# SYNTHESIS AND PHARMACOLOGICAL STUDY OF PROMEDOL ANALOGS WITH ALKYLAMINOALKYL SUBSTITUENTS IN POSITION 1

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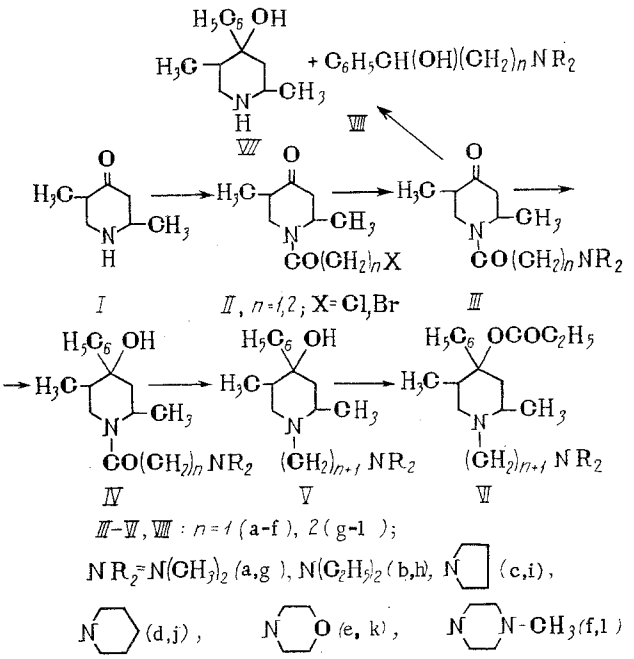
The high analgesic activity of Promedol, which has found wide use in medical practice [1, 2], has given rise to the appearance of a large number of investigations on the synthesis and pharmacological study of analogs of this compound. Moreover, these varied in the nature and position of the substituents in the piperidine and phenyl rings, in the acylating group on the tertiary hydroxyl, and in the alkyl and aralkyl groupings on the piperidine nitrogen atom. Analogs of Promedol with alkylaminoalkyl substituents in position 1 have not been reported previously.

We have carried out the synthesis of this new type of compound according to the scheme:




Acylation of 2,5-dimethyl-4-piperidone (I) with the acid chloride of chloracetic or β-bromopropionic acid and subsequent treatment of the halo-amides (II) with various secondary amines (dimethylamine, diethylamine, pyrrolidine, piperidine, morpholine, and N-methylpiperazine) led to the preparation of the corresponding 1-alkylaminoacyl-2,5-dimethyl-4-piperidone (III) in 59–73% yield based on I (Table 1).

In the course of the further synthesis, when studying the products of the interaction of the keto-amides

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TABLE 1. 1-Alkylaminoacyl-2,5-dimethyl-4-piperidones

| Compound | Yield (in %) | Boiling point (deg) | Found (in %) | | | Empirical formula | Calculated (in %) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N |
| IIIc | 53 | 148—50 (2 mm) | 66,02 | 9,35 | 11,89 | $C_{13}H_{22}N_2O_2$ | 66,51 | 9,30 | 11,75 |
| IIId | 67 | 171—3 (4 mm) | 66,68 | 9,31 | 10,93 | $C_{14}H_{24}N_2O_2$ | 66,62 | 9,58 | 11,10 |
| IIIe | 68 | 168—170 (0,6mm) | 61,13 | 8,63 | 10,91 | $C_{13}H_{52}N_2O_3$ | 61,39 | 8,71 | 11,01 |
| IIIf | 59 | 178—180 (3 mm) | 63,00 | 9,33 | 16,08 | $C_{14}H_{25}N_3O_2$ | 62,88 | 9,42 | 15,71 |
| IIIi | 63 | 175—7 (3 mm) | 66,83 | 9,35 | 10,93 | $C_{14}H_{24}N_2O_2$ | 66,62 | 9,58 | 11,10 |
| IIIj | 69 | 185—7 (4 mm) | 67,63 | 9,89 | 10,47 | $C_{15}H_{26}N_2O_2$ | 67,63 | 9,83 | 10,51 |
| IIIk | 65 | 190—2 (3 mm) | 62,67 | 8,87 | 10,50 | $C_{14}H_{24}N_2O_3$ | 62,65 | 9,01 | 10,44 |
| IIIl | 62 | 188—190 (2 mm) | 64,22 | 9,80 | 14,84 | $C_{15}H_{27}N_3O_2$ | 64,34 | 9,67 | 14,93 |

