was added to incipient crystallization. The crude product, m.p. 175–205°, was recrystallized once from acetic acid to give 0.3 g. (25%), orange needles, m.p. 210–212°.

Treatment of Dibenzalacetone DNPH with 90% Acetic Acid and Hydrobromic Acid.—A solution of 1.2 g. (0.003 mole) of dibenzalacetone DNPH in 150 ml. of 90% acetic acid containing 0.25 ml. of 48% hydrobromic was refluxed 6.5 hours. The solution was concentrated to 50 ml. and water was added to incipient crystallization. The crude product, m.p. 207–210°, was recrystallized from acetic acid to give 0.7 g. (58%), orange needles, m.p. 212–214°. The infrared spectrum showed no NH peak at 3.07 μ (3257 cm.$^{-1}$).

Reaction of 2,4-Dinitrochlorobenzene with 3-Styryl-5-phenyl-2-pyrazoline.—The 3-styryl-5-phenyl-2-pyrazoline which was used was a crude pale-yellow viscous oil; the N-nitroso derivative, m.p. 149–150°, was prepared to identify the pyrazoline.[6] A solution of 7.5 g. (0.030 mole) of 3-styryl-5-phenyl-2-pyrazoline in 100 ml. of ethanol was added to a solution of 6.8 g. (0.034 mole) of 2,4-dinitrochlorobenzene in 100 ml. of ethanol. The mixture was refluxed 2 hours during which time it turned deep red. After much of the solvent was removed, the material was refrigerated. The deep-red crude product which was recovered was taken up in hot ethanol, from which an orange product, m.p. 207–209°, was recovered. The crude product was recrystallized from ethyl acetate to give 6.1 g. (59%), orange crystals, m.p. 212–213°. This product did not depress the melting point of the product obtained by the treatment of dibenzalacetone DNPH with acetic acid. The infrared spectra (2–15 μ) of these products were identical.

Anal. Calcd. for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 67.73, 67.32; H, 4.36, 3.34; N, 12.85.

Reaction of 2,4-Dinitrochlorobenzene with 5-Phenyl-2-pyrazoline in Absolute Ethanol in the Presence of Fused Sodium Acetate.—The 5-phenyl-2-pyrazoline which was used was a colorless oil and distilled at 120–124° (1 mm.); the picrate derivative, m.p. 115–116°, was prepared to identify the pyrazoline.[5] A solution of 6.0 g. (0.041 mole) of 5-phenyl-2-pyrazoline in 25 ml. of absolute ethanol was added to a solution of 8.5 g. (0.042 mole) of 2,4-dinitrochlorobenzene in 350 ml. of absolute ethanol containing 4 g. of fused sodium acetate. The solution was refluxed for a period of 3.5 hours and then cooled. The sodium chloride which came down was filtered off and the solution was concentrated to about 50 ml. A red oil came down which after 24 hours crystallized. The crude product was recrystallized first from methanol and then from acetic acid to give 6.3 g. (49%), yellow crystals, m.p. 157–158°. The infrared spectrum showed no NH peak at 3.07 μ (3257 cm.$^{-1}$).

Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.33, 57.34; H, 3.79, 3.79; N, 17.89.

When, on the other hand, 2,4-dinitrochlorobenzene and 5-phenyl-2-pyrazoline were treated in 95% ethanol in the absence of sodium acetate, an orange product, m.p. 214–217°, was obtained. This material did not depress the melting point of 1-(2,4-dinitrophenyl)-3-phenyl-2-pyrazoline.

Preparation of the Low-melting Isomer of Cinnamaldehyde DNPH.—A mixture of 10 g. (0.05 mole) of 2,4-dinitrophenylhydrazine in a sixfold excess of cinnamaldehyde was allowed to react at room temperature. After an hour the excess cinnamaldehyde with the dissolved derivative was separated by suction filtration. To the filtrate was added 200 ml. of ethanol, followed by 200 ml. of a 1:1 mixture of water–ethanol. The voluminous orange precipitate was collected and dried. The crude product was recrystallized from benzene to give a low yield of orange needles, m.p. 196–197°. The melted material solidified and re-melted at 248–250°. The low-melting derivative was quantitatively converted to the high-melting derivative when treated with hot acetic acid. The ultraviolet spectra in chloroform of the materials were different. The infrared spectra of these isomeric cinnamaldehyde derivatives were almost identical from 3 to 8 μ. The region from 8 to 15 μ showed variations in the positions and in the intensities of the corresponding absorption peaks.

(6) N. Kishner, *Chem. Zentr.*, **88**, II, 318 (1916).

UNIVERSITY PARK, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN SCHOOL OF PHARMACY]

The Quasi-Favorskii Rearrangement. II.[1] Stereochemistry and Mechanism

BY EDWARD E. SMISSMAN AND GILBERT HITE[2,3]

RECEIVED MAY 4, 1959

The skeletal rearrangement of (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV) provides a means by which the mechanism and the stereochemistry of the quasi-Favorskii rearrangement may be studied. The (−)-α-halogenated ketone IV afforded racemic rearrangement acid X and residually dextrorotatory α-hydroxy ketone VI. Both chemical evidence and optical rotatory dispersion (o.r.d.) studies indicate that the rearrangement is intermediated by ion pairs. A unified mechanism has been presented for the skeletal rearrangement of α-halogenated ketones possessing no α-hydrogen (the quasi-Favorskii rearrangement).

Stevens and Farkas[4] have obtained 1-phenylcyclohexanecarboxylic acid (III) from the rearrangement of α-chlorocyclohexyl phenyl ketone (I) with powdered sodium hydroxide in refluxing xylene. To explain the high yield (53%) of rearrangement acid III, they have suggested a surface-catalyzed reaction in which the anionoid transition state is formed by initial nucleophilic attack of a hydroxide ion at the carbonyl carbon of the α-halogenated ketone I. Tchoubar and Sackur[5] were the first to observe this reaction. They favored a similar semi-benzilic rearrangement in which the migrating and the departing groups and the two continguous carbon atoms might be expected to be planar with the groups *trans*.[6] Equally as important as the mechanistic sequence is the tangible but unobservable (in this case) stereochemical result predicted by these[4,5] rationalizations: that is, inversion at the reaction terminus.

