The Mechanism and Stereochemistry of Formation of (+)-1-Methyl-3-benzoyl-3-hydroxypiperidine from the (−)-3-Halo Analog under Quasi-Favorskii Conditions[1a]

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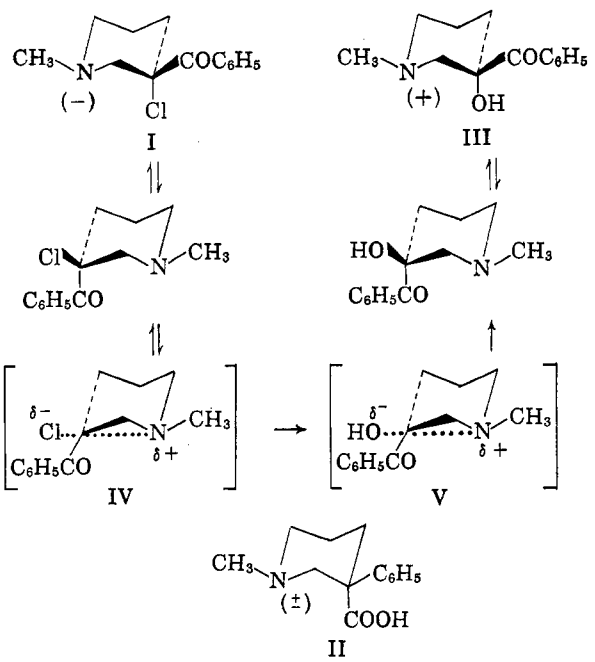
Received April 21, 1965

Under quasi-Favorskii conditions,[2] (−)-1-methyl-3-benzoyl-3-chloropiperidine (I) affords racemic rearrangement acid II and (+)-1-methyl-3-benzoyl-3-hydroxypiperidine (III) which is 88% racemic. It was proposed that a configuration retaining ion pair IV, formed by nucleophilic attack on the α-carbon by the electron pair on nitrogen, is involved in the formation of (+)-III by anion exchange to give V and subsequent collapse of the latter at the surface of the dry, powdered sodium hydroxide in refluxing xylene.[2]

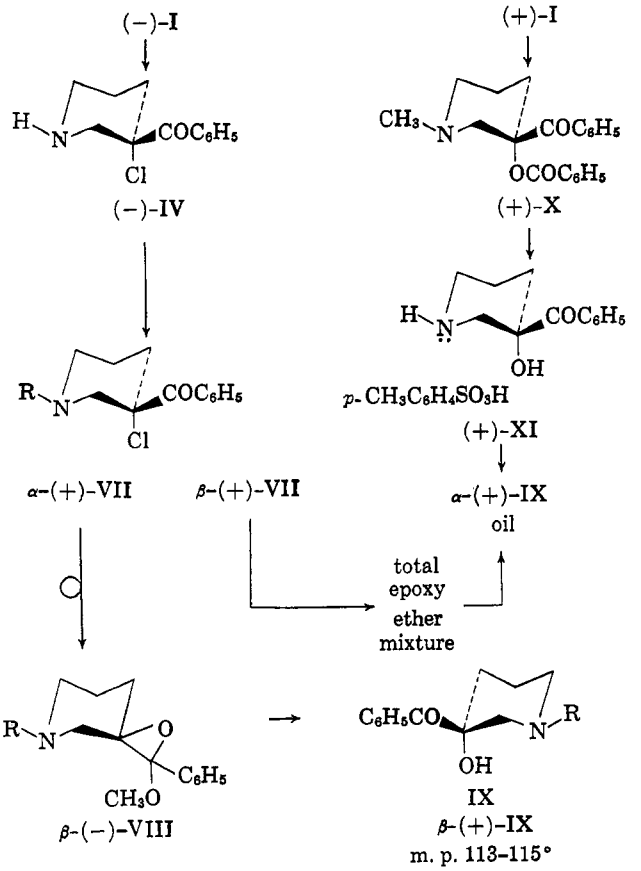
That (−)-I and (+)-III have the same relative configuration, as required by the suggested mechanism, was supported only by rotatory dispersion studies.[2]



At best, this evidence was considered tenuous in view of the failure of some α-oxygenated ketones to conform to the extension of the axial α-halo ketone optical rotatory dispersion rule.[3] However, with the establishment of the mechanism and stereochemistry of epoxy ether formation [α-(+)-VII → β-(−)-VIII] and cleavage [β-(−)-VIII → β-(+)-IX],[4] it became possible to relate the configurations of I and III.

