2 *N* ammonium hydroxide saturated with hydrogen sulfide was stirred at room temperature for one hour and cooled to 5°. The bright red diamine (18.74 g., 95%), melting at 256–258°, was purified by dissolving it in dimethylformamide, followed by the addition of water to induce crystallization. This resulted in 17.84 g. of deep maroon plates with a melting point of 260–262°.

Anal. Calcd. for $C_7H_8N_4O_3$: C, 42.85; H, 4.11; N, 28.56. Found: C, 42.65; H, 4.06; N, 28.61.

4-Nitro-6-carboxamidobenzimidazole.—Ethyl orthoformate (200 ml.) containing 9.80 g. (0.05 mole) of 3,4-diamino-5-nitrobenzamide was refluxed for two hours. The orange residue, consisting of 4.50 g. of crude 4-nitro-6-carboxamidobenzimidazole (m.p., 300–305°, with decomposition), was removed. This was dissolved in dimethylformamide and precipitated by adding an ether–petroleum ether mixture (2:1) giving 4.10 g. of product with a decomposition point of 318–320°.

The ethyl orthoformate solution was cooled and treated with two volumes of petroleum ether whereupon 5.13 g. of 5-nitro-3(or 4)-amino-4(or 3)-(ethyl isoformamido)-benzamide was obtained. In the vicinity of 165° this compound is converted to the benzimidazole with or without melting, depending upon the rate of heating. It was purified for analysis by repeated recrystallization from ethyl orthoformate.

Anal. Calcd. for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.77; H, 4.92; N, 22.26.

The intermediate ethyl isoformanilide was converted to the benzimidazole by placing the 5.13 g. of material in an oil-bath at 150° and raising the temperature to 200° over a 30-minute period. The yield of 4-nitro-6-carboxamidobenzimidazole from this treatment was 4.67 g., m.p. 320–325°, giving a total yield of 8.77 g. (85%). A sample, purified for analysis by precipitation from dimethylformamide with a mixture of ether and petroleum ether (2:1), melted at 325°, with decomposition.

Anal. Calcd. for $C_8H_6N_4O_3$: C, 46.59; H, 2.93; N, 27.17. Found: C, 46.86; H, 3.01; N, 27.35.

4-Nitro-6-aminobenzimidazole.—Cold water was added with stirring to 4.12 g. (0.02 mole) of 4-nitro-6-carboxamidobenzimidazole in 40 ml. of 0.5 *N* alkaline sodium hypochloride solution[16] until the solid dissolved (final volume, approximately 200 ml.). After heating on the steam-bath for one hour, the solution was cooled and adjusted to neutrality. This was extracted with ethyl acetate (yellow solution) giving 1.02 g. (29%) of the red free base, m.p. 286–288°, on evaporating the solvent. This was reprecipitated from dilute hydrochloric acid solution with sodium bicarbonate. Further purification was accomplished by adding petroleum ether to an ethyl acetate solution of the material; final m.p., 292–294°.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 47.34; H, 3.36; N, 31.52.

Hydrochloride and Picrate.—The red-orange hydrochloride, prepared by adding absolute alcohol to a solution of the free base in 2 *N* hydrochloric acid, melted at 330–332° with decomposition.

Anal. Calcd. for $C_7H_7N_4O_2Cl$: C, 39.17; H, 3.29; N, 26.11. Found: C, 39.31; H, 3.36; N, 26.25.

The picrate was prepared by dissolving the free base in hot aqueous picric acid solution (saturated at room temperature) and cooling. Recrystallization from water gave bright orange plates which melted at 231–233°.

Anal. Calcd. for $C_{13}H_9N_7O_7$: C, 38.34; H, 2.23; N, 24.08. Found: C, 38.52; H, 2.34; N, 24.23.

4-Nitro-6-acetamidobenzimidazole.—The procedure for acetylating 4-amino-6-nitrobenzimidazole was applied to the 4-nitro-6-amino-isomer (1.8 g., 0.01 mole) giving 2.02 g. (92%) of light yellow product, melting at 330° with decomposition. Recrystallization from water gave light yellow needles decomposing at 341–343°.

Anal. Calcd. for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 48.84; H, 3.67; N, 25.39.