With the realization of the rearrangement of (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV), it became possible, for the first time, to observe the

(1) For the first paper in this series, see: E. E. Smissman and G. Hite, THIS JOURNAL, **81**, 1201 (1959).

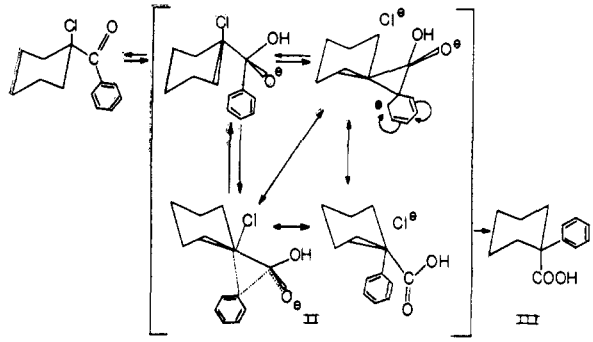
(2) This and the previous publication comprise a portion of the thesis presented by G. H. in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Chemistry at the University of Wisconsin. Recipient of the Lunsford Richardson Pharmacy Award, First Prize, Central Section, 1959.

(3) This work was presented, in part, at the 135th Meeting of the American Chemical Society in Boston, Mass., April, 1959.

(4) C. L. Stevens and E. Farkas, THIS JOURNAL, **74**, 5352 (1952).

(5) B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

(6) D. Y. Curtin and P. I. Pollak, THIS JOURNAL, **73**, 992 (1951).



stereochemistry and to elucidate the mechanism of the quasi-Favorskii rearrangement.

The rearrangement was effected by refluxing the (−)-α-halogenated ketone IV with dry, powdered sodium hydroxide in anhydrous xylene or high boiling petroleum ether (Skelly E). The reaction yielded (±)-1-methyl-3-carboxy-3-phenylpiperidine (X), (+)-1-methyl-3-benzoyl-3-hydroxypiperidine (VI), which was 85–90% racemic, benzoic acid (XII), and an unidentified amine fragment. No rearrangement acid X was obtained when ether or Skelly A were employed as the solvents.

The dehydrohalogenated derivatives of the α-halogenated ketones have been sought but never detected among the products of these rearrangement reactions.

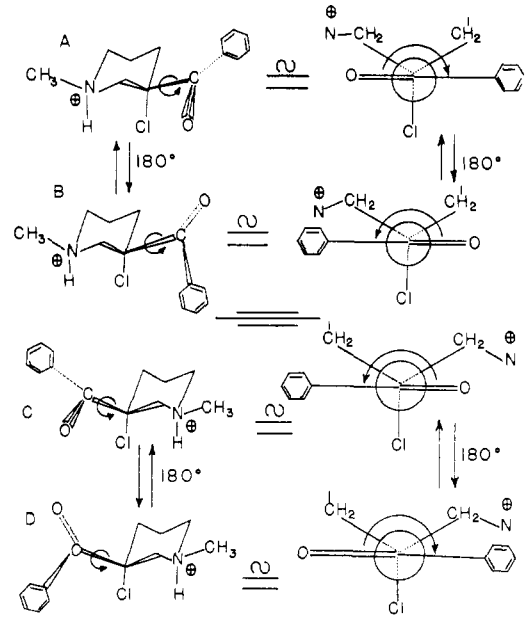


Fig. 1.—Acyl-to-ring rotamers in the halogen-axial conformations of the two enantiomers of 1-methyl-3-benzoyl-3-chloropiperidine in acidic solution.

The (−)-α-halogenated ketone IV was quantitatively dehalogenated in less than 15 minutes, whereas α-chlorocyclohexyl phenyl ketone (I) appears to react at a much slower rate.[4]

The optically active ketone IV was 10% racemized after thirty minutes in anhydrous refluxing xylene.

The (+)-α-hydroxy ketone VI was optically stable to treatment with dry powdered sodium hydroxide in anhydrous xylene after refluxing for thirty minutes.

The rearrangement of 1-methyl-4-chloro-4-benzoylpiperidine is sensitive to both the solvent volume and the sodium hydroxide content of the system.[7]

When treated with sodium hydroxide in aqueous acetone at room temperature for four hours, IV was quantitatively dehalogenated. It gave (±)-α-hydroxy ketone XI. No rearrangement acid X could be isolated from this reaction nor was any found after refluxing IV or XI with 5% or 30% sodium hydroxide in aqueous dioxane.

Treatment of racemic IV with methanolic sodium methoxide gave a product with no carbonyl absorption in the infrared.[4,8] However, using methanol-free sodium methoxide suspended in anhydrous refluxing xylene, IV gave a chlorine free, dextrorotatory oil which had the same infrared spectrum except for a carbonyl band at 5.97 μ. No rearrangement was detected.

Optical Rotatory Dispersion Studies.—The empirical axial α-halogenated ketone dispersion rule,[9] developed by Djerassi and co-workers,[9–11] provides a means of determining the absolute configuration of α-halogenated ketones without reference to compounds of known configuration.[10,11] Recent work with 17α-halo-20-ketopregnanes has suggested that the rule also may be employed to differentiate free rotational isomers in these acetylcycloalkanes.[12] Most likely this is applicable to the general class of α-halogenated acylcycloalkanes of this type.

The halogen atom maintains the axial orientation by virtue of structural constraints in the axial α-halo-keto steroids.[9,10] In the α-halo acylcycloalkanes, the halogen is attached to the ring carbon and the quasi-axial orientation with respect to the carbonyl group is achieved by rotation about the acyl-to-ring bond. This is stabilized by conformational constraints in the 17α-halo-20-ketopregnanes,[12] and by electrostatic constraints[13,14] in the 3-halo-3-acylpiperidines.

(7) The rearrangement of I is reported to be insensitive to the particle size of the sodium hydroxide; ref. 4.

(8) R. E. Lyle, S. A. Leone, H. J. Troscianiec and G. H. Warner, *J. Org. Chem.*, **24**, 330 (1959).

(9) The α-halogenated ketone dispersion rule may be stated as follows: "In viewing the optically active chromophore [for nomenclature, see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957)]

(X = Cl, Br, not F, I), along the carbonyl bond with the oxygen closer to the observer's eye and with the halogen down, if the halogen atom is to the right of the carbonyl group, the sign of the single Cotton effect curve will be positive; if to the left, negative, providing the halogen atom bears an axial or quasi-axial orientation with respect to the carbonyl group."

