one separated from triphenylethoxyethylene and diphenylacetophenone by the process of fractional crystallization employed for the isolation of diphenylpropiophenone. The pure diphenylbutyrophenone thus isolated (0.35 g.) melted at 97–98° and was not hydrolyzed by 2 *N* hydrochloric acid.

Anal. Calcd. for $C_{22}H_{20}O$: C, 88.0; H, 6.7. Found: C, 88.2; H, 6.7.

1,2,2-Triphenyl-1-propoxyethylene.—Diphenylacetophenone (2.7 g.) was condensed with 2.1 g. of propyl iodide as described above. The crude reaction product (1.6 g.) was recrystallized from ethanol to give crystalline material melting at 84–85°. Fractional crystallization from petroleum ether (60–80°) as outlined above gave 0.5 g. of pure triphenylpropoxyethylene melting at 92–93° and 0.15 g. of diphenylacetophenone.

Anal. Calcd. $C_{23}H_{22}O$: C, 87.9; H, 7.1. Found: C, 87.9; H, 7.1.

α,α-Diphenylvalerophenone.—As the alcoholic mother liquors of the preceding experiment did not furnish a crystalline product on concentration, the material was subjected to hydrolysis by dilute aqueous alcoholic hydrochloric acid. Addition of water and cooling of the reaction mixture gave 0.2 g. of diphenylacetophenone. The filtrate was evaporated to dryness under reduced pressure and the residue distilled to give 0.2 g. of a yellow oil which boiled at 195° (2.5 mm.) (oil-bath temperature). Attempts to crystallize this material from petroleum ether or alcohol failed.

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.9; H, 7.1. Found: C, 87.8; H, 7.0.

α,α-Diphenyl-γ-N-morpholino-butyrophenone.—A benzene solution of Grignard reagent prepared from 9.5 g. of bromobenzene and 1.44 g. of magnesium was added to a solution of 6.15 g. of α,α-diphenyl-γ-N-morpholino-butyronitrile.[11] After refluxing for 18 hours, the reaction mixture was poured onto a mixture of cracked ice and concentrated hydrochloric acid. The benzene layer was separated and the aqueous part heated on the water-bath for 3 hours. On cooling 7 g. (83%) of crystalline hydrochloride of III ($R_1 = C_6H_5$, $R_2 = H$, $R_3 = C_4H_8NO$) was obtained. After recrystallization from acetone, it melted at 235–237°.

Anal. Calcd. for $C_{26}H_{28}O_2NCl$: C, 74.0; H, 6.7; N, 3.3. Found: C, 74.1; H, 6.6; N, 3.2.

Acknowledgment.—I wish to express my gratitude to Mr. H. Schubert of the Forsanose Fabrik in Switzerland for the laboratory facilities and hospitality extended to me during the first stages of this investigation and to Dr. C. Niemann of the California Institute of Technology for his helpful criticism and encouragement in this work.

(11) D. J. Dupre, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

PASADENA 4, CALIF. RECEIVED JANUARY 22, 1951

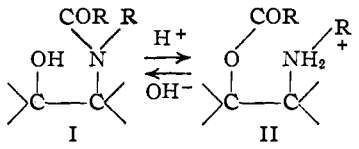
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Mechanism of Nitrogen–Oxygen Acyl Migrations

BY EUGENE E. VAN TAMELEN

Both *cis*- and *trans*-N-(*p*-nitrobenzoyl)-2-aminocyclopentanol have been converted by means of hydrogen chloride to the hydrochloride of *cis*-2-aminocyclopentyl *p*-nitrobenzoate. The latter result is attributed to the suppressed formation of a *trans*-fused, bicyclic intermediate and constitutes strong evidence for a cyclic intermediate in nitrogen–oxygen acyl migrations which proceed with retention of configuration.

Nitrogen to oxygen (N→O) and oxygen to nitrogen (O→N) acyl migrations, which may be represented generally as

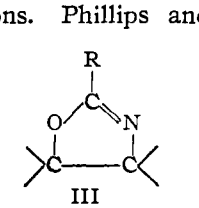


I II

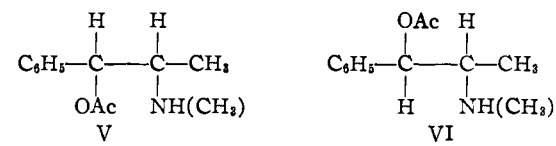
have been critically investigated in several laboratories during recent years. Ordinarily the former rearrangement is effected by treatment of an N-acyl-1,2-aminoalcohol (I) with mineral acid. The resulting salt of the O-acyl-1,2-aminoalcohol (II) can be reconverted, *via* the free O-acylamino-alcohol,[1] to I through the agency of aqueous alkali.

