ESTERS OF HETEROCYCLIC γ-AMINO ALCOHOLS

III. CINNAMATES AND PHENOXYACETATES OF 5-AMINOMETHYL-4-PHENYL-1,2,5-TRIMETHYLPIPERID-4-OLS

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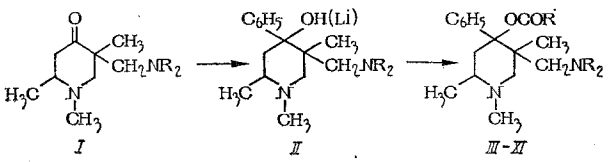
We have previously reported on the synthesis and pharmacology of a series of esters of 5-aminomethyl-4-phenyl-1,2,5-trimethylpiperid-4-ols [1, 2]. Among these compounds, a number of benzoates and p-aminobenzoates proved to have considerable local anesthetic activity [2]. Indeed, in some cases their effectiveness exceeded that of Xycaine [Lidocaine] both in terminal as well as in infiltrative anesthesia. These esters, however, while of relatively low toxicity, showed some irritant effects, and in these circumstances it seemed of interest to prepare and examine the cinnamate and phenoxyacetate esters of these same piperidine γ-amino alcohols.



The stated compounds were obtained by the action of cinnamic or phenoxyacetic acid chloride on the appropriate 5-aminomethyl-4-phenyl-1,2,5-trimethylpiperid-4-ols (II) (or upon their O-lithium derivatives, prepared by treating the respective 5-aminomethyl-1,2,5-trimethylpiperid-4-ones (I) with phenyllithium [1]). The resulting cinnamates (III-IX) and phenoxyacetates (X, XI) were isolated and characterized as dihydrochlorides (Table 1).

Pharmacologically, one of the more interesting of these products was 5-diethylaminomethyl-4-phenyl-1,2,5-trimethylpiperid-4-ol cinnamate (IV); and in order to effect a comparison of its activity, several of its salts, in addition to the dihydrochloride itself, were prepared (see Table 2). These substances included the oxalate, D-tartrate, citrate, and ascorbate, and in each case the salt, not only with one, but also with two molecules of the dibasic acid per molecule of the ester base, was obtained and examined. The dimethiodide was also prepared.

The pH values of the salts described in this paper have been determined in 1% aqueous solution.

Pharmacological examination of the cinnamates showed that in 0.25-0.5% concentration most of these compounds could induce prolonged infiltrative anesthesia, the effect lasting, in the majority of cases, some 2-4 h. High infiltrative anesthesia in this series of compounds was related to their ability to induce also some degree of terminal anesthesia, and the least active of these products [viz., the morpholine (IX) and dimethylamino (III) derivatives] were also the least able to induce terminal anesthesia of any considerable duration. The remaining, more highly active cinnamates had very highly pronounced and closely similar anesthetic properties.

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TABLE 1. Dihydrochlorides of the Cinnamate and Phenoxyacetate Esters of 5-Aminomethyl-4-phenyl-1,2,5-trimethyl-piperid-4-ols

Compound	NR_2	R′	Yield,* %	pH of solution	mp,† °C	Found, %		Empirical formula	Calculated, %	
						Cl	N		Cl	N
III	$N(CH_3)_2$	$CH=CHC_6H_5$	53,0 —	—	135—7	14,77 14,99	5,87 5,70	$C_{26}H_{34}N_2O_2 \cdot 2HCl$	14,79	5,84
IV	$N(C_2H_5)_2$	$CH=CHC_6H_5$	47,0 —	2,56	146—8	14,10 14,18	5,88 5,63	$C_{28}H_{38}N_2O_2 \cdot 2HCl$	13,97	5,51
V	$N(n\text{-}C_3H_7)_2$	$CH=CHC_6H_5$	46,3 —	—	160—2	13,37 13,38	5,11 5,25	$C_{30}H_{42}N_2O_2 \cdot 2HCl$	13,24	5,23
VI	$N(n\text{-}C_4H_9)_2$	$CH=CHC_6H_5$	39,6 94,8	—	119—21	12,66 12,65	4,89 4,77	$C_{32}H_{46}N_2O_2 \cdot 2HCl$	12,58	4,97
VII	$N(CH_2)_5$	$CH=CHC_6H_5$	35,0 73,0	2,65	156—8	13,78 13,93	5,24 5,17	$C_{29}H_{38}N_2O_2 \cdot 2HCl$	13,65	5,39
VIII	$N(CH_2)_6$	$CH=CHC_6H_5$	58,0 82,0	2,56	150—2	13,32 13,27	5,15 5,08	$C_{30}H_{40}N_2O_2 \cdot 2HCl$	13,29	5,25
IX	$N(CH_2CH_2)_2O$	$CH=CHC_6H_5$	32,0 71,0	2,39	143—5	13,89 13,76	5,18 5,12	$C_{28}H_{36}N_2O_3 \cdot 2HCl$	13,60	5,37
X	$N(C_2H_5)_2$	$CH_2OC_6H_5$	35,0 —	—	137—9	13,70 13,88	5,53 5,61	$C_{27}H_{38}N_2O_3 \cdot 2HCl$	13,87	5,47
XI	$N(CH_2)_6$	$CH_2OC_6H_5$	53,5 96,0	—	143—5	12,99 13,23	5,05 4,95	$C_{29}H_{40}N_2O_3 \cdot 2HCl$	13,19	5,21

*Numerator shows yield calculated in terms of the amino-ketone (I) used; denominator indicates yield in terms of amino alcohol (II)

† The dihydrochlorides were recrystallized from a mixture of chloroform and ether; their mp, as given in this column, are "to decomposition."