(10) C. Djerassi and W. Klyne, THIS JOURNAL, **79**, 1506 (1957).

(11) C. Djerassi, J. Osiecki, R. Rinicker and B. Rinicker, *ibid.*, **80**, 1216 (1958).

(12) C. Djerassi, I. Fornaguera and O. Mancera, *ibid.*, **81**, 2383 (1959).

(13) Electrostatic interactions can be used to predict the preferred rotational isomers of a pair of enantiomers; however, there is no rigorous chemical proof that 3-halo-3-acylpiperidines, in which such interactions are operable, will conform to the rule. This tentative extension was suggested by C. Djerassi (personal communication).

(14) For more subtle electrostatic effects observed with o.r.d., see C. Djerassi and L. E. Geller, *Tetrahedron*, **3**, 319 (1958).

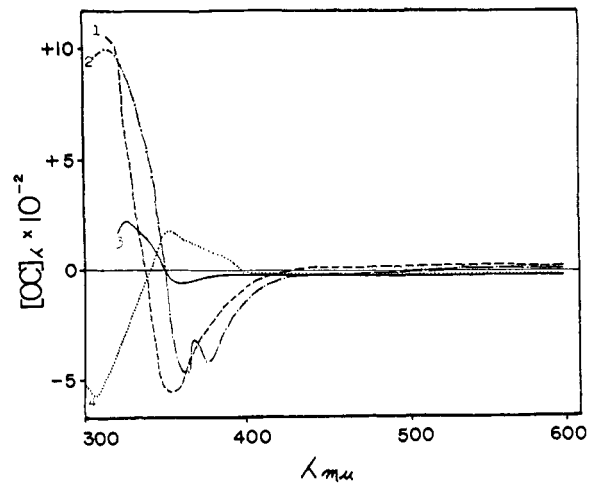


Fig. 2.—The optical rotatory dispersion curves of: 1, (+)-1-methyl-3-benzoyl-3-hydroxypiperidine (VI) in 0.1 *N* hydrochloric acid; 2, (+)-1-methyl-3-benzoyl-3-hydroxypiperidine (VI) in octane; 3, (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV) in 0.1 *N* hydrochloric acid; 4, (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV) in octane.

Examination of molecular models reveals that the more stable conformations of the two enantiomorphic forms of 1-methyl-3-benzoyl-3-chloropiperidine are those in which the chlorine is axial with respect to the ring. In acidic solution, the preferred antipodal rotational conformers are those in which the carbonyl oxygen electrons are closer to the cationoid nitrogen (Fig. 1, A, C not B, D).

Application of the dispersion rule to A and C requires that A represents the absolute configuration of (−)-1-methyl-3-benzoyl-3-chloropiperidine (*cf.* IV) since A predicts a negative single Cotton effect curve in agreement with the observed result (Fig. 2).

The o.r.d. curve of the same enantiomer was obtained in octane solution. It exhibited a positive Cotton effect (Fig. 2). Inversion of the sign of the Cotton effect by changing solvent is rationalized in the following manner. There was an electrostatic attraction between the cationoid nitrogen and the carbonyl oxygen electrons in an acidic medium. In a non-polar medium, an electrostatic repulsion between the free electron pair on nitrogen and the carbonyl oxygen electrons exists. Therefore, the more stable forms of the antipodal rotational conformers can be chosen (Fig. 3, F, H not E, G).

The dispersion rule requires that F represents the absolute configuration of the (−)-α-halogenated ketone (*cf.* IV), the same conclusion arrived at in the argument above.

Inspection of molecular models indicates that the more stable conformations of the two enantiomorphs of 1-methyl-3-benozyl-3-hydroxypiperidine are those in which the hydroxyl is axial with respect to the ring. By the same reasoning used for the α-halogenated ketones, the more representative rotational conformers in acidic solution will be J and K (Fig. 4).

Application of the dispersion rule to these projections indicates that J, which predicts a negative Cotton effect curve, in accordance with the observed result (Fig. 2), represents the absolute configuration of the (+)-α-hydroxy ketone (*cf.* VI).[15]

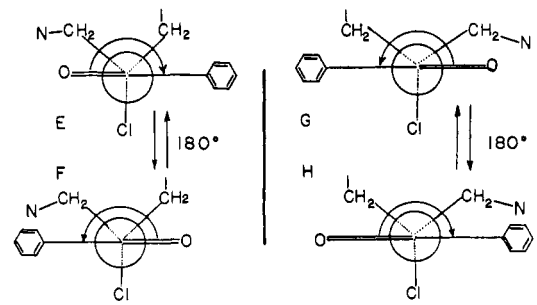


Fig. 3.—Acyl-to-ring rotamers in the halogen-axial conformations of the two enantiomers of 1-methyl-3-benzoyl-3-chloropiperidine in octane.

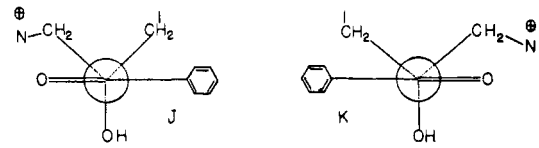


Fig. 4.—The preferred acyl-to-ring rotamers in the hydroxyl-axial conformations of the two enantiomers of 1-methyl-3-benzoyl-3-hydroxypiperidine in acidic solution.

In octane solution, the (+)-α-hydroxy ketone shows a negative Cotton effect curve (Fig. 2). Unlike the α-halogenated ketone, no inversion in the sign of the Cotton effect is observed in passing between octane and 0.1 *N* acid. The bases upon which acceptance of the applicability of the dispersion rule to these α-hydroxy ketones rests[15] could only be valid if the same configurational rotamer were responsible for the negative Cotton effect observed in both acid and octane solutions, that is, J (Fig. 4).

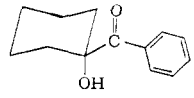
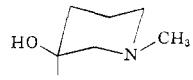
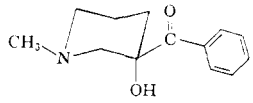
It was predicted that a stabilizing influence of the hydroxyl group favored that rotamer in which the carbonyl oxygen was closer to the nitrogen (J or its antipode).

Inspection of molecular models suggested that intramolecular hydrogen bonding of the C_3-hydroxyl to the tertiary amine function would account for a negative Cotton effect from J, not its antipode, by virtue of the partial positive charge imparted to the nitrogen. The prediction was confirmed by infrared evidence (Table I).

