## EXPERIMENTAL

The synthesis of the substances has been described earlier [2]. MAO-inhibiting activity was established by the generally accepted methodology [9].

## LITERATURE CITED


1. I. E. Virsis, B. A. Grinberg, D. G. Tsedere, and A. A. Prikulis, Khim.-farm. Zh., No. 8, 953-956 (1985).
2. V. N. Garalene, A. P. Stankyavichyus, L. I. Mazhilis, et al., Khim.-farm. Zh., No. 11, 1305-1308 (1986).
3. V. E. Grinshtein, A. A. Prikulis, B. A. Grinberg, et al., Izv. Akad. Nauk LatvSSR, Ser. Khim., No. 3, 299-304 (1976).
4. G. I. Zhungietu, and M. A. Rekhter, Isatin and Its Derivatives [in Russian], Kishinev (1977).
5. L. I. Mazhilis, A. P. Stankyavichyus, P. B. Terent'ev, et al., Khim.-farm. Zh., No. 5, 580-583 (1987).
6. A. A. Prikulis, B. A. Grinberg, V. E. Grinshtein, and G. R. Strelka, Biokhimiya, No. 2, 313-319 (1983).
7. A. P. Stankyavichyus, L. I. Mazhilis, V. N. Garalene, et al., Khim.-farm. Zh., No. 12, 31-34 (1981).
8. D. G. Tsedere, Z. V. Lyaksa, B. A. Grinberg, et al., Izv. Akad. Nauk LatvSSR, Ser. Khim., No. 2, 223-226 (1982).
9. D. G. Tsedere, B. A. Grinberg, A. S. Roska, et al., Khim.-farm. Zh., No. 5, 555-558 (1984).


# SYNTHESIS AND ANTIHYPERTENSIVE ACTION OF N-β-ACETYL HYDRAZIDE OF 1-(β'-MERCAPTOPROPIONYL)-6-METHYLPIPECOLIC ACID


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One promising method of investigating potential antihypertensive agents is to identify inhibitors of dipeptidylcarboxypeptidase (DCP) (Pharmacopoeia Code [PC] 3.4.15.1) [15] which is an enzyme responsible for the inactivation of the depressor peptide bradykinin and for the conversion of the slightly active angiotensin I into the pressor octapeptide angiotensin II.

According to literature data [9] the synthesis of N-acylated amino acids containing a thiol group in the side chain [7] constitutes an advisable way of finding selective DCP inhibitors.

Recent studies have shown that the combination of captopril [1] or derivatives of amidine mercapto acids [2] with hydrazide acids such as acetyl hydrazide and isonicotinic hydrazide resulted in intensified or prolonged antihypertensive action (the hydrazides of the acids themselves did not exhibit antihypertensive activity).

The purpose of the present work was to synthesize a compound which includes a cyclic amino acid hydrazide acylated on the nitrogen atom of the ring by a ω-mercaptoacyl group, and then to investigate its antihypertensive action was as to study its inhibitor properties against DCP.

The compound selected as the starting material was cis-6-methyl-pipecolic acid (I), the ethyl ester (II) which was converted to the hydrazide (III) in the usual manner.

Inasmuch as the next stage of the synthesis required a selective acylation of the cyclic NH-group, the primary amino group of the hydrazide function had to be protected. We selected isopropylidene protection whose easy preparation is combined with its easy removal in a weak acid [3]. When hydrazide III was boiled in acetone we obtained cis-6-methylpipecolic isopropylidene hydrazide (IV).


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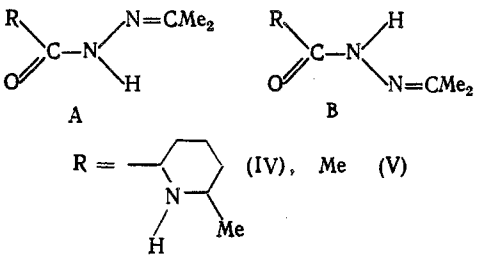
The large values for the $J_{H(2)H(3A)}$ and $J_{H(5A)H6)}$ (>10 Hz) constants in the NMR $^1H$ spectrum of hydrazide III (Table 1) are indicative of the primarily axial orientation of protons H(2) and H(6) of the piperidine ring which exists in an "armchair" conformation [4]. This corresponds to the cis-configuration of compound III and the predominance of the conformation which has a diequatorial positioning of the substituents. The diastereoisomer identity of hydrazide III emanates from its NMR $^{13}C$ spectrum (Table 2) which exhibits carbon atom signals of the only isomer of this compound.

