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Advances in the Search for Medicinal Drugs Based on γ-Aminobutyric Acid

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Problems associated with the search for new psychotropic agents based on γ-aminobutyric acid—a mediator of central inhibition—are examined, the principles of the rational synthesis of new medicinal drugs in the series of γ-aminobutyric acid derivatives are discussed, and methods for their chemical synthesis are described. Data are presented on the conformation of γ-aminobutyric acid and the structure of its receptor; certain features of the relation between structure and biological activity in the above series of compounds are considered.
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I. INTRODUCTION

Since it was observed in 1950 that γ-aminobutyric acid (GABA) is present at high concentrations in the central nervous system (CNS), workers in various fields carried out extensive studies designed to establish the role of this compound in the functioning of the brain. New data have been obtained in recent years showing that GABA is a mediator of inhibition in vertebrates, including mammals [1-3]. The development of improved methods for the identification of GABA and its metabolites yielded additional information about the metabolism of GABA in the central and peripheral nervous systems, about the enzymes involved in its synthesis and decomposition [4], and about the mechanism of inhibition with participation of the GABA system [5]. It was noted that in certain mental illnesses the GABA metabolism is affected [6]. These findings have served in recent years as a basis for a number of hypotheses concerning the pathogenesis of mental illness [7,8], although the use of GABA and its derivatives as medicinal drugs began much earlier. Pharmacological and clinical tests on GABA, begun at the beginning of the 1950s, have been completed by the synthesis of an effective medicinal drug [9], although its application in the treatment of diseases of the nervous system is complicated by the low permeability of the haemato-encephalic barrier (HEB) to this compound. Studies have therefore been carried out for a number of years on the synthesis of substances close to GABA in structure and having an analogous activity as well as GABA derivatives capable of penetrating into the brain and acting on CNS, and a combined investigation of the properties of such substances has been carried out.

The importance of GABA is not apparently restricted to its mediating function. It is encountered not only in the brain but also in other organs, playing a definite role in the metabolism of carbohydrates, aminoacids, biogenic amines, hormones, and phospholipids [10] and serving as a precursor of many physiologically active substances [11]. Studies in recent years demonstrated the important role of GABA in the synthesis of proteins [12,13]. These data lead to the possibility of using GABA derivatives not only as neurotropic preparations but also in many other fields of medicine.

In view of the considerable interest in the study of the mediating function of GABA, the literature on this field is exceptionally extensive. In recent years alone a series of reviews have been published on the physiological role of GABA [1,2], its biochemical functions [4,14], and clinical applications [9,15]. However, the reviews virtually do not reflect problems associated with the chemical aspects of the search for new medicinal drugs based on GABA, although during the past 10–15 years chemists have synthesised a considerable number of derivatives of this aminoacid. In the course of this research extensive data have accumulated on the methods of synthesis, physiochemical properties, and biological activity of the compounds; a survey of these data can play a definite role in the specific search for medicinal drugs based on GABA. The present review is mainly devoted to methods of synthesis and properties of GABA derivatives used as medicinal drugs or studied experimentally on animals, and to the determination of the relation between structure and biological activity in this series; attention has been concentrated on studies carried out in the last 5–10 years.

II. THE CONFORMATION OF GABA AND THE STRUCTURE OF THE GABA-RECEPTOR

It is generally accepted that the physiological action of GABA is similar to that of the "inhibition factor" discovered by Florey in 1953. [16] Until recently it was believed that this factor is identical with GABA. However, in 1975 Florey showed experimentally that the inhibiting action of the inhibition factor is only 35% due to the presence of GABA in it [17]. Aspartic acid, glutamic acid, and taurine, forming part of the factor, exhibit a similar effect (30%); the remainder of the inhibiting effect is apparently due to the presence of β-guanidinopropionic, γ-guanidinobutyric, and γ-amino-β-hydroxybutyric acids [17,18]. A large group of natural and synthetic compounds, similar to GABA in structure and in inhibiting activity, is also known. These findings indicate the possibility of the interaction of GABA and its analogues with the same biochemical system present in the CNS; this system can be defined as the GABA-receptor. A number of studies in recent years have been

devoted to the determination of the characteristics of the structure of this receptor, the methods for its isolation, and the conditions for the interaction of GABA derivatives with it.

On the basis of ideas concerning the complementarity of the structures of the medicinal drug and the receptor, one of the ways of solving the problem of the structure of the GABA-receptor consisted in the investigation of the structural features of GABA and its agonists which ensure the optimum interaction with the receptor. Kier[19] suggested that the energetically preferred conformation of the substance is identical to that in which it interacts with the receptor. This hypothesis was found to be justified in the study of a large and varied group of preparations, including anti-inflammatory, adrenergic histamine derivatives, etc. The preferred GABA conformation was determined by the molecular orbital method (LCAO-MO) taking into account the principle of the minimisation of the total energy of the molecule. Calculations showed[20] that in this conformation the ammonium and α-methylene groups of GABA (I) are in the transoid positions, while the COO^- group can rotate freely. The distance between N^+ and O^- is in the range 5.0–6.1 Å. Calculation on the muscimol (II) molecule, which has an inhibiting effect similar to that of GABA[21] and acts on the same receptor[22], showed that in the preferred conformation the side chain is coplanar with the ring and is directed towards the ring oxygen. In this conformation the charged exocyclic oxygen atom is located at a distance of 5.8 Å from the 'onium nitrogen atom[20]. A similar calculation for a group of GABA-like substances showed that the distance between N^+ and O^- in γ-amino-β-hydroxybutyric acid (III),[23] β-hydrazinopropionic acid (IV), homotaurine (V), and imidazolylacetic acid (VI)[24] is 5–6 Å. It was also established that substances with a "rigid conformation"—γ-aminotetrolic acid (VII)[25] and *trans*-γ-aminocrotonic acid (VIII),[26] which are similar to GABA in its fully extended form and have an N^+–O^- distance in the range 5.2–5.8 Å—have an inhibiting effect similar to that of GABA. In the alkaloid bicuculline (IX),[27] which is a powerful competitive antagonist of GABA[28], the distance between the 'onium group and the oxygen atom of the carbonyl is 5.6 Å. Thus the distances between the charged groups in GABA and in compounds (II)–(IX) are approximately the same, demonstrating the importance of the extended conformation of GABA for its interaction with the central inhibition receptor, whose active section should have two charged regions of opposite sign located at a distance of 5–6 Å from one another. However, van Gelder proposed a folded conformation for GABA with a distance between nitrogen and oxygen atoms of 3.7–4.5 Å.[29] X-Ray diffraction study of the GABA zwitterion in the crystalline state also led to the conclusion that its molecule is to some extent folded[30,31], while crystalline GABA hydrochloride has an extended structure[32]. On the basis of molecular orbital calculations, Pullman suggested a folded conformation for the isolated GABA molecule, which is a consequence of the strong interaction of its two charged ends[33]. From the pharmacological point of view, the conformation in solution, where the inhibiting effect is manifested under physiological conditions, is of greatest importance. According to Pullman's data, a large number of stable conformations of the GABA molecule exist in solution, which apparently enables it to interact with different receptors[33].

During the last 3–4 years a number of publications concerning the direct investigation of GABA by methods used for the choline receptor have appeared[34–39]. Although these studies do not exhaust all the aspects of the problem associated with the structure of the GABA receptor, the information obtained can greatly facilitate the search for new synthetic GABA agonists and antagonists. On the other hand, systematic investigation of the relation between structure and pharmacological activity in this series of compounds makes it possible to obtain a more complete idea about the structure of the GABA receptor.

