*p*H 7.2 and treated with a strong aqueous solution of benzylisothiouronium chloride. The colorless crystalline salt that separated was filtered off, washed and recrystallized from hot water. It formed colorless rectangular plates melting at 195–196°. *Anal.* Calcd. for $C_{12}H_{13}N_2SO_3$ ($C_4H_3O_3 \cdot C_8H_{10}N_2S$): C, 54.32; H, 4.94; N, 10.56; S, 12.08; OCH_3, 11.70. Found: C, 54.11; H, 5.24; N, 10.57; S, 12.83; OCH_3, 9.11. The ratio of N/S is the same as that in benzylisothiuronium chloride and confirms the absence of nitrogen in xanthomycinic acid II.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Stereochemistry of 10-Hydroxycodeine Derivatives[1,2]

BY HENRY RAPOPORT AND SATORU MASAMUNE

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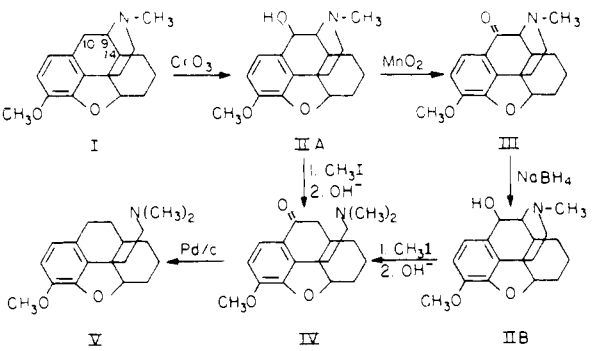
Oxidation of dihydrodesoxycodeine with cold chromic acid in dilute sulfuric acid led to the formation of 10-*trans*-hydroxydihydrodesoxycodeine. With manganese dioxide this alcohol was oxidized to the ketone, and reduction of the latter with sodium borohydride gave exclusively 10-*cis*-hydroxydihydrodesoxycodeine. The relative configuration of the epimers was established by oxazolidone formation in the case of the *cis* compound. Distinct differences were found between the epimers in regard to hydrogen bonding, partition coefficient, and dissociation constant as well as susceptibility to hydrogenolysis, Hofmann degradation, and a variety of oxidation procedures.

Cold chromic acid oxidation of a number of codeine derivatives has led in each case to the 10-hydroxy compound,[3] and it was the objective of the present work to determine the stereochemistry of the 10-hydroxyl group introduced by this general reaction. For this purpose, 10-hydroxydihydrodesoxycodeine (IIa) appeared to be the ideal compound since the absence of other reactive groups in the molecule should confine reaction to the position under study.

The general procedure of chromic acid oxidation was applied therefore to dihydrodesoxycodeine (I), conveniently prepared by lithium aluminum hydride hydrogenolysis of *p*-toluenesulfonylcodeine followed by hydrogenation.[4] A hydroxy compound was isolated in 95% yield, its purification being easily effected by recourse to the enhanced water solubility conferred by introduction of the hydroxyl group. That this new hydroxyl was at the 10-position seemed reasonable to assume, since such had been the case upon oxidation of codeine, dihydrocodeine and dihydrocodeinone.[3] However, it was established beyond question in the same manner as with the previous compounds, namely, by degradation to the methine. This compound, 10-ketotetrahydrodesoxycodeine methine (IV), had an ultraviolet absorption spectrum typical of *p*-methoxy aromatic ketones and practically identical with the ketomethine previously obtained,[3] and underwent facile hydrogenolysis to the methylene compound, tetrahydrodesoxycodeine methine (V).

Obviously, any study of the steric relationship of the 10-hydroxyl group and the nitrogen at position nine would be aided greatly if the epimeric alcohols were available. Since a detailed examination of the chromic acid reaction mixture indicated that only one isomer (IIa) had been formed, attention was directed to possible oxidation of this alcohol to the ketone III, from which the epimer might be prepared by reduction.



A very small amount of 10-ketodihydrodesoxycodeine (III) (<1%) had been isolated from the dihydrodesoxycodeine recovered after several recyclings in the chromic acid oxidation. However, direct preparation of the ketone by further chromic acid oxidation of the alcohol was possible only in poor yield due to continued oxidation of the ketone.

The recent numerous successful oxidations of allyl alcohols by manganese dioxide in an inert solvent[5] prompted us to apply this procedure to the benzyl alcohol[6] IIa. When a chloroform solution of the alcohol and manganese dioxide were shaken at room temperature, oxidation readily occurred and was complete in 21 hours, as indicated by the new absorption peak at 322 mμ. This successful oxidation of the alcohol to a ketone conjugate with the benzene ring is, incidentally, further confirmation of C_{10} as the position of the hydroxyl.

Both on catalytic hydrogenation and reduction with lithium aluminum hydride the ketone III gave an oily mixture of isomers from which crystalline material could be separated only with great difficulty and in very poor yield. However, the action of sodium borohydride on the ketone resulted in a quantitative yield of a single, crystalline product.

(1) Supported by a grant from the National Institutes of Health, Bethesda, Md.

(2) Reported in part in Abstracts of Papers, Am. Chem. Soc., **126**, 3-O (1954).

(3) H. Rapoport and C. W. Stevenson, THIS JOURNAL, **76**, 1796 (1954).

(4) H. Rapoport and R. M. Bonner, *ibid.*, **73**, 2872 (1951).

(5) F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953), and several references therein.

(6) After this work had been completed, a report appeared by D. L. Turner [*ibid.*, **76**, 5175 (1954)] in which a number of benzyl alcohols were oxidized to ketones with manganese dioxide in about 50% yields. Also, M. Harfenist, A. Bayley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954), report the successful oxidation of several benzyl alcohols using specially activated manganese dioxide.