Results and Discussion

Treatment of (−)-I to the conditions of the von Braun dealkylation gave an oily, levorotatory cyanamide which was hydrolyzed to the corresponding amine, (−)-VI. The crude product was sulfonated with the sulfonyl chloride prepared from (+)-10-camphorsulfonic acid to afford α-(+)-VII in 54% over-all yield. Thus, (−)-I is epimeric to β-(+)-IX about the α-carbon. Failure of III to undergo demethylation[5] necessitated benzoylation to give (+)-X which afforded



R = 10-camphorsulfonyl moiety derived from (+)-10-camphorsulfonic acid

(+)-XI upon subjection to von Braun conditions. Treatment of the free amine prepared from (+)-XI with the sulfonyl chloride derived from (+)-10-camphorsulfonic acid afforded an oil, $[\alpha]^{28}D$ +34.0 ± 0.4°, α-(+)-IX, which we have not been able to crystallize and which has also been obtained,[4c] $[\alpha]^{28}D$ +34.5 ± 0.3°, from β-(+)-VII through the total epoxy ether mixture. The former is undoubtedly optically pure since it was prepared from optically pure (+)-III and since racemization of (+)-III[2] and its acetate ester[4a] is known not to occur under more drastic conditions than those employed here.

Since α-(+)-IX is derived from (+)-III and has the same configuration as (−)-I about the α-carbon, the latter compounds have the same configuration, and

(1) (a) This investigation was supported by Grant NB-3593 from the National Institute of Neurological Diseases and Blindness, U. S. Public Health Services. Abstracted, in part, from the thesis of H. P., submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Presented at the 149th Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) Recipient of the Lunsford-Richardson Award, 1964, Second Prize, Northeast Section. (c) Author to whom inquiries should be addressed.

(2) E. E. Smissman and G. Hite, *J. Am. Chem. Soc.*, **82**, 3375 (1960).

(3) W. Klyne, *Tetrahedron*, **13**, 32 (1961); C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(4) (a) T. B. Zalucky, L. Malspeis, and G. Hite, *J. Org. Chem.*, **29**, 3143 (1964); (b) T. B. Zalucky, S. Marathe, L. Malspeis, and G. Hite, *ibid.*, **30**, 1324 (1965); (c) H. Patel and G. Hite, *ibid.*, **30**, 4337 (1965).

(5) (a) T. B. Zalucky, L. Malspeis, H. Patel, and G. Hite, *J. Pharm. Sci.*, **54**, 687 (1959); (b) *cf.* A. Shafi'ee, H. Patel, and G. Hite, in preparation.

the mechanism proposed earlier[2] is thus confirmed. Accordingly, the extension of the α-halo ketone optical rotatory dispersion rule to α-oxygenated ketones has become a matter of continuing interest in these laboratories.

Experimental Section

α-(+)-1-(10-Camphorsulfonyl)-3-benzoyl-3-chloropiperidine [α-(+)-VII] from (−)-I.—A solution of 1.1 g. of (−)-I (4.40 mmoles based on optical purity), $[\alpha]^{26}D$ −3.8 ± 0.3° (*c* 10.00, absolute ethanol), lit.[2] $[\alpha]^{25}D$ −4.2°, was slowly added to a warm (40–45°) solution of 1.5 g. (14 mmoles) of cyanogen bromide in 20 ml. of benzene. After 48 hr. the solid quaternary bromide (50 mg., 0.15 mmole) was filtered off and the benzene was removed under reduced pressure to give the levorotatory (benzene) cyanamide: infrared, 2212 (–CN), 1660 cm.$^{-1}$ (C=O). The cyanamide and 20 ml. of concentrated hydrochloric acid were refluxed for 48 hr. Following removal of the excess acid at the water pump, the syrup was treated with aqueous sodium bicarbonate and extracted with chloroform. A solution of the labile[5a] free amine VI in benzene is levorotatory. The chloroform extracts were added to a benzene solution (40 ml.) of the sulfonyl chloride, prepared as described earlier,[5a] from 2.5 g. (10.8 mmoles) of (+)-10-camphorsulfonic acid. The solution was refluxed for 3 hr., treated with an aqueous slurry of sodium bicarbonate, and stirred for an additional 1 hr. After washing with diluted aqueous hydrochloric acid, the dried organic solution separated from the reaction mixture was evaporated under reduced pressure. The resulting gum was crystallized from methanol and afforded 0.98 g. (2.3 mmoles, 54%) of α-(+)-VII, m.p. 131–132°, lit.[5a] m.p. 131–132°.

