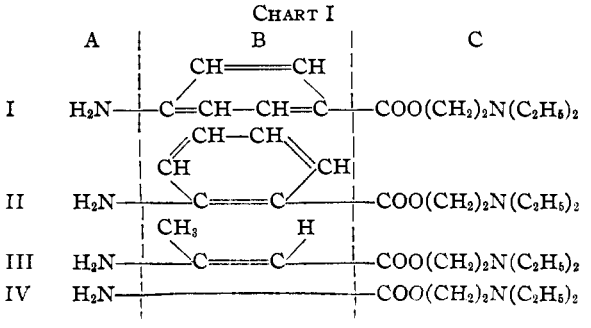
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

β′-Diethylaminoethyl β-Aminocrotonate

BY R. L. SHRINER AND LOUIS S. KEYSER

A survey of the structural variations which have been made in molecules of the procaine type, I in Chart I, shows that many changes have been made in the portion of the molecule marked "C" in an effort to find compounds with superior pharmacological action.[1] Some variations have been made in the "A" portion but very few in the "B" part. Changes in the latter part have consisted in preparing and studying the esters of *m*- and *o*-aminobenzoic acids[2] (II) and cinnamic acids.[3] The compound III in Chart I is an aliphatic analog of the ester of *o*-aminobenzoic acid (II). Both of these are vinylogs[4] of I and all three, I, II,

CHART I



III, may be considered as derived from the parent urethan, IV. Compounds of the type III have not been prepared and the specific compound IV has not been studied although numerous urethans are known to possess some general anesthetic and hypnotic properties.[5] The phenyl urethans[6] have been studied extensively as local anesthetics.

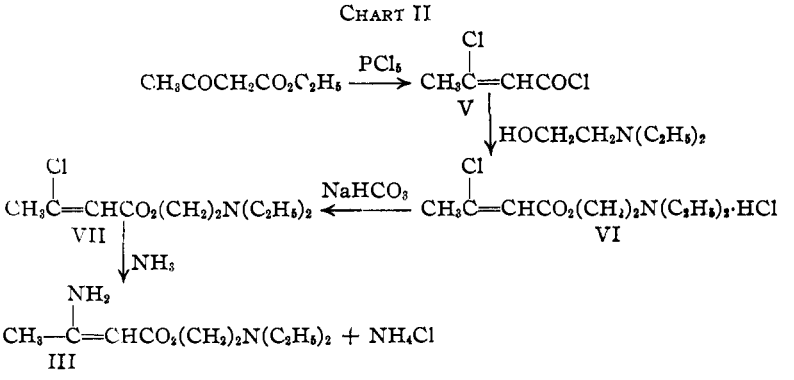
The present investigation was concerned with the synthesis of the compound shown in formula III. It was prepared in good yields by the reactions which are summarized in Chart II.

The β-chlorocrotonyl chloride (V) was prepared by the action of phosphorus pentachloride on ethyl acetoacetate. Treatment of this acid chloride with β-diethylaminoethanol yielded the hydrochloride of the amino ester, VI. After conversion to the free base (VII) it was treated with liquid ammonia in a sealed tube to produce β′-diethylaminoethyl β-aminocrotonate (III). This ester was a colorless oil which formed unstable, noncrystalline salts with acids. Treatment with phenyl isocyanate gave the crystalline substituted urea, β′-diethylaminoethyl β-(N-phenylureido)-crotonate, which served as a solid derivative. The ester was soluble in water to the extent of about 2.5% and this aqueous solution was buffered to give a solution with a *p*H of 7.0 for use in the pharmacological test.

Through the courtesy of the Lilly Research Laboratories the local anesthetic action of this buffered solution was determined. It caused no local anesthesia when applied either topically to the rabbit's cornea or injected intracutaneously in the rabbit's skin. Its M.L.D. in mice was 155 mg. per kg.

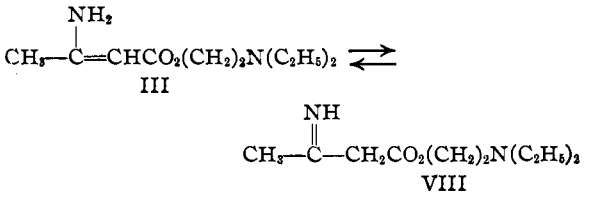
The absence of any local anesthetic activity of this compound is rather surprising in view of the close structural similarities outlined in Chart I.

