CH_3), 2.033 ($COCH_3$), 4.15 (CH_2OH), 4.6 (3 —H), 5.25 (C = C_{20}H—), 5.35 (C = C_6H—). The treatment of 0.1 g of the acetate (III) with acetic anhydride in pyridine at 20°C for 48 h gave 0.1 g of trans-pregna-5,17(20)-diene-3β,21-diol diacetate (IV), with mp 130-133°C (ether–hexane). According to the literature: mp 128-129°C (MeOH) [7].

Oxidation of 17β-Hydroxy-17α-vinylandrost-4-en-3-one (V). The oxidation of 5 g of the alcohol (V) was carried out with 5.8 g of pyridine chlorochromate, as for the alcohol (I). The oil obtained after dilution of the reaction mixture with ether (7 g) was filtered and evaporated and then it was passed in benzene through 10 g of silica gel. In this way, 4.5 g of a colorless oil was isolated, 3.5 g of which was chromatographed on 90 g of silica gel. Methylene chloride eluted fractions containing the aldehyde (VI) contaminated with substances of low polarity, and then methylene chloride and 5% of ether in methylene chloride eluted the aldehyde (VI) containing more polar compounds as impurities. After evaporation of the solven from these fractions, an oil retained which did not crystallize. By preparative TLC, 0.3 g of this oil yielded 0.12 g of 3-oxo-trans-pregna-4,17(20)-dien-21-al (VI), with mp 130-132°C (MeOH) (according to the literature: mp 142-147°C [1]). IR spectrum (cm^{-1}): 2720, 1670, 1610. NMR spectrum (ppm): 0.92 (18-CH_3), 1.22 (19-CH_3), 5.74 (C= C_{20}—H), 9.83 (CHO). Fractions containing 10-20% of ether in methylene chloride eluted from the column 0.3 g of 3-oxo-trans-pregna-4,17(20)-dien-21-cic acid (VII), $C_{21}H_{28}O_3$, mp 261-263°C. IR spectrum (cm^{-1}): 2500-2750, 1670, 1640, 1610. NMR spectrum (ppm): 0.89 (18-CH_3), 1.21 (19-CH_3), 5.62 (C=C_{20}—H). Mass spectrum: M 328.

SUMMARY

By oxidation with pyridine chlorochromate, 17α-vinylandrostene-3β,17β-diol has been converted into 3β-hydroxy-trans-pregna-5,17(20)-dien-21-al acetate.

LITERATURE CITED

1. U.S. Patent No. 4,059,575 (1977).
2. P. Sundararaman and W. Herz, J. Org. Chem., 42, 813 (1977).
3. G. Ortar, E. Morera, and A. Romeo, J. Org. Chem., 43, 2927 (1978).
4. G. L. Olson, K. D. Morgan, and G. Saucy, Synthesis, 25 (1976).
5. L. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. 1, Wiley, New York (1967).
6. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).
7. J. Romo and A. Romo de Vivar, J. Am. Chem. Soc., 79, 1118 (1957).

SYNTHESIS AND PHARMACOLOGY OF SOME DIISOQUINOLINE ALKALOIDS

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A number of tetrahydrodiisoquinoline alkaloids has been synthesized by various routes. Some connections between the chemical structures of the compounds obtained and their pharmacological effects have been found.

Diisoquinoline alkaloids are physiologically active substances. Some of them are widely used in medical practice as sedatives and cholagogues [1].

The aim of the present work was to synthesize and find new physiologically active preparations among derivatives of the tetrahydroisoquinoline alkaloids, and also to find connections between their chemical structure and pharmacological action.

Several methods of obtaining photoberberine bases are known [2-10]. From the practical point of view, the most acceptable, in our opinion, is the following scheme of synthesis:

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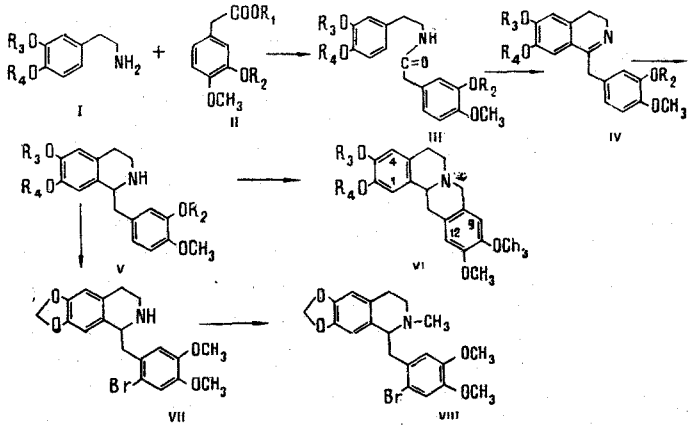


Scheme 1

Below we give information on the study of the individual stages of this scheme.