That this was the epimeric alcohol IIb was established by (a) oxidation to the ketone III using manganese dioxide and (b) methiodide formation and Hofmann degradation to 10-ketotetrahydrodesoxycodeine methine (IV), identical with the product from the alcohol IIa.

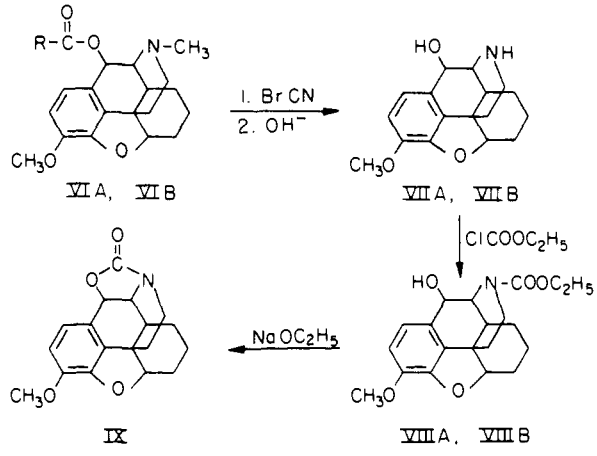
With the epimeric pair of alcohols, IIa and IIb, thus easily available, evidence was now sought as to the relative configuration of the hydroxyl and amino group in each. The first indication was encountered in the Hofmann degradation. Under identical conditions (ten minutes reflux in 20% aqueous potassium hydroxide), the methiodide of alcohol IIa was degraded to the extent of 9% whereas the epimeric methiodide of IIb gave methine IV in 96% yield. Since it has been shown that the Hofmann degradation is a bimolecular elimination proceeding with greatest facility when both carbons, the nitrogen and the β-hydrogen are coplanar,[7] this marked difference in reactivity should be explicable in terms of the relative configuration of the epimers.

From the known stereochemistry of morphine[8] and the fact that C_{10}, C_{11}, C_{12} and C_{13} are coplanar, ring B exists as a distorted chair form with C_9 above and C_{14} below this plane. Although the bonds from this ring are not true axial and equatorial bonds, they are similar enough to allow these designations to be used. The C_9-nitrogen bond must be axial for the piperidine ring to be formed. Thus in one epimer, the *trans*-alcohol, the C_{10}-oxygen bond will be axial and the C_{10}-hydrogen equatorial. In the *cis*-alcohol, the C_{10}-oxygen bond will be equatorial and the C_{10}-hydrogen will be axial. Only this latter conformation satisfies the coplanarity requirement, and hence should undergo degradation with extreme facilitiy. On this basis, alcohol IIb was assigned the *cis* configuration and alcohol IIa, the original chromic acid oxidation product, was assigned the *trans*.

Additional stereochemical evidence was sought in reactions involving ring formation between the hydroxyl and amino groups. For this purpose, the corresponding nor compounds were needed and they were prepared in the conventional manner by acylation of the hydroxyl, treatment with cyanogen bromide, and hydrolysis to the epimeric secondary amino alcohols VIIa and VIIb. In this regard, it is of interest to note that treatment of the *cis* compound IIb with refluxing acetic anhydride gave a 59% yield of the *trans*-acetate. This unexpected inversion is very likely due to the easily formed carbonium ion as a result of the *p*-methoxyl group. Benzoates then were prepared by treating IIa and IIb with benzoyl chloride in chloroform and aqueous alkali.

Migration of an acyl group from nitrogen to oxygen, which has been shown to involve a cyclic intermediate[9] and has been used successfully in stereochemical studies with a number of amino alcohols,[9,10] was inapplicable in the present instance. Hydrogen chloride, invariably used as catalyst in the previous cases, resulted in complete replacement of the hydroxyl by chloride with the present compounds, and when perchloric acid was substituted, no reaction occurred.

A cyclization reaction which finally did provide definite chemical evidence and confirmed the stereochemical assignment made above was found in the formation of the oxazolidone IX. Both the *trans*- and *cis*-N-carbethoxy compounds (VIIIa and VIIIb) were prepared by reaction with ethyl chloroformate and subjected to the action of sodium ethoxide in xylene.[11] The *trans* compound was recovered unchanged after this treatment, whereas the *cis* epimer afforded the oxazolidone.



With the configuration of the amino alcohols IIa and IIb thus established as *trans* and *cis*, respectively, it was of interest to examine the properties of the two epimers as a function of their configuration. The infrared spectrum[12] of the *trans* epimer IIa displayed normal absorption at 2.75 μ characteristic of the O–H stretching vibration. However, with the *cis* epimer IIb this band was completely absent and a new, broad absorption appeared at 3.0 μ, typical of the hydrogen-bonded hydroxyl. The intensity of this band was independent of concentration over the range 2.5 to 25 mg. per ml. of carbon tetrachloride. This evidence indicates the absence of any hydrogen bonding (even intermolecular) in the *trans* compound and practically complete intramolecular hydrogen bonding in the *cis*.

On the basis of the infrared data, the *cis* epimer would be expected to be less soluble in water than the *trans*, since the latter would more easily hydrogen bond with this solvent. When the apparent partition coefficients (P') of both compounds were determined for a benzene–$M/15$ phosphate buffer (*p*H 7.17) system, a P' of 3.55 was found for the *cis* compound and 1.90 for the *trans*. The true partition coefficients then were calculated from these values and the dissociation constants (see Table I),

(7) M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Wolff, *J. Chem. Soc.*, 2093 (1948); D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(8) H. Rapoport and J. B. Lavigne, THIS JOURNAL, **75**, 5329 (1953).