TABLE 2. 1-Alkylaminoacyl-2,5-dimethyl-4-hydroxy-4-phenylpiperidines

| Compound | Yield (in %) | Boiling point (deg) | Found (in %) | | | Empirical formula | Calculated (in %) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N |
| IVa | 27 | 188—90 (0,6 mm) | 70,33 | 8,86 | 9,52 | $C_{17}H_{26}N_2O_2$ | 70,30 | 9,02 | 9,64 |
| IVb | 30 | 188—90 (0,4 mm) | 71,61 | 9,49 | 8,79 | $C_{19}H_{30}N_2O_2$ | 71,65 | 9,49 | 8,79 |
| IVc | 36 | 198—200 (0,3mm) | 72,31 | 8,75 | 8,67 | $C_{19}H_{28}N_2O_2$ | 72,11 | 8,92 | 8,85 |
| IVd | 33 | 208—10 (0,4 mm) | 72,90 | 8,89 | 8,12 | $C_{20}H_{30}N_2O_2$ | 72,70 | 9,15 | 8,48 |
| IVe | 26 | 197—9 (0,4 mm) | 68,88 | 8,73 | 8,44 | $C_{19}H_{28}N_2O_3$ | 68,64 | 8,49 | 8,42 |
| IVf | 43 | 208—10 (0,4 mm) | 69,17 | 9,10 | 12,40 | $C_{20}H_{31}N_3O_2$ | 69,52 | 9,04 | 12,16 |
| IVi | 33 | 195—7 (1 mm) | 72,53 | 9,45 | 8,14 | $C_{20}H_{30}N_2O_2$ | 72,70 | 9,15 | 8,48 |
| IVj | 34 | 198—200 (0,4 mm) | 72,66 | 8,98 | 8,38 | $C_{21}H_{32}N_2O_2$ | 73,21 | 9,36 | 8,13 |

Note: Compounds IV g, h, k, and *l* were not isolated in the pure state but were immediately subjected to lithium aluminium hydride reduction.

TABLE 3. 1-Alkylaminoalkyl-2,5-dimethyl-4-hydroxy-4-phenylpiperidines

| Compound | Yield (in %) | Boiling point (deg) | Found (in %) | | | Empirical formula | Calculated (in %) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N |
| Va | 41 | 148—50 (0,5 mm) | 74,25 | 10,12 | 9,79 | $C_{17}H_{28}N_2O$ | 74,63 | 10,16 | 10,16 |
| Vb | 49 | 152—4 (0,5 mm) | 74,98 | 10,61 | 9,15 | $C_{19}H_{32}N_2O$ | 74,94 | 10,59 | 9,20 |
| Vc | 61 | 173—5 (0,7 mm) | 75,70 | 9,95 | 9,17 | $C_{19}H_{30}N_2O$ | 75,44 | 9,99 | 9,26 |
| Vd | 69 | 178—180 (0,6 mm) | 75,99 | 10,05 | 8,76 | $C_{20}H_{32}N_2O$ | 75,89 | 10,19 | 8,85 |
| Ve | 66 | 178—180 (0,4 mm) | 71,82 | 9,64 | 9,10 | $C_{19}H_{30}N_2O_2$ | 71,65 | 9,49 | 8,79 |
| Vf | 52 | 183—5 (0,6 mm) | 72,46 | 10,02 | 12,40 | $C_{20}H_{33}N_3O$ | 72,46 | 10,01 | 12,67 |
| Vg | 12 | 152—5 (0,4 mm) | 74,28 | 10,08 | 9,21 | $C_{18}H_{30}N_2O$ | 74,47 | 10,31 | 9,64 |
| Vh | 10 | 178—180 (0,4 mm) | 75,12 | 10,75 | 9,05 | $C_{20}H_{34}N_2O$ | 75,41 | 10,76 | 8,79 |
| Vi | 52 | 187—190 (0,6 mm) | 75,42 | 9,95 | — | $C_{20}H_{32}N_2O$ | 75,89 | 10,19 | — |
| Vj | 67 | 189—2 (0,5 mm) | 76,42 | 10,45 | 8,13 | $C_{21}H_{34}N_2O$ | 76,31 | 10,38 | 8,47 |
| Vk | 10 | 177—180 (0,6 mm) | 71,95 | 9,66 | 8,44 | $C_{20}H_{32}N_2O_2$ | 72,24 | 9,70 | 8,42 |
| Vl | 22 | 189—2 (1 mm) | 72,97 | 10,10 | 11 93 | $C_{21}H_{35}N_3O$ | 72,99 | 10,21 | 12,16 |