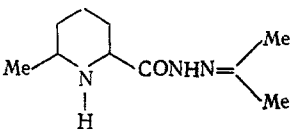
In contrast to hydrazide III, its isopropylidene derivative IV exists as a mixture of two forms which is indicated by the presence of two sets of closely positioned signals in the NMR $^1H$ and $^{13}C$ spectra that strongly differ in intensity. Each set of signals H(2) and H(6) is characterized by large values for the constants $^3J_{H(2)H(3A)}$ and $^3J_{H(5A)H(6)}$ ($\sim$11 Hz) which in turn indicates a cis-configuration for the piperidine residue in both forms. The relative configuration of the minor form depends on the solvent and varies from 10% in $CHCl_3$ to 35% in pyridine. The average life of each form, based on saturation transfer experiments [11], does not exceed 10 sec (at room temperature).

Further study of compound IV was undertaken in comparison to a model compound represented by acetic isopropylidene hydrazide (V) which also exists in two forms. In accordance with the NMR $^{13}C$ spectra for hydrazide V that were recorded without uncoupling from the protons, both forms of this compound exhibited marked differences in the $J_{CH}$ constants that characterize spin–spin transfer through the amide bond ($^2J_{CO,\ NH}$, $^3J_{CR,\ NH}$) and the coincidence of the constants $^3J_{NH,CN}$, that characterize the same effect through the hydrazide bond. This allows us to affirm that the two forms of compounds IV and V constitute long-life forms (A and B) relative to the amide bond CO–NH, but not the hydrazide bond NH–N=* [12].




Reference of the forms to conformations A and B was made on the basis of the $[^3J_{CR,NH}]_{trans} > [^3J_{CR,\ NH}]_{cis}$ ratios [13] and confirmed by examining the effect of aromatic solvent additions on the chemical shifts of the NH-group protons [14]. Conformer A with cis-positioned substituents relative to the amide CO–N bond is preferable for compound V. On the other hand, this conformer is a minor one for compound IV. This is probably tied to the increased size of the substituent on the carbonyl carbon and correspondingly to the increased steric interaction of the cis-substituents on the amide bond.

The TLC data for the acylation of compound IV by β-acetylthiopropionyl chloride (VI) [10] in the presence of $ET_3N$ are not clear so that the separation of the target product required double column chromatography of the resultant mixture. The first silica gel chromatography run resulted in a mixture which according to the PMR-spectroscopic data contained ~70% isopropylidene hydrazide (VII). The mixture also contained separation products in VII of the isopropylidene residue and S → N acyl migration. A repeated chromatography and separation of the reaction product resulted in the complete splitting off of isopropylidene protection and S → N migration with the formation of 1-(β'-mercaptopropionyl)-6-methylpipecolic N-β-acetyl hydrazide (VIII).



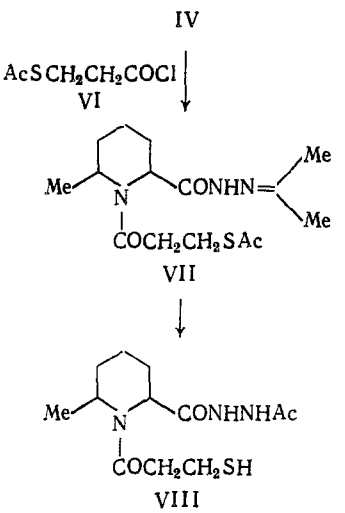

IV

*Compounds IV and V cannot exist in the syn- and anti-isomer forms relative to the C=N bond since both substituents on the carbon of the imine group are the same (Me). However, in each of these forms the substituents are nonequivalent since they can be in a syn- or anti-orientation to the hydrazide bond.

TABLE 1. Chemical Shifts of $^1H$ in the Piperidine Derivatives III, IV, VII, VIII, and the Model Compound V (δ, ppm)