Among the numerous studies of natural and synthetic GABA analogues, derivatives with substituents in the hydrocarbon chain, compounds with modified COOH and NH_2 groups or with a trimethylene chain (structural analogues), as well as esters and *N*-acyl derivatives of GABA (bound forms) occupy an important place and these will be considered further.

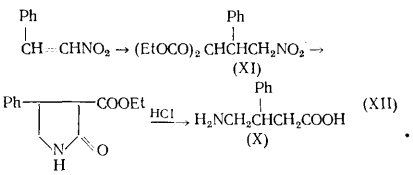
III. γ-AMINOACIDS WITH SUBSTITUENTS IN THE HYDROCARBON CHAIN

The main methods for the synthesis of GABA have been described[9] and they will not therefore be considered in the present review. We need only examine the single-step method for the preparation of GABA[40] by the selective oxidation of *p*-hydroxyphenylpropylamine with ruthenium tetroxide (in 69% yield). Labelled [^{14}C]GABA is synthesised by reducing the ethyl ester of labelled β-cyanopropionic acid under pressure[41]. Selective substitution of α-hydrogen atoms by deuterium yielded α-deutero-GABA in a high yield[42]. Enzymatic decarboxylation of glutamic acid and the microbiological synthesis of GABA from L-glutamic acid or ornithine may be of some interest for the preparation of GABA[43].

Up to the middle of the 1950s, the methods of synthesis of substituted γ-aminobutyric acids were little investigated and only after the mediating function of GABA in mammals had been discovered was the attention of synthetic chemists drawn to this problem. The aim of the investigations was the synthesis of compounds retaining the GABA carbon skeleton and both its functional groups but containing in the side chain lipophilic substituents capable of increasing the solubility of the entire molecule in fats and thus improving its permeation through HEB.

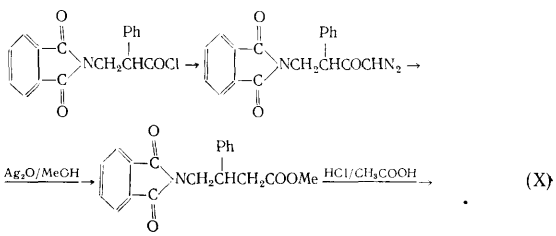
Systematic studies on the synthesis and chemical properties of unsaturated compounds have been carried out for many years in the Department of Organic Chemistry of the Leningrad State Pedagogic Institute, one series of which led to the preparation of GABA derivatives and α-pyrrolidinones. In 1954 Perekalin and Sopovoi[44] synthesised γ-amino-β-phenylbutyric acid (X), the pharmacological study of which demonstrated that it has the properties of a mild tranquiliser[45]. The subsequent cycle of investigations, carried out by members of this Department and the Bekhterev Leningrad Psychoneurological Institute, was completed by the synthesis of a new psychotropic preparation phenybut (β-phenyl derivative of GABA)[46]. A symposium devoted mainly to the chemistry, pharmacology, and clinical applications of Phenybut was held in 1974 in Olaine; the industrial manufacture of this preparation has now been organised. Phenybut was synthesised by the condensation of β-nitrostyrene with diethyl malonate, the subsequent reduction of the resulting ethyl ester of α-ethoxycarbonyl-γ-nitro-β-phenylbutyric acid (XI) in the presence of a nickel catalyst to 3-ethoxycarbonyl-4-phenylpyrrolidinone (XII), and treatment of the latter with 20% hydrochloric acid[44]. In recent years Perekalin and coworkers developed and patented a technological version of this synthetic scheme[47].

Scheme 1



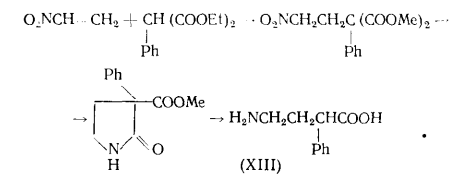
Kupryszewski and coworkers[48] obtained compound (X) by the reduction of β-cyano-β-phenylpropionic acid. A similar method of synthesis of the β-phenyl derivative of GABA by the reaction of phenylacetonitrile with ethyl bromoacetate and subsequent reduction and hydrolysis of the resulting ethyl β-cyano-β-phenylpropionate was described recently[49].

A new synthesis of compound (X) from α-phenyl-β-alanine using the Arndt-Eistert reaction was described in 1974[50]:

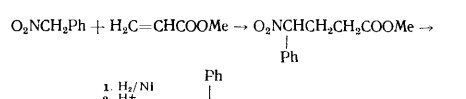


Studies by Perekalin and coworkers, devoted to the development of a general method of synthesis of substituted γ-aminobutyric acids, led to the preparation of various derivatives, which helped to elucidate the relation between the structure and pharmacological activity of compounds of this type. When other nitro-olefins were used instead of nitrostyrene, β-isopropyl, β-*p*-methoxyphenyl, β-*p*-hydroxy-*m*-methoxyphenyl, β-2-furyl and β-2-thienyl derivatives of GABA[51], β-(*o*-tolyl), β-(*n*-tolyl),[52,53] and β-(*p*-tolyl)[54] derivatives, as well as a number of derivatives of γ-amino-β-phenylbutyric acid containing various substituents in the benzene ring[55] were obtained via Scheme 1.

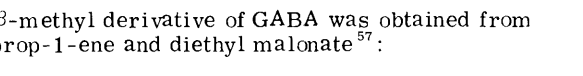
In order to synthesise the α-phenyl derivative of GABA (XIII),[56] nitroethylene was condensed with the phenylmalonic ester and the resulting ester of the γ-nitrocarboxylic acid was reduced to the corresponding ester of α-pyrrolidinone-β-carboxylic acid; hydrolysis of the latter led to compound (XIII):



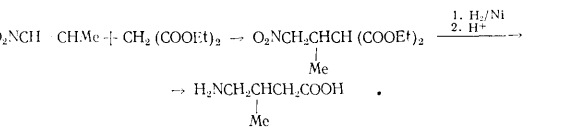
The interaction of phenylnitromethane with methacrylate[52] in the presence of potassium fluoride yielded methyl γ-nitro-γ-phenylbutyrate, which was then converted in the usual way into γ-amino-γ-phenylbutyric acid:



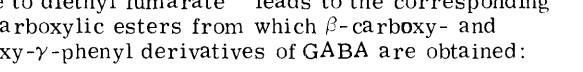
The methyl esters of α-methyl-γ-nitrobutyric acid (XIV) and γ-nitrovaleric acid (XV) were obtained similarly by the nucleophilic addition of nitromethane to methyl methacrylate and of nitroethane to methyl acrylate[57] and were then converted into α- and γ-methyl derivatives of GABA:



The β-methyl derivative of GABA was obtained from 1-nitroprop-1-ene and diethyl malonate[57]:

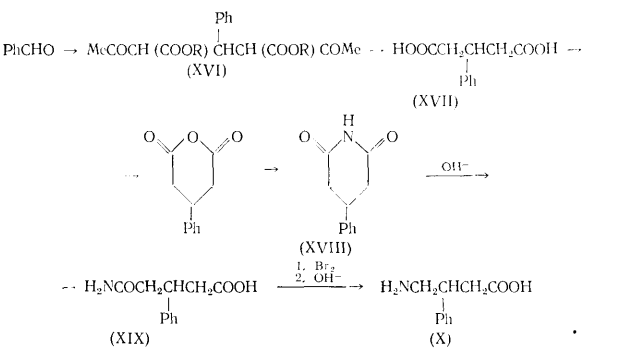


The nucleophilic addition of nitromethane and phenylnitromethane to diethyl fumarate[58] leads to the corresponding nitrodicarboxylic esters from which β-carboxy- and β-carboxy-γ-phenyl derivatives of GABA are obtained:



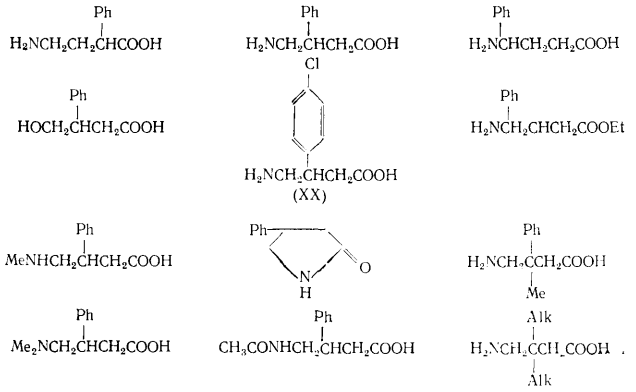
The pharmacological properties of Phenybut have been examined in detail in reviews [1,15] and in another publication[45]. Clinical and pharmacological studies of compounds of this series are still being continued. A report was published in 1975 concerning a comparative study of α-, β-, and γ-phenyl derivatives of GABA and the corresponding lactams. The β-phenyl derivative of GABA proved to be the most active in tests on the potentiation of the effects of barbiturates, ethanol, and morphine[59]. In contrast to the aminoacids, the corresponding lactams exhibited an anticonvulsant activity[60]. Individual compounds of this series were found to possess hypotensive and hypertensive activities[61].

A similar search for medicinal drugs among phenyl derivatives of GABA was carried out in the pharmaceutical chemistry division of the Ciba-Geigy Company[62,63]. γ-Amino-β-phenylbutyric acid (X) was initially synthesised via the mechanism



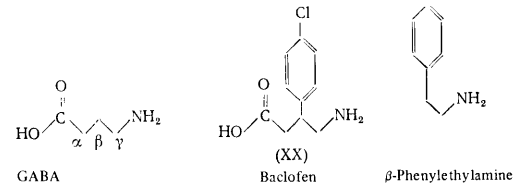
Condensation of 1 mole of benzaldehyde with 2 moles of acetoacetic ester leads to the ester of α,α'-diacetyl-β-phenylglutaric acid (XVI), which splits off both acetyl groups on treatment with alkali and is hydrolysed to β-phenylglutaric acid (XVII). Dehydration and cyclisation of the acid (XVII) in the presence of acetic anhydride and subsequent heating with ammonia lead to β-phenylglutarimide (XVIII), which is then converted into the amide (XIX). After the Hofmann rearrangement, the latter yields γ-amino-β-phenylbutyric acid. Intensive synthetic studies,

carried out by chemists of the Ciba-Geigy Company, led to the preparation of a whole series of GABA derivatives[62,63]:



Among the derivatives obtained, capable of permeating through the HEB,[62] γ-amino-β-(*p*-chlorophenyl)butyric acid (XX) showed the greatest pharmacological activity. After extensive clinical tests, it was found that this compound is an effective muscle relaxant, and a preparation based on it began to be manufactured for medical applications under the commercial name Lioresal or Baclofen (the latter name is more common). In 1971 an international symposium devoted to the applications of this preparation in therapeutic practice was held in Vienna. Baclofen is mainly used in the treatment of spastic paralysis[64] including disseminated sclerosis[65]. Reports concerning the use of Baclofen in combination with phenothiazine preparations in the treatment of chronic schizophrenia are of considerable interest[66]. It has been suggested that the use of Baclofen (and a number of other GABA derivatives) in combination with neuroleptic agents ensures a more effective suppression of the dopaminergic mechanisms of the brain and hence a more successful treatment of schizophrenia with a reduced dose of neuroleptic agents[67].

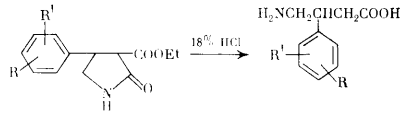
The similarity of the chemical structures of γ-amino-β-(*p*-chlorophenyl)butyric acid and GABA suggested that the mechanism of the action of Baclofen is associated with the activation of the GABA receptor and that it can also influence the GABA formation and degradation processes. However, an experiment on an isolated frog brain established that Baclofen has only a weak inhibiting effect compared with GABA[68]. Furthermore, since the inhibiting effect of Baclofen was not reduced under the influence of bicuculine (a GABA antagonist)[69,70] and strychnine (a glycine antagonist)[69], its action on the CNS cannot be explained by the activation of the GABA and glycine receptors on spinal neurons. The administration of large doses of Baclofen to animals (30 mg kg^{-1}) had no appreciable influence on the GABA concentration in the brain[71]. All these findings give grounds for the hypothesis that GABA and Baclofen act via different mechanisms. It is believed[67] that the action of Baclofen is due to the activation of the adrenoreceptor and not the GABA receptor. Presumably the therapeutic activity of Baclofen as well as Phenybut is associated with the presence of the β-phenylethylamino-group in their molecules, particularly since a similarity has been noted between the inhibiting effects of catecholamines and derivatives of γ-amino-β-phenylbutyric acid[72].



GABA Baclofen (XX) β-Phenylethylamine

The action of the β-(*m*-chlorophenyl), β-(*o*-chlorophenyl), β-(*p*-fluorophenyl), β-(*p*-isopropylphenyl), and β-(2-naphthyl) derivatives of GABA on the cortical activity in animals has also been studied[72]. All the derivatives investigated exhibited an inhibiting activity which was not weaker than that of Baclofen.

A number of derivatives of γ-amino-β-phenylbutyric acid, including Baclofen, have been suggested as sedatives. They have been synthesised by the acid hydrolysis of 3-alkoxycarbonyl-4-(R,R′-phenyl)-2-pyrrolidinones[73]:



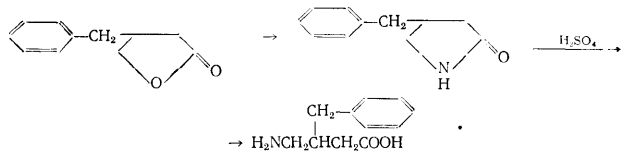
R = H, R′ = *o*-, *m*-, or *p*-Cl; R = R′ = Cl.

An analogous method of synthesising a whole series of β-phenyl derivatives of GABA, consisting in the hydrolysis of the corresponding pyrrolidinones, has been patented[74].

$H_2NCH_2CH(R)CH_2COOH$
R = *o*-ClC_6H_4, *p*-BrC_6H_4, *p*-tolyl, mesityl, *p*-dimethylaminophenyl, *p*-HOC_6H_4, 2-pyridyl, or 3-pyridyl.

In order to elucidate the relation between the structure of a substance and its physiological activity, it may be of interest to investigate the heterocyclic analogues of Phenybut; however, detailed data concerning biological activity are absent from the relevant patent[74] and it is merely stated that all the compounds obtained exhibit a sedative and soporific activity.

