ESTERS OF HETEROCYCLIC γ-AMINO ALCOHOLS.

IV. PROPIONATES, BENZOATES, CINNAMATES, AND PHENOXYACETATES OF 5-AMINOMETHYL-2,2-DIMETHYL-4-PHENYLTETRAHYDROPYRAN-4-OLS

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Current theories concerning the mechanism of anesthetic action suggest that the aqueous and lipoid solubilities, surface activity, and ionizability at physiologically significant pH levels are among the physicochemical properties which play an important part in determining the efficacy of a compound as an anesthetic agent [1, 2].

We have previously carried out an examination of a large series of esters of various 5-aminomethyl-4-phenyl-1,2,5-trimethylpiperidino-4-ols [3]. The esters comprised acetates, propionates, benzoates, p-nitrobenzoates, p-aminobenzoates, cinnamates, and phenoxyacetates, and among these compounds, which were in the form of dihydrochlorides, were some which had marked anesthetic properties and were nevertheless of a low degree of toxicity. The greatest anesthetic activity was found among the cinnamates, benzoates, p-aminobenzoates, and phenoxyacetates of piperidinols containing the diethylamino- or hexamethyleneimino-group; and compounds of this type, at concentrations 0.25-0.5%, could induce deep and prolonged anesthesia, both terminal and infiltrative, lasting up to 2-4 h. In this respect, the new compounds exceeded in activity that of the well-known anesthetic agent, xycaine (lidocaine), and were, in addition, less toxic than the latter. Unfortunately however, as well as possessing these properties, the stated dihydrochlorides had an irritant action and, being rather acid in character (the pH values of the most active among them, determined in 1% aqueous solution, fell within the range 2.2-2.7), their use in actual practice finally proved to be contraindicated.

The esters in question were piperidine derivatives and, apart from the heterocyclic nitrogen atom in the ring, carried an amino group in the side chain. The excessively acid character of solutions of their dihydrochlorides may be ascribed to these structural features, and there was a reasonable expectation therefore that by replacing the basic piperidine ring by a neutral tetrahydropyran residue compounds would result which would be more lipophilic, and would give rise to salts less acidic in character.

With these ideas in mind, we have now renewed our earlier attempts [3] to find anesthetic agents among hitherto unexamined esters of heterocyclic γ-amino alcohols, and have undertaken the preparation and pharmacological investigation of a series of compounds of a structure analogous to that of the amino esters previously studied [3] but derived from tetrahydropyran instead of piperidine. Our results are recorded in the present communication.

The starting material for the preparation of the new esters was 2,2-dimethyl-4-tetrahydropyran which,

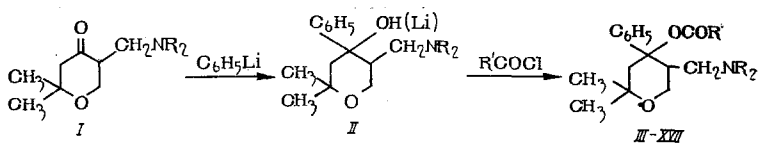

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TABLE 1. Esters of 5-Aminomethyl-2,2-dimethyl-4-phenyltetrahydropyran-4-ols