Consequently, J represents the absolute configuration of the (+)-α-hydroxy ketone (*cf.* VI). This conclusion is in accord with the o.r.d. data obtained in acid solution.

(15) The use of the dispersion rule to assign absolute configurations to the α-hydroxy ketones is justified on these bases: (a) The hydroxy group is not expected to produce any new conformational or electrostatic changes in these structures in acidic media. (b) Both the (−)-α-halogenated ketone and the (+)-α-hydroxy ketone give negative Cotton effect curves in 0.1 *N* acid, a fact which indicates that in both compounds the stereochemical environment about the carbonyl group is the same. (c) In a series of twenty axial or quasi-axial α-hydroxy and α-acyloxy steroidal ketones whose o.r.d. characteristics have been reported in the literature, all but four have been correctly accompanied by this extension of the rule [C. Djerassi, O. Halpern, V. Halpern, O. Schindler and Ch. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958); E. W. Foltz, A. E. Lippman and C. Djerassi, THIS JOURNAL, **77**, 4359 (1955)].

TABLE I[16,17]

Compound	Non-bonded hydroxyl, cm.$^{-1}$	Intramolecularly bonded hydroxl, cm.$^{-1}$
	3618	..
	3603	3466
	3623	3538
	Absent	3455 3340

Discussion

The mechanism involves an initial unimolecular-type ionization of the (−)-α-halogenated ketone IV. The charge separation is facilitated by a 1–3 internal, bimolecular-type, nucleophilic substitution "1–3 SN2i" on the α-carbon bearing the halogen by the electron pair on nitrogen.[18] This affords a configuration retaining intimate (internal)[19] ion pair (V) which yields (+)-alcohol VI of retained configuration by anion exchange and subsequent collapse to VI. Greater separation of the charges in V gives an "internally solvated" racemic cation which is probably present as a solvent separated (external) ion pair (VII). Participation of the phenyl group through a phenonium ion intermediate (quasi-cyclopropanone intermediate, IX), anion exchange and collapse of this external ion pair IX leads to racemic acid X. Racemic α-hydroxy ketone (XI) is formed from VII upon anion exchange and collapse of the resulting racemic ion pair. Participation of the carbonyl oxygen (VII → VIII) gives, by anion exchange and collapse of the resulting ion pair, unstable, racemic, internal hemi-ketal VIII. Stabilization of VIII constitutes an alternate route to racemic α-hydroxy ketone XI.

It was stated above that the rearrangement of 1-methyl-4-chloro-4-benzoylpiperidine is sensitive to both solvent volume and sodium hydroxide content of the system. Therefore, in view of the experimental evidence, hydroxyl ion in solution need not play a role in the rearrangement and the reaction is postulated to occur at the sodium hydroxide ionic surface.

The validity of the mechanism is dependent upon the fact that the (−)-α-halogenated ketone (IV) and the (+)-α-hydroxy ketone (VI) have the same relative configuration. The interpretation of the o.r.d. data bears this out and leads to the assignment of the absolute configurations shown in IV and VI. The optical specificity and the racemization of IV in refluxing anhydrous xylene place the ion pair postulate on a secure foundation. Classical theory used to rationalize the chemical results provides further evidence to justify this mechanism.

While it is impossible to say which of the two conformers (IVa, IVe) is the more abundant at 135°, the IVa conformation would be the more likely precursor of dehydrohalogenated products. Facile unimolecular elimination in a non-polar solvent is considered improbable. Bimolecular eliminations are less hindered in non-polar media, but this is considered unlikely since experimental evidence indicates that the nucleophile concentration [OH] is low or non-existant in these anhydrous media. The rate differential, attributed to the anchimeric effect of the nitrogen, has precedent in the higher rates of reaction of halogenated piperidines compared with their cyclohexyl counterparts.[18] The SN2i attack postulated is not without precedent in the classical Favorskii rearrangement.[20] Since the conformation in which the chlorine is equatorial (IVe) is the only one in which this type of attack could be effected, it is not surprising that no dehydrohalogenation products can be detected. Consequently the reaction proceeds entirely through the IVe conformation.

The isolation of racemic acid X is in agreement with the common intermediate VIII from which it and the remainder of the alcohol (racemic, XI) is derived. The rearrangement takes place in the racemic external ion pairs and not by a semi-benzilic mechanism. To explain the high yield of rearrangement acid III nucleophilic attack at the carbonyl group should be deferred. If Cβ–O$^{\ominus}$ is present together with Cβ–OH and Cβ–C_6H_5 on one carbon atom, high yields of rearrangement acid III are difficult to rationalize in view of the known facility of participation of neighboring groups in some pinacolic displacement reactions that is, Cβ–O$^{\ominus}$ >> Cβ–C_6H_5 > Cβ–OH.[21,22]

If ion pairs were intermediates in these rearrangements, compound I would give a higher yield of rearrangement acid III than its bromo analog.[4] Since the C–Br bond is more polarizable than the C–Cl bond, the bromo analog would be less able to maintain the configuration of external ions VII and IX. Anion exchange and formation of VI and XI would predominate. Rearrangement should be favored by high temperature and non-polar solvents. These trends are evident in the α-halocyclohexyl phenyl ketone series[4] and in our own work. The still lower yields of 1-methyl-4-carboxy-4-phenylpiperidine (25%)[1] and (±)-1-methyl-3-carboxy-3-phenylpiperidine (5–10%) also fit this rationalization since the carbon-to-chlorine bond is made more polarizable in the latter due to the proximity of the lone pair of electrons on nitrogen in their respective precursors.

(16) These data were abstracted from a paper by G. Hite, E. E. Smissman and R. West, THIS JOURNAL, **82**, 1207 (1960).

(17) The spectra were run in carbon tetrachloride using a Perkin-Elmer, model 112, single beam, infrared spectrophotometer (0.01 *M*, cell path 10 mm.).