CHART II



There appear to be two possible explanations for this result. First, the compound III may tautomerize[7] into VIII. It is only the enamine form, III, which is structurally similar to I and II. In the second place, β-aminocrotonic esters are known to be readily hydrolyzed[8] to keto esters.

(1) Hirschfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).
(2) German Patent 170,587 (1906).
(3) Wildman and Thorp, U. S. Patent 1,193,649 (1916).
(4) Fuson, *Chem. Rev.*, **16**, 1 (1935).
(5) Dixon, "Manual of Pharmacology," Edward Arnold, London, 1908, p. 68.
(6) Fromherz, *Arch. expil. Path. Pharm.*, **76**, 257 (1914); Rider, *J. Pharmacol.*, **39**, 457 (1930); **47**, 255 (1933); THIS JOURNAL, **52**, 2115 (1930); **58**, 1079 (1936).
(7) See Baker, "Tautomerism," George Routledge and Sons, London, 1934, p. 122 ff., for a summary of this type of tautomerism.
(8) Collie, *J. Chem. Soc.*, **71**, 303 (1897).



If this hydrolysis took place rapidly when the compound (III or VIII) came in contact with the body fluids then of course the structural analogy would be destroyed. Neither the keto ester, nor the imino form, VIII, contains the carboxyl group of the ester attached to a carbon atom carrying a double bond—a structural set-up which seems to be necessary for local anesthetic action.[9]

Experimental

β-Chlorocrotonyl Chloride.—An adaptation of the method of Michael and Schulthess[10] was used in the preparation of this compound. Three hundred grams of phosphorus pentachloride was covered with 100 cc. of dry benzene in a 3-necked 1-liter flask fitted with a mercury-sealed stirrer, separatory funnel, and a reflux condenser connected to a gas absorption apparatus *via* a calcium chloride tube. The mixture was cooled in ice and 100 g. of ethyl acetoacetate added dropwise over a period of four hours with frequent manual stirring. Near the end of the reaction the ice-bath was lowered and the reaction mixture was brought to room temperature for one hour and then heated at 50° for one hour with vigorous stirring. The dark reddish brown liquid was then fractionally distilled through a 20-inch (51-cm.) column and the fraction boiling from 122–140° was collected. This wide boiling range corresponds to that observed by Autenrieth,[11] who prepared this compound by the action of phosphorus pentachloride on the *cis* and *trans* β-chlorocrotonic acids. Further purification is difficult since the compound hydrolyzes readily. It fumes strongly in air and has an extremely irritating effect on the nose and eyes. The crude product which weighed 94 g. (84% of the theoretical) was used in the following step.

β′-Diethylaminoethyl β-Chlorocrotonate.—Twenty grams of the acid chloride was dissolved in 300 cc. of anhydrous ether and 16.8 g. of diethylaminoethanol in 100 cc. of anhydrous ether was added dropwise with stirring. The flocculent light brownish solid which separated was filtered, washed once with dry ether and mixed into a slurry with 40 g. of sodium bicarbonate and a minimum of water. This pasty mass was then extracted with six 50-cc. portions of ether and the combined extracts distilled. After removal of the ether, 9.4 g. of colorless liquid having a faint ester like odor came over at 94–95° (4 mm.). The ether in the first mother liquor was evaporated and the residue distilled under diminished pressure. An additional 3.4 g. of the fraction above was obtained along with a low boiling portion which distilled at 67–78° (4 mm.) and consisted largely of unreacted β-diethylaminoethanol. The total yield of the β′-diethylaminoethyl β-chlorocrotonate was 12.8 g. (41% of the theoretical); d^{20}_4 1.0300; $n^{20}D$ 1.4675; M_D calcd. 59.56; M_D found 59.0.

Anal. Calcd. for $C_{10}H_{18}O_2NCl$: Cl, 16.14. Found: Cl, 15.94.