A sedative and anticonvulsant activity is also shown by γ-amino-β-benzylbutyric acid, which was obtained by aminating β-benzyl-γ-butyrolactone with liquid ammonia under pressure and subsequent treatment of the resulting 4-benzyl-2-pyrrolidinone with barium hydroxide and sulphuric acid[75]:



4-Phenyl-2-pyrrolidinone, formed on cyclisation of the β-phenyl derivative of GABA[76], as well as 4-(polyalkoxyphenyl)-2-pyrrolidinones also show a psychotropic activity[77].

It is noteworthy that the racemates of the β-phenyl derivatives of GABA were used in pharmacological and clinical tests. In order to investigate the molecular mechanism of the action of these compounds, it is of great interest to study their stereospecificity. The first step in this direction was taken by Kupryszewski and coworkers[78], who were able to resolve the racemic γ-amino-β-phenylbutyric acid into its enantiomers $\{[\alpha]_D = +3.2°$ and $-3.7°\}$ by the fractional crystallisation of the diastereoisomeric salts of γ-amino-*N*-benzyloxycarbonyl-β-phenylbutyric acid with cinchonidine. In order to determine the absolute

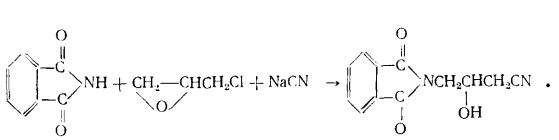
configurations of the enantiomers, they were correlated with β-phenylbutyric acid, the configuration of which is known, by deamination with nitrosyl bromide and subsequent reduction of the resulting γ-bromo-β-phenylbutyric acids with sodium amalgam. It was established that the dextrorotary isomer has the L-configuration (or the *S*-configuration in the Prelog–Kahn system), while the laevorotatory isomer has the D(*R*)-configuration. Khaunina[79] showed that the L-β-phenyl derivative of GABA is twice as active as the DL-compound, while the D-isomer is completely inactive. The increase of activity on passing from the racemate to the L-isomer is not accompanied by an increase of toxicity, which according to the author[79] justifies the assumption that the L-isomer has a greater therapeutic effect and a greater range of the latter compared with the racemate used at the present time. Presumably one of the enantiomers of Baclofen is also more effective than the racemate.

Data concerning the presence of γ-amino-β-hydroxybutyric acid (III) in the brain were first published by Hayashi in 1956, and his subsequent investigations led to the hypothesis that this substance plays an important role in the activity of the brain. It was shown that compound (III) is an extremely interesting pharmacological agent and, under the commercial name Hamibetal, it has now found extensive applications in clinical practice[15]. The β-hydroxy-derivative of GABA was obtained for the first time by Tomita[80] in 1923. In the USSR the synthesis of this preparation, which was given the name Buksamin, was achieved by Mamaev and Shkuro at the Institute of Organic Chemistry of the Siberian Division of the USSR Academy of Sciences[81]. Japanese chemists[82] synthesised compound (III) from GABA, which is chlorinated in the β-position on irradiation with light from a mercury lamp. Treatment of the β-chloro-derivative of GABA with alkali leads to compound (III).

Another method of synthesis, consists in the treatment of γ-chloro-β-hydroxybutyronitrile with hydrogen peroxide and subsequent amination and hydrolysis of the resulting γ-chloro-β-hydroxybutyramide[83]:

$$ClCH_2\underset{\underset{OH}{|}}{CH}CH_2CN \rightarrow ClCH_2\underset{\underset{OH}{|}}{CH}CH_2CONH_2 \rightarrow \underset{\underset{OH}{|}}{H_2NCH_2CH}CH_2COOH \quad (III)$$

A convenient method of preparation of compound (III) involves the interaction of epichlorohydrin with phthalimide and sodium cyanide followed by the hydrolysis of the resulting β-hydroxy-γ-phthalimidobutyronitrile[84]:



The β-chloro-derivative of GABA, obtained by treating the methyl ether of the β-hydroxy-derivative of GABA with PCl_5 and the acid hydrolysis of the resulting ester, exhibits an anti-epileptic activity[49].

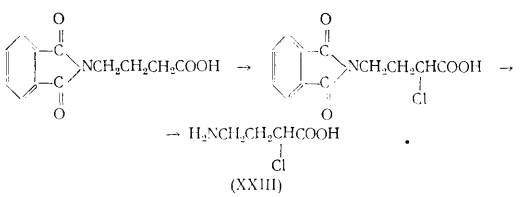
The β-phosphono-derivative of GABA (**XXI**), which exhibits a sedative activity and can be used in the treatment of epilepsy according to the authors, has been synthesised[85] by the reaction of *N*-substituted γ-aminocrotonic acid with trialkyl(allyl)phosphites and subsequent elimination of the protecting groups by refluxing with hydrobromic acid:

$$\begin{array}{ccc} XNHCH_2\underset{\underset{SO_3H}{|}}{CH}CH_2COOH & \leftarrow & XNHCH_2CH{=}CHCOOH \rightarrow XNHCH_2\underset{\underset{O{=}P(OR)_2}{|}}{CH}CH_2COOH \\ \downarrow & & \downarrow \\ H_2NCH_2\underset{\underset{SO_3H}{|}}{CH}CH_2COOH & & H_2NCH_2\underset{\underset{O{=}P(OH)_2}{|}}{CH}CH_2COOH \\ \text{(XXII)} & & \text{(XXI)} \end{array} ;$$

X = CH_3CO, C_6H_5CO, $CH_3C_6H_3SO_2$, or phthalide R = Me, Et, CH_2Ph, or Ph.

Treatment of γ-phthalimidocrotonic acid with sodium or potassium bisulphite leads to the β-sulpho-derivative of GABA (**XXII**), which has anti-epileptic and anticonvulsant activities[86].

Among the α-substituted GABA derivatives, the chloro-, amino-, hydroxy-, and mercapto-derivatives (the α-amino- and α-hydroxy-derivatives have been detected in the mammalian brains) have been subjected to extensive pharmacological tests[1]. γ-Amino-α-chlorobutyric acid (**XXIII**) is synthesised by hydrolysing with hydrochloric acid ethyl α-bromo-γ-phthalimidobutyrate, which leads to the replacement of the bromine atom by chlorine together with the removal of the phthaloyl group[87]. An improved method, consisting in the interaction of γ-phthalimidobutyric acid with gaseous chlorine and subsequent hydrolysis with hydrochloric acid, was described in 1971[88]:



A pharmacological experiment showed that the α-chloro-derivative of GABA apparently permeates readily through the HEB and has a normalising activity in disturbances of the function of the brain[89]. In order to obtain optically active isomers, the phthaloyl derivative of the racemate (**XXIII**) was resolved using quinine[90], but the pharmacological properties of the resulting enantiomers $\{[\alpha]_D^{25} \pm 9.2°\}$ were not described.

α,γ-Diaminobutyric acid is highly neurotoxic[91]. The administration of this compound to animals leads to clonic spasms, which terminate in the death of the animals[92]. This acid is one of the principal structural elements of many peptide antibiotics and this is why its synthesis has been studied in detail[93]. An anticonvulsant activity, comparable to that of the β-hydroxy-derivative of GABA, is shown by the α-hydroxy-derivative of GABA (**XXIV**) when the latter is administered intraabdominally, and its toxicity is smaller than that of GABA; the α-mercapto-derivative of GABA does not exhibit an anticonvulsant activity[94].