| Compound | Piperidine ring | | | 1-R | 2-R[f] | 6-$CH_3$ |
|---|---|---|---|---|---|---|
| | 2-H | 3-H—5H | 6-H | | | |
| III | 3,31q (11,3, 3,0)[a] | 1,0—2,2 | 2,69m (11,0, 2,6)[b] | | 8,0 (NH) 3,0 ($NH_2$) | 1,26[e] |
| $IV_T$[c] | 3,39q (11,0, 3,0) | 1,0—2,2 | 2,70m (11,0, 2,5) | ~1,7 | 1,89S 2,10S ($CH_3$), 9,68 (NH) | 1,07[e] |
| $IV_{cis}$ | 4,08q (11,0, 3,0) | 1,0—2,2 | 2,70 m (11,0, 2,5) | | 1,82S, 2,00S ($CH_3$), 8,18 (NH) | 1,07[e] |
| VII | 5,04[e] (5,7)[d] | 1,4—2,4 | 4,16m (~6)[d] | 2,8—3,2 ($CH_2CH_2$) 2,34S ($COCH_3$) | 9,85 (NH) 2,07S, 1,87S ($CH_3CN$) | 1,22[e] |
| VIII | 5,14[e] (~6)[d] | 1,4—2,4 | 4,2m[e] | 1,7—1,95 ($CH_2CH_2$) | 2,01S ($COCH_3$) 8,90d, 9,00d | 1,26[e] |
| $V_T$[g] | 1,90S; 2,11S; 2,12S ($CH_3$); 8,07m (NH) | | | | | |
| $V_{cis}$ | 1,84S; 2,02S; 2,28 S($CH_3$); 8,27m (NH) | | | | | |

Note. a) $J_{H(2)H(3A)}$ and $J_{H(2)H(3B)}$ values are given in parentheses; b) $J_{H(5A)H(6)}$ and $J_{H(5B)(H(6)}$ are given in parentheses; c) cis(T) — conformers with a cis—(trans)-positioning of substituents (piperidine and hydrazide residues) relative to the amide bond; d) broadened signal, the largest of the vicinal constants are given in parentheses; e) strongly broadened signal; f) coupling constant of hydrazide residue protons ~4 Hz; g) see note c, conformer ratio in $CDCl_3$ is 1 (T): 8 (cis). Spectra recorded in $CDCl_3$.




A marked broadening of the signals, primarily the nuclear signals in positions 2 and 6 of the piperidine ring, is characteristic of the NMR $^1H$ and $^{13}C$ spectra for the N-acylated products of VII and VIII. This broadening is evidently due to the existence of compounds VII and VIII in two conformer forms relative to the amide bond N(1)—CO that transfer from one to the other. An analogous effect of delayed rotation relative to the $N_1$—CO bond was previously observed by us in the case of the N-acylated derivatives of 2,4- and 2,5-piperidine dicarboxylic acids [8]. As was the case in the latter compounds, the N-acylated products of VII and VIII are characterized by markedly lower vicinal $J_{H(2)H(3A)}$ and $J_{H(6)H(5A)}$ constant values in comparison to the initial nonacylated derivatives III and IV.

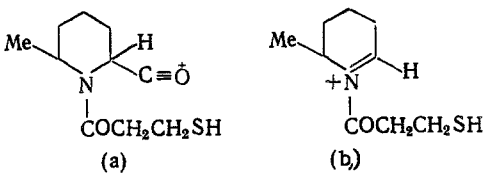
The proton signals of the isopropylidene group that were observed in the spectrum for hydrazide VII were absent in the NMR $^1H$ spectrum for compound VIII, but the acetyl group signal was markedly shifted to the strong field relative to the analogous signal of hydrazide VII and the earlier examined 1-(3'-acetylmercaptoacyl)-2-piperidine carboxylic acids [8]. This strong field shift, as well as the multiplicity of proton signals of the hydrazide chain, correspond to the AB system and indicate the presence of an acetyl substituent on the ω-amino group of the hydrazide fragment.

The structure of the acetyl hydrazide VIII was also confirmed by mass spectrometry which exhibited a low intensity molecular ion peak with m/z 287 which quickly decomposes with the formation of characteristic ions with m/z 214 (a) and 186 (b):

TABLE 2. Chemical Shifts of $^{13}C$ in Derivatives of Piperidine III, IV, VIII, and the Model Compound V (δ, ppm)

