[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES AND THE NAVAL MEDICAL RESEARCH INSTITUTE]

An Anomalous Esterification of *cis*-DL-2-Dimethylaminocyclohexanol

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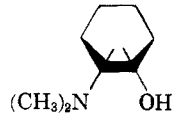
Received July 15, 1957

It has been observed that the hindered hydroxyl function of *cis*-DL-2-dimethylaminocyclohexanol (I) is difficultly esterified, with an aromatic acid chloride of moderate bulk. In the case of the acetate of mandelyl chloride (II) as the esterifying agent, the small yield of ester of I that is actually obtained has resulted from an unexpected reduction in which the acetoxyl function has been eliminated. A rationale is suggested in which the *cis*-orientation of substituents in the ester of I affords the proper geometry for intervention of a displacement reaction on the carbon atom bearing the acetoxyl group, in a process accompanied by reductive cleavage of the resulting heterocyclic ring.

Previous study[2] of the *cis*-aminocyclanol I revealed an unexpected order of strength as an *in*

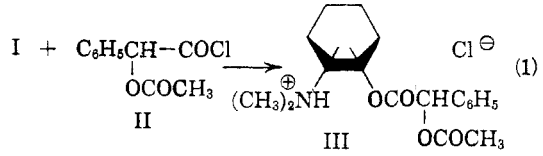


I

vitro inhibitor of purified acetylcholinesterase, as well as evidence of blocking activity in the frog rectus preparation[2] and with respect to the propagated impulse in desheathed bullfrog sciatic nerve.[3] Accordingly, it was of considerable interest to prepare esters of this aminoalcohol with a spectrum of aromatic acids possessing some physiological function, for evaluation of possible atropinic and/or local anesthetic activity. Pharmacological results of this work will be reported elsewhere.

In one of the first of these esterifications, attempted with the acetate of mandelyl chloride (II), an anomalous course of reaction was observed which appears to be a peculiar consequence of the spatial orientation of the two polar substituents in the highly hindered aminoalcohol I.

It was anticipated that under relatively mild conditions the reaction of I and II might be driven essentially to completion, since it was noted previously[4] that the reaction of I with ketene in ether



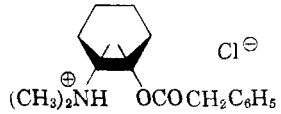
(1)

II III

proceeds in good yield at room temperature. However, preliminary experiments on refluxing equimolar quantities of I and II in chloroform for periods up to 30 hours, even in the presence of sufficient toluene added to the solvent to give a reflux temperature of about 85°, resulted only in recovery of starting materials. This reflection of the difficult steric requirements of I in the course of reaction with the bulky acid chloride II prompted the use of considerably greater amounts of toluene in the reaction solvent, permitting reflux near 105° for 50 hours.

Under these conditions, considerable quantities of the starting amino alcohol I (isolated as the hydrochloride) were recovered, but in addition a small (7.1%) yield of an ester hydrochloride presumed to be III was isolated and purified. This compound crystallized in rosettes of fine needles from ether-chloroform mixture, with m.p. 152.5–153.5°. However, instead of the elementary analysis expected for the C_{18} compound III, results on C, H, N, and Cl gave an excellent fit to the empirical formula $C_{16}H_{24}NO_2Cl$, corresponding to a *reduction* and loss of the —OAc function. Further, the compound gave no olfactory trace of acetic acid in the *O*-acetyl determination, although a volatile acid was steam-distilled and titrated. Under the conditions of this *O*-acetyl determination, mandelic acid was found to be completely non-volatile.

Accordingly, it appeared that the sole product isolated from reaction (1) was not the expected diester III, but rather the hydrochloride IV of the reduced product in which the —OAc function has



IV

been eliminated. This has been verified by independent synthesis of IV from I and phenylacetyl chloride, with comparison of the two products by melting and mixed melting points (152.5–153.5°) proving them to be identical. Further, the infrared spectra of the product from reaction (1) and authentic IV at equivalent concentrations in chloroform solution are virtually superimposable.

This finding of the anomalous course of the esterification reaction (1), occurring under vigorous conditions that only furnish an ester product in poor

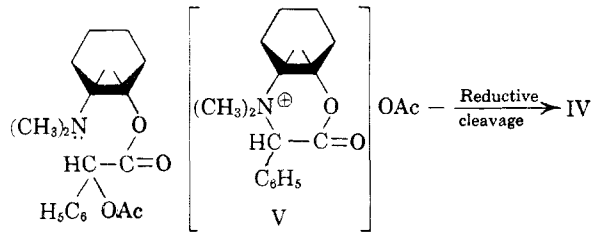
(1) The opinions in this paper are those of the authors and do not necessarily reflect the views of the Navy Department.

(2) S. L. Friess, *J. Am. Chem. Soc.*, **79**, 3269 (1957).