A considerable interest has been shown in recent years in the α-hydroxy-derivative of GABA after it was established that new aminoglycosidic antibiotics, butyrosines A and B, which show a high antimicrobial activity, contain this aminoacid. In this connection a whole series of modified aminoglycosidic antibiotics, acylated by γ-amino-α-hydroxybutyric acid, have been synthesised[96–98] and new methods have been developed for the preparation of the aminoacid itself. A simple method for the synthesis of (**XXIV**) involves the replacement of the α-amino-group in α,γ-diaminobutyric acid by the hydroxy-group with the aid of diazotisation[99,100]. Japanese investigators obtained high yields of *R*- and *S*-enantiomers (**XXIV**) by the reaction

of *RS*-α-hydroxy-γ-butyrolactone with potassium phthalimide in dimethylformamide (DMF), the subsequent resolution of the phthalimide derivative into optical isomers via the L-amphetamine salts, and their hydrolysis with hydrochloric acid [101]. When sodium L-glutamate is treated with sodium nitrite and hydrochloric acid, γ-carboxy-γ-butyrolactone is formed and its interaction with ammonia results in its conversion into L-2-hydroxyglutaramic acid; the reaction of the latter with hypochlorite leads to the L-isomer of (**XXIV**) [102]:

$$NaOOCCH_2CH_2CH(NH_2)COOH \rightarrow NaOOCCH_2CH_2CH(OH)COOH \rightarrow$$

$$\rightarrow \text{HOOC-(C}_4\text{H}_3\text{O)-O} \rightarrow HOOCCH(OH)CH_2CH_2CONH_2 \rightarrow H_2NCH_2CH_2CH(OH)COOH.$$

(XXIV)

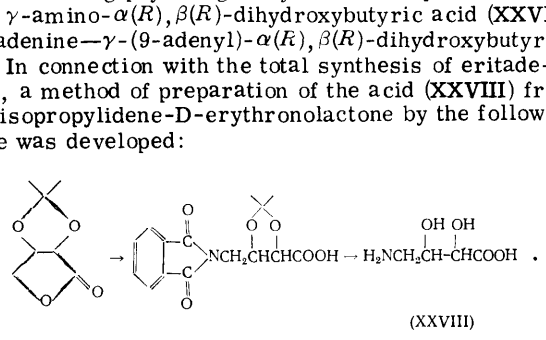
The L-enantiomer of (**XXIV**) can also be obtained in 15.3% yield by the aerobic fermentation of certain *Acetobacter* strains in a nutrient medium containing the racemic mixture [103]. A fundamentally new method of synthesis of the α-hydroxy-derivative of GABA has been recently proposed by Japanese investigators [104]. The regiospecific dipolar cycloaddition of the nitronic ester (**XXV**) to methyl acrylate leads to the formation of 2-ethoxy-5-methoxycarbonylisoxazolidine (**XXVI**). Heating of compound (**XXVI**) at 100°C leads to the ethoxyimino-compound (**XXVII**), the hydrogenation of which and subsequent acid hydrolysis give rise to γ-amino-α-hydroxybutyric acid [104]:

$$CH_2{=}\overset{+}{N}(O^-)(OEt) + CH_2{=}CHCOOMe \rightarrow \text{(XXVI)} \rightarrow EtON{=}CHCH_2CH(OH)COOMe \rightarrow \text{(XXIV)}$$

(XXV); (XXVI); (XXVII)

Using methyl crotonate, α-amino-α-hydroxy-β-methylbutyric acid can be obtained by a similar scheme [104]. One may also note that the reaction of pantolactone (α-hydroxy-β,β-dimethyl-γ-butyrolactone) with potassium phthalimide and subsequent elimination of the phthaloyl group led to the synthesis of γ-amino-α-hydroxy-β,β-dimethylbutyric acid (γ-pantonine)—an analogue of pantoic acid, which is a precursor of panthothenic acid (vitamin B_3). [105]

An interesting physiologically active compound containing γ-amino-$\alpha(R),\beta(R)$-dihydroxybutyric acid (**XXVIII**) is eritadenine—γ-(9-adenyl)-$\alpha(R),\beta(R)$-dihydroxybutyric acid. In connection with the total synthesis of eritadenine [106], a method of preparation of the acid (**XXVIII**) from 2,3-*O*-isopropylidene-D-erythronolactone by the following scheme was developed:



(XXVIII)

Together with a study of β-phenyl derivatives of GABA, the synthesis and pharmacology of the α-phenyl derivatives have been widely investigated [107]. However, the compounds obtained exhibited only a slight stimulating activity, so that further studies on these lines were not continued.

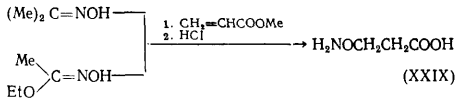
In analysing the available information about the pharmacological properties of GABA derivatives substituted in the carbon chain, one may reach certain conclusions concerning the relation between chemical structure and physiological activity in this series of compounds. The introduction of substituents (chlorophenyl, hydroxy-, sulpho-, and phosphono-groups) in the β-position leads to substances with a strong inhibiting activity. This suggests that such compounds permeate through the HEB, although direct evidence for their penetration into the brain has not been obtained in most cases. The migration of these groups to the α- or γ-position does not affect their permeation through the HEB, but leads to an appreciable decrease of the inhibiting effect, although in many instances the introduction of the substituents in the α-position (chloro-, hydroxy-, and amino-groups) imparts valuable pharmacological properties to the compounds. The presence of the phenyl and alkyl groups simultaneously in the β-position of the GABA molecule as well as one or two alkyl groups does not result in the appearance of neurotropic properties in these compounds. At the same time, γ-amino-α-hydroxy-β-phenylbutyric acid does not differ from γ-amino-β-phenylbutyric acid as regards the intensity of its action on the CNS [108]. An increase of activity was noted after the introduction of substituents into the benzone ring of γ-amino-β-phenylbutyric acid and an appreciable increase was noted for the *para*-derivatives [63].

As already mentioned, the inhibiting effect of HEBA is due to its interaction with the receptor. Presumably β-substitution is most favourable for the retention of the conformation of the molecule which corresponds to the postulated structure of the GABA receptor (this has been demonstrated by calculations for the β-hydroxy-derivative of GABA), and the presence of certain substituents can ensure an additional interaction with the active surface of the receptor. The important role of the steric structure of the molecule is convincingly demonstrated by the finding that pharmacological activity is shown only by one of the stereoisomers of γ-amino-β-phenylbutyric acid.

IV. STRUCTURAL ANALOGUES OF GABA

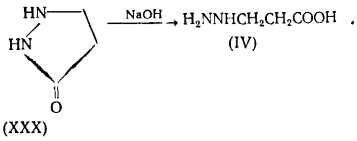
One of the procedures used to synthesise new medicinal drugs with specific activities consisted in the replacement of the CH_2, COOH, and NH_2 groups in the GABA molecule by structurally related groups. Such modifications led in many instances to the formation of substances which inhibit specifically the activity of enzymes involved in the metabolism of GABA and therefore influence its content in the brain. The most interesting substances of this type are isosteric analogues of GABA—β-aminohydroxypropionic acid (**XXIX**) and β-hydrazinopropionic acid (**IV**), in which the CH_2 group of GABA has been replaced by an oxygen atom and an NH group respectively. These compounds exhibit an exceptionally high inhibiting activity in relation to the GABA transaminase; this activity is determined by the presence of hydroxylamine [109] and hydrazine [110] residues, capable of reacting with the aldehyde group of pyridoxal 5′-phosphate, and also by the similarity of the structures of the compound and the substrate. Presumably compounds (**XXIX**) and (**IV**), which inhibit the transamination of GABA and thereby increase its content, possess psychotropic activity.

