68. I. E. Starik, Kh. A. Arslanov, and I. R. Klener, Radiokhimiya, 5, 198 (1963).
69. P. Chini, G. De Venuto, T. Salvatori, and M. De Maldé, Chimica e Industria, 46, 1049 (1964).
70. A. T. Blomquist and P. M. Maitlis, J. Amer. Chem. Soc., 84, 2329 (1962).
71. W. C. Lanning and A. Clark, U. S. P. 2 819325; Chem. Abs., 52, 5807 (1958).
72. I. Shapiro and H. G. Weiss, J. Amer. Chem. Soc., 79, 3294 (1957); U. S. P. 2 867 675; Chem. Abs., 53, 8071 (1959).
73. M. Tsutsui, Chem. and Ind., 780 (1962).
74. I. Jadot and M. Neuray, Bull. Soc. roy. Sci. Liège, 30, 52 (1961).
75. L. B. Luttinger, J. Org. Chem., 27, 1591 (1962).
76. L. B. Luttinger and E. C. Colthup, J. Org. Chem., 27, 3752 (1962).
77. G. Schröder and R. Criegee, Annalen, 623, 1 (1959); Angew. Chem., 71, 70 (1959).
78. W. Hübel and E. H. Braye, J. Inorg. Nuclear Chem., 10, 250 (1959).
79. R. P. Dodge and V. Schomaker, Nature, 186, 798 (1960).
80. A. Nakamura and N. Hagihara, Bull. Chem. Soc. Japan, 34, 452 (1961).
81. L. Malatesta, G. Santarella, L. Vallarino, and F. Zingales, Angew. Chem., 72, 34 (1960).
82. M. E. Vol'pin, V. A. Dubovitskii, O. V. Nogina, and D. N. Kursanov, Dokl. Akad. Nauk SSSR, 151, 1100 (1963).
83. G. N. Schrauzer, J. Amer. Chem. Soc., 81, 5307 (1959).
84. W. Strohmeier, H. Laporte, and D. Van Hobe, Chem. Ber., 95, 455 (1962).
85. A. Nakamura, Mem. Inst. Sci. Ind. Res., Osaka Univ., 19, 81 (1962).
86. T. H. Coffild, K. G. Ihrman, and W. Barns, J. Amer. Chem. Soc., 82, 1251 (1960).
87. C. McKinley, Ind. Eng. Chem., 44, 995 (1952).
88. G. N. Schrauzer and S. Eichler, Chem. Ber., 95, 550 (1962).
89. H. C. Longuett-Higgins and L. E. Orgel, J. Chem. Soc., 1969 (1956).
90. G. N. Schrauzer, P. Glockner, and S. Eichler, Angew. Chem., 76, 28 (1964).
91. W. Metlesics and H. Zeiss, J. Amer. Chem. Soc., 81, 4117 (1959).
92. C. E. Berkoff, R. C. Cookson, J. Hudec, and R. O. Williams, Proc. Chem. Soc., 312 (1961).
93. J. Chatt, G. A. Rowe, and A. A. Williams, Proc. Chem. Soc., 208 (1957).
94. R. Criegee and G. Schröder, Angew. Chem., 74, 703 (1962).
95. U. Kruerke and W. Hübel, Chem. Ber., 94, 2829 (1961).
96. G. Wilke, Angew. Chem., 72, 581 (1960); 75, 10 (1963).
97. G. Pilcher and H. A. Skinner, J. Inorg. Nuclear Chem., 7, 8 (1958).
98. E. Duck, J. Polymer Sci., 34, 86 (1959).
99. A. Malatesta, J. Polymer Sci., 51, S45 (1961).
100. H. Uelzman, J. Polymer Sci., 32, 457 (1958).
101. U. S. P. 3 082 269 (19th March 1963).
102. German P. 1 159 951 (2nd July 1964).
103. Austral. P. 232 995 (10th April 1964); B. P. 973 934 (4th November 1964).
104. A. Furlani-Donda and A. Guerrieri, Ricerca sci. Rend., A6, 287 (1964).
105. E. M. Arnett, J. M. Bollinger, and J. C. Sanda, J. Amer. Chem. Soc., 87, 2050 (1965).
106. A. Della-Site and A. Mele, Gazzetta, 93, 1279 (1963).
107. French P. 1 377 677 (6th November 1964); Chem. Abs., 62, 9061 (1965).
108. S. Ikeda and A. Tamani, Radioisotopes, 12, 368 (1963).
109. S. V. Butomo, V. O. Reikhsfel'd, and K. L. Makovetskii, Radiokhimiya, 7, 364 (1965).
110. W. Hübel and R. Merènyi, Chem. Ber., 96, 930 (1963).
111. A. J. Hubert and J. Dale, J. Chem. Soc., 3160 (1965).
112. M. I. Prince and K. Weiss, J. Organometal. Chem. (Amsterdam), 2, 251 (1964).
113. R. Huettel and H. Neugebauer, Tetrahedron Letters, 3541 (1964).
114. P. M. Maitlis, O. Pollock, M. L. Games, and W. J. Pryde, Canad. J. Chem., 43, 470 (1965).
115. P. M. Maitlis and A. Efraty, J. Organometal. Chem. (Amsterdam), 4, 172 (1965).
116. P. M. Maitlis and S. McVey, J. Organometal. Chem. (Amsterdam), 4, 254 (1965).
117. E. H. Braye and W. Hübel, J. Organometal. Chem. (Amsterdam), 3, 25 (1965).
118. M. R. Churchill and R. Mason, Proc. Chem. Soc., 365 (1963).
119. C. E. Berkoff, R. C. Cookson, J. Hudec, D. W. Jones, and R. O. Williams, J. Chem. Soc., 194 (1965).
120. L. Watts, J. D. Fitzpatrick, and R. Pettit, J. Amer. Chem. Soc., 87, 3253 (1965).
121. G. N. Schrauzer, in "Advances in Organometallic Chemistry" (Edited by F. G. A. Stone and R. West), Academic Press, New York, 1964, Vol. 2, p. 31.

Lensovet Leningrad Technological Institute

U.D.C. 547.659.2

COMPOUNDS OF THE β-TETRALONE SERIES

V. F. Shner and N. M. Przhiyaglovskaya

CONTENTS

I. Introduction 523

II. Methods for obtaining compounds of the β-tetralone series 524

III. Chemical properties of compounds of the β-tetralone series 526

IV. Synthesis of natural products and their analogues on the basis of compounds of the β-tetralone series 527

I. INTRODUCTION

β-Tetralone — tetralone-2 [name used throughout in Russian text (Ed. of Translation)], or 3,4-dihydro-1*H*--naphthalen-2-one, or 1,2,3,4-tetrahydro-2-oxonaphthalene — and its derivatives are characterised by high reactivity and can be used for the synthesis of various compounds. Interest in them heightened after Robinson showed that they could serve as raw materials for the synthesis of steroids and terpenes. Subsequently β-tetralone was successfully used for the synthesis of compounds similar to morphine and chrysene derivatives.

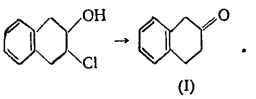
In several instances the interest lies not so much in β-tetralone itself as in various of its derivatives.

The problems of the synthesis of β-tetralone and its substituted derivatives and also the use of β-tetralone in syntheses have not been systematically covered in the

literature. The present review aims at a complete picture of work in the field of the chemistry of the compounds of the β-tetralone series.