It is the purpose of this study to gain some insight into the nature of the intermediates involved in this type of interconversion.

Evidence bearing on the mechanism of acyl migrations has been brought out in several investigations. Phillips and Baltzly[2] rejected an oxazoline (III) as a possible intermediate, because an oxazoline, which should ordinarily be stable in neutral or alkaline medium, could not be isolated in the O→N reaction. Alternately, a cyclic, hemiacetal-like structure (IV) was suggested.[3] Welsh[4] has demonstrated that the initial products resulting from the acyl migration involving N-acetylephedrine are O-acetylephedrine (V)—arising through retention of configuration—and a greater amount of its epimer, O-acetyl-Ψ-ephedrine (VI), the product of inversion at the benzylic position. N-Acetyl-Ψ-ephedrine, on the other hand, gave rise to only O-acetyl-ψ-ephedrine—reaction with exclusive retention. Welsh[5] correlated these results with the probable conformations of the diastereo-



III IV

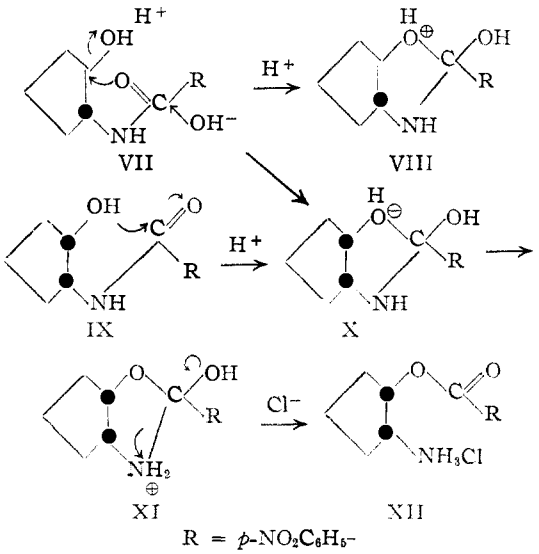


V VI

(1) G. Fodor and J. Kiss, THIS JOURNAL, 73, 3495 (1950).
(2) A. P. Phillips and R. Baltzly, *ibid.*, 69, 202 (1947).
(3) There still remains the possibility of an oxazoline intermediate in the N → O migration, which might well form through dehydration with cyclization; cleavage with strong acid to 1,2-amino ester salts (II) is a reaction characteristic of oxazolines. The isolation of some 2-phenyloxazoline[2] in the N → O migration with N-(2-hydroxyethyl)-benzamide supports this formulation. However, it seems likely that—at least in the retention mechanism (*vide infra*)—cyclization of I to an oxazoline should proceed *via* IV and that IV would also intermediate the conversion of III to II; thus the formation of an oxazoline does not preclude the presence of IV nor invalidate the retention mechanism.
(4) L. H. Welsh, THIS JOURNAL, 69, 128 (1947).
(5) L. H. Welsh, *ibid.*, 71, 3500 (1949).

isomeric ephedrines and suggested plausible mechanisms for both the retention and inversion steps, which are applied herein to the cases under present consideration. The possibility of inversion was not realized in the cyclohexane series, in that Fodor and Kiss[1] reported that the benzoates of *both cis-* and *trans*-2-aminocyclohexanols undergo N→O and O→N acyl exchange with retention in each step. The more rapid O→N migration of the *cis*-isomer is consistent with the concept of an intermediate IV (the bicyclic system derived from the *cis* form should involve lower energy requirements than that from the *trans*), but any such interpretation must be regarded as tentative, since the difference is small and the steric situation not a simple one.

