N-ARYL-N-[1,2,5-TRIMETHYLPIPERIDYL-4-PROPAMIDES] AND THEIR ANALGESIC ACTIVITY

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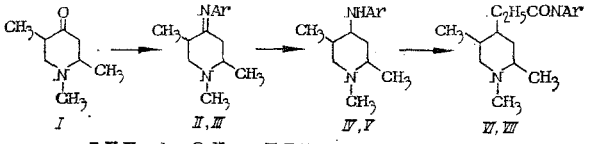
In an attempt to find effective analgesics which are nontoxic and nonaddictive, considerable attention has been given to esters of tertiary γ-piperidoles. At the present time, prodine (1,3-dimethyl-4-phenyl-4-propionoxypiperidine) and promedol (1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine) are widely used in medicine [3, 8]. It has been shown that the stereosiomeric α- and β-prodine, and also the stereoisomeric promedol, isopromedol, and α-promedol differ considerably from each other in analgesic activity [7, 8].

At the present time, propionic acid amides with an aryl or γ-piperidyl substituent are being widely studied as possible effective analgesics. These compounds are structurally analogous to the γ-piperidinol propionates.

The discovery of the analgesic properties of one member of this series —N-[1-(β-phenylethyl)piperidyl-4]propanilide (fentanyl) — stimulated work on the synthesis of this compound and its analogs. The present communication describes two compounds of this type.

The intermediate promedol derivative — 1,2,5-trimethylpiperidine-4-one (I) — was used as starting material for this synthesis [2]. The condensation of this ketone with aniline, and also with p-toluidine to give N-(1,2,5-trimethylpiperidylidene-4)aniline (II) and p-methylaniline (III) are described in [4]. The first of these Schiff's bases was reduced with sodium borohydride to 1,2,5-trimethyl-4-phenylaminopiperidine (IV) which was isolated as a mixture of the δ- and γ-isomers in the ratio of ∿1:1 [9]. Analogously, the reduction of compound III gave 1,2,5-trimethyl-4-p-tolylaminopiperidine (V). The δ- and γ-isomers, which have chromatographic mobilities very similar to the isomers of IV, were separated by column chromatography.



The amines IV and V (either individual isomers or mixtures of isomers) gave N-(1,2,5-trimethylpiperidyl-4)-propa-p-methylanilide (VII) when reacted with propionic anhydride.

The analide VI, obtained from the δ-isomer of the amine IV, is a crystalline substance; its hydrochloride is stable in air. The analogous anilide of the corresponding γ-isomer of compound IV is a viscous liquid whose hydrochloride is very hygroscopic. From a mixture of the isomers of the amine IV was obtained the propanilide VI (mixture of isomers); it was converted to the stable nonhygroscopic hydrochloride. The results of the pharmacological study of this compound are given below.

Propionylation of the mixture of isomers of the amine V gave one of the isomers of p-methylanilide VII in crystalline form (gives a stable hydrochloride), and also a mixture of isomers.

The patent [10] describes the preparation and results of a study of the analgesic activity of N-(1,2,5-trimethylpiperidyl-4)propanilide (VI). The method of preparation differs from ours; the final stage of the synthesis was hydrogenation in the presence of palladium

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with simultaneous N-methylation of N-(2,5-dimethylpyridyl-4)propanilide. The compounds studied were found to possess no analgesic activity.

EXPERIMENTAL CHEMISTRY

Infrared spectra were taken on a Specord IR-75 (GDR) instrument; samples were measured as films between KBr plates and as CCl_4 solutions (in a KBr cell). Mass spectra were obtained using an MX-1303 with direct introduction of the sample into the ion source at an ionization voltage of 70 V and a temperature of 60-90°C. TLC was carried out using standard plates with aluminum oxide activity 2.

1,2,5-Trimethyl-4-(p-tolylamino)piperidine (V). A. A solution of 1.19 g (5 mmoles) of the Schiff's base III in 40 ml of ethanol was added with mixing to 2 g (0.053 mmoles) of sodium borohydride. The mixture was refluxed for 7 hours, then cooled and poured into 160 ml of water and heated until no more hydrogen was evolved. The alcohol and some of the water were distilled off. The reaction product was extracted with ether and the ether extract dried with sodium sulfate. Evaporation of the ether gave 1.17 g (98%) of a mixture of the isomers of the base V as a colorless liquid which was chromatographed on aluminum oxide (360 g; column: h = 75 cm, d = 2.3 cm, eluant — a mixture of hexane and ethyl acetate 5:1). The δ-isomer of compound V (0.29 g; 25%) was eluted first as a viscous, bright-yellow liquid, R_f 0.65 (hexane—ethyl acetate, 2:1). IR spectrum, ν, cm^{-1}: 3400 (N—H), 2775 (N—CH_3). Found, %: C 77.7; H 10.6; N 11.9. M^+ 232. $C_{15}H_{24}N_2$. Calculated, %: C 77.6; H 10.3; N 12.1. M 232.

