# ESTERS OF HETEROCYCLIC γ-AMINO ALCOHOLS

## ACETATES AND PROPIONATES OF 1,2,5-TRIMETHYL-5-AMINOMETHYL-4-PHENYL-4-PIPERIDOLS

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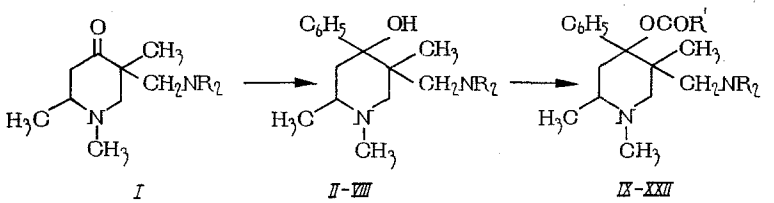
In the search for physiologically active substances we synthesized a large series of esters (acetates, propionates, benzoates, p-nitro-, and p-aminobenzoates, phenoxyacetates, and cinnamates) of 1,2,5-trimethyl-5-aminomethyl-4-phenyl-4-piperidols.

The present communication is concerned with the synthesis and evaluation of the data on the pharmacological studies of the acetates and propionates.

As starting substances in the synthesis, we used 1,2,5-trimethyl-5-aminomethyl-4-piperidones (I) obtained by the Mannich reaction from 1,2,5-trimethyl-4-piperidone [1].

1,2,5-Trimethyl-5-aminomethyl-4-phenyl-4-piperidols, II-VIII, were obtained by the action of phenyllithium on I with yields from 45 to 60%. The experimental data are given in Table 1.

Acylation with acid chlorides of acetic and propionic acids of lithium alcoholates of amino alcohols II-VIII, produced in phenylation reactions, gave the appropriate esters IX-XXII in yields from 40 to 70% (based on amino ketones). The data are given in Table 2.



I II-VIII IX-XXII

Amino alcohols II-VIII and their esters IX-XXII are very viscous substances. Their distillation in vacuo was performed with difficulty and possibility of decomposition. Compounds XI, XII, XIV, XVII, XIX, and XXI could not be distilled and were purified and determined as dihydrochlorides. Dihydrochlorides of amino alcohols and of their esters are very hygroscopic substances, and therefore their crystallization and purification were done with difficulty.

Compounds IX, X, XVI, and XVIII were also used to prepare diiodomethylates (Table 3).

A pharmacological study of the synthesized acetates and propionates has shown anesthetic properties. The activity of the substances was determined from their ability to cause terminal anesthesia on the mucous membrane of the eye in rabbits and to cause infiltrative anesthesia in guinea pigs. Widely used anesthetic xycaine (lidocaine) was tested for comparison.

The longest lasting infiltrative anesthesia was exhibited by dihydrochlorides of XIa and XIVa [$NR_2$ = $N(n\text{-}C_3H_7)_2$, $N(CH_2CH_2)_2O$] and diiodomethylate of Xb [$NR_2 = N(C_2H_5)_2$]. In this respect the cited substances

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TABLE 1. 1,2,5-Trimethyl-5-aminomethyl-4-phenyl-4-piperidols

| Compound | $NR_2$ | Yield, % | Bp, deg | Found, % | | | Empirical formula | Calc., % | | | Dipicrates* | Dihydrochlorides† |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | | C | H | N | mp, deg | mp, deg |
| II | N $(CH_3)_2$ | 62,7 | 150—4(1 mm) | 74,02<br>73,71 | 10,27<br>9,99 | 10,38<br>10,37 | $C_{17}H_{28}N_2O$ | 73,86 | 10,21 | 10,14 | 87—8 | 122—4 |
| III | N $(C_2H_5)_2$ | 55,2 | 178—80(2 mm) | 74,96<br>75,02 | 10,76<br>10,70 | 9,30<br>9,04 | $C_{19}H_{32}N_2O$ | 74,95 | 10,59 | 9,20 | 99—101 | 132—4 |
| IV | N $(\kappa\text{-}C_3H_7)_2$ | 48,7 | 177—80(1 mm) | 75,67<br>75,73 | 10,72<br>10,84 | 8,10<br>8,13 | $C_{21}H_{36}N_2O$ | 75,85 | 10,92 | 8,42 | 83—5 | 75—8 |
| V | N $(\kappa\text{-}C_4H_9)_2$ | 60,4 | 220—2(2 mm) | 76,25<br>76,42 | 11,29<br>11,28 | 7,69<br>7,64 | $C_{23}H_{40}N_2O$ | 76,61 | 11,18 | 7,77 | 87—9 | 87—9 |
| VI | N $(CH_2)_5$ | 47,9 | 190—2 (2 mm) | 75,67<br>75,82 | 9,84<br>9,98 | 8,83<br>9,15 | $C_{20}H_{32}N_2H$ | 75,90 | 10,19 | 8,85 | 114—6 | 114—6 |
| VII | N $(CH_2)_6$ | 55,8 | 177—80(1 mm) | 76,27<br>76,38 | 10,30<br>10,35 | 8,56<br>8,25 | $C_{21}H_{34}N_2O$ | 76,31 | 10,37 | 8,48 | 118—20 | 124—6 |
| VIII | N $(CH_2CH_2)_2O$ | 45,3 | 210—3(2 mm) | 71,31<br>71,11 | 9,33<br>9,20 | 8,99<br>8,67 | $C_{19}H_{30}N_2O_2$ | 71,66 | 9,49 | 8,80 | 98—100 | 153—5 |

