ACYL AND AROYL DERIVATIVES OF 4-AMINO-1,2,5-TRIMETHYLPIPERIDINE

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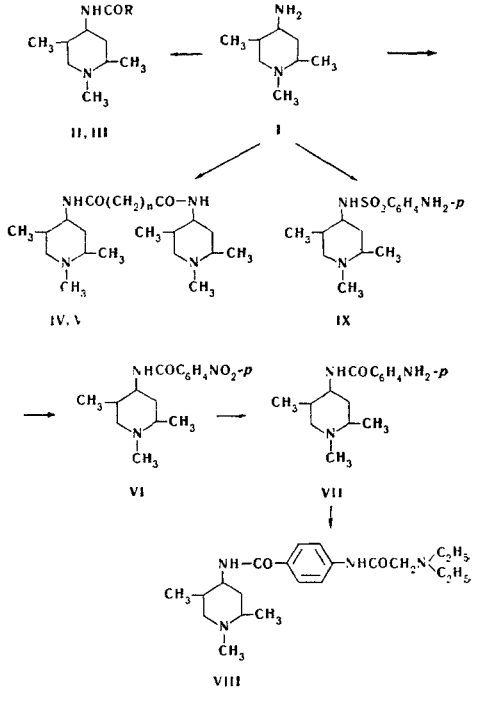
N-Substituted amides of some aliphatic and aromatic acids, respectively, have been obtained by the acylation and aroylation of 4-amino-1,2,5-trimethylpiperidine.

In preceding communications [1, 2], the preparation and some reactions of 4-amino-1,2,5-trimethylpiperidine (I) have been described. In view of the fact that the substituted amides of a number of acids frequently exhibit physiological activity we decided to use the substituted aminopiperidine I to synthesize the corresponding amides of some aliphatic and aromatic acids.

By the direct acylation and aroylation of I with acetyl, oxalyl, adipyl, benzoyl, and p-nitrobenzoyl acids we obtained 4-acetamido-, 4-benzamido-, and 4-p-nitrobenzamido-1,2,5-trimethylpiperidines (II, III, and VI, respectively), and the bis(1,2,5-trimethylpiperidin-4-yl)amides of oxalic and adipic acids (VI and V).



II R=CH_3, III R=C_6H_5; IV n=0, V n=4

From VI by reduction of the nitro group and the subsequent acylation of the 4-p-aminobenzamido-1,2,5-trimethylpiperidine (VII) so formed with diethylaminoacetyl chloride we obtained 4-[p-(diethylaminoacetamido)benzamido]-1,2,5-trimethylpiperidine (VIII). With p-acetamidobenzenesulfonyl chloride we synthesized the (1,2,5-trimethylpiperid-4-yl)amide of sulfanilic acid (IX).

As a rule, the acylation and aroylation reactions took place with satisfactory yields.

EXPERIMENTAL

Acylation and aroylation of 4-amino-1,2,5-trimethylpiperidine. A) With cooling, 18 ml (0.18 mole) of acetic anhydride was added to 3 g (0.021 mole) of I in 50 ml of 20% aqueous caustic soda, and the mixture was stirred for 3 hr. Then it was saturated with caustic soda and the organic base was extracted with a mixture of ether and benzene. This gave 3.4 g (0.18 mole) of II (yield 86%) mp 150–151° C (from ether). Found, %: N 15.02, 14.89. Calculated for $C_{10}H_{20}N_2O$, %: N 15.21.

B) At 50° C, 17 ml (0.1 mole) of benzoyl chloride in 20 ml of benzene was added to a mixture of 5 g (0.035 mole) of I, 130 ml of anhydrous benzene, and 30 ml of triethylamine. The mixture was stirred for 24 hr and then the benzene and triethylamine were distilled off. The residue was dissolved in water, treated with caustic potash, and extracted with ether. This gave 4.2 g (0.017 mole) of III (yield 48.6%) in the form of white crystals with mp 166–167° C. Found, %: N 11.29, 11.40. Calculated for $C_{15}H_{22}N_2O$, %: N 11.43.