1. Methyl 3,4-dimethoxyphenylacetate (II, $R_1 = R_2 = CH_3$) was obtained by the reaction of veratraldehyde with hippuric acid followed by methylation [11] with an overall yield of 40%.

2. A. The condensation [12] of homoveratrylamine (I, $R_3 = R_4 = CH_3$) with the ester (II, $R_1 = R_2 = CH_3$) yielded the amide (III, $R_2 = R_3 = R_4 = CH_3$) in the form of colorless crystals with mp 121-123°C. Yield 80%.

B. By heating homopiperonylamine (I, $R_3 + R_4 = CH_2$) with the ester (II, $R_1 = R_2 = CH_3$) for three hours at 180°C we obtained the amide (III, $R_3 + R_4 = CH_2$, $R_2 = CH_3$). Yield 70%, mp 134-136°C (from ethanol) [13].

3. A. Bischler–Napieralski cyclization of the amide (III, $R_2 = R_3 = R_4 = CH_3$) with $POCl_3$ in absolute benzene led to the 3,4-dihydroisoquinoline (IV, $R_2 = R_3 = R_4 = CH_3$). The latter, without purification, was reduced with $NaBH_4$ in methanol to tetrahydropapaverine (V, $R_2 = R_3 = R_4 = CH_3$). Melting point of the hydrochloride 217-218°C (from ethanol). The yield of (V), reckoned on the (III) was 70%.

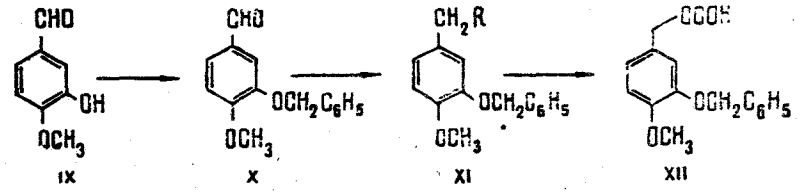
B. The analogous cyclization of amide (III, $R_3 + R_4 = CH_2$, $R_2 = CH_3$) followed by reduction formed 6,7-methylenedioxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (V, $R_3 + R_4 = CH_2$, $R_2 = CH_3$) with an overall yield of 80%. Melting point of the hydrochloride 234-235°C (from methanol).

4. A modified Mannich reaction of compounds (V) with formalin in methanol in the presence of HCl [14] yielded, respectively, xylopinine (VI, $R_3 = R_4 = CH_3$) with mp 157-158°C and tetrahydropseudoberberine (VI, $R_3 + R_4 = CH_2$), mp 175°C (from ethanol). Yield 70%.

Hoping to effect a transition from the benzyltetrahydroisoquinoline (V, $R_3 = R_4 = CH_2$, $R_2 = CH_3$) to tetrahydroberberine, we brominated (V) in 10% acetic acid [16] and obtained 1-(2-bromo-4,5-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VII), mp 158-160°C, with 80% yield. All attempts at Pictet–Spengler cyclization of the resulting bromine derivative (VII) to give 12-bromotetrahydroberberine were unsuccessful; either the starting material (VII) was recovered, or 1-(2-bromo-4,5-dimethoxybenzyl)-2-methyl-6,7-methylenedioxytetrahydroisoquinoline (VII) was obtained, which completely confirms the results obtained by Kametani [16].

It is known that 9,10-substituted tetrahydroprotoberberines can be obtained by Pictet–Spengler cyclization if the substituent at C_9 is a hydroxy, and not a methoxy, group [17, 9]. Thus, Kametani et al. [18] showed that at pH 1.2 the yield of nandinine (XV) in this reaction was 71% (Scheme 3).