*Dipicrates of compounds II and VII were recrystallized from alcohol, III, V, VI, and VIII from 50% acetone; melted with decomposition and determined by an analysis for nitrogen.

†Dihydrochlorides of compounds II and III were recrystallized from anhydrous alcohol with ether, IV -VIII from chloroform with ether; melted with decomposition and determined by an analysis for chlorine.

TABLE 2. Acetates and Propionates of 1,2,5-Trimethyl-5-aminomethyl-4-phenyl-4-piperidols

| Compound | $NR_2$ | $R^1$ | Yield, % | Bp, deg | Found, % C | Found, % H | Found, % N | Empirical formula | Calc., % C | Calc., % H | Calc., % N | Dihydrochlorides* compound | Dihydrochlorides* mp, deg | Dihydrochlorides* infiltrative anesthesia (effectiveness in min, inserted into the skin of guinea pigs, 1% solutions†) | Terminal anesthesia applied to the mucous membrane of the eye in rabbits: Renier index‡ for 0,5% solution | Terminal anesthesia applied to the mucous membrane of the eye in rabbits: effectiveness (in min) for 1% solutions** | $LD_{50}$ (in mg/kg) inserted under the skin in white mice |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IX | $N(CH_3)_2$ | $CH_3$ | 50,3 | 162—8 (2 mm) | 71,32<br>71,37 | 9,48<br>9,49 | 9,08<br>9,14 | $C_{19}H_{30}N_2O_2$ | 71,66 | 9,49 | 8,80 | IXa | 178—80 | 10—25 (4) | — | $\frac{0—5}{0—5}$ (4) | — |
| X | $N(C_2H_5)_2$ | $CH_3$ | 43,5 | 156—67 (1,5 mm) | 72,91<br>73,09 | 9,49<br>9,59 | 8,06<br>8,05 | $C_{21}H_{34}N_2O_2$ | 72,79 | 9,89 | 8,09 | Xa | 265—6 | 10 | 35 | $\frac{30—60}{60}$ (4) | 317,4 |
| XI | $N(n\text{-}C_3H_7)_2$ | $CH_3$ | 66,2 | — | — | — | — | — | — | — | — | XIa | 117—9 | 80; >150 (20) | 63 | $\frac{0}{15}$ (4) | 300 |
| XII | $N(n\text{-}C_4H_9)_2$ | $CH_3$ | 72,6 | — | — | — | — | — | — | — | — | XIIa | 119—21 | 35; 20 (2) | 418 | — | — |
| XIII | $N(CH_2)_5$ | $CH_3$ | 43,5 | 198—201 (1 mm) | 73,73<br>73,68 | 9,62<br>9,86 | 8,17<br>8,32 | $C_{22}H_{34}N_2O_2$ | 73,70 | 9,56 | 7,81 | XIIIa | 88—90 | 40 | — | $\frac{10—15}{15}$ (4) | 267 |
| XIV | $N(CH_2)_6$ | $CH_3$ | 57,3 | — | — | — | — | — | — | — | — | XIVa | 93 | — | 39 | — | 384 |
| XV | $N(CH_2CH_2)_2O$ | $CH_3$ | 44,0 | 195—200 (2,5 mm) | — | — | 7,60<br>7,34 | $C_{21}H_{32}N_2O_3$ | — | — | 7,77 | XVa | 98—9 | >120 | — | $\frac{3}{15}$ (2) | 343 |
| XVI | $N(CH_3)_2$ | $C_2H_5$ | 50,5 | 139—50 (0,5 mm) | 72,54<br>72,40 | 9,76<br>10,05 | 8,28<br>8,09 | $C_{20}H_{32}N_2O_2$ | 72,25 | 9,70 | 8,43 | XVIa | 109—10 | — | — | $\frac{0—15}{0—30}$ (4) | 441 |
| XVII | $N(C_2H_5)_2$ | $C_2H_5$ | 39,4 | 160—8 (1 mm) | 73,56<br>73,65 | 9,81<br>9,71 | 7,45<br>7,55 | $C_{22}H_{36}N_2O_2$ | 73,29 | 10,06 | 7,77 | XVIIa | 273—4 | 20; 35 (2) | 36 | $\frac{60—90}{—}$ (5) | 323,8 |
| XVIII | $N(n\text{-}C_3H_7)_2$ | $C_2H_5$ | 50,4 | — | — | — | — | — | — | — | — | XVIIIa | 107—9 | >125 | 52 | $\frac{5}{5}$ (4) | 390 |
| XIX | $N(n\text{-}C_4H_9)_2$ | $C_2H_5$ | 56,7 | — | — | — | — | — | — | — | — | XIXa | 111—3 | — | — | — | 580 |
| XX | $N(CH_2)_5$ | $C_2H_5$ | 38,4 | 205—10 (1 mm) | 73,76<br>73,96 | 9,78<br>9,77 | 7,78<br>7,75 | $C_{23}H_{36}N_2O_2$ | 74,15 | 9,74 | 7,52 | XXa | 94—6 | 45 | — | $\frac{15}{30}$ (4) | 242 |
| XXI | $N(CH_2)_6$ | $C_2H_5$ | 70,7 | — | — | — | — | — | — | — | — | XXIa | 104—6 | — | 40 | — | 350 |
| XXII | $N(CH_2CH_2)_2O$ | $C_2H_5$ | 42,6 | 171—3 (1 mm) | — | — | 7,36<br>7,46 | $C_{22}H_{34}N_2O_3$ | — | — | 7,48 | XXIIa | 88—91 | 50; 75 (2) | — | $\frac{0}{10—15}$ (4) | 434 |
| | | | | | | | | | | | | Xycaine | | 30—40 (4) | 539 | | 285 |

