SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF 2,2,6,6-TETRAMETHYL-4-ARYL(ARALKYL)AMINOPIPERIDINES

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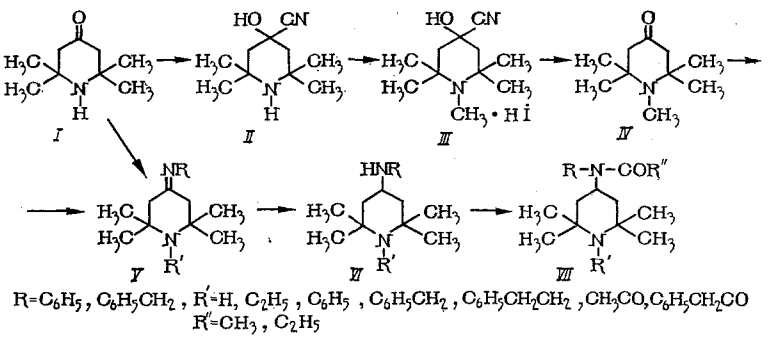
UDC 615.212:547.834.4

It was previously shown that in contrast to ganglioblocking substances of the quinuclidine and piperidine series, where the shielding of the ring nitrogen atom leads to a considerable increase in activity (temequine, imequine, and pirilen) [1,2], similar changes in the molecules for analgesics of the type 4-aminopiperidyl-4-carboxamide cause a loss in their pharmacological activity [3].

In order to establish how shielding of the ring nitrogen atom will affect the pharmacological properties of the derivatives of another group of analgesic compounds, the N-acylated 4-arylaminopiperidines of the pentanyl type, we synthesized and investigated the compounds of this series containing four methyl groups in the α positions to the ring nitrogen atom.

The synthesis was accomplished by the following scheme:



The method developed earlier [5] for synthesizing N'-substituted 4-aminopiperidines from triacetone amine (I) through cyanohydrin (II) and the appropriate aminonitriles with the reductive decyanidation of the latter permitted one to obtain 4-benzylamino-2,2,6,6-tetramethylpiperidine (VI, R = $C_6H_5CH_2$, R' = H) easily, but did not yield positive results when R = C_6H_5.

Therefore, the synthesis of the 4-phenylamino compound VI (R = C_6H_5, R' = H) was carried out from I through the 4-phenylamino derivative V (R = C_6H_5, R' = H), which was obtained by reacting I with aniline in boiling xylene to which catalytic amounts of glacial acetic acid were added. The reaction of I also proceeds similarly with benzylamine.

It is interesting to note that in the case of derivatives of I substituted on the nitrogen, as was demonstrated with 1,2,2,6,6-pentamethyl-4-piperidone (IV), the reaction with primary amines is not limited to the formation of imino derivatives but is accompanied by the rupture of the piperidine ring and subsequent cyclization in which the primary amine introduced into the reaction participates. Thus, when IV was heated with aniline in boiling xylene, 1-phenyl-2,2,6,6-tetramethyl-4-phenyliminopiperidine (V, R = R' = C_6H_5) was obtained, and during an analogous reaction of IV with benzylamine, 1-benzyl-2,2,6,6-tetramethyl-4-benzyliminopiperidine (V, R = R' = $CH_2C_6H_5$) was formed.

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific-Research Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 8, No. 2, pp. 16-21, February, 1974. Original article submitted February 15, 1973.

The synthesis of IV is easily accomplished by treating II with methyl iodide followed by the alkalization of the N-methyl hydriodide derivative (III) formed. The dehydrocyanidation process proceeds quantitatively in the cold. The introduction of larger substituents by the indicated route encounters steric hindrances.

The alkylation of the imino derivatives V (R' = H, R = C_6H_5; $CH_2C_6H_5$) with alkyl halides also generates steric difficulties. Thus, the 1-β-phenylethyl derivative of V (R = C_6H_5; R' = $CH_2CH_2C_6H_5$) was obtained by alkylating V (R = C_6H_5; R' = H) with β-phenylethylbromide with a yield of 28.8%, and the 1-ethyl derivative was obtained with a yield of 13.2% in an analogous reaction of V (R = C_6H_5; R' = H) with ethyl iodide.