TABLE 2. Salts of 5-Diethylaminomethyl-4-phenyl-1,2,5-Trimethylpiperid-4-ol Cinnamate (IV)

Salt	ph of solution	mp,* °C	N (found, %)	Empirical formula	N (calculated, %)	Terminal anesthesia. Effect (Renier index† given) of a 0.5% solution on the mucous membrane of the eye in rabbits
Oxalate	3,70	62—4	5,54 5,69	$C_{28}H_{38}N_2O_2 \cdot C_2H_2O_4$	5,33	18 (16—20)
Dioxalate	2,80	54—6	4,75 4,85	$C_{28}H_{38}N_2O_2 \cdot 2C_2H_2O_4$	4,56	157 (141,2—172,8)
D-tartrate	4,60	77—9	5,02 4,89	$C_{28}H_{38}N_2O_2 \cdot C_4H_6O_6$	4,79	34 (29,8—38,1)
Di-D-tartrate	3,77	77—9	3,68 3,64	$C_{28}H_{38}N_2O_2 \cdot 2C_4H_6O_6$	3,81	29 (26,4—31,6)
Citrate	4,50	68—70	4,35 4,27	$C_{28}H_{38}N_2O_2 \cdot C_6H_8O_7$	4,47	16 (13,9—18,1)
Dicitrate	3,94	77—9	3,27 3,25	$C_{28}H_{38}N_2O_2 \cdot 2C_6H_8O_7$	3,42	32 (28,2—35,8)
Ascorbate	—	85—7	4,95 4,87	$C_{28}H_{38}N_2O_2 \cdot C_6H_8O_6$	4,66	20 (15,1—24,9)
Diascorbate	4,84	85—7	3,52 3,60	$C_{28}H_{38}N_2O_2 \cdot 2C_6H_8O_6$	3,60	713 (693—732,6)
Di-iodomethylate	8,13	75—7	3,85 3,71	$C_{30}H_{44}I_2N_2O_2$	3,90	47 (42,4—51,6)

*With decomposition. Mono- and di-salts admixed together show a depression of mp.

† Probable limits at P = 0.05 are given in parentheses. The higher the value of the Renier index, the greater the anesthetic activity: the maximum possible value is 1300.

Generally speaking, our cinnamates can be described as belonging to the group of highly active, all-purpose anesthetic agents. Their effects are of long duration, and their toxicity, which is inconsiderable, is lower than that of Xycaine and, in many instances, lower even than that of Novocaine. Unfortunately, however, these substances have marked irritant properties: in 2-5% concentration, the irritant effects of the most highly active of our compounds may persist for 24-48 h, or even for 7-14 days. Such compounds can evidently find no application in clinical medicine.

The dihydrochlorides of the compounds shown in Table 1 were strongly acid in solution, and for this reason other salts were examined having different pH values (see Table 2), but these were in all cases only feebly anesthetic.

The two phenoxyacetates (X, XI) likewise belong to the group of powerful, long-acting anesthetic agents, but their toxicity is higher than that of the cinnamates, and once again, they exercise marked and prolonged irritant effects.

EXPERIMENTAL

5-Dimethylaminomethyl-5-phenyl-1,2,5-trimethylpiperid-4-ol Cinnamate (III). An ethereal solution of phenyllithium was prepared from lithium (1.4 g) and bromobenzene (16 g). The solution was cooled to −10°C and kept stirred while a solution of 5-dimethylaminomethyl-1,2,5-trimethylpiperid-4-one (I; R = CH_3) (10 g) in anhydrous ether (20 ml) was admitted dropwise in a current of dry nitrogen gas. The resulting mixture was then allowed to warm up, and the stirring continued and the ether kept refluxing for a further 5 h. The temperature was then lowered again to −10° and a solution of cinnamic acid chloride (10 g) in ether (20 ml) added. After standing at room temperature for 24 h, the reaction mixture was treated with iced water; diluted hydrochloric acid (equal parts of conc HCl and water) was then added, enough acid being used to dissolve the precipitate. The ether layer was discarded, and the aqueous layer, after further extraction with ether, was cooled and saturated with solid sodium carbonate. The basic reaction product so obtained was transferred to ether, and the ethereal solution dried over magnesium sulfate and filtered. Dry hydrogen chloride gas was then passed in. This furnished the dihydrochloride of (III) in 53% yield [calculated on the aminoketone (I; R = CH_3)].

The compounds (IV), (V), (VI), and (X) were obtained in an analogous manner.

4-Phenyl-5-piperidinomethyl-1,2,5-trimethylpiperid-4-ol Phenoxyacetate (XI). A solution of 4-phenyl-5-piperidinomethyl-1,2,5-trimethylpiperid-4-ol [II; NR_2 = piperidine $N(CH_2)_6$] (5 g) and phenoxyacetic acid chloride (3.4 g) in benzene (30 ml) was treated with finely divided magnesium metal (0.3 g) and refluxed for 1 h. After standing at room temperature for 24 h, the benzene was evaporated in vacuo and the residue dissolved in a mixture of equal parts of conc HCl and water. The solution so obtained was worked up as described in the foregoing example. The ether extract furnished 4.65 g of (XI), and this base was converted to dihydrochloride in the customary manner. The yield was 96%, calculated on the aminoalcohol [II; NR_2 = $N(CH_2)_6$], or 53.5% on the corresponding ketone (I). The compounds (VI)-(IX) were prepared analogously.

The salts of (IV) with oxalic, D-tartaric, citric, and ascorbic acids were prepared by mixing an ethereal solution of (IV) base with an acetone or alcohol solution of one equivalent (or of two equivalents, as the case may be) of the appropriate acid. In each case, an oil separated on standing; this was crystallized from an anhydrous mixture of acetone, methanol, and ether.

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