* Dihydrochlorides Xa, XVIa, and XVIIa were recrystallized from anhydrous alcohol with ether, IXa, XIa-XVa, and XVIIIa-XXIIa from chloroform with ether; melted with decomposition and determined by an analysis for nitrogen and chlorine.

†The number of observations is given in parentheses.

‡Mean values are given for the Renier index.

**The numerator shows the duration of deep anesthesia; the denominator gives the duration of incomplete anesthesia; the number of observations is given in parentheses.

TABLE 3. Diiodomethylates of Acetates and Propionates of 1,2,5-Trimethyl-5-aminomethyl-4-phenyl-4-piperidols (IX, X, XVI, and XVII)

| Compound | Melting point deg* | Infiltrative anesthesia (effectiveness, min, inserted into the skin in guinea pigs, 1% soln) | Terminal anesthesia, applied to the mucous membrane of the eye in rabbits, 1% soln. (effectiveness, min) | $LD_{50}$ (in mg/kg) inserted under the skin in white mice |
|---|---|---|---|---|
| IXb | 176-80 (from an alcohol–ether mixture | 5 (2) | $\frac{0}{0\text{-}10}$ (6) | 300 |
| Xb† | 126-8 | 80<br>150 (2) | $\frac{15\text{-}30}{60}$ (4) | – |
| XVIb | 165-8 | – | $\frac{0}{0\text{-}10}$ (4) | 175 |
| XVIIb | 62-4 (from a chloroform–ether mixture | 90-150 (4) | $\frac{5\text{-}90}{10\text{-}90}$ (8) | 116.6 |

*Melted with decomposition, characterized by an analysis for iodine.
†Shows curaremimetic properties.
Other comments, see Table 2,

are comparable with xycaine. At the same time in most of the compounds the terminal anesthesia lasted for a short time and had been observed mainly at relatively high concentrations (1%). Compound Xa[$NR_2 = N(C_2H_5)_2$] exhibited the longest terminal anesthesia.

