Russian Chemical Reviews

Uspekhi Khimii

August 1960

ADVANCES IN THE CHEMISTRY OF BARBITURIC ACIDS

R.Ya.Levina and F.K.Velichko

CONTENTS

Introduction 437

I. Advances in the synthesis of barbituric and thiobarbituric acids 438

A. Reactions in an acid or neutral medium 438

1. Preparation of barbituric and thiobarbituric acids from malonic acid chlorides 438

2. Preparation of barbituric and thiobarbituric acids from malonic acids 438

3. Preparation of barbituric acids from other nitrogenous heterocyclic compounds 439

B. Reactions in an alkaline medium 440

4. Preparation of barbituric and thiobarbituric acids from malonic esters 440

5. Preparation of barbituric and thiobarbituric acids from lactonic esters 442

6. Preparation of barbituric and thiobarbituric acids from cyanoacetic esters 442

7. Preparation of barbituric acids from amides of malonic acids 443

8. Preparation of barbituric and thiobarbituric acids by cyclisation of *N*-substituted ureas 443

II. Reactivity of barbituric and thiobarbituric acids 444

1. Tautomerism 444

2. General stability of the 2,4,6-trioxohexahydropyrimidine nucleus 445

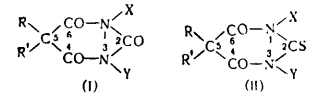
3. Reactions of barbituric acids involving the mobile hydrogen atoms 446

4. Reactions of barbituric and thiobarbituric acids involving the carbonyl (thiocarbonyl) groups 451

III. Detection, identification, and determination of barbituric acids 452

INTRODUCTION

Barbituric acids (I) and (II) are compounds containing the 2,4,6-trioxohexahydropyrimidine or 2-thio-4,6-dioxohexahydropyrimidine ring; in the latter case they are designated as 2-thiobarbituric or simply as thiobarbituric acids:



(I) (II)

Although one representative of this class of substances — hydurilic acid (5,5'-bisbarbituric) — had been prepared by Schlieper[1] as long ago as 1845, very little was known about the barbituric acids until the beginning of the 20th century, when Fischer and coworkers worked out a convenient method for their synthesis[2] and observed their well-known therapeutic properties[3].

In the course of the last 25 years our knowledge of the barbituric acids has extended remarkably. In addition to their soporific and analgesic properties, barbituric acids possess antiinflammatory[4], antisclerotic[5], and bacteriostatic[6-8] properties; they lower the blood pressure[9-11], they find use in the treatment of sugar diabetes[12] and as antidotes against adder poison[13]. Barbituric, and especially thiobarbituric acids, are used in photography[14-31], as antioxidants[32-34], and as catalysts for the polymerisation of

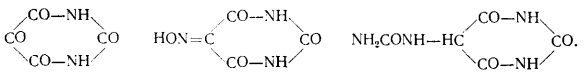
halogenated vinyl monomers[35] and of styrene[36]. Azo-dyes containing the 2,4,6-trioxohexahydropyrimidine nucleus possess a good covering power, and are suitable for the dyeing of wool, silk, and cellulose[37-39].

Barbituric acids are finding more and more applications in analytical chemistry: for the preparation of buffer solutions in the range pH 6–9, where only a few substances are suitable[40], as very sensitive indicators in acidimetric titration[41], as reagents for the determination of small quantities of Ag, Hg, Cu, Pd, Pt, Ir, In, Au[42], and also of chloride and cyanide ions[43]. Barbituric acid (I) (where R = R' = X = Y = = H) condenses with formaldehyde, giving useful resins[44]. The insecticide[45] and herbicide[46] action of barbituric acids may also be mentioned.

Apparently, barbituric acids play a not insignificant part in biological processes. Desoxyribonucleic acids, which are supposed[47] to carry the hereditary factors in chromosomes, contain thymine groups, which gives barbituric acid on biological oxidation[48,49]. The pyrimidine ring enters into the molecule of vitamin B_2 (riboflavine); among the metabolic products of *Lactobacillus casei*, barbituric acid is found after introduction of this vitamin into the nutritional medium[50]. A series of microorganisms assimilate barbituric acid, using the energy of its decomposition to CO_2, NH_3, and malonic acid for their life processes[48,51-53].

Up to the present, nearly 2000 barbituric acids have been synthesised. Some of these are produced on a commercial scale. In the USA the yearly production of barbituric acids amounts to 300–400 tons[54]; in the USSR the production is rapidly growing and the output of barbituric acids in 1955 exceeded that of 1950 by 204%[54].

In a review article we cannot deal with all the details of the chemistry of barbituric acids; in what follows the most important aspects of their synthesis and chemical properties are considered, with a brief mention of all secondary questions and a list of the relevant literature. As a basis, only "typical" barbituric and thiobarbituric acids are taken, in which the substituents in position 5 are linked with the hexahydropyrimidine nucleus by a carbon–carbon bond, while X and Y may be any groups. Such a limitation may be artificial to a certain extent, but at the same time, it is necessary to separate the barbituric acids from derivatives of alloxan (III), and violuric (IV) and pseudouric acids (V):



(III) (IV) (V)

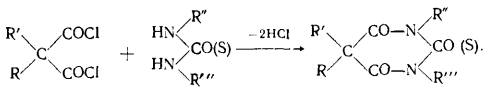
I. ADVANCES IN THE SYNTHESIS OF BARBITURIC AND THIOBARBITURIC ACIDS

From the practical point of view it is important to distinguish between methods applicable in acid (or neutral) and in alkaline media. The first include syntheses of barbituric acids from malonic acids and their acid chlorides and also from alloxan and other heterocyclic compounds related to barbituric acids; the second includes the synthesis of barbituric acids from malonic and cyanoacetic esters, from amides of malonic acids, from lactonic esters, and also from derivatives of urea, cyclised for the most part in the presence of alkaline condensing agents.

A. REACTIONS IN AN ACID OR NEUTRAL MEDIUM

1. Preparation of Barbituric and Thiobarbituric Acids from Malonic Acid Chlorides

One of the oldest methods of preparation of barbituric acids is the reaction of the acid chlorides of substituted malonic acids (malonyl chlorides) with urea* or thiourea[56-73]:



This reaction does not require condensing agents and occurs in neutral solution under relatively gentle conditions (~ 100°, 5–6 h); therefore synthesis of barbituric acids unstable under the conditions of alkaline condensation is possible. Thus, 5,5-diphenylbarbituric acid, which could not be synthesised from 5,5-diphenylmalonic ester[74], has been prepared from the acid chloride of diphenylmalonic acid[75]. The reaction with malonyl chlorides is particularly convenient for the preparation of 1,3-disubstituted barbituric acids[63,76]. *N,N'*-diphenylthiourea in general does not react with malonic esters, while its condensation with the acid chlorides of malonic acids takes place spontaneously[67].

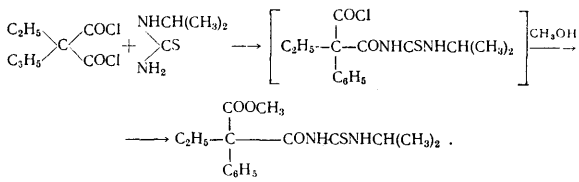
The condensation of the acid chlorides of malonic acids with urea usually occurs with equimolar proportions of the components without a solvent[56,57,62-64,68], or in ether[77], chloroform[65], toluene[58], xylene[62], dioxane[61], or pyridine[70].

In the reaction of thiourea with malonyl chloride many resinous reaction products are formed together with the thiobarbituric acid[60,78].

The principal side reactions in the barbituric acid synthesis are acylation of the barbituric acid already formed and the thermal dissociation of the *N*-substituted urea[67]. The following series of *N*-substituted ureas is arranged in order of increase of thermal instability[79,80]:

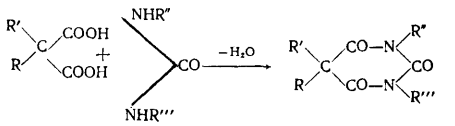
$$CO(NH_2)_2 \leqslant CO(NHCH_2C_6H_5)_2 < CO(NHC_6H_{13})_2 \leqslant CO(NHC_3H_5)_2 = $$
$$= CO[NHCH(CH_3)_2]_2 < CO[NHC(CH_3)_3]_2.$$

According to the observations of Boon and coworkers[78], α-ethyl-α-phenylmalonyl chloride reacts anomalously with *N*-isopropylthiourea, forming (after working up the product with CH_3OH) *N*-(α-methoxycarbonyl-α-phenylbutyryl)-*N'*-isopropylthiourea:



2. Preparation of Barbituric and Thiobarbituric Acids from Malonic Acids

The condensation of malonic acids with urea in the presence of a dehydrating agent,

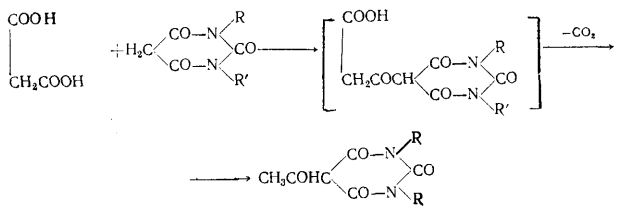


was the first preparative method for the synthesis of barbituric acids[81]. Since then, this reaction has been repeatedly

* Instead of urea 1-cyanoguanidine, NH = $C(NH_2)NHCN$, can be used[55].

used for the synthesis of *N*-substituted barbituric acids[57,67,68,73,76,82-94]. Phosphorus oxychloride[57,76,81,84,85,88,90,92,93], acetic anhydride[68,82,83,86,89,91,94], and acetyl chloride[76,87] have been used as condensing agents. The advantage of the latter two agents is that under the action of the water removed during the condensation, they decompose into acetic acid, easily removable from the reaction medium; however, the possibility of acetylating the already-formed barbituric acids is a serious drawback. None of the condensing media mentioned possesses an obvious advantage[76]. With phosphorus oxychloride, the reaction is carried out in chloroform; the acetic anhydride and acetyl chloride themselves serve as solvents, or the reaction is carried out in glacial acetic acid; the temperature varies between 50° and 100°.

The sphere of application and effectiveness of the methods of preparing barbituric acids from malonic acids and from malonyl chlorides are approximately the same. However, the significantly smaller thermal stability of the malonic acids[95], in comparison with their esters or acid chlorides, gives rise to a variety of side reactions, which much reduces the value of the method, making it impossible to synthesise a number of barbituric acids in this way (e.g. 5-halogeno or 5-alkenyl derivatives). The important side reaction is the acylation of the barbituric acid already formed by a second molecule of malonic acid[57,67,85,92]. A part of the malonic acid is also expended on the acylation of the second component of the reaction — urea or its derivatives[57]:

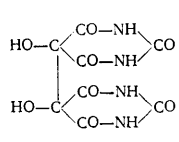


On increasing the scale, the quantity of acylated side products increases disproportionately quickly[57], which lowers the yields of barbituric acids in large batches; in order to suppress this side reaction, it is necessary to avoid excess of urea[91] and prolonged heating of the reaction mixture[92]. The formation of malonuric acids[89] and their amides[94] as by-products has also been noted.

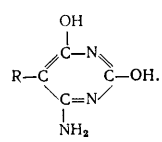
Attempts to avoid the difficulties due to the instability of the malonic acids by replacing the latter by cyanoacetic acid[56], and also by the use of 1-cyanoguanidine[55] were unsuccessful.

3. Preparation of Barbituric Acids from Other Nitrogenous Heterocyclic Compounds

The initial heterocyclic compounds for the synthesis of barbituric acids are most often alloxan, alloxantin (VI), and derivatives of aminouracil (VII):



(VI)



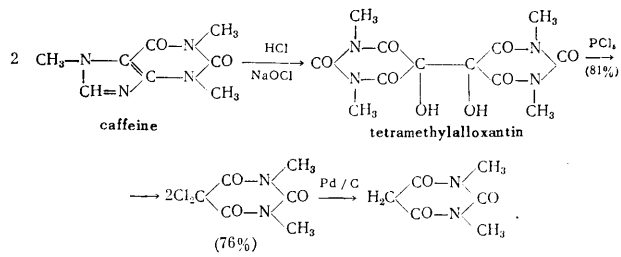
(VII)

Alloxan condenses with compounds containing an active methylene group in the presence of 20% oleum, acetic anhydride, or concentrated hydrochloric acid, to form 5-alkylidenebarbituric acids or 5-substituted-5-hydroxybarbituric acids which are later transformed into 5-mono-substituted barbituric acids[62,96-99].

In the reaction of alloxan with benzene in the presence of sulphuric acid 5,5-diphenylbarbituric acid is formed with a five-membered oxide as a by-product[62,98,99].

A series of syntheses of barbituric acids from their 5,5-dihalogeno-, 5-hydroxy-, 5-nitroso-, and other derivatives has been described, starting usually with alloxan[77,100-103].

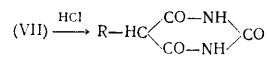
Alloxantin was already used at the time of Bayer[104] for the preparation of *N*-substituted barbituric acids, which are formed by heating alloxantin with concentrated sulphuric acid. A very economical synthesis of 1,3-dimethylbarbituric acid from tetramethylalloxantin (prepared from caffeine) has been described[86]:



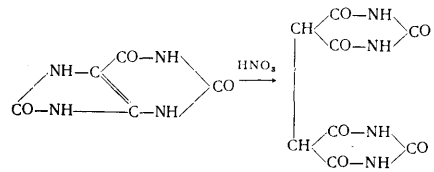
caffeine — tetramethylalloxantin

In the preparation of 1,3-dimethylbarbituric acid from malonic ester and dimethylurea the yield does not exceed 37%.

It is easy to prepare barbituric acids from aminouracil (VII)[105-107]:



Uric acid can be converted into 5,5'-bisbarbituric acid[1,108]:



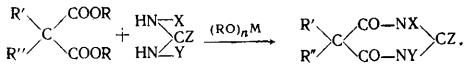
Other examples of the preparation of barbituric and thiobarbituric acids[67,109] from related heterocyclic compounds have been described.

B. REACTIONS IN AN ALKALINE MEDIUM

4. Preparation of Barbituric and Thiobarbituric Acids from Malonic Esters

At the present time the most commonly used method of preparation of barbituric and thiobarbituric acids is the condensation of malonic esters with urea, thiourea, guanidine, or their derivatives, in an alcoholic medium in

the presence of alcoholates of alkali- or alkaline-earth metals:



where Z = 0.5 or NH*; n = 1 or 2.

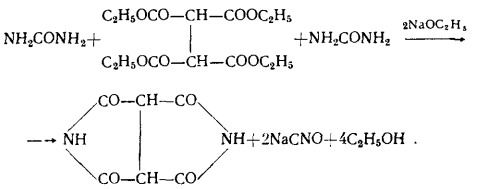
The majority of known barbituric and thiobarbituric acids have been synthesised by this method[11,30,37,55,62,68,73,74,78,105,108,110-263].

The merits of the method described are its universality, the relative accessibility of the original malonic esters, the high yields (70–98%) of barbituric acids, and their purity, which is particularly important in pharmacological investigations[200].

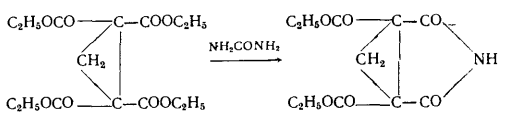
At the same time, the method has definite limitations. The malonic esters containing, for example, 1-alkenyl[110,149], cyclopropyl[264-268], β-hydroxyalkyl[242], or heterocyclic[121,146,162,267] radicals, and also substituted malonic esters with a keto group in the β-position[268-270], are not stable in an alkaline medium. However, for this group of esters the suggestion of Jacobson[271] that the monosodio derivative of urea, $NH_2C[ONa]=NH$, be used as second component may prove fruitful, because the monosodio derivative reacts with malonic esters in the absence of a condensing agent at room temperature giving barbituric acids in a yield of ~80%.

Arylalkyl-, diaryl-, and t-alkylbarbituric acids cannot be conveniently prepared from the corresponding malonic esters on account of the difficulty of obtaining these, and the low yields of the barbituric acids[62,151,228,272,273]. It was not possible to synthesise 5,5-diphenyl-[74], 5-p-nitrophenyl-[274], 1-methyl-5-isopropyl-5-β-diethoxyphosphoryloxyethyl-[11], 5-propyl-5-α-ethoxyvinyl-[110], and 5-ethyl-5-α-butoxyvinylbarbituric[110] acids in this way. Bisalkylmalonic esters, $(C_2H_5OCO)_2CRCR(COOC_2H_5)_2$, and also certain alkylidenemalonic esters, do not react with urea in the presence of sodium ethylate[275]. It is also impossible to prepare 1,3-dialyl- and 1,3-diarylbarbituric acids by the condensation of malonic esters with substituted ureas[275,276].

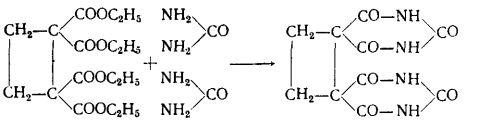
Unexpectedly, ethanetetracarboxylates and urea do not form bisbarbituric acid, but ethanetetracarboxydiimide[252]:



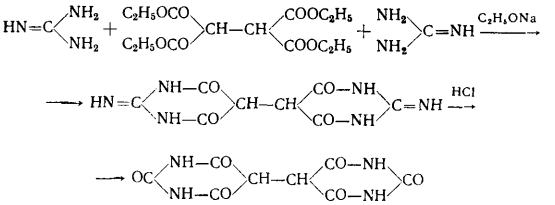
The reaction between cyclopropanetetracarboxylates and urea proceeds analogously[277]:



It should be noted that the cyclobutanetetracarboxylates under the same conditions give the "normal" product of the reaction, cyclobutanebisspirobarbituric acid[277]:

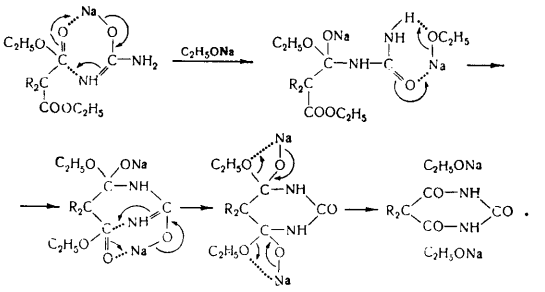


Ethanetetracarboxylates react normally with guanidine hydrochloride forming diiminohydurilic acid, which on boiling with hydrochloric acid is transformed to hydurilic acid[108]:



The mechanism of the condensation of malonic esters with urea in the presence of sodium ethylate has not been investigated in detail. It is quite probable that, as suggested by Skinner and coworkers[278], the reaction proceeds via the formation of the sodio derivative of urea.

Considering, according to the theory of Nesmeyanov and coworkers[279,280], the possibility that the process proceeds with the transfer of the reaction centre, one can regard the condensation mechanism as a threefold "diene" synthesis with the participation of σ,π-conjugated bonds:

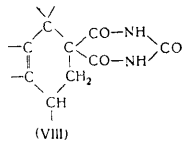


The great facilitation of the reaction on replacing the urea by guanidine, thiourea[278], or monosodiourea[271] favours such a scheme, as does also the need for an excess of alcoholate to obtain maximum yields of the barbituric acids[281].

