Mechanism and Stereochemistry of Epoxy Ether Formation and Cleavage IV

By HARSHADKUMAR PATEL* and GILBERT HITE

An independent proof of the mechanism and stereochemistry of epoxy ether formation from (−)-1-methyl-3-benzoyl-3-chloropiperidine[(−)-I] is presented.

IN PREVIOUS PAPERS on this subject (1–5) the anomalous racemization observed in the sequence, (−)-I → (−)-II → (±)-III (1) was rationalized on the basis of an asymmetric induction at the carbonyl carbon followed by halide ejection with concomitant participation of the free electron pair on nitrogen and α-C-symmetrization (*cf.* IV). This requires formation of identical amounts of the two possible diastereoisomeric epoxy ethers, epimeric at the spiro carbon, both arising from IV. The antipodal intermediate formed in the asymmetric induction would give rise to the remaining two diastereoisomeric epoxy ethers, also epimeric at the spiro carbon, but enantiomorphic to the first set. Since the product must then be a unique mixture consisting of identical quantities of erythro and threo epoxy ethers in identical degrees of optical purity, the optical activity of II must be attributed to the ketal carbon and not to the carbon common to both rings.

The *total* optical specificity of the reaction sequence, α-(+)-I $\xrightarrow{O}$ β-(−)-II → β-(+)-III (2,3) in which participation of the electron pair on nitrogen is obviated, has made possible this study. The interjection of an analogous but symmetrical cyano blocking group, following epoxy ether [(−)-II] formation, permitted observation of the opticochemical course of the conversion of (−)-I to (−)-II. (Scheme I.)

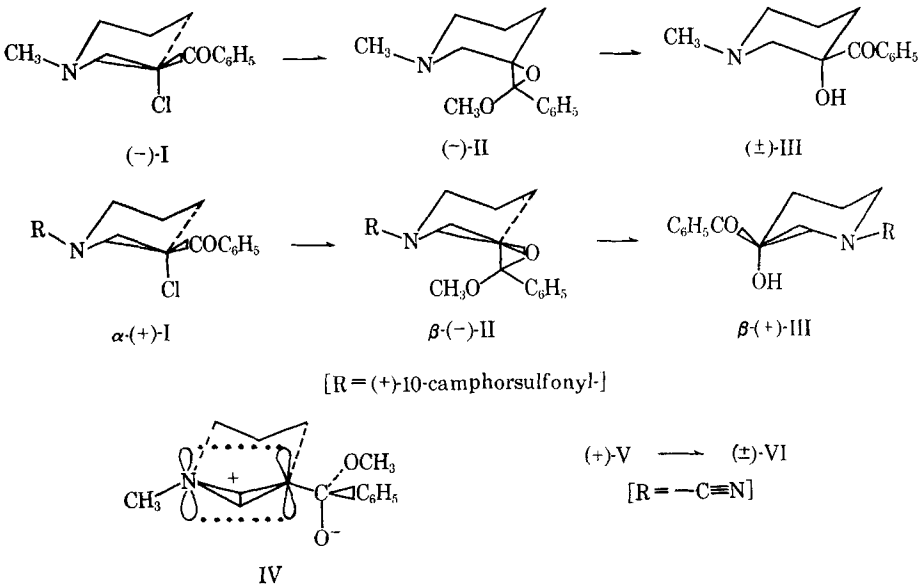
After treatment of (−)-1-methyl-3-benzoyl-3-chloropiperidine [(−)-I] with sodium methoxide in methanol, the total levorotatory mixture containing 2 - methoxy - 2 - phenyl - 5 - methyl - 1 - ox - 5 azaspiro[2.5]octanes (II) was isolated and was allowed to react with cyanogen bromide in order to effect demethylation. The total, dextrorotatory, benzene soluble fraction, containing 2-methoxy-2-phenyl-5-cyano-1-ox-5-azaspiro[2.5]octanes (V), was treated with dilute aqueous acid to give racemic 1-cyano-3-benzoyl-3-hydroxypiperidine (VI).

Since this epoxy ether cleavage is analogous to the totally optically specific transformation of β-(−)-II to β-(+)-III (2, 3), it is clear that the carbon common to both rings in (+)-V, and thus in (−)-II, must be present in both configurations, *equally*. Accordingly, the previously proposed (1) salient features of epoxy ether [(−)-II] formation from (−)-I are unequivocally established.

EXPERIMENTAL[1]

(−) - 2 - Methoxy - 2 - phenyl - 5 - methyl - 1-ox-5-azaspiro[2.5]octanes [(−)-II]—This was prepared, as described earlier (1), from (−)-I, $[\alpha]_D^{25}$ (ethanol) −4.2° (c 15.00).

(+) - 2 - Methoxy - 2 - phenyl - 5 - cyano - 1-ox-5-azaspiro[2.5]octanes [(+)-V]—A solution of 4.67 Gm. (20 mmoles) of (−)-II, $[\alpha]_D^{28}$ (ethanol) −1.28° (c 15.32), in 20 ml. of dry benzene was slowly added to a solution of 8.5 Gm. (60 mmoles) of cyanogen bromide in 30 ml. of dry benzene. The mixture was heated to 50° and stirred for 48 hr. The insoluble salts (0.8 Gm.) were filtered off



Scheme I

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[1] See Footnote 15 in *Reference 1.*

and the benzene and cyanogen bromide were removed under reduced pressure. The residual oil was dissolved in dry benzene and treated with carbon. The mixture was filtered through sintered glass. The solvent was removed under reduced pressure (0.01 mm. Hg/24 hr.) to give a colorless oil, 3.04 Gm. (12.3 mmoles, 61.5%), $[\alpha]_D^{28}$ (benzene) +2.1° (c 3.04), exhibiting a band at 2208 cm.$^{-1}$ (film) (C≡N) in the infrared spectrum. There were no bands in the —OH or C=O region.

Anal.—Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6. Found: C, 69.3; H, 6.2.

(±) - 1 - Cyano - 3 - benzoyl - 3 - hydroxypiperidine [(±)-VI]—To 2.44 Gm. (10 mmoles) of (+)-V in 40 ml. of methanol was added 10 ml. of 1 *N* hydrochloric acid. After standing for 24 hr., the methanol was removed under reduced pressure to give, on cooling, 1.87 Gm. (8.1 mmoles, 81%) of product which was optically inactive.[1] There were bands in the infrared spectrum (benzene solution) at 1665 (C=O), 2218 (C≡N), and 3285 cm.$^{-1}$ (OH). The spectrum was identical to that of an authentic sample prepared as previously described (5) melting point and mixed melting point of crystals from methanol, 131.5–132.5°.

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Synthesis of Aldoxime Analogs of Arecoline as Reactivators of Organophosphorus Inhibited Cholinesterase

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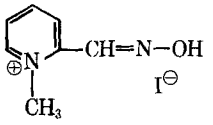
A series of arecoline-like aldoximes were synthesized and evaluated as potential reactivators of organophosphate-inhibited cholinesterase. These arecoline analogs were patterned after the potent quaternary oximes 2-PAM and TMB-4 and were synthesized by sodium borohydride reduction of the corresponding pyridinium aldoxime. Biological results show that although these aldoximes are less toxic than the quaternary aldoximes, they are much less effective as reactivators. They did exhibit weak muscarinic activity (1/60 that of arecoline) on dog blood pressure and guinea pig ileum.

THE EFFICIENT reactivating property of 2-pyridine aldoxime methiodide (2-PAM) has been attributed to the affinity of its quaternary nitrogen for the anionic site of cholinesterase (1). This affinity could cause the nucleophilic aldoxime oxyanion to be in a favorable position for reactivating phosphorylated cholinesterase.



2-PAM

The cholinergic agent arecoline contains a tertiary amine. Since the muscarinic activity of arecoline has been shown to be dependent on its protonated cationic nitrogen (2), the arecolinium ion might also possess a marked affinity for the anionic site of cholinesterase. Therefore, aldoxime analogs of arecoline, which should enter the CNS readily, might be expected to provide good reactivation of phosphorylated cholinesterase in the brain.

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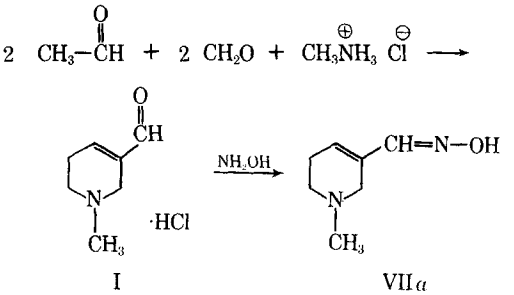
DISCUSSION

The authors have prepared a few 1,2,5,6-tetrahydropyridine aldoximes and report here the chemistry and pharmacological data. 1-Methyl-1,2,5,6-tetrahydropyridine-3-aldoxime (VII*a*) has been prepared by the reaction of formaldehyde, methylamine hydrochloride, and acetaldehyde to give 1-methyl-1,2,5,6 - tetrahydropyridine - 3 - carboxaldehyde (I) which was isolated as the oxime (3). (Scheme I.)



Scheme I

This reaction is quite laborious and gave poor yields of impure VII*a*. Thus, a more general method was sought which would be applicable to 1-alkyl-1,2,5,6-tetrahydro-3- and 4-aldoximes.

Potassium borohydride has been shown to reduce *N*-methylpyridinium iodide (II) to 1-methyl-1,2,3,6-tetrahydropyridine (III) (4). Similarly, the reduction of methyl nicotinate methiodide (IV) with