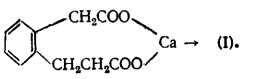
II. METHODS FOR OBTAINING COMPOUNDS OF THE β-TETRALONE SERIES

β-Tetralone (I) was first obtained in 1893 by Bamberger and Lodter [1] by the action of alkali at high temperature on 3-chloro-1,2,3,4-tetrahydro-2-naphthol. The yield of the product was somewhat increased on using quinoline or magnesium carbonate [2,3]:



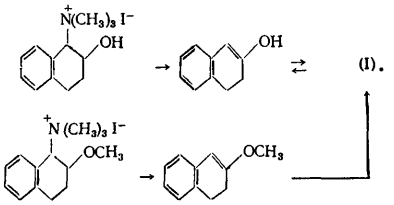
(I)

Somewhat later Einhorn and Lumsden [4] showed that β-tetralone is formed in the dry distillation of calcium 2-(carboxylatomethyl)phenylpropionate:

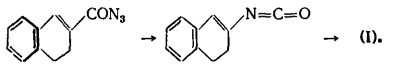


Soviet investigators [5-7] obtained β-tetralone by pyrolysis of 2-carboxymethylphenylpropionic anhydride and by Dieckmann condensation of the diethyl ester of the acid. However, their attempts to synthesise β-tetralone derivatives substituted in the aromatic nucleus by this method were unsuccessful.

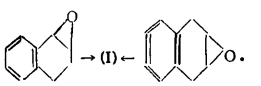
Braun and coworkers [8] obtained β-tetralone, together with α-tetralone, by the oxidation of tetralin with chromyl chloride (Étard reaction); it was shown later [9] that in this reaction both ketones are formed in approximately equal amounts. β-Tetralone is formed in the pyrolysis of trimethyl-(1,2,3,4-tetrahydro-2-hydroxynaphth-1-yl)ammonium iodide [8] and of trimethyl-(1,2,3,4-tetrahydro-2-methoxynaphth-1-yl)ammonium iodide [10] with subsequent hydrolysis of the 3,4-dihydronaphth-2-yl methyl ether:



Crowley and Robinson [11] describe the synthesis of β-tetralone and 6-methoxy-β-tetralone by the Curtius decomposition of the azides of the corresponding 3,4-dihydro-2-naphthoic acids and hydrolysis of the resulting isocyanates:

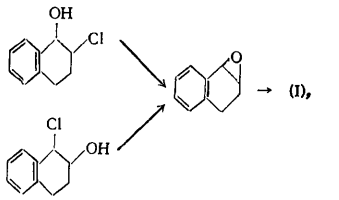


Straus and Rohrbacher [12] obtained β-tetralone in the decomposition of epoxy-3,4- and epoxy-1,4-dihydronaphthalenes and also by dehydrobromination of 1-bromo-1,2,3,4-tetrahydro-2-naphthol:



Tchoubar [13] obtained similar results. Probably the intermediate formation and decomposition of an oxide formed the basis of the production of β-tetralone in the autoxidation of 3,4-dihydronaphthalene by air [14].

The reaction for the preparation of β-tetralone from chlorotetrahydronaphthols also passes through a stage in which epoxynaphthalenes are formed [15]:



and therefore the same ketone is obtained from both isomers.

The method of decomposing epoxydihydronaphthalenes subsequently proved to be extremely useful for synthesising substituted β-tetralone derivatives.

Tchoubar [16] describes the formation of β-tetralone from the cyanohydrin of indan-2-one by hydrogenation and then deamination of the aminoalcohol obtained by the action of nitrous acid.

Compounds of the 2-naphthol series were found to be valuable starting materials for preparing β-tetralone and its derivatives. Thus Robinson and coworkers [17] obtained β-tetralone by the reduction of methyl 2-naphthyl ether with sodium and alcohol followed by hydrolysis of the 3,4-dihydronaphth-2-yl methyl ether formed. Ethyl 2-naphthyl ether behaves similarly [18].

The structure of the intermediate 3,4-dihydronaphth-2-yl methyl ether is confirmed by ozonolysis [19]. β-Tetralone, 7-methoxy-β-tetralone, and 7,8-dimethoxy-β-tetralone [20] are obtained in high yield in the electroreduction of the methyl ethers of the corresponding naphthols.

Birch [21] reduced 2-naphthol to β-tetralone by the action of sodium and alcohol in liquid ammonia. Subsequently the reaction was studied more thoroughly [22] and the side-products were investigated.

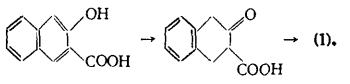
The Robinson–Cornforth and Birch methods are widely used for the synthesis of various substituted β-tetralone derivatives.

2-Naphthol is hydrogenated under severe conditions to β-tetralone [23,24] over palladium deposited on carbon, in the presence of organic bases, and over copper chromite — to 1,2,3,4-tetrahydro-2-naphthol [25], which is dehydrated by ethylene over a catalyst to β-tetralone.

Weil [26,27] obtained β-tetralone by reducing 2-hydroxy-3-naphthoic acid with sodium amalgam, but erroneously ascribed to the product the structure 1,2,3,4-tetrahydronaphthalene-3-carbaldehyde; the same product was obtained by him in reducing various 1-substituted (acetyl, amino-, chloro-, bromo-) 2-hydroxy-3-naphthoic acids.

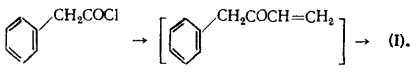
Weil's erroneous opinion about the structure of his product was corrected by Przhiyalgovskaya and coworkers [28], who showed that when 2-hydroxy-3-naphthoic acid is reduced by sodium amalgam it gives the 3-carboxylic acid of

β-tetralone, which is readily decarboxylated into β-tetralone:



2-Hydroxy-1-naphthoic acid is reduced similarly, but in somewhat less yield[29].

Phenylacetyl chloride gives β-tetralone on reacting with ethylene in the presence of aluminium chloride[30]:



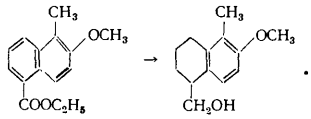
7-Methoxy-β-tetralone is obtained similarly. Much earlier this reaction was used for the synthesis of 4,4-dimethyl- and 3,4,4-trimethyl-β-tetralones[31,32] and 1-isopropyl-4,7--dimethyl-β-tetralone[33].

Of the methods for making β-tetralone which have been described, the following are sufficiently universal, that is, suitable for the synthesis of substituted derivatives: reduction of compounds of the 2-naphthol series after Robinson–Cornforth and Birch, amalgam reduction of hydroxynaphthoic acids, and decomposition of epoxydihydronaphthalenes.

Thus, reduction of the corresponding naphthyl ethers has yielded: 5-methoxy-β-tetralone[27,34-36], 6-methoxy-β--tetralone[17], 7-methoxy-β-tetralone[37-40], 5-methoxymethyl-β-tetralone[41], 5-methoxy-1-methyl-β-tetralone[17,42], 5-hydroxy-1-methyl-β-tetralone[34], 5,8-dimethoxy-β--tetralone[43-47], 7,8-dimethoxy-β-tetralone[38,48], 5-acetamido-β-tetralone[42], 1-methyl-β-tetralone[17], 6-methyl-β--tetralone, and 6-vinyl-β-tetralone[49,50], 6-n-hexyl-β--tetralone[51], 6-(1-hydroxyethyl)-β-tetralone[52], 6-vinyl--β-tetralone[52], 5-(1-ethyl-1,3-dihydroxy-2,2-dimethylpropyl)-β-tetralone[52], 2-(2-hydroxy-2-methylpropyl)--1-methyl-3-(5,6,7,8-tetrahydro-6-oxo-2-naphthyl)cyclopentanol[52], 5-acetamido-4-carboxy-β-tetralone[53].