C) With cooling, 2 g (0.016 mole) of oxalyl chloride in 30 ml of benzene was added to a mixture of 4 g (0.028 mole) of I, 12 ml of triethylamine, and 50 ml of benzene. The mixture was heated at 60° C for 15 min. After 12 hr, the benzene and triethylamine were distilled off and the residue was dissolved in water and acidified with dilute hydrochloric acid. The neutral substances were extracted with ether and the aqueous solution was treated with sodium carbonate. The white precipitate that deposited was insoluble in ether and benzene. The yield of IV was 3 g (0.009 mole; 64%), mp 248–250° C (from ethanol). Found, %: C 63.72, 63.80; H 9.95, 10.09; N 16.02. Calculated for $C_{18}H_{34}N_4O_2$, %: C 64.00; H 10.05; N 16.75. **Dipicrate of IV,** mp 247–248° C (from ethanol). Found, %: N 17.30. Calculated for $C_{18}H_{34}N_4O_2 \cdot 2C_6H_3(NO_2)_3OH$, %: N 17.59. The IR spectrum of IV exhibited the following bands: 1664 cm^{-1} (—CO—); 1537, 3300, and 3080 cm^{-1} (—NH—), and 2790 cm^{-1} (N≡).

D) The experiment was carried out similarly with 3.5 g (0.024 mole) of I, 12 ml of triethylamine, 2.5 g (0.014 mole) of adipoyl chloride, and 80 ml of benzene. This gave 4.5 g (0.011 mole) of V (yield 91.6%), mp 272–274° C (from ethanol). Found, %: C 66.80, 66.88; H 10.84, 10.96; N 14.63, 14.40. Calculated for $C_{22}H_{42}N_4O_2$, %: C 67.00; H 10.62; N 14.21. **Dipicrate of V,** mp 217–218° C (from ethanol). Found, %: N 16.12, 16.31. Calculated for $C_{22}H_{42}N_4O_2 \cdot 2C_6H_3(NO_2)_3OH$, %: N 16.43. The IR spectrum of V showed the following bands: 1644 cm^{-1} (—CO—); 1563, 3300, and 3100 cm^{-1} (—NH—), and 2790 cm^{-1} (N≡).

4-[p-(Diethylaminoacetamido)benzamide]-1,2,5-trimethylpiperidine. A) A mixture of 3.7 g (0.025 mole) of I, 6 g (0.032 mole) of p-nitrobenzoyl chloride, 15 ml of triethylamine, and 100 ml of benzene was heated at 60° C for 1 hr. After the usual working up, 6.3 g (0.022 mole) of VI was obtained (yield 88%), mp 193–195° C (from benzene). **Picrate of VI,** mp 236–237° C (from ethanol). Found, %: N 15.80, 15.84. Calculated for $C_{15}H_{21}N_3O_3 \cdot C_6H_3(NO_2)_3OH$, %: N 16.15.

B) Compound VI (6 g; 0.02 mole), dissolved in 100 ml of absolute ethanol, was hydrogenated at room temperature in the presence of palladium on carbon, 1240 ml of hydrogen being absorbed. The ethanolic solution yielded 4.5 g (0.017 mole; 85%) of VII, mp 165–166° C (from gasoline). Found, %: N 15.73, 15.32. Calculated for $C_{15}H_{23}N_3O$, %: N 16.09.

C) A mixture of 1.2 g (4.6 mM) of VII, 0.5 ml of pyridine, 0.63 g (5.6 mM) of monochloroacetyl chloride, and 30 ml of chloroform was heated to the boil for 5 hr. Then the solvent was distilled off and the residue was treated with 50 ml of absolute ethanol and 5 ml of di-

ethylamine. The mixture was heated to the boil for 10 hr and then the ethanol and the excess of diethylamine were distilled off. The residue was dissolved in water and acidified. The neutral reaction products were extracted with ether and the aqueous solution was saturated with sodium carbonate. The organic bases that separated out were extracted with benzene, giving 0.25 g (0.7 mM) of **VIII** in the form of crystals deliquescing in the air; after washing with petroleum ether, mp 114–124° C. Found, %: N 14.19. Calculated for $C_{21}H_{34}N_4O_2$, %: N 14.97. **Dihydrochloride of VIII,** crystals rapidly deliquescing in the air. Found, %: Cl 16.22, 16.11. Calculated for $C_{21}H_{34}N_4O_2$, %: Cl 15.84. **Dipicrate of VIII,** mp 238–239° C (from ethanol). Found, %: N 16.31, 15.04. Calculated for $C_{21}H_{34}N_4O_2 \cdot 2C_6H_3(NO_2)_3OH$, %: N 16.82.