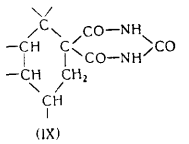
The structure of both components exerts an enormous influence on the course of the reaction and the yield of barbituric acids. As a rule[117,118], monosubstituted malonic esters condense more easily with urea than do the disubstituted derivatives; with increase of branching of the substituent, particularly at the α-carbon atom, the reactivity of the malonic esters is reduced[118,166]. This explains the difficulty

* When Z = NH, the product of the reaction is transformed to barbituric acid by hydrolysis with hydrochloric acid.

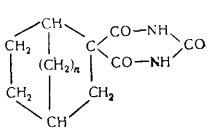
encountered by Levina and coworkers[128,170,172,180,277,282] in the synthesis of "spiro"-barbituric acids of types (VIII), (IX), and (X):



(VIII)



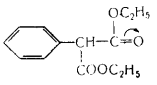
(IX)



(X)

n = 1 or 2

A phenyl group at the α-carbon atom of the malonic ester[98,283] powerfully inhibits the condensation; this is evidently connected with a reduction of the electron density on the O atom in the system (cf. the above scheme of condensation):

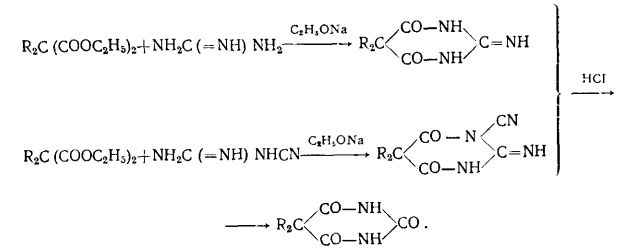


Electron-donating *ortho*- or *para*-substituents in the benzene ring considerably weaken its inhibiting action[74]. The inhibiting influence of the naphthyl radical is weaker in comparison with the phenyl[204]. Electron-acceptor substituents (such as the NO_2 group, for example) in the α-position to the ethoxycarbonyl group of the malonic ester makes the condensation more difficult[147,148,152,201]. Difficulty has also been encountered in the preparation of 5-trimethylsilylmethyl-[171] and 5-alkylsulphonylmethylbarbituric acids[207] from the corresponding malonic esters:

$(CH_3)SiCH_2CH(COOC_2H_5)_2$; $RSO_2CH_2CH(COOC_2H_5)_2$.

In place of the ethyl esters of malonic acids, the butyl[167,200] or methyl esters can enter into the reaction[62]. Sodiomalonic ester has also been used[140].

As second component of the condensation, urea, guanidine[112,155,167,187,191,238,244,261,263,284], and 1-cyanoguanidine[55,202,285] are employed. The use of the last two reagents leads to the formation of products requiring additional working up for transformation to barbituric acids:



The length of the carbon-carbon chain of the substituents of the N-alkylureas does not influence the course of the reaction[125]. N-Phenylurea condenses with malonic esters more easily than N-alkylurea[281]; symmetrical N,N'-diarylureas do not form barbituric acids with disubstituted malonic esters[2,86], while with monoalkylmalonic esters the reaction goes easily and the yields of barbituric acids exceed 60%[86].

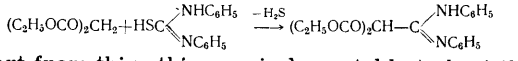
The best condensing agent is sodium ethylate[82,130,281,286-288], but CH_3ONa[62,78,82,139,141,162,167], iso-C_3H_7ONa[114], C_4H_9ONa[138,145,227], $C_5H_{11}ONa$[289], $(CH_3O)_2Mg$[111,122,124,130,153,177,190,286], caustic alkalis, $NaNH_2$, Na-cyanamide[290], and $CaCl_2$[226,290] have also been used. Most commonly, the condensation in the presence of sodium ethylate is carried out in absolute ethyl alcohol. Reactions in toluene[129] or without solvent[163,193] have also been described. Constancy of temperature during the reaction ensures constancy of yields[286].

The condensation of malonic esters with urea is often complicated by side reactions. Among the products formed in this way the following have been separated: esters of carbonic acid[115,194], esters and amides of monocarboxylic acids, esters of carbamic acid*, and esters of malonamic acids[74,76,113,115,162,194,291].

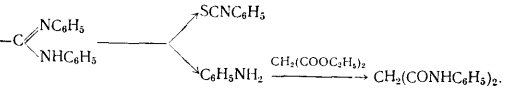
The very reactive 5-monoalkylbarbituric acids are oxidised by atmospheric oxygen to 5-hydroxy-5-alkylbarbituric acids[293-295].

Malonic esters react more easily with thiourea than with urea[140,278], and form 2-thiobarbituric acids. However, the yields are, as a rule, lower than those of the corresponding O-analogues, which is explained by the greater complexity of the reaction.

In view of the relatively great tendency to thiol formation[296], thiourea may react in the thiol form with the CH_2 group of the malonic ester[276]:



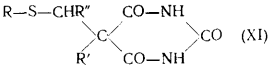
Apart from this, thiourea is less stable to heat than urea, and one of the products of its thermal decomposition may in its turn condense with the malonic ester[276]:



With a large excess of thiourea, the malonic ester may condense with two of its molecules[291]; for example:

$$R_2C(COOC_2H_5)_2 + 2NH_2CSNHCH_2CH = CH_2 \rightarrow$$
$$\rightarrow R_2C(CONHCSNHCH_2CH = CH_2)_2 + 2C_2H_5OH.$$

Comparison of a series of results from the literature shows that in the preparation of thiobarbituric acids by this method the behaviour of the reaction system is often the reverse of that observed for barbituric acids. While branched malonic esters give better yields of barbituric acids when sodium butylate is used, than with sodium ethylate, the reverse is generally true in the condensation with thiourea[166]. In the synthesis of barbituric acids of structure (XI),



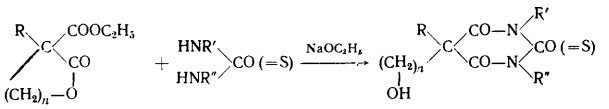
(XI)

an excess of sodium ethylate usually favours the condensation[118], but thiobarbituric acids of the same type can be prepared only with an equivalent quantity of sodium ethylate[117,118]. The condensation of malonic esters with urea in the presence of $(CH_3O)_2Mg$ gives barbituric acid in a 96% yield; the analogous synthesis with thiourea leads to the formation of only an insignificant yield of thiobarbituric acid[298]. In the synthesis of barbituric acids an excess of alcohol is immaterial, but the yield of thiobarbituric acid is sharply lowered thereby[297]. The best condensing agent for the synthesis of thiobarbituric acid is apparently lithium ethylate[297].

* Esters of carbamic acid may be formed during the alcoholysis of urea[292].

5. Preparation of Barbituric and Thiobarbituric Acids from Lactonic Esters

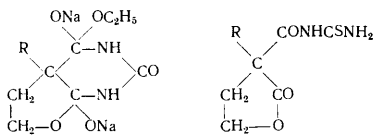
The particular method of the synthesis of barbituric acids from lactonic esters,



is directly related to the possibility of preparing barbituric acids from malonic esters, as lactonic esters are easily prepared from the latter, but differs in its gentler reaction conditions. The advantages of this method are clearly shown in the case where the reactants are unstable to heat, particularly in the presence of alkali, e.g. the preparation of 5-(β-hydroxyethyl)- and, in particular, of 5-(2-hydroxyprop-2-enyl)barbituric acid[299]*.

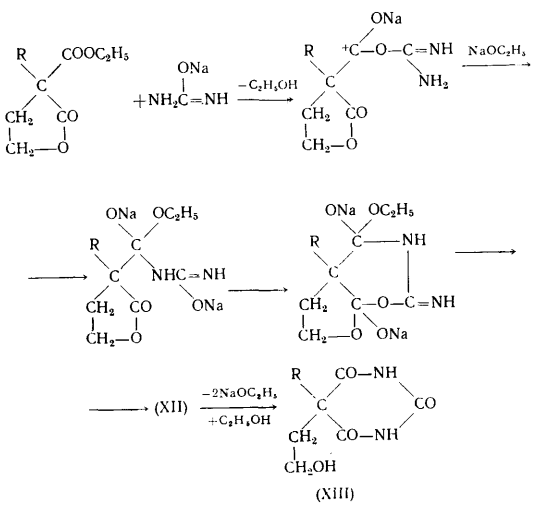
The application of the method has been limited, because, up to the present, only γ-lactonic esters have been used[112, 146,148,165,278,299-303]. Also, according to the investigations of van Zyl and van Tamelen[303], monosubstituted barbituric acids cannot be prepared by the condensation of the corresponding lactonic esters with urea.

The following intermediates have been isolated[278,302]:

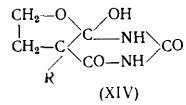


(XII)

on the basis of which Skinner and coworkers[278] have suggested the following scheme for this reaction:



The product of the reaction can have the β-hydroxyethyl (XIII) or the hemiacetal (XIV) structure,

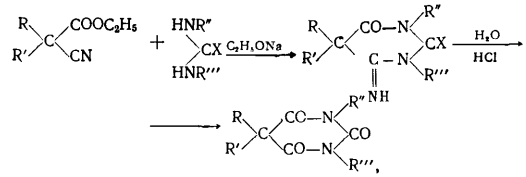


(XIV)

the consequence of which is that there is a certain dualism in the chemical behaviour of barbituric acids of this kind[148]. As alcohols they form chloroalkylbarbituric acids with fuming hydrochloric acid; at the same time, alkaline hydrolysis does not give a trace of unsaturated acids.

6. Preparation of Barbituric and Thiobarbituric Acids from Cyanoacetic Esters

By the interaction of cyanoacetic esters with urea (or guanidine) in the presence of an alkaline condensing agent, an iminobarbituric (or diiminobarbituric) acid is first formed, and subsequently hydrolysed to barbituric acid by mineral acids:



where X = O or = NH.

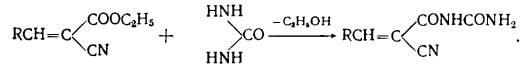
In the USSR this method is used for the commercial synthesis of hexenal (sodium salt of 5-cyclohexenyl-3,5-dimethylbarbituric acid)[304].

Having much in common with the syntheses of barbituric acids from malonic esters (for example identical conditions of reaction, the same condensing agents), this method possesses the defect of involving two stages, although the loss of product at the stage of the hydrolysis of the imino-acid is usually not great*.

The yields of barbituric acids synthesised by this method[132,137,169,178,263,304-321], are lower in the majority of cases, than by synthesis from malonic esters[137,311].

However, inhibition due to steric hindrance is not so strong in the case of cyanoacetic esters as in condensations with malonic esters, and this explains the advantages of this method for the preparation of barbituric acids with α-branched substituents[306], spirobarbituric[175], and 5-substituted 5-phenylbarbituric acids[307].

Alkylidene- or arylidenecyanoacetic esters do not form the corresponding iminobarbituric acids[315]; the reaction stops at the stage of the alkylidenecyanoacetyl urea:



It was not possible to prepare 5-(4-thiazolyl)barbituric acid by this method in consequence of resinification of the reaction mixture[315].

* The reference (299) is incorrect (Ed. of Translation).

* The hydrolysis of 2-thioiminobarbituric acids is accompanied by the formation of the corresponding barbituric acids[175,318].

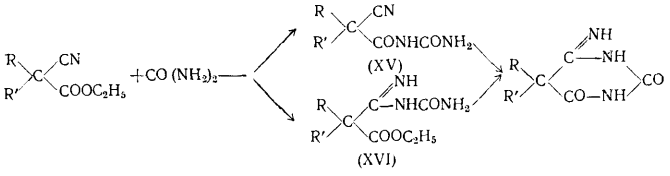
As the synthesis of barbituric acids from cyanoacetic esters is a two-stage reaction, the use of guanidine instead of urea [242,263,305,310,312,313,315,318] is completely justified in all cases, since the number of stages is not increased, and the duration of the reaction is diminished [305,322]. Instead of urea 1-cyanoguanidine [313] can also be used.

In the reaction mixture the cyanoacetic esters also undergo some alcoholysis involving splitting off the ethoxycarbonyl group and the formation of the nitrile, the yield of which may amount to 60% [305,311]:

$$R_2C(CN)COOC_2H_5 + C_2H_5OH \xrightarrow{NaOC_2H_5} R_2CHCN + CO(OC_2H_5)_2.$$

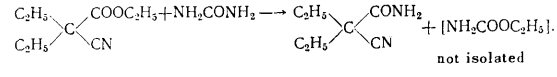
The replacement of sodium ethylate by isopropylate, and of urea by guanidine, diminishes the extent of alcoholysis [305].

In Lund's opinion [315] the formation of iminobarbituric acids from cyanoacetic esters proceeds in two ways:



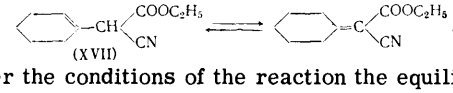
As the cyclisation of compound (XVI) occurs very easily, it is not possible to detect it in the reaction mixture; the cyclisation of compound (XV) occurs with difficulty. Thus, the results of the condensation depend on the rates of formation of (XV) and (XVI), in view of which the ratio of the iminobarbituric acid and cyanoacetyl urea (XV) remains almost constant on carrying out the reaction under various conditions. Cyanoacetyl urea has been repeatedly found among the products of the reaction [318,321].

Conrad and Zart [319] separated diethylcyanoacetamide from the reaction mixture in the preparation of 5,5-diethylbarbituric acid from diethylcyanoacetic ester and urea:



Lund [315] noticed an interesting complication in a reaction involving cyanoacetic esters with a double bond in the β-position to the CN group: α-(cyclohex-1-enyl)cyanoacetic ester (XVII) does not form iminobarbituric acid, decomposing only to α-(cyclohex-1-enyl)cyanoacetylurea, while the α-ethyl derivative (XVIII) condenses with urea to 5-ethyl-5-(cyclohex-1-enyl)-4-iminobarbituric acid.

The reason for such a difference in the behaviour of substances (XVII) and (XVIII) consists, according to the author, in the presence of tautomers in the first of them:



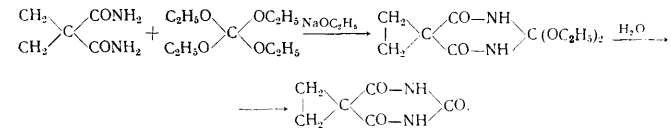
(XVII)

Under the conditions of the reaction the equilibrium is almost wholly driven to the side of the alkylidene derivative incapable of cyclisation with urea (cf. p. 442). Such an isomerisation is impossible for (XVIII) and the reaction proceeds normally.

7. Preparation of Barbituric Acids from Amides of Malonic Acids

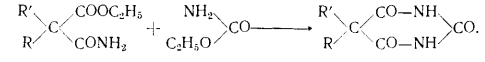
The possibility of preparing barbituric acids from amides of malonic acids bridges the gap to syntheses carried out in an acid medium, since this reaction can occur not only in alkaline, but also in neutral and even in an acid medium, according to the stability of the second component.

The condensation of malonic diamides with orthocarbonates takes place in the presence of sodium ethylate without heating [323], for example:



Diphenyl carbonate forms diethylbarbituric acid with diethylmalonic diamide only on heating for 18 h at 200°–280° [324]. 5-Phenyl- and 5,5-diphenylbarbituric acids were prepared by heating the corresponding malonic diamides with oxalyl chloride in benzene without a condensing agent [62,162]. A series of barbituric acids have been synthesised by the condensation of malonic diamides with phosgene (in toluene, 150°) [62,187].

Tanaka and Sugawa [325] found that the esters of carbamic acid condense with esters of malonamic acids in the presence of isopropylate, cyclohexylate or sodium amide to the corresponding barbituric acids:

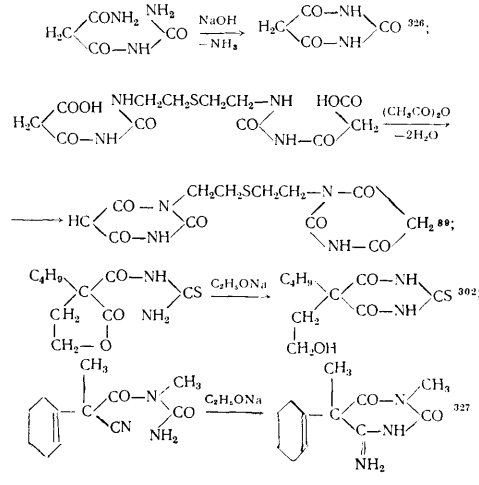


Malonamic esters condense in the presence of sodium ethylate with urea, forming barbituric acids [319].

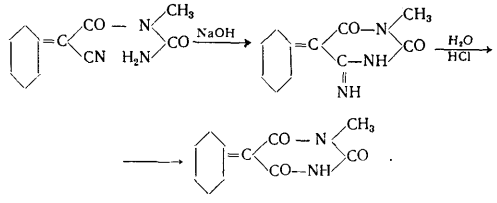
Esters [94] and ureides [70] of malonuric acids have also been used for the preparation of barbituric acids, without much success.

8. Preparation of Barbituric and Thiobarbituric Acids by Cyclisation of *N*-Substituted Ureas

The cyclisation of derivatives of urea to barbituric and thiobarbituric acids has no value for synthesis, but it indirectly indicates the possibility of *N*-derivatives of urea capable of cyclisation to barbituric acids being intermediates in the above reactions. For example:



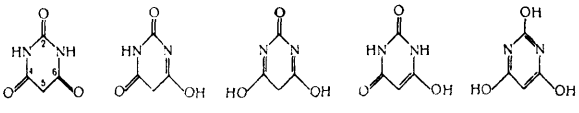
Nakamura[328] synthesised 1-methyl-5-cyclohexylidene-barbituric acid in 90% yield by heating cyclohexylidene cyanoacetylmethylurea with 10% caustic soda and subsequent acid hydrolysis of the reaction product:



This fact clearly contradicts Lund's view that alkylidene-cyanoacetic esters are not capable of forming barbituric acids with urea[315]. By an analogous method Nakamura prepared some 5-Δ^1-cyclohexenylbarbituric acids[328].

II. REACTIVITY OF BARBITURIC AND THIO-BARBITURIC ACIDS

The hexahydropyrimidine nucleus of barbituric acid, which contains three carbonyl groups and four mobile hydrogen atoms, possesses a high degree of reactivity. The variety of possible chemical transformations of barbituric acids is further increased because trioxohexahydropyrimidines are capable of a multiplicity of enolic forms. To date, derivatives of the following forms of barbituric acid have been described:



The possibility of the formation of the conjugated-bond systems,

$$\overset{\frown}{CH}=C^{+}-\overset{\frown}{O}^{-} \text{ and } \overset{\frown}{O}=C-\overset{\frown}{N}-H$$

determines the power of trioxohexahydropyrimidines to react at different active centres; for example, alkylation occurs under some conditions at the nitrogen, and under other conditions at carbon atom 5.

