ESTERS OF HETEROCYCLIC γ-AMINO-ALCOHOLS

II. BENZOATES, p-NITRO- AND p-AMINOBENZOATES OF 1,2,5-TRIMETHYL-5-AMINOMETHYL-4-PHENYLPIPERIDIN-4-OLS

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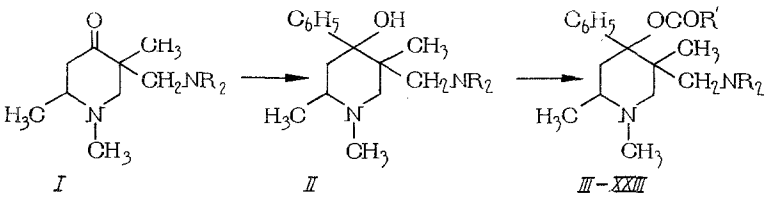
In this work the benzoates, p-nitro- and p-aminobenzoates of 1,2,5-trimethyl-5-aminomethyl-4-phenylpiperidin-4-ols were synthesized.

The benzoic (III–IX) and the p-nitrobenzoic (X–XVI) esters were prepared by the action of the acid chloride of benzoic and p-nitrobenzoic acids on the lithium alcoholate of 1,2,5-trimethyl-5-aminomethyl-4-phenylpiperidin-4-ols (II) made by the reaction of phenyllithium with 1,2,5-trimethyl-5-aminomethyl-piperid-4-ones (I). Some esters were also prepared by the reaction of acid chlorides with the same amino alcohols (II).



I II III–XXIII

Reduction of the p-nitrobenzoic esters X–XVI with stannous chloride and hydrochloric acid yielded the p-aminobenzoic esters (XVII–XXIII).

Experimental data on the synthesized esters is given in Table 1.

The esters prepared were very viscous liquids, difficult to distill in vacuo. Therefore the majority of them were purified and characterized only as their hydrochloride salts. The methyl iodides of the benzoates III and IV were also prepared. The pH values of 1% aqueous solutions of the salts of the most active esters were determined.

Pharmacological investigation revealed that the dihydrochlorides and the dimethyliodides of the benzoates caused deep and prolonged terminal and infiltrating anesthesia. For the majority of the compounds of this group, subcutaneous dosage of guinea pigs with a 0.5% solution produced anesthesia lasting 60-200 min, which is significantly longer than the action of xycain.

For terminal anesthesia, the dihydrochlorides were significantly more effective than the dimethyliodides, which, apparently, was due to the poor permeability of the latter through tissue membranes. The dihydrochlorides IV–VI were the most active. The longest-lasting of all were the compounds IV · 2HCl and V · 2HCl. An unfavorable aspect of the majority of the benzoates was their irritating action, observed even at 0.5% concentration. The LD_{50} of the dihydrochlorides varied from 186 to 629 mg/kg. The dimethyliodides were significantly more toxic (LD_{50} 71-91 mg/kg).

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TABLE 1. Benzoates, p-Nitro- and p-Aminobenzoates of 1,2,5-Trimethyl-5-aminomethyl-4-phenylpiperidols