Compound*	NR_2	R'	Yield (%) [based on (I)]	R_f (petroleum ether–diethyl ether, 1 : 3)	mp of Hydrochloride† (°C)	Found (%) Cl	Found (%) N	Empirical formula	Calculated (%) Cl	Calculated (%) N
III	$N(C_2H_5)_2$	C_2H_5	82,0	0,62	194—5	9,48 9,49	3,74 3,86	$C_{21}H_{33}NO_3 \cdot HCl$	9,25	3,64
IV	$N(C_3H_7)_2$	C_2H_5	83,5	0,71	182—3	8,68 8,41	3,04 3,03	$C_{23}H_{37}NO_3 \cdot HCl$	8,60	3,39
V	$N(n\text{-}C_4H_9)_2$	C_2H_5	50,4	0,75	165—6	8,05 8,31	3,10 3,11	$C_{25}H_{41}NO_3 \cdot HCl$	8,05	3,18
VI	$N(CH_2)_6$	C_2H_5	79,5	0,60	116—7	9,10 9,47	3,60 3,69	$C_{23}H_{35}NO_3 \cdot HCl$	9,09	3,49
VII	$N(CH_2CH_2)_2O$	C_2H_5	73,6	0,61	166—7	9,05 9,09	3,98 4,10	$C_{21}H_{31}NO_4 \cdot HCl$	8,90	3,87
VIII	$N(C_2H_5)_2$	C_6H_5	83,0	0,62	193—4	8,02 8,07	3,32 3,26	$C_{25}H_{33}NO_3 \cdot HCl$	8,20	3,24
IX	$N(C_3H_7)_2$	C_6H_5	83,4	0,71	175—6	7,52 7,38	2,69 2,67	$C_{27}H_{37}NO_3 \cdot HCl$	7,70	3,04
X	$N(n\text{-}C_4H_9)_2$	C_6H_5	41,8	0,70	173—4	7,24 7,25	2,78 2,59	$C_{29}H_{41}NO_3 \cdot HCl$	7,26	2,86
XI	$N(CH_2)_5$	C_6H_5	60,0	0,63	194—5	8,28 8,30	2,89 2,82	$C_{26}H_{33}NO_3 \cdot HCl$	7,98	3,15
XII	$N(CH_2)_6$	C_6H_5	78,0	0,53	193—4	7,96 7,97	3,03 3,02	$C_{27}H_{35}NO_3 \cdot HCl$	7,74	3,05
XIII	$N(CH_2CH_2)_2O$	C_6H_5	64,5	0,64	161—2	7,52 7,60	2,86 2,79	$C_{25}H_{31}NO_4 \cdot HCl$	7,77	3,07
XIV	$N(C_2H_5)_2$	$CH{=}CHC_6H_5$	80,4	0,57	187—8	7,59 7,54	2,77 2,98	$C_{27}H_{35}NO_3 \cdot HCl$	7,74	3,05
XV	$N(CH_2)_6$	$CH{=}CHC_6H_5$	71,5	0,56	162—3	7,57 7,55	2,55 2,65	$C_{29}H_{37}NO_3 \cdot HCl$	7,32	2,89
XVI	$N(C_2H_5)_2$	$CH_2OC_6H_5$	82,0	0,55	182—3	7,60 7,54	3,03 3,02	$C_{26}H_{35}NO_4 \cdot HCl$	7,66	3,03
XVII	$N(CH_2)_6$	$CH_2OC_6H_5$	56,4	0,50	167—8	7,02 7,15	2,94 2,94	$C_{28}H_{37}NO_4 \cdot HCl$	7,26	2,89

*Mp of crystalline bases (°C): (VI) 81-82 (from heptane), (IX) 81.5-82.5 (from heptane), (XII) 146-147 (from heptane/ethanol), (XIII) 190-191 (from heptane/ethanol), (XIV) 153-154 (from heptane/ethanol), (XV) 151-152 (from heptane/ethanol).

†Hydrochlorides of the fifteen bases (all melt with decomposition) crystallized from: (III) acetone/ethanol, (IV) acetone, (V) dioxane, (VI) ethyl acetate/methanol, (VII) acetone/methanol, (VIII) ethyl acetate/methanol, (IX) ethanol, (X) dioxane, (XI) dioxane, (XII) ethyl acetate/methanol, (XIII) acetone/methanol, (XIV) ethyl acetate/methanol, (XV) ethyl acetate/methanol, (XVI) ethyl acetate/methanol, (XVII) ethyl acetate/methanol.

on aminomethylation with formaldehyde and various secondary bases, furnished a series of aminomethyl derivatives (I), and these, with phenyllithium, gave the lithium alcoholates of the corresponding phenyltetrahydropyranols (II). The two-dimensional and stereochemical structures of these β-amino ketones (I) and γ-amino alcohols (II) were confirmed by means of PMR measurements as well as by IR- and mass-spectrometry. The desired amino esters (III-XVII) were obtained by interacting the lithium alcoholates with the chlorides of propionic, benzoic, cinnamic, and phenoxyacetic acids. The fifteen compounds so prepared (see Table 1) differed among themselves in structure only with respect to (a) the nature of the basic residue (NR_2) in the side-chain aminomethyl group and (b) the nature of the acid radical (R'CO) in the ester grouping.

Vacuum distillation of the products presented difficulties and was attended by the risk of decomposition; the compounds were therefore isolated and characterized as hydrochlorides. The bases recovered from these salts proved, in the case of the six compounds (VI), (IX), (XII), (XIII), (XIV), and (XV), to be crystalline substances; but the remaining nine, viz. (III), (IV), (V), (VII), (VIII), (X), (XI), (XVI), and (XVII), were viscous liquids. In all fifteen cases, the purity and homogeneity of the compounds were controlled by thin layer chromatography (TLC).

