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Alkaloids of the Amaryllidaceae. X. The Structure of Caranine[1]

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A combination of degradative experiments substantiates the structure I for the alkaloid caranine.

In previous papers[2,3] of this series the alkaloid caranine, isolated from *Amaryllis belladonna* L., was characterized as a base, $C_{16}H_{17}NO_3$. One of the two simplest Amaryllidaceae alkaloids, it contained a methylenedioxyphenyl group, a hydroxyl group, a tertiary nitrogen atom and one double bond.

Preliminary tests on caranine have now shown it to be unaffected by hot 10% hydrochloric acid, hot 90% formic acid, hot 10% ethanolic potassium hydroxide and lithium aluminum hydride. The alkaloid was not oxidized to an α,β-unsaturated ketone by active manganese dioxide although part of the base was destroyed by the reagent. Caranine contained no N-methyl or methoxyl groups, and a Rast molecular weight determination showed the molecular formula to be $C_{16}H_{17}NO_3$.

Hydrogenation of caranine in acetic acid over platinum gave α-dihydrocaranine (IV), m.p. 170.5–172°, $[\alpha]_D$ $-126°$, which proved to be different from β-dihydrocaranine (V), m.p. 166.5–168°, $[\alpha]_D$ $-191°$, obtained from the reduction of caranine in ethanol over palladium.[2]

On the basis of an unusual, but reproducible, modified Oppenauer oxidation of caranine to the phenanthridinium compound II,[3] the base I was postulated to have the lycorine[4] carbon skeleton with a hydroxyl group in the 1-position. The unprecedented nature of the above oxidation does not exclude the possibility of a molecular rearrangement or the possibility that the hydroxyl present in II is not that originally present in caranine but may have been introduced by the air oxidation occurring during the reaction work-up. Hence it was felt desirable to provide additional evidence for each structural feature and in particular for the size of each ring of caranine.

Potassium permanganate oxidation of caranine (I) gave hydrastic acid isolated as its anhydride III, m.p. 179–180.5°, to establish the nature and position of the substituents on ring A.

The size of the B-ring of caranine was determined in the same way as for lycorine.[5] Acetylation of α-dihydrocaranine or hydrogenation of acetylcaranine in acetic acid over platinum gave the same α-dihydroacetylcaranine (VI). This was oxidized with permanganate to the lactam VII whose infrared spectrum in chloroform showed a peak at 6.10 μ characteristic of a 6-membered lactam ring.[5] The lactam was reduced with lithium aluminum hydride to α-dihydrocaranine (IV) to prove that no rearrangement had taken place.

Ring C was investigated through the ketone α-dihydrocaranone (VIII). When a benzene solution of α-dihydrocaranine was stirred for 1.5 hours at room temperature with potassium *t*-butoxide and fluorenone, a 65% yield of pure α-dihydrocaranone was isolated. Its chloroform infrared spectrum had a carbonyl peak at 5.87 μ characteristic of a ketone in a six-membered ring. From the oxidation, in addition to the ketone VIII, there was obtained, in 3% yield, a neutral keto-lactam, $C_{16}H_{13}NO_4$, m.p. 251.5–253°, which must have the structure IX since its complex ultraviolet spectrum is almost identical with the model compound X prepared previously.[3,6]

The isolation of the keto-lactam IX provides additional evidence for the placement of the caranine hydroxyl group in the 1-position. Unequivocal evidence for this point was obtained when the treatment of α-dihydrocaranone with acetic anhydride gave an enol acetate conjugated with the aromatic ring, λ_{max} 264 mμ (ϵ 12,000), possible only with a 1-keto structure. The enol acetate proved too sensitive to oxidation and hydrolysis to be separated from a second product of the reaction, the neutral keto-amide XII, which could have been formed either by direct attack of the anhydride on the nitrogen atom of VIII or by acetylation of the nitrogen after its β-elimination from the C-ring.

The results of the Hofmann degradation of caranine are consistent with the above findings Caranine, like lycorine,[7] gives an α- and a β methiodide XIII but in the proportion of 2:1. The β-methiodide, m.p. 312–314°, $[\alpha]_D$ $+62°$, crystallized from ethanol–water while the α-methiodide, m.p. 254–255°, $[\alpha]_D$ $-111°$, could be obtained from the filtrates by evaporation to dryness and trituration with ethanol. The Hofmann reaction on the mixture of methiodides was carried out at 120°. The optically inactive caranine anhydromethine, $C_{17}H_{17}NO_2$, m.p. 92–92.5°, obtained by chromatography of the crude product contained no hydroxyl group and did not absorb hydrogen in the presence of palladium. The oxidation of the anhydromethine to 4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid (XVa), m.p. 262.5–263.5°, together with the fact that the nitrogen atom is benzylic to the methylenedioxyphenyl ring

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(1) Paper IX, H. M. Fales and W. C. Wildman, THIS JOURNAL, **78**, 4151 (1956).

(2) L. H. Mason, E. R. Puschett and W. C. Wildman, *ibid.*, **77**, 1253 (1955).