| Compound | Solvent | Piperidine ring | | | 1-R | 2-R | 6-$CH_3$ |
|---|---|---|---|---|---|---|---|
| | | 2-C | 3-C—5-C | 6-C | | | |
| III | $CDCl_3$ | 59,9 | 33,5; 29,6; 24,1 | 51,4 | — | 174,0 (CO) | 22,7 |
| IVt[a] | $CDCl_3$ | 60,2 | 32,9; 29,6; 24,8 | 50,9 | — | 169,5 (CO), 154,5 (CN); 16,0, 24,8 ($CH_3$) | 22,6 |
| IVcis | $CDCl_3$ | 56,1 | 33,7; 28,2 | 50,7 | — | 174,7 (CO); 148,7 (CN); 15,3 | 22,4 |
| VIII | $CDCl_3$ | 47,9[b] | 36,9; 29,7; 24,3 | 48,1[b] | 14,6, 19,7 ($CH_2$), 167,6 c (CO) | 171,9c 170,6c (CO) | 18,5 |
| Vt[d] | DMSO-$d_6$ + $C_6D_6$ (2:1) | 21,6 ($\underline{C}H_3CO$), 17,4; 25,0 ($\underline{C}H_3CN$), 165,7 (CO), 153,9 (CN) $^2J_{NH,\ CO}$=7,5 Hz; $^2J_{NH,\ CH_3}$ <1,5 Hz; $^2J_{CN,\ NH}$=3,3 Hz | | | | | |
| Vcis[d] | | 20,7 ($\underline{C}H_3CO$), 16,9, 25,1 ($\underline{C}H_3CN$), 172,3 (CO), 149,3 (CN); $^2J_{NH,\ CO}$ <3 Hz; $^2J_{NH\ (1),\ CH_3}$=3,2 Hz; $^2J_{CN,\ NH}$=3,1 Hz | | | | | |

Note: a) cis (T) – conformers with cis–(trans)-positioning of substituents (of piperidine and hydrazide residues) relative to the amide bond; b, c) possible inverse reference of labeled signals; d) see note a, conformer ratio in the indicated solvent ∿1 (T): 2.5 (cis).




## EXPERIMENTAL

NMR spectra were recorded on a XL-200 spectrometer (Varian, Switzerland) with a working frequency of 200 mHz on the $^1H$ nuclei and 52.3 mHz on the $^{13}C$ nuclei; internal standard was TMS ($\delta^1_H = \delta^{13}_C = 0$).

Solvents are indicated in Tables 1 and 2. IR-spectra were obtained on a Perkin-Elmer 599 spectrometer in petroleum jelly. Mass spectra were recorded on a MAT-112 chromatomass spectrometer (Varian). Ionizing electron energy was 70 eV, temperature of the ionization chamber was 180°C upon direct input of sample into the ion source. Silufol UV-254 plates were used for TLC. Mobile phases: EtOH–ammonia–water (24:4:3); system A), MeOH–$CuCl_2$ (1:20, system B). Developer was a 2% solution of ninhydrin in EtOH upon heating for 5 min to 110°C. For the sulfur-containing compounds a 10% solution of phosphomolybdic acid in EtOH was used (in the case of VIII – upon heating for 5 min to 110°C). The found element analysis values corresponded to the calculated ones.

Cis-methylpipecolic Hydrazide (III). A mixture of 30 g (180 mmole) of II (obtained from I) [6] in 4 ml of EtOH and 10.6 g (198 mmole) of 85% hydrazine-hydrate was stirred for 3 h at 60°C, then cooled and triturated with 300 ml of ether. The precipitate was filtered off and washed with ether (3 × 50 ml), resulting in 20.9 g (73%) of the hydrazide III. White crystals, mp 103-104°C. $R_f$ 0.42 (A). The substance was soluble in water, alcohols and $CHCl_3$, and poorly soluble in acetone, and insoluble in ether and benzene. Mass spectrum: $M^+$ 157. $C_7H_{15}N_3O$.

6-Methylpipecolic Isopropylidene Hydrazide (IV). A solution of 6 g of hydrazide III in 600 ml of anhydrous acetone was boiled for 3 h, vacuum-evaporated, and recrystallized from 60 ml of hexane to yield 6.7 g (89%) of isopropylidene hydrazide IV. Colorless crystals, mp 93-95°C. Substance soluble in water, $CHCl_3$, and ether. Mass spectrum: $M^+$ 197. $C_{10}H_{19}N_3O$.

