

The Preparation of Some Dialkylaminoalkyl Esters of Phenoxyacetic Acids*

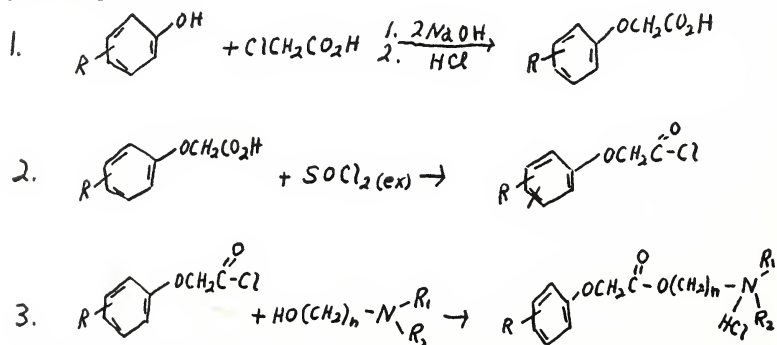
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Ever since the elucidation of the structure of cocaine by Willstätter et al (1) in 1898, attempts have been made to synthesize better local anesthetics without the undesirable physiological properties of the natural product. One of the first of the synthetic local anesthetics, which was not closely related to cocaine in structure, was prepared by Einhorn and Uhlfelder (2) in 1909. This compound was the diethylamino-ethyl ester of p-aminobenzoic acid and was called "novocaine" or more recently "procaine."

Since the synthesis of "procaine," there have been literally thousands of compounds prepared and tested for local anesthetic activity; but, as yet, no one has managed to prepare a more versatile anesthetic. The results which have been obtained in this search are conflicting and vary over wide limits, and no general correlation of structure with physiological activity has been made in this field. This lack of correlation is most striking when one considers the lack of specificity in the acids which have been esterified with amino alcohols.

A search of the literature failed to reveal the preparation of dialkylaminoalkyl esters of any phenoxyacetic acids. The high activity of certain substituted phenoxyacetic acids as plant hormones (3) suggested the possibility of other physiological action. Therefore, a series of basic esters was prepared for test as local anesthetics. Meanwhile, Truitt et al (4) and Martin and Hafziger (5) reported the preparation of a large number of basic esters of various substituted phenoxyacetic acids for testing as antihistaminic agents. However, neither group reported any work on the esters of p-nitrophenoxyacetic acids and p-aminophenoxyacetic acids with which this work is concerned.

The procedure used for the preparation of the esters is illustrated by the equations:



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R=H, NO₂-, 2, 6-diCH₃

N=2, 3

R₁ and R₂=CH₃, C₂H₅, N-C₃H₇, N-C₄H₉, β-morpholino

R₁=Φ, R₂=C₂H₅

The method of Jacobs and Heidelberg (6) was used to prepare both the p-nitrophenoxyacetic acid and the p-nitrophenoxyacetyl chloride. The esterification reaction was run in dry benzene from which the product usually separated as a heavy oil which crystallized on cooling. Absolute ether was added to the cold benzene solution to precipitate the remainder of the salt. All the hydrochlorides but one (the morpholino derivative) were very hygroscopic so that the isolation and recrystallization were difficult. In general the compounds were recrystallized from absolute alcohol-absolute ethyl acetate mixtures or from the latter solvent.

Attempts to isolate the products obtained after reduction using Adam's Catalyst (on the free bases) and Palladium on charcoal (on the hydrochlorides) presented many difficulties and at best only small yields of impure product were obtained. The p-aminophenoxyacetic acid esters obtained were oxidized even on very brief exposure to air, causing the reduced alcohol solutions to become intensely colored. Since these compounds were being prepared to be tested as local anesthetics, this extreme instability was very disadvantageous. Attempts to distill the free bases under reduced pressure resulted in decomposition and only tars were obtained as a residue. The hydrochlorides were precipitated with absolute ether and were highly colored viscous oils or glasslike amorphous solids which would not crystallize.

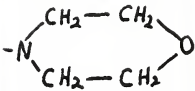
The decomposition of p-aminoethers in the presence of mild oxidizing agents was studied quite thoroughly in the case of p-anisidine (7) as early as 1910. Wieland assumed that the decomposition occurred with the formation of an intermediate quinoid structure. Aniline, methanol and anisole were isolated from the reaction mixtures even after the reactions had been run only a few minutes. It is then reasonable to assume that similar decomposition probably occurs with the p-aminophenoxy acetates. No attempts were made to isolate any of the probable breakdown products in this decomposition reaction.



Experimental

Diethylaminoethyl phenoxyacetate hydrochloride: A solution of 8g (0.046 mole) of phenoxyacetyl chloride in 65 ml of dry benzene was placed in a three-necked flask equipped with a reflux condenser, a mechanical stirrer and a dropping funnel. A solution of 8g (0.068 mole) of β-diethylaminoethanol in 30 ml of dry benzene was added drop-wise to the vigorously stirred cold acid chloride solution at such a rate that no hydrogen chloride fumes were perceptible. A light yellow oil, which crystallized to a white amorphous solid, separated from the reaction

TABLE I. Properties of Esters.

