served. The structures of the other compounds follow by analogy, and from their spectral and analytical data.

Dodecyltrimethylphosphonium Bromide.—After phenol was steam distilled from one preparation of dimethyldodecylphosphine oxide, the residue was extracted with hot benzene by decantation, the solvent was evaporated, and the residue was recrystallized from hexane. A hexane-insoluble product was observed, which was recrystallized from benzene–ethanol, and shown to be dodecyltrimethylphosphonium bromide. The yield was 5.5%.

Anal. Calcd. for $C_{15}H_{34}BrP$: C, 55.4; H, 10.5; Br, 24.5; P, 9.52. Found: C, 55.5; H, 10.5; Br, 24.5; P, 9.53.

The infrared spectrum (KBr pellet) showed P–CH_3 (7.70 μ) and strong P–C (10.0–10.3 μ) absorption, but no phosphoryl bands. The compound was readily soluble in water, titrated as a neutral compound towards both acid and base, and gave an immediate precipitate with silver nitrate reagent. A sample was converted to the chloride using Dowex 2-X8 ion-exchange resin. The infrared spectrum and powder X-ray diffraction pattern of the chloride were identical with those of an authentic sample, prepared by treating dimethyldodecylphosphine[9] with methyl chloride (16 hr. at 100° in ether in a sealed tube).

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The Mechanism and Stereochemistry of Formation and Cleavage of Epoxy Ethers.[1] II[2,3]

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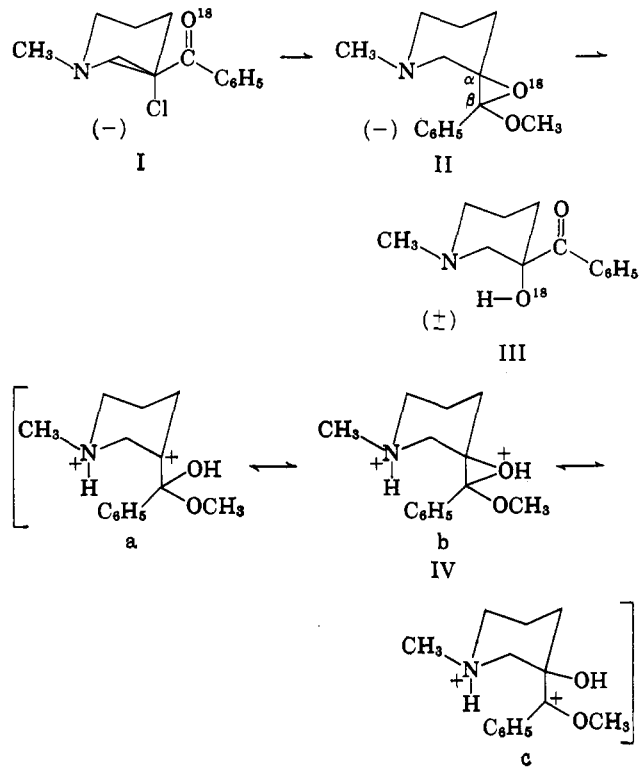
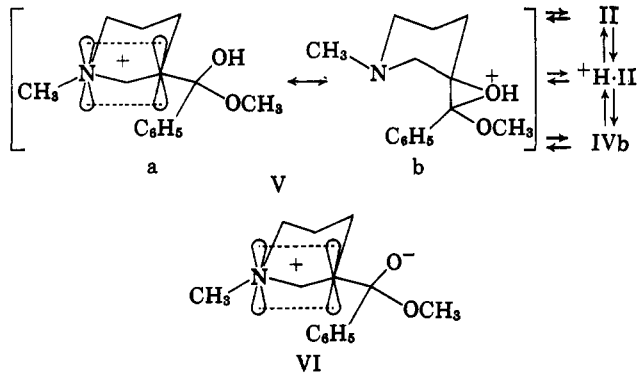
The mechanism of epoxy ether formation from α-halo ketones, proposed by Stevens and Weinheimer,[5] leads to inversion of the α-carbon. It has also been shown that epoxy ether cleavage proceeds by O–β-C scission which would result in retention of configuration at the α-carbon.[6]

However, while treatment of the β-amino α-halo ketone (−)-I with methanolic sodium methoxide or with a methanol-free slurry of sodium methoxide in xylene afforded optically active epoxy ethers, (−)-II or (+)-II, respectively, acidolysis of the epoxy ethers gave racemic α-hydroxy ketone III.[3]

It has been pointed out that inversion in the reaction (−)-I → (+)- or (−)-II must be followed by racemization through IV.[3] It may be argued that stabilization of IVa could be effected by N-deprotonation and participation (*cf.* V) as invoked in the corresponding conjugate base, VI, proposed, with some precedent,[3] as an intermediate in epoxy ether formation.



The more likely alternative involves asymmetric induction of the ketone carbon prior to or concurrent with α-carbon symmetrization[7] (*cf.* VI) in the former reaction, followed by epoxy ether cleavage through IVa and its SN2 counterpart and/or IVc and its SN2 counterpart.[3]



A reinvestigation of this sequence was initiated using isotopically (O^{18}) tagged α-halo ketone (−)-I in an attempt to detect participation of IVa, Va, and the SN2 counterpart.

A sample of (−)-1-methyl-3-benzoyl-3-chloropiperidine,[8] (−)-I, containing 3.04 atom % excess of O^{18} was treated with methanolic sodium methoxide and afforded the epoxy ether (−)-II, containing 1.52 atom % excess of O^{18}. The epoxy ether was subjected to acidolysis: method A, by refluxing in aqueous hydrochloric acid; or method B, by warming in glacial acetic acid followed by hydrolysis of the intermediate acetate ester (not isolated) in aqueous hydrochloric acid.

The racemic ketonic products (III) were freed of exchangeable (C=O^{18}) isotope before elemental and

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(2) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963.

(3) Paper I: T. B. Zalucky, L. Malspeis, and G. Hite, *J. Org. Chem.*, **29**, 3143 (1964).

(4) Author to whom inquiries should be addressed at Columbia University.

(5) C. L. Stevens and H. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1959).

(6) C. L. Stevens and S. J. Dykstra, *ibid.*, **75**, 5975 (1953); *cf.* C. L. Stevens and T. H. Coffield, *J. Org. Chem.*, **23**, 336 (1958).

(7) See ref. 3 for a definition of this term.

(8) (a) E. E. Smissman and G. Hite, *J. Am. Chem. Soc.*, **81**, 1201 (1959); (b) *ibid.*, **82**, 3375 (1960).

isotopic analyses. Since the dextrorotatory acetate ester has been hydrolyzed under more drastic conditions than those employed to remove carbonyl bound O^{18}, without loss of optical activity,[3] it is unlikely that hydroxyl-bound O^{18} is affected. The analytically pure α-hydroxy ketone samples obtained by methods A and B contained 1.54 and 1.50 atom % excess of O^{18}, respectively

Within the limits of confidence of the isotopic analyses, the O^{18} distribution can be interpreted on the basis of a stereospecific, O–β-C, epoxy ether cleavage through IVc and/or its SN2 counterpart, in agreement with the Stevens mechanism. The intervention of other intermediates (*cf.* IVa, Va) would have resulted in a substantial loss of O^{18}. Thus, the anomalous α-C symmetrization, induced by the amino function, must occur during epoxy ether, (+)- or (−)-II, formation and following asymmetric induction of the ketone carbon.[3]

Experimental[9]

Labeling of (−)-I.—To 23.8 g. (0.1 moles) of (−)-I, prepared as previously described,[8] $[\alpha]^{25}D$ −3.6° (*c* 10.10, absolute ethanol), lit.[8] $[\alpha]^{27}D$ −4.2° (absolute ethanol), was added 110 ml. of 1 *N* hydrochloric acid. The solution was lyophilized and afforded a white crystalline material, m.p. 165.5–166.5°, $[\alpha]^{25}D < \pm 0.1°$ (*c* 10.00, water), $[\alpha]^{27}_{330}$ +90 ± 20° (*c* 0.0233, water), lit.[8b] $[\alpha]^{27}_{330}$ +130 (*c* 0.023, water). A small sample of the salt was used to regenerate the free amine, $[\alpha]^{25}D$ −3.8° (absolute ethanol).

A 21.9-g. (80-mmoles) sample of the hydrochloride salt was added to 20 ml. of O^{18}-enriched (5.85 atom % excess) water and warmed on a steam bath to effect complete solution. One drop of concentrated hydrochloric acid was added and heating (50°) was continued for 72 hr. The solution was lyophilized yielding a tan powder which was recrystallized from chloroform, m.p. 165–166°, afforded free amine, $[\alpha]^{25}D$ −3.6° (*c* 9.85, absolute ethanol), and contained 3.04 atom % excess of O^{18}.

Anal. Calcd. for $C_{13}H_{17}Cl_2NO$: C, 56.94; H, 6.25; Cl, 25.86. Found: C, 56.63; H, 6.48; Cl, 25.22.

(−)-2-Methoxy-2-phenyl-5-methyl-1-ox^{18}-5-azaspiro[2.5]octane [(−)-II].—Treatment of 5.58 g. (20 mmoles) of (−)-I hydrochloride with sodium methoxide in anhydrous methanol as described earlier[3] afforded 3.26 g. (14 mmoles, 70%) of (−)-II, b.p. 70–71° (0.08 mm.), containing 1.52 atom % excess of O^{18}: $[\alpha]^{26}D$ −1.3° (*c* 15.80, absolute ethanol).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.90; H, 8.28; N, 6.25.

Acidolysis of (−)-2-Methoxy-2-phenyl-5-methyl-1-ox^{18}-5-azaspiro[2.5]octane [(−)-II].—Two 0.70-g. (3-mmoles) samples of (−)-II were treated according to methods A and B previously described.[3] However, in the case of cleavage with acetic acid (method B) the intermediate acetate ester was not isolated but was hydrolyzed directly. The reaction mixtures, after completion of the acidolysis and subsequent hydrolysis (method B), were made basic with sodium hydroxide and extracted with petroleum ether (b.p. 40–60°). The extract from each reaction mixture was re-extracted with 0.1 *N* hydrochloric acid. The acidic aqueous extract was heated (50–60°) in a water bath for 24 hr., made basic, and extracted with petroleum ether. After two additional cycles, the alcohols were recrystallized from the petroleum ether solution which had been dried over sodium sulfate, treated with charcoal, filtered through sintered glass, and concentrated. From reactions A and B there were obtained 0.550 g. (2.5 mmoles, 83%) and 0.631 g. (2.7 mmoles, 90%), respectively, of racemic α-hydroxy ketone, (±)-III, m.p. 56–57°, lit.[3] m.p. 56–57°, containing 1.54 and 1.50 atom % excess of O^{18}.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81. Found (reaction A): C, 71.19; H, 7.61. Found (reaction B): C, 71.39; H, 7.86.

Acknowledgment.—We are indebted to Dr. H. Fales and Miss Katherine Warren of the National Institute of Health for the rotatory dispersion measurements.

(9) All melting points were obtained in a Hershberg [E. B. 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 silicone 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. Isotopic (O^{18}) analyses were performed by Analytica Corp., New York, N. Y. Specific rotations were determined with a Zeiss 0.01° polarimeter in a modified [G. Hite and J. Lyons, *Chemist-Analyst*, **53**, 84 (1964)] 2-dm. (2-ml.) syringe-filling tube. The criterion for racemic products obtained from optically active starting materials was a level base line in the range 700–320 mμ as determined with a Rudolph manual spectropolarimeter. The O^{18}-enriched water was obtained from Isomet, Inc., Palisades Park, N. J.

A-Norsteroids. Ketalization of A-Nortestosterone

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The ketalization of Δ^4-3-keto steroids has been shown to give Δ^5-3-ketals,[1] Δ^4-3-ketals,[2] or mixtures of both[2] by varying conditions of acid strength or acid concentration. We wish to report our findings on the ketalization of a ring A steroidal α,β-unsaturated ketone in the A-nor series.[3]

The preparation of the ethylene ketal derivative of A-nortestosterone[4] (I) was carried out under reaction conditions (benzene, ethylene glycol, *p*-TsOH)[1,2] similar to those used for testosterone and 17β-hydroxy-A-nor-5α-androstan-2-one,[5] except that we found it necessary to conduct the reaction for a longer period of time (5–7 days) in order to obtain the ethylene ketal derivative (II) in reasonable yields. With varying concentrations of *p*-toluenesulfonic acid, however, only one ethylene ketal was obtained.

Evidence concerning the position of the double bond in II was obtained from the physical and chemical properties of the compound: (a) the change in optical rotation in going from the parent ketone to the ethylene ketal was dextrorotatory (−22° → +34°); this conversion is generally accompanied by a levorotatory shift in the formation of Δ^5-3-ketals[6]; (b) a relatively strong band appeared in the infrared spectrum at 6.03 μ; Δ^4-3-ethylene ketals are reported to absorb at 6.00 μ[2a,b]; and (c) when a solution of II in chloroform containing a trace of water was left overnight at room temperature, A-nortestosterone was obtained. The susceptibility of allylic ketals to mild acid hydrolysis has previously been noted.[2a,c]

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(3) J. Fried and E. Sabo [*J. Am. Chem. Soc.*, **84**, 4356 (1962)] have reported the ketalization of a Δ^5-3-keto-A-norsteroid with *p*-toluenesulfonic acid gives a mixture consisting mainly of the Δ^5-5β-3-ethylene ketal and a Δ^5-3-ethylene ketal.

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