Note: The indicated yields of Vg, h, k, and *l* are based on IIIg, h, k, and *l*.

(III) with phenyllithium by a gas—liquid chromatographic method (GLC), it was established that the reaction does not proceed unambiguously. Together with the normal products of the reaction at the keto group of the piperidine ring (the acylcarbinols IV, Table 2), the formation of 2,5-dimethyl-4-phenylpiperidine (VII) and the corresponding phenylalkylaminoalkylcarbinols VIII (owing to the attack of the amide groups of III by phenyllithium and subsequent cleavage of the C–N bond) was observed in all cases. In the case of 1-(4'-methylpiperazinylacetyl)-2,5-dimethyl-4-piperidone (IIIf) the quantity of VII and VIII formed was 44-51% according to the GLC data, while the yield of IVf did not exceed 45%. In a number of cases the compounds VIII were isolated from the reaction products in a pure state and their structure confirmed by elemental analysis, IR, and mass spectra. The ambiguous course of the reaction of III with phenyllithium is responsible for the comparatively low yields of the 1-alkylaminoacyl-2,5-dimethyl-4-hydroxy-4-phenylpiperidines (IV) (26-43%).

The reduction of the amide group in IV by lithium aluminium hydride (Table 3) and the subsequent acylation of the tertiary hydroxyl in position 4 of the piperidine ring by propionyl chloride caused no difficulty and led to the preparation of 12 analogs of Promedol (VI) having various alkylaminoalkyl groups (Table 4) in place of the methyl group in position 1.

As in the case of Promedol, compounds VI have three asymmetric centers (in positions 2, 4, and 5 of the piperidine ring) and exist as mixtures of diastereoisometric products. In contrast to Promedol, the