(9) W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950); G. Fodor and J. Kiss, *ibid.*, **72**, 3495 (1950); E. van Tamelen, *ibid.*, **73**, 5773 (1951).

(10) G. Fodor and J. Kiss, *J. Chem. Soc.*, 1589 (1952), and references therein; G. Fodor and K. Nador, *ibid.*, 721 (1953); A. Nickon and L. F. Fieser, THIS JOURNAL, **74**, 5566 (1952).

(11) A. H. Homeyer, U. S. Patent 2,399,188 (1946).

(12) Infrared spectra were taken in carbon tetrachloride solution with a Baird spectropholometer.

using the equation[13]

$$P = P'(1 + ([H^+]/K_a))$$

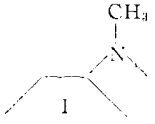
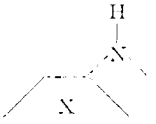
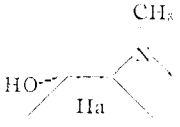
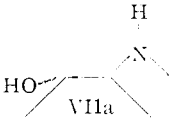
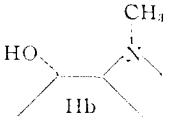
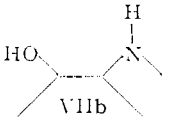
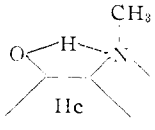
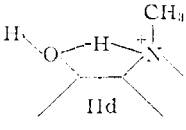
and found to be 620 and 8.5 for the *cis* and *trans* epimers, respectively. This ratio of seventy-three to one in the partition coefficients between benzene and water for these isomers is consistent with the striking difference in hydrogen bonding revealed by the infrared studies.

Although some difference in the dissociation constants of IIa and IIb was expected, the unusually large difference actually found (1.7 pK units) prompted a more detailed examination. For this purpose, the pK_a''s of the non-hydroxylated compound and both 10-hydroxy epimers were determined[14] for the tertiary amines and for the corresponding nor series. These values are given in Table I. The decreased basicity of 10-*trans*-hydroxydihydrodesoxycodeine (IIa) as compared to dihydrodesoxycodeine (I) is what might be expected from the inductive effect of an adjacent hydroxyl group.[15] However, to rationalize the marked increase of basicity of 10-*cis*-hydroxydihydrodesoxycodeine (IIb), hydrogen bonding interactions between the hydroxyl and amino groups must be considered.

Hydrogen bonding in a 1,2-aminoalcohol may be interpreted as base weakening if it occurs in the amine form IIc or base strengthening (stabilizing the ion) if it occurs in the ammonium form IId.

TABLE I

pK_a''S OF VARIOUS DIHYDRODESOXYCODEINES

Compound	pK_a'	Compound	pK_a
 I	8.83	 X	9.62
 IIa	7.71	 VIIa	8.72
 IIb	9.41	 VIIb	9.17
 IIc		 IId	

Since hydrogen bonding is most probably greater to the ion than to the free amine,[16] a base-strengthening effect would be expected. The profound difference in basicity of the epimeric pair IIa and IIb thus can be explained[17] if one recalls the infrared spectral data (above) which indicated very strong hydroxyl and amino interaction in the *cis* isomer IIb, and no interaction of this type in the *trans* isomer IIa.[18]

The effect of replacing the methyl group on nitrogen by a hydrogen is of considerable interest to this argument. Dihydrodesoxynorcodeine (X)[19] is a stronger base than 10-*trans*-hydroxydihydrodesoxynorcodeine (VIIa) by approximately the expected amount. However, the *cis* epimer VIIb, although still a stronger base than the *trans*, is weaker than the non-hydroxylated compound X. A reasonable explanation for this observation may be found in the fact that in the nor series a secondary amine is involved and therefore a non-hydrogen bonded hydrogen is available for dissociation. Thus stabilization of the ion is not as great and the base-strengthening effect in the *cis* isomer has been decreased. Accordingly, the maximum effect in base-strength variation with configuration for cyclic 1,2-aminoalcohols would be found with the tertiary amines.[20]

In a number of chemical reactions, major differences also were found between the epimers IIa and IIb. The fact that the Hofmann degradation proceeded so much more easily with IIb than with IIa led initially to the *cis* assignment for the former and has been discussed above. Both isomers were subjected to the action of hydrogen at room temperature and whereas the *cis* compound was recovered unchanged, the *trans* underwent hydrogenolysis and gave a quantitative yield of dihydrodesoxycodeine (I). If one considers that in general adsorption on a catalyst surface *trans* to the ethanamine chain is subject to interference from the benzene ring (which extends rearward), this result becomes explicable.

Three different oxidation methods were applied to the epimeric pair. In the Oppenauer reaction, a

(13) J. Cymerman-Craig and A. A. Diamantis, *J. Chem. Soc.*, 1619 (1953).

(14) Determinations were made by dissolving the alkaloid in excess hydrochloric acid and titrating the solution with alkali using a Beckman model G pH meter. Calculations were made for about ten points between 15 and 85% titrated using the equation $pK_a' = \log (a - x)/x + pH$, where x is the equivalent of alkali added at any point and a is the equivalent added at complete neutralization. Agreement was within ± 0.05 pK unit.

(15) *Cf.* cyclohexylamine (pK_a' 10.2) and 2-hydroxycyclohexylamine (*trans*, pK_a' 9.5; *cis*, pK_a' 9.6); G. E. McCasland, THIS JOURNAL, **73**, 2295 (1951).

(16) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1949, p. 287. G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p.229. A. F. Trotman-Dickensen, *J. Chem. Soc.*, 1293 (1949).