Compound	NR_2	R'	Yield, % (based on I)	Hydrochlorides		
				compound	pH	mp, °C
III	$N(CH_3)_2$	C_6H_5	52,6*	III·2HCl	2,36	74—6**
IV	$N(C_2H_5)_2$	The same	38,9†	IV·2HCl	2,55	135—7
V	$N(n\text{-}C_3H_7)_2$	» »	71,5	V·2HCl	2,61	134—6
VI	$N(n\text{-}C_4H_9)_2$	» »	57,7	VI·2HCl	2,75	118—20
VII	$N(CH_2)_5$	» »	48,6	VII·2HCl	2,47	155—7
VIII	$N(CH_2)_6$	» »	42,3	VIII·2HCl	2,22	154—6
IX	$N(CH_2CH_2)_2O$	» »	40,1‡	IX·2HCl		80—2
X	$N(CH_3)_2$	$p\text{-}No_2C_6H_4$	70,5	X·2HCl		174—6
XI	$N(C_2H_5)_2$	The same	58,0	XI·2HCl		151—3
XII	$N(n\text{-}C_3H_7)_2$	» »	47,6	XII·2HCl		138—40
XIII	$N(n\text{-}C_4H_9)_2$	» »	36,3	XIII·2HCl		131—3
XIV	$N(CH_2)_5$	» »	44,2	XIV·2HCl		166—8
XV	$N(CH_2)_6$	» »	38,8	XV·2HCl		147—9
XVI	$N(CH_2CH_2)_2O$	» »	36,4	XVI·2HCl		163—5
XVII	$N(CH_3)_2$	$p\text{-}NH_2C_6H_4$	55,7	XVII·3HCl		192—4
XVIII	$N(C_2H_5)_2$	The same	58,1	XVIII·3HCl	1,46	142—4
XIX	$N(n\text{-}C_3H_7)_2$	» »	64,0	XIX·3HCl		170—2
XX	$N(n\text{-}C_4H_9)_2$	» »	52,2	XX·3HCl	3,01	171—3
XXI	$N(CH_2)_5$	» »	51,8	XXI·3HCl		187—9
XXII	$N(CH_2)_6$	» »	44,1	XXII·3HCl		156—8
XXIII	$N(CH_2CH_2)_2O$	» »	59,5	XXIII·3HCl		187—9

* Bp 160-175°C (0.5 mm). Found %: C 75.97, 75.56; H 8.49, 8.55; N 7.18, 7.33. $C_{24}H_{32}N_2O_2$. Calculated %: C 75.75; H 8.48; N 7.36. Dimethyliodide, mp 135-137°C (decomp., from alcohol with ether), characterized by iodine analysis.

† Bp 162-176°C (0.2 mm). Found %: N 6.75, 6.68. $C_{26}H_{36}N_2O_2$. Calculated %: N 6.86. Dimethyliodide, mp 78-79°C (decomp., from chloroform with ether), characterized by iodine analysis.

‡ Bp 201-203°C (0.5 mm). Found %: N 6.44, 6.70. $C_{26}H_{34}N_2O_3$. Calculated %: N 6.63.

** Melted with decomposition. III·2HCl and X·2HCl were recrystallized from alcohol with ether, XI·2HCl from acetone with ether, IV·2HCl–IX·2HCl and XII·2HCl–XVI·2HCl from chloroform with ether, XVII·3HCl–XXIII·3HCl from alcohol with ether. All the hydrochlorides were characterized by chlorine and nitrogen analysis.

p-Nitrobenzoates were noticeably inferior in their effectiveness to benzoates. The most prolonged infiltrating anesthesia was registered by the compounds XI·2HCl, XIV·2HCl and XV·2HCl. The terminal anesthesia of the p-nitrobenzoates was less pronounced and not prolonged. Compound XI·2HCl was an exception: it had a Renier index of 1248. The toxicity of the compounds of this group was small. They were all less toxic than xycain.

A very prolonged infiltration anesthesia was characteristic for the p-aminobenzoates. The high anesthetizing activity was retained in the series of compounds on applying them on the mucous membrane of a rabbit's eye. This was attributed, in the main, to the trihydrocholorides XVIII–XX. However, these compounds showed an irritating activity, which, as in the case of the benzoates, is contra-indicative to their practical use. The toxicity of the p-aminobenzoates was rather significant. Only one compound, XX·3HCl, is less toxic than xycain.

If the tested groups of compounds are compared as a whole, they can be arranged in the following order: a) according to activity and duration of activity for terminal anesthesia – benzoates > p-aminobenzoates > p-nitrobenzoates; b) according to duration of infiltration anesthesia – p-aminobenzoates > benzoates > p-nitrobenzoates; c) according to toxicity – p-aminobenzoates > benzoates > p-nitrobenzoates.