β′-Diethylaminoethyl β-Chlorocrotonate Hydrochloride and β′-Diethylaminoethyl β-Chlorocrotonate Hydrobromide.—These salts were prepared by passing anhydrous hydrogen chloride and hydrogen bromide into an ether solution of the ester with subsequent recrystallization from a mixture of alcohol and petroleum ether. The salt was dissolved in boiling alcohol and just enough petroleum ether added to start precipitation in the hot solution. After addition of a few drops of alcohol to clear up the hot solution, it was then allowed to cool. In both cases small white crystalline plates were obtained. The hydrochloride melted at 114.2–115.2° and the hydrobromide melted at 140–141°. The following analyses are for ionizable halogen only.

Anal. Calcd. for $C_{10}H_{19}O_2NCl_2$: Cl, 13.85. Found: Cl, 14.16. Calcd. for $C_{10}H_{19}O_2NClBr$: Br, 26.58. Found: Br, 26.68.

β′-Diethylaminoethyl β-Aminocrotonate.—Ten cc. of the β′-diethylaminoethyl β-chlorocrotonate was sealed with 30 cc. of liquid ammonia in a tube cooled in a bath of acetone and solid carbon dioxide. The tube was allowed to come to room temperature and after inverting several times to ensure complete mixing the tube was set aside for seventy-two hours. At the dry ice temperature the two liquids were immiscible, but at room temperature and under the pressure of the ammonia a perfectly homogeneous solution resulted. This solution was colorless at first but on standing a greenish tint developed. The tube was again cooled in the dry ice–acetone bath and opened. As the solution cooled crystals of ammonium chloride separated. The ammonia was allowed to evaporate, and the light yellow oil which remained admixed with the ammonium chloride crystals was taken up with ether and distilled. The yield of colorless oil boiling at 121–122° (3 mm.) was 9.0 g. (96% of the theoretical although on the basis of the amount of ammonium chloride produced the reaction was quantitative); d^{20}_4 0.9985; $n^{20}D$ 1.5020. M_D calcd. for enamine structure,[12] 59.27; for imine structure, 56.10. Found: 58.90.

Anal. Calcd. for $C_{10}H_{20}O_2N_2$: C, 59.99; H, 10.07; N, 14.00. Found: C, 60.24; H, 9.98; N, 14.16.

β′-Diethylaminoethyl β-(N-Phenylureido)-crotonate.—One cc. of phenyl isocyanate was added to 1 cc. of the β′-diethylaminoethyl β-aminocrotonate in a test-tube and shaken. The tube was heated slightly whereupon the mixture became thick and sirupy. On standing several days the mass became crystalline. Slow recrystallization from alcohol gave beautiful white cubes which melted sharply at 87.5°.

(9) Kamm, THIS JOURNAL, **42**, 1030 (1920); Gilman and Pickens, *ibid.*, **47**, 245 (1925).

(10) Michael and Schulthess, *J. prakt. Chem.*, [2] **46**, 236 (1892).

(11) Autenrieth, *Ber.*, **29**, 1665 (1896).

(12) In calculating the molecular refractivities for the two structures, the data of von Auwers and Susemihl, *Ber.*, **63**, 1072 (1930) were used. The factor of 2.05 was used for the exaltation in the conjugated system of the enamine form. A value of 3.05 was used for the imino nitrogen in the imine structure.

Anal. Calcd. for $C_{17}H_{28}O_3N_2$: N, 13.15. Found: N, 13.13.

Summary

β'-Diethylaminoethyl β-aminocrotonate has been synthesized from ethyl acetoacetate through the sequence: ethyl acetoacetate ⟶ β-chlorocrotonyl chloride ⟶ β'-diethylaminoethyl β-chlorocrotonate ⟶ β'-diethylaminoethyl β-aminocrotonate. This ester possessed no local anesthetic activity.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

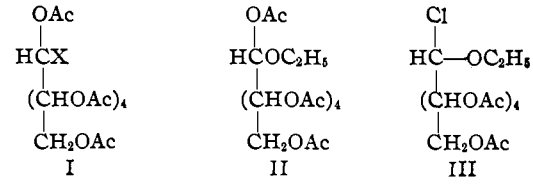
Esters of the Aldehydrol Form of Sugars. II

BY M. L. WOLFROM AND M. KONIGSBERG

Crystalline substances that may be considered as esters of the aldehydrol forms of the aldoses have been reported from this Laboratory and from others.[1] Felton and Freudenberg[2] obtained *aldehydo*-1-bromo-*l*-arabinose pentaacetate as a by-product in the large scale preparation of acetobromo-*l*-arabinose. Montgomery, Hann and Hudson[3] have reported a number of novel derivatives of *d*-arabinose of this same general type, obtained by the hydrolysis of the acetylated methyl-*d*-arabinosides under acetylating conditions.