(17) T. A. Geissman, B. D. Wilson and R. B. Medz, THIS JOURNAL, **76**, 4182 (1954), used a similar approach in considering the base strengths and configurations of the 1,3-aminoalcohols tropine and ψ-tropine. In that case, the results were anomalous.

(18) Since in 14-hydroxydihydrocodeinone the hydroxyl and amino groups have been shown to be *cis* [C. Schöpf and F. Borkowsky, *Ann.*, **452**, 249 (1927)], this generalization would lead to the prediction that 14-hydroxydihydrocodeinone is a stronger base than dihydrocodeinone. This is the case since a pK_a' of 8.58 has been found for the 14-hydroxy compound (G. W. Stevenson, this Laboratory), and that of dihydrocodeinone is 7.95 [N. Schrool, *Pharm. Weekblad*, **76**, 1497 (1939)].

(19) The fact that dihydrodesoxynorcodeine is a stronger base than the parent compound dihydrodesoxycodeine (I) is consistent with what G. W. Stevenson of this Laboratory has found for normorphine, pK_a' 9.76 (morphine, 8.05) and norcodeine, pK_a' 9.10 (codeine, 8.04).

(20) V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **33**, 2021 (1950), studied several acyclic 1,2-aminoalcohols and reached the same conclusion, *viz.*, the isomer in which the hydroxyl and amino groups have the closer proximity is the stronger base, and this effect is most pronounced with tertiary amines. The effects they observed were much smaller than the difference between IIa and IIb. In this regard it might be of interest to see if the difference (0.1 pK unit) in base strength between *cis*- and *trans*-2-aminocyclohexanol (ref. 15) could be magnified by conversion to the tertiary amines, although this difference undoubtedly would be smaller than that found for the rigid system of IIa, IIb.

96% yield of ketone III was obtained from the *cis* isomer while identical conditions gave only a 77% yield from the *trans*. This difference probably is due to the interference provided by the *trans*-amino group to the formation of the necessary pseudo-cyclic intermediate.[21] Again in the case of oxidation by chromic acid in dilute sulfuric acid, the *cis* compound gave a better yield than the *trans* (71% *vs.* 21%). In this reaction, the rate-controlling step has been shown to be the breaking of the C–H bond,[22] and the result thus may be explained by hindrance to this process in the *trans* isomer, especially if a cyclic intermediate is involved. Finally, oxidation with manganese dioxide in chloroform, a relatively recent reaction[5,6] of as yet unknown mechanism, showed the same preference for the *cis* isomer as had the previous two procedures. Although quantitative oxidation to ketone occurred with both isomers, only a 3-hour reaction time was required for the *cis*-alcohol whereas 19 hours were necessary for the *trans*.

Experimental[23]

10-*trans*-Hydroxydihydrodesoxycodeine (IIa).—Over a six-hour period, a solution of 12 g. of chromic acid in 614 ml. of 10 *N* sulfuric acid was added slowly and with moderate stirring to a solution of 51.4 g. (0.18 mole) of dihydrodesoxycodeine (I)[4] in 9 liters of 1 *N* sulfuric acid maintained at 3–3.5°. Addition was made from a funnel with a capillary tip extending below the surface of the reaction mixture, and after an additional hour of stirring, excess oxidant was destroyed with 30 g. of sodium bisulfite. The *p*H was brought to 4 by addition of sodium carbonate and then to 10.5 with 15 *N* ammonia, and the reaction mixture was extracted continuously with benzene after adjusting the volume to 20 liters. When all the alkaloidal material had been extracted into the benzene (as shown by a negative color test[3] with sulfuric acid), the benzene solution was extracted with 0.7 *N* hydrochloric acid (4 × 750 ml.) and the aqueous solution in turn was washed with benzene (2 × 1 liter) and hexane (1 liter) and the *p*H then adjusted to 10.5 in the previous fashion. Dilution to 20 liters followed by continuous extraction with hexane for 42 hours gave, on evaporation of the hexane, 33.0 g. (64%) of recovered, crude dihydrodesoxycodeine suitable for direct use in another oxidation. Continuous extraction of the aqueous solution with benzene and evaporation of the benzene then gave 18.5 g. (34% conversion, 95% yield based on recovered dihydrodesoxycodeine) of 10-*trans*-hydroxydihydrodesoxycodeine (II), m.p. 145–147°. Repeated crystallization from ethyl acetate (90% recovery) and sublimation at 130°(20 μ) afforded material of m.p. 149–150°, $[\alpha]^{25}D$ −51.1° (*c* 1.1, ethanol).

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.7; H, 7.7; equiv. wt., 301. Found: C, 71.5; H, 7.7; equiv. wt., 299.

After 2 g. of 10-*trans*-hydroxydihydrodesoxycodeine in 60 ml. of acetic anhydride was heated under reflux for 20 hours and the cooled solution was made alkaline with excess aqueous ammonia, benzene extraction and evaporation of the benzene gave **10-*trans*-acetoxydihydrodesoxycodeine (VIa)** in 98% yield, m.p. 127–128° after crystallization from methylcyclohexane; $[\alpha]^{26}D$ +56.0° (*c* 1.1, ethanol).

Anal. Calcd. for $C_{20}H_{25}O_4N$: C, 70.0; H, 7.3; C–CH_3, 4.4. Found: C, 70.0; H, 7.4; C–CH_3, 4.4.