The benzylhomoisovanilic acid (XII) required for this scheme could not be obtained with a yield of more than 10% by the method described above for compound (II). This forced us to select a different route for the synthesis of (XII):



Scheme 2

Below we give brief information on each stage of the preparation of 3-benzyloxy-4-methoxyphenylacetic acid (XIII). The selective demthylation of 3,4-dimethoxyphenylacetic acid in concentrated HCl (at HCl:H_2O ratios of 2:1, 1:2, and 1:1) with a variation of the time of heating from 1.5 to 3 h led to 3-hydroxy-4-methoxyphenylacetic acid in low yield.

1. Isovanillin (IX) was obtained by the dimethylation of veratraldehyde by heating it in concentrated H_2SO_4 at 65°C for 20-25 hours [19]. The yield of isovanillin ranged from 60 to 70%.

2. The benzylation of (IX) with benzyl chloride in ethanol in the presence of potassium carbonate gave benzylisovanillin (X), mp 60-62°C, with a yield of 70%.

3. The reduction of (X) with $NaBH_4$ in methanol at 20°C gave the alcohol (XI, R = OH). Yield 95%, mp 75-76°C.

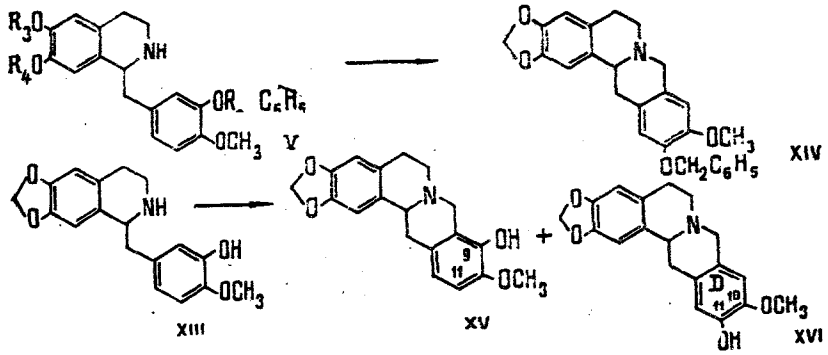
4. The chlorination of the alcohol (XI, R = OH) with freshly-distilled thionyl chloride in absolute benzene followed by the replacement of the chlorine by a cyano group in methyl ethyl ketone [20] gave the nitrile (XI, R = CN) in the form of an oil. This was saponified by being heated in a mixture of 60% aqueous caustic soda, methanol, and dioxane for 15 hours. The 3-benzyloxy-4-methoxyphenylacetic acid (XII) isolated with a yield of 70% had mp 127-128°C after recrystallization.

5. Heating 3-benzyloxy-4-methoxyphenylacetic acid (XII) with 3,4-methylenedioxyphenylethylamine at 180°C for three hours gave the amide (III, $R_3 + R_4 = CH_2$, $R_2 = CH_2C_6H_5$) with mp 128-130°C. The yield of the amide (80%) did not depend on whether the reaction was performed in a current of nitrogen or without it.

6. Cyclization of the amide (III, $R_3 + R_4 = CH_2$, $R_2 = CH_2C_6H_5$) followed by reduction of the product (IV) with $NaBH_4$ led to (V, $R_3 + R_4 = CH_2$, $R_2 = CH_2C_6H_5$) in the form of an oil with a yield of 65% (reckoned on the (III)). Melting point of the hydrochloride 224-226°C (from acetone).

7. The debenzylation in a mixture of ethanol and concentrated HCl (7:1) at the boil for 7 h of the (V) obtained led to the benzyltetrahydroisoquinoline (XIII) with mp 164-166°C (decomp.). Yield 92%.

8. Pictet–Spengler cyclization.



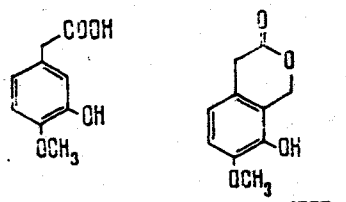
Scheme 3a

A. When (V) (Scheme 3) was boiled in methanol containing 37% formalin and a few drops of concentrated HCl for three hours, 11-benzyloxy-10-methoxytetrahydroprotoberberine (IV) with mp 216-218°C (decomp.) was obtained with a yield of 60%.