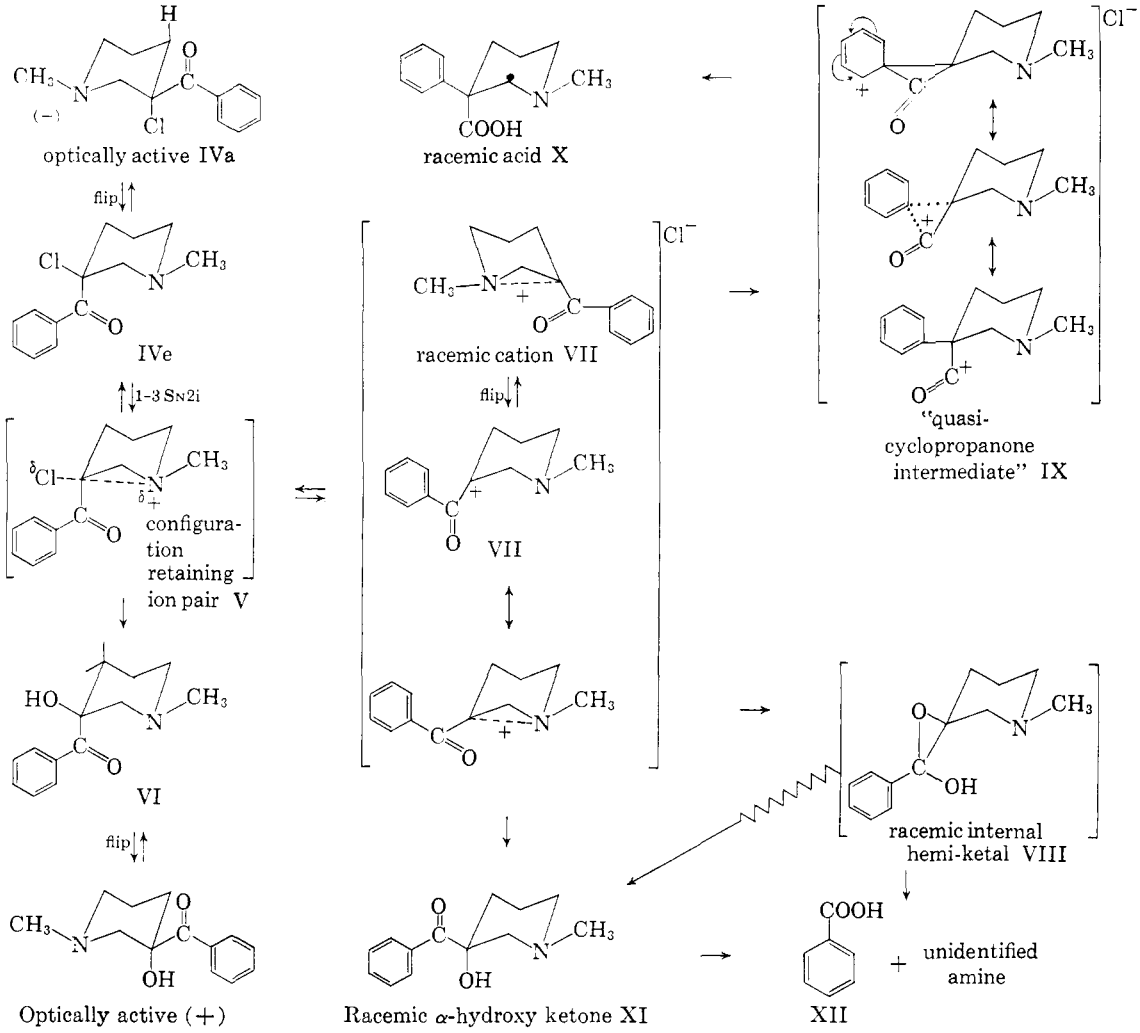
(18) A. T. Bottini, C. A. Grob and E. Schumacher, *Chemistry & Industry*, 757 (1958).

(19) For nomenclature, see S. Winstein, E. Clippinger, A. A. Fainberg, R. Heck and C. G. Robinson, THIS JOURNAL, **78**, 328 (1956).

(20) R. B. Loftfield, *ibid.*, **73**, 4707 (1951); I. J. Borowitz, Ph.D. Thesis, Columbia University, 1956; A. S. Kende, "Organic Reactions," in press; and N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(21) J. F. Lane and D. R. Walters, THIS JOURNAL, **73**, 4238 (1951).

(22) This order of aptitude is observed in the reaction of IV with sodium methoxide in methanol. This, and the methoxide reaction in non-polar solvents, is the subject of a paper now in preparation by E. E. S. and G. H.; *cf.* ref. 8.



The mechanism suggested by Stevens and Farkas[4] and by Tchoubar and Sackur[5] are contravened by the ion pair mechanism. Because of the dominant role played by the nitrogen in the piperidines, it may be argued that this does not represent a "classical quasi-Favorskii rearrangement." Ultimate resolution of this point can be achieved by rearrangement of a suitably constituted, non-nitrogenous, optically active, α-halogenated ketone which is now being prepared.

Acknowledgments.—We are indebted to Parke-Davis and Co. for financial support of this research; to Dr. C. Djerassi of Syntex, S.A., for his helpful comments and suggestions on the interpretation of the o.r.d. data; to Dr. E. Eisenbraun and Mrs. T. Nakano of Wayne University for the o.r.d. measurements; to Dr. R. West of the University of Wisconsin for the high resolution infrared spectra and his helpful comments thereon; to Dr. Jackson Hester for a sample of (−)-10-camphorsulfonic acid; and to Dr. W. Wildman of the National Institutes of Health for an O.R.D. measurement of the acid X.

Experimental

All melting points were obtained in a Hershberg-type, silicone filled melting point apparatus equipped with Anschütz 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° per minute. Elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England. A Zeiss–Winkel polarimeter was used to determine specific rotations ($\alpha^{t}D$).

Resolution of (+)-1-Methyl-3-benzoyl-3-hydroxypiperidine (XI).—The racemic alcohol XI and (+)-10-camphorsulfonic acid were dissolved in equimolar amounts in two separate portions of ethyl acetate and then mixed. Recrystallization from ethyl acetate afforded the (+)-10-camphorsulfonate salt of (+)-1-methyl-3-benzoyl-3-hydroxypiperidine (VI), m.p. 145–146° dec., $\alpha^{25}D$ (absolute ethanol) +28.4°.