10-*trans*-Benzoxydihydrodesoxycodeine (VIa) was prepared by setting aside a cooled (0°) solution of 150 mg. of the 10-hydroxy compound and 0.09 ml. of benzoyl chloride in 5.8 ml. of dry pyridine for one day. Addition of 5 ml. of 1 *N* sodium carbonate precipitated a viscous oil which was chromatographed on an alumina column (2 × 15 cm.) after drying thoroughly. The fractions (190 mg., 94%) eluted easily with benzene crystallized on long standing and were combined and recrystallized from petroleum ether (30–60°); m.p. 113–114°, $[\alpha]^{26}D$ +85.5° (*c* 0.78, ethanol).

Anal. Calcd. for $C_{25}H_{27}O_4N$: C, 74.1; H, 6.7. Found: C, 73.9; H, 7.0.

The methiodide of 10-*trans*-hydroxydihydrodesoxycodeine crystallized when 450 mg. of the base in 4 ml. of methanol was treated with 0.6 ml. of methyl iodide at room temperature for six hours and the solution was placed in the cold. Recrystallization from methanol yielded 480 mg. (73%) of methiodide, m.p. 239–240° dec., $[\alpha]^{25}D$ −32.2° (*c* 0.68, methanol).

Anal. Calcd. for $C_{19}H_{26}O_3NI$: C, 51.5; H, 5.9; I, 28.6. Found: C, 51.2; H, 6.0; I, 28.6.

10-Ketodihydrodesoxycodeine (III).—A solution of 300 mg. of 10-*trans*-hydroxydihydrodesoxycodeine (IIa) in 30 ml. of dry chloroform was shaken at room temperature with 3 g. of manganese dioxide[5] and the course of the oxidation was followed by observing the absorption maximum at 322 mμ. When this reached a constant value after 21 hours, indicating 98% conversion to ketone, the mixture was filtered, the precipitate was washed well with chloroform, and the combined washings and filtrate, after washing with 1 *N* aqueous ammonia and drying, were evaporated. Solution of the residue (278 mg.) in 2 ml. of ethanol and addition of saturated, ethanolic picric acid solution resulted in a crystalline precipitate which was recrystallized from ethanol (to m.p. 219–220°) and then dissolved in benzene and applied to an alumina column (1 × 14.5 cm.). All the material eluted with benzene was distilled onto a cold finger at 60–70° (10 μ), and the resulting oil (110 mg.) became crystalline after long standing (two months) at room temperature, m.p. 86–87°, $[\alpha]^{27}D$ +32.4° (*c* 0.55, ethanol); λ_{max}^{EtOH} 245, 289, 322 mμ, log ε 4.22, 4.08, 3.72.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.2; H, 7.1. Found: C, 72.4; H, 7.0.

The picrate was prepared as described above and was recrystallized from ethanol and benzene; m.p. 219–220°, $[\alpha]^{25}D$ +9.4° (*c* 0.46, benzene).

Anal. Calcd. for $C_{24}H_{24}O_{10}N_4$: C, 54.5; H, 4.6. Found: C, 54.8; H, 4.8.

To prepare the **oxime**, a solution of 200 mg. of ketone III and 200 mg. of hydroxylamine hydrochloride in 2 ml. of absolute ethanol and 0.2 ml. of pyridine was heated under reflux for two days. Concentration to half the original volume and addition of 6 ml. of water and 0.3 g. of sodium carbonate precipitated 185 mg. of the oxime which was recrystallized from ethyl acetate several times, m.p. 187–188°, $[\alpha]^{29}D$ +54.0° (*c* 0.35, ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3N_2$: C, 68.8; H, 7.1; N, 8.9. Found: C, 69.1; H, 6.9; N, 9.2.

10-*cis*-Hydroxydihydrodesoxycodeine (IIb).—With ice-cooling, a solution of 150 mg. of sodium borohydride in aqueous methanol (made by dissolving the borohydride in 3 ml. of water and then adding 12 ml. of methanol) was added to 250 mg. of 10-ketodihydrodesoxycodeine (III) dissolved in 10 ml. of methanol and the reaction mixture was allowed to stand at room temperature for 24 hours by which time the absorption at 322 mμ had disappeared. After the addition of 5 ml. of 1 *N* sodium hydroxide, the methanol was evaporated from the solution, water was added, and the aqueous phase was now extracted with chloroform (6 × 10 ml.). Evaporation of the chloroform resulted in 248 mg. (98% yield) of the 10-*cis*-hydroxydihydrodesoxycodeine, m.p. 91–92°, which was recrystallized from hexane; m.p. 91–92°, $[\alpha]^{28}D$ −53.5° (*c* 0.86, ethanol).

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.7; H, 7.7. Found: C, 72.0; H, 7.8.

Acetylation of 200 mg. of 10-*cis*-hydroxydihydrodesoxycodeine proceeded as in the case of the *trans* isomer above and the crude acetylation product was chromatographed on an alumina column (1 × 15 cm.) using benzene–hexane, (1:1) at the start. With a benzene–hexane ratio of 4:1 material was eluted, the early fractions being oily and the later ones crystalline. Combination of the crystalline fractions and recrystallization from methylcyclohexane gave 134 mg. (59% yield) of **10-*trans*-acetoxydihydrodesoxycodeine (VIa)** melting at 122–124° alone and at 122–

(21) L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 2641 (1949); W. von E. Doering and R. W. Young, THIS JOURNAL, **72**, 631 (1950).

(22) A. Leo and F. H. Westheimer, *ibid.*, **74**, 4383 (1952).

(23) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California.

125° with authentic *trans*-acetoxy compound (m.p. 127–128°).

10-*cis*-Benzoxydihydrodesoxycodeine (VIb) was prepared by shaking a solution of 0.15 g. of the hydroxy compound and 0.42 g. of benzoyl chloride in 3 ml. of chloroform with 5 ml. of 1 *N* sodium hydroxide. The aqueous layer then was extracted with five 20-ml. portions of benzene, and the residue on evaporation of the benzene was chromatographed on alumina. The benzoate (185 mg., 91%) was eluted with benzene, and recrystallized from hexane; m.p. 123–124°, $[\alpha]^{28}D$ −2.5° (*c* 0.63, ethanol).