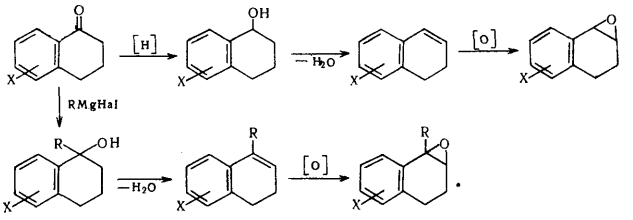
The reaction is usually carried out in an excess of alcohol — sometimes in an inert solvent (toluene)[51] — or in liquid ammonia[19,34,41,42,54].

The reduction of naphthyl ethers does not always proceed smoothly. Robinson and coworkers[17] note that the 1-methyl-β-tetralones are obtained in poor yield, but in a subsequent communication[42] they report a higher yield. The yield was low also for 5-acetamido-β-tetralone[42] owing to the loss of the acetyl residue during the reaction and the tarring of the aminoketone produced. In the reduction of 6-bromo-2-naphthyl methyl ether[52] debromination occurs; sometimes dehydration takes place when there is an alcohol group in a side-chain[52]; with ethyl 6-methoxy--5-methyl-2-naphthoate[52] the nucleus which contains the ethoxycarbonyl group is reduced; simultaneously hydrogenation and esterification of the group occurs and 1,2,3,4-tetrahydro-2-hydroxymethyl-6-methoxy-5-methyl naphthalene is obtained:



6-n-Hexyl-β-tetralone[51] and 6-isopropyl-β-tetralone[54,55] were obtained by reduction by the Birch method. Among the merits of the method are the mild conditions (low temperature, no large excess of sodium); sometimes, however, the yield is worse[51] than by the Robinson–Conforth method.

Decomposition of epoxydihydronaphthalenes provides a rather simple method of obtaining compounds of the β-tetralone series, as epoxy-3,4-dihydronaphthalenes can be synthesised from α-tetralones:



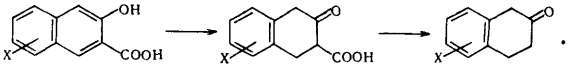
Hence a simple conversion from the readily available α-tetralones to the more difficultly accessible β-tetralones is provided. The following have been synthesised by this method: 6-methoxy-β-tetralone[56-61], 1-methyl-β-tetralone[62-65], 1-ethyl-β-tetralone[65], 1-phenyl-β-tetralone[66,68-71], 1-(2-biphenylyl)-β-tetralone[63,73], 5-methoxy-1-methyl-β--tetralone[63,74,75], 7-methoxy-1,6-dimethyl-β-tetralone[76,77], 7-isopropyl-6-methoxy-1-methyl-β-tetralone[78], 6,7-dimethoxy-1-methyl-β-tetralone[63], 5,8-dihydroxy-1-methyl--β-tetralone and its ethers at the hydroxyl group[79-81], 5,6-dimethoxy-1-methyl-β-tetralone[82], 5-isopropyl-6--methoxy-1-methyl-β-tetralone[83]. This is the best of all the known methods for synthesising 1-alkyl-β-tetralones.

The following oxidants have been proposed for the conversion of 3,4-dihydronaphthalenes into β-tetralone: peracids: perbenzoic[56-59,62,63,68,69,71,72,75-79,83], perphthalic[56,58,72,79], peracetic[60,61,66]; or a solution of hydrogen peroxide in acetic acid in the presence of ammonium molybdate[65,70]; and also inorganic oxidants: osmium tetroxide[79-81], Pb_3O_4 in acetic acid and lead tetra-acetate[63,64,67,73,74,79,82], or potassium permanganate in alkali[62]. Howell and Taylor[63] consider that the best results are given by perbenzoic acid.

After oxidation, ketones are often obtained directly[56-58,62,63,72,75,79], but sometimes an intermediate epoxide is obtained, which on decomposition (for example, by sulphuric acid) gives a diol, which is immediately dehydrated to a ketone[59,63,68,72]. The diols were isolated as diacetates when Pb_3O_4 in acetic acid was used for the oxiation; the diacetates were readily hydrolysed into ketones.

It is noted[65,66,70] that in the oxidation of dehydronaphthalenes by peracetic acid products of the oxidation of the hydrogenated naphthalene nucleus are formed as well as the ketone and diol.

Comparatively recently there was an interesting proposal of a new method for obtaining β-tetralone by reducing 2-hydroxy-3-naphthoic acid by sodium amalgam. It is found that substituted 2-hydroxy-3-naphthoic acids are converted, like the unsubstituted acid, into the corresponding β-tetralones:



6-Bromo-β-tetralone[84], 6-acetamido-β-tetralone[85], and 7-methoxy-β-tetralone[86] were obtained in this way.

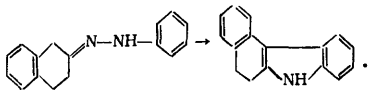
The method of indirect electroreduction differs favourably from the methods described above for preparing β-tetralones, by its mild reaction conditions. The substance to be reduced is treated in neutral or weakly acid medium (pH 6–7) at room or reduced temperature with very dilute sodium amalgam. Thanks to this even in the most complex instances, such as the preparation of halogenotetralones and acylaminotetralones, the reaction proceeds unambiguously and the substituted β-tetralones are obtained in good yields.

Other preparations of certain substituted β-tetralones have been described but have a partial nature and will not be described here. This relates to 1,1-dimethyl-β-tetralone[87,88], 1,3,3-trimethyl- and 1,3,3,7-tetramethyl-β-tetralones[89], 1-chloromethyl-1-methyl-β-tetralone[87], 1-dichloromethyl-1-methyl-β-tetralone[90], 5-bromo-7,8-dimethoxy--1-methoxycarbonyl-β-tetralone[91], 5,8-dimethoxy-β-tetralone[20,47], and 1,1,4,4-tetramethyl-β-tetralone[92].

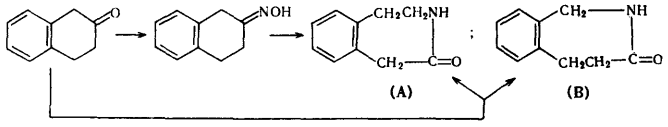
III. CHEMICAL PROPERTIES OF COMPOUNDS OF THE β-TETRALONE SERIES

β-Tetralone forms derivatives at the keto-group; the semicarbazone[8,12], phenylhydrazone[8,12], oxime[12,96], and 2,4-dinitrophenylhydrazone[28] have been described.

Some of these derivatives have been used in organic syntheses. Thus β-tetralonephenylhydrazone[93,94] and 5-, 6-, and 8-quinolylhydrazones[95] are cyclised by the method of Fischer into the corresponding dihydrobenzocarbazoles:



Knunyants and Fabrichnyi[96] carried out a Beckmann rearrangement of the β-tetralone oxime, and obtained the lactam (A):



In addition to this, lactams (A) and (B) were obtained[96] by the action of hydrazoic acid on β-tetralone.

The Beckmann rearrangement of the 1,1-dimethyl-β--tetralone and 1,1,4,4-tetramethyl-β-tetralone have also been studied[97].

β-Tetralone gives a crystalline bisulphite compound[1-3], but one is not formed (probably because of steric hindrance) when there is a basic substituent in position 1 of β-tetralone[17].

β-Tetralone forms an enol acetate when heated with acetic anhydride and sodium acetate[98].

The formation of a cyclic ketal with ethylene glycol has been described for 5-bromo-7,8-dimethoxy-1-methoxycarbonyl-β-tetralone[91].