β-Aminohydroxypropionic acid has been synthesised by the Michael reaction of acetoxime [109] or hydroxyiminoacetic ester [111] with methyl acrylate and subsequent elimination of the protecting groups:



(XXIX)

Van Gelder [110] obtained β-hydrazinopropionic acid by hydrolysing 3-pyrazolidinone (XXX):



(IV)

(XXX)

Another method of synthesising compound (IV) is based on the interaction of β-chloropropionic acid [112] or its t-butyl ester [113] with hydrazine. In the usual methods of administration β-hydrazinopropionic acid permeates through HEB and gives rise to a distinct sedative effect in mice, which is associated, according to the author [114], with the increased content of GABA in the brain.

The synthesis of γ-aminotetrolic acid by the amination of γ-chlorotetrolic acid has been reported [115]:

$$ClCH_2C\equiv CCOOH \rightarrow H_2NCH_2C\equiv CCOOH \rightarrow cis\text{-}H_2NCH_2CH{=}CHCOOH \quad . \qquad (XXXI)$$

The acid (VII) is the simplest analogue of GABA with a fixed conformation owing to the presence of an acetylenic bond.

cis-4-Aminocrotonic acid (XXXI) has been synthesised by the reduction of compound (VII) over 10% palladium on barium sulphate; the *trans*-isomer (VIII) is formed on dehydration of γ-amino-β-hydroxybutyric acid with concentrated sulphuric acid. In view of the presence of the double bond, which restricts the mobility of the molecule, compounds (VIII) and (XXXI) can be regarded as rigid analogues of GABA in the open and folded conformations [26] respectively. In experiments on the upper neck ganglion in rats, analogues of compounds (VII) and (VIII) exhibit an inhibiting effect similar to that of GABA [116]. The acetylenic derivative (VII) is also a powerful competitive inhibitor of GABA transaminase [117]; it is extremely likely that the ethylenic analogue (VIII) also suppresses the activity of this enzyme.

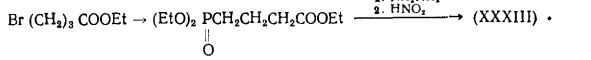
3-Aminopropanesulphonic acid (homotaurine) (XXXII), the sulpho-analogue of GABA, has an inhibiting effect [118] and manifests hypotensive and cardiotonic activities [119]. It is stated in a patent [120] that homotaurine is used as a CNS depressant. The anti-epileptic activity of homotaurine has also been reported. The sulphonic acid (XXXII) is synthesised by converting 3-aminopropanol into 3-amino-1-chloropropane, which is then treated with sodium sulphite [120]:

$$H_2N(CH_2)_3OH \xrightarrow[\text{or } PCl_5]{SOCl_2} H_2N(CH_2)_3Cl \xrightarrow{Na_2SO_3} H_2N(CH_2)_3SO_3H \quad . \qquad (XXXII)$$

γ-Aminopropylphosphonic acid (XXXIII), the phosphono-analogue of GABA, has been obtained by the addition of nitromethane to diethyl vinylphosphonate with subsequent reduction of the nitro-group and the hydrolysis of the phosphonate ester [122]:

$$CH_2{=}CHP(O)(OEt)_2 \rightarrow O_2NCH_2CH_2CH_2P(O)(OEt)_2 \rightarrow$$
$$\rightarrow H_2NCH_2CH_2CH_2P(O)(OEt)_2 \rightarrow H_2NCH_2CH_2CH_2P(O)(OH)_2 \quad . \qquad (XXXIII)$$

The synthesis of compound (XXXIII) by the interaction of the γ-bromobutyric acid ester with triethyl phosphite and subsequent Curtius amination has also been described [123]:



(XXXIII) .

Unfortunately the available information about the pharmacological properties of compounds (VII), (VIII), (XXIX), (XXXI), and (XXXIII) is extremely limited or is altogether lacking.

The replacement of the NH_2 group in GABA by OH leads to γ-hydrobutyric acid. In the form of its sodium salt, this compound is widely used in medicine as a relatively non-toxic non-inhalation narcotic. A number of reviews have been devoted to studies on this preparation [124,125].

V. BOUND FORMS OF GABA

In the course of its metabolism in the brain tissue GABA is deaminated, which leads to the formation of γ-hydroxybutyric acid and the semialdehyde of succinic acid [1]. In the animal and human organisms there are other ways of utilising this compound which lead to physiologically active bound forms of GABA. The content of these substances in the brain varies from 0.0002 to 0.012%, but the specific metabolic pathways leading to the formation of the majority of them have not been investigated; very little is known about their physiological importance in the normal functioning of the brain. An experimental study of the bound forms of GABA showed that they possess valuable pharmacological properties and the possibility of their use in medical practice continues to be investigated. An extremely promising pathway in the search for new medicinal drugs based on GABA was found to involve the chemical combination of the GABA molecule with other physiologically active substances via the amino- or carboxy-groups, which tends to decrease the polarity and in many cases to enhance the lipophilic properties of the molecule and leads to substances which readily permeate through HEB and exhibit a predominantly central activity.

The esterification of GABA yielded its esters, which, when administered in the usual way, exhibited a distinct neurotropic activity similar to that of GABA itself [126]; the highest activity in doses much below the toxic level is shown by the cetyl ester, which has the longest chain among all the esters investigated [127], with the exception of the octadecyl ester [128]. γ-Aminobutyrylcholine, the choline ester of GABA, which has been detected in mammalian brains, has an inhibiting effect in various parts of the brain [129]. Howells [130] believes that γ-aminobutyrylcholine is a mediator of the inhibition in the nervous system, since it exhibits a greater degree of stereochemical similarity to bicuculline, a specific GABA antagonist, than γ-aminobutyric acid; however, this hypothesis did not receive additional experimental confirmation. Very few data are available on the pharmacological effect of γ-aminobutyrylcholine, which is apparently associated with its high toxicity (600 times greater than that of GABA [131]); it has an anticonvulsant activity [129].