The acylation of the above imino derivatives V (R = C_6H_5, $C_6H_5CH_2$; R' = H) by the action of acyl halides yields the best results. The reactions proceed in the presence of triethylamine at low temperatures and permit one to obtain 1-acyl substituted V (R = C_6H_5 or $C_6H_5CH_2$; R' = $COCH_3$ or $COCH_2C_6H_5$) with a yield of 60-61%.

The reduction of imino derivatives V to the corresponding amines VI is smoothly accomplished with hydrogen in the presence of a platinum catalyst. When an N-acyl moiety is present in V, it is necessary to reduce it preliminarily with lithium aluminum hydride because the catalytic hydrogenation of the double bond in C = N in the N-acylated imines V is accompanied by secondary processes and it is difficult to purify the final products.

It is interesting that the reduction with lithium aluminum hydride of the phenyliminopiperidines and benzyliminopiperidines acylated with respect to the piperidine nitrogen (V, R = C_6H_5) and (V, R = $C_6H_5CH_2$) respectively proceeds differently. For V, where R = C_6H_5, the reduction of the phenylimino group to the phenylamino group and the reductive deacylation with respect to the piperidine nitrogen forming 2,2,6,6--tetramethyl-4-phenylaminopiperidine (VI, R = C_6H_5, R' = H) are characteristic. The same compound was obtained when 2,2,6,6-tetramethyl-4-phenyliminopiperidine (V, R = C_6H_5; R' = H), which is unsubstituted with respect to the ring nitrogen, was reduced with lithium aluminum hydride. For V, where R = $C_6H_5CH_2$, the benzylimino group remains unchanged by the action of lithium aluminum hydride, but the acyl moiety on the piperidine nitrogen is reduced normally, without splitting off, to the alkyl group. In this way, VI (R = $C_6H_5CH_2$; R' = $C_6H_5CH_2CH_2$) was obtained from V (R = $C_6H_5CH_2$; R' = $COCH_2C_6H_5$) by reducing the latter with lithium aluminum hydride followed by hydrogenation over platinum. This route proved to be the most convenient for synthesizing 1-substituted 4-benzylaminopiperidines VI, where R $\neq$ R'. This scheme does not yield positive results in the case of 1-substituted 4-phenylaminopiperidines VI where R $\neq$ R', and one succeeds in obtaining this type of compound by just alkylating V (R = C_6H_5; R' = H) followed by reducing the imino derivatives V (R = C_6H_5; R' = C_2H_5; $C_6H_5CH_2CH_2$) to VI over a platinum catalyst.

The presence of four α-methyl groups in the piperidine ring in compounds VI causes definite steric hindrances during acylation with respect to the exocyclic nitrogen atom. These hindrances increase with an increase in the bulk of R' and R". Thus, whereas the N'-methylation of VI (R = $C_6H_5CH_2$; R' = C_2H_5) using formic acid and formalin proceeds with a yield of 66.5%, the N'-acylation with a yield of 34%, and the N'-propionylation with a yield of 10%, compound VI, where R = C_6H_5; R' = $C_6H_5CH_2CH_2$, is acylated both by acetic and propionic anhydride to an extent of just 10-13% according to gas-liquid chromatography even under more drastic conditions (boiling for 8 h with a considerable excess of anhydride).

Compounds VII (R = $C_6H_5CH_2$; R' = C_2H_5; R" = CH_3) and VII (R = $C_6H_5CH_2$; R' = R" = C_2H_5) were investigated in relation to their analgesic activity and also their effect on arterial pressure, respiration, and the smooth muscles; their antihistaminic, local anesthetic activity, and toxicity were investigated. It was established that both substances do not prove to have any expressed analgesic activity in experiments on mice (the method of Woolfe and MacDonald) and on rats (electrical stimulation of the tail). The compounds were injected into the mice subcutaneously in doses of 5, 10, 50, and 100 mg/kg and into rats in doses of 10 and 25 mg/kg. Promedol (3-4 mg/kg) gave rise to an expressed analgesic effect. Beginning at a dose of 0.5-1 mg/kg, which was injected intravenously, both compounds cause a short-lived and moderate drop in arterial pressure (10-20 mm Hg) in cats narcotized with ethyl carbamate. At doses of 5-10 mg/kg, a stronger hypotensive effect is observed; bradycardia and some increase in respiration are noted. At doses of 15-25 mg/kg, the arterial pressure sharply decreases (by 80-100 mm Hg); the effect lasts for 30-50 min. The animals in a fraction of the experiments perish at this dose. Neither of the compounds possess an expressed antihistaminic activity (experiments in which histamine was intravenously injected into cats) and cholinolytic activity (experiments on a section of rabbit's intestine), do not cause dilation or contraction of the vessels in an isolated rabbit's ear, and their 0.5-1% solutions prove to have no local anesthetic effect (Renier method on rabbits). The LD_{50} for VII (R = $C_6H_5CH_2$; R' = C_2H_5; R" = CH_3) when injected into