Anal. Calcd. for $C_{25}H_{27}O_4N$: C, 74.1; H, 6.7. Found: C, 74.3; H, 6.5.

When 200 mg. of 10-*cis*-hydroxydihydrodesoxycodeine, 0.2 ml. of methyl iodide and 2 ml. of benzene are heated in a sealed tube at 100° for eight hours, an oil precipitate results which becomes solid on washing with several portions of warm benzene. All attempts to crystallize this **methiodide** (290 mg., 99% yield) failed and gas was evolved when it was warmed to 80–90°. It was degraded (below) without further purification.

10-Ketotetrahydrodesoxycodeine Methine (IV). A. From 10-*trans*-Hydroxydihydrodesoxycodeine Methiodide.—To 160 mg. of *trans*-methiodide dissolved in 15 ml. of 0.5 *N* sodium hydroxide was added 15 ml. of 40% aqueous potassium hydroxide and the solution was heated under reflux for ten minutes. The cooled mixture was extracted with chloroform (4 × 50 ml.) and the chloroform was evaporated leaving 11 mg. (9% yield) of keto methine, m.p. 118–119°. By extending the reflux time an additional seven hours, the yield could be increased to 85%.

B. From 10-*cis*-Hydroxydihydrodesoxycodeine Methiodide.—The crude *cis*-methiodide prepared above (290 mg.) was degraded exactly as described for the case of the *trans* isomer. A ten-minute reflux period resulted in isolation of 200 mg. (96%) of methine, m.p. 117–119°. Recrystallization from ethyl acetate gave pure 10-ketotetrahydrodesoxycodeine methine, m.p. 119–120°, $[\alpha]^{28}D$ +4.8° (*c* 0.67, ethanol); λ_{max}^{EtOH} 244, 283, 322, log ε 4.23, 4.07, 3.67.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 71.7; H, 7.7. Found: C, 71.7; H, 8.0.

10-Ketotetrahydrodesoxycodeine methine oxime was prepared using the same procedure employed for the undegraded ketone III above. From 200 mg. of ketone there was obtained 160 mg. of oxime after recrystallization from ethanol; m.p. 215–216°, $[\alpha]^{27}D$ −12.1° (*c* 0.51, dioxane).

Anal. Calcd. for $C_{19}H_{26}O_4N_2$: C, 69.1; H, 7.9; N, 8.5. Found: C, 68.8; H, 7.8; N, 8.6.

Tetrahydrodesoxycodeine Methine (V).—Hydrogenation of 92 mg. of 10-ketotetrahydrodesoxycodeine methine in 10 ml. of absolute ethanol containing 0.5 ml. of 60% perchloric acid and with 50 mg. of 5% palladized carbon as catalyst proceeded with the absorption of one mole of hydrogen in 20 minutes and a second mole in two hours after which absorption ceased. Dilute aqueous sodium hydroxide then was added, the mixture was filtered free of catalyst, and the filtrate was extracted with four 10-ml. portions of chloroform. Evaporation of the chloroform left an oil[24] which could not be crystallized and showed no absorption in the region 320–340 mμ. It was converted to the **perchlorate**, 70 mg., m.p. 218–219° dec. after crystallization from absolute ethanol; $[\alpha]^{26}D$ +4.7° (*c* 0.70, pyridine).

Anal. Calcd. for $C_{19}H_{28}O_6NCl$: C, 56.8; H, 7.0. Found: C, 57.0; H, 7.1.

10-*trans*-Acetoxy-N-cyanodihydrodesoxynorcodeine.—A solution of 660 mg. of cyanogen bromide in 12 ml. of chloroform was added to a cold solution of 1.54 g. of 10-*trans*-acetoxydihydrodesoxycodeine (VIa) in 8 ml. of chloroform and, after two hours reflux, the solvent and excess cyanogen bromide were removed under reduced pressure to give 1.6 g. of crude N-cyano compound. This product was warmed with water on the steam-bath, the mixture was filtered, and the insoluble material was crystallized from 75% aqueous ethanol, resulting in 1.3 g. (82% yield) of N-cyano compound, m.p. 184–185°, $[\alpha]^{25}D$ +7.7° (*c* 0.53, ethanol).

Anal. Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.6; H, 6.5; N, 7.9. Found: C, 67.6; H, 6.3; N, 7.9.

(24) E. Speyer and K. Koulen [*Ann.*, **438**, 34 (1924)] report what is presumably tetrahydrodesoxycodeine methine as one of two isomers (one crystalline the other oily) resulting from hydrogenation of chloro-α-methylmorphimethine.

10-*cis*-Benzoxy-N-cyanodihydrodesoxynorcodeine.—The reaction of 610 mg. of 10-*cis*-benzoxydihydrodesoxycodeine (VIb) with 220 mg. of cyanogen bromide followed the same course as with the analogous *trans* compound above and the crude N-cyano compound, dissolved in benzene, was washed with 1 *N* hydrochloric acid and water. Evaporation of the benzene left a glassy residue which showed a single elution peak (600 mg., 95% yield) on chromatographing on alumina, but which could not be obtained crystalline.

10-*trans*-Hydroxydihydrodesoxynorcodeine (VIIa).—After being heated under reflux for 17 hours, a solution of 0.35 g. of 10-*trans*-acetoxy-N-cyanodihydrodesoxycodeine in 10 ml. of ethanol and 30 ml. of water containing 3 g. of sodium hydroxide was concentrated to 20 ml. and extracted thoroughly with chloroform. Evaporation of the chloroform left 0.29 g. of residue, m.p. 186–188°, which after crystallization from isopropyl alcohol and sublimation at 170° (30 μ) melted at 189–190°, $[\alpha]^{26}D$ −60.3° (*c* 0.91, ethanol).