N-(1,2,5-Trimethylpiperid-4-yl)sulfanilamide. With cooling, 11.4 g (0.048 mole) of p-acetamidobenzenesulfonyl chloride was added in portions to 5.35 g (0.038 mole) of **I** in 20 ml of pyridine. The reaction was accompanied by pronounced heating and resinification. The mixture was diluted with water and the oil that floated to the top was extracted with benzene. The benzene was distilled off and the residue was treated with 100 ml of 6% caustic soda solution and heated at 100° C for 1.5 hr. Then the solution was acidified and the neutral reaction products were extracted with ether. The aqueous solution was treated with sodium carbonate and ether. The ethereal extract yielded 1.73 g (0.006 mole) of **IX** in the form of white crystals with mp 191–193° C (from acetone). Found, %: N 14.09, 13.98. Calculated for $C_{14}H_{23}N_3O_2S$, %: N 14.14.

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SOME METHYL AND BROMO DERIVATIVES OF 9-AMINO-6-NITROACRIDINE

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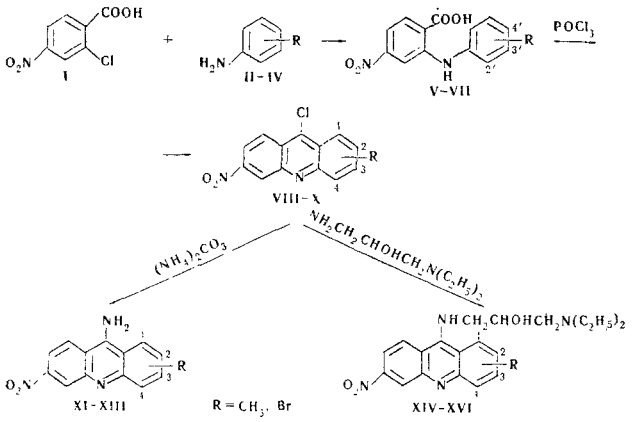
2-Methyl, 4-methyl, and 2-bromo derivatives of 9-amino-6-nitroacridine and of 9-(γ-diethylamino-β-hydroxypropylamino)-6-nitroacridine, and a number of intermediates in their synthesis, have been obtained.

It is known that alkoxy-substituted 9-amino-6-nitroacridines possess antimicrobial activity [1, 2]. At the same time, derivatives of 9-amino-6-nitroacridine containing other substituents have been studied inadequately. It appeared of interest to synthesize for biological tests some of its methyl and bromo derivatives. The synthesis was carried out in the following way:



The diphenylamine-2-carboxylic acids (V–VII) were obtained by the Ullman reaction from 2-chloro-4-nitrobenzoic acid (I) and the appropriate arylamines (o- and p-toluenes and p-bromoaniline) (II–IV). The acids **V–VII** were cyclized by treatment with phosphorus oxychloride in chloroform into the 9-chloro-6-nitroacridine derivatives (XI–XIII) or 9-(γ-diethylamino-β-hydroxypropylamino)-6-nitroacridines XIV–XVI.

Compounds V–XVI (see table) have been obtained for the first time, with the exception of 4'-methyl-5-nitrodiphenylamine-2-carboxylic acid [3]. The 2-methyl, 4-methyl-, and 2-bromo derivatives of 9-(γ-diethylamino-β-hydroxypropylamino)-6-nitroacridine (**XIV–XVI**) were isolated in the form of the dihydrochlorides, which are readily soluble in water. According to preliminary results, their antibacterial activity is higher than that of the corresponding methoxy derivatives [2]. The biological tests were carried out by I. Yu. Kholupyak under the direction of O. V. Chuiko.

EXPERIMENTAL

Diphenylamine-2-carboxylic acids (V–VII). A mixture of 0.15 mole of 2-chloro-4-nitrobenzoic acid, 0.3 mole of the required arylamine (o-toluidine, p-toluidine, or p-bromoaniline), 30 g of potassium carbonate, and 1 g of copper powder was heated in 150 ml of