(16) Refs. 11 and 12.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND CHEMISTRY, UNIVERSITY OF WISCONSIN]

Xanthomycin A. Degradation Studies[1]

BY K. V. RAO, W. H. PETERSON AND E. E. VAN TAMELEN

RECEIVED MARCH 22, 1954

Hydrolysis of xanthomycin ($C_{23}H_{29-31}N_3O_7$) with hydrochloric acid produced ethanolamine, ammonia, methylamine and a large amount of a dark humin-like material. A derivative, methyltetrahydroxanthomycin, suitable for degradation purposes was obtained by simultaneous reduction and methylation of xanthomycin. Oxidation of methyltetrahydroxanthomycin with permanganate produced two crystalline products, xanthomycinic acid I and xanthomycinic acid II. The first contained nitrogen and analyzed for the empirical formula $C_7H_{11}N_3O_{10}$. The second acid was obtained crystalline as the benzylisothiouronium salt and proved to be free of nitrogen. Analysis indicated the empirical formula of this salt was $C_4H_3O_3 \cdot C_8H_{10}N_2S$.

The isolation, purification and properties of the antibiotic xanthomycin A have been described in previous publications.[2,3] The data indicated that xanthomycin A has the molecular formula C_{23}-$H_{29-31}N_3O_7$ and contains a quinonoid nucleus attached to a dibasic nitrogenous moiety.

Xanthomycin A is very sensitive to many of the common reagents, even under mild conditions. It undergoes pronounced decomposition in acidic or basic solutions. Attempted acetylation, benzoylation or methylation at room temperature results in highly colored amorphous products. Almost all the derivatives of xanthomycin A obtained thus far are of very hydrophilic nature and tend to form glassy or amorphous solids. Another difficulty in obtaining useful derivatives of xanthomycin A is the fact that it has two tertiary nitrogen atoms which retain their basic character during many reactions.

Two lines of approach were pursued in the degradation of xanthomycin A. First, drastic acid hydrolysis was employed in the hope of obtaining information regarding the function of the nitrogen atoms in the molecule. Second, reduction of the quinonoid grouping, protection of the resulting hydroxyl groups and oxidation was studied with a view toward determining the nature of the quinone residue.

Degradation of Xanthomycin A.–Hydrolysis of xanthomycin A with 6 *N* hydrochloric acid invariably led to the formation of 35–45% by weight

(1) This investigation was supported in part by research grants from Merck and Co., Inc., and Parke, Davis and Co. Presented in part at the 121st Meeting American Chemical Society, Milwaukee, 1952.

(2) K. V. Rao and W. H. Peterson, THIS JOURNAL, **76**, 1335 (1954).

(3) K. V. Rao and W. H. Peterson, *ibid.*, **76**, 1338 (1954).

of dark brown, humin-like material. The soluble fraction gave a positive reaction with ninhydrin and when analyzed by the photometric method of Moore and Stein[4] showed an amino nitrogen content amounting to approximately 50–70% of the total. The yields of soluble amino nitrogen decreased with the formation of increasing quantities of humin.

Cation exchange resin chromatography with Dowex-50 according to the method of Stein and Moore[5] was used to resolve the components of the hydrolysate. Three fractions were obtained on the basis of the ninhydrin color reaction. Hydrolysates from several batches of xanthomycin A gave rise only to these three components which were termed fractions I, II and III in the order of their emergence (Fig. 1).

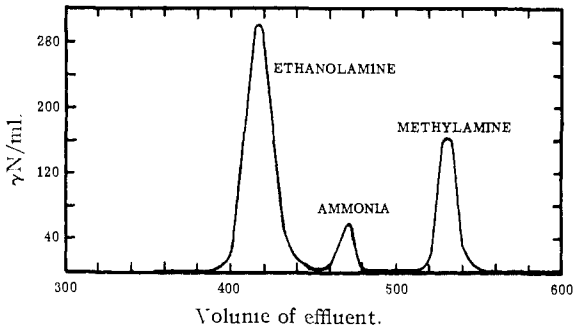


Fig. 1.—Chromatographic separation of ninhydrin-positive components of xanthomycin hydrolysate.

Fraction I yielded a crystalline chloroplatinate which on analysis gave an equivalent weight of 61 and an empirical formula C_2H_7ON for the free base. It underwent smooth oxidation with potassium periodate. One mole of the oxidant was consumed per atom of nitrogen giving rise to two moles of formaldehyde and one mole of ammonia. These reactions showed that fraction I was ethanolamine. Fraction II was identified as ammonia by the Nessler color reaction. Fraction III gave a crystalline chloroplatinate which analysis showed had an equivalent weight of 31 and an empirical formula of CH_5N for the free base. It was identified as methylamine on the basis of volatility and paper chromatography.