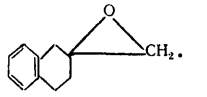
The keto-group in the compounds of the β-tetralone series is reduced after Kishner into a CH_2 group[43,99,100] and also into a hydroxyl group, by aluminium isopropoxide[101,102], lithium tetrahydroaluminate[41,92], and hydrogen over Raney nickel[33].

2,2-Dichloro-1,2,3,4-tetrahydronaphthalene is formed in the reaction of β-tetralone with phosphorus pentachloride.

The ketones of the β-tetralone series react with organomagnesium compounds[8,40,50,51,104,105] and organolithium compounds[106], and undergo a Reformatsky reaction[89,107,108] to form tertiary alcohols.

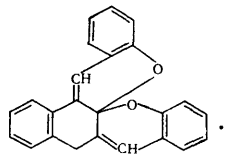
However, the yields in these reactions are usually low because the enols which are readily formed by β-tetralones decompose the organometallic compounds.

Mosettig and Burger[109] carried out the reaction of β-tetralone with diazomethane; ring expansion did not occur but an epoxide of the following structure was formed:

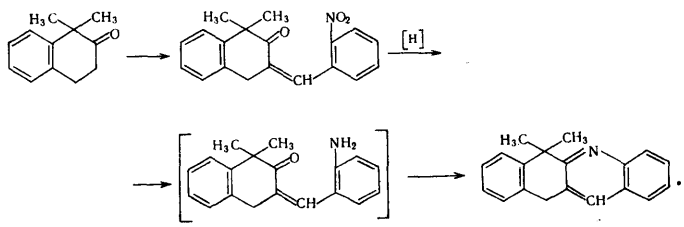


The authors did not isolate the reaction product, but its structure is confirmed by various transformations.

Braun and coworkers[8] condensed β-tetralone with aldehydes in alkali but could not isolate any definite product. Condensation proceeded normally in acid[110]; 1,3-dibenzylidene-β-tetralone and 1,3-disalicylal-β-tetralone (the latter in the form of a ketal) were obtained:



Cromwell and David[111] condensed 1,1-dimethyl-β-tetralone with *o*-nitrobenzaldehyde to synthesise substituted dihydrobenzacridines:

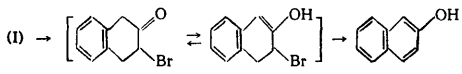


Condensation with aldehydes can be used to characterise substituted β-tetralones[106].

Braun and coworkers[8] studied the bromination of β-tetralone but did not establish the structure of the product. Soffer and coworkers[112] showed that on bromination in ether β-tetralone is dehydrated and forms 2-naphthol with a yield close to quantitative.

In chlorination, β-tetralone gives the stable 3-chloro--β-tetralone[102]; the same compound is obtained[103] by the decomposition of 3-chloro-1,4-dihydronaphthalene.

The formation of 2-naphthol in the bromination of β-tetralone becomes understandable when it is assumed that the first stage of the reaction is the formation of 3-bromo--β-tetralone, which is dehydrobrominated to form 2-naphthol:



The method of converting β-tetralones into 2-naphthols can be applied to a variety of β-tetralones substituted either in the aromatic or in the aliphatic nuclei of the molecule, dehydrogenation by bromine giving the best results[84-86,113].

The methods of studying the structure of compounds of the β-tetralone series have not been developed in the literature. The 2-naphthol derivatives formed in dehydrogenation by bromine have been rather fully described in the literature; therefore the method described above can be recommended for finding the structure of various compounds in the β-tetralone series.

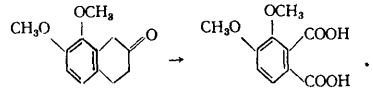
1,1-Dialkyl-substituted β-tetralones — 1,1-dimethyl-β--tetralone[114,115] and 1-(2-dimethylaminoethyl)-1-methyl--β-tetralone[100,116,117] — are brominated in position 3.

Einhorn and Lumsden[4] in oxidising β-tetralone with dilute nitric acid, obtained a dibasic acid to which was ascribed the structure of *o*-phenylenediacetic acid. However, Hückel and Friedrich[118] found that this compound is 2-(2-carboxyphenyl)propionic acid, that is, the bond between the first and second carbon atoms in the hydrogenated ring is broken.

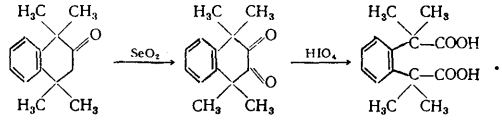
There are analogous results in the oxidation of β-tetralone by peracetic acid[119].

The formation of 2-(2-carboxyphenyl)propionic acid has also been observed in the vacuum distillation of β-tetralone in a stream of air[29].

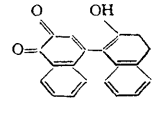
Oxidation under more drastic conditions completely destroys the hydrogenated ring; thus, on oxidation by permanganate in alkali 7,8-dimethoxy-β-tetralone gives the corresponding dimethoxyphthalic acid[38]:



The oxidation of 1,1,4,4-tetramethyl-β-tetralone has been described[120,121]; *o*-di-t-butyl benzene is obtained through *o*-phenylenedi-isobutyric acid:



On treating β-tetralone with alkali in the air it becomes intensely blue[12]. An analogous coloration is also produced in the presence of aliphatic amines[119]. The reaction is characteristic for all the β-tetralones unsubstituted in the first position[11]. The reaction is very sensitive and can be used to detect traces of β-tetralones. In studying this reaction, German investigators[110] showed that β-tetralone is rapidly oxidised in alkali by atmospheric oxygen, with the formation of 4-(3,4-dihydro-2-hydroxynaphth-1-yl)--1,2-naphthaquinone:



to which the blueness of the solution is due.

The Cornforths and Robinson[17] observed that β-tetralone is methylated in position 1 on heating with methyl iodide and sodium isopropoxide in isopropyl alcohol; by this method they obtained 1-methyl-β-tetralone.

The great ease of alkylation of β-tetralone compared with the aliphatic ketones explains its tendency to enolisation in alkali by conjugation of the double bond formed with the aromatic nucleus.

Subsequently similar reactions were studied both for β-tetralone and various substituted β-tetralones. Some think[91] that the process takes place in a single stage and that a mixture of products of 1-mono- and 1,1-di--alkylation is formed, this being difficult to separate. Some compounds, for example, 5-methoxy-β-tetralone[17,34] and 5,8-dimethoxy-β-tetralone[43] are methylated so readily that the monoalkylation product is not obtained at all, or is obtained in only insignificant quantities. The use of potassium t-butoxide[87,99,122] in this reaction improves the yield of monoalkylation products.

It is much more convenient to carry out the reaction not in alcohol, but in an inert solvent using as the base metallic sodium, potassium, sodium hydride, or sodium amide. By varying the molar ratio of the reagents it proved possible to introduce sharply one or two alkyl substituents, including also those instances when alkylation in alcohol was unsuccessful.

It is also possible to introduce two different radicals into position 1 of the β-tetralones, by performing the alkylation successively with different alkyl halides[106,116,123].

The following is the order of activity of the condensing media:

$$NaH \simeq NaNH_2 > K > Na \simeq t\text{-}C_4H_9OK > (CH_3)_2CHONa > CH_3ONa.$$

Carrying out the reaction in an atmosphere of inert gas is recommended, as β-tetralone in alkali is oxidised by air.

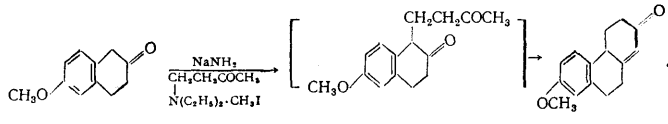
Examples of the alkylation of compounds of the β-tetralone series which have been described are given in the Table.