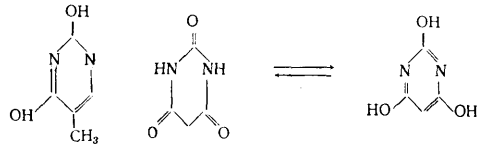
As it possesses two mobile atoms of hydrogen in position 5, barbituric acid may enter into almost all the reactions characteristic of malonic esters. In addition to this, the carbonyl group is capable of being reduced, of condensing with compounds containing mobile hydrogen atoms, and of exchanging its oxygen for halogen atoms.

Thiobarbituric acids are even more reactive, as the sulphur in position 2 may become quadrivalent and the C=S bond is relatively easily reduced.

1. Tautomerism

In the light of all that has been said above, the question of the possibility, the nature and the direction of tautomeric transformations in the series of barbituric acids is highly significant. Unfortunately, in spite of the large number of investigations in this field[19,57,75,79,85,251,293,294,329,337], the problem has not received a final solution.

The spectra show that barbituric acids enolise in solutions. Heyroth and Loofbourow[331], comparing the ultraviolet spectra of different pyrimidines, discovered that as the number of double bonds increases the absorption maxima shift to the long-wave part of the spectrum. Noticing the proximity of λ_{max} for barbituric acids and thymine,

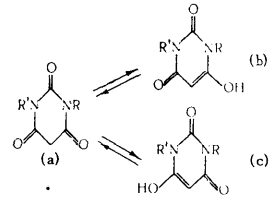


thymine barbituric acid

the authors suggested that the trienol tautomer of barbituric acids exist, but only in a strongly alkaline medium[338]. The existence of the trienol form, however, became doubtful when it was established[329], in 1952, that barbituric acid has a spectrum similar to that of 1-methylbarbituric acid, in which the trienol form is impossible. Even earlier[251,336], the analogy in the spectra of barbituric, 5-methylbarbituric, and 1,5-dimethylbarbituric acids was noted. In addition, in view of its aromatic structure, the trienol form should give a considerably lower extinction coefficient than is actually observed[329].

Erlenmeyer and coworkers[339] showed that in heavy water all four hydrogen atoms of barbituric acid are replaced by deuterium. From this it follows that the enolisation can proceed at least in one pair of neighbouring atoms, for example, in the following positions: 1, 2; 1, 6; and 5, 6; or 2, 3; 3, 4; and 4, 5.

The majority of investigators[57,251,329,336,340] consider that mono- and disubstituted barbituric acids in aqueous solutions undergo only single enolisation; for example, for 1,3-disubstituted barbituric acid the forms (a), (b), and (c) are possible:



Form (a) should be stable in acid, and forms (b) and (c) in alkaline solutions (pH = 7–11)[57,329]. With a rise of alkalinity of the medium, the degree of enolisation increases, as shown by the increase of u.v. absorption[57,251,333].

Sheinker and Pomerantsev[341] have demonstrated that barbituric acid is trioxohexahydropyrimidine in the crystalline state; in its infra-red spectrum there are intense bands corresponding to the CO groups and no absorption band is observed, which could be related to C=C or C=N linkages.

Interesting data on the barbituric acid tautomerism in solution may be gained from the investigation of their acid properties. In view of the high ionisation constant of barbituric acid in comparison with those of 5,5-dialkylbarbituric acids, Wood and Anderson[94] concluded that unsubstituted barbituric acid exists in solution in the enol form. However, alkylation of the sodium salts of barbituric acids yields *C*- or *N*- derivatives, not those of the enol form.

According to the observations of Biggs[334], 5,5-diethyl--1,3-dimethylbarbituric acid cannot enolise, neither does it exhibit acid properties. Its alcoholic solutions do not possess a band in the region of 241 mμ, where less substituted barbituric acids possess more or less intense absorption

bands. 5-Cyclohexenyl-1,5-dimethylbarbituric acid, in which enolisation is possible only in the 2,3- or 3,4-positions, shows weak acidity. If neither nitrogen atom carries substituents, the enolisation being thereby appreciably facilitated, the acidity is strongly increased. Barbituric, 1-methylbarbituric, and 1,3-dimethylbarbituric acids have close pK values, apparently because the enolisation in the 2,3- and 3,4-positions in the first two is weak.

The chemical transformations of barbituric acids are complicated, as it is necessary to assume the existence of all the forms described above in equilibrium with one another. Apparently, such difficulties can be overcome by considering charge displacement.

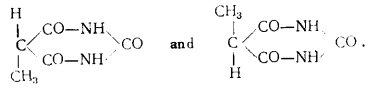
$$H-\overset{\frown}{N}-C=\overset{\frown}{O}^{(-)} \text{ or } H-\overset{\frown}{CH}-C=\overset{\frown}{O}^{(-)},$$

in the ring of the barbituric acids under the influence of various factors (medium, irradiation, chemical reagents). The trioxohexahydropyrimidine system is strongly polarisable, and such electron displacements may be accomplished in it with relative ease.

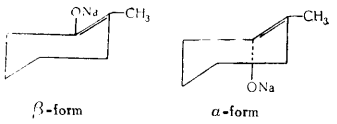
Thus, derivatives of numerous "tautomers" can be formed in the reaction, as a consequence of the distribution of electron density in the pyrimidine ring* characteristic of each case [75,92,105,133,293,332,335,342-344].

The spectra of the barbituric acids apparently reflect differences of the degree of polarisability of the trioxohexahydropyrimidine system dependent on the nature and distribution of substituents in the nucleus.

In the series of 5-monosubstituted barbituric acids stereoisomerism is possible as a consequence of the hindrance to the rotation of the ring by heteroatoms**:



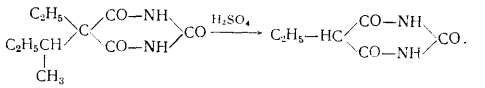
Nishikawa [294] succeeded in separating α- and β-forms of the sodium salts of these acids, differing in solubility and pH of their solutions**:



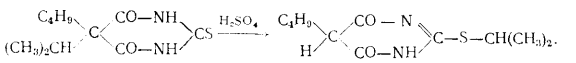
On heating, the α-form is transformed into the β-form. Stereoisomerism may also arise due to asymmetric centres in the side chains of barbituric acids [63,345]. In the case of tetraalkylbarbituric acids, the separation of such stereoisomers into their enantiomorphs is extraordinarily difficult, because they are neutral substances and do not give salts with optically active bases or acids [63].

2. General Stability of the 2,4,6-Trioxohexahydropyrimidine Nucleus

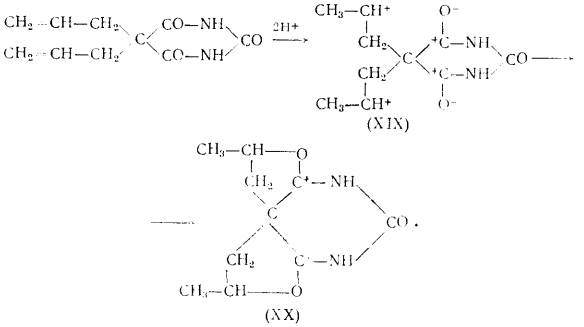
The 2,4,6-trioxohexahydropyrimidine nucleus is, in general, fairly stable to the action of various chemical reagents. It is not affected by such reducing agents as $SnCl_2/HCl$ [101,346-248] and zinc-dust in CH_3COOH [349] or water [350], or on hydrogenation in the presence of PtO_2 [37,274]. The aromatic nuclei of phenylbarbituric acids can be nitrated [37,274,351-353] and sulphonated [352] under the usual conditions without disruption of the pyrimidine ring. The pyrimidine nucleus of barbituric acids containing an amino group in the substituent chain is not ruptured during diazotisation and coupling [37,274,278,347,353]. Cold concentrated H_2SO_4, as a rule, does not split the nucleus of barbiturates [208,354,355]; however, in the case of 5,5-dialkylbarbituric acids containing a secondary alkyl, the latter is split off by the action of H_2SO_4 [355,356]:



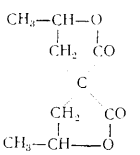
Monoalkylbarbituric acids, even those containing a secondary alkyl, are not changed by the action of H_2SO_4 [355]. Under analogous conditions, thiobarbituric acids isomerise into S-alkylated reaction products [357]:



Allyl groups in position 5 diminish the stability of the trioxohexahydropyrimidine nucleus, evidently on account of the possible formation of the unstable carbonium ion (XIX), later cyclising to (XX) [355]:



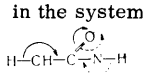
The ion (XX) becomes later stabilised in one way or another. Actually, 5,5-diallylbarbituric acid is easily transformed by concentrated H_2SO_4 into the lactone



Apparently the same substance was obtained by Leuchs and Lemcke [358] by the action of fuming HBr on diallylbarbituric acid.

Spirobarbituric acids can also be split by the action of HBr [150]. The nucleus of 5,5-dialkylbarbituric acids is not split on boiling with concentrated HBr, and only sometimes is a secondary alkyl removed, as by the action of H_2SO_4 [152,355]. On heating barbituric acid with concentrated HCl to 200°, the pyrimidine ring is broken down, malonic acid, urea, ammonia, acetic acid, and CO_2 being formed [109].

* This distribution may be anticipated from a knowledge of the electron structure of the reactants and the influence of the medium. In particular, in the system



the electron displacement in the direction of the continuous arrows is preferred to that of the dotted arrows.

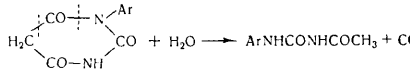
** These statements follow the abstract quoted [294]; they would not now be considered valid (Ed. of Translation).

Aluminium chloride, like sulphuric acid, removes alkyl groups from barbituric acids; but it does not form *S*-alkyl derivatives from thiobarbituric acids[355].

Fialkov and Rapaport[359] remark that the nuclei of 5,5 diallylbarbituric and 5-s-pentyl-5-β-bromoallylbarbituric acids are not decomposed by a solution of ICl in HCl, even at 70°–80°.

Chromic acid (at ~20°)[360], $K_2Cr_2O_7$ in H_2SO_4[350,361], and 30% H_2O_2 do not disrupt the nucleus of barbituric acid in the cold.

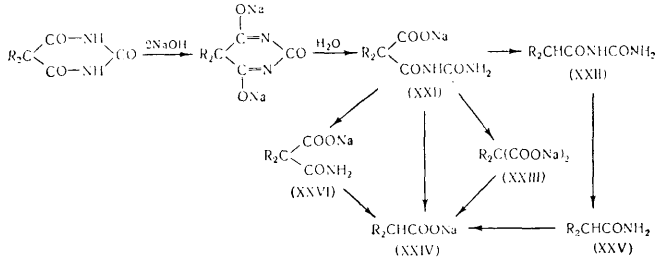
Usually, barbituric acids are stable to water — they are decomposed by it only on many hours' boiling at 5–10 atm[362]; however, *N*-arylbarbituric acids, according to Ridi's observations[84], are broken down as follows on boiling in water:



Spirobarbituric acids, on prolonged heating with water, decompose with separation of ammonia[323] and formation of the corresponding malonic acids[145]. Tetrasubstituted barbituric acids are still less stable[363].

In contrast to the barbituric acids, their sodium and potassium salts (and consequently the barbituric acids themselves in the presence of alkali) are extremely unstable, particularly in aqueous or alcoholic solution. As the instability of the sodium salts of barbituric acids in aqueous solutions has great significance in medical practice, considerable attention has been devoted to the hydrolysis of these salts[84,98,202,229,234,238,254,281,283,284,323,362,364-373].

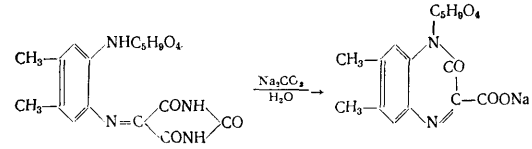
The literature gives information on the formation of the following products of barbituric acid hydrolysis: (XXI)[202,229,238,283,362,372]; (XXII)[202,229,354,362,365]; (XXIII)[84,202,234,283,284,323,367,373]; (XXIV)[98,284,365,367-369]; (XXV)[362,368]; (XXVI)[369].



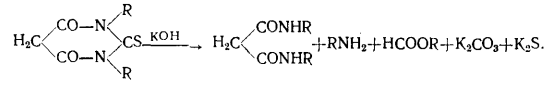
The scheme indicates the possibility of the formation of at least six substances according to the conditions of hydrolysis. Compounds of type (XXI) are products of the hydrolysis of the sodium salts of barbituric acids at ordinary temperatures; sometimes, however, (XXI) may not be formed, because the relatively most stable 5,5-dialkylbarbituric acids are not decomposed by cold alkali. In the case of the most unstable barbituric acids (those with unsaturated and *N*-aryl groups, and spirobarbituric acids) hydrolysis in the cold leads to (XXII), (XXIII), and even to (XXV); in the majority of cases, for the formation of these hydrolysis products, boiling the barbituric acids (or their sodium salts) with 10–20% NaOH is required. The compounds (XXVI) and (XXIV) are formed only on boiling the reaction mixture. The sodium salt of a substituted acetic acid (XXIV), urea, ammonia, carbon dioxide, $NaHCO_3$, and Na_2CO_3 are the final products of the hydrolysis of barbituric acids. In separate experiments, the decomposition of (XXI) to (XXII), (XXIII), and (XXIV), of (XXII) to (XXIV), and of (XXVI) to (XXIV) has been demonstrated.

Addition of alcohol or glycerol to solutions of sodium barbiturates decreases the rate of their hydrolysis[254].

The sodium salt of a substituted malonamic acid (XXVI) is formed in the hydrolysis of 1-(*N*-barbiturylidene)-4,5-dimethyl-2-D-ribitylaminoaniline* by boiling with 27% Na_2CO_3:[371]



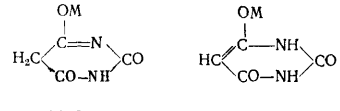
The action of KOH on *N*,*N*-disubstituted thiobarbituric acids splits the pyrimidine ring[364]:



The 2,4,6-trioxohexahydropyrimidine ring is also destroyed by caustic alkalis without a solvent. Molle and Kleinst[374], by slow fusion of 5,5-diethylbarbituric acid with NaOH, obtained the sodium salt of diethylacetic acid and ammonia. Later Jorissen[326] discovered cyanoacetic acid among the products of this reaction.

3. Reactions of Barbituric Acids Involving the Mobile Hydrogen Atoms

(a) Acid properties. Barbituric and thiobarbituric acids, by the action of hydroxides or salts, can exchange one or two atoms of hydrogen for a metal, forming salts of the types (XXVII) and (XXVIII), apparently according to whether the metal–oxygen[94,279] bond is strongly or weakly ionised:



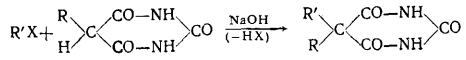
With the silver ion, a salt is formed (XXVIII) that gives on subsequent alkylation, C_5-derivatives[92,342]; alkali metals form salts of the type (XXVII), capable of being alkylated not only at the N atom, but also at the C_5 atom. If two substituents are present in position 5, only the form (XXVII) is possible.

Salts of alkali metals[370,375-377], Al[378,379], Ca[380], Ba[373], Ag[373,381,382], Hg[383-386], Cu[373,387-389], Co[379,390,391], Ni, Mn, Fe, Mg[379], and Pb[373] have been described. The salts of Co, Ni, and Cu have a complex composition and have been little investigated. Barbituric acids form stable salts with organic bases[392]. The imide hydrogen of barbituric acids reacts with organomagnesium compounds[393].

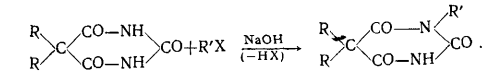
In these reactions, the trioxohexahydropyrimidines behave as typical acids. However, with strong mineral acids barbituric acids also behave as bases; in particular, they are readily titrated with perchloric acid[394].

* D-Ribityl = D-ribose residue – $CH_2CHOHCHOHCHOHCH_2OH$ (– $C_5H_{11}O_4$).

(b) *C*- and -alkylation (arylation). Alkyl (aryl) derivatives of barbituric acids may arise by substitution on carbon 5 or on the nitrogen; the hydrogen on the nitrogen is replaced with more difficulty than on carbon 5, and accordingly, when a choice is possible, it is the latter, and not the imide hydrogen, that is replaced in the first instance[337,395-398]:



or



These reactions are widely utilised for the synthesis of 5-substituted and *N*-substituted barbituric acids (particularly for those that cannot stand vigorous conditions of synthesis), because the process occurs under gentle conditions, and gives good yields of the desired reaction product. Thus, this reaction is convenient for the introduction of unsaturated radicals into the nucleus of barbituric acid (cf. Table).

TABLE. Comparison of various methods of synthesis of barbituric acids (according to Goldhahn and Barth[368]).

5,5-Substituents in the synthesised barbituric acid	Yield of acid, %	
	from malonic esters	by the introduction of unsaturated radical into the 5-monosubstituted barbituric acids
Allyl, allyl	37	84
Crotyl, crotyl	75	97.5
Ethyl, crotyl	50	97
Ethyl, allyl	50	65
Allyl, crotyl	49	68

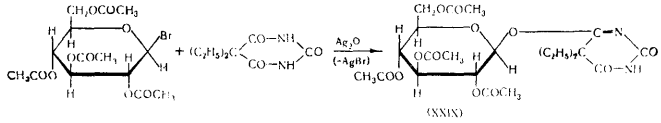
By this method, it is possible to synthesise barbituric acids that are impossible to prepare from malonic esters, in view of the instability of the latter. In particular, 5-acetanilidobarbituric acids were thus prepared[399]. From the corresponding malonic ester, 1,3,5-trimethyl-5-β--diethylaminoethylbarbituric acid could not be prepared; but it is easily synthesised by the interaction of 1,3,5-trimethylbarbituric acid with $ClCH_2CH_2N(C_2H_5)_2$.[363]

A second advantage of this method is the high purity of the product obtained. This is particularly important in the synthesis of low-melting *N*-substituted barbituric acids, which in the presence of impurities separate in the form of non-crystallising syrups[400].

In some cases, however, the reaction is complicated. In the alkylation of 5-isopropylbarbituric acid by α,α-dimethylallyl bromide in the cold, the yield of 5-isopropyl--5-(3-methylbut-2-enyl)barbituric acid is 27% (on heating even less), whereas this acid is prepared from malonic esters in a yield of 67%[193].

The preparation of *C*-alkylbarbituric acids by the interaction of monoalkylbarbituric acids with α-$C_{10}H_7CH_2Br$[203] was not successful. Even such an active agent as allyl bromide does not form a 5-allyl-derivative with 1-ethoxycarbonylmethyl-5-acetylbarbituric acid[57]. It was not possible to prepare 5-phenyl-5-cyclohexylbarbituric acid by the interaction of cyclohexyl bromide with 5-phenylbarbituric acid[62] or 5-methyl-5-cyclooctylbarbituric acid from 5-cyclooctylbarbituric acid and methyl iodide[184].