Since the direct acid hydrolysis of xanthomycin A led to marked decomposition, this procedure proved unsuitable for the isolation of the products of hydrolysis. It was felt that the highly reactive quinonoid grouping probably was responsible for the formation of the large quantities of humin and that a reduction derivative of xanthomycin A would be more suitable for such a purpose. Hydrolysis of the dihydro derivative (obtained by reduction of xanthomycin A with sulfur dioxide or stannous chloride) showed no improvement over hydrolysis of xanthomycin A. In contrast, tetrahydroxanthomycin A, obtained by catalytic hydrogenation of xanthomycin A,[3] remained unchanged when refluxed with 6 *N* hydrochloric acid for 12 hours in an inert atmosphere.

(4) S. Moore and W. H. Stein, *J. Biol. Chem.*, **176**, 367 (1948).

(5) W. H. Stein and S. Moore, *Cold Spring Harbor Symp., Quant. Biol.*, **14**, 179 (1950).

Tetrahydroxanthomycin A readily underwent oxidation by hydrogen peroxide in alkaline medium giving a small yield of a basic substance which was isolated as the reineckate. Analysis of this material indicated an empirical formula of $C_{12}H_{19\text{-}31}N_2O_6 \cdot HCr(CNS)_4(NH_3)_2$. This derivative contained no methoxyl groups. Owing to the small yield and the consequent difficulty of purification, this substance was not studied further.

Ozonization appeared to be a convenient method to attack the quinonoid and other centers of unsaturation in xanthomycin A. When xanthomycin A was treated with ozone in chloroform solution at −70°, approximately 8 moles of ozone were consumed. When the ozonide was worked up by oxidative procedure with peracetic acid, a light cream-colored substance was obtained. This substance analyzed for the empirical formula $C_{12}H_{14\text{-}16}N_2O_{10}$. Acid hydrolysis of the ozonization product resulted in the formation of considerable quantities of humin. From the soluble fraction, ethanolamine, ammonia and methylamine were isolated.

The methylation product of tetrahydroxanthomycin A was prepared by the simultaneous catalytic hydrogenation and methylation of xanthomycin A. This methyl ether was colorless and stable in acid and alkaline solutions. It was oxidized with neutral potassium permanganate, the oxidation mixture was acidified and extracted with ether, whereupon an acidic fraction was obtained. This acidic fraction could be separated into two components by fractional crystallization from ether. The ether-insoluble component was termed xanthomycinic acid I and the ether-soluble one, xanthomycinic acid II.

Xanthomycinic acid I appears to have the empirical formula $C_7H_{11}N_3O_{10}$ and exhibits a neutralization equivalent of 100. Infrared absorption spectrum indicated the presence of primary amide and carboxyl groups. Xanthomycinic acid II crystallized as the free acid and also as the benzylisothiouronium salt. Analysis of the latter indicated the empirical formula of the free acid to be $C_4H_3O_3$.

Experimental

Acid Hydrolysis of Xanthomycin A.—A mixture of redistilled hydrochloric acid (6 *N*, 5 ml.) and 85% formic acid (5 ml.) was added to xanthomycin A hydrochloride (100 mg.) in a test-tube (25 × 200 mm.). The tube was sealed and heated in an autoclave at 15 lb. pressure for six hours. The dark colored mixture was evaporated to dryness three times with additional quantities of distilled water. The residue was taken up in water (10 ml.) and treated with 50 mg. of Norit A which previously had been washed thoroughly with boiling 2 *N* acid and 2 *N* alkali. The filtered solution was nearly colorless and contained 80–90% of the original nitrogen as determined by the micro Kjeldahl procedure.[6] This solution was concentrated to about 5 ml. and used directly on the Dowex-50 chromatographic column.

Chromatographic Resolution of Xanthomycin A Hydrolysate.—The chromatographic column (550 × 18 mm.) was packed with Dowex-50 which already had been washed successively with 2 *N* sodium hydroxide, water, 2 *N* hydrochloric acid and water. The resin was made into a slurry with 1.5 *N* hydrochloric acid and poured into the column. After about 500 ml. of acid had been run through the column the sample was added. The column was developed

(6) M. J. Johnson, *J. Biol. Chem.*, **181**, 707 (1949).

with 1.5 *N* hydrochloric acid and about 400 ml. of eluate was collected. Then 2.5 *N* hydrochloric acid was substituted until the volume of the eluate was 1000 ml. Finally 4 *N* hydrochloric acid was added and the chromatogram continued until a total of about 1500 ml. was collected. Fractions of 5 ml. were collected with the help of an automatic fraction collector. For analysis of the fractions suitable aliquots were taken, evaporated to dryness at 70–80° under reduced pressure and analyzed by the photometric ninhydrin method of Moore and Stein.[4] The fractions containing an individual ninhydrin-positive component were pooled together and evaporated to dryness (Fig. 1).