TABLE 4. 1-Alkylaminoalkyl-2,5-dimethyl-4-propionyloxy-4-phenylpiperidines

| Compound | Yield (in %) | Boiling point (deg) | Found (in %) | | | $LD_{50}$ in mg/kg | Empirical formula | Calculated (in %) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | | C | H | N |
| VI *a* | 39 | 178—80 (1 mm) | 72,45 | 9,72 | 8,16 | 570 | $C_{20}H_{32}N_2O_2$ | 72,24 | 9,70 | 8,42 |
| | | Ditartrate 70 | 50,75 | 7,25 | — | | $C_{20}H_{32}N_2O_2 \cdot 2C_4H_6O_6 \cdot 2H_2O$ | 50,29 | 7,23 | — |
| V' b | 60 | 166—8 (0,6 mm) | 73,27 | 10,20 | 7,74 | 350 | $C_{22}H_{36}N_2O_2$ | 73,28 | 10,06 | 7,77 |
| | | Ditartrate 75 | 51,90 | 7,55 | — | | $C_{22}H_{36}N_2O_2 \cdot 2C_4H_6O_6 \cdot 2H_2O$ | 51,71 | 7,52 | — |
| VIc | 42 | 172—4 (0,4 mm) | 73,90 | 9,42 | 7,91 | 275 | $C_{22}H_{34}N_2O_2$ | 73,69 | 9,55 | 7,81 |
| | | Ditartrate 75—77 | 51,44 | 7,39 | — | | $C_{22}H_{34}N_2O_2 \cdot 2C_4H_6O_6 \cdot 2H_2O$ | 51,86 | 7,25 | — |
| VId | 27 | 163—5 (0,4 mm) | 74,54 | 9,93 | 7,66 | 157 | $C_{23}H_{36}N_2O_2$ | 74,19 | 9,74 | 7,52 |
| | | Ditartrate 78—80 | 54,20 | 7,44 | — | | $C_{23}H_{36}N_2O_2 \cdot 2C_4H_6O_6 \cdot H_2O$ | 53,90 | 7,29 | — |
| VIe | 27 | 166—8 (0,4 mm) | 70,54 | 9,41 | 7,54 | 142 | $C_{22}H_{34}N_2O_3$ | 70,55 | 9,15 | 7,48 |
| | | Ditartrate 90—92 | 52,35 | 7,34 | — | | $C_{22}H_{34}N_2O_3 \cdot 2C_4H_6O_6 \cdot H_2O$ | 52,77 | 7,08 | — |
| VI f | 38 | 174—6 (0,4 mm) | 70,87 | 9,64 | 10,84 | 590 | $C_{23}H_{37}N_3O_2$ | 71,27 | 9,62 | 10,84 |
| | | Tritartrate 110—12 | 48,10 | 6,80 | — | | $C_{23}H_{37}N_3O_2 \cdot 3C_4H_6 \cdot 2H_2O$ | 48,55 | 6,87 | — |
| VI g | 48 | 183—5 (0,6 mm) | 72,59 | 9,91 | 7,89 | 275 | $C_{21}H_{34}N_2O_2$ | 72,78 | 9,89 | 8,02 |
| | | Ditartrate 75—77 | 52,53 | 7,58 | — | | $C_{21}H_{34}N_2O_2 \cdot 2C_4H_6O_6 \cdot H_2O$ | 52,39 | 7,27 | — |
| VIh | 34 | 150—2 (0,6 mm) | 73,60 | 10,38 | 7,54 | 400 | $C_{23}H_{38}N_2O_2$ | 73,74 | 10,22 | 7,45 |
| | | Ditartrate 75—77 | 53,65 | 7,53 | — | | $C_{23}H_{38}N_2O_2 \cdot 2C_4H_6O_6 \cdot H_2O$ | 53,74 | 7,56 | — |
| VIi | 35 | 168—70 (0,6 mm) | 73,78 | 9,52 | — | 435 | $C_{23}H_{36}N_2O_2$ | 74,12 | 9,74 | — |
| | | Ditartrate 60—62 | 54,18 | 7,35 | — | | $C_{23}H_{36}N_2O_2 \cdot 2C_4H_6O_6 \cdot 2H_2O$ | 53,89 | 7,29 | — |
| VI j | 45 | 168—70 (0,4 mm) | 74,69 | 9,64 | — | | $C_{24}H_{38}N_2O_2$ | 74,56 | 9,90 | — |
| | | Ditartrate 75—77 | 55,07 | 7,42 | — | 245 | $C_{24}H_{38}N_2O_2 \cdot 2C_4H_6O_6 \cdot 0,5H_2O$ | 55,23 | 7,38 | — |
| VI k | 29 | 183—5 (0,6 mm) | 71,50 | 9,25 | 7,40 | | $C_{23}H_{36}N_2O_3$ | 71,09 | 9,33 | 7,21 |
| | | Ditartrate 78—80 | 51,55 | 7,29 | — | 400 | $C_{23}H_{36}N_2O_3 \cdot 2C_4H_6O_6 \cdot 2H_2O$ | 51,23 | 7,23 | — |
| VIl | 45 | 198—200 (0,6 mm) | 71,59 | 9,75 | 10,06 | | $C_{24}H_{39}N_3O_2$ | 71,77 | 9,78 | 10,46 |
| | | Tritartrate 116-118 | 49,80 | 7,05 | — | 510 | $C_{24}H_{39}N_3O_2 \cdot 3C_4H_6O_6 \cdot H_2O$ | 49,70 | 6,83 | — |