In view of the ability of barbituric acids to enolise, a competing formation of *O*- and *N*-derivatives might have been expected on straight alkylation of the sodium salts of 5,5-dialkylbarbituric acids. However, until very recently, no indisputable examples of *O*-alkylation were known; the claim of Marotta and Rosanova[330] to have prepared *O*-derivatives by the methylation of 5,5-diethylbarbituric acid by diazomethane was proved erroneous[63]. However, in 1953 Snyder and Link[109] succeeded in preparing *O*-derivatives (XXIX) by the interaction of tetraacetyl-D-glucosylbromide with 5,5-diethylbarbituric acid in the presence of an excess of Ag_2O and of quinoline:

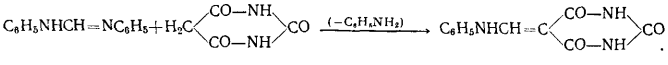


(XXIX)

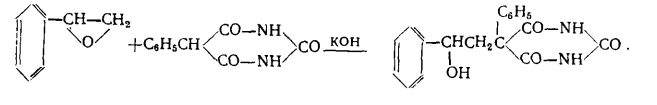
A synthesis of (XXIX) directly from the silver salt of 5,5-diethylbarbituric acid did not succeed.

Most frequently, alkylation* has been used for the preparation of 5-substituted barbituric acids.

Alkyl[87,153,284,290,400-402] and alkenyl[6,57,62,161,184,193,200,257,290,368,403-409] iodides and bromides, halogenoarylmethanes[60,86,203], halogenopyridines[367,410,411], α-halogenoketones[369,399,412-414], *N*-chloro-*N*-acylanilines[415], and various α-halogenomethyl derivatives of heterocyclic compounds[24,130,159,416] have been used as *C*-alkylating agents. Alkylation by alkyl halides is difficult[153,402]. Instead of alkyl halides, alkyl *p*-toluene sulphonates[417] can be utilised. Formamidines[60] also react at the C atom:



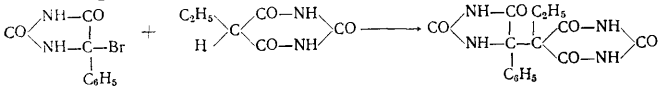
By interaction with the alkali-metal salts of 5-monobarbituric acids, epoxides give small yields of 5,5-disubstituted barbituric acids[303], containing an alcohol group in the substituent:



Thiobarbituric acids polymerise under these conditions[418]. *C*-alkylated barbituric acids may arise in the presence or absence of strong alkali; in the latter case alkylating agents containing mobile halogen atoms are used, for example, allyl halides[6,57,290,404], bromophenylhydantoin[419], α-$C_{10}H_7CH_2Br$[203], $C_6H_5COCH_2Br$[412], *p*-$C_2H_5OC_6H_4NCl$.$COCH_3$[415], $ClCH_2COCH_3$[399], and $ClCH_2CONHC_6H_5$[399].

* Barbituric acid is easily acylated in the 5-position by acid anhydrides and chlorides[91,364]. Urea forms with barbituric acid a 5-NH_2CO-derivative[364].

The reaction is carried out in an aqueous-alcoholic medium by heating in the presence of an equimolar quantity of sodium acetate. The addition of potassium or sodium iodide considerably accelerates the reaction and raises the yield of *C*-alkylated barbituric acid[399,415]. Phenylbromohydantoin, possessing an extremely active bromine atom, reacts with barbituric acids even in the cold and in acetic acid, forming 5-alkyl-5-phenylhydantoinylbarbituric acids, for example:



In most cases, *C*-alkylation is carried out in aqueous alcohol in the presence of $N-3N$ NaOH, since in this case it is easily reproducible and gives high yields of *C*-alkylated barbituric acids[57,193,202,233,250,254,369,398,405,413,416,417,420,421]. Even here the addition of iodides facilitates the yield of the desired product[233,257] (for example, in the synthesis of 5-acetonylbarbituric acids, the yield is raised from 10 to 75%[413]). Apparently, the influence of the NaI added in the alkylation of barbituric acids (or bromides) involves the conversion of the chlorides by sodium iodide into alkyl iodides which react much more easily with the barbituric acids[233]. The addition of Cu powder[416] or $CuSO_4$[57,369,405,408] also acts favourably. The reaction proceeds also in the absence of alcohol, but usually more slowly[254]; the yields of substituted barbituric acids reach 90%[202]. 5-Triphenylmethylbarbituric acid was prepared by fusing $(C_6H_5)_3CCl$ with barbituric acid in vacuo[284]. The preparation of tri- and tetraalkylated acids by direct alkylation of barbituric acid has, up to the present, not been successful[337], but tetra-*p*-nitrobenzylbarbituric acid was prepared[395] by the reaction of barbituric acid with an excess of *p*-nitrobenzylchloride.

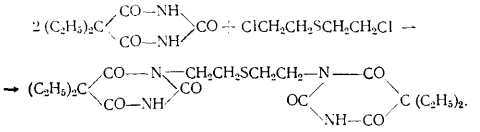
Among the side reactions we should mention *N*-alkylation in those cases where it is possible[63,396-398], and dehydrohalogenation when polyhalogeno compounds[401] (for example, 1,2,3-tribromopropane) or compounds with a mobile halogen atom (triphenylchloromethane)[250] are used on alkylating agents.

2-Thiobarbituric acids, in particular 5-alkyl-substituted compounds, are capable of alkylation on the sulphur atom[408,422-424].

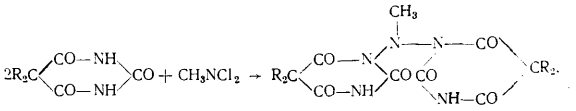
A comparison of the influence of alkylation conditions on the yield of barbituric acids is given by Gabel'[290] and Halpern and coworkers[425].

N-Alkylation of 5,5-disubstituted barbituric acids proceeds under the same conditions and with the same catalysts as does *C*-alkylation[9,57,62,193,284,285,319,354,370,425-449]. Among *N*-alkylating agents, *p*-nitrobenzyl bromide and phenacyl bromide are relatively important, because these *N*-derivatives of barbituric acids crystallise well, have definite melting points, and serve for the identification of barbituric acids[435,442,444,445,449,450]. A microchemical modification of the reaction has been described by Reimers[443].

It is interesting that solutions of veronal inactivate mustard gas, forming a non-poisonous compound with it[447]:



Dichloromethylamine forms with 5,5-dialkylbarbituric acids the very unstable methylaminobisbarbituric acid[446]:



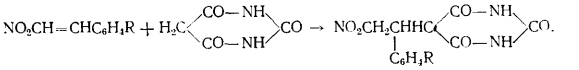
Cases of intramolecular *N*-alkylation have been described[451].

It is possible to alkylate 2-iminobarbituric acids (primary products of the interaction of malonic ester with guanidine) or 4-iminobarbituric acids (prepared from cyanoacetic ester and urea). The products can easily be converted into barbituric acids[261,285,319].

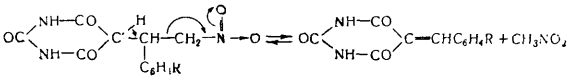
Some reagents usually react with the 1,3 hydrogen atoms. These include compounds of the type RHgX[386,452], phenylmercury hydroxide[453], dimethyl sulphate in alkaline solution[101,127,345,454-457], diethyl sulphate[345,456], diazomethane, and diazoethane[62,63,350,456,458]. Biltz and Wittek[91] introduced a single methyl group into position 5 of 1,3-dimethylbarbituric acid with the help of a large excess of diazomethane, but they did not succeed in substituting the second H atom in position 5 by a CH_3 group in the same way. The hydrogen atoms on both nitrogen atoms seemed to be quite equivalent in chemical reactions[63,91].

Not all derivatives of barbituric acid are equally easily methylated; thus, hydurilic acid is not methylated by dimethyl sulphate[100]. *N*-Allyl derivatives of thiobarbituric acid cannot be synthesised by the reaction of allyl bromide with the sodium salt of thiobarbituric acid in aqueous or alcoholic solution; ring rupture occurs with the formation of 2-propenethiol[370].

(c) Substitution by addition. Barbituric acid and its 5-monoalkyl derivatives enter into a series of reactions involving addition[459,460]. Compounds with conjugated double bonds combine with barbituric acid without any catalyst[459]:



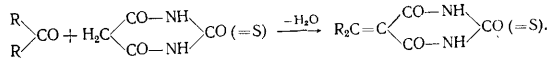
The velocity of the reaction depends on the concentration of barbituric acid. Reduction of the electron density on the carbon atom which is attacked by the anion of the barbituric acid increases the speed of the reaction. Increase of the dielectric constant of the reaction medium has the same effect[461]. The final products of the reaction are unstable and rapidly decompose on storage[459]:



Attempts to use in this reaction $C_6H_5C \equiv CCH_2OH$[462], $CH_2=CHPO(OR)_2$[11], cinnamic and acrylic acids, methyl acrylate and benzalmalonic ester were unsuccessful.

(d) Condensation reactions. A considerable number of communications[60,66,76,82,88,199,241,344,349,364,421,463-489] have been published about investigations of the condensation of barbituric and thiobarbituric acids and their

1,3-disubstituted derivatives, with aldehydes and ketones:

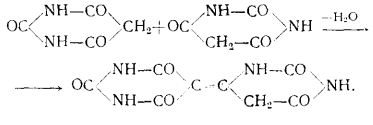


The ketones react with appreciably greater difficulty than the aldehydes; this is the basis of a method of separating them by boiling their mixtures with an aqueous solution of barbituric acid[223,464].

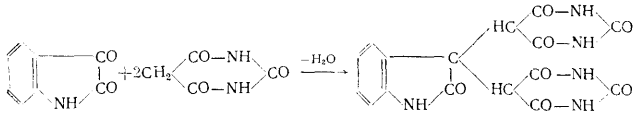
The reaction is carried out by boiling an equimolar mixture of the reagents in alcohol[82,344,421,481,482], water[199,344,349,469,483], pyridine[375,482,486], glycerol[373], or glacial acetic acid[467,488]. Sparingly soluble, sometimes coloured, compounds are thereby produced: in consequence, this reaction has been frequently suggested for the identification and quantitative estimation of aldehydes[76,384,463,490-492] and barbituric acids[379].

Aliphatic aldehydes form compounds without sharp melting points and often of a resinous nature, but the reaction goes smoothly with aromatic and heterocyclic aldehydes, and the condensation product separates quantitatively[464]. Substitution on the nitrogen does not influence the rate of the reaction[66,76]. In a number of cases the reaction is accelerated by the addition of bases: trimethylamine[486], hydrazine hydrate[484], piperidine[480].

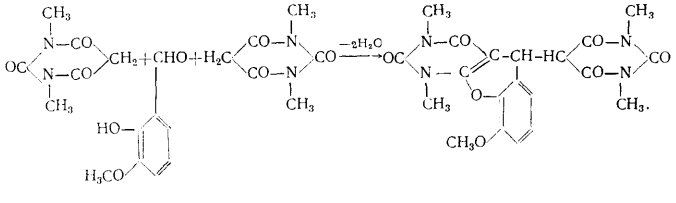
A second molecule of barbituric acid may act as carbonyl component[373]:



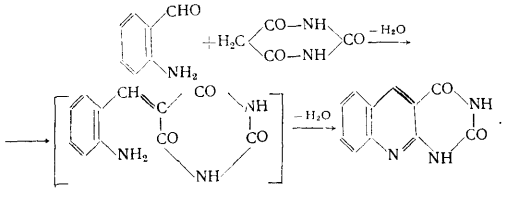
Some limitations and complications in the reaction of aldehydes and ketones with barbituric acids are known, particularly in the case of ketones. Thus, in an alkaline medium barbituric acid does not condense with isatin; in an acid medium bisbarbituric acids are formed[472]:



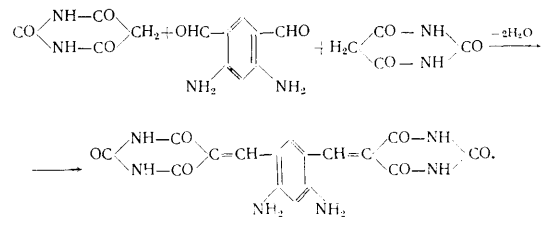
An analogous reaction is given by salicylic aldehyde[349,464]. Orthovanillin forms with 1,3-dimethylbarbituric acid *o*-vanillylidenebisdimethylbarbituric anhydride[464]:



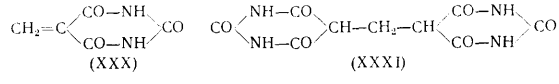
By the condensation of *o*-aminobenzaldehyde[349], and also of 2-amino-4-nitrobenzaldehyde[344] with barbituric acid, a diazoacridine ring is formed:



When 4,6-diaminoisophthalic aldehyde is used, the reaction follows the normal path[482]:

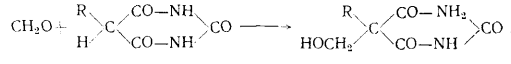


It is impossible to prepare methylenebarbituric acid (XXX)[464] from formaldehyde and barbituric acid; however, its ammonium salt was synthesised by the reaction of barbituric acid and urotropine[474]; on neutralisation of this salt by hydrochloric acid, methylenebisbarbituric acid (XXXI) was obtained instead of (XXX).

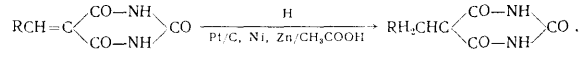


(XXX) (XXXI)

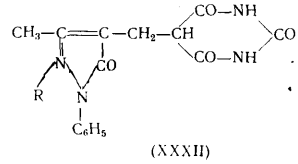
Formaldehyde condenses with 5-substituted barbituric acids forming methylol derivatives[493]:



The condensation of barbituric acids with aldehydes may be important for the preparation of 5-monosubstituted barbituric acids, which are easily formed in quantitative yield by the catalytic hydrogenation or reduction by zinc and acetic acid of arylidene- or alkylidenebarbituric acids:



In this, in spite of the additional stage in the reaction, the yields of 5-substituted barbituric acids are usually higher than in their syntheses from malonic esters[199]. With some types of barbituric acids, e.g. (XXXII), this reaction is the only means of preparation, since the corresponding malonic and cyanoacetic acids and esters cannot stand the conditions of the condensation:

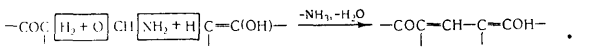


(XXXII)

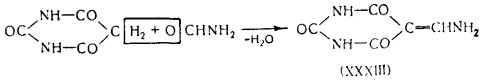
The synthesis of 5-monoalkylbarbituric acids from aliphatic carbonyl compounds may be achieved, even in a one-stage hydrogenation of a mixture of aldehydes and barbituric acids in the presence of palladium in an alcoholic solution[494,495]. The aldehydes react more rapidly than the ketones, and among the ketones the low-molecular more rapidly than the high-molecular. Cyclic ketones are more active in this reaction than aliphatic ketones with the same number of carbon atoms; unsaturated carbonyl compounds react more rapidly than the saturated analogues.

Formamide and its *N*-derivatives[364,470,474,487] condense with barbituric acids in the same way as aldehydes. It is

interesting that at the same time formamide reacts with $-CH_2CO-$ groups in the usual way, dimerising them into oxonols:

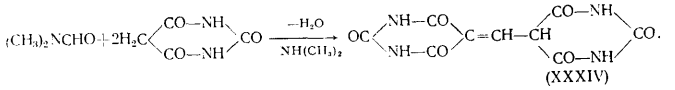


For barbituric and thiobarbituric acids the basic reaction is the formation of aminomethylene compounds (XXXIII), evidently as a result of the high mobility of the hydrogen in the methylene groups[475]:



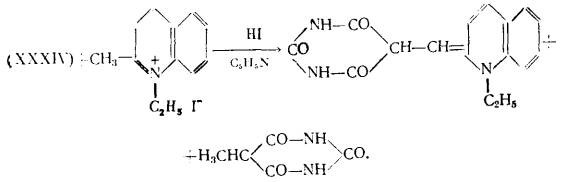
(XXXIII)

Oxonols of type (XXXIV) (see below) are formed in insignificant quantities in this way. In the preparation of (XXXIII) instead of formamide, ammonium formate[470] can be used and even formic acid itself[237]; the reaction of barbituric acid with *N*-formylaniline proceeds in this way[467]. However, if in place of formamide, dimethylformamide is used, the normal product of the reaction, methylidynebisbarbituric acid[475] (XXXIV), is almost exclusively formed:



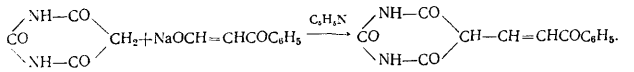
(XXXIV)

Oxonols of type (XXXIV) can react with compounds possessing an active CH_3 group to form merocyanines, for example[496]:



The merocyanines of barbituric and thiobarbituric acids may also be prepared by another method[497-504]; they find application as sensitisers for photographic emulsions[496-506].

The reactions of barbituric acids with $C_6H_5COCH = CHONa$[505] proceed analogously, for example:

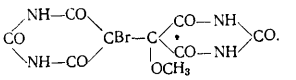


(e) Halogenation. The trioxohexahydropyrimidine nucleus is easily halogenated. By passing chlorine into an aqueous suspension of barbituric acid[85,91] or its 5-alkyl derivatives[103] at 30°–40°, or into an alcoholic solution of barbituric acid at 0°[100], 5,5-dichlorobarbituric and 5-alkyl-5-chlorobarbituric acids, respectively, are formed in good yield.

Sulphuryl chloride (SO_2Cl_2) in chloroform acts similarly to chlorine[103]. The chlorination of barbituric acids with potassium perchlorate in hydrochloric acid has been described[90,100]. By the action of calcium hypochlorite in acetic acid on 5,5-diethylbarbituric acid, 1,3-dichloro-5,5-diethylbarbituric acid is formed[507]; this is a good chlorinating agent for unsaturated compounds.

The bromination of barbituric acids proceeds just as easily, leading to 5-bromo-[81,508] and 5,5-dibromobarbituric acids[85,90-92,509,510], tribromoacetureides[508] being formed as side products.

Hydurilic acid, on bromination in the presence of methanol, decomposes into the compounds[101,346]



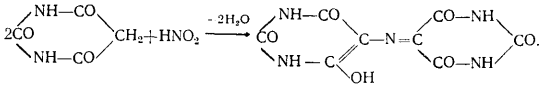
By the action of iodine chloride on 5-alkylbarbituric acids, Fresenius[511] prepared 5-iodo-5-alkylbarbituric acids; 5-hydroxy- and 5-chlorobarbituric acids were also formed.

(f) Oxidation. Various products are obtained by the oxidation of barbituric acids. Chromic acid oxidises barbituric acid to alloxan, and a mixture of $NaClO_3 + V_2O_5 + H_2SO_4$[512] acts in the same way. Alloxan is also formed on the oxidation of alkylidene- or arylidenebarbituric acids[483]. Nitric acid reacts vigorously with monoalkylbarbituric acids, forming numerous products, including alloxan[90].

5-Mono-substituted barbituric acids are easily oxidised to the corresponding dialuric (5-hydroxybarbituric) acids, even by atmospheric oxygen[294,295,513]. $K_2Cr_2O_7$ in water or glacial acetic acid[123,514] and H_2O_2 and Na_2O_2[123,513,515] act similarly.

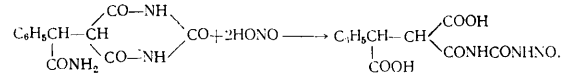
5,5-Dialkylbarbituric acids are much more stable to oxidation than monoalkylbarbituric acids[293].