mice intravenously is 86 mg/kg; when injected subcutaneously it is 590 mg/kg; for compound VII (R = $C_6H_5CH_2$; R' = R" = C_2H_5), it is 100 mg/kg when intravenously injected and 520 mg/kg when subcutaneously injected.

Thus, the introduction of four α-methyl groups into 4-aryl(aralkyl)aminopiperidines, as for analogous changes in the molecule of analgesics of the 4-aminopiperidylcarboxamide series, leads to the formation of compounds which possess no analgesic activity.

EXPERIMENTAL

1,2,2,6,6-Pentamethyl-4-hydroxy-4-cyanopiperidine Hydriodide (III). A mixture of 5 g of II, 8.95 g of methyl iodide, and 12 ml of isopropyl alcohol was allowed to stand with periodic agitation for 48 h at room temperature. The sediment consisting of compound II dissolved completely and another new precipitate separated out within 24 h, was filtered off, washed with isopropyl alcohol, and with ether. A total of 5.47 g (61.5%) of III was obtained, mp 185-186°C, colorless crystals, soluble in water, poorly soluble in organic solvents. Found %: C 40.90; H 6.35; I 39.17; N 8.36. $C_{11}H_{20}N_2O \cdot HI$. Calculated %: C 40.74; H 6.53; I 39.14; N 8.64.

1,2,2,6,6-Pentamethyl-4-piperidone (IV). A. A total of 3.9 g of III was dissolved in 10 ml of water, made alkaline with a 20% sodium hydroxide solution, and extracted with ether. The dried ether extract was evaporated. Two grams (98%) of IV was obtained, colorless liquid, bp 88°C (8 mm), n_D^{20} 1.4682. Found %: C 70.97; H 11.28; N 8.21. $C_{10}H_{19}NO$. Calculated %: C 70.95; H 11.31; N 8.27. B. A solution of 5 g of III in 160 ml of methanol was passed through a column filled with 45 ml of AV-17 ion exchange resin which had been washed with methanol (or 27 g of the dry resin) which was then washed with 45 ml of methanol. The first 174 ml of eluate had a pH of 8.0-9.0 after which the eluate became neutral. The methanol was vacuum distilled off at 30°C, the residue was dissolved in anhydrous ether, filtered, and the ether was evaporated. A total of 2.8 g (86%) of IV was obtained, bp 88°C (8 mm), n_D^{20} 1.4681. The IR spectra of samples of IV obtained by methods A and B were identical.

1-Phenyl-2,2,6,6-tetramethyl-4-phenyliminopiperidine (V, R = R' = C_6H_5). A mixture of 5 g of IV, 4.1 g of aniline, 25 ml of xylene, and several crystals of p-toluenesulfonic acid was boiled for 13 h in a flask to which a Dean and Stark trap was attached. The xylene was distilled off, the residue was made alkaline with a 50% potassium carbonate solution, and extracted with ether. The dried extract was vacuum distilled. The fraction with a bp of 153-156°C (10 mm) was collected. Two grams (22%) of V (R = R' = C_6H_5) was obtained, a viscous light-yellow liquid which quickly darkened on standing, n_D^{20} 1.5520. Found %: C 82.50; H 8.30; N 9.15. $C_{21}H_{26}N_2$. Calculated %: C 82.30; H 8.55; N 9.14.

1-Benzyl-2,2,6,6-tetramethyl-4-benzyliminopiperidine (V, R = R' = $C_6H_5CH_2$). A mixture of 5 g of IV, 4.74 g of benzylamine, 25 ml of toluene, and several drops of glacial acetic acid was boiled for 13 h in a flask to which a Dean and Stark trap was attached. Further treatment was carried out as in the preceding experiment. A total of 2.05 g (20.7%) of V (R = R' = $C_6H_5CH_2$) was obtained, bp 128-130° (1.5 mm). Found %: C 82.10; H 9.32; N 8.45. $C_{23}H_{30}N_2$. Calculated %: C 82.58; H 9.04; N 8.37.