Anal. Calcd. for $C_{23}H_{33}NO_6S$: C, 61.17; H, 7.37; N, 3.10; S, 7.10. Found: C, 61.00, H, 7.39; N, 3.18; S, 6.34

Treatment of the racemic amine XI with (−)-10-camphorsulfonic acid afforded the (−)-10-camphorsulfonate salt of (−)-1-methyl-3-benzoyl-3-hydroxypiperidine, m.p. 145–146° dec., $\alpha^{25}D$ (absolute ethanol) −28.3°.

The free (+)-amino alcohol VI was recrystallized from Skelly A; m.p. 72.5 − 73°, $\alpha^{25}D$ (absolute ethanol) +11.4°; R.D. (Fig. 2) in 0.1 *N* hydrochloric acid (*c* 0.072), 25°, negative Cotton effect curve: $[\alpha]_{700}$ + 15°, $[\alpha]_{589}$ + 25°, $[\alpha]_{500}$ + 35°, $[\alpha]_{400}$ −25°, $[\alpha]_{380}$ −150°; (*c* 0.014) $[\alpha]_{360}$ −430°, $[\alpha]_{347.5}$ −545°, $[\alpha]_{340}$ −450°, $[\alpha]_{330}$ + 55°, $[\alpha]_{325}$ + 355°, $[\alpha]_{320}$ + 700°, $[\alpha]_{315}$ + 985°, $[\alpha]_{310}$ + 1045°; R.D. (Fig. 2) in octane (*c* 0.089), 25°, negative Cotton effect curve: $[\alpha]_{700}$ + 15°, $[\alpha]_{589}$ + 10°, $[\alpha]_{500}$ + 5°, $[\alpha]_{400}$ − 85°, $[\alpha]_{375}$ − 345°, $[\alpha]_{370}$ − 420°, $[\alpha]_{362.5}$ − 335°, $[\alpha]_{355}$ − 435°, $[\alpha]_{350}$ −340°; (*c* 0.017) $[\alpha]_{340}$ + 210°, $[\alpha]_{320}$ + 880°, $[\alpha]_{310}$ + 1000°, $[\alpha]_{300}$ + 955°.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.18; H, 8.07; N, 6.28.

The free (−)-amino alcohol was recrystallized from Skelly A, m.p. 72.5–73°, $\alpha^{25}D$ (absolute ethanol) −11.6°, and gave o.r.d. curves in both octane and 0.1 *N* hydrochloric acid which were perfectly antipodal to the curves obtained for the (+)-amino alcohol VI in these solvents.

Resolution of (+)-1-Methyl-3-benzoyl-3-chloropiperidine.—The racemic amine was dissolved in cold (0°) absolute ethanol. This was added slowly to an equimolar amount of (+)-10-camphorsulfonic acid in warm absolute ethanol. The crystals were redissolved in absolute ethanol (3 ml. per g. of salt) and to the warm solution was added hot ethyl acetate (6 ml. per g. of salt). After eleven recrystallizations, the pure (+)-10-camphorsulfonate salt of (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV), m.p. 182–183° dec., $\alpha^{25}D$ (water) +11.6°, was obtained.

Anal. Calcd. for $C_{23}H_{32}NClO_5S$: C, 58.78; H, 6.86; N, 2.98; Cl, 7.54; S, 6.82. Found: C, 58.70; H, 6.94; N, 3.02; Cl, 7.74; S, 6.72.

Pure (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV) was obtained from the above salt by the method described for the preparation of amines for use in the rearrangement; m.p. 25–26°, $\alpha^{27}D$ (absolute ethanol) −4.2°; R.D. (Fig. 2) in octane (*c* 0.082), 27°, positive Cotton effect curve: $[\alpha]_{700}$ −19°, $[\alpha]_{589}$ −15°, $[\alpha]_{400}$ −5°, $[\alpha]_{380}$ + 70°; (0.016) $[\alpha]_{360}$ + 125°, $[\alpha]_{350}$ + 175°, $[\alpha]_{340}$ + 25°, $[\alpha]_{320}$ −375°, $[\alpha]_{307.5}$ − 600°, $[\alpha]_{300}$ − 550°; R.D. (Fig. 2) in 0.1 *N* hydrochloric acid (*c* 0.119), 29°, negative Cotton effect curve: $[\alpha]_{700}$ −1°, $[\alpha]_{589}$ −12°, $[\alpha]_{380}$ −15°, $[\alpha]_{360}$ −32°, $[\alpha]_{352.5}$ − 55°, $[\alpha]_{345}$ − 32°; (*c* 0.023) $[\alpha]_{340}$ + 43°, $[\alpha]_{330}$ + 130°, $[\alpha]_{330}$ + 218°, $[\alpha]_{320}$ + 218°, $[\alpha]_{317.5}$ + 235°, $[\alpha]_{315}$ + 182°.

Anal. Calcd. for $C_{13}H_{16}NOCl$: Cl, 14.91. Found: Cl, 14.86.[23]

Rearrangement of (−)-1-Methyl-3-benzoyl-3-chloropiperidine (IV).—An analytically pure sample of the (+)-10-camphorsulfonate salt of the (−)-amine IV was dissolved in water treated with excess sodium bicarbonate and extracted with purified Skelly A. After drying over sodium sulfate, the solvent was removed under a stream of dry nitrogen until the concentration of free amine was about 6 g. per 25 ml. of solution. If cloudy, the solution was treated with carbon, filtered through sintered glass, and rapidly cooled in an acetone–Dry Ice-bath. Scratching usually initiated crystallization. The remainder of the solvent was removed under reduced pressure at 0°. The crystals were dried (0° (0.1 mm.)) overnight, stored under vacuum, and placed in the refrigerator until used.

A dry reaction vessel was charged with 200 ml. of anhydrous xylene and 10.0 g. (0.25 mole) of freshly prepared, finely powdered, dried (150–160° (0.01 mm.), 12 hours) sodium hydroxide. The slurry was brought to reflux and 50 ml. of a solution containing 5.943 g. (0.025 mole) of (−)-amine IV in anhydrous xylene was introduced in a period of 10 minutes. The mixture was immediately cooled in an acetone–Dry Ice-bath and flushed with carbon dioxide gas.[24]

Test for Unreacted α-Halo Ketone.—Twenty-five ml. of the xylene solution was siphoned, mixed with 100 ml. of anhydrous ether, filtered through sintered glass, mixed with filter cell and carbon, and refiltered. The amines were extracted with 0.2 *N* hydrochloric acid. The aqueous layer was washed with purified Skelly A, treated with sodium bicarbonate, and extracted with Skelly A. After drying over sodium sulfate and treating with carbon, the solvent was removed leaving a colorless chlorine-free oil, 0.450 g. of which crystallized on cooling.