B. A mixture of the hydrochloride of the phenolic base (III), 37% formalin, concentrated HCl (pH of the reaction mixture 1.2), and methanol was boiled under reflux for 1

to 2 h. Chromatography of the reaction products on silica gel gave: nandinine (XV, 45%) with mp 182-184°C from benzene) and 11-hydroxy-10-methoxy-2,3-methylenedioxytetrahydroprotoberberine (XVI, 43%) with mp 243-245°C (from ethanol). When this reaction was repeated several times, the yields of nandinine (XV) varied between 15 and 45%. The performance of the reaction at other pH values and at room temperature [18] likewise did not give a stable yield of (XV).

In the synthesis of scoulerine published by Battersby et al. [9], the route to 9,10-substituted protoberberines lay through the selective orthoformylation of homoisovanillin acid (XVII) by the Reimer–Tieman reaction; however, according to our results and those of Battersby et al. [9], the yield in this stage did not exceed 15%.



XVII XVIII

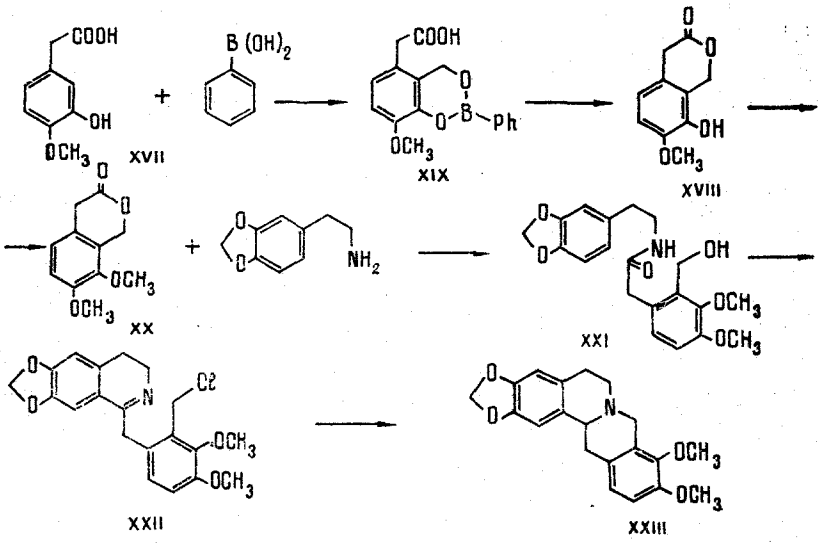
Scheme 3b

The preparation of the hydroxylactone (XVIII) already having the necessary arrangement of the substituents in ring D is the most difficult problem of the whole synthesis of scoulerine, since all the subsequent stages take place smoothly and with good yields.

The Vilsmeier–Haack formylation ($POCl_3$ in dry DMFA) of 6-bromo-3,4-dimethoxyphenylacetic acid and the chloromethylation of the same acid and of the bromobenzyltetrahydroisoquinoline (VII) with chloromethyl methyl ether likewise did not give satisfactory results.

Nagata et al., using phenylboric acid, which favors ortho-hydroxymethylation, obtained the lactone (XVIII) from homoisovanillic acid and paraformaldehyde with 83% yield [22].

Having perfected some details in individual stages, we obtained tetrahydroberberine (XXIII) by Scheme 4.



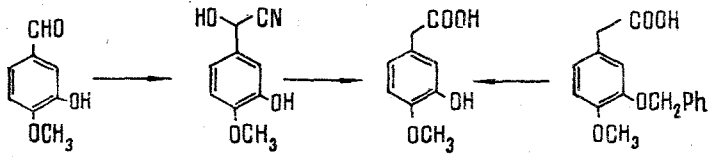
XVII XIX XVIII XX XXI XXII XXIII

Scheme 4

1. We performed the synthesis of the required 3-hydroxy-4-methoxyphenylacetic acid (XVII) in two ways: by the debenzylation of the acid (XII), and from isovanillin. In the first case, the reaction was performed in mixtures of hydrochloric acid and ethanol (1:2 and 1:1), and also in glacial acetic acid with the addition of various amounts of concentrated hydrochloric acid. The highest yield was obtained in the following experiment: by heating in the water bath at 90°C a mixture of glacial acetic acid, concentrated hydrochloric acid, and the acid (XII) (40:3:10, ratio by weight) for 2.5 h and rapidly eliminating the solvent

by distillation in vacuum. On trituration with chloroform, the residue gave a 60% yield of (XVII) with mp 116-118°C.