2,2,6,6-Tetramethyl-4-phenyliminopiperidine (V, R = C_6H_5; R' = H). A mixture of 10 g of I, 9 g of aniline, 50 ml of xylene, and 0.5 ml of glacial acetic acid was boiled in a flask to which a Dean and Stark trap was attached. The xylene was distilled off, the residue was treated with a 50% potassium carbonate solution and extracted with ether. The dried extract was vacuum distilled. The fraction with a bp of 125-127°C (3 mm) was collected. The yield was 5.2 g (35%). The substance crystallized upon cooling (colorless crystals, mp 41-42°C). The substance was highly soluble in the usual organic solvents and poorly soluble in water. Found %: C 77.94; H 9.60; N 12.14. $C_{15}H_{22}N_2$. Calculated %: C 78.20; H 9.62; N 12.16.

2,6,6,6-Tetramethyl-4-benzyliminopiperidine (V, R = $C_6H_5CH_2$, R' = H). This compound was obtained analogously from 10 g of I and 10.35 g of benzylamine. The yield was 7.6 g (48.2%), light yellow liquid, bp 137-139°C (1 mm), n_D^{20} 1.5315 [5]. Found %: C 78.67; H 9.61; N 11.28. $C_{16}H_{24}N_2$. Calculated %: C 78.64; H 9.89; N 11.46.

1-Acetyl-2,2,6,6-tetramethyl-4-phenyliminopiperidine (V, R = C_6H_5; R' = CH_3CO). To a solution of 5 g of V (R = C_6H_5; R' = H) in 40 ml of anhydrous benzene was added 3.2 g of triethylamine and then after cooling to 0-5°C, a solution of 25 g of acetyl chloride in 10 ml of benzene was added with agitation. The mixture was agitated for 6 h at room temperature, and the triethylamine hydrochloride precipitate was filtered off and washed with benzene. The combined benzene solutions were washed with a 20% aqueous potassium carbonate solution, dried with magnesium sulfate, and evaporated. A total of 3.6 g (61%) of V

($R = C_6H_5$; $R' = CH_3CO$) was obtained as a viscous liquid which was highly soluble in the usual organic solvents and poorly soluble in water, bp 138-140°C (0.4 mm). Found %: C 75.00; H 8.81; N 9.92. $C_{17}H_{24}N_2O$. Calculated %: C 74.95; H 8.88; N 10.28.

1-Acetyl-2,2,6,6-tetramethyl-4-benzyliminopiperidine (V, $R = C_6H_5CH_2$; $R' = CH_3CO$). This compound was analogously obtained from 6.5 g of V ($R = C_6H_5CH_2$; $R' = H$) with a yield of 4.6 g (60.4%), bp 158-160°C (0.7 mm). Found %: C 75.66; H 9.27; N 9.65. $C_{18}H_{26}N_2O$. Calculated %: C 75.47; H 9.15; N 9.78.