(g) Other reactions involving the mobile hydrogen atoms. Barbituric and thiobarbituric acids and also their monoalkyl derivatives are very easily attacked by HNO_2, yielding violuric acid[87,90-92,516-518]. From barbituric acid, purpuric acid is formed as a by-product:

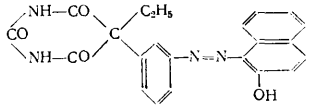


By reacting thiobarbituric acid with ethyl nitrite in alcohol, the analogous thiopurpuric acid is obtained as the chief product of the reaction[519].

Diazotisation of α-(5-barbituryl)phenylacetamide by sodium nitrite at -5° leads, unexpectedly, to the breakdown of the ring[234]:



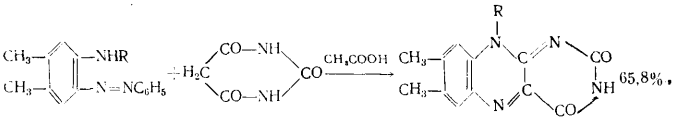
The nucleus of 5,5-disubstituted barbituric acids is usually not affected on diazotisation; thus, from 5-(*m*-aminophenyl)-5-ethylbarbituric acid a diazonium salt was obtained, which gave the azo-dye (XXXV)[351] with β-naphthol:



(XXXV)

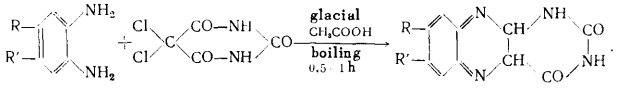
By reaction with nitrogen-containing compounds, barbituric acids form a series of technically valuable substances. Thus, p-$(CH_3)_2NSO_2C_6H_4NHSO_2C_6H_4NH_2$-$p$, after diazotisation, reacts with barbituric acid forming an orange azo-dye[520].

Tischler and coworkers[521], starting from barbituric acid, accomplished a direct synthesis of riboflavine (vitamin B_2):

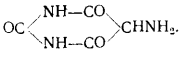


where R = D-ribityl (cf. p. 446).

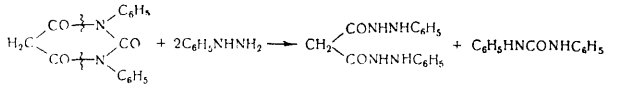
Alloxazines, related to riboflavine, are also formed in the reaction of substituted o-phenylenediamines with 5,5-dichlorobarbituric acids[522], for example



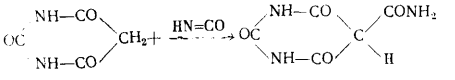
By boiling with phenylhydrazine in water, in acetic acid, or without a solvent, barbituric acid gives uramil[523,524]:



N-substituted barbituric acids, under these circumstances, react with rupture of the ring[524]:



Isocyanic acid reacts with barbituric acid to give malobiuric acid[525]*:



The interaction of barbituric acid with mercury fulminate, $Hg(CNO)_2$, in a KCN solution leads also to the formation of malobiuric acid[474].

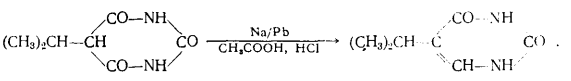
4. Reactions of Barbituric and Thiobarbituric Acids Involving the Carbonyl (Thiocarbonyl) Groups

The reactivity of the carbonyl group of barbituric acids depends to a considerable extent on the nature of the substituents in the 5-position.

On electrolytic reduction of barbituric acid, the reaction stops at the stage of formation of hydrouracil or trimethyleneurea[526]; hexahydropyrimidine is not obtained in this way.

The 5-monoalkylbarbituric acids are reduced similarly, but with much more difficulty. The introduction of two alkyls in position 5 changes the behaviour of the acid: as a consequence of the small tendency to enolisation in the 5,5-dialkyl barbituric acid, only the urea-type carbonyl group is reduced, and not the malonic ester residue[78,526,527].

5-Isopropyluracil is obtained from 5-isopropylbarbituric acid by the action of a sodium–lead alloy (30% Na) in a mixture of hydrochloric and acetic acids:

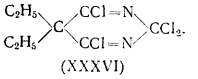


Lithium tetrahydroaluminate reduced 5,5-disubstituted barbituric acids only to the corresponding trimethyleneurea[528].

It should be mentioned that, in comparison with CO groups in a carbon chain, the 4,6-carbonyl groups in barbituric acid possess a somewhat lowered activity as a consequence of the mutual influence of the CO and NH groups. They are not reduced by the action of Raney nickel or sodium amalgam in HCl[78]; 4-chloroquinaldine, which usually reacts with $-CH_2-CO-$ groups, does not enter into reaction with barbituric acids[529].

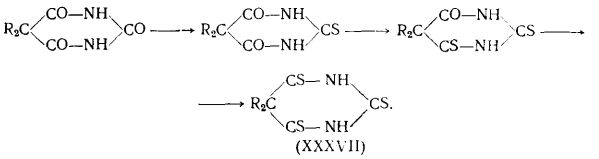
On boiling with $POCl_3$, monoalkylbarbituric acids react in the trioxopyrimidine form[244,293], forming 2,4,6-trichloropyrimidines; in the presence of $C_6H_5N(CH_3)_2$, 4,6-dichloro-2-(*N*-methylanilino)pyrimidine[530,531] is formed as a side product.

By the action of PCl_5 on 5,5-diethylbarbituric acid, a tetrachloro derivative (XXXVI) is obtained in small yield with a considerable quantity of diethylcyanoacetyl chloride[293,343]:



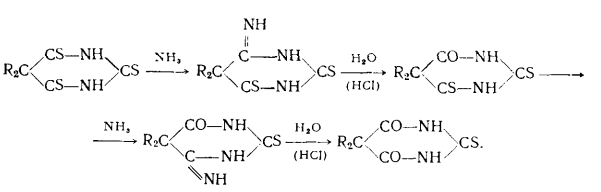
(XXXVI)

Heating barbituric acids with phosphorus trisulphide in tetralin at 225° leads to the formation of trithiobarbituric acids of the type (XXXVII)[532,533]. When phosphorus pentasulphide is used, 2-thiobarbituric and 2,4-dithiobarbituric acids can be isolated from the reaction mixture, in addition to trithiobarbituric acids; the replacement of oxygen by sulphur evidently occurs in stages[532]:



(XXXVII)

By the subsequent action of ammonia and hydrochloric acid, it is easy to prepare monothiobarbituric acids from di- and trithio-derivatives[532]:

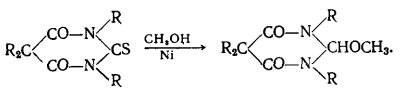


The CS group of 2-thiobarbituric acids is considerably more reactive than the carbonyl group of the barbituric

* At this point the original contains an error, which has been amended in accordance with Curtius' paper[525] (Ed. of Translation).

acids. While sodium amalgam in water hardly acts on veronal, and on prolonged contact, splits it into diethylmalonic acid and urea, 5,5-diethyl-2-thiobarbituric acid is easily reduced in the cold by sodium amalgam to 2-desoxyveronal[70]; the reduction proceeds similarly in the presence of Raney nickel[78,534-536].

On boiling with Raney nickel in methanol, thiobarbituric acids give 2-methoxyhexahydropyrimidine-4,6-diones[537]



2-Phenylimino- and 2-phenylhydrazinobarbituric acids are formed by the action of aniline or phenylhydrazine on thiobarbituric acids[70].

Thiobarbituric acids are easily transformed to barbituric acids by oxidising agents. This reaction can be accomplished with the help of H_2O_2 or $KMnO_4$ in an alkaline medium[484], SeO_2 in acetic acid[538], ICl[539] in hydrochloric acid, sulphuric acid[252,540], nitric acid[318], and by other means[418,541].

III. DETECTION, IDENTIFICATION, AND DETERMINATION OF BARBITURIC ACIDS*

Various colour reactions have been suggested for the detection of barbituric acids. Cobalt salts[542-546] give coloured precipitates or coloured solutions, which may be utilised for the colorimetric determination of barbituric acids.

Barbituric acids form coloured solutions with benzoquinone[547], resorcinol[548,549], H_2SeO_3[379,556], aminoantipyrine in the presence of $K_3Fe(CN)_6$[551], vanillin[548], *m*-nitrobenzaldehyde[552], Fehling's solution[553], formaldehyde, salicylaldehyde[379], and aniline[76].

Many barbituric acids can be identified by microscopic examination of the crystals[554]. However, in view of the wide occurrence of polymorphism among the barbituric acids[57,156,408,435,443,555-559], it is better to use the microscopic method on their compounds with benzylthiourea[560], xanthydrol[57,543,561-565], pyridine[566], urotropine[567], pyrazolones[568,569], ethylenediamine in the presence of $CuSO_4$[571], or with salts of mercury[384,561,565], silver[381], yttrium[572], iron[573], or copper[573].

It is also possible to identify barbituric acids by the different rates of precipitation of dialkylacetylurea ($R_2CHCONHCONH_2$) on heating them to 150° with 0.1 *N* NaOH in sealed capillaries[574].

Mixtures of barbituric acids can be separated by chromatography[545,565,575,576] and electrophoresis[577].

For the quantitative estimation of barbituric acids, acidimetric[578], argentometric[579,580], bromometric[57,578], mercurimetric[581], spectrophotometric[87,582-586], potentiometric[581] and polarographic[587,588] methods have been worked out.

* Methods of determination of barbituric acids are considered in detail in the review of Stainier et al.[570].

1. A. Schlieper, Annalen, 55, 251 (1845); 56, 1 (1845).
2. E. Fischer and A. Diltey, Annalen, 335, 334 (1904).
3. E. Fischer and J. Mering, Therap. Gegenwart., 44, 97 (1903).
4. H. Hofman, Arch. exp. Path. Pharmak., Chem. Abs., 35, 2607 (1941).
5. H. Seel, Deut. med. Woch., 64, 444 (1938); Chem. Abs., 32, 8559 (1938).
6. O. Schales, Ber., 71B, 1116 (1938).
7. V. Rovati and A. Zirondoli, Boll. Soc. ital. Biol. sper., 28, 1006 (1952); Chem. Abs., 48, 9452 (1954).
8. J. Suzuki and T. Kishida, Kaguka, 24, 153 (1954); Chem. Abs., 48, 12 229 (1954).
9. E. Gryszkiewicz-Trochimowski, Arch. Chem. Farm., 2, 1 (1934); Chem. Abs., 30, 1127 (1936).
10. M. Ruhnek and F. Sandberg, Svensk. Farm. Tid., 56, 70, 95, 120 (1952); Chem. Abs., 46, 11 113 (1952).
11. H. Goldhahn and B. Fiebig, Pharmazie, 9, 964 (1954).
12. M. Vigante, Acta univ. Latviensis, Med. Fakul. Serija, 2, 193 (1935); Chem. Abs., 30, 5307 (1956).
13. Takadzi and Sekiguti, Jap. Pat. 6599 (1954); Referat Zhur. Khim., 22 504 (1958).
14. F. W. H. Mueller and A. Bavley, Canadian Pat. 449 834, 449 835 (1948); Chem. Abs., 42, 6685 (1948).
15. R. H. Sprague, U. S. Pat. 2 622 082 (1952); Chem. Abs., 47, 3159 (1953).
16. G. H. Keyes, U. K. Pat. 710 846 (1954); Chem. Abs., 49, 85 (1955).
17. D. W. Heseltine and L. G. S. Brooker, U. S. Pat. 2 719 151 (1955); Chem. Abs., 50, 5435 (1956).
18. A. H. Herz and G. H. Keyes, U. S. Pat. 2 719 088 (1955); Chem. Abs., 50, 2334 (1956).
19. H. Grassmann, Z. wiss. Phot., 45, 233 (1950); Chem. Abs., 46, 2433 (1952).
20. K. Marobushi, H. Ichifuji, and E. Ashikawa, J. Chem. Soc. Japan, Ind. Chem. Sect., 56, 539 (1953); Chem. Abs., 48, 11 963 (1954).
21. J. J. Jennen and O. H. Vandenbrocle, U. S. Pat. 2 644 754 (1953); Chem. Abs., 48, 67 (1954).
22. D. E Sargent, U. S. Pat. 267 023 (1954); Chem. Abs., 48, 6300 (1954).
23. D. E. Sargent, U. S. Pat. 2 636 821 (1953); Chem. Abs., 47, 5435 (1953).
24. L. G. S. Brooker and H. W. J. Cressman, U. S. Pat. 2 398 999 (1946); Chem. Abs., 40, 3691 (1946).
25. C. F. H. Allen and P. W. Wittum, U. S. Pat. 2 313 498 (1943); Chem. Abs., 37, 4979 (1943).
26. F. Dersch and N. Heimbach, U. S. Pat. 2 384 897 (1945); Chem. Abs., 40, 530 (1946).
27. H. Zenno, J. Soc. Sci. Phot. Japan, 15, 99 (1953); Chem. Abs., 48, 11 063 (1954).
28. M. Fujisawa and S. Ohba, Jap. Pat. 2661 (1952); Chem. Abs., 47, 6579 (1953).
29. G. Van Zandt and L. G. S. Brooker, U. S. Pat. 2 485 679 (1949); Chem. Abs., 44, 7694 (1950)
30. E. J. Van Lare and L. G. S. Brooker, U. S. Pat. 2 691 652 (1954); Chem. Abs., 49, 2916 (1955).
31. H. Glahn and L. N. Stanley, U. S. Pat. 2 542 848 (1951); Chem. Abs., 45, 6522 (1951).
32. F. P. Mazza and O. Carere, Boll. Soc. ital. Biol. sper., 9, 177 (1934); Chem. Abs., 28, 5409 (1934).
33. K. Weber and M. Rae, Kem. Vjestnik, 15–16, 67 (1941–1942); Chem. Abs., 40, 4895.
34. K. Seshadri, J. Sci. Ind. Res., 13B, 575 (1954).
35. H. F. Park, U. S. Pat. 2 664416 (1953); Chem. Abs., 48, 4252 (1954).
36. G. Swann and E. L. Humberger, U. K. Pat. 684 489 (1952); Chem. Abs., 47, 7257 (1953).

37. J. S. Buck, J. Amer. Chem. Soc., 59, 1249 (1937).
38. Ciba Ltd., Swiss Pat. 238518 (1945); Chem. Abs., 43, 7697 (1949).
39. R. Gunst, U. S. Pat. 2686178 (1954); Chem. Abs., 49, 2741 (1955).
40. L. Michaelis, J. Biol. Chem., 87, 33 (1930).
41. T. Pavolini, Rivista ital. essenze e profumi, 12, 93 (1930); Chem. Abs., 24, 3456 (1930).
42. T. Pavolini and F. Gambarin, Anal. Chem. Acta, 3, 27 (1949).
43. E. Asmus and H. Garschagen, Z. analyt. Chem., 138, 404, 414 (1953).
44. W. Zerweck and M. Shubert, German Pat. 734139 (1943); Chem. Abs., 38, 1302 (1944).
45. V. V. Prey, F. Beran, and H. Bohm, Mitt. Chem. Forsch.-Inst. Wirtsch. Osterr., 6, 28 (1952); Chem. Abs., 46, 8802 (1952).
46. A. Ber, Endokrinologie, 30, 54 (1953); Chem. Abs., 47, 8841 (1953).
47. F. Krik, Khim. Nauka i Prom., 1, 472 (1956).
48. F. J. S. Lara, J. Bact., 64, 271, 279 (1952).
49. O. Hayaishi and A. Kornberg, J. Amer. Chem. Soc., 73, 2975 (1951).
50. E. E. Haley and J. P. Lambooy, ibid., 76, 2926 (1954).
51. S. Zamenhof and G. Griboff, Nature, 174, 307 (1954).
52. O. Hayaishi and A. Kornberg, J. Biol. Chem., 197, 717 (1952).
53. T. P. Wang and J. O. Lampen, ibid., 194, 775, 785 (1952).
54. A. G. Natradze and E. V. Yakovleva, Khim. Nauka i Prom., 1, 461 (1956).
55. I. G. Farbenindustrie, A.-G., French Pat. 753178 (1933); Chem. Abs., 28, 781 (1934).
56. O. Rosen, Swedish Pat. 131141 (1951); Chem. Abs., 46, 9590 (1952).
57. O. Rosen and F. Sandberg, Acta Chem. Scand., 4, 666, 675 (1950).
58. S. R. Safir, I. J. Hlavka, and I. H. Williams, J. Org. Chem., 18, 106 (1953).
59. E. Mulder, Chem. Ber., 12, 465 (1879).
60. D. Nightingale and C. H. Alexander, J. Amer. Chem. Soc., 58, 794 (1936).
61. E. W. Maynert and E. Washburn, J. Org. Chem., 15, 259 (1950).
62. H. J. Morsman, Helv. Chim. Acta, 18, 1254 (1935).
63. A. W. Dox, J. Amer. Chem. Soc., 58, 1633 (1936).
64. C. H. Vasey, U. K. Pat. 741097 (1955).
65. M. Göttler, Chem Ber., 48, 1765 (1915).
66. D. Nightingale and L. C. Morris, J. Amer. Chem. Soc., 58, 1469 (1936).
67. H. Schulte, Ber., 87, 820 (1954).
68. B. Hepner and S. Frenkenberg, Chem. Ber., 65B, 123 (1932).
69. I. G. Farbenindustrie, A.-G., U. K. Pat. 468683 (1937); Chem. Abs., 32, 730 (1938).
70. A. Einhorn, Annalen, 359, 145 (1908).
71. R. Sellery and W. Chiti, Farmaco. Ed. Scient., 12, No. 1, 3 (1957).
72. C. Vasei, German Pat. BDP 896491 (1953), 22447 (1958).
73. O. Zima and F. Werder, German Pat. BDP 946804 (1956); 51325 (1958).
74. A. Dox and W. Thomas, J. Amer. Chem. Soc., 45, 1811 (1923).
75. M. Ridi, Gazzetta, 82, 23 (1952).
76. N. V. Koshkin, Zhur. Obshch. Khim., 5, 1460 (1935).
77. H. Biltz and T. Hamburger, Chem. Ber., 49, 635 (1916).
78. W. R. Boon, H. C. Carrington, N. Greenhalgh, and C. H. Vasey, J. Chem Soc., 3263 (1954).
79. T. Mukajyama, S. Ozaki, and T. Hoshino, Bull. Chem. Soc. Japan, 27, 578 (1954).
80. T. Mukajyama and Y. Iujita, ibid., 29, 54 (1956).
81. E. Grimaux, Bull. Soc. chim. France, 31, (4), 146 (1879).
82. G. Brückmann and S. D. Isaacs, J. Amer. Chem. Soc., 71, 390 (1949).
83. D. Nightingale and R. G. Taylor, ibid., 61, 1015 (1939).
84. M. Ridi, Ann. Chim. (Italy), 42, 25 (1952).
85. A. K. Macbeth, T. H. Nunan, and D. Traill, J. Chem. Soc., 1248 (1926).
86. A. C. Cope, D. Heyl, D. Reck, C. Eide, and A. Arrayo, J. Amer Chem. Soc., 63, 356 (1941).
87. J. N. D. Dass and S. Dutt, Proc. Indian Acad. Sci., 8A, 145 (1938).
88. M. Lora-Tamayo, J. M. Gamboa, and E. F. Alvarez, Anales real Soc. espan. Fis. Quim., 48B, 889 (1952); Chem. Abs., 48, 1278 (1945).
89. E. J. Mills and M. T. Bogert, J. Amer. Chem. Soc., 62, 1173 (1940).
90. K. Sembritzki, Chem. Ber., 30, 1814 (1897).
91. H. Biltz and H. Wittek, ibid., 54, 1035 (1921).
92. M. Conrad and M. Guthzeit, ibid., 15, 2844 (1882).
93. J. K. Wood, J. Chem. Soc., 89, 1831 (1906).
94. J. K. Wood and E. A. Anderson, ibid., 95, 979 (1909).
95. J. F. Norris and H. F. Tucker, J. Amer. Chem. Soc., 55, 4697 (1933).
96. F. P. Ruskin and S. L. Ruskin, U. S. Pat. 2013717 (1933); Chem. Zentr., I, 113 (1936).
97. O. Kühling, Chem. Ber., 43, 2406 (1910).
98. S. M. McElvain, J. Amer. Chem. Soc., 57, 1303 (1935).
99. H. M. Barnes and S. M. McElvain, ibid., 59, 2348 (1937).
100. H. Biltz and T. Hamburger, Chem. Ber., 49, 655 (1916).
101. H. Biltz and M. Heyn, ibid, 52, 1313 (1919).
102. W. Techow, ibid., 27, 3084 (1894).
103. G. K. Hughes and A. K. Macbeth, J. Chem. Soc., 1622 (1938).
104. C. Finck, Lieb. Ann., 132, 304 (1864).
105. T. Ukai, Y. Yamamoto, and Sh. Kanetomo, J. Pharm. Soc. Japan, 74, 674 (1954); Chem. Abs., 48, 10743 (1954).
106. T. U. Kai, Y. Yamamoto, and Sh. Kanetomo, ibid., 74, 678 (1954); Chem. Abs., 48, 10743 (1954).
107. C. E. Kaslow and W. E. Bacon, U. S. Pat. 2491815; Chem. Abs., 44, 3016 (1950).
108. M. Conrad, Annalen, 356, 24 (1907).
109. J. A. Snyder and K. P. Link, J. Amer. Chem. Soc., 75, 1881 (1953).
110. S. M. McElvain and H. Burkett, ibid., 64, 1831 (1942).
111. F. F. Blicke and M. F. Zienty, ibid., 63, 2991 (1941).
112. D. Heyl and A. C. Cope, ibid., 65, 669 (1943).
113. A. C. Cope, W. H. Hartung, E. M. Hancock, and F. S. Crosley, ibid., 62, 1199 (1940).
114. S. M. McElvain and R. F. Taylor, ibid., 63, 2513 (1941).
115. A. C. Cope and E. M. Hancock, ibid., 61, 636 (1939).
116. J. S. Buck and A. M. Hjort, ibid., 59, 2567 (1937).
117. L. A. Walter, L. H. Goodson, and R. J. Fosbinder, ibid., 67, 655 (1945).
118. L. A. Walter, L. H. Goodson, and R. J. Fosbinder, ibid., 67, 657 (1945).
119. L. A. Walter, L. H. Goodson, and R. J. Fosbinder, ibid., 67, 659 (1945).
120. H. W. Coles, ibid., 59, 2468 (1937).
121. S. M. McElvain and M. A. Goese, ibid., 65, 2226 (1943).
122. F. F. Blicke and M. F. Zienty, ibid., 63, 2945 (1941).
123. H. Aspelund, Acta Acad. Aboensis, Math. Phys., 10, No. 14 (1937).
124. H. Aspelund, Finska Kemistsamfundets Medd., 48, 87 (1939); Chem. Abs., 33, 8182 (1939).
125. J. S. Buck, A. M. Hjort, W. S. Ide, and E. J. De Beer, J. Amer. Chem. Soc., 60, 461 (1938).
126. M. M. Katsnel'son and D. A. Brodskii, Dokl. Akad. Nauk SSSR, 17, 471 (1937).
127. F. Hoffmann-La Roche, A.-G., U. K. Pat. 454779 (1936); Chem. Abs., 31, 1555 (1937).
128. R. Ya. Levina, N. I. Mezentsova, and O. V. Lebedev, Zhur. Obshch. Khim., 25, 1097 (1955).
129. F. F. Blicke and C. E. Maxwell, J. Amer. Chem. Soc., 61,