(3) Private communication from Mr. E. Whitcomb, National Institutes of Health.

(4) H. D. Baldridge, W. J. McCarville, and S. L. Friess, *J. Am. Chem. Soc.*, **77**, 739 (1955).

yield, has a curious feature in the reductive loss of the —OAc group leading to IV. One possible explanation for this facet of the reaction draws on the special geometry resulting from the *cis*-relationship of functional groups in I, permitting a nucleophilic attack of the basic $(CH_3)_2N$- group (*i.e.*, that small fraction present in equilibrium with the protonated form) on the mandelic carbon displacing acetate ion;



Such a process eliminating acetate ion and yielding the intermediate quaternary cycle V would have to be paired with a reductive cleavage step leading to the observed product IV. The most likely hydrogen donor in this step under these reaction conditions would be the excess amino alcohol I present, with the reductive cleavage being accompanied by its concomitant oxidation to amino ketone.

EXPERIMENTAL[5]

The *acetate of mandelyl chloride* (II) was prepared from purified mandelic acid, m.p. 118–119°, in standard fashion by successive reactions with acetic anhydride and thionyl chloride; b.p. 150° (14 mm.), reported[6] 142° (18 mm.). The product solidified in the receiver on standing; yellow solid, m.p. 34–36°. The *cis*-aminoalcohol I was prepared from the corresponding aminoketone by reduction with Pt and H_2 in ethanol solution as in the previous work.[4]

After preliminary studies indicating that reflux of I and II in chloroform for extended intervals gave only starting materials, toluene was incorporated into the reaction mixture to give a higher reflux temperature. In a typical esterification run, 10 g. (0.047 mole) of the acid chloride II and 6.78 g. (0.047 mole) of the solid amino alcohol I were dissolved in 50 ml. of chloroform and this solution diluted with 50 ml. of toluene. The mixture was brought to reflux and sufficient chloroform stripped off to bring the reflux temperature to about 105°, at which point it was held for 50 hr. The cooled solution was then saturated with HCl gas, resulting in separation of an oil that was found to consist largely of I as its hydrochloride. The supernatant solution was then stripped of solvent and the residual oil subjected to crystallization from chloroform-ether mixture. There was obtained 1.0 g. (7.1%) of crystals of the hydrochloride IV, white rosettes of needles, m.p. after repeated recrystallization 152.5–153.5° (Fisher-Johns).

Anal. Calcd. for $C_{16}H_{24}NO_2Cl$ (the phenylacetic ester): C, 64.52; H, 8.12; N, 4.70; Cl, 11.91. Found: C, 64.37; H, 7.96; N, 4.71; Cl, 11.94.

For comparison purposes, an authentic sample of IV was prepared by prolonged reflux of equimolar portions of I and phenylacetyl chloride, in chloroform-toluene mixture, followed by several recrystallizations of the product from chloroform and ether. M.p. 152.5–153.5°, mixed m.p. with the product from the acid chloride II, 152.5–153.5° (Fisher-Johns).

The compound prepared in reaction (1) was subjected to an *O*-acetyl determination essentially according to the procedure of Clark,[7] with the results described in the discussion section above.

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(5) Analyses by courtesy of the Microanalytical Laboratory, National Institute of Arthritis and Metabolic Diseases. Infrared spectra were obtained by Mr. W. M. Jones.

(6) R. Anschutz and R. Bocker, *Ann.*, **368**, 59 (1909).

(7) E. P. Clark, *Semimicro Quantitative Organic Analysis*, Academic Press, 1943, p. 73.

[CONTRIBUTION FROM THE NAVAL STORES RESEARCH SECTION, U. S. DEPARTMENT OF AGRICULTURE]

A New Method for Isolating Isodextropimaric Acid from Pine Oleoresin and Rosin

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Received July 9, 1957

A method is described for isolating isodextropimaric acid from pine oleoresin and gum rosin. The piperidine salt of the resin acids is precipitated from *n*-heptane solution, recrystallized from ethanol, and converted to the acid in acetone with hydrochloric acid. The yield of pure isodextropimaric acid varies from 3% to 5% depending on the species of oleoresin or rosin used. A new derivative, isodextropimarinol, was prepared and characterized.

In 1948 Harris and Sanderson[2] reported the presence of isodextropimaric acid in *Pinus palustris* oleoresin, wood rosin, and gum rosin. It was isolated by reacting the acid-isomerized, conjugated-diene acids with maleic anhydride and then separating the unreacted acids, isodextropimaric and dextropimaric acids, from the maleic anhydride adduct by precipitating them from aqueous alkaline solution at *p*H 6.2. Further fractionation of the mixture by recrystallization of the 2-amino-2-methyl-1-propanol salt yielded isodextropimaric acid.

The method described in this paper is based on the precipitation of the piperidine salt of the resin acids from *n*-heptane solution of pine oleoresin or rosin followed by selective recrystallization of the

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 2079 (1948).