In recent years the Stork reaction has been used with success for the alkylation of β-tetralones — alkylation of the enamines of the β-tetralones[37,54,55,67,117,132-134]. 1-Alkyl-β-tetralones are obtained by this method in good yields and free from 1,1-dialkyl-β-tetralones as impurities.

Biquard[135-137] described the ultraviolet and Raman spectra of β-tetralone. The infrared spectra of some substituted β-tetralones have also been described. The relation between the structure and the infrared spectra of β-tetralones substituted in the aromatic and aliphatic nuclei of the molecule have also been studied[138].

IV. SYNTHESIS OF NATURAL PRODUCTS AND THEIR ANALOGUES ON THE BASIS OF COMPOUNDS OF THE β-TETRALONE SERIES

Crowley and Robinson[11] suggested a method of constructing phenanthrene systems by starting from compounds of the β-tetralone series:



Methyl vinyl ketone[73,79,139] and ethyl vinyl ketone[73,139] can also be used in this reaction.

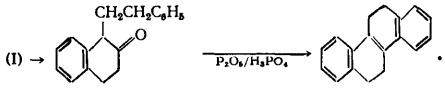
The synthesis opens great possibilities, as the most diverse substituted β-tetralones can be used in it. The

TABLE. Preparation of 1-substituted β-tetralone derivatives.

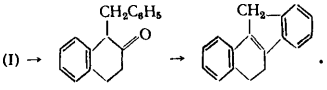
Initial ketone	Substituent introduced	Degree of substitution	Reference
β-Tetralone	methyl	mono-	17,67,123
	methyl	di-	48,87,115
	allyl	mono-	101,124
	benzyl	mono-	125
	m-methoxybenzyl	mono-	125
	phenethyl	mono-	59,125
	2-dimethylaminoethyl	mono-	126
	2-diethylaminoethyl	mono-	125,127
	2-piperidinoethyl	mono-	127
	3-piperidinopropyl	mono-	127
	2-methoxyethyl	mono-	126
	2-benzyloxy	mono-	104
	1-methoxycarbonylethyl	mono-	128
	2-ethoxycarbonylethyl	mono-	129
	3-methoxycarbonylpropyl	mono-	129
	3-cyanopropyl	mono-	129
	methoxycarbonylmethyl	di-	48,99
	cyanomethyl	di-	48
	2-methoxycarbonylethyl	di-	48
	2-ethoxycarbonylethyl	di-	99,129
	2-cyanoethyl	di-	99
	3-methoxycarbonylpropyl	di-	129
	3-cyanopropyl	di-	129
1-Methyl-β-tetralone	2-dimethylaminoethyl		100
	2-diethylaminoethyl		116
	2-ethoxycarbonylethyl		123
3-Methyl-β-tetralone	methyl	mono-	113
5-Methoxy-β-tetralone	methyl	mono-	34,35
	methyl	di-	17
	phenethyl	mono-	122,130
	3-methoxyphenethyl	mono-	122,130
6-Methoxy-β-tetralone	3-methoxybenzyl	mono-	125
	3-methoxyphenethyl	mono-	59,125
	2-ethoxycarbonylethyl	mono-	129
	3-methoxycarbonylpropyl	mono-	
	3-cyanopropyl	mono-	
7-Methoxy-β-tetralone	methyl	mono-	37
	ethyl	mono-	117
5,8-Dimethoxy-β-tetralone	methyl	mono-	43,131
	methyl	di-	43,131
7,8-Dimethoxy-β-tetralone	methyl	mono-	106
	ethyl	mono-	
	2-ethyl-1-methyl	di-	
7,8-Dimethoxy-1-methyl-β-tetralone	ethyl		106
7-Methoxy-1,6-dimethyl-β-tetralone	4-oxo-hexyl		76,77

phenanthrene group is present in extremely important natural products — steroids, the alkaloids of the morphine series, terpenes, resin acids. It is understandable, therefore, that the synthesis proposed by Robinson immediately aroused lively interest and work in this direction is continuing even now [34-37,43,54,55,63,67,74-78,80-82,123,126,134,139-142]. As a result of these investigations several complex natural compounds and their synthetic analogues have been obtained.

Salzer [59,143] used β-tetralone and 6-methoxy-β-tetralone for the synthesis of the tetracyclic chrysene system:

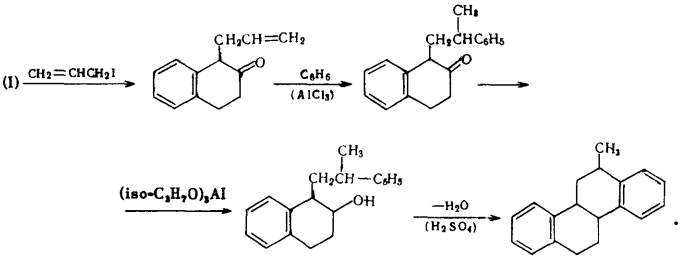


Pentacyclic systems can be obtained similarly by using naphthylethyl bromide for the alkylation [144]. Benzofluorenes have also been synthesised like this [143,145]:

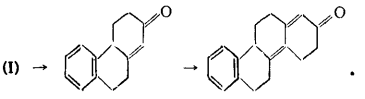


5-Methoxy-β-tetralone was alkylated with 2-phenylethyl bromide and 2-(*o*-methoxyphenyl)ethyl bromide and the compounds obtained were cyclised to chrysenes [122,130].

Indian investigators [101,124] propose an original method for synthesising chrysenes [101,124]:

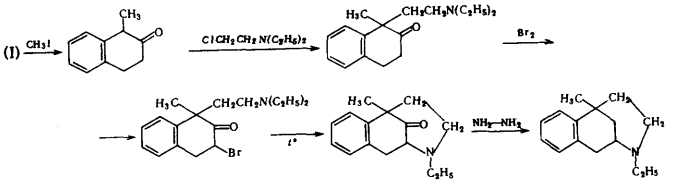


A method for obtaining tetracyclic compounds by successive repetition of the Robinson phenanthrene synthesis has been described [139,146,147]:



Among the compounds of the chrysene series which have been synthesised there are steroid analogues with a six-membered *D* ring and also carcinogenic substances.

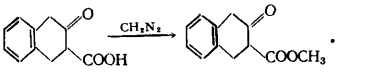
The compounds of the β-tetralone series have been used for building heterocyclic structures similar to morphine. A bicyclic analogue of morphine (benzomorphan) was thus obtained [116]:



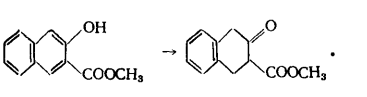
and then the tricyclic analogue [126]. May and coworkers have studied the chemistry of the benzomorphanes [100,105,117,148].

As is evident from what has been said above, various syntheses are based on the high reactivity of the hydrogen atoms in position 1 of the β-tetralone molecule. The first stage of a synthesis is usually the introduction of a substituent into this position of the molecule and then further substitutions are carried out.