1780 (1939).
130. G. J. Martin and S. Avakian, U. S. Pat. 2448 722 (1948); Chem. Abs., 42, 9093 (1948).
131. H. Goldhahn, Pharmazie, 12, 549 (1957).
132. Lilly and Co., Ltd., U. K. Pat. 725 589 (1955).
133. A. Merkatz, Chem. Ber., 52, 872 (1919).
134. M. Conrad and C. A. Bischoff, Annalen, 214, 70 (1882).
135. R. de V. Huber and W. F. Bruce, U. S. Pat. 2 721 201 (1955); Chem. Abs., 50, 7879 (1956).
136. E. Profft and G. Buchmann, Chem. Techn. Ztg., 1, 138 (1955); Chem. Abs., 50, 7070 (1956).
137. K. Abe, J. Pharm. Soc. Japan, 75, 885–896 (1956); Chem. Abs., 50, 4978 (1956).
138. D. Twomey, Proc. Roy. Irish Acad., 57B, 39 (1954); Chem. Abs., 50, 340 (1956).
139. D. M. Dvornik, S. M. Djokic, and R. Hammes, Archiv Kem., 26, 15 (1954); Chem. Abs., 50, 312 (1956).
140. A. Michael, J. prakt. Chem., (2), 35, 449 (1887).
141. H. Tsukamoto, H. Yoshimura, and S. Toki, Pharm. Bull. (Japan), 3, 239 (1955); Chem. Abs., 50, 11246 (1956).
142. C. R. Jacobson, A. B. Kerr, and E. D. Anstutz, J. Org. Chem., 19, 1909 (1954).
143. F. G. P. Remfry, J. Chem. Soc., 99, 610 (1911).
144. S. Bezzi, A. Cestari, and A. Cocco, Farm. Sci. e. tec. (Pavia), 3, 269 (1948); Chem. Abs., 42, 8419 (1948).
145. A. C. Cope, P. Kovacic, and M. Burg, J. Amer. Chem. Soc., 71, 3658 (1949).
146. H. Beyer and H. Höhn, Ber., 83, 14 (1950).
147. E. R. van Tamelen and G. van Zyl, J. Amer. Chem. Soc., 72, 2979 (1950).
148. G. S. Skinner and R. de V. Huber, ibid., 73, 3321 (1951).
149. G. S. Skinner, G. Limperos, and R. H. Pettebone, ibid., 72, 1648 (1950).
150. J. Büchi, K. Lauenberger, and R. Lieberherr, Farm. Sci. e. tec., 6, 429 (1951); Chem. Abs., 46, 8015 (1952).
151. M. T. Bush and W. D Beauchamp, J. Amer. Chem. Soc., 75, 2949 (1953).
152. G. S. Skinner and D. J. Lymen, ibid., 75, 5909 (1953).
153. K. Tanaka and T. Miyaiji, Ann. rept. Takeda Research Lab., 8, 29 (1949); Chem. Abs., 47, 4846 (1953).
154. F. D. Gunstone and R. M. Heggie, J. Chem. Soc., 1354 (1952).
155. E. M. van Heyningen, U. S. Pat. 2 621 183 (1952); Chem. Abs., 47, 10 001 (1953).
156. E. Campaigne and R. L. Patrick, J. Amer. Chem. Soc., 77, 5425 (1955).
157. R. Gebauer and Heyden, A.-G., German Pat. 623 373 (1935). Chem. Abs., 30, 2203 (1936).
158. C. S. Kuhn and G. H. Richter, J. Amer. Chem. Soc., 57, 1927 (1935).
159. Joachim Wiernik and Co., A.-G., French Pat. 797 152 (1936); Chem. Abs., 30, 6768 (1936).
160. W. Kropp and L. Taub, German Pat. 606 499 (1934); Chem. Abs., 29, 1587 (1935).
161. H. A. Shonle and J. H. Waldo, J. Amer. Chem. Soc., 55, 4649 (1933).
162. T. Reichstein and H. J. Morsman, Helv. Chim. Acta, 17, 1119 (1934).
163. A. Sonn and W. Litten, Ber., 66B, 1512 (1933).
164. F. E. Hooper and T. B. Jonson, J. Amer. Chem. Soc., 56, 484 (1934).
165. E. F Rosenberg, R. F. Kneeland, and G. S. Skinner, ibid., 56, 1339 (1934).
166. M. Kropp and B. Tchoubar, Bull. Soc. chim. France, 30 (1951).
167. I. E. Balaban and B. F. Wilde, U. K. Pat. 650 354 (1951); Chem. Abs., 45, 8553 (1951).
168. L. J. Smith and S. McKenzie, J. Org. Chem., 15, 74 (1950).
169. W. J. Doran, U. S. Pat. 2 666 057 (1954); Chem. Abs., 49, 371 (1955).
170. R. Ya. Levina and N. N. Godovikov, Zhur. Obshch. Khim., 24, 1572 (1954).
171. L. H. Sommer, G. M. Goldberg, G. H. Barnes, and L. S. Stone, J. Amer. Chem. Soc., 76, 1609 (1954).
172. R. Ya. Levina and N. N. Godovikov, Zhur. Obshch. Khim., 24, 1242 (1954).
173. H. A. Shonle, J. H. Walde, A. K. Keltch, and H. W. Coles, J. Amer. Chem. Soc., 58 585 (1936).
174. Laboratoires francais de chemiotherapie, U. K. Pat. 701 660 (1953); Chem. Abs., 49, 10 363 (1955).
175. E. Van Heyningen, J. Amer. Chem. Soc., 76, 2241 (1954).
176. E. E. Haley and G. P. Lambooy, ibid., 76, 2926 (1954).
177. F. Korosy, Magyar Kem. Lapja, 2, 61 (1947); Chem. Abs., 42, 4533 (1948).
178. E. C. Kleiderer and H. A. Shonle, J. Amer. Chem. Soc., 56, 1772 (1934).
179. J. S. Buck, ibid., 56, 1607 (1934).
180. R. Ya. Levina, N. N. Godovikov, and F. K. Velichko, Zhur. Obshch. Khim., 25, 2522 (1955).
181. M. Hudlicky, Chem. Listy, 40, 125 (1946); Chem. Abs., 560 (1950).
182. W. F. Bruce, G. Mueller, J. Seifter, and J. Szabo, U. S. Pat. 2 494 084 (1950); Chem. Abs., 45, 177 (1950).
183. G. Holmberg, Acta. Acad. Aboensis, Math. Phys, 16, 138 (1948); Chem. Abs., 45, 558 (1951).
184. W. O. Janes and D. S. Withey, J. Chem. Soc., 3490 (1954).
185. Compagnie de Béthune, U. K. Pat. 349 455 (1930); Chem. Abs., 26, 5313 (1932).
186. J. Tanaka, K. Miyanagy, and T. Okami, Bull. Hyg. Research Inst., 35, 105 (1929); Chem. Abs., 24, 1086 (1930).
187. Compagnie de Béthune, French Pat. 684 111 (1929); Chem. Abs., 24, 5308 (1930).
188. M. Ohara, S. Tamura, K. Ohmori, and K. Hochizuki, J. Pharm. Soc. Japan, 71, 911 (1951); Chem. Abs., 46, 4548 (1952).
189. K. N. Campbell, J. R. Corrigan, and B. K. Campbell, J. Org. Chem., 16, 1712 (1951).
190. M. Renard and G. Dony, Ind. chim. Belge, 16, 479 (1951); Chem. Abs., 46, 10 108 (1952).
191. W. J. Doran and E. M. van Heyningen, U. S. Pat. 2 561 688(1951); Chem. Abs., 46, 9589 (1952).
192. W. J. Doran and E. M. van Heyningen, U. S. Pat. 2 561 689 (1951); Chem. Abs., 46, 9589 (1952).
193. H. Walton, J. Doczi, and J. A. King, J. Amer. Chem. Soc., 72, 4319 (1950).
194. A C. Cope and S. M. McElvain, ibid., 54, 4319 (1932).
195. V. Nadkarni and J. W. Jones, J. Amer. Pharmaceut. Assoc. (Sci. Edn.), 39, 207 (1950); Chem. Abs., 44, 6525 (1950).
196. J. D. Riedel - E. de Häen, A.-G., French Pat. 778 031 (1935); Chem. Abs., 29, 4378 (1935).
197. H. A. Shonle, Canadian Pat. 353 477 (1935); Chem. Abs., 29, 8239 (1935).
198. V. Prelog and V. Hahn, Coll. Czech. Chem. Comm., 8, 219 (1936).
199. L. J. Owen and F. F. Nord, J. Org. Chem., 15, 988 (1950).
200. H. Goldhahn, Pharmazie, 8, 1016 (1953).
201. E. B. Hodge, J. Amer. Chem. Soc., 72, 5771 (1950).
202. H. Goldhahn, Pharmazie, 8, 324 (1953).
203. D. T. Keach, J. Amer. Chem. Soc., 55, 2975 (1933).
204. D. T. Keach, ibid., 55, 3440 (1933).
205. R. B. Maffott, J. E. Stafford, and C. A. Hart, J. Amer. Pharmaceut. Assoc. (Sci. Edn.), 42, 720 (1953); Chem. Abs., 48, 12 677 (1954).
206. H. G. Morren, G. Dony, and S. Levis, J. Pharm. Belg., 7, 65 (1952); Chem. Abs., 47, 5895 (1953).
207. H. Böhme and G. Greve, Pharm. Zentralhalle, 91, 259 (1952); Chem. Abs., 47, 7446 (1953).
208. E W. Maynert, J. M. Dawson, and E. Washburn, J. Biol. Chem., 195, 403 (1952).

209. G T. Tatevosyan and M G. Tuteryan, Izv. Akad. Nauk Armyansk. SSR, 29 (1944).
210. T. B. Johnson,and A. J. Hill, Amer. Chem. J., 46, 537 (1911).
211. E. Preisewerk and E. Grether, U. S. Pat. 1 042 265 (1912); Chem. Abs., 6, 3495 (1912).
212. H. Hörlein and W. Kropp, U. S. Pat. 1 056 793 (1913); Chem. Abs., 7, 2218 (1913).
213. E. H. Volwiler, J. Amer. Chem. Soc., 47, 2236 (1925).
214. A. W. Dox, U. S. Pat. 1 615 870 (1927); Chem. Abs., 21, 916 (1927).
215. F. Boedecker, U. S. Pat. 1 622 129 (1927); Chem. Abs., 21, 1464 (1927).
216. L. Taub, L. Schötz, and K. Meisenburg, U. S. Pat. 1 511 919 (1924); Chem. Abs., 19, 153 (1925).
217. M. Brockmühl and G. Ehrhart, U. S. Pat. 1 682 062 (1928); Chemie., 1928, 11, 1823.
218. H. A. Shonle, U. S. Pat. 2 066 280 (1937); Chem. Abs., 31, 1163 (1937).
219. W. Shulemann and K. Meisenburg, U. S. Pat. 1 690 796 (1928); Chem. Abs., 23, 483 (1929).
220. R. Chaux, Compt. Rend., 194, 1193 (1932).
221. A. Meyer, Compt. Rend., 152, 1677 (1911).
222. M. Taggart and G. Richter, J. Amer. Chem. Soc., 55, 1110 (1933).
223. S. Akabori, J. Chem. Soc. Japan, 52, 601 (1931).
224. S. Kirner and G. Richter, J. Amer. Chem. Soc., 51, 3131 (1929).
225. A. Dox and W. Jones, ibid., 50, 2033 (1928).
226. R. J. Nicholson, Australian Pat. 116 407 (1946); Chem. Abs., 41, 991 (1947).
227. J. Gillois-Doucet, Ann. Chim., 10 (12), 498 (1955).
228. M. Rising and J. Stieglitz, J. Amer. Chem. Soc., 40, 723 (1918).
229. G. S. Skinner, H. R. Krysiak, and J. A. Perregrino, ibid., 77, 2248 (1955).
230. A. J. Hill and D. T. Keach, ibid 48, 257 (1926).
231. H. A. Shonle and A. Moment, ibid., 45, 243, (1923).
232. F. P. Underhill and O. R. Johnson, J. Pharmacol., 35, 441 (1929); Chemie., 1929, 11, 1709.
233. I. F. Suknevich and T. M. Grafova, Sborn. Nauch. Trud. Leningrad Khim. Fiz. Inst. 2. 23 (1957).
234. Z. Jerzmanowska and M. Jaworska-Królikowska, Roczniki Chem., 28, 417 (1954).
235. J. D. Riedel-E. de Häen, A.-G., German Pat 575 470 (1933); Chem. Abs., 27, 3559 (1933).
236. P. Sharpentier, French Pat. 980 507; Chem. Abs., 48, 5213 (1954).
237. H. Gysling and G. Schwarzenbach, Helv. Chim. Acta, 32, 1848 (1949).
238. A. Allais and J. Mathien, Ann. Pharm. Franc., 9, 271 (1951); Chem. Abs., 45, 10499 (1951).
239. M. S. Taggart and G. H. Richter, J. Amer. Chem. Soc., 55, 1110 (1933).
240. A. W. Dox, ibid., 55, 1230 (1933).
241. J. Ledrut and G. Combes, Bull Soc. Chim. France, 786, (1950).
242. L. H. Cretcher, J. A. Koch, and W. H. Pittinger, J. Amer. Chem. Soc., 47, 3083 (1925).
243. S. M. McElvain and H. Burkett, U. S. Pat. 2 415 897 (1947); Chem. Abs., 41, 3482 (1947).
244. H. Kast, Chem. Ber., 45, 3124 (1910).
245. P. Ruggli O. Leupin, and A. Businger, Helv. Chim. Acta, 24, 339 (1941).
246. Winthrop Chemical Corp., Inc., U. S. Pat. 1 584 156 (1924); Chemie., 1926, 11 829.
247. B. Reichert and W. Wilke, Arch. Pharm., 276, 596 (1938); Chem. Abs., 33, 3797 (1939).
248. T. Wagner-Jauregg and H. Arnold, Annalen. 529, 274 (1937).
249. J. Motti, Anesthesie et Analgesie, 2, 52 (1936); Chem. Abs., 31, 3010 (1937).
250. G. A. Holmberg, Svensk. Kem. Tidskr., 57, 193 (1945); Chem. Abs., 40, 4028 (1946).
251. R. E. Stuckey, J. Pharm. Pharmacol., 15, 370, 377 (1942); Chem. Abs., 37, 2992 (1943).
252. G. Roeder, Chem. Ber., 46, 2560 (1913).
253. E. H. Volwiler and D. L. Tabern, J. Amer. Chem. Soc., 52, 1676 (1930).
254. H. A. Shonle, A. K. Keltch and E. E. Swanson, ibid., 52, 2440 (1930).
255. H. Oliyama, Y. Hasegawa, and H. Matsumura, J. Pharm. Soc., Japan, No. 533, 28 (1926); Chemie., 1926, 11, 2725.
256. A. W. Dox and W. G. Bywater, J. Amer. Chem., Soc., 58, 731 (1936).
257. J. D. Riedel, A.-G., Canadian Pat. 253 554 (1924); Chemie., 1926, 11, 1336.
258. T. B. Johnson and N. A. Shepard, J. Amer. Chem. Soc., 35, 994 (1913).
259. D. Waldi, Angew. Chem., 62, 430 (1950).
260. E. Miller, J. C. Munch, F. S. Crossley, and W. H. Hartung, J. Amer. Chem. Soc., 58, 1090 (1936).
261. R. Majima, Chem. Ber., 41, 174 (1908).
262. I. G. Alizade, Uch. Zap. Azerbaidzh Univ., 1957, No. 6, 49.
263. H. Aspelund, Acta Acad. Aboensis, Math. Phys., 20, No. 12 16 (1956).
264. A. W. Dox and H. Yoder, J. Amer. Chem. Soc., 43, 677 (1921).
265. A. W. Dox and H. Yoder, ibid., 43, 1366 (1921).
266. A. W. Dox and H. Yoder, ibid., 43, 2097 (1921).
267. A. Walter and S. M. McElvain, ibid., 57, 4891 (1935).
268. A. Dittrich and C. Paal, Chem. Ber., 21, 3453 (1888).
269. W. Kues and C. Paal, ibid., 18, 3324 (1885).
270. H. Goubt and T. Salomon, Chem. Rev., 174, 755 (1922).
271. R. A. Jacobson, J. Amer. Chem. Soc., 58, 1984 (1936).
272. A. Dox and W. Bywater, ibid., 58, 731 (1936).
273. A. Morton and F. Fallwell, ibid., 60 1428 (1938).
274. E. W. Bousquet and R. Adams, ibid., 52, 224 (1930).
275. C. M. Marberg and D. W. Stanger, ibid., 61, 2736 (1939).
276. N. V. Koshkin, Zhur. Obshch. Khim., 4, 1021 (1934).
277. R. Ya. Levina, Uch. Zap. Mosk. Gos. Univ., 175, 123 (1956).
278. G. S. Skinner, A. Stokes, and G. Spiller, J. Amer. Chem. Soc., 69, 3083 (1947).
279. A. N. Nesmeyanov and M. I. Kabachnik, Zhur. Obshch. Khim., 25, 41 (1955).
280. O. A. Reutov, "Teoreticheskie Problemy Organicheskoi Khimii" (Theoretical Problems of Organic Chemistry) Chapter X, Moskow. Gos. Univ., 1956.
281. H. Aspelund and L. Lindt, Acta Acad. Aboensis, Math. Phys., 11, No. 10 (1937).
282. R. Ya. Levina and N. N. Godovikov, Zhur. Obshch. Khim., 25, 986 (1955).
283. H. Aspelund and O. Backman, Acta Acad. Aboensis, Math. Phys., 14, No. 14, 19 (1944); Chem. Abs., 42, 373 (1943).
284. C. Berggardh, ibid., 9, No. 3, (1935).
285. L. Taub and W. Kropp, U. S. Pat. 2 061 14 (1937); Chem. Abs., 31, 709 (1937).
286. H. Aspelund and L. Lindh, Acta Acad. Aboensis, Math. Phys., 12, 13 (1939).
287. E. H. Volwiler, J. Amer. Chem. Soc., 47, 2238 (1925).
288. M. M. Katsnel'son and M. I. Kabachnik, Dokl. Akad. Nauk SSSR, 4, 397 (1936).
289. A. Wacker, French Pat. 757 655 (1933); Chem. Abs., 28, 2728 (1934).
290. Yu. O. Gabel', I. Yu. Zbarskii, and V. F. Lavrushin, Pratsi Ukrain. Inst. Exp. Farm., 1, 84 (1938).
291. F. S. Crossley, E. Miller, W. H. Hartung, and M. L. Moore, J. Org. Chem., 5, 238 (1940).
292. A. Hofmann, Chem. Ber., 4, 267 (1871).