Crystalline Chloroplatinate of Fraction I.—An aliquot of a solution containing about 5 mg. of nitrogen (Kjeldahl) in 1 ml. of 0.1 *N* HCl was treated with a slight excess of chloroplatinic acid in 95% ethanol. The solution was evaporated to dryness and treated with a mixture of absolute ethanol and ether (3:1). The solid was removed by filtration, washed and recrystallized from a mixture of ethanol and ethyl acetate (1:1). It separated as bright yellow glistening rectangular plates, melting with decomposition at 244°. *Anal.* Calcd. for $(C_2H_7ON)_2 \cdot H_2PtCl_6$: C, 9.02; H, 3.01; Pt, 36.67. Found: C, 9.12; H, 2.90; Pt, 36.45.

Periodate Oxidation of Fraction I.—Three ml. of a solution of fraction I containing about 300 γ of nitrogen was treated with 1 ml. of 0.1 *N* sulfuric acid and 2 ml. of 0.01 *M* potassium periodate. After 30 minutes at room temperature the mixture was made up to 10 ml. with 0.5 *M* phosphate buffer of *p*H 7.5. Unchanged periodate, ammonia and formaldehyde were determined on suitable aliquots. Calculated per atom of nitrogen the following results were obtained: moles of periodate consumed, 1.01; moles of formaldehyde formed, 1.97; moles of ammonia, 1.09.

Crystalline Chloroplatinate of Fraction III.—The chloroplatinate was prepared in a manner similar to that described for fraction I and was crystallized from aqueous ethanol. It separated out as short, yellow prisms, melting with decomposition at 236°. *Anal.* Calcd. for $(CH_5N)_2 \cdot H_2PtCl_6$: C, 5.09; H, 2.56; Pt, 41.34. Found: C, 5.70; H, 2.65; Pt, 41.88.

The analysis does not distinguish between methylamine and ethylenediamine, but the identity of fraction III was established from volatility and chromatographic data. Aliquots of fraction III, methylamine and ethylenediamine containing approximately 20 γ in 10 ml. were distilled separately after the addition of 1 ml. of 1 *N* sodium hydroxide. The distillates were collected in 0.1 *N* HCl and the amino nitrogen determined by the ninhydrin method. The following recoveries were obtained for the three samples: fraction III, 95%, methylamine, 95%, and ethylenediamine, 5%.

Two systems were used for the paper chromatograms: 1, phenol (200 g.) and 0.01 *N* HCl (50 ml.); 2, *n*-butyl alcohol (200 ml.) and 0.01 *N* HCl (50 ml.). Aliquots of samples containing 1–2 γ were spotted on 0.5-inch strips of Whatman No. 1 filter paper.

	Rf-Values		
System	Fraction III	Methylamine	Ethylenediamine
1	0.50	0.50	0.14
2	.16	.16	.02

Attempted Hydrolysis of Tetrahydroxanthomycin A.—Xanthomycin A hydrochloride (50 mg.) was dissolved in ethanol and hydrogenated in the presence of 50 mg. of platinum oxide catalyst to form tetrahydroxanthomycin A.[3] After one hour the solvent was evaporated and 5 ml. of 6 *N* hydrochloric acid was added. The mixture was refluxed while hydrogen was being bubbled through. After heating for 12 hours the mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in ethanol, treated with 20 mg. of platinum oxide catalyst and hydrogenated for one hour. The catalyst was removed by filtration and the filtrate treated with an equal volume of ether. The colorless solid that separated out was filtered off and washed with ether. The product was an amorphous solid which did not melt below 320°. *Anal.* Calcd. for $C_{23}H_{33-35}N_3O_7 \cdot 2HCl$: Cl, 13.9. Found: Cl, 14.2. The absorption spectrum of the substance showed a maximum at 292 mμ with a specific extinction value of 83.

Oxidation of Tetrahydroxanthomycin A.—One hundred mg. of xanthomycin A hydrochloride was hydrogenated in 5 ml. of water in the presence of 100 mg. of platinum oxide catalyst. The mixture was filtered to remove the catalyst, 3 ml. of 1 *N* sodium hydroxide was added to the filtrate and the solution was treated with 0.3 ml. of 30% hydrogen peroxide added drop by drop during the course of 30 minutes. The temperature of the reaction was maintained at 50–60°. The initially colorless solution turned bright pink and gradually changed to light yellow. The solution was extracted with ether, acidified and again extracted with ether. The ether extracts gave only traces of products. The aqueous layer was treated with a slight excess of a strong solution of ammonium reineckate. The light rose-colored precipitate that separated was filtered, washed with water and crystallized from a mixture of methanol and ethanol. *Anal.* Calcd. for $C_{12}H_{19-21}N_2O_6 \cdot HCr(CNS)_4(NH_3)_2$: C, 31.58; H, 4.61; N, 18.42; S, 21.05. Found: C, 31.88; H, 4.52; N, 17.92; S, 20.40.