1-(β'-mercaptopropionyl)-6-methylpipecolic N-β-Acetylhydrazide (VIII). A 10.3 ml portion (74 mmole) of $Et_3N$ was added dropwise to a solution of 14.5 g (74 mmole) of hydrazide IV in 240 ml of anhydrous ethyl acetate after which 12.41 g (74 mmole) of freshly distilled β-acetylthioacetic chlorane hydride was also added. The mixture was stirred for 1 h at 25°C and for 1 h at 50°C, and cooled. The $Et_3N \cdot HCl$ was filtered off and washed with ethyl acetate (2 × 25 ml). The solution was then evaporated and the residue was treated by column chromatography (silica gel L 100/160, $CHCl_3$). The fractions containing the substance with $R_f$ 0.8 (B) were combined and the solvent was evaporated to yield 10.7 g of a transparent yellowish

oil with $R_f$ (0.8 (B) and $R_f$ 0.3* (B) containing up to 70% of VII according to PMR-spectroscopy. The solutions containing the substance with $R_f$ 0.3 (B) were combined and the solvent was evaporated to yield 5 g of substance VIII with $R_f$ 0.2† (B).

A 10.7 g portion of technical grade VII was treated again by chromatography, eluting $CHCl_3$. The solutions containing the substance with $R_f$ 0.3 (B) were combined and the solvent was evaporated. The yield was 4.7 g of substance VIII which was combined with 5 g of the substance VIII from the first column. This was dried over $P_2O_5$ and retriturated with 300 ml of hexane. The precipitate was filtered off and dried to yield 6.7 g (32%) of the hydrazide VIII. Colorless crystals, mp 39-41°C. The substance was soluble in water, alcohols, acetone, ethyl acetate, benzene, and $CHCl_3$, insoluble in hexane, ether, and $CCl_4$. IR-spectrum, $\nu_{max}$, $cm^{-1}$: 2500-2600, 3300. Mass-spectrum: $M^+$ 287, fragmentation: 214, 186, 98. $C_{12}H_{21}N_3S_1O_3$.

## EXPERIMENTAL (PHARMACOLOGICAL)

Antihypertensive activity was tested on nonanesthetized spontaneous-hypertensive male rats of the Okamato-Aioki line weighing 200-250 g. Arterial pressure (AP) was indirectly measured by the exsanguinate method in the caudal artery with photoelectric sensor through a Mod 29 amplifier and recorded on a Mod 45 autoscribe (instrument set manufactured by the IITC firm, USA). During the measurements the animals were in a chamber with an air temperature of 28°C. Compound VIII was administered orally to the rats at a dose of 10 mg/kg in the form of an aq. solution.

The effect of compound VIII on the depressor effect of bradykinin (BK, 1 μg/kg, iv) was tested on urethane-anesthetized (0.7 ml of a 25% solution per 100 g of body weight, ip) normal tensive Kyoto—Wistar line male rats. Compound VIII, dissolved in an NaCl isotonic solution was administered through a catheter into the jugular vein. AP was measured in the common carotid artery by a Statcham 23Gb (Gould, USA) sensor through a type 551-A pressure block (Hugo Sachs Electronic, FRG) and recorded on a Gemini Ugo Basile (Italy) automatic recorder.

The experiments on the spontaneous-hypertensive rats demonstrated that AP was reduced by 32 ± 5 mm Hg 1 h after the oral administration of compound VIII at a dose of 10 mg/kg, after which the antihypertensive effect gradually diminished over a period of 2.5-3.0 h. In comparative experiments captopril at the same dosage reduced AP by 45 ± 4 mm Hg and its effect lasted more than 4 h.

In experiments on anesthetized rats compound VIII did not exhibit any appreciable effect on the degree or duration of BK depressor effect when the compound was administered at a dose of 0.1 and 0.5 mg/kg. An increase in dosage to 1 and 2 mg/kg resulted in the appearance of BK-potentiating properties that are characteristic of angiotensin inhibitors of the I-converting enzyme. Moreover, there was a two to threefold increase in depressor effect and a 1.5-3 fold increase in its duration. The BK-potentiating effect of compound VIII was more than 10 times weaker than that of captopril.

According to the test data on the inhibiting activity of compound VIII with regard to DCP obtained by spectrofluorometry, at a concentration of $4 \cdot 10^{-5}$ M it retarded this enzyme's activity by 50% ($IC_{50} = 4 \times 10^{-5}$ M), i.e., it exhibits DCP-like effects [2, 3].

Thus, our experiments have demonstrated that compound VIII exhibits elements of antihypertensive and BK-potentiating activity which is apparently related to its ability to inhibit DCP by binding the functional groups of compound VIII to the enzyme's active center.