293. A. W. Dox, J. Amer. Chem. Soc., 53, 1559 (1931).
294. T. Nishikawa, Mem. Ryojun. Coll. Eng., 3, 277 (1931); Chem. Abs., 25, 5390 (1931).
295. H. Aspelund, J. Prakt. Chem., 136, 329 (1933).
296. J. L. Walter, J. A. Ryan, and T. J. Lanc, J. Amer. Chem. Soc., 78 5560 (1956).
297. L. N. Goldyrev and L. N. Zakharov "Sbornik, Statei po Obshchie, Khimii" (Collected papers on General Chemistry), Vol. 2, 1953, p.1273.
298. H. Lund, Kgl. Danske Videnskob. Selskob. Math. Fys. Med., 13, No. 13, 11 (1935); Chem. Abs., 30, 1362 (1936).
299. G. S. Skinner, J. Amer. Chem. Soc., 59, 322 (1937).
300. G. S. Skinner and A. P. Stuart, ibid., 63, 2993 (1941).
301. G. S. Skinner and R. E. Herbener, ibid., 75, 3031 (1953).
302. G. S. Skinner and J. Mitchell, ibid., 67, 1252 (1945).
303. G. van Zyl and E. E. van Tamelen, ibid., 72, 1357 (1950).
304. N. V. Khromov-Borisov and I. M. Yurist, Zhur. Obshch. Khim., 22, 847 (1952).
305. A. C. Cope and E. M. Hancock, J. Amer. Chem. Soc., 61 776 (1939).
306. D. L. Tabern and E. H. Volwiler, ibid., 56, 1139 (1934).
307. J. S. Chamberlain, J. J. Chap, J. E. Doyle, and L. B. Spaulding, ibid., 57, 352 (1935).
308. J. H. Boothe and C. O. Wilson, ibid., 68, 448 (1946).
309. M. Momoi, Jap. Pat. 1562 (1951); Chem. Abs., 47, 5435 (1953).
310. M. Tsuruta, Y. Okajima, and M. Tomita, J. Chem. Soc, Japan. Ind. Chem. Sect., 54, 722 (1951); Chem. Abs., 42, 3915 (1954).
311. A. C. Cope and E. M. Hancock, J. Amer. Chem. Soc., 61 353 (1939).
312. Sharp and Dome, Inc., U. K. Pat. 639 946 (1950); Chem. Abs., 44, 110 040 (1950).
313. J. R. Geigy, A.-G., French Pat. 870 714 (1942); Chem. Abs., 43, 5038 (1949).
314. J. W. Opie, J. Seifter, W. F. Bruce, and G. Mueller, U. S. Pat. 2 538 322 (1951); Chem. Abs., 45, 6657 (1951).
315. H. Lund. Ber., 69B, 1621 (1936).
316. M. A. Phillips, U. K. Pat. 590 714 (1947); Chem. Abs., 42, 2987 (1948).
317. I. G. Farbenindustrie A.-G., U. K. Pat. 401 693 (1933); Chem. Abs., 28, 2850 (1934).
318. M. Conrad, Annalen, 340, 310 (1905).
319. M. Conrad and A. Zart, ibid., 340, 326 (1905).
320. D. M. Dvornik and S. M. Djokic, Archiv. Kem., 26, 115 (1954) Chem. Abs., 50, 312 (1956).
321. M. Conrad and A. Zart, Annalen, 340, 335 (1905).
322. Z. Eckstein, Przemysl Chem., 9, 390 (1953); Chem. Abs., 49, 11668 (1955).
323. Ya. M. Slobodin and I. N. Shokhor, "Sbornik. Statei po Obshchei. Khimii" (Collected Papers on General Chemistry), Vol. 2, 1953, p. 850.
324. A. Einhorn and C. Ladisch, German Pat. 158 553; Annalen, 359, 184 (1908).
325. K. Tanaka and T. Sugawa, J. Pharm. Soc. Japan, 70, 162 (1950); Chem. Abs., 44, 5814 (1950).
326. K. Jorissen, J. Pharm. Chim, 478 (1910).
327. Shionogri Drug Manuf. Co., Jap. Pat. 153 514 (1942); Chem. Abs., 43 3463 (1949).
328. M. Nakamura, Jap. Pat. 178 454.(1949); Chem. Abs., 46, 526 (1952).
329. J. J. Fox and D. Shugar, Bull. Soc. Chim. Belg., 61, 44 (1952)
330 D. Marotta and G. Rosanoya, Atti Accad. naz. Lincei, Rend. 15 (6), 753 (1932).
331. F. F. Heyroth and J. R. Loofbourow, J. Amer. Chem. Soc., 56, 1728 (1934).
332. M. Ridi, Gassetta, 80, 121 (1950).
333. G. Florence and M. Possi, Compt. rend., 195, 614 (1932)
334. A. J. Biggs, J. Chem. Soc., 1956, 2485.
335. A. H. Nathan and M. T. Bogert. J. Amer. Chem. Soc., 63, 2361 (1941).
336. R. E. Stuckey, Quart. J. Phamacol, 13 312 (1940); Chem. Abs., 35, 3169 (1941).
337. A. W. Dox and E. G. Jones, J. Amer. Chem. Soc., 51, 316 (1929).
338. J. R. Loofbourow and M. M. Stimson, J. Chem. Soc., 1940, 1275.
339. H. Erlenmeyer, A. Epprecht, H. Lobeck, and H. Gartner Helv. Chim. Acta, 19, 354 (1936).
340. A. J. Petro, C. P. Smyth, and L. G. S. Brooker, J. Amer. Chem. Soc., 78 3040 (1956).
341. Yu. I. Sheinker and Yu. I. Pomerantsev, Zhur. Fiz. Khim., 30, 79 (1956).
342. M. Conrad and M. Guthzeit, Chem. Ber., 14, 1643 (1881).
343. A. W. Dox, J. Amer. Chem. Soc., 53, 2741 (1931).
344. F. E. King and T. J. King, J. Chem. Soc., 1947, 726.
345. H. A. Shonle and W. J. Doran, J. Amer. Chem. Soc., 58, 1358 (1936).
346. H. Biltz, M. Heyn, and T. Hamburger, Chem. Ber., 49, 662 (1916).
347. Heyden, A.-G., German Pat. 589 146 (1933); Chem. Abs., 28, 2359 (1934).
348. R. Gebauer, Heyden A.-G., German Pat. 626 411, (1936); Chem. Abs., 30, 5594 (1936).
349. M. Conrad and H. Reinbach, Chem. Ber., 34, 1339 (1901).
350. B. Bobranski, T. Jakobiec, and D. Prelicz, Roczniki Chem., 30, 165 (1956).
351. M. M. Rising, J. H. Schroyer, and J. Stieglitz, J. Amer. Chem. Soc., 55, 2817 (1933).
352. M. M. Rising and A. Pierce, ibid., 55, 3895 (1933).
353. A. E. Pierce and M. M. Rising, ibid., 58, 1361 (1936).
354. J. W. Loubrid, ibid., 56, 1968 (1934). 355.
355. E. W. Maynert and E. Washburn, ibid., 75, 700 (1953).
356. E. W. Maynert and J. M. Dawson, J. Biol. Chem., 195, 389 (1952).
357. W. G. Bywater, U. S. Pat. 2 200 538 (1940); Chem. Abs., 34, 6019 (1940).
358. H. Leuchs and H. Lemcke, Chem. Ber., 47. 2573 (1914).
359. Ya. A. Fialkov and L. I. Rapaport, Zhur. Obshch. Khim., 25, 2265 (1955).
360. E. W. Maynert, J. M. Dawson, and E. Washburn, J. Biol. Chem., 195, 397 (1952).
361. B. B. Bobranski, T. Jakóbiec, and D. Prelicz, Roczniki Chem., 30, 175 (1956).
362. H. Ruhkopf, Ber., 73, 938 (1940).
363. H. Goldhahn, Pharmazie, 12, 549 (1957).
364. M. Ridi, Gazzetta, 80, 542 (1950).
365. A. E. Boyley, Pharm. J., 136, 620 (1936); Chem. Abs., 30, 7785 (1936).
366. J. S. Buck, J. Amer. Chem. Soc., 58, 2059 (1936).
367. R. L. France and R. K. Phillips, ibid., 71, 2804 (1949).
368. H. Goldhahn and H. Barth, Pharmazie, 8, 913 (1953).
369. A. V. Kirsanov and Ya. N. Ivashchenko, Zhur. Obshch. Khim., 8, 1576 (1938).
370. D. L. Tabern and E. H. Volwiler, J. Amer. Chem. Soc., 57, 1961 (1935).
371. M. Tisher, J. W. Wellmann, and K. Ladenburg, ibid., 67, 2165 (1945).
372. H. Aspelund and L. Skoglund, Acta Acad. Aboensis Math. Phys., 10, (1937).
373. A. Bayer, Lieb. Ann., 130, 129 (1864).
374. B. Molle and H. Kleinst, Arch. Pharm., 242, 401, (1904); Chemie, 1904, 11, 1005.
375. D. L. Tabern and E. H. Volwiler, J. Amer. Chem. Soc., 58, 1354 (1936).
376. D. L. Tabern and N. A. Hansen, Canadian Pat. 355 872 (1936); Chem. Abs., 30, 2708 (1936).
377. Abbott Laboratories, U. K. Pat. 404 038 (1934); Chem. Abs.,

28, 3742 (1934).
378. S. Quesada, Rev. Asoc. biquim . argentina, 12, 195 (1945); Chem. Abs., 40, 400 (1946).
379. K. Okazaki, N. Kitamura, and H. Hamada J. Pharm. Soc., Japan, 71, 889, 893, (1951); Chem. Abs., 46, 1711 (1952).
380. H. P. Kaufmann, German Pat. 652712 (1937); Chem. Abs., 32, 1407 (1938).
381. B. Danielsson, Svensk. Farm. Tidskr., 58, 511 (1954); Chem. Abs., 48, 13539 (1954).
382. L. I. Rapaport and G. A. Vaksman, Ukrain. Khim. Zhur., 20, 424 (1954).
383. C. N. Anderson, U. S. Pat. 2 118 133 (1938); Chem. Abs., 32, 5584 (1938).
384. L. Rosenthaler, Microchimie, 21, 215 (1937).
385. C. N. Andersen, U. S. Pat. 2 155 922 (1939); Chem. Abs., 33, 6000 (1939).
386. H. P. Andersen and M. C. Hart, J. Amer. Chem. Soc., 59, 1115 (1937).
387. T. Nisikawa, Mem. Ryojun Coll. Eng., 13, 195 (1940); Chem. Abs., 35, 5466 (1941).
388. T. Nisikawa, J. Chem. Soc. Japan, 61, 81 (1940); Chem. Abs., 36, 2864 (1942).
389. T. Nisikawa, ibid., 61, 559, 564, 686 (1940); Chem. Abs., 37, 344 (1943).
390. H. Gomahr and H. Kresbach, Scientia Pharm., 19, 148 (1951); Chem. Abs., 46, 2237 (1952).
391. E. Vascantanu and R. Cernatescu, Bull. Sect. Sci. Acad. Roumaine, 25, 459 (1943); Chemie., 1944, 1, 1180.
392. H. J. Tormey and J. S. Griffo, Sci. Studies St. Bonaventure Univ., 18, 15 (1956); Chem. Abs., 51, 8107 (1957).
393. A. W. Dox. J. Amer. Chem. Soc., 49, 2275 (1927).
394. T. Kashima, J. Pharm. Soc., Japan, 74, 101 (1954); Chem. Abs., 48, 5440 (1954).
395. E. Lyons and A. W. Dox, J. Amer. Chem. Soc., 51, 288 (1929).
396. J. D. Riedel - E. de Haen, A. -G., German Pat. 605 567 (1934); Chem. Abs., 29, 1101 (1935).
397. W. J. Doran and H. A. Shonle, J. Amer. Chem. Soc., 59 1625 (1937).
398. J. D. Riedel - E. de Haen, A. - G., German Pat. 610 502 (1935); Chem. Abs., 29, 5861 (1935).
399. J. A. Timm, J. Amer. Chem. Soc., 57 1943 (1935).
400. W. Braker, E. J. Pibyl, and W. A. Lott, Ibid., 69, 866 (1947).
401. J. D. Riedel-E. de Haen, A. -G., German Pat. 482 841 (1924); Chem. Abs., 24, 628 (1930).
402. Compagnie de Bethûne, French Pat. 38 860 (1930); Chem. Abs., 26 1623 (1932).
403. J. D. Reidel-E. de Haen, A. -G., German Pat. 481 733 (1923); Chem. Abs., 24, 628 (1930).
404. K. O. Rosen, Swedish Pat. 131, 142 (1951); Chem. Abs., 46, 9591 (1952).
405. F. Hoffmann-La Roche and Co., A. -G., German Pat. 526 854 (1930); Chem. Abs., 25, 4893 (1931).
406. W. F. Bruce, Matt-Ban., U. S. Pat. 2 786 057 (1957); Chem. Abs., 51, 18015 (1957).
407. B. Siegfried, Swiss Pat. 151 516 (1930); Chem. Abs., 26 4828 (1932).
408. W. J. Doran and H. A. Shonle, J. Amer. Chem. Soc., 60 2880 (1938).
409. O. Wichterle and O. Nemecek, Chem. Listy, 37, 281 (1943); Chem. Abs., 45 561 (1951).
410. Heyden, A. -G., German Pat. 642 794 (1937); Chem. Abs., 31, 6676 (1937).
411. A. - G., French Pat. 773 774 (1934); Chem. Abs., 29, 1437 (1935).
412. W. T. Keach and A. J. Hill, J. Amer. Chem. Soc., 48, 2743 (1926).
413. E. D. Hurd and M. L. McAuley, ibid., 70, 1650 (1948).
414. J. A. Timm and J. B. Howard, ibid., 58, 1805 (1936).
415. J. A. Timm, ibid., 61, 2962 (1939).
416. K. Duschinsky and L. A. Dolan, ibid., 70, 657 (1948).
417. D. Chandanayigyong, J. Pharm. Assoc. Siam, (3) 1, No. 5 4 (1948); Chem. Abs., 46, 2502 (1952).
418. C. C. J. Culvenor, W. Davies, and N. S. Heath, J. Chem. Soc., 1949, 278
419. S. L. Ruskin and M. Pfalz, J. Amer. Chem. Soc., 60, 1471 (1938).
420. H. A. Shonle, U. S. Pat. 1 954 429 (1934); Chem. Abs., 28 3743 (1934).
421. B. Hepner and S. Frenkenberg, J. Prakt. Chem., 134, 249 (1932).
422. J. Lee, J. Amer. Chem. Soc., 60, 933 (1938).
423. T. Nisikawa, J. Chem. Soc., Japan, 56, 1487 (1935).
424. T. Nisikawa, ibid., 58, 97 (1937).
425. A. Halpern, J. W. Jones, and E. G. Gross, J. Amer. Pharmacuet. Assoc. (sci. Edn.) 37, 333 (1948); Chem. Abs., 43, 2169 (1949).
426. H. Rosenberg, German Pat. 631 097 (1936); Chem. Abs., 30, 6136 (1936).
427. K. Bodendorf, Arch. Pharm., 282, 78 (1944); Chem. Abs., 44, 8059 (1950).
428. E. Profft, F. Runge, and A. Jumar, J. Prakt. Chem., (4), 1, 57 (1954).
429. H. K. Henze and J. J. Spurlook, J. Amer. Chem. Soc., 63, 3360 (1941).
430. F. Bertrand, Bull. Soc. Chim. France, 1948 1079.
431. H. J. Tormey and G. W. Humphreys, Sci. Studies, St. Bonaventure Univ. 8, No. 2, 9 (1940); Chem. Abs. 34, 2848 (1940).
432. T. Kaku, Y. Kase, and M. Nagai, J. Pharm. Soc. Japan, 74, 122 (1954); Chem. Abs., 49, 1569 (1955).
433. T. Ukai, Y. Yamamoto, Sh. Kanatomo, and A. Kawakami, Ann. Report Fac. Pharm., Kanazawa Univ., No. 3, 42 (1953); Chem. Abs., 50, 10737 (1956).
434. E. Profft, F. Runge, and A. Jumar, J. Prakt. Chem., (4) 1, 59 (1954).
435. M. E. Hultquist and C. F. Poe, Ind. Eng. Chem., Anal. Ed., 7, 398 (1935).
436. Heyden, A. - G., German Pat. 590 174 (1933); Chem. Abs., 28, 2016 (1934).
437. F. Hoffmann-La Roche and Co., A. -G., U. K. Pat. 391 741 (1933); Chem. Abs., 27, 5085 (1933).
438. J. D. Riedel-E. de Haen, A. -G., German Pat. 621 964 (1935); Chem. Abs., 30, 2207 (1936).
439. F. Hoffmann-La Roche and Co., A. -G., Berlin Chem. Fabr., German Pat. 587 192 (1933); Chem. Abs., 28, 2370 (1934).
440. H. R. Henze, U. S. Pat. 2 314 537 (1943); Chem. Abs., 37, 1014 (1943).
441. F. Sandberg, Acta. Physiol. Scand., 24, 7 (1951); Chem. Abs., 46 3154 (1952).
442. M. E. Hultquist, C. F. Poe, and N. F. Witt, Ind. Eng. Chem. Anal. Ed., 14, 219 (1942).
443. F. Reimers, Analyt. Chim. Acta, 2, 1 (1948).
444. C. F. Poe, N. F. Witt, and A. S. Snodgrass, Mikrochem. Acta, 34, 235 (1939).
445. R. N. Castle and C. F. Poe, J. Amer. Chem. Soc., 66 1440 (1944).
446. L. Jezo and P. Selecky, Chem. Zvesti, 5, 121 (1951); Chem. Abs., 47, 106 (1953).
447. S. Moore, W. Stein, and J. S. Fruton, J. Org. Chem., 11, 675 (1946).
448. J. W. Jones and A. Halpern, J. Pharm. Sci. Ed., 36, 376 (1947); Chem. Abs., 42, 3533 (1948).
449. L. G. Chatten and L. Levi, Appl. Spectroscopy, 11, 177 (1957).