Note: Melting points are shown for the tartrates; they melt with decomposition.

analysis of these mixtures by the PMR method proved to be difficult because the signals of the alkylaminoalkyl groups were superimposed on the signals of the piperidine-ring protons and formed a very complex overall picture for the PMR spectra.

For the pharmacological tests, the synthesized 1-alkylaminoalkyl-4-propionyloxy-4-phenylpiperidines (VIa-*l*) as the sum of the diastereoisomers were converted into the tartrates, which exist in crystal hydrate forms and are readily soluble in water.

Compounds VIa-*l* were studied for a number of pharmacological properties: the effect on the central nervous system (analgesic action, influence on the soporific effect of Hexenal, antispasmodic activity, etc.), on smooth muscle, and on the cardivascular system (the local anesthetic and antihistamine activity, and the general action and toxicity). In addition, for substances VIg-k the effect on adreno- and cholinoreactive systems was studied.

Compound VIe displayed sedative activity in experiments on mice (the method of Woulfe and MacDonald), when injected subcutaneously or into the abdominal cavity, and in experiments on rats (electrical stimulation), when injected subcutaneously. The analgesic effect developed 5 min after injection of the compound starting at doses of 5-10 mg/kg. Compound VIe is two to three times weaker than Promedol in strength of action. The remaining compounds VI did not possess marked analgesic activity in doses up to 100 mg/kg.

In experiments on mice compound VIe intensified the soporific effect of Hexenal but was inferior in this respect to Promedol. The remaining compounds did not possess this property.

Compounds VIa-*l* did not display spasmolytic, antihistamine, local anesthetic, and antipasmodic activity. All the substances exerted a weak cholinolytic action (in experiments on isolated sections of rabbit intestine). Substances VIa-*l*, beginning with doses of 1-2.5 mg/kg, caused a short-lived hypotensive effect in experiments with urethan-treated cats. Compounds VIh-*l* did not display an effect on peripheral adrenergic receptors and ganglia. Compound VIg at a dose of 2.5-5 mg/kg possessed weak cytisinolytic activity.

The $LD_{50}$ of compounds VIa-*l* for intravenous (VIa-f, *l*) and intraperitoneal (VIg-k) injection in mice are given in Table 4.

## EXPERIMENTAL

1-(N-Pyrrolidinoacetyl)-2,5-dimethyl-4-piperidone (IIIc). A solution of 10 g of chloracetyl chloride in 10 ml of benzene was added to 10 g of I and 8.9 g of triethylamine in 100 ml of anhydrous benzene while stirring and cooling with ice. On completing the addition, the reaction mixture was stirred for 30 min at 0-5°C and 4 h at room temperature, after which the precipitate of triethylamine hydrochloride (11.6 g) was filtered off and washed with anhydrous benzene. The combined benzene filtrates were washed with 25% potash solution and dried with magnesium sulfate. After distilling off the solvent, 11.7 g (73%) of a viscous dark brown liquid was obtained. It was dissolved in 50 ml of absolute alcohol; 6.2 g of pyrrolidine was added, and the mixture was heated to boiling for 5 h. The alcohol was distilled off, and the residue was treated with an excess of 50% potash solution and extracted with ether. After drying the extract with magnesium sulfate and distilling off the solvent, the residue was distilled under vacuum. This gave 9.9 g of IIIc.

The remaining compounds III (see Table 1) were prepared similarly. Compounds IIIa, b, g, and h have been reported previously [3].