2,2,6,6-Tetramethyl-4-phenylaminopiperidine (VI, $R = C_6H_5$; $R' = H$). A. A total of 13.85 g of V ($R = C_6H_5$; $R' = COCH_3$) was reduced with 7.4 g of lithium aluminum hydride for 30 h in a boiling mixture of ether and benzene. The calculated amount of water was added, the solution was filtered, evaporated, and 5.57 g (47.5%) of VI ($R = C_6H_5$; $R' = H$) was obtained, bp 125-127°C (2 mm), mp 48-49°C. Found %: C 77.49; H 10.24; N 11.89. $C_{15}H_{24}N_2$. Calculated %: C 77.53; H 10.40; N 12.06. B. A total of 13.55 g of V ($R = C_6H_5$; $R' = H$) was reduced under the same conditions with 8.95 g of lithium aluminum hydride. Nine grams (66.1%) of VI ($R = C_6H_5$; $R' = H$) were obtained, mp 48-49°C. C. To 10.9 g of V ($R = C_6H_5$; $R' = H$) and 6.35 g of triethylamine dissolved in 90 ml of anhydrous benzene, then cooled to 0-5°C was added with agitation a solution of 9.5 g of phenylacetyl chloride in 10 ml of anhydrous benzene. After standing for 30 min at 5-10°C and 1 h at 18-20°C, the triethylamine hydrochloride precipitate was filtered off, the benzene filtrate was washed with a 20% potassium carbonate solution, dried, and evaporated. The residue, 16.05 g of V ($R = C_6H_5$; $R' = COCH_2C_6H_5$), was reduced with 7 g of lithium aluminum hydride for 30 h in a boiling mixture of ether and benzene without additional purification. The reduction product (10.2 g) was dissolved in 100 ml of absolute alcohol and hydrogenated in the presence of a platinum catalyst (from 1 g of platinum oxide). The catalyst was filtered off, the filtrate was evaporated, the residue was dissolved in 8% hydrochloric acid, the nonbasic substances were extracted with ether, and the aqueous layer was made alkaline with a 50% potassium carbonate solution and extracted with ether. The ether extract was evaporated. A total of 4.5 g (40.5%) of VI ($R = C_6H_5$; $R' = H$) was obtained, mp 48-49°C, bp 125-127°C (2 mm). The samples obtained by methods A, B, and C were identical in their mixed melting points and IR spectra.

1-Ethyl-2,2,6,6-tetramethyl-4-benzylaminopiperidine (VI, $R = C_6H_5CH_2$; $R' = C_2H_5$). A total of 7.35 g of V ($R = C_6H_5CH_2$; $R' = CH_3CO$) was reduced with 3.9 g of lithium aluminum hydride for 30 h in a boiling mixture of ether and benzene. The mixture was treated as described above and 5.9 g of V ($R = C_6H_5CH_2$; $R' = C_2H_5$) was obtained, which was dissolved in 90 ml of absolute alcohol without further purification and hydrogenated at room temperature and a pressure of 30-40 cm water gauge in the presence of 0.5 g of platinum oxide. A total of 4.2 g (59.6%) of VI ($R = C_6H_5CH_2$; $R' = C_2H_5$) was obtained as a colorless oily liquid which was highly soluble in the usual organic solvents, bp 142-144°C (1 mm), n_D^{20} 1.5040. Found %: C 78.67; H 10.94; N 10.12. $C_{18}H_3ON_2$. Calculated %: C 78.77; H 11.01; N 10.20.

1-Ethyl-2,2,6,6-tetramethyl-4-(N-methyl-N-benzylamino) Piperidine. A mixture of 4 g of VI ($R = C_6H_5CH_2$; $R' = C_2H_5$), 2.02 g of formic acid, 1.37 g of 37% formalin, and 2.6 ml of water was heated for 15 h on a boiling water bath, cooled, made alkaline with a 50% potassium carbonate solution, and extracted with ether. After distilling the ether off, 2.8 g (66.5%) of N'-methylated VI ($R = C_6H_5CH_2$; $R' = C_2H_5$) was obtained, colorless liquid, bp 145-147°C (4 mm), n_D^{20} 1.5110. Found %: C 79.02; H 11.19; N 10.06. $C_{19}H_{32}N_2$. Calculated %: C 79.10; H 11.18; N 9.71. The dihydrochloride is composed of colorless crystals, mp 75-77°C (decomp.). Found %: Cl 17.77; N 6.82. $C_{19}H_{32}N_2 \cdot 2HCl \cdot 2H_2O$. Calculated %: Cl 17.99; N 7.05. The monoiodomethylate consists of colorless crystals, mp 204-206°C. Found %: I 29.22; N 9.71. $C_{20}H_{35}IN_2$. Calculated %: I 29.48; N 6.51.

1-Ethyl-2,2,6,6-tetramethyl-4-phenylaminopiperidine (VI, $R = C_6H_5$; $R' = C_2H_5$). A mixture of 10 g of V ($R = C_6H_5$; $R' = H$), 10 g of ethyl iodide, 13.8 g of anhydrous sodium carbonate, and 100 ml of toluene was boiled for 48 h. After removing the precipitate due to the inorganic salts, the solution was evaporated in vacuo, and the residue of 10.1 g of V ($R = C_6H_5$; $R' = C_2H_5$) was dissolved in 130 ml of absolute alcohol without further purification and hydrogenated under the usual conditions with 0.5 g of platinum oxide. The catalyst was filtered off, the solution was evaporated, and the residue was distilled. A total of 1.5 g (13.2%) of VI ($R = C_6H_5$; $R' = C_2H_5$) was obtained as a viscous liquid, bp 142-145°C (4 mm). Found %: C 78.00; H 10.55; N 10.44. $C_{17}H_{28}N_2$. Calculated %: C 78.40; H 10.83; N 10.75.