The therapeutic latitude of the substances was determined from their toxicity. The experiments were carried out on white mice with a single introduction of the compounds. The average fatal dose ($LD_{50}$) was established.

The acetates under study are characterized by moderate toxicity close to that of xycaine. Curaremimetic properties have been found in diiodomethylate Xb[$NR_2 = N(C_2H_5)_2$].

The propionates also possess low anesthetic activity and low effectiveness. Infiltrative anesthesia in dihydrochlorides XVIIIa and XXIIa [$NR_2 = N(n\text{-}C_3H_7)_2$, morpholyl] lasts longer.

The propionates cause terminal anesthesia also, but it was less pronounced. The longest lasting anesthesia was produced upon the introduction of dihydrochloride of XVIIa and iodomethylate of XVIIb [$NR_2 = N(C_2H_5)_2$] into the eye. The application of 1-5% solutions of most of the substances, in the group under study, to the mucous membrane of the eye in rabbits has shown no irritating effects.

A study of the toxicity of propionates has established that diiodomethylates are markedly more toxic than dihydrochlorides. $LD_{50}$ in the dihydrochloride series deviated from 242 to 600 mg/kg, in xycaine $LD_{50}$ was equal to 285 mg/kg. Compound XIXa [$NR_2 = N(n\text{-}C_4H_9)_2$] was the least toxic.

Thus, the tested acetates and propionates of $\gamma$-amino alcohols in the piperidine series possess anesthetizing properties and relatively low toxicity.

A long-lasting infiltrative anesthesia has been observed in the application of a number of compounds. The terminal anesthesia was a little pronounced and lasted for a short time.

As compared with the known anesthetizing agent xycaine, the tested group of compounds as a whole shows no advantages.

## EXPERIMENTAL

Preparation of Phenyllithium. To 2 g-atoms of fine lithium shavings in anhydrous ether, while passing through dry nitrogen and stirring, was added dropwise a solution of one mole of bromobenzene in ether. The mixture was stirred and the ether boiled until lithium was completely dissolved.

1,2,5-Trimethyl-5-dimethylaminomethyl-4-phenyl-4-piperidol (II). To a solution of phenyllithium in anhydrous ether, obtained from 2.8 g of lithium and 31.4 g of bromobenzene, in a stream of dry nitrogen, with stirring and cooling to −10°, a solution of 19.7 g of 1,2,5-trimethyl-5-dimethylaminomethyl-4-piperidine [I; $NR_2 = N(CH_3)_2$] in 20 ml of anhydrous ether was added. The reaction mixture was stirred for 5 h at room temperature and 1 h while the ether boiled. The resulting lithium alcoholate of amino alcohol II, with cooling by ice water, was decomposed with diluted (1:1) hydrochloric acid (to an acid reaction). The ether layer was separated, the aqueous layer extracted again several times with ether, and then, with cooling by ice water, neutralized with sodium carbonate, saturated with solid sodium hydroxide, and repeatedly extracted with ether. The combined ether extracts were dried over magnesium sulfate. The ether was distilled off and the residue distilled in vacuo. Yield of II 17.3 g (62.7%), bp 150-154° (1 mm), viscous substance.

Compounds III-VIII were prepared similarly to II.

Acetate of 1,2,5-trimethyl-5-dimethylaminomethyl-4-phenyl-4-piperidol (IX). Lithium alcoholate of II was obtained, as described above, from 1.4 g of lithium, 16 g of bromobenzene, and 10 g of I ($NR_2 = N(CH_3)_2$] in the presence of anhydrous ether. A solution of 8 g of acetyl chloride in 10 ml of anhydrous ether was then added dropwise, with cooling by ice water and stirring. The reaction mixture was stirred for 3 h at room temperature and 5 h while the ether boiled. Water was then added, the ether layer separated, the aqueous layer extracted with ether, saturated with sodium carbonate, and repeatedly extracted with ether. The ether extracts were dried over magnesium sulfate, the ether distilled off, and the residue distilled in vacuo. Yield, 8 g (50.3%), bp 162-168° (2 mm), thick liquid.

Acetates X-XV and propionates XVI-XXII of amino alcohols II-VIII were obtained similarly to IX by the action of acetyl chloride or propionyl chloride on the lithium alcoholates, respectively.

## LITERATURE CITED

1. E. T. Golovin and A. P. Nikiforova, Chemistry of Heterocyclic Compounds [in Russian] (1968), p. 268.