X	n	R ₁	R ₂	Yield %	*M.P. °C	Chlorine%	
						Calcd.	Found
H	2	C ₂ H ₅ -	C ₂ H ₅ -	79	112-3.5	12.04	11.79
NO ₂	2	CH ₃ -	CH ₃ -	71	164-5	11.63	11.40
NO ₂	2	C ₂ H ₅ -	C ₂ H ₅ -	83	107-8	10.66	10.45
NO ₂	2	n-C ₄ H ₉ -	n-C ₄ H ₉ -	52	88-90	9.12	9.23
NO ₂	2	C ₂ H ₅ -	C ₆ H ₅ -	41	133-4	9.13	9.18
NO ₂	2			63	192-3	10.22	10.19
NO ₂	3	n-C ₃ H ₇ -	n-C ₃ H ₇ -	72	88-9	9.43	9.28
NO ₂	3	n-C ₄ H ₉ -	n-C ₄ H ₉ -	72	108-9	8.80	8.51
NO ₂	3	n-C ₄ H ₉ -	n-C ₄ H ₉ -	20-5	144-7	9.51	9.52

* Uncorrected.

mixture. The ester hydrochloride was recrystallized twice from an absolute alcohol-absolute ether mixture. (Properties in Table I.)

Dialkylaminoalkyl esters of p-nitrophenoxyacetic acid:

Diethylaminoethyl p-nitrophenoxyacetate hydrochloride: This compound was prepared using the same procedure as was used for the diethylaminoethyl phenoxyacetate hydrochloride except that in this case the reaction mixture was allowed to reflux for about 30 minutes after complete addition to the aminoalcohol. A solution of 22g (0.19 mole) of diethylaminoethanol in 100 ml of dry benzene was added to a solution of 40g (0.19 mole) of p-nitrophenoxyacetyl chloride (6) in 150 ml of dry benzene. A viscous light brown oil, which solidified on cooling, separated from the reaction mixture. About 200 ml of absolute ether was added to the benzene solution to insure complete precipitation. The ester hydrochloride was recrystallized twice from 5% absolute methanol in absolute ethylacetate. (An alternative recrystallization procedure was to dissolve the ester hydrochloride in absolute alcohol and add absolute ether until a cloudiness develops.) (Properties in Table I.)

The same general procedure was used in the preparation of all the p-nitrophenoxyacetate hydrochlorides.

Dialkylaminoalkyl p-aminophenoxyacetates: Distilled water solutions of 20g (0.05-0.065 mole) of the p-nitrophenoxyacetate hydrochlorides were treated with dilute sodium carbonate solution until the solution was basic. The heavy oils which separated from the basic solution were extracted with three 50-75 ml portions of ether and the ether extracts combined and placed over anhydrous sodium sulfate. The dried extracts were filtered and the ether removed under reduced pressure leaving close to the theoretical amount (95-100%) of viscous light yellow

oils. The free bases were taken up in 125 ml of absolute alcohol and 0.2g of platinum oxide catalyst added. The reductions were done using low pressure hydrogenation apparatus (initial pressure about 40-45 lbs.) and the reduction began immediately. The reaction mixture warmed considerably as the reduction proceeded and the theoretical amount of hydrogen was used up in about 15-30 minutes, depending on the ester being reduced. The catalyst was removed by filtration or centrifugation and the alcohol solutions concentrated under reduced pressure yielding highly colored concentrates which were taken up in ether. Dry hydrogen chloride gas was passed into the ether solutions to precipitate the amine hydrochlorides.

Reduction of the p-nitrophenoxyacetate hydrochlorides was done in the same manner using Palladium on charcoal as a catalyst. Absolute ether was added directly to the filtered absolute alcohol solution to precipitate the amine hydrochlorides.

Summary

The following esters have been prepared from the appropriate acid chloride and aminoalcohol: β -diethylaminoethyl phenoxyacetate hydrochloride, β -dimethylaminoethyl p-nitrophenoxyacetate hydrochloride, β -diethylaminoethyl p-nitrophenoxyacetate hydrochloride, β -di-n-butylaminoethyl p-nitrophenoxyacetate hydrochloride, β -ethyl- β -phenylaminoethyl p-nitrophenoxyacetate hydrochloride, β -morpholinoaminoethyl p-nitrophenoxyacetate hydrochloride, γ -di-n-propylaminopropyl p-nitrophenoxyacetate hydrochloride, γ -di-n-butylamino-propyl p-nitrophenoxyacetate hydrochloride, and γ -di-n-butylaminopropyl p-aminophenoxyacetate hydrochloride.

The difficulties encountered in the attempted catalytic reduction of the p-nitrophenoxyacetates are discussed.

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