1-(β-Phenylethyl)-2,2,6,6-tetramethyl-4-phenylaminopiperidine (VI, $R = C_6H_5$; $R' = C_6H_5CH_2CH_2$). A mixture of 12 g of V ($R = C_6H_5$; $R' = H$), 14 g of β-phenylethyl bromide, 16.6 g of anhydrous sodium carbonate, 150 ml of xylene, and a catalytic amount of potassium iodide was boiled with agitation for 48 h. The inorganic salt precipitate was filtered off, the solution was evaporated in vacuo, and the 21.9 g of V ($R = C_6H_5$, $R' = C_6H_5CH_2CH_2$) obtained was dissolved in 400 ml of absolute alcohol without further purification

and hydrogenated under the usual conditions with 1 g of platinum oxide. The catalyst was filtered off. The alcoholic solution was evaporated, the residue was dissolved in 8% hydrochloric acid, the nonbasic substances were extracted with ether, then the hydrochloric acid solution was made alkaline with an excess of potassium carbonate and extracted with ether. After drying and evaporating the ether extract, 11.1 g of a crystallizable mass was obtained which was recrystallized from 25 ml of n-hexane. A total of 5.04 g (28.8%) of VI ($R = C_6H_5$; $R' = C_6H_5CH_2CH_2$) was obtained, colorless crystals, mp 96-97°C. The substance was highly soluble in the usual organic solvents and poorly soluble in hexane and water. Found %: C 82.39; H 9.72; N 8.17. $C_{23}H_{32}N_2$. Calculated %: C 82.08; H 9.58; N 8.32.

1-Ethyl-2,2,6,6-tetramethyl-4-(N-acetyl-N-benzylamino)piperidine (VII, $R = C_6H_5CH_2$; $R' = C_2H_5$; $R'' = CH_3$). To a solution of 4.07 g of VI ($R = C_6H_5CH_2$, $R' = C_2H_5$) and 2.54 g of triethylamine in 40 ml of benzene which was then cooled to 0-5°C was added with agitation 1.93 g of acetyl chloride in 10 ml of benzene, the mixture was agitated for 6 h at room temperature, the triethylamine hydrochloride precipitate was filtered off, the filtrate was washed with a 20% potassium carbonate solution, dried, and evaporated. A total of 1.6 g (34%) of VII ($R = C_6H_5CH_2$; $R' = C_2H_5$; $R'' = CH_3$) was obtained, bp 158-160°C (0.4 mm). Found %: C 75.63; H 10.20; N 8.69. $C_{20}H_{32}N_2O$. Calculated %: C 75.89; H 10.19; N 8.85. The D-tartrate consisted of colorless crystals, highly soluble in water, mp 169-171°C. Found %: C 61.25; H 8.51; N 5.86. $C_{20}H_{32}N_2O \cdot C_4H_6O_6$. Calculated %: C 61.77; H 8.20; N 6.00.

1-Ethyl-2,2,6,6-tetramethyl-4-(N-propionyl-N-benzylamino) piperidine (VII, $R = C_6H_5CH_2$; $R' = R'' = C_2H_5$). This compound was analogously obtained from 5.3 g of VI ($R = C_6H_5CH_2$, $R' = C_2H_5$), 3.26 g of triethylamine in 40 ml of benzene, and 2.98 g of propionyl chloride in 10 ml of benzene. The yield was 0.64 g (10%), bp 157-160°C (0.3 mm). Found %: C 76.14; H 10.43; N 8.47. $C_{21}H_{34}N_2O$. Calculated %: C 76.31; H 10.36; N 8.47.

The D-tartrate consisted of colorless crystals highly soluble in water, mp 85-87°C (decomp.). Found %: C 60.13; H 8.40; N 5.31. $C_{21}H_{35}N_2O \cdot C_4H_6O_6 \cdot H_2O$. Calculated %: C 60.21; H 8.49; N 5.61.

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