The methyl ester of β-tetralone-3-carboxylic acid has recently become available, having been obtained for the first time by the authors of the present review [149]:



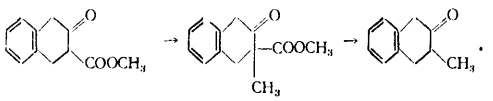
A convenient preparative method for obtaining this ester is the reduction of methyl 3-hydroxy-2-naphthoate with sodium and alcohol in liquid ammonia [150]:



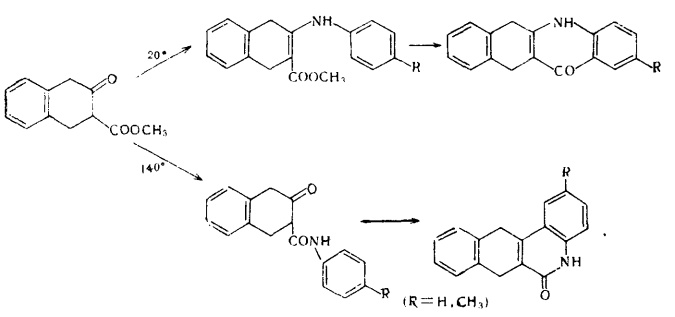
The methyl esters of the 6-bromo-, 6-acetamido-, and 7-methoxy-β-tetralone-3-carboxylic acids have been obtained from the substituted β-tetralone-3-carboxylic acids [84-86].

Pelletier and Parthasarathy [151] obtained 5-methoxy--β-tetralone-3-carboxylic acid and its methyl ester by treating 5-methoxy-β-tetralone with methylmagnesium carbonate. All these compounds contain a labile hydrogen atom in position 3 and therefore are of independent synthetic interest.

By the example of the simplest of these, methyl β-tetralone-3-carboxylate, Przhivalgovskaya and coworkers carried out a series of transformations. This ester was unambiguously methylated in position 3, which makes possible the simple preparation, after ketonic cleavage, of previously inaccessible 3-substituted β-tetralones [113]:



The condensation of methyl β-tetralone-3-carboxylate with aromatic amines [152] takes place at the carbonyl or the ester group according to the conditions. Further conversion of the condensation products allows them to be changed into complex heterocyclic compounds of the benzacridine and benzophenanthridine series containing a dihydronaphthalene nucleus.



The use of the esters of β-tetralone-3-carboxylic acid and the substituted acids for other synthetic purposes is very promising.

1. E. Bamberger and W. Lodter, Ber., 26, 1833 (1893).
2. E. Bamberger and A. Voss, Ber., 27, 1547 (1894).
3. E. Bamberger and W. Lodter, Annalen, 288, 74 (1895).
4. A. Einhorn and J. S. Lumsden, Annalen, 286, 257, 275 (1895).
5. M. O. Iodko, Candidate's Thesis, Mendeleev Moscow Chemical Technology Institute, Moscow, 1955.
6. M. O. Iodko and N. S. Vul'fson, Ukrain. Khim. Zhur., 23, 489 (1957).
7. N. S. Vul'fson and M. O. Iodko, Sbornik Statei, Nauch.-Issled. Inst. Org. Poluprod. i Krasitelei im. Voroshilova, No. 2, 143 (1961).
8. J. von Braun, O. Braunsdorf, and G. Kirschbaum, Ber., 55, 3648 (1922).
9. O. M. Wheeler, Canad. J. Chem., 38, 2137 (1960).
10. J. von Braun and K. Weissbach, Ber., 63, 3052 (1930).
11. P. G. Crowley and R. Robinson, J. Chem. Soc., 2001 (1938).
12. F. Straus and A. Rohrbacher, Ber., 54, 40 (1921).
13. B. Tchoubar, Compt. rend., 214, 117 (1942).
14. H. Hock and F. Depke, Chem. Ber., 83, 317 (1950).
15. H. Bodot, J. Jullien, and E. Leblanc, Bull. Soc. chim. France, 41 (1962).
16. B. Tchoubar, Compt. rend., 215, 224 (1942).
17. J. W. Cornforth, R. H. Cornforth, and R. Robinson, J. Chem. Soc., 689 (1942).
18. M. D. Soffer, M. Bellis, H. E. Gellerson, and R. Stuart, Org. Synth., 32, 97 (1952).
19. W. Hückel and E. Vevera, Chem. Ber., 89, 2105 (1956).
20. G. B. Diamond and M. D. Soffer, J. Amer. Chem. Soc., 74, 4126 (1952).
21. A. J. Birch, J. Chem. Soc., 430 (1944).
22. A. J. Birch, A. R. Murray, and H. Smith, J. Chem. Soc., 1945 (1951).
23. G. Stork and E. L. Foreman, J. Amer. Chem. Soc., 68, 2172 (1946).
24. U. S. P. 2 526 859; Chem. Abs., 45, 1165 (1951).
25. H. Adkins, A. G. Rossow, and J. E. Carnahan, J. Amer. Chem. Soc., 70, 4247 (1948).
26. H. Weil, Ber., 44, 3058 (1911).
27. H. Weil and H. Ostermeier, Ber., 54, 3217 (1921).
28. N. M. Przhiyalgovskaya, L. N. Lavrishcheva, and V. N. Belov, Zhur. Obshch. Khim., 27, 1266 (1957).
29. L. N. Lavrishcheva, N. M. Przhiyalgovskaya, and V. N. Belov, Zhur. Obshch. Khim., 31, 2762 (1961).
30. J. H. Burckhalter and J. R. Campbell, J. Org. Chem., 26, 4232 (1961).
31. J. Colonge and J. Chambion, Compt. rend., 224, 128 (1947).
32. J. Colonge and J. Chambion, Bull. Soc. chim. France, 1002 (1947).
33. J. Colonge and J. Chambion, Compt. rend., 222, 557 (1946).
34. J. W. Cornforth and R. Robinson, J. Chem. Soc., 676 (1946).
35. J. W. Cornforth and R. Robinson, J. Chem. Soc., 1855 (1949).
36. W. S. Johnson, B. Bannister, B. M. Bloom, A. D. Kemp, R. Pappo, E. R. Rogier, and J. Szmuszkovicz, J. Amer. Chem. Soc., 75, 2275 (1953).
37. M. E. Kuehne, J. Amer. Chem. Soc., 83, 1492 (1961).
38. M. D. Soffer, J. C. Cavagnol, and H. E. Gellerson, J. Amer. Chem. Soc., 71, 3857 (1949).
39. B. W. Horrom and H. E. Zaugg, J. Amer. Chem. Soc., 72, 721 (1950).
40. H. Cassebaum, Chem. Ber., 90, 2876 (1957).
41. J. F. Eastham and D. R. Larkin, J. Amer. Chem. Soc., 80, 2887 (1958).
42. J. W. Cornforth, O. Kauder, J. E. Pike, and R. Robinson, J. Chem. Soc., 3348 (1955).
43. C. A. Grob and W. Yundt, Helv. Chim. Acta, 31, 1691 (1948).
44. Danish P. 65 800; Chem. Abs., 44, 7351 (1950).
45. Danish P. 67 887; Chem. Abs., 46, 2580 (1952).
46. B. P. 677 442; Chem. Abs., 47, 9363 (1953).
47. U. S. P. 2 632 024, 2 632 025; Chem. Abs., 48, 2113 (1954).
48. M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson, and E. A. Bowler, J. Amer. Chem. Soc., 72, 3704 (1950).
49. R. Royer and N. Buu-Höi, Compt. rend., 222, 746 (1946).
50. R. Royer, Ann. Chim. (France), 1, 395 (1946).
51. B. Bannister and B. B. Elsner, J. Chem. Soc., 1061 (1951).
52. K. W. Bentley, J. Chem. Soc., 2398 (1955).
53. German P. 1 000 811; Chem. Abs., 54, 8769 (1960).
54. G. Stork and J. W. Schulenberg, J. Amer. Chem. Soc., 78, 250 (1956).
55. G. Stork and J. W. Schulenberg, J. Amer. Chem. Soc., 84, 284 (1962).
56. U. S. P. 2 223 664; Chem. Abs., 35, 1808 (1941).
57. German P. 708 114; Chem. Abs., 37, 2748 (1943).
58. German P. 714 848; Chem. Abs., 38, 2052 (1942).
59. W. Salzer, Z. physiol. Chem., 274, 39 (1942).
60. W. Nagata and T. Terasawa, Chem. Pharm. Bull. (Tokyo), 9, 267 (1961); Chem. Abs., 55, 27 227 (1961).
61. W. Nagata and T. Terasawa, Chem. Pharm. Bull. (Tokyo), 9, 745 (1961); Chem. Abs., 57, 7333 (1962).
62. J. English and G. Cavagliery, J. Amer. Chem. Soc., 65, 1085 (1943).
63. F. H. Howell and D. A. H. Taylor, J. Chem. Soc., 1248 (1958).
64. T. Fujita and A. Ayada, Tanabe Seiyaku Keukyn Nempô, 3,