The remainder of the reaction mixture was diluted with 400 ml. of anhydrous ether, and extracted with small portions of water until the washings were neutral. Extraction of the amines as outlined above afforded an additional 4.10 g. of material.

Test for Dehydrohalogenated Products (Unsaturation).—One gram of the above oil was dissolved in glacial acetic acid or in 5% hydrobromic acid and treated with bromine. After neutralizing with sodium bicarbonate, extracting with Skelly A, drying, and decolorizing with carbon, the oil obtained was bromine free.

(23) This was a gravimetric analysis performed in our laboratory due to the instability of this compound.

(24) Continued heating does not increase the yield of rearrangement acid X; it lowers the yield of α-hydroxy ketone (VI, XI) and increases the yield of benzoic acid. Flushing quenches the reaction.

Optical Rotation of the Amine Fraction.—The isolated amines were recrystallized from Skelly A yielding residually dextrorotatory 1-methyl-3-benzoyl-3-hydroxypiperidine (VI) $\alpha^{25}D$ + 1.3° (88% racemic). The total yield was 4.55 g. (0.021 mole, 84%).

Isolation of Benzoic Acid (XII).—The aqueous extract from the reaction mixture was acidified to *p*H 2.0 with hydrochloric acid and extracted with ether. After drying and removing the solvent, the solid was placed under vacuum (0.1 mm.) overnight. Titration showed the presence of 1.150 g. (0.013 mole, 5%) of benzoic acid which was isolated and crystallized, m.p. 120°.

Isolation of Rearrangement Acid (X).—The acidic aqueous solution from which the benzoic acid had been extracted was neutralized to *p*H 7.00. The *p*H was checked intermittently as the solvent was removed. The residue was dried (80° (0.01 mm.), 8 hours), ground to a fine powder, and extracted with chloroform in a soxhlet apparatus for 10 hours. Removal of the solvent gave 0.600 g. of a solid which, when recrystallized from chloroform, yielded 0.385 g. (0.017 mole, 7.0%) of pure rearrangement acid *m*, m.p. 250–250.5° dec. (lit.[1] m.p. 250–250.5° dec.).

Neither a 20% aqueous solution nor a 3% methanolic solution of this material (1 dm.) showed optical activity in the Zeiss–Winkel polarimeter. An o.r.d. curve further corroborated this finding.

The hydrochloride salt of (±)-1-methyl-3-carboxy-3-phenyl-piperidine was prepared from a sample of the rearrangement acid isolated from the rearrangement of the (±)-1-methyl-3-benzoyl-3-chloropiperidine.[1] Recrystallization from acetic acid–benzene gave white crystals, m.p. 274.5–275.5° dec. (lit.[25] m.p. 265°).

Anal. Calcd. for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.05; H, 7.09; N, 5.48; Cl, 13.86. Found: C, 61.11; H, 7.10; N, 5.39, Cl, 13.92.

The ethyl ester hydrochloride was synthesized from the above material by treatment with thionyl chloride and subsequent ethanolysis of the acyl halide hydrochloride. Recrystallization from ethyl acetate afforded ethyl (±)-1-methyl-3-phenyl-3-piperidine-carboxylate hydrochloride, m.p. 177.5–178.5° dec. (lit.[23] m.p. 177–180°).

The melting points of the known racemic rearrangement acid, its hydrochloride salt and its ethyl ester hydrochloride were identical with and undepressed by admixture with samples of these materials derived from the rearrangement acid isolated from the rearrangement of (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV).

Reaction of (−)-1-Methyl-3-benzoyl-3-chloropiperidine (IV) with Sodium Hydroxide in Acetone–Water.—When 0.405 g. (0.0017 mole) of the optically active amine IV was treated for 4 hours at room temperature with 0.100 g. (0.0025 mole) of sodium hydroxide in 50% acetone–water, an optically inactive, chlorine-free oil, 0.325 g. (0.0015 mole, 87%), was obtained. The infrared spectrum and melting point were identical to those of (±)-1-methyl-3-benzoyl-3-hydroxypiperidine (XI).

Reaction of (+)-1-Methyl-3-benzoyl-3-chloropiperidine with Methanolic Sodium Methoxide.—To 50 ml. of freshly prepared absolute methanol was added 1.15 g. (0.05 mole) of clean sodium. After the sodium had reacted, 4.75 g. (0.02 mole) of the racemic amine was added. The solvent was removed at reduced pressure after allowing the reaction mixture to stand overnight at room temperature. The residue was extracted with petroleum ether, treated with carbon, and filtered through sintered glass. Removal of the solvent afforded a colorless, chlorine-free oil. The infrared spectrum showed neither hydroxyl nor carbonyl bands. On this basis and from the results of Lyle,[8] the oil (4.25 g., 0.018 mole, 91%) obtained from this reaction is assigned the structure of an epoxy ether, 2-methoxy-2-phenyl-5-methyl-1-ox-5-azaspiro[2.5]octane.

Reaction of (−)-1-Methyl-3-benzoyl-3-chloropiperidine with a Methanol-free Slurry of Sodium Methoxide in Anhydrous Refluxing Xylene.—To 50 ml. of freshly prepared absolute methanol was added 2.3 g. (0.10 mole) of clean sodium. After the sodium had reacted the methanol was removed under reduced pressure and the residue was dried at 100° (0.5 mm.) for 2 hours. The white powder was harvested, quickly powdered in a mortar, and redried at 100° (0.1 mm.) for 12 hours. To the methanol-free slurry of

(25) F. Bergel, N. C. Hindley, A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 271 (1944).

sodium methoxide in 50 ml. of anhydrous refluxing xylene was added 50 ml. of a xylene solution containing 4.75 g. (0.02 mole) of (−)-1-methyl-3-benzoyl-3-chloropiperidine (IV). After refluxing for 30 minutes the mixture was cooled in a Dry Ice–acetone-bath and filtered through sintered glass. The solvent was removed under reduced pressure and replaced with 100 ml. of petroleum ether. This solution was treated with carbon and refiltered. Removal of the solvent gave a chlorine-free, colorless, dextrorotatory oil. The infrared spectrum showed no hydroxyl absorption, but did have a carbonyl absorption at 5.97 μ. In all other respects the spectrum was identical to that of 2-methoxy-2-phenyl-5-methyl-1-ox-5-azaspiro[2.5]octane.