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.1; H, 7.4; N, 4.9. Found: C, 70.9; H, 7.4; N, 5.0.

Shaking a chloroform solution (20 ml.) of 10-*trans*-hydroxydihydrodesoxynorcodeine (3.2 mmoles) and benzoyl chloride (3.0 mmoles) with 3.5 ml. of 1 *N* aqueous alkali led to the formation of the **N-benzoyl** derivative. This was isolated by washing the chloroform layer with dilute acid, evaporating the chloroform, and crystallizing the residue from ethyl acetate; m.p. 156–157° (95% yield), $[\alpha]^{25}D$ −109° (*c* 0.74, ethanol).

Anal. Calcd. for $C_{24}H_{25}O_4N$: C, 73.7; H, 6.4. Found: C, 73.7; H, 6.6.

Following the same procedure as was used above to prepare the N-benzoyl derivative, the residue from the reaction of 145 mg. of 10-*trans*-hydroxydihydrodesoxynorcodeine and 54.3 mg. of ethyl chloroformate was isolated and chromatographed on alumina (2 × 10 cm.). A mixture of benzene–chloroform (1:1) eluted the **N-carbethoxy** compound (VIIIa) which resisted crystallization and was sublimed at 130° (30 μ), $[\alpha]^{24}D$ −125° (*c* 0.94, ethanol).

Anal. Calcd. for $C_{20}H_{25}O_5N$: C, 66.8; H, 7.0. Found: C, 67.2; H, 7.0.

10-*cis*-Hydroxydihydrodesoxynorcodeine (VIIb).—Hydrolysis of 10-*cis*-benzoxy-N-cyanodihydrodesoxynorcodeine was carried out in the same manner as for the *trans*-acetoxy compound and a 91% yield of crude, m.p. 178–180°, was obtained. This was purified further by crystallization from ethyl acetate and sublimation to give pure 10-*cis*-hydroxydihydrodesoxynorcodeine, m.p. 180–181°, $[\alpha]^{26}D$ −64.3° (*c* 0.89, ethanol).

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.1; H, 7.4; equiv. wt., 287. Found: C, 71.0; H, 7.3; equiv. wt., 290.

Treatment with benzoyl chloride as in the case of the *trans* compound above gave the **N-benzoyl** derivative, m.p. 164–165° after crystallization from ethyl acetate; $[\alpha]^{25}D$ −77.7° (*c* 0.36, ethanol).

Anal. Calcd. for $C_{24}H_{25}O_4N$: C, 73.7; H, 6.4. Found: C, 73.9; H, 6.4.

10-*cis*-Hydroxy-N-carbethoxydihydrodesoxynorcodeine (VIIIb) was prepared by a procedure parallel to that employed for the *trans* compound, except that benzene served as the organic phase instead of chloroform. After chromatography, sublimation at 120° (30 μ) gave a crystalline sublimate of N-carbethoxy compound, m.p. 144–145°, $[\alpha]^{25}D$ −141° (*c* 0.91, ethanol).

Anal. Calcd. for $C_{20}H_{25}O_5N$: C, 66.8; H, 7.0. Found: C, 67.1; H, 7.2.

Cyclization Reactions. A. Oxazolidone (IX) from 10-*cis*-Hydroxy-N-carbethoxydihydrodesoxynorcodeine (VIIIb).—Sodium ethoxide (from 100 mg. of sodium) and 200 mg. of 10-*cis*-hydroxy-N-carbethoxydihydrodesoxynorcodeine in 10 ml. of xylene were heated under reflux for 3.5 hours with stirring in a nitrogen atmosphere. Ice and 2 *N* sodium hydroxide were added to the cooled reaction mixture and the aqueous phase was extracted exhaustively with chloroform, after which the combined organic extracts were evaporated and the residue was dissolved in 25 ml. of benzene. Washing with 1 *N* sulfuric acid followed by chloroform extraction of the basified aqueous phase left 85 mg. (53%) of 10-*cis*-hydroxydihydrodesoxynorcodeine on evaporation of the chloroform. The washed benzene solu-

tion was applied to an alumina column (1.5 × 10 cm.), and after 400 ml. of benzene was passed through, 66 mg. (38%) of the oxazolidone was eluted with 450 ml. of chloroform–benzene (3:7). Crystallization from benzene and then ethyl acetate gave oxazolidone IX of m.p. 201.5–202°, $[\alpha]^{25}D$ +148° (*c* 0.24, ethanol).

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 69.0; H, 6.1. Found: C, 69.0; H, 6.1.

B. Attempted Cyclization of 10-*trans*-Hydroxy-N-carbethoxydihydrodesoxynorcodeine (VIIIa).—A procedure identical with that applied to the *cis* isomer above was followed with 350 mg. of 10-*trans*-hydroxy-N-carbethoxy dihydrodesoxynorcodeine, and the reaction product was separated into neutral and basic fractions. The neutral material was recovered *trans*-N-carbethoxy compound ($[\alpha]^{24}D$ −122°, 255 mg., 73% recovery) and the basic fraction was 10-*trans*-hydroxydihydrodesoxynorcodeine (53 mg., 19%).