The other route consisted in obtaining the cyanohydrin from isovanillin (IX) by the method of Grewe and Fisher [23] with the replacement of KCN by NaCN. The cyanohydrin obtained (yield 85-98%, mp 98-100°C), on being heated with stannous chloride in a solution of acetic and concentrated hydrochloric acids, gave the acid (XVII) with a yield of 80%.



IX XVII XII

2. The phenylboric acid used for ortho-hydroxymethylation was prepared by the method of Bean and Johnson [24].

3. The condensation of the phenylboric and homoisovanillic acids was performed in boiling benzene with the azeotropic elimination of water for 2-3 h with successive additions of paraformaldehyde every hour during the whole period of boiling, followed by the saponification of the isolated product (XIX) with hot water. This gave the lactone (XVIII), mp 183-184°C.

The performance of this stage by the method of Nagata et al. [22] required in our case the time of the reaction to be doubled (to 40 h). However, the use of a stirrer and the addition of a few drops of propionic acid with each portion of paraformaldehyde enabled the reaction time to be shortened to 20-24 h. Under these conditions, the yield of (XVIII) was 84.4%.

4. Methylation of the lactone (XVIII) with dimethyl sulfate in acetone in the presence of potassium carbonate gave the dimethoxylactone (XX). Yield 95%, mp 97-99°C (from ethanol–petroleum ether).

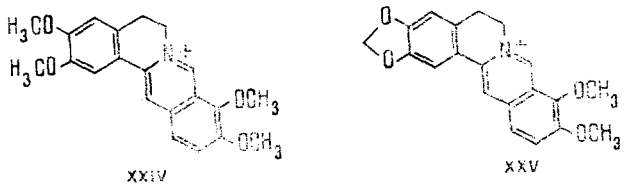
The succeeding stages were performed in a similar manner to that used by Nagata et al. [22], but in place of 4-benzyloxyphenylethylamine we used 3,4-methylenedioxyphenylethylamine.

5. The dimethoxyisochromanone (XX) was condensed with homopiperonylamine in boiling ethanol, giving the amide (XX) (mp 156-158°C). Benzene, a mixture of benzene and dioxane, ethanol, and absolute ethanol were used as solvents. The corresponding yields of (XXI) were 63, 65, 82, and 85%. The highest yields were obtained in ethanol, although the reactants were completely soluble only in a mixture of benzene and dioxane. It has been established that there is no necessity for performing the reaction in a current of nitrogen and in absolute ethanol, but it is desirable that the 18-hour condensation should be a continuous process.

6. The Bischler–Napieralski cyclization of the amide (XXI) with phosphorus oxychloride followed by reduction of the product obtained with sodium tetrahydroborate led to tetrahydroberberine (XXIII), mp 169-170°C, melting point of the hydrochloride 204-206°C (from acetone). The yield of tetrahydroberberine was 74%, calculated on the amide (XXI), and 38%, calculated on isovanillin.

PHARMACOLOGY

Of the diisoquinoline alkaloids, those that have been subjected to the most detailed pharmacological study are palmatine (XXIV), berberine (XXV), dl- and l-tetrahydropalmatine (dl- and l-THP), and dl-tetrahydroberberine (dl-THB).



XXIV XXV

Palmatine and berberine possess weak anticholinesterase effects and stimulate the smooth musculature of the intestine and the uterus [1, 25-27]. In addition to this, berberine has a pronounced cholagogic action [28, 29].

dl-THP and dl-THB (XXIII, dl-canadine) exert a marked suppressive influence on the cen-

tral nervous system [30-33, 35]. l-THP, which has been isolated from the plant *Staphonia glabra* Miers, cultivated on the Black Sea slopes of the Caucasus, also possesses a pronounced sedative action, and has been approved for use in medicine under the name "hyndarin" [1, 34, 37].

It has been established [30], when the methoxy groups are replaced by other alkoxy or ester groups, and also when the two methoxy groups in positions 2 and 3 of the dl-THP molecule are replaced by a methylenedioxy group (dl-THB) the nature of the effect is retained but the sedative-tranquillizing activity is slightly reduced [30, 32, 33].