(+)-1-Methyl-3-benzoyl-3-benzoyloxypiperidine [(+)-X] from (+)-III.—To 13.0 g. (59.3 mmoles) of optically pure (+)-III, $[\alpha]^{25}D$ +11.1 ± 0.3° (*c* 5.00, absolute ethanol), lit.[2] $[\alpha]^{25}D$ +11.4°, was added 18 g. (80 mmoles) of benzoic anhydride in 100 ml. of pyridine. After refluxing for 24 hr., the pyridine was removed under reduced pressure, and the syrup was treated with ether and 10% hydrochloric acid. The resulting precipitate was filtered off, washed with ether, and dissolved in water. Both aqueous solutions were extracted with ether, neutralized with excess sodium bicarbonate, and extracted with chloroform. The organic phase was dried over sodium sulfate, filtered, and evaporated to give an oil which afforded crystals of (+)-X, 9.0 g. (28.7 mmoles, 47%), m.p. 65–66°, $[\alpha]^{25}D$ +61.4 ± 0.4°, (*c* 4.00, absolute ethanol), from petroleum ether (b.p. 40–60°): infrared, 1676 (ketone), 1705 cm.$^{-1}$ (ester), no OH bands.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.41; H, 6.54; N, 4.33. Found: C, 74.00; H, 6.62; N, 4.14.

(+)-3-Hydroxy-3-benzoylpiperidine *p*-Toluenesulfonic Acid Salt [(+)-XI] from (+)-X.—When subjected to the von Braun conditions described above, 8.0 g. (25.7 mmoles) of (+)-X afforded a dextrorotatory cyanamide [infrared, 2205 (–CN), 1678 (ketone), 1718 cm.$^{-1}$ (ester)] and 0.40 g. (1.0 mmole) of the quaternary bromide. Hydrolysis of the cyanamide afforded the corresponding desmethyl α-hydroxy ketone, isolated as its (+)-*p*-toluenesulfonic acid salt, (+)-XI, 4.0 g. (10.6 mmoles, 41%), m.p. 124–125°, $[\alpha]^{29}D$ +11.4 ± 0.4° (*c* 2.73, absolute methanol), from ethanol–ether.

Anal. Calcd. for $C_{19}H_{23}NO_5S$: C, 60.50; H, 6.16. Found: C, 60.59; H, 6.30.

α-(+)-1-(10-Camphorsulfonyl)-3-benzoyl-3-hydroxypiperidine [α-(+)-IX] from (+)-XI.—The free base, obtained from 3.11 g. (8.25 mmoles) of (+)-XI, was dissolved in 50 ml. of 1:1 benzene–chloroform and slowly added to a benzene solution (40 ml.) of the sulfonyl chloride, prepared as described earlier,[5a] from 1.90 g. (8.0 mmoles) of (+)-10-camphorsulfonic acid. After refluxing for 24 hr., 2.0 g. of sodium bicarbonate was added and refluxing was continued for an additional 2 hr. On cooling, the mixture was extracted with aqueous base and acid. The organic extract was removed under reduced pressure and replaced with benzene. After treating with anhydrous sodium sulfate and carbon, filtering through sintered glass, and completely removing the solvent under reduced pressure (0.01 mm.), there was obtained a colorless oil, **α-(+)-IX**, 2.07 g. (4.95 mmoles, 60%), $[\alpha]^{25}D$ +34.0 ± 0.4° (*c* 5.19, 0.2 *N* HCl in 4:1 acetone–water), which could not be crystallized and which had been obtained earlier[5a] from β-(+)-VII, through the total epoxy ether mixture, $[\alpha]^{25}D$ +34.5 ± 0.3° (*c* 5.54, 0.2 *N* HCl in 4:1 acetone–water). The infrared spectra (liquid films) were superimposable.