Last to be eluted from the column was 0.36 g (31%) of the γ-isomer of compound V as a viscous yellow liquid, R_f 0.23. IR spectrum, ν, cm^{-1}: 3340 (N—H associated), 2780 (N—CH_3). Found, %: C 77.4; H 10.5; N 12.0. M^+ 232. $C_{15}H_{24}N_2$. Calculated, %: C 77.6; H 10.3; N 12.1. M 232.

B. Freshly prepared Schiff's base III (6.7 g; 29.5 mmoles) in 100 ml of ethanol was hydrogenated in the presence of 2 g of pyrophoric nickel. The catalyst was filtered off and the filtrate evaporated. The residue was distilled to give 1.5 g (22%) of starting material III, bp 55-60°C (2 mm), n_D^{22} 1.5130, and 4.97 g (72.6%) of a mixture of isomers of compound V, bp 130-134°C (2 mm), n_D^{22} 1.5430; R_f 0.65 and 0.23.

N-(1,2,5-Trimethylpiperidyl-4)-propanilide (VI). A. A solution of 1.7 g (7.8 mmoles) of the δ-isomer of the amine IV in 5 ml (40 mmoles) of propionic anhydride was refluxed for 9 hours. After cooling, 50 ml of water was added and the solution saturated with sodium hydroxide. The reaction product was extracted with ether, and the ether extract dried with magnesium sulfate. After evaporation of the ether, the residue (3.68 g) yielded 2.03 g (83.3%) of the hydrochloride of VI (colorless crystals, sublimed) mp 216-217°C (from acetone; sealed tube). Found, %: Cl 11.7. $C_{17}H_{26}N_2O \cdot HCl$. Calculated, %: Cl 11.4.

Decomposition of 0.32 g of the hydrochloride gave 0.24 g (85%) of the base VI as a liquid, which crystallized on standing to give colorless crystals with mp 55-57°C (from petroleum ether), R_f 0.52 (hexane—ethyl acetate, 2:1). IR spectrum, ν, cm^{-1}: 1660 (C=O of the tertiary amide). Found, %: C 74.4; H 9.5; N 10.2. M^+ 274. $C_{17}H_{26}N_2O$. Calculated, %: C 74.4; H 9.5; N 10.2. M 274.

B. In the same way, 0.95 g (4.4 mmoles) of the γ-isomer of the amine IV and 3 ml (24 mmoles) of propionic anhydride gave 1.03 g of the base, which was chromatographed on aluminum oxide (200 g; column: h = 50 cm, d = 2.3 cm, eluant — hexane and ethyl acetate, 5:1) to give 0.21 g (17.4%) of compound VI as bright yellow liquid, R_f 0.39. IR spectrum, ν, cm^{-1}: 1650 (C=O, tertiary amide). Found, %: N 10.3. M^+ 274. $C_{17}H_{26}N_2O$. Calculated, %: N 10.2. M 274.

The hydrochloride was a very hygroscopic crystalline material. Subsequently, 0.41 g (34%) of the third isomer of VI (undetermined configuration) was isolated as a similar liquid, R_f 0.16. IR spectrum, ν, cm^{-1}: 1660 (C=O, tertiary amide). Found, %: N 10.0. M^+ 274. $C_{17}H_{26}N_2O$. Calculated, %: N 10.2. M 274.

C. Similarly, 3.28 g (15 mmoles) of the amine IV (mixture of isomers) and 18 ml (140 mmoles) of propionic anhydride gave 3.88 g (92.5%) of the base VI (mixture of isomers: R_f 0.52, 0.39, 0.16), which were converted to the hydrochlorides. The mixture of hydrochlorides (3.84 g, 80%) was isolated as a colorless crystalline material with mp 215-217°C (from acetone; sealed tube). Found, %: Cl 11.7. $C_{17}H_{26}N_2O \cdot HCl$. Calculated, %: Cl 11.4.

TABLE 1. Effect of Propanilide VI on Pain Sensitivity of Mice to Heat (A), Mechanical (B), and Electric-Shock (C) Stimulation

Compound	Dose, mg/kg	A: latent period of defensive react. % of initial				B: suppression of squeaking react., %				C
		5 min	15 min	30 min	60 min	5 min	15 min	30 min	60 min	pain thresh. aft. 20 min, % of initial
Propanilide VI	5	126	145	126	0	0	0	0	—	—
	10	253*	280*	150	...	16	16	0	...	—
	15	298*	328*	194*	...	33*	33*	0	...	—
	20	275*	362*	275*	210	66*	50*	33*	16	—
	25	380*	439*	479*	360*	66*	100*	100*	50*	118*
Promedol	5	210*	191*	125	...	66*	83*	16	0	—
	10	374*	...	268*	231*	100*		33*	16	113
	25	—	—	—	—	—	—	—	—	127*
Morphine	5	144	228*	270*	238*	0	0	33*	...	—
	10	...	390*	...	...	...	...	50*	...	—
Fentanyl	0,1	...	179*	...	...	83*	0	...	...	—
	0,5	...	642*	...	...	100*	100*	50*	...	—

*$P < 0.05$.

N-(1,2,5-Trimethylpiperidyl-4)propa-p-methylanilide (VII). Using the method described above, 4.95 g (21.4 mmoles) of a mixture of the isomers of the amine V and 5 ml (40 mmoles) of propionic anhydride gave 4.06 g (66.2%) of the base VII, which was chromatographed on aluminum oxide (80 g; column: h = 20 cm, d = 2.3 cm, eluant — hexane and ethyl acetate, 1:1). One of the isomers of VII (0.6 g, 9.8%) was obtained as a bright-yellow liquid with R_f 0.52, which crystallized on standing to give colorless crystals mp 70-72°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 1650 (C=O, tertiary amide). Found, %: N 9.6; M^+ 288. $C_{18}H_{28}N_2O$. Calculated, %: N 9.7. M 288. Hydrochloride, mp 228-229°C (from acetone; sealed tube). Found, %: Cl 10.6. $C_{18}H_{28}N_2O \cdot HCl$. Calculated, %: Cl 10.9. At the end of the chromatographic run 2.5 g of a mixture of compounds with R_f 0.52, 0.47, 0.36, and 0.1 was eluted.

EXPERIMENTAL BIOLOGY

The LD_{50} for intraperitoneal injection of the propanilide VI into mice was 180 mg/kg. Death was preceded by motor excitation accompanied by symptoms such as the Straub phenomenon, circling, decrease in rectal temperature to 33-34°C, breathing disturbances, and convulsions, all of which are characteristic of the action of narcotic analgesics. In nontoxic doses (10-100 mg/kg), intraperitoneal injection of the test compound into mice caused excitation lasting from 20 min to 2 hours, and in rats, catalepsy varying in seriousness (up to three Wirth points [11]).

The analgesic activity of the propanilide VI on intraperitoneal injection was studied in 140 mice weighing from 15-20 g using the following tests: the "tail-clip" test for mechanically-stimulated pain (Haffner modification [6]), thermal stimulation using the "hot plate" method [1], and electrical shock stimulation by the method of Polevois [5].

As can be seen from Table 1, these tests showed the propanilide VI to possess some pain-relieving properties. The analgesic threshold occurs at a dose of 10 mg/kg; injection of this amount at 5 and 15 minutes increased the pain threshold by 130% in the "hot plate" test, and suppressed reaction to mechanically produced pain by 16%.

The propanilide VI exhibited pronounced pain-relieving properties toward both heat and mechanically stimulated pain at a dosage of 20 mg/kg and an even greater effect at a dosage of 25 mg/kg. For the first of these, the threshold increased by 213% (15 minutes), and for the second, by 290% (15 minutes), and 327% (30 minutes); reaction to the "tail clip" was suppressed in all mice.

In the case of the more severe electrically-stimulated pain, the test compound at a dosage of 25 mg/kg (single test) acted as an analgesic on all animals, increasing the pain threshold on the average by 2.2 V.

The duration of the effect of the propanilide VI was closely related to the dose and varied from 15 minutes (10 mg/kg) to 1 hour (25 mg/kg). A biological study of both the δ-isomer and a mixture of the δ- and γ-isomers of compound VI showed that neither the acute toxicity nor the general character of activity nor the effectiveness of analgesic activity varied between isomers.

A comparison shows that the propanilide VI was a less effective pain reliever than promedol, morphine, and fentanyl in all the tests.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF AMINOMETHYL DERIVATIVES OF 4-HYDROXY-5-METHOXYINDOLE

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During the course of a search for compounds with antiviral activity, the 2-, 3-, and 7-aminomethyl derivatives of 1-phenyl-2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromoindole [1] have been synthesized.

The hydroxy group in compound I was protected by acetylation with acetic anhydride, giving the O-acetyl derivative (II), which on bromination with N-bromosuccinimide was converted to the 2-promomethyl derivative (III). Treatment of III with isopropylamine gave 1-phenyl-2-isopropylaminomethyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromoindole (IV), which was isolated as the hydrochloride.

Aminomethylation of compound I gave the 7-aminomethyl derivatives 4-hydroxy-5-methoxyindole (V, VI), also isolated as the hydrochlorides.

Hydrolysis of compound I with alcoholic base gave the 3-carboxylic acid (VII), which on refluxing in glycol was converted to 1-phenyl-2-methyl-4-hydroxy-5-methoxy-6-bromoindole (VIII): Methylation of the latter with dimethyl sulfate in the presence of potassium hydroxide gave 1-phenyl-2-methyl-4,5-dimethoxy-6-bromoindole (IX). Aminomethylation of IX with formaldehyde and dimethylamine hydrochloride gave 1-phenyl-2-methyl-3-dimethylaminomethyl-4,5-dimethoxy-6-bromoindole (X).

The antiviral properties of compounds I, IV-VII, and X were studied. The 3-aminomethyl derivative X exhibited pronounced antiviral activity against influenze type A virus in *in*

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