1-(Dimethylaminoacetyl)-2,5-dimethyl-4-hydroxy-4-phenylpiperidine (IVa). To a solution of phenyllithium prepared from 1.5 g of lithium and 16.85 g of bromobenzene in 130 ml of anhydrous ether, 9.05 g of IIIa in 40 ml of anhydrous ether was added over 30 min with stirring and cooling to 0°. The stirring was continued for a further 30 min at 0° and 2 h at room temperature, after which 40 ml of water was added dropwise while cooling with ice. Then concentrated hydrochloric acid was added until the reaction was acid to congo red. The ether layer was separated, the water was washed several times with ether, it was saturated with solid potassium hydroxide, and the oily substance which separated was extracted with ether. The ether extract was dried with magnesium sulfate, the solvent was evaporated, and the residue distilled under vacuum. The yield of IVa was 3.4 g. The viscous, hardly mobile liquid was readily soluble in the usual organic solvents.

The remaining compounds IV (see Table 2) were prepared similarly.

On fractional distillation of the products of the reaction of III with phenyllithium, the appropriate

phenylalkylaminoalkylcarbinol (VIII) was isolated from the first fraction. Thus, for example, in the case of IIId, phenyl-N-piperidinomethylcarbinol (VIIId) was obtained, bp 120-122° (2 mm), mp 65-66° (from ethyl acetate). Found, %: C 76.00; H 9.45; N 7.13. Mol. wt. 205 (mass spectrum). $C_{13}H_{19}NO$. Calculated, %: C 76.07; H 9.33; N 6.82. Mol.wt. 205. In the case of IIIf, phenyl-N-(N'-methylpiperazinyl)-methylcarbonyl (VIIIf) was obtained, bp 129-131° (0.4 mm), mp 96-97° (from ethyl acetate). Found, %: C 70.86; H 9.15: N 12.71 Mol. wt. 220. $C_{13}H_{20}N_2O$. Calculated, %: C 70.88; H 9.00; N 12.63. In the case of IIIi, phenyl-N-pyrrolidylethylcarbonyl (VIIIi) was obtained, bp 165-168° (0.35 mm). Found %: C 76.04; H 9.51; N 6.82. $C_{13}H_{19}NO$. Calculated, %: C 76.09; H 9.27; N 6.82.

1-(β-Dimethylaminoethyl)-2,5-dimethyl-4-hydroxy-4-phenylpiperdine (Va). Compound IVa (2.55 g) was reduced in a mixture of ether and benzene (3:5) by the action of 0.67 g of lithium aluminium hydride. This gave 1 g of Va as a colorless, hardly mobile, caramel-like mass.

The remaining compounds V (see Table 3) were prepared similarly.

1-(β-Dimethylaminoethyl)-2,5-dimethyl-4-propionyloxy-4-phenylpiperidine (VIa). A solution of 3.6 g of Va and 1.72 g of triethylamine in 35 ml of anhydrous benzene was cooled to 0-3° and 1.57 g of propionyl chloride was added dropwise, after which the reaction mixture was heated to boiling while stirring for 4 h. The precipitate of triethylamine hydrochloride (2.3 g) was filtered off. The filtrate was washed with a saturated solution of sodium carbonate, dried with magnesium sulfate, and evaporated. This gave 1.7 g of VIa as an oily liquid readily soluble in the usual organic solvents.

The ditartrate was a white, finely crystalline substance readily soluble in water.

The remaining compounds VI and their tartrates (see Table 4) were prepared similarly.

## LITERATURE CITED


1. M. D. Mashkovskii, I. N. Nazarov, V. A. Rudenko, et al., Klin. Med., No. 8, 60 (1952).
2. I. N. Nazarov, N. S. Prostakov, and N. I. Shvetsov, Zh. Obshch. Khim., 26, 2798 (1956).
3. E. S. Nikitskaya, E. I. Levkoeva, G. S. Arutyunyan, et al., Khim.-Farmats. Zh., No. 12, 3 (1973).