1 (1958); Chem. Abs., 52, 20 016 (1958).
65. J. Odaira and S. Tsutsumi, Technol. Reports Osaka Univ., 8, 455 (1958); Chem. Abs., 53, 18 920 (1959).
66. J. Odaira and S. Tsutsumi, Technol. Reports Osaka Univ., 9, 209 (1959); Chem. Abs., 54, 9853 (1960).
67. J. Delobelle and M. Fetizon, Bull. Soc. chim. France, 1632 (1961).
68. H. E. Zaugg, M. Freifelder, and B. W. Horrom, J. Org. Chem., 15, 1197 (1950).
69. B. Mills and K. Schofield, J. Chem. Soc., 4213 (1956).
70. J. Odaira and S. Tsutsumi, Bull. Chem. Soc. Japan, 32, 564 (1959); Chem. Abs., 54, 7660 (1960).
71. J. K. Stille and R. A. Newson, J. Org. Chem., 26, 1375 (1961).
72. F. I. Weisenborn and D. Taub, J. Amer. Chem. Soc., 74, 1329 (1952).
73. M. Fetison and J. Delobelle, Compt. rend., 245, 850 (1957).
74. K. Raman and P. N. Rao, Experientia, 12, 472 (1956).
75. P. N. Rao, Tetrahedron, 4, 294 (1958).
76. P. C. Dutta and P. K. Ramachandran, Chem. and Ind., 997 (1960).
77. P. K. Ramachandran and P. C. Dutta, J. Chem. Soc., 4766 (1960).
78. J.-L. Chow, Acta Chem. Scand., 16, 1301 (1962).
79. W. F. Newhall, S. A. Harris, F. W. Holly, E. L. Johnson, J. W. Richter, E. Walton, A. N. Wilson, and K. Folkers, J. Amer. Chem. Soc., 77, 5646 (1955).
80. U. S. P. 2 720 542; Chem. Abs., 50, 4226 (1956).
81. B. P. 702 012; Chem. Abs., 49, 1810 (1955).
82. N. F. Elmore and T. J. King, J. Chem. Soc., 4425 (1961).
83. D. A. H. Taylor, J. Chem. Soc., 3319 (1961).
84. N. M. Przhiyalgovskaya, V. F. Shner, and V. N. Belov, Zhur. Obshch. Khim., 33, 3292 (1963).
85. N. M. Przhiyalgovskaya, V. F. Shner, and V. N. Belov, Zhur. Obshch. Khim., 34, 508 (1964).
86. N. M. Przhiyalgovskaya, V. F. Shner, and V. N. Belov, in Collected Papers, "Problemy Organicheskogo Sinteza" (Problems of Organic Synthesis), Izd. Nauka, Moscow–Leningrad, 1965, p. 151.
87. R. M. Dodson and W. P. Webb, J. Amer. Chem. Soc., 73, 2767 (1951).
88. E. Wenkert, R. D. Youssefyeh, and R. G. Lewis, J. Amer. Chem. Soc., 82, 4675 (1960).
89. C. Broguet-Borgel and R. Quelet, Bull. Soc. chim. France, 1882 (1962).
90. K. Isogai, J. Chem. Soc. Japan, Pure Chem. Sect., 82, 1241 (1963); Chem. Abs., 59, 521 (1963).
91. G. Stork and H. Conroy, J. Amer. Chem. Soc., 73, 4743 (1951).
92. H. A. Bruson, F. W. Grant, and E. Bobko, J. Amer. Chem. Soc., 80, 3633 (1958).
93. E. Ghigi, Gazzetta, 60, 194 (1930).
94. E. Ghigi, Gazzetta, 61, 43 (1931).
95. N. P. Buu-Höi, F. Périn, and P. Jacquignon, J. Chem. Soc., 4500 (1960).
96. I. L. Knunyants and B. P. Fabrichnyi, Dokl. Akad. Nauk SSSR, 68, 523 (1949).
97. R. T. Conley and R. J. Lange, J. Org. Chem., 28, 210 (1963).
98. M. Mousseron, Bull. Soc. chim. France, 419 (1943).
99. U. S. P. 2 644 836; Chem. Abs., 48, 7061 (1954).
100. E. L. May and J. G. Murphy, J. Org. Chem., 20, 257 (1955).
101. V. S. Gaind, M. L. Vashisht, and S. M. Mukherji, Current Sci., 24, 373 (1955); Chem. Abs., 50, 12 010 (1956).
102. M. Mousseron and R. Grander, Bull. Soc. chim. France, 428 (1943).
103. M. Mousseron and R. Jacquier, Bull. Soc. chim. France, 648 (1950).
104. E. M. Fry, J. Org. Chem., 22, 1710 (1957).
105. E. L. May, H. Kugita, and J. H. Ager, J. Org. Chem., 26, 1621 (1961).
106. L. J. Sargent, J. Org. Chem., 26, 1754 (1961).
107. W. G. Dauben and R. Teranishi, J. Org. Chem., 16, 550 (1951).
108. H. Ahmed and N. Campbell, J. Chem. Soc., 4115 (1960).
109. E. Mosettig and A. Burger, J. Amer. Chem. Soc., 53, 2295 (1931).
110. H. W. Wanzlick, M. Lehmann-Horchler, and S. Mohrmann, Chem. Ber., 90, 2521 (1957).
111. N. H. Cromwell and J. C. David, J. Amer. Chem. Soc., 82, 1138 (1960).
112. M. D. Soffer, R. A. Stewart, and G. L. Smith, J. Amer. Chem. Soc., 74, 1556 (1952).
113. N. M. Przhiyalgovskaya, V. F. Shner, and V. N. Belov, Zhur. Obshch. Khim., 31, 1678 (1961).
114. E. N. Marvell and J. L. Stephenson, J. Amer. Chem. Soc., 77, 5177 (1955).
115. N. H. Cromwell and R. D. Campbell, J. Org. Chem., 22, 520 (1957).
116. J. A. Barltrop, J. Chem. Soc., 399 (1947).
117. S. Saito and E. L. May, J. Org. Chem., 26, 4536 (1961).
118. W. H. Hückel and H. Friedrich, Annalen, 451, 132 (1927).
119. J. Odaira and S. Tsutsumi, J. Chem. Soc. Japan, Ind. Chem. Sect., 62, 91 (1959); Chem. Abs., 57, 8512 (1962).
120. L. R. C. Barclay, C. E. Milligan, and N. D. Hall, Canad. J. Chem., 40, 1664 (1962).
121. A. W. Burgstahler and M. O. Abdel-Rahman, J. Amer. Chem. Soc., 85, 173 (1963).
122. I. N. Nazarev and S. I. Zav'yalov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1233 (1958).
123. K. D. Zwahlen, W. J. Horton, and G. I. Fujimoto, J. Amer. Chem. Soc., 79, 3131 (1957).
124. V. S. Gaind, M. L. Vashisht, and S. M. Mukherji, J. Indian Chem. Soc., 33, 697 (1956).
125. U. S. P. 2 271 674; Chem. Abs., 36, 3514 (1942).
126. J. A. Barltrop and J. E. Saxton, J. Chem. Soc., 1038 (1952).
127. J. A. Barltrop, J. Chem. Soc., 958 (1946).
128. R. A. Clement and Tsu Chia Shieh, J. Org. Chem., 25, 1850 (1960).
129. U. S. P. 2 599 650; Chem. Abs., 47, 10 002 (1953).
130. J. E. Collins and H. Smith, J. Chem. Soc., 4308 (1956).
131. T. R. Lewis, W. R. Dickinson, and S. Archer, J. Amer. Chem. Soc., 74, 5321 (1952).
132. U. S. P. 2 773 099; Chem. Abs., 51, 9703 (1957).
133. G. Stork and H. K. Landesman, J. Amer. Chem. Soc., 78, 5128 (1956).
134. J. A. Findlay, W. A. Henry, T. C. Jain, Z. Valenta, K. Wiesner, and C. M. Wong, Tetrahedron Letters, 869 (1962).
135. D. Biquard, Compt. rend., 208, 1096 (1939).
136. D. Biquard, Bull. Soc. chim. France, 55 (1941).
137. D. Biquard, Bull. Soc. chim. France, 725 (1941).
138. V. F. Shner, Zhur. Obshch. Khim., 35, 977 (1965).
139. B. P. 873 019; Chem. Abs., 56, 2399 (1962).
140. J. P. Kutney, W. McCrae, and A. By, Canad. J. Chem., 40, 982 (1962).
141. G. Stork, A. Meisels, and J. E. Davies, J. Amer. Chem. Soc., 85, 3419 (1963).
142. U. S. P. 3 098 098; Chem. Abs., 60, 483 (1964).
143. German P. 725 278; Chem. Abs., 37, 6787 (1943).
144. D. N. Mukherji, Sci. Cult. (Calcutta), 27, 209 (1961); Chem. Abs., 55, 27 243 (1961).
145. D. N. Mukherji, Sci. Cult. (Calcutta), 27, 405 (1961); Chem. Abs., 56, 3431 (1962).
146. W. Nagata, S. Hirai, I. Terasawa, T. Kikkawa, and K. Takeda, Chem. Pharm. Bull. (Tokyo), 9, 756 (1961); Chem. Abs., 57, 7334 (1962).
147. W. S. Johnson, J. C. Collins, R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann,