When one of the methoxy groups is displaced from position 9 to 11 (VI, dl-xylopinine) the toxicity of the substance rises 3- to 6-fold as compared with dl-THP, and the sedative activity decreases slightly. The LD_{50} value of dl-xylopinine on intraperitoneal administration to white mice is 108 mg/kg, and on intravenous injection 51.5 mg/kg. In experiments on white mice, dl-xylopinine in doses of 20-40 mg/kg markedly suppressed motor activity not only in intact animals but also in mice with increased motor activity caused by the subcutaneous injection of phenocoll (10 mg/kg). Under the influence of dl-xylopinine in a dose of 20 mg/kg, the toxicity of phenocoll in grouped mice falls. Consequently, the sedative action is connected with its central adrenolytic effect. Hence, for the manifestation of a pronounced sedative action the arrangement of two OCH_3 groups in the 9 and 10 positions is the optimum, as was confirmed by subsequent investigations of derivatives of dl-THB.

Thus, on passing from dl-THB to dl-tetrahydropseudoberberine (dl-THPB) (VII, two methoxy groups in positions 10 and 11), the toxicity of the substance increased by a factor of 4-5. Beginning with a dose of 50 mg/kg, dl-THPB exhibited a sedative effect on white mice, while the sedative action to dl-THB was shown in doses of 10-15 mg/kg. Consequently, the sedative effect of dl-THPB is greater than that of dl-THB by a factor of 3-5. It must be mentioned that under the influence of dl-THPB white mice were not only sedated by also showed a tremor which was not removed but, on the contrary, was aggravated by atropine and amizil [benactyzine].

When the OCH_3 group in position 11 was replaced by OH, the toxicity of the substance (XVI) fell sharply, and only at a dose of 1000 mg/kg did some of the mice in a group die. A sedative action of the preparation was shown in doses of 200-300 mg/kg.

2,9-Dihydroxy-3,10-dimethoxytetrahydrodiisoquinoline (l-scoulerine) proved to be more toxic than t-THP. Thus, the LD_{50} value of l-scoulerine on subcutaneous injection into white mice was 275 mg/kg. A sedative action of l-scoulerine appeared in doses of 1-5 mg/kg. The sedative effect of the substance is connected with its central adrenolytic property. It must be mentioned that the action of l-scoulerine proved to be short in comparison with that of l-THP. l-Scoulerine apparently penetrates very well into the brain, since its central depressing effect appears 3-5 min after subcutaneous injection, and that of l-THP only after 10-15 min. In contrast to other diisoquinoline drugs, l-scoulerine possesses a pronounced antiemetic effect. In experiments on dogs, l-scoulerine in a dose of 0.05 mg/kg completely arrested the vomiting caused by the intravenous administration of apomorphine [36].

Thus, a pharmacological investigation of dl-THB, dl-THPB, dl-xylopinine, and l-scoulerine and some of their derivatives has been performed. It has been found that the presence of alkoxy radicals in positions 2, 3, 9, and 10 of the diisoquinoline nucleus is necessary for a pronounced sedative effect. A displacement of an OH or OCH_3 group from position 9 to 11 leads to a marked decrease in activity and to an increase in the toxicity of the compounds.

The dl-tetrahydroberberine and l-scoulerine preparations studied are of not only theoretical but also practical interest as tranquillizers.

SUMMARY

A series of tetrahydroberberine alkaloids have been synthesized: tetrahydroberberine, xylopinine, tetrahydropseudoberberine, 11-benzyloxy-10-methoxytetrahydroprotoberberine, and nandinine.

The greatest sedative activity is possessed by substances with substituting groups in positions 9 and 10 of the protoberberine skeleton — tetrahydroberberine and scoulerine.