Comparison of Reactivity 10-*trans*- and 10-*cis*-Hydroxydihydrodesoxycodeine (IIa, IIb). A. Hydrogenolysis.—During an overnight period at room temperature, one mole of hydrogen was absorbed by a solution of 159 mg. of 10-*trans*-hydroxydihydrodesoxycodeine in 8.5 ml. of acetic acid and 0.3 ml. of 60% aqueous perchloric acid containing 150 mg. of 5% palladized carbon. From the reaction mixture there was isolated in the usual way 130 mg. (86% yield) of dihydrodesoxycodeine, m.p. 103–106°; *d*-acid tartrate, m.p. 154–156° (reported[4] m.p. 106–107° and 155–156°, respectively).

Identical conditions with the *cis*-alcohol resulted in no hydrogen absorption and recovery of starting material.

B. Oppenauer Oxidation.—Using the procedure previously described[25] 600 mg. (2 mmoles) of 10-*trans*-hydroxydihydrodesoxycodeine was subjected to oxidation by benzophenone for 3.5 hours in the presence of potassium *t*-butoxide and the product was separated by chromatography on alumina. Benzene eluted 460 mg. (77% yield) of 10-ketodihydrodesoxycodeine (identified by its ultraviolet absorption spectrum) and benzene–chloroform (1:1) removed 110 mg. (18%) of the *trans*-alcohol, m.p. 145–147°.

From 10-*cis*-hydroxydihydrodesoxycodeine under the same conditions, the only isolable product was 10-ketodihydrodesoxycodeine in 96% yield.

C. Chromic Acid Oxidation.—The same procedure used for the introduction of the 10-hydroxyl group into dihydrodesoxycodeine (I) was applied to 10-*trans*-hydroxydihydrodesoxycodeine (IIa). From 200 mg. of *trans*-alcohol, 149 mg. of alkaloidal material was isolated from the oxidation reaction and this was rectified in the usual manner by chromatography on alumina. A 21% yield (42 mg.) of ketone and a 53% recovery (105 mg.) of *trans*-alcohol were obtained.

With the *cis*-alcohol, the same oxidation procedure resulted in a 71% yield of ketone and a 5% recovery of crude *cis*-alcohol.

D. Manganese Dioxide Oxidation.—A solution of 100 mg. of the 10-hydroxy compound in 10 ml. of chloroform was shaken at room temperature with 1 g. of manganese dioxide[5] and the progress of the oxidation was followed by withdrawal of aliquots and examination of the absorption at 322 mμ. Complete conversion to ketone required 19 hours with the *trans*-alcohol and only 3 hours with the *cis*. In each case, a quantitative yield of 10-ketodihydrodesoxycodeine was isolated.

Dihydrodesoxynorcodeine (X).—After a 2.5-hour reflux, a solution of 550 mg. (5.2 mmoles) of cyanogen bromide and 1.14 g. (4 mmoles) of dihydrodesoxycodeine in 15 ml. of chloroform was evaporated, the residue was dissolved in benzene, and the benzene solution was concentrated to dryness after being washed with 1 *N* hydrochloric acid and filtered. The residue thus obtained was hydrolyzed by heating under reflux for 20 hours with 60 ml. of 2 *N* hydrochloric acid and 10 ml. of ethanol. The ethanol then was evaporated, the aqueous solution was washed with benzene before being made alkaline with 6 *N* sodium hydroxide, and the alkaline solution was extracted thoroughly with chloroform. Evaporation of the chloroform left a residue which, with aqueous *d*-tartaric acid, was converted to the *d*-acid tartrate, m.p. 200–210° with decomposition after crystallization from aqueous ethanol and drying at 140° (10 μ); $[\alpha]^{20}D$ −26.0° (*c* 0.53, ethanol).

Anal. Calcd. for $C_{21}H_{27}O_8N$: C, 59.9; H, 6.5. Found: C, 59.6; H, 6.4.

Treatment of the *d*-acid tartrate with aqueous sodium hydroxide and extraction with chloroform gave, on evaporation, dihydrodesoxynorcodeine of m.p. 113–114° after sublimation at 90° (30 μ); $[\alpha]^{20}D$ −75.6° (*c* 1.09, ethanol).

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.2; H, 7.8. Found: C, 75.2; H, 7.9.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF CIBA PHARMACEUTICAL PRODUCTS, INC.]

Rauwolfia Alkaloids. XIX.[1] The Constitution of Deserpidine and Reserpine

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The previously reported Rauwolfia alkaloid deserpidine has been degraded by two routes to known compounds. This was accomplished by converting methyl deserpidate tosylate (IV) to methyl 18-iodo-18-desoxydeserpidate (VII). Treatment of this substance with zinc and acetic acid removed the halogen and yielded methyl 18-desoxydeserpidate (VIII). Cleavage of the 17-methoxyl group and reesterification of the 16-carboxyl function gave α-yohimbine (rauwolscine) (X). In another series of reactions IV on treatment with lithium aluminum hydride was found to yield deserpidinol (V). Cleavage of the methoxyl group produced a substance identical with α-yohimbyl alcohol (VI). Evidence is presented which shows that reserpine and its derivatives and, with less ease, also deserpidine and its derivatives, undergo an epimerization at the C-3 center. The stereochemical implications of these findings as related to the structure of deserpidine and reserpine are discussed.

In a previous communication from this Laboratory[2] the isolation of a new Rauwolfia alkaloid, deserpidine, has been reported. On the basis of the analytical data, the isolation of 3,4,5-trimethoxybenzoic acid on hydrolysis, the interpretation of infrared and ultraviolet absorption spectra and the similarity of its pharmacological and chemical properties with those of reserpine,[3,4] it was proposed that this new alkaloid is 11-desmethoxyreserpine. In a recent communication[1] the conversion of deserpidine to α-yohimbine (rauwolscine)[5] was described. The stereochemical implications of this interrela-

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