J. Amer. Chem. Soc., 85, 1409 (1963).
148. E. L. May and E. M. Fry, J. Org. Chem., 22, 1366 (1957).
149. N. M. Przhiyalgovskaya, L. N. Lavrishcheva, and V. N. Belov, Zhur. Obshch. Khim., 30, 1617 (1960).
150. N. M. Przhiyalgovskaya, V. F. Shner, M. I. Mel'nikova, and V. N. Belov, Zhur. Obshch. Khim., 33, 635 (1963).
151. S. W. Pelletier and P. G. Parthasarathy, Tetrahedron Letters, 103 (1964).
152. N. M. Przhiyalgovskaya, V. F. Shner, and V. N. Belov, Zhur. Obshch. Khim., 33, 3690 (1963).

Mendeleev Moscow Chemical
Technology Institute

U. D. C. 547.963.3

CHEMICAL METHODS OF SYNTHESIS OF POLYNUCLEOTIDES

S. M. Zhenodarova and M. I. Khabarova

CONTENTS

I. Introduction 531
II. Methods of polymerisation 531
III. Homopolynucleotides 533
IV. Homopolynucleotides with different terminal nucleotides 534
V. Polynucleotides with a random distribution of purine and pyrimidine bases along the chain 535
VI. Polynucleotides with regularly alternating purine and pyrimidine bases 535

I. INTRODUCTION

The problems of the synthesis of polynucleotides are now attracting attention from scientists. Enzymes have been used to obtain deoxyribopolynucleotides [1] and ribopolynucleotides [2-5] of high molecular weight (from 30 000 to 2 000 000) and a random distribution of purine and pyrimidine bases along the polynucleotide chain, which have played an exceptionally important role in investigations which have been undertaken as the start of the study of the amino-acid code [6,7]. For several investigations there is a need for polynucleotides of definite composition and comparatively low molecular weight [8,9]. In studying the influence of the chain length of polyuridylic acid on the inclusion of phenylalanine in a cell-free yeast system it was found that the polyuridylic acid is active from the nonanucleotide onwards [10]. A sharp increase in the inclusion of phenylalanine was noted on going from U_8† to U_9 from U_{11} to U_{12} and from U_{14} to U_{16} (up to U_{22} studied), but for definite conclusions it was necessary to check the results on pure specimens of the polynucleotides.

† The nomenclature, abbreviations, and representation in diagrams corresponds to that generally accepted [11,12].

Preliminary experiments with hexauridylic acid having a terminal 3'-phosphate group showed that in a mixture with a high-polymer polyuridylic acid the hexanucleotide inhibits its activity by ~30% in relation to the synthesis of polyphenylalanine [13]. When hexauridylic acid is treated with dicyclohexylcarbodiimide (DCC) under conditions leading to the cyclisation of the 3'-monophosphate into the 2',3'-cyclic phosphate, inhibition is not observed. An analogous effect, but with oligouridylic acids having a terminal 5'-phosphomonoester group was observed by Jones and coworkers [14]. The dependence of the synthesis of peptides of lysine on the length of the polyadenylic acid chain has also been noted [15].

Homopolynucleotides with different terminal groups are frequently used in work to determine the specificity of nucleases [16-18] and as formerly is of interest for determining the sequence of the purine and pyrimidine bases in the nucleic acids and in the investigations of enzymes which synthesise the nucleic acids [19].

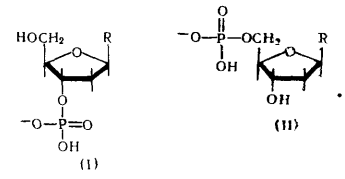
The availability of polynucleotide with a chain of known dimensions, known composition, and with known terminal groups should facilitate the study of systems which synthesise polypeptides, and apparently show the direction of further work on the synthesis of specific ribopolynucleotides of interest in the study of the amino-acid code [20]. The problems connected with obtaining such polynucleotides should also be solved by chemical methods of polynucleotide synthesis.

Chemical methods of synthesising polynucleotides are developing in two directions: (1) the stepwise synthesis of oligonucleotides, and (2) polycondensation. The stepwise synthesis of oligonucleotides recently formed the subject of a special review [21]. The present review will consider methods of synthesising polynucleotides by condensation‡ of mononucleotides or other "monomeric" units.

II. METHODS OF POLYMERISATION

1. Types of "Monomers"

It must be specially emphasised that in developing methods of synthesis of polynucleotides it must be taken into account that the polymeric chain should be formed by molecules of sugar (deoxy-D-ribose or D-ribose) joined by residues of phosphoric acid through the OH-group at the $C_{(3')}$ atom of one carbohydrate molecule and the OH group at the $C_{(5)}$ atom of another. In accordance with this requirement, the "monomers" for obtaining the polynucleotides can be derivatives of nucleotides of the following types: (a) for the deoxyribopolynucleotides series:



‡ Usually in the literature devoted to the problems of obtaining polynucleotides this method is inaccurately termed polymerisation; we will keep to this name subsequently as it is the most widely employed.