Ozonization of Xanthomycin A.—Xanthomycin A (100 mg.) was dissolved in chloroform (10 ml.) and the solution cooled in a bath of Dry Ice and chloroform. Ozone was bubbled through the solution and the exit gases passed through a trap containing a 10% solution of potassium iodide to analyze the excess of ozone. The initial reddish-brown color of the solution gradually turned pale yellow within 15 minutes and the ozonide started to separate out as a light yellow solid. After bubbling for 30 minutes the mixture was removed from the freezing bath and treated with 3 ml. of glacial acetic acid and 2 ml. of 40% peracetic acid. It was set aside at room temperature for 12 hours and heated on a water-bath at 60° for one hour. The solvent then was evaporated to dryness and the residue taken up in a mixture of ethanol and ethyl acetate. The solution was decolorized with Norit A and concentrated to a small volume. Addition of ether precipitated a light cream-colored solid which did not melt below 320°. *Anal.* Calcd. for $C_{12}H_{14-16}N_2O_{10}$: C, 41.50; H, 4.32; N, 8.07. Found: C, 41.11; H, 4.42; N, 8.25.

When the ozonization product was hydrolyzed by refluxing with 6 *N* hydrochloric acid for six hours the solution turned dark and deposited a dark brown solid. The mixture was evaporated to dryness, dissolved in water and treated with Norit A. The carbon was removed by filtration and the filtrate concentrated to a small volume. No product could be extracted from this solution with ether under either alkaline or acidic conditions. The hydrolysate was added to an acid washed Dowex-50 chromatographic column and developed with 1 *N* hydrochloric acid. Three ninhydrin-positive components which were identified as ethanolamine, methylamine and ammonia, were obtained.

Oxidation of Methyltetrahydroxanthomycin A.—Methyltetrahydroxanthomycin A was prepared as previously described[3] and a solution of it (500 mg. in 20 ml., *p*H 7.2) was treated at 50–60° with 5% aqueous potassium permanganate. The oxidant was added until the purple color remained for 10 minutes after the addition. The mixture was then treated drop by drop with a solution of sodium bisulfite to decompose the excess reagent. The manganese dioxide was filtered off and the pale yellow solution (*p*H 10) was extracted three times with chloroform to remove any basic or neutral impurities. The aqueous layer was acidified with sulfuric acid and extracted continuously with ether for 48 hours. The ether extract was dried over sodium sulfate, filtered and evaporated to dryness. The semi-solid residue was triturated with small amounts of ether and filtered. The residue (xanthomycinic acid I) was crystallized from a mixture of ethanol and benzene. It separated as colorless prisms melting at 147–148°. *Anal.* Calcd. for $C_7H_{11}N_3O_{10}$: C, 28.29; H, 3.73; N, 14.14. Found: C, 28.95; H, 4.03; N, 14.59.

The ether filtrate after the removal of xanthomycinic acid I was evaporated to dryness and treated with ice-water. The crystalline solid that separated (xanthomycinic acid II) was filtered off and recrystallized from cyclohexane. It formed long colorless needles melting at 118–119°. Tests for nitrogen were negative.[7]

A solution of xanthomycinic acid II was neutralized to

(7) Elementary analysis on acid II, and molecular weight determinations by the Rast method on both acids were unsatisfactory and insufficient material was available for trying other methods. Because the first author was obliged to return to India at this time, further work on the degradation products has been discontinued for an indefinite period.

*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

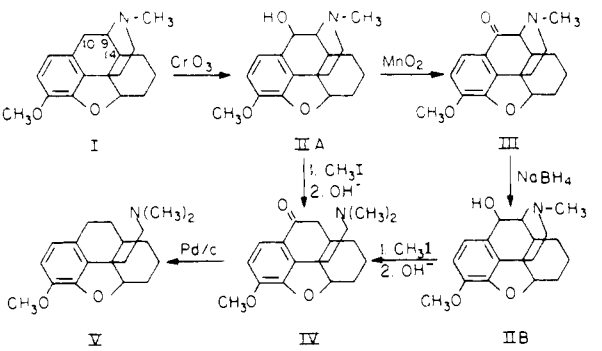
RECEIVED APRIL 4, 1955

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. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954), report the successful oxidation of several benzyl alcohols using specially activated manganese dioxide.