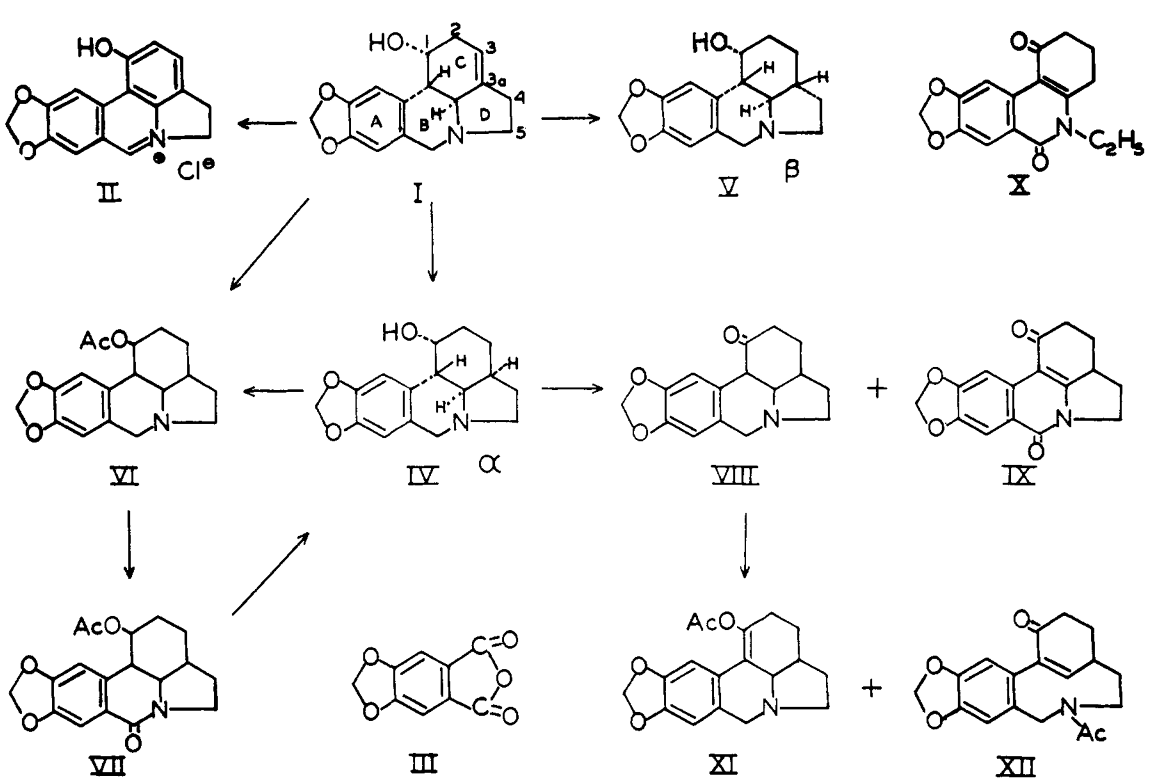
(3) H. M. Fales, E. W. Warnhoff and W. C. Wildman, *ibid.*, **77**, 5885 (1955).

(4) L. G. Humber, *et al.*, *J. Chem. Soc.*, 4622 (1954).

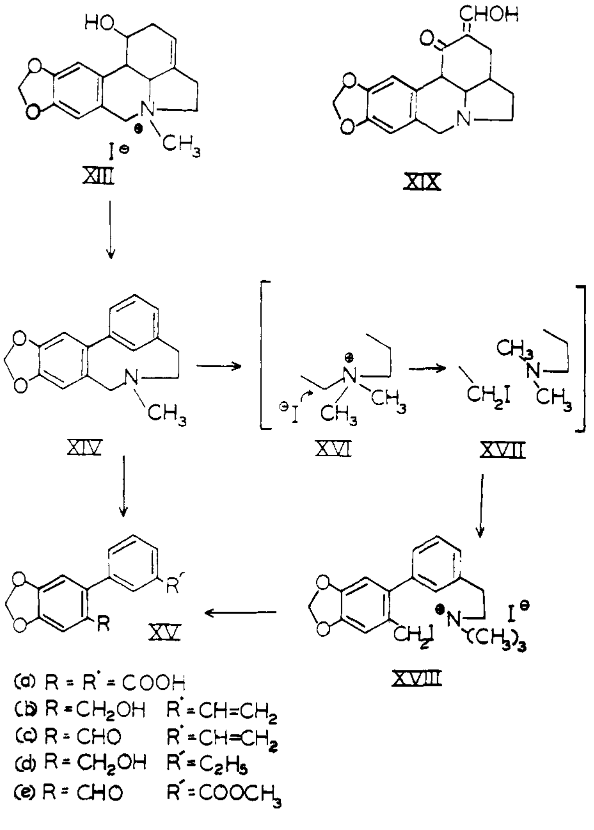
(5) K. Wiesner, W. I. Taylor and S. Uyeo, *Chemistry & Industry*, 46 (1954), found the lactam infrared peak of dihydrolycorinone at 6.13 μ compared to 6.10 μ for N-methyloxyhydrastinine and 5.97 μ for N-methyl-1-oxo-2,3-dihydroisoindole.

(6) Probably IX was formed by air oxidation. In acidic or basic solution α-dihydrocaranone absorbs oxygen rapidly. See also the ultraviolet spectrum of a similar compound from lycorine, S. Takagi, W. I. Taylor, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 4003 (1955).

(7) H. Kondo, H. Katsura and S. Uyeo, *Ber.*, **71