(6) Melting points were obtained in a Hershberg [*Ind. Eng. Chem., Anal Ed.*, **8**, 312 (1936)], silicone (550-Dow) filled melting point apparatus equipped with Anschutz full-immersion thermometers. The samples were placed in the circulating bath 10° below the reported melting points and heated at the rate of 1–2°/min. Elemental analyses were performed by Weiler and Strauss, Oxford, England. Infrared survey spectra (Nujol mulls) were determined with a Perkin-Elmer Model 421 spectrophotometer. Band assignments are believed accurate to within ±5 cm.$^{-1}$. Specific rotations were determined with a Zeiss 0.01° polarimeter in a modified [G. Hite and J. Lyons, *Chemist-Analyst*, **43**, 84 (1964)] 1-dm. (1-ml.) syringe-filling tube.

The Mechanism and Stereochemistry of Formation and Cleavage of Epoxy Ethers.[1] III[2]

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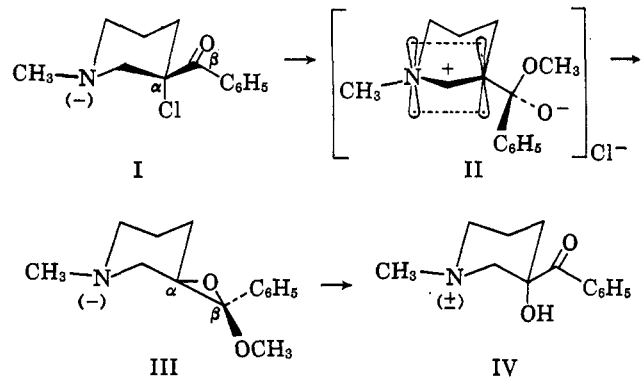
Received April 21, 1965

The work of Stevens, *et al.*,[3] indicates that epoxy ether cleavage[3c,f] and epoxy ether formation from α-halo ketones[3] are stereospecific processes resulting in retention and inversion of configuration of the α-carbon, respectively.

The *anomalous* α-C symmetrization in the epoxy ether, (−)-III, formation–cleavage sequence, (−)-I → [II] → (−)-III → (±)-IV, has been rationalized[4] by



invoking participation of the free electron pair of the piperidine nitrogen (*cf.* II). Accordingly, it was of interest to examine an analog of (−)-I in which the methyl group is replaced by an electronegative moiety designed to preclude such participation.

The syntheses and rationale for use in these studies of the two diastereoisomers, α-(+)- and β-(+)-1-(10-camphorsulfonyl)-3-benzoyl-3-chloropiperidine [α-(+)- and β-(+)-V], have been recorded.[5]

(1) See H. Patel and G. Hite, *J. Org. Chem.*, **30**, 4336 (1965), footnote 1.

(2) Paper II: T. B. Zalucky, S. Marathe, L. Malspeis, and G. Hite, *ibid.*, **30**, 1324 (1965).

(3) (a) C. L. Stevens and A. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1958); (b) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *ibid.*, **75**, 3977 (1953); (c) C. L. Stevens and T. H. Coffield, *J. Org. Chem.*, **23**, 336 (1958); (d) C. L. Stevens, W. Malik, and R. Pratt, *J. Am. Chem. Soc.*, **72**, 4758 (1950); (e) C. L. Stevens and T. H. Coffield, *ibid.*, **80**, 1919 (1958); (f) C. L. Stevens and S. J. Dykstra, *ibid.*, **75**, 5975 (1953).

(4) T. B. Zalucky, L. Malspeis, and G. Hite, *J. Org. Chem.*, **29**, 3143 (1964).

(5) T. B. Zalucky, L. Malspeis, H. Patel, and G. Hite, *J. Pharm. Sci.*, **54**, 687 (1965).