## LITERATURE CITED


1. V. G. Granik, G. Ya. Shvarts, I. F. Faermark, et al., Khim.-farm. Zh., No. 7, 778-782 (1985).
2. V. G. Granik, G. Ya. Shvarts, S. I. Grizik, et al., Khim.-farm. Zh., No. 12, 1428-1433 (1987).
3. J. F. W. McOmie, in: Advances in Organic Chemistry, Vol. 3, R. A. Raphael et al., eds., Wiley-Interscience, NY (1963).
4. L. I. Mastafanova, K. F. Turchin, M. I. Evstratova, et al., Khim. Geterotsikl. Soed., No. 3, 367-371 (1985).
5. V. N. Orekhovich, Yu. B. Eliseeva, and L. V. Pavlikhina, Vestn. AMN SSSR, No. 9, 34-38 (1982).


*Hydrolysis of acetonitrile protection was observed during column chromatography.
†Change in $R_f$ related to S → N-migration of the acetyl residue.

6. USA Patent No. 3,388,128, 1968, Chem. Abstr., 69, No. 17, 6301 (1968).
7. G. Ya. Shvarts and V. G. Granik, Khim.-farm. Zh., No. 3, 271-283 (1984).
8. L. N. Yakhontov, L. I. Mastafanovoa, M. I. Evstratova, et al., Khim.-farm. Zh., No. 10, 1185-1190 (1984).
9. D. W. Cushman, H. S. Cheung, E. F. Sabo, et al., Angiotensin Converting Enzyme Inhibitors, Mechanisms of Action and Clinical Implications, ed. Z. P. Horovitz, Baltimore (1981), pp. 3-25.
10. H. U. Daeniker and J. Druey, Helv. Chim. Acta., 40, 2148-2156 (1957).
11. S. Forsen and R. A. Hoffmann, J. Chem. Phys., 39, No. 11, 2892-2899 (1963).
12. P. E. Hansen, Progress in Nuclear Magnetic Resonance Spectroscopy, eds. J. W. Emsley et al., Vol. 14, No. 4, Oxford (1981), pp. 223-226.
13. A. DeMarco and M. Llinas, Org. Magn. Res., 12, 454-465 (1979).
14. W. E. Stewart and T. H. Siddall, Chem. Rev., 70, No. 5, 517-551 (1970).

# SYNTHESIS AND NEUROTROPIC ACTIVITY OF 3(5)-OXYMETHYLPYRROLIZIDINE COMPLEX ESTERS WITH AROMATIC ACIDS

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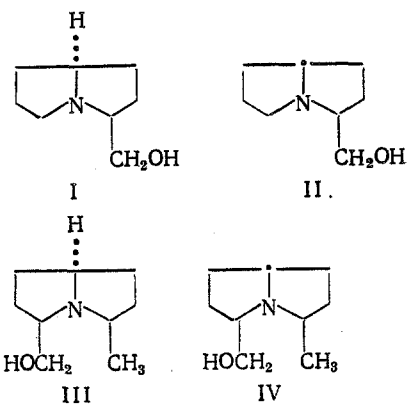
Complex esters of amino alcohols and carboxylic acids are known to possess variable biological activity and primarily, cholinolytic activity [3, 12, 13].

We felt it would be of interest to synthesize and investigate the pharmacological properties of pyrrolizidine alcohol complex esters with benzoic, diphenylacetic, and benzilic acids. We selected two pairs of isomers from among the pyrrolizidine alcohols — cis (I) and trans-3,8H-3-oxymethylpyrrolizidine (II), cis-3,8H-3-methyl-cis-5,8H-(III) and trans-3,8H-3-methyl-trans-5,8H-5-oxymethylpyrrolizidine (IV) — which can be viewed as derivatives of 1,2-aminoethanol.

The pyrrolizidines have been noted to be strong bases [1, 6]. The steric accessibility of the nitrogen atom in the pyrrolizidine derivatives with type I and III configurations has been considered to be a factor conducive to neurotropic activity [11-13, 15].




Compounds I-IV were obtained by the direct hydrogenation of 5-oxymethyl-(V) and 3-methyl-5-oxymethyl 1,2-dihydropyrrolizidine (VI) [7]. Instead of the previously employed 5% $Rh/Al_2O_3$ catalyst [7], we used $RuO_2$ in this process [5]. The mixtures of the I, II isomers and the four isomers of 3-methyl-5-oxymethylpyrrolizidines were treated and converted by methods [7, 8] in order to separate each one from compounds I-IV.

Acylation of the pyrrolizidine alcohols I-IV with benzoic (VII) and diphenylacetic (VIII) chloranhydrides and treatment with HCl in the same manner as described in [9, 10, 14] resulted in the corresponding hydrochlorides EX-XVI.

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