LITERATURE CITED

1. V. V. Berezhinskaya, in: Advances in the Field of Drugs of Plant Origin [in Russian], Poznan (1972), p. 164.

2. C. K. Bradscher and N. L. Duta, J. Am. Chem. Soc., 82, 1145 (1960); K. Pelz, chem. Listy, 57, 1107 (1963).
3. T. R. Govindachari, S. Rayaduroi, M. Subramanian, and N. Viswanathan, J. Chem. Soc., 2943 (1957).
4. J. Ninomiya and T. Naito, Chem. Commun., 4, 137 (1973).
5. L. W. Deady, N. H. Pirzada, R. D. Topsom, and J. M. Bobbitt, Aust. J. Chem., 26, 2063 (1973).
6. A. A. Akhrem, A. M. Moisenkov, and V. S. Malishevskii, Dokl. Akad. Nauk SSSR, 208, 1089 (1973).
7. T. R. Govindachari, K. Nagarajan, S. Natarajan, and B. R. Rai, Indian J. Chem., 9, 1313 (1971).
8. T. Kametani, K. Ogasawara, and T. Takahoshi, Chem. Commun., 675 (1972).
9. A. R. Battersby, R. Southgate, J. Stanton, and M. Hirst, J. Chem. Soc., 1052 (1966).
10. T. Kametani, I. Hirai, F. Saton, K. Ogasawara, and K. Fukumoto, Chem. Pharm. Bull., 21, 907 (1973).
11. Organic Syntheses [Russian translation], Moscow, Coll. 2 (1949), p. 164.
12. A. Pictet and M. Finkelstein, Ber., 42, 1986 (1909).
13. R. D. Haworth, W. H. Perkin, Jr., and J. Rankin, J. Chem. Soc., 125, 1686 (1924).
14. T. Kametani, J. Noguchi, K. Saito, and S. Kaneda, J. Chem. Soc., 15, 2036 (1969).
15. T. Kametani and M. Ihara, J. Chem. Soc., 530 (1967).
16. T. Kametani, J. Noguchi, and K. Saito, J. Heterocycl. Chem., 6, 869 (1969).
17. T. Kametani, K. Fukumot, H. Agui, H. Vagi, K. Kigasawa, T. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, J. Chem. Soc. (C), 112 (1968).
18. T. Kametani, K. Fukumoto, T. Terui, K. Yamaki, and E. Taguchi, J. Chem. Soc. (C), 2709 (1971).
19. A. Brossi, H. Gurien, A. J. Rachlin, and S. Teitel, J. Org. Chem., 32, No. 4, 1435 (1967).
20. T. Kametani, K. Fukumoto, S. Shibuya, H. Nemoto, T. Nakano, T. Sugahara, T. Takahashi, Y. Aizawa, and M. Toriyama, J. Chem. Soc., Perkin I, 1435 (1972).
21. T. Kametani, K. Fukumoto, H. Vagi, H. Lida, and T. Kikuchi, J. Chem. Soc. (C), 1178 (1968).
22. W. Nagata, H. Itazek, and K. Okada, Chem. Pharm. Bull., 83, 2867 (1975).
23. R. Grewe and H. Fisher, Chem. Ber., 96, 1520 (1963).
24. F. R. Bean and J. R. Johnson, J. Am. Chem. Soc., 54, 4415 (1932).
25. K. Shimamoto, Ref. Zh. Biokhim., 17, 22720 (1958).
26. Z. Supek, Farmakol. Toksikol., 6, 12 (1946).
27. A. D. Turova, M. N. Konovalov, and A. I. Leskov, Med. Prom. SSSR, 6, 58 (1964).
28. C. C. Velluda, T. Goins, and J. Tiesa, Lucrarile presentate conf. natl. farm. [in Romanian], Bucharest (1958), pp. 351-354.
29. T. Furuya, Ref. Zh. Biokhim., 20, 26971 (1958).
30. Hsii Ping and Jin Go-ch'ang, in: The Pharmacology of Neurotropic Agents [in Russian], Leningrad (1963), pp. 126-137.
31. F. Sadritdinov and M. B. Sultanov, in: The Pharmacology and Pharmacotherapy of Alkaloids and Glycosides [in Russian], Tashkent (1966), p. 22.
32. F. Sadritdinov, Med. Zh. Uzb., 4, 48 (1966).
33. F. Sadritdinov and N. Tulyaganov, Med. Zh. Uzb., 9, 12 (1968).
34. V. V. Berezhinskaya and P. T. Kondratenko, Farmatsiya, 2, 84 (1968).
35. Jin Go-ch'ang and T'ang Hsing-ts'ang, Ref. Zh. Biologiya, Farmakol. Toksikol., 11, N. 263 (1963).
36. I. Khamdamov and F. S. Sadritdinov, Dokl. Akad. Nauk UzbSSR, 7, 39 (1977).