γ-Guanidinobutyric acid (XXXIV), the guanidine derivative of GABA, has been detected in various animal organs, including the brain. It has been suggested that this compound is formed in the animal organism when GABA combines with the guanidino-group of arginine and that it is subsequently cleaved with formation of urea and GABA. In contrast to GABA, compound (XXXIV) has a stimulating

effect on the CNS.[132] γ-Guanidino-β-phenylbutyric acid exhibits a central activity, although it is weaker than that of γ-amino-β-phenylbutyric acid[63]. It has been shown recently that the amide (XXXV) lowers the content of urea and glucose in the blood of diabetics[133]. The acid (XXXIV) has been synthesised by the interaction of GABA with *O*-methylisothiourea[134]; the amide (XXXV) has been obtained in the usual way via the ester (XXXVI)[135]:

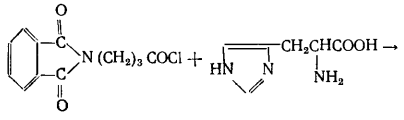
$$H_2N(CH_2)_3COOH \rightarrow \underset{\underset{NH}{\|}}{H_2NCNH}(CH_2)_3COOH \rightarrow$$

(XXXIV)

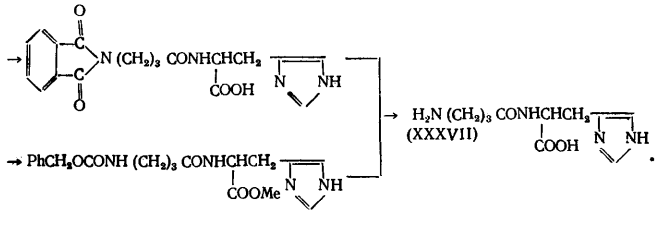
$$\rightarrow \underset{\underset{NH}{\|}}{H_2NCNH}(CH_2)_3COOMe \rightarrow \underset{\underset{NH}{\|}}{H_2NCNH}(CH_2)_3CONH_2 \quad .$$

(XXXVI) (XXXV)

During the last 15 years, a series of γ-aminobutyric acid dipeptides, including γ-aminobutyryl-L-histidine, homocarnosine (XXXVII), γ-aminobutyryl-*N*-methylhistidine, homoanserine, and α-(γ-aminobutyryl)-L-lysine (XXXVIII), have been detected in the brain tissues of various animals. Homocarmosine was isolated for the first time from ox brain in 1961 and was later detected in the brains of other animals (in appreciable amounts in the human brain). The pharmacological properties of homocarmosine, particularly its action on the CNS, have been described[136]; the anticonvulsant activity of homocarnosine had been noted earlier[137]. Together with carnosine and other histidine peptides, this compound has been proposed as one of the agents for increasing the resistance of the human and animal organism to various bacterial infections[138]. It is synthesised by the usual methods for the synthesis of peptides. The reaction of *N*-phthaloyl-γ-aminobutyric acid with L-histidine and the subsequent removal of the phthaloyl protective group lead to the dipeptide (XXXVII). In another procedure the *N*-benzyloxycarbonyl derivative of GABA is condensed with the methyl ester of L-histidine in the presence of ethyl chloroformate and homocarnosine (XXXVII) is obtained in high yields after the removal of the protective groups[139]:



$$PhCH_2OCONH(CH_2)_3COOH + \text{His-OMe} \rightarrow$$



The *p*-nitrophenyl ester of the *N*-benzyloxycarbonyl derivative of GABA can also be used as the starting compound for the synthesis of compound (XXXVII)[140].

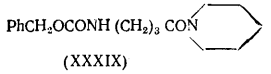
Nakajima's group detected in the rabbit brain tissues[141] and isolated in a crystalline form[142] a dipeptide which was identified as α-(γ-aminobutyryl)lysine (XXXVIII). The concentration of this peptide in the brain is much lower than that of homocarnosine; it has been noted that its content in the brain and in the cerebrospinal fluid of the adult man is higher than in children, while the content of homocarnosine in the same tissues is higher in children[142]. It may be that the level of peptides (XXXVII) and (XXXVIII) in brain tissues is physiologically important, but their function has not so far been established. α-(γ-Aminobutyryl)-L-lysine has been synthesised by the mixed anhydride method involving the condensation of the *N*-benzyloxycarbonyl derivatives of GABA and L-lysine in the presence of ethyl chloroformate followed by the removal of the protective groups over palladium oxide[141]:

$$PhCH_2OCONH(CH_2)_3COOH + \underset{\underset{COOH}{|}}{H_2NCH}(CH_2)_4NHCOOCH_2Ph \xrightarrow[2.\ H_2/PdO_2]{1.\ ClCOOEt} \rightarrow$$

$$\rightarrow H_2N(CH_2)_3CONH\underset{\underset{COOH}{|}}{CH}(CH_2)_4NH_2 \quad .$$

(XXXVIII)

Fosker and Low[143] obtained various glutamyl derivatives of GABA in the hope that these would permeate through the HEB and would serve as an additional source of GABA; however, the compounds obtained were inactive in the biological systems tested. *N*-Benzyloxycarbonyl-γ-aminobutyric acid, which is an intermediate in the synthesis of GABA peptides, has a distinct anticonvulsant activity according to the corazole spasm and electric shock tests[94]; this is probably associated with the improvement of the transport of GABA to the brain. *N*-Benzyloxycarbonyl-γ-aminobutyrylpiperidine (XXXIX), which exhibits analgesic and antiacetylcholine activities, is obtained by the reaction of the *N*-benzyloxycarbonyl derivative of GABA with piperidine in the presence of condensing agents[144]:



(XXXIX)

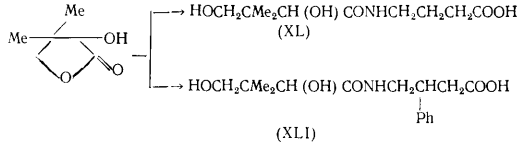
Perekalin and coworkers[145] achieved the synthesis of the dipeptides of γ-amino-β-phenylbutyric acid in order to prolong its action and to improve its permeation through the HEB. The condensation of the methyl ester of γ-amino-β-phenylbutyric acid with the *N*-benzyloxycarbonyl derivatives of α-, β-, and γ-aminoacids or of the methyl esters of α-, β-, and γ-aminoacids with *N*-benzyloxycarbonyl-γ-amino-β-phenylbutyric acid in the presence of phosphoryl chloride leads to the corresponding protected dipeptides, whose acid hydrolysis removes the protective groups and leads to the formation of the free dipeptides.

D-*N*-pantoyl-γ-aminobutyric acid (homopantothenic acid) (XL), which is a natural homologue of D-pantothenic acid (vitamin B_3), has been found in animal brain tissues, where it is present in amounts of 4–5 μg per gram of tissue[146].

It has been reported that the acetone powder of calf brain tissue contains an enzyme which can catalyse the condensation of pantoic acid and GABA, resulting in the formation of D-homopantothenic acid[147]; a similar enzyme has also been detected in rats[146]. However, the above synthetase has not been isolated in a pure form and its specificity has not been studied. A doubt has been expressed in a review[4] concerning the presence of homopantothenic acid in the brain.

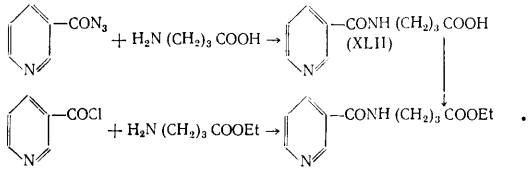
Homopanthothenic acid readily permeates into the brain[148], which indicates the importance of the pantoyl component of the molecule in passing through the HEB-lipid membrane. The distribution of [^{14}C] homopantothenic acid in various components of the mouse brain after parenteral administration[149] and its pharmacodynamics in the mouse brain have been recently investigated[150]. Extensive studies have been carried out on the biological properties[148] and therapeutic action[148,151] of compound (XL); the results suggest that the preparation is a new effective

medicinal drug. The acid (XL) is synthesised by condensing D-pantolactone with GABA salts [152-154]. The introduction of the phenyl residue into the β-position of the aminoacid component of D-homopantothenic acid greatly increased its anticonvulsant activity, antagonistic in relation to thiosemicarbazide. The D-pantoyl derivative of γ-amino-β-phenylbutyric acid (XLI) has been synthesised by the action of D-pantolactone on γ-amino-β-phenylbutyric acid in the presence of diethylamine [155]:

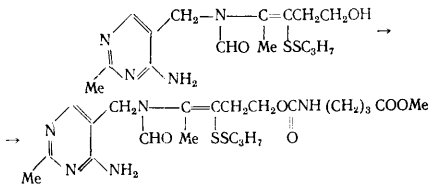


(XLI)

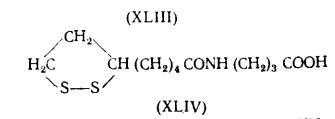
One of the hypotheses concerning the causes responsible for mental illness, put forward by Pauling [156], attributes them to the disturbance of the optimum concentration of vitamins in the brain and it is suggested that high doses of vitamins be used in its treatment. In particular, it has been shown that the use of ultralarge doses of pantothenic acid [157] and particularly nicotinic acid [158] is helpful to schizophrenics. These ideas constitute the basis of the search for new neurotropic substances based on GABA and vitamins, taking into account also the transport functions of certain vitamins and their influence on the nervous system. In particular, it appeared useful to investigate the pharmacological properties of the nicotinoyl derivative of GABA (XLII), which was obtained by the reaction of nicotinoyl azide with GABA; its ethyl ester was synthesised by condensing nicotinoyl chloride with a GABA ester or by esterifying the acid (XLII). [159]



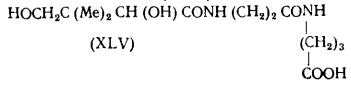
The nicotinoyl derivative of GABA and its ester exhibit a high physiological activity [160]. The GABA derivative of thiamine (XLIII) was synthesised for pharmacological study. When thiamine propyl disulphide is acted upon by phosgene, the product is *O*-chlorocarbonylthiamine propyl disulphide, the reaction of which with the methyl ester of GABA gives rise to the corresponding urethane derivative (XLIII) [161]:



(XLIII)



(XLIV)

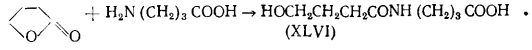


(XLV)

The detoxicating activity of the *N*-α-lipoyl derivative of GABA (XLIV) in poisoning with mercury and arsenic has been reported [162]. Compound (XLIV) has been obtained by condensing the mixed anhydride of α-lipoic acid [163] or its chloride [164] with GABA.

The *N*-D-pantothenoyl derivative of GABA (XLV) has been synthesised by the reaction of the mixed anhydride of D-pantothenic and ethylcarbonic acids with GABA [164]. There is no doubt that extensive investigation of the pharmacological properties of compounds (XLIII)–(XLV) as well as derivatives of GABA combines with other vitamins can be of great practical interest.

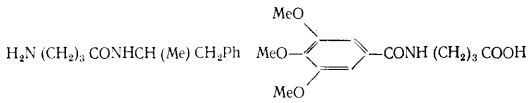
The addition of the GABA molecule to certain biologically active substances also resulted in many instances in the formation of compounds having different spectra of pharmacological activity. Bearing in mind the relatively high permeating capacity of γ-hydroxybutyric acid (GHBA) and its high neurotropic activity, γ-amino-γ-hydroxybutyrylbutyric acid (XLVI) was synthesised by condensing γ-butyrolactone with GABA [165,166]:



(XLVI)

The intra-abdominal administration of (XLVI) has a stronger sedative and hypothermic effect than the administration of GHBA or GABA. This is apparently due primarily to the specific influence of the entire molecule of the γ-hydroxybutyryl derivative of GABA on membranes and energetic processes in the brain tissue and not the activity of its decomposition products [167].

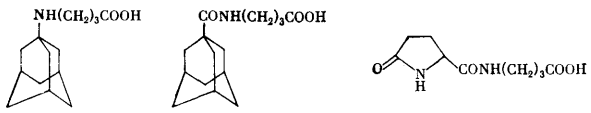
Gamophen (XLVII), the product of the condensation of GABA with phenamine, readily permeates through HEB and inhibits the orienting effects in white mice. The preparation has a hypothermic activity and potentiates the action of barbamyl and chloral hydrate, but, in contrast to the majority of depressants, it enhances the convulsant activity of corazole [168].



(XLVII) (XLVIII)

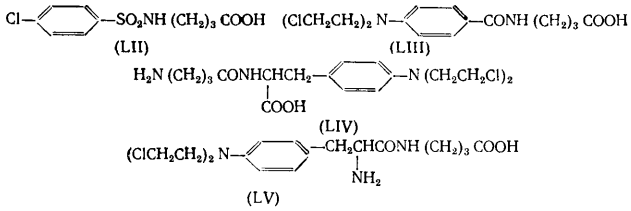
3,4,5-Trimethoxybenzoyl-γ-aminobutyric acid (XLVIII), which is a derivative of gallic acid, effectively prevents and suppresses in a pharmacological experiment (in doses of 100 μg kg^{-1}) the muscular tremor in white mice induced by tremorine or oxotremorine. Preliminary kinetic experiments demonstrated the possibility of using this compound in the treatment of Parkinson's disease [169] and the myocardial infarct [170]. The derivative (XLVIII) has been synthesised by the Schotten–Baumann acylation of GABA with 3,4,5-trimethoxybenzoyl chloride [171] or by the reaction of the mixed anhydride of 3,4,5-trimethoxybenzoic and ethylcarbonic acids with the ethyl ester of GABA followed by the hydrolysis of the resulting ester [170].

The introduction of the adamantyl group into the GABA molecule gives rise to γ-(1-adamantylamino)butyric acid (XLIX), which can be used in the treatment of Parkinson's desease [172]. However, it has been reported [128] that the ethyl ester of this acid does not exhibit signs of neurotropic activity. Together with antibiotic activity, the adamantoyl derivative (L) [173] exhibited a sedative effect [174]. The amide derivative of L-pyroglutamic acid and GABA (LI) shows a psychotropic activity [175].



(XLIX) (L) (LI)

In order to obtain new antidiabetic agents, the *N*-(*p*-chlorobenzenesulphonyl) derivative of GABA (**LII**) was synthesised among other compounds [176]. Attempts have been made to use GABA derivatives as antitumour agents by inserting GABA into the structure of a carcinolytic agent. GABA peptides containing the cytotoxic *N*-bis-(2-chloroethyl)amino-group, namely compounds (**LIII**) [177], (**LIV**), and (**LV**) [178], exhibited a high and selective antitumour activity.



(LII) (LIII)

(LIV)

(LV)

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Thus the study of the pharmacological properties of a large number of GABA derivatives made it possible to discover and introduce into medical practice many effective preparations and to obtain much information about the relation between structure, physicochemical properties, and activity. In particular, it has been shown that the most active substances with depressant activity are those with substituents in the β-position and free amino- and carboxy-groups. Some data show that the manifestation of the pharmacological activity of GABA requires the presence of free amino- and carboxy-groups. At the same time, many natural and synthetic amides or esters of GABA have valuable pharmacological, including neurotropic, properties; on the one hand, this can be due to their high capacity for permeation through biological membranes with subsequent hydrolysis of the ester or amide group in the organism and, on the other hand, it may indicate the importance of the properties of the residue introduced into the GABA molecule. Analysis and survey of the results obtained empirically can play an important role in promoting a more rational synthesis of physiologically active GABA derivatives. However, the most important condition governing the specific search for new psychotropic preparations in this series is the elucidation of the molecular mechanisms of the action of GABA and its active derivatives.

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