We have continued our studies in the preparation from *aldehydo*-acetates of esters of the aldehydrol forms of the aldoses. We wish to report herein the extension to the *d*-glucose and *l*-arabinose series of the *aldehydo*-acetohalogen compounds (I) previously reported for *d*-galactose.[1a] The sugar derivatives of this type now known are tabulated in Table I. Similar carbonyl acyl halide addition compounds of the common, non-carbohydrate aldehydes have been studied extensively by Adams and co-workers.[4]

We have found acetylating conditions wherein it is possible to acetylate the ethyl hemiacetal of *aldehydo*-*d*-galactose pentaacetate[5] and obtain the crystalline *aldehydo*-1-ethoxy-*d*-galactose hexaacetate (II). Replacement of the acetate on the aldehydic carbon with chlorine was feasible and produced the *aldehydo*-1-chloro-1-ethoxy-*d*-galactose pentaacetate (III). These substances are of interest as the acyclic analogs of structures which have been of importance in the chemistry of the cyclic forms of the sugars.



Experimental

Preparation of *aldehydo*-1-Bromo-*l*-arabinose Pentaacetate.—*aldehydo*-*l*-Arabinose tetraacetate[6] (5 g.) was dissolved in 25 cc. of acetyl bromide and the solution, after standing at room temperature for one hour, was poured into 100 cc. of ice and water. A colorless, crystalline product separated that was removed by filtration, after an hour of standing, and was washed with cold water; yield 6.5 g. Pure material was obtained on recrystallization from ether; m. p. 130–131°; $[\alpha]^{23}$ −134° (*c*, 4; $CHCl_3$, alcohol free; no mutarotation).[7] For the crystalline substance which they called pentaacetylbromoarabinose, Felton and Freudenberg[2] recorded the constants: m. p. 132°; $[\alpha]^{23}$ −135°.

Synthesis of Other Acyclic Acetohalogen Compounds of *l*-Arabinose and *d*-Glucose.—These compounds were synthesized in crystalline condition by the following general procedure. The solution of 5 g. of the *aldehydo*-acetate in 50 cc. of the acyl halide was allowed to stand at room temperature for twenty-four hours, whereupon it was poured into 800 cc. of ice and water and the crystalline precipitate was removed by filtration and washed with cold water; yield, 4 to 6.5 g. The chloroacetates were recrystallized from absolute ethanol and the bromoacetate from ordinary ether. The properties of the purified compounds are tabulated in Table II.

***aldehydo*-1-Ethoxy-*d*-galactose Hexaacetate (II).**—Acetic anhydride (250 cc.) was added slowly to a solution of 10 g. of *aldehydo*-galactose pentaacetate ethyl hemiacetal[5] in 125 cc. of pyridine, previously cooled to 0°. The mixture was kept at 0° for thirty minutes and then at ice-box temperature for eighteen hours, whereupon it was poured

(1) (*a*) M. L. Wolfrom, THIS JOURNAL, **57**, 2498 (1935); (*b*) F. Micheel, H. Ruhkopf and F. Suckfüll, *Ber.*, **68**, 1523 (1935); (*c*) N. W. Pirie, *Biochem. J.*, **30**, 374 (1936).

(2) G. E. Felton and W. Freudenberg, THIS JOURNAL, **57**, 1637 (1935).

(3) Edna M. Montgomery, R. M. Hann and C. S. Hudson, *ibid.*, **59**, 1124 (1937).

(4) R. Adams and E. H. Vollweiler, *ibid.*, **40**, 1732 (1918); H. B. French with R. Adams, *ibid.*, **43**, 651 (1921); L. H. Ulich with R. Adams, *ibid.*, **43**, 660 (1921).

(5) M. L. Wolfrom, *ibid.*, **52**, 2464 (1930).

(6) M. L. Wolfrom and Mildred R. Newlin, *ibid.*, **52**, 3619 (1930).

(7) All rotations are recorded to the D-line of sodium light.