450. M. E. Hultquist, C. F. Poe, and N. F. Witt, J. Amer. Chem. Soc., 67, 688 (1945).
451. R. J. Meltzer and A. D. Lewis, J. Org. Chem., 21, 256 (1956).
452. Yuzura, Yamamoto, Kanatomo, and Kawakami, Rept. Fac. Pharm. Univ. Kanazawa, 3, 42 (1953). 37687, (1957).
453. C. N. Andersen, U. S. Pat. 2 087 959 (1937); Chem. Abs., 31, 6827 (1937).
454. R. E. Stuckey, Quart. J. Parm. Pharmacol., 14, 217 (1941); Chem. Abs., 36, 705 (1942).
455. J. D. Riedel-E. de Häen. A.-G., German Pat. 613 403, 648 001, 650 431 (1937); Chem. Abs., 32, 1406 (1938).
456. M. T. Bush and T. C. Butler, J. Pharmacol., 61, 139 (1937); Chem. Abs., 32, 118 (1938).
457. M. Nakamura, Jap. Pat. 180 248 (1949); Chem. Abs., 46, 4027 (1952).
458. H. Rudy, Österreich. Chem. Ztg., 42 329 (1939).
459. M. J. Kamlet, J. Amer. Chem. Soc., 77, 4896 (1955).
460. C. T. Bahner, U. S. Pat. 2 527 293 (1950); Chem. Abs., 45, 9087 (1951).
461. M. J. Kamlet and D. J. Glover, J. Amer. Chem. Soc., 78, 4556 (1956).
462. P. Fresenius, Arzneimittel-Forsch., 1, 128 (1951); Chem. Abs., 46, 6596 (1952).
463. A. Weinschenk, Chem. Ber., 34, 1685 (1901).
464. S. Akabori, ibid., 66B, 139 (1933).
465. M. Nguyên-Hoan, Compt. rend., 238, 1136 (1954).
466. H. Willstaedt, Atti X congr., intern. chim., 3, 390 (1939).
467. H. Zenno, J. Pharm. Soc. Japan, 74, 199 (1954); Chem. Abs., 49, 1570 (1955).
468. P. Pfeiffer and E. Enders, Ber., 84, 313 (1951).
469 T. Ukai, Y. Yamamoto, and S. Kanetomo, J. Pharm. Soc. Japan, 74, 678 (1954); Chem. Abs., 48, 10 743 (1954).
470. P. Papini and R. Cimmarustĭ, Gazzetta, 77, 142 (1947).
471. P. Ruggli and P. Hindermann, Helv. Chim. Acta, 20, 172 (1937).
472. F. E. King, T. J. King, and G. B. Thompson, J. Chem. Soc., 552 (1948).
473. F. Mueller and A. Bavley, Canadian Pat. 449 834 (1948); Chem. Abs., 42, 6685 (1948).
474. M. Ridy, Gazzetta, 82, 756 (1952).
475. S. Hünig, Annalen, 574, 106 (1951).
476. V. A. Maslennikova and G. V. Lazur'evskii, Dokl. Akad. Nauk SSSR, 72, 305 (1950).
477. T. Iseki, J. Biochem. (Japan), 19, 7 (1934); Chem. Abs., 28, 2709 (1934).
478. M. Ridi and P. Papini, Gazzetta, 78, 11 (1948).
479. R. Kitamura and S. Suzuki, J. Pharm. Soc. Japan, 57, 659 (1937); Chem. Abs., 33, 1726 (1939).
480. R. B. Van Order and H. G. Zinwall, J. Org. Chem., 10, 128 (1945).
481. M. Krakowski, Arch. Chem. Farm., 2, 164 (1935); Chem. Abs., 30, 1031 (1936).
482. P. Ruggli, P. Hindermann, and H. Frey, Helv. Chim. Acta, 21, 1066 (1938).
483. "Organic Syntheses", 21, 5 (1941).
484. M. Ridi, Gazzetta, 80, 533 (1950).
485. T. Pavolini, F. Gambarin, and C. Zanini, Ann. Chim. (Italy), 41, 438 (1951).
486. G. H. Keyes and L. G. S. Brooker, U. S. Pat. 2 611 696 (1952); Chem. Abs., 47, 990 (1953).
487. M. Ridi, Gazzetta, 79, 175 (1949).
488. T. Sasaki, Pharm. Bull., 2, 123 (1954); Chem. Abs., 50, 971 (1956).
489. Yu. K. Yur'ev and N. I. Mezentsova, Zhur. Obshch. Khim., 28, 3041 (1958).
490. R. Jager and E. Unger, Ber., 35, 4443 (1902).
491. E. Unger, and R. Jäger, ibid., 36, 1229 (1903).
492. A. Dox and L. Pleasance, J. Amer. Chem. Soc., 38, 2164 (1916).
493. W. Kropp and L. Taub, U. S. Pat. 1 947 944 (1934); Chem. Abs., 28, 2850 (1934).
494. W. Wenner, Jubilee Vol. Emil Barell, 435 (1946); Chem. Abs., 41, 4107 (1947).
495. W. Wenner, U. S. Pat. 2 446 504 (1948); Chem. Abs., 43 1799 (1949).
496. H. Zenno, J. Pharm. Soc. Japan, 73, 1063 (1953); Chem. Abs., 48, 8543 (1954).
497. L. G. S. Brooker, G. H. Keyes, R. H. Sprague, R. H. Van Dyke, E. Van Lare, G. Van Zandt, and F. L. White, J. Amer. Chem. Soc., 73, 5326 (1951).
498. L. G. Brooker, G. H. Keyes, R. H. Sprague, R. H. Van Dyke, E. Van Lare, G. Van Zandt, F. L. White, H. W. Cressmann, and S. G. Dent, ibid., 73, 5332 (1951).
499. L. G. S. Brooker and F. L. White, U. S. Pat. 2 739 964 (1956); Chem. Abs., 50, 12 708 (1956).
500. G. H. Keyes and L. G. S. Brooker, U. S. Pat. 2 611 696 (1953); Chem. Abs., 47, 990 (1953).
501. E. B. Knott, J. Chem. Soc., 3038 (1951).
502. H. Zenno, J. Pharm. Soc. Japan, 73, 301 (1953); Chem. Abs., 48, 2044 (1954).
503. H. Zenno, ibid., 73, 1065 (1953); Chem. Abs., 48, 8545 (1954).
504. S. Kanao, Jap. Pat. 5682 (1953); Chem. Abs., 49, 47 301 (1955).
505. H. Zenno, J. Phar. Soc. Japan, 74, 196 (1954); Chem. Abs., 49, 1569 (1955).
506. H. Zenno, ibid., 74, 1236 (1954); Chem. Abs., 49, 14 736 (1955).
507. K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, Annalen, 551, 80 (1942).
508. W. Bock, Chem. Ber., 56, 1222 (1923).
509. H. Aspelund and L. Lindh, Acta Acad. Aboensis, Math. Phys., 11, No. 2 (1937).
510. A. M. Clover, Canadian Pat. 245 806 (1924); Chem. Abs., 19, 657 (1925).
511. P. Fresenius, Pharm. Zentralhalle, 95, 361 (1956).
512. W. Wenner, U. S. Pat. 2 445 898 (1948); Chem. Abs., 43, 2227 (1949).
513. H. Aspelund, Acta Acad. Aboensis, Math. Phys., 10, No. 2 (1936).
514. H. Aspelund and L. Mandel, ibid., 20, No. 11, 18 (1956).
515. H. Aspelund and J. Kronlöf, ibid., 21, No. 5, 15 (1957).
516. H. T. Clarke, "Handbook of Organic Analysis" (Translated into Russian), NTI Ukrainy, 1934, p. 212.
517. R. Robinson and M. Tomlinson, J. Chem. Soc., 467 (1935).
518. N. S. Drozdov and V. P. Krylov, Nauch. Dokl. Vys. Shkoly., Khim. i Khim. Tekhnol., 342 (1958).
519. J. Lifschitz, Chem. Ber., 47, 1068 (1914).
520. A. Mossini, Ann. chim. farm., (Suppl. to Farm. ital.), Dec., 1939, p. 47; Chem. Abs., 34, 2175 (1940).
521. M. Tischler, K. Pfister, R. D. Babson, K. Ladenburg, and A. J. Fleming, J. Amer. Chem. Soc., 69, 1487 (1947).
522. M. Tischler, J. W. Wellman, and K. Ladenburg, ibid., 67, 2165 (1945).
523. M. Ridi and P. Papini, Gazzetta, 78, 13 (1948).
524. M. Ridi, P. Papini, and S. Checchi, ibid., 84, 781 (1958).
525. T. Curtius, Chem. Ber., 56, 1577 (1923).
526. J. Tafel and A. Weinschenk, ibid., 33, 3383 (1900).
527. A. Einhorn and H. Diesbach, ibid., 40, 4902 (1907).
528. F. J. Marshall, J. Amer. Chem. Soc., 78, 3696 (1956).
529. A. Meyer and G. Bouchet, Compt. rend., 227, 345 (1948).
530. F. E. King, T. J. King, and P. C. Spensley, J. Chem. Soc., 1147 (1947).
531. J. Baddiley and A. Topham, ibid., 678 (1944).
532. H. C. Carrington, ibid., 124 (1944).

533. H.R. Henne and P.E. Smith, J. Amer. Chem. Soc., 65, 1090 (1943).
534. W.B. Walley, E.L. Anderson, F. Duggan, J.W. Wilson, and G.E. Ullot, ibid., 77, 745 (1955).
535. J. Stanek and J. Sidlo, Ceskoslov. Farm., 2, 117 (1953); Chem. Abs., 49, 6123 (1955).
536. N.R. Boon and C.H. Vasey, U.S. Pat. 2660 056 (1954); Chem. Abs., 49, 9045 (1955).
537. C.H. Vasey, U.K. Pat. 734 511 (1955); Chem. Abs., 50, 7881 (1956).
538. L. Monti and G. Tranchi, Gazzetta, 81, 764 (1951).
539. L.I. Rapaport and Ya.A. Fialkov, Zhur. Obshch. Khim., 26, 279 (1956).
540. A. Einhorn, Annalen, 359, 145 (1908).
541. R. Bârre and A. Jaques, Rev. Can. biol., 1, 454 (1942); Chem. Abs. 36, 3853 (1942).
542. C. Lapière, Analyt. Chim. Acta, 1, 390 (1947).
543. J. Zwikker, Pharm. Weekblad, 68, 975 (1931).
544. J. Kubis and N. Liskova, Casopis Lekaru Cekých., 93, 602 (1954); Chem. Abs., 48, 11 724 (1954).
545. K.P. Agrilês and J.M. Beguiristain, Arch. med. exptl., 16, 145 (1953); Chem. Abs., 48, 5738 (1954).
546. G.G. Robles, Bol. Soc. quim. Peru, 15, 70 (1949); Chem. Abs., 44, 1648 (1950).
547. W. Bock, Chem. Ber., 55, 3400 (1922).
548. M. Pesez, J. Pharm. Chim., 28, 379 (1938); Chem. Abs., 33, 7961 (1939).
549. H. Rafalowska, Roczniki Panstwowego Zakladu Hig., 2, 226 (1951); Chem. Abs., 46, 4747 (1952).
550. E.B. Parkes, Analyst, 75, 448 (1950).
551. E. Emerson and L.C. Beegle, J. Org. Chem., 8, 425 (1943).
552. J. Deshusses, Pharm. Acta Helv., 20, 199 (1945); Chem. Abs., 42, 6055 (1948).
553. Han Chen Ho and Chu Ning Tao, J. Chinese Chem. Soc. (Formosa), 17, 79 (1950); Chem. Abs., 44, 5270 (1950).
554. B. Lilliman, Analyst, 75, 626 (1950).
555. A. Kofler, Mikrochem., 33, 4 (1947).
556. M. Brandstätter and H. Grimm, Mikrochim. Acta, 1175 (1956).
557. O. Schales, Chem. Ber., 71B, 116 (1938).
558. M. Brandstätter, Z. phys. Chem., 191A, 227 (1942).
559. Tso' Yuck Huang, Acta Pharm. Intern., 2, 43, 95 (1951); Chem. Abs., 46, 4172, 7284 (1952).
560. V. Hahn, Z. Kochansky, J. Gustak-Masek, and K. Jemric, Croat. Chem. Acta, 28, 119 (1958).
561. C. Stainier, J. Pharm. Belg., (N.S.), 5, 26 (1950); Chem. Abs., 44, 6575 (1950).
562. R. Fabre, Bull. Soc. chim. France, 33, 781 (1923).
563. R.S. McCutcheon and E.M. Plein, J. Amer. Pharmaceut. Assoc. (Sci. Edn.), 38, 24 (1949).
564. A. Lespanol and R. Delsarte, Ann. méd. légale criminol. police Sci., 16, 601 (1936); Chem. Abs., 31, 1954 (1937).
565. C. Stainier, C. Lapiere and S. de Tiège-Robinet, Ann. pharm. franc., 14, 384 (1956).
566. C. Raeth and R. Gebauer, U.S. Pat. 2 134 672 (1939); Chem. Abs., 33, 994 (1939).
567. P. Bouchereau, J. Pharm. Chim., 28, 484 (1938); Chem. Abs., 33, 8565 (1939).
568. P. Beiersdorf and Co., A.-G., German Pat. 659 221 (1938); Chem. Abs., 32, 5592 (1938); Chem. Abs., 32, 5592 (1938).
569. H. Ruhkopf, Chem. Ber., 70, 939 (1937).
570. C. Stainier, C. Lapiére, and S. de Tiége-Robinet, Ann. pharm. franc., 14, 476 (1956).
571. G.H. Wagenaar, Pharm. Weekblad, 78, 345 (1941); Chem. Abs., 38, 2454, (1944).
572. G. Beck, Mikrochem., 29, 206 (1941).
573. H. Kaiser and W. Lang, Pharm. Zentralhalle, 91, 281 (1952); Chem. Abs., 47, 675 (1953).
574. C.J. de Molf, Pharm. Weekblad, 84, 537 (1949); Chem. Abs., 44, 279 (1950).
575. W. Paulus and H.J. Mallach, Arzneimittel - Forsch., 4, 391 (1954); Chem. Abs., 48, 11 001 (1954).
576. A. Kyaer and K. Rubinstein, Acta Chem. Scand., 7, 528 (1953).
577. A. Calo, A. Mariani, and O. Mariani-Morelli, Rend. 1-st Super Sanita, 20, 811 (1957).
578. A.N. Kurteva, Zavod. Lab., 9, 307 (1940).
579. M. Schubert, Z. analyt. Chem., 107, 374 (1936).
580. P. Chavanne and H. Maric, Ann. pharm. franc., 11, 91 (1953); Chem. Abs., 47, 6605 (1953).
581. R. Heiz, Dansk. Tidsskr. Farm., 26, 69 (1952); Chem. Abs., 46, 6551 (1952).
582. S. Goldschmidt, W. Lamprecht, and E. Helmreich, Z. physiol. Chem., 292, 125 (1953).
583. A. Grieg, Nature, 170, 845 (1952).
584. L.K. Goldbaum, Analyt. Chem., 24, 1604 (1952).
585. C.J. Umberger and G. Adams, ibid., 24, 1309 (1952).
586. L. Levi and C.E. Hubley, ibid., 28, 1591 (1956).
587. A. Kalvoda and J. Zyka, Cesk. Farm., 2, 154 (1953); Chem. Abs., 48, 9672 (1954).
588. O. Manousek and P. Zuman, ibid., 5, 193 (1956); Chem. Abs., 50, 17 334 (1956).

Faculty of Chemistry,
Lomonosov Moscow State
University

BORAZOLE AND ITS DERIVATIVES

B.M. Mikhailov

CONTENTS

Introduction

I. Methods of synthesis of borazole and its derivatives 460
   1. Synthesis from diborane and its alkyl derivatives 460
   2. Synthesis from boron trialkyls 461
   3. Synthesis from boron trichloride 461
   4. Synthesis from ammonium salts and lithium tetrahydroborate 462
   5. Synthesis from *N*-substituted aminoboron dichlorides 462
   6. Synthesis from alkyl- and arylboron dichlorides 463
   7. Synthesis from *N*-substituted alkyl- and aryl(diamino)borines 463
   8. Synthesis from arylchloroboric esters 464
   9. Synthesis from organothioboric esters 464
   10. Synthesis from tetraalkylthiodiboranes 464

II. Synthetic methods based on reactions of functional derivatives of borazole 465
   1. Synthesis of borazole and its derivatives from *B*-chlorinated borazoles 465