We wish to report results which bring into sharp focus the structural requirements of acyl migrations and leave little doubt as the reality of the cyclic intermediate IV or a closely related equivalent. Recently we have utilized the concept of a prohibited ionic intermediate comprised of two five-membered rings fused in the *trans* sense, to support a mechanism for the conversion of 1,2-oxides to 1,2-sulfides.[6] Applying the concept to the case at hand, we regard the intermediate (VIII) as a highly strained structure obtainable only with difficulty from the amide of *trans*-2-aminocyclopentanol (VII); thus, acyl migrations leading to *trans*-2-aminocyclopentyl ester hydrochlorides should be considerably or completely suppressed. On the other hand, the N→O acyl migration involving the



R = *p*-$NO_2C_6H_5$-

corresponding *cis*-isomer (IX) should proceed with a facility approximately equal to that described in the cyclohexane series,[1] because the intermediate (X) should be essentially strain-free. Actually it was found that mere saturation of a dry dioxane solution of IX with anhydrous hydrogen chloride results in a 61% yield of the hydrochloride of *cis*-2-aminocyclopentyl *p*-nitrobenzoate (XII).[7] In the *trans* case VII, similar conditions led, as suspected, to complete recovery of starting material. Refluxing the hydrogen chloride–dioxane solution for three hours gave only an 80% recovery of VII. Finally, in contrast to the result obtained with *cis*-N-benzoyl-2-aminocyclohexanol, *refluxing for 24 hours led to an 18% yield of the hydrochloride of cis-2-aminocyclopentyl p-nitrobenzoate (XII)*, along with 69% of VII. Thus, when the retention mechanism is prevented by steric factors, the inversion mechanism becomes operative. Although, in comparison to IX, the *trans* amide VII is favorably oriented for a Walden inversion, eliminating hydroxyl according to the scheme presented above, comparatively vigorous conditions are required for a reasonable conversion. In any case, no evidence for the formation of *trans*-2-aminocyclopentyl *p*-nitrobenzoate from VII was forthcoming; and we interpret these results as strong evidence for a reaction sequence involving a transient cyclic intermediate.

Experimental[8]

cis- and *trans*-N-(*p*-Nitrobenzoyl)-2-aminocyclopentanol (VII and IX).—The isomers were prepared according to the directions of McCasland.[7]

cis-2-Aminocyclopentyl *p*-Nitrobenzoate Hydrochloride (XII). From *cis*-N-(*p*-nitrobenzoyl)-2-aminocyclopentanol.—Five hundred milligrams (2.00 millimoles) of the amide was dissolved in 25 cc. of dry dioxane and the resulting solution rapidly saturated with dry hyrogen chloride. Suitable precautions were taken to exclude atmospheric moisture. After cooling to room temperature, the solution was reduced in volume (*in vacuo*) to about 10 cc. The colorless crystals which had precipitated were removed by filtration and dried. Three hundred and fifty milligrams (61%) of ester was obtained, melting at 178–179°. The mixed melting point with an authentic sample was undepressed,[7] as was that of the regenerated *cis*-N-(*p*-nitrobenzoyl)-2-aminocyclopentanol.

From *trans*-N-(*p*-Nitrobenzoyl)-2-aminocyclopentanol.—One gram (4.00 millimoles) of amide dissolved in 100 cc. of dry dioxane was saturated with dry hydrogen chloride. A reflux condenser equipped with a drying tube was attached. After refluxing for about an hour, the evolution of hydrogen chloride had subsided considerably, and the system was closed with a rubber stopper to prevent further escape of gas. Refluxing was continued for 24 hours. The solvent was removed *in vacuo*, whereupon the flask contents crystallized. The solid was triturated thoroughly with 15 cc., then 5 cc. of hot water and the mixture filtered each time, yielding a total of 580 mg. of starting material. The filtrate was evaporated on the steam-bath to a volume of 10 cc. and then cooled; 110 additional mg. of starting amide crystallized. After filtration, the aqueous solution was evaporated to dryness on the steam-bath. There was obtained 210 mg. (18%) of crude *cis*-2-aminocyclopentyl *p*-nitrobenzoate hydrochloride, m.p. 173–176°. After recrystallization from ethanol–petroleum ether, the ester melted at 176–178° and was identified as described above.

MADISON, WISCONSIN RECEIVED JUNE 15, 1951

(6) E. van Tamelen, THIS JOURNAL, **73**, 3444 (1951).

(7) G. E. McCasland and H. Smith, *ibid.*, **72**, 2190 (1950).

(8) All melting points are corrected.