Pharmacological examination of the new compounds consisted in (a) instillation of 0.25-5.0% solutions into rabbit's eye, and (b) subcutaneous administration of similar solutions to guinea pigs. The former of these two techniques served to establish the production of terminal anesthesia, while the latter furnished

the criterion for the corresponding infiltrative effect. The results showed that, of the compounds tested, the most stable form of anesthesia was produced by the phenoxyacetate (XVII), a 0.25% solution of which could induce effects lasting 120-150 min (terminal) and 90-225 min (infiltrative). Relatively deep and prolonged terminal anesthesia, lasting 30-90 min, was also recorded with the phenoxyacetate (XVI) and the cinnamate (XIV). On the other hand, the terminal anesthesia produced by the propionates and benzoates was either only partially developed, or else of short duration and inconsiderable in degree. Thus, the only benzoates which, in 0.5% solution, were able to induce full terminal anesthesia for as long as 15-30 min were (VIII) and (XI); the same two compounds, on the other hand, showed a more marked effect as infiltrative anesthetic agents. Of the benzoates, the most lasting infiltrative effects (up to 120-220 min) were produced by compounds (VIII), (X), and (XIII), while among the propionates, the infiltrative effects of compounds (III) and (VII) could endure for 50-165 min.

The compounds described in this paper were of low toxicity, and showed no irritant effects.

In conclusion it may be stated therefore that although esters of γ-amino alcohols of the tetrahydropyran series are devoid of irritant action, the compounds are, as anesthetic agents, rather less successful than were their earlier piperidine analogs.

EXPERIMENTAL METHOD

Thin layer chromatography was carried out with unmounted alumina plates. The alumina was of Grade II activity, and the solvent system was petroleum ether : diethyl ether : : 1 : 3.

Preparation of Phenyllithium. A suspension of 2 g-atom of lithium metal, in the form of fine shavings, in anhydrous ether was stirred in a current of dry nitrogen and treated dropwise with a solution of 1 mole of bromobenzene in ether. The solvent was kept boiling and the mixture stirred until the metal had completely dissolved.

Propionate of 5-Diethylaminomethyl-2,2-dimethyl-4-phenyltetrahydropyran-4-ol (III). An ethereal solution of phenyllithium, prepared from lithium metal (1.4 g) and bromobenzene (16 g), was stirred, cooled to –10°, and treated with the hydrochloride of 5-diethylaminomethyl-2,2-dimethyl-4-tetrahydropyran (I); R = C_2H_5. The mixture was boiled (36°) for 3 h, then cooled to –10° and treated dropwise with a solution of propionyl chloride (18.5 g) in 20 ml of anhydrous ether; this mixture was stirred and the solvent kept boiling during 24 h. When the reaction was complete (as shown by TLC) the mixture was treated with diluted hydrochloric acid (1 : 1) until the precipitate had dissolved. The ethereal layer was separated, and the aqueous layer, after being washed with ether to remove neutral substances, was saturated with potassium carbonate and repeatedly extracted with ether. The resulting extracts were dried over magnesium sulfate, the solvent removed by evaporation, and the residue so obtained dried to constant weight in a vacuum desiccator. This was (III) base, a thick liquid weighing 14.3 g, representing a yield of 82% calculated on amino ketone (I). The hydrochloride was obtained by dissolving the base in ether and adding a saturated solution of dry hydrogen chloride in anhydrous ether.

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

Benzoate of 5-Diethylaminomethyl-2,2-dimethyl-4-phenyltetrahydropyran-4-ol (VIII). The lithium alcoholate of the amino alcohol (II) (R = C_2H_5) was obtained, as in the foregoing example, from metallic lithium (1 g), bromobenzene (12 g), and 6.3 g of the hydrochloride of (I) (R = C_2H_5) in an anhydrous ethereal medium. The resulting solution was cooled to –10°, stirred, and treated dropwise with a solution of benzoyl chloride (14 g) in 30 ml of anhydrous ether. The solvent was then brought to the boil and stirring continued for 1 h, whereupon the reaction mixture was allowed to stand at room temperature for 48 h. Diluted hydrochloric acid (1 : 1) was next added to pH 2.0, and the resulting precipitate of the hydrochloride of (VIII) filtered off and washed, first with more of the same hydrochloric acid solution and finally with ether. The yield, after drying, was 8.9 g (83%).

The benzoates (IX), (X), (XI), (XII), and (XIII) were obtained in an analogous manner.

The Cinnamates (XIV) and (XV), and the Phenoxyacetates (XVI) and (XVII). The method of preparing these compounds was the same as that, described above, used for the preparation of compound (III), viz. by the action of cinnamic or phenoxyacetic acid chloride, as the case may be, on the lithium alcoholate of the appropriate amino alcohol (II).

The Amino-Ester Bases (III-XVII). These were recovered from their purified salts by treating the aqueous solutions of the latter with potassium carbonate followed by extraction with ether. The extracts were dried over magnesium sulfate and the solvent then driven off in each case. In the case of compounds (VI), (IX), (XII), (XIII), (XIV), and (XV), the residues so obtained crystallized; but in the remaining nine cases the residues remained as viscous oils, and these were converted back to hydrochlorides by the method described above for the reconversion of (III) to its hydrochloride.

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