EXPERIMENTAL

Benzoate of 1,2,5-Trimethyl-5-dimethylaminomethyl-4-phenylpiperidol-4 (III). To a solution of phenyllithium freshly-prepared by the usual method (from 1.4 g of lithium and 16 g of bromobenzene) in

anhydrous ether was added 100 ml of dry benzene; while stirring and cooling to −10°C in a stream of dry nitrogen, a solution of 10 g of 1,2,5-trimethyl-5-dimethylaminomethylpiperidone-4 [I, $NR_2 = N(CH_3)_2$] in 20 ml of benzene was added dropwise. The mixture was agitated at the boiling point of benzene for two hours, then, while cooling with ice water, 14 g of benzoyl chloride in 20 ml of benzene was added dropwise. The reaction mass was left at room temperature for 24 h, and, while cooling with ice water, it was worked up with dilute (1 : 1) hydrochloric acid until the precipitate was completely dissolved. The organic layer was separated; the aqueous layer, while being cooled, was neutralized and saturated with sodium carbonate, and then extracted many times with ether. The combined ether extracts were dried with magnesium sulfate, filtered, the ether was distilled off, and the residue was distilled in vacuo. Yield 10 g (52.6%), bp 160-175°C (0.5 mm); it was a very viscous liquid. The base III was then converted to the dihydrochloride and the dimethyl iodide.

p-Nitrobenzoate of 1,2,5-Trimethyl-5-dimethylaminomethyl-4-phenylpiperidol-4 (X). This was prepared analogously to the previous experiment from 1.4 g of lithium, 16 g of bromobenzene, 10 g of 1,2,5-trimethyl-5-dimethylaminomethylpiperidone-4 [I, $NR_2 + N(CH_3)_2$] and 18.5 g of p-nitrobenzoyl chloride. After distillation of the ether, the residue was dried in a vacuum desiccator. Yield was 15 g (70.5%). The base X was converted to the dihydrochloride. Yield was 13.7 g (78%).

p-Nitrobenzoate of 1,2,5-Trimethyl-5-diethylaminomethyl-4-phenylpiperidol-4 (XI). To a solution of 10 g of 1,2,5-trimethyl-5-diethylaminomethylpiperidol-4 [II, $NR_2 = N(C_2H_5)_2$] in 20 ml of dry benzene was added a solution of 11 g of p-nitrobenzoyl chloride in 20 ml of benzene and 1 g of magnesium turnings. The mixture was boiled 3 h and left at room temperature for 24 h. The benzene was distilled off in vacuo. The residue, on cooling, was worked up with a saturated solution of sodium carbonate and extracted with ether. The extract was dried with magnesium sulfate and filtered. The ether was distilled off. Yield was 12.4 g (82.8%). The base XI was converted to the dihydrochloride in 85% yield.

The benzoates V−VIII and the p-nitrobenzoates XII−XVI were prepared in the same way as X or XI, the benzoates IV and IX the same as III.

p-Aminobenzoate of 1,2,5-Trimethyl-5-dimethylaminomethyl-4-phenylpiperidol-4 (XVII). To a solution of 5 g of the dihydrochloride of X in 80 ml of alcohol, heated to 50°C, with stirring, was added a solution of 20 g of stannous chloride in 20 ml of alcohol and 20 ml of concentrated hydrochloric acid. The reaction mixture was heated at the boiling point of alcohol for 5 h, the alcohol was distilled off in vacuo; the residue was washed with ether and, with cooling with ice water, was neutralized with sodium carbonate. The reaction product was extracted with ether, dried with magnesium sulfate, filtered, the ether distilled off, and the residue dried in a vacuum desiccator. Yield was 2.2 g (55.7%). The trihydrochloride was prepared from the base XVII in 88.6% yield.

The other p-aminobenzoates (XVIII−XXIII) were prepared analogously.