Optical Stability of (−)-1-Methyl-3-benzoyl-3-chloropiperidine (IV) in Refluxing Anhydrous Xylene.—To 50 ml. of anhydrous refluxing xylene was added 0.463 g. (0.0019 mole) of (−)-1-methyl-3-benzoyl-3-chloropiperidine ($\alpha^{35}D$ (absolute ethanol) −5.0°). The solution was refluxed for 30 minutes, cooled, and extracted with 0.2 *N* hydrochloric acid. The acid aqueous was washed with petroleum ether, treated with excess sodium bicarbonate, and extracted with petroleum ether. The solvent was removed after dryng the extract over sodium sulfate, treating with carbon, and filtering through sintered glass. The resulting colorless oil showed an $\alpha^{35}D$ (absolute ethanol) −4.1° corresponding to 10% racemization.

The optical rotations were obtained using the conventional method as well as an analytical method based on the organic chlorine[23] content of an aliquot of the solutions taken for the polarimetric examinations.

Optical Stability of (+)-1-Methyl-3-benzoyl-3-hydroxypiperidine (VI) under the Conditions of the Quasi-Favorskii Rearrangement.—Optically active amine, $\alpha^{32}D$ (absolute ethanol) +10.6°, was recovered after subjection to the conditions described above for the quasi-Favorskii rearrangement. The optical rotation of the material was unchanged.

The Effect of Solvent Volume and Sodium Hydroxide Concentration on the Rearrangement of 1-Methyl-4-benzoyl-4-chloropiperidine.—The rearrangements were carried out as reported earlier.[1] In a series of three reactions 3.45 g. (0.0145 mole) of 1-methyl-4-benzoyl-4-chloropiperidine in 50 ml. of anhydrous petroleum ether, b.p. 125° (Skelly E), was added to 50, 200 or 200 ml., of Skelly E containing 3.50, 3.50 or 18.0 g. of finely powdered, dry (180° 0.1 mm.), 12 hours) sodium hydroxide (0.0875, 0.0875 and 0.450 mole), respectively. These reactions yielded 0.540, 0.191 and 0.730 g. of 1-methyl-4-carboxy-4-phenylpiperidine (0.00247, 0.00087 and 0.00333 mole) corresponding to 17, 6 and 23% yields, respectively.

MADISON, WISC.

[CONTRIBUTION FROM LEDERLE LABORATORIES, AMERICAN CYANAMID CO.]

The 6-Deoxytetracyclines.[1] Further Studies on the Relationship between Structure and Antibacterial Activity in the Tetracycline Series

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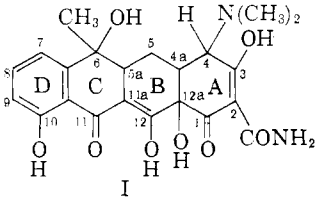
The preparation by hydrogenolysis and the properties of 6-deoxytetracycline, 6-deoxy-6-demethyltetracycline and 6-deoxy-5-hydroxytetracycline are described. A description is given of a hydrogenation sequence starting with the tetracyclines and proceeding, apparently by way of the anhydrotetracyclines, to some 8-hydroxytetralone derivatives; some of these products are characterized. Relationships between structure and antibacterial activity in the tetracycline series are described.

Continuing work on the broad-spectrum antibiotic, tetracycline (I),[2−4] has shown that three changes can be made in the fundamental structure



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of this compound with retention of its characteristic antimicrobial activity. For purposes of this study, a compound is considered to possess characteristic tetracycline activity if it exhibits as much as one-tenth the activity of tetracycline against all of a number of organisms in both *in vitro* and *in vivo* tests. These changes are replacement of 5-hydrogen by hydroxyl,[5] 7-hydrogen by chlorine[3,4] or bromine,[6] and 6-methyl by hydrogen.[7] The first two changes are in the direction of more complex structures, confer additional modes of instability on the molecule,[5,8,9] and give little information on the minimal structural requirements for antimicrobial activity. On the other hand, the third change, replacement of 6-methyl by hydrogen, produces a simplified molecule retaining high activity and possessing enhanced stability toward both acid and base.[7] Other localized changes in the tetracycline molecule, reported earlier and pertinent to the question of the structural requirements for activity, resulted in marked decreases in antimicrobial activity. These changes were (Table I): conversion of 2-carboxamide to nitrile,[10] replace-

(1) J. R. D. McCormick and E. R. Jensen, South African Patent 512/58, June 6, 1958; J. R. D. McCormick and E. R. Jensen, South African Patent 513/58, June 6, 1958. Abridgements of these patents were published in the *Union of South Africa Patent Journal*, issue of July 9, 1958, p. 22. A later preliminary communication of Stephens, *et al.* (THIS JOURNAL, **80**, 5324 (1958)) described two members of this series (6-deoxytetracycline and 6-deoxy-5-hydroxytetracycline).

(2) The trade mark of the American Cyanamid Co. for tetracycline is Achromycin.

(3) J. H. Boothe, J. Morton, J. P. Petisi, R. G. Wilkinson and J. H. Williams, THIS JOURNAL, **75**, 4621 (1953).

(4) L. H. Conover, W. T. Moreland, A. R. English, C. R. Stephens and F. J. Pilgrim, *ibid.*, **75**, 4623 (1953).

(5) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75**, 5455 (1953).

(6) P. Sensi, *Il. Farmaco Sci. Ed.*, **10**, 346 (1955); A. P. Doerschuk, J. R. D. McCormick, J. J. Goodman, S. A. Szumski, J. A. Growich, P. A. Miller, B. A. Bitler, E. R. Jensen, M. A. Petty and A. S. Phelps, THIS JOURNAL, **78**, 1508 (1956).

(7) J. R. D. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen and A. P. Doerschuk, *ibid.*, **79**, 4561 (1957).

(8) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

(9) C. W. Waller, B. L. Hutchings, C. F. Wolf, A. A. Goldman, R. W. Broschard and J. H. Williams, *ibid.*, **74**, 4981 (1952).

(10) Prepared from tetracycline by the method presented in ref. 12 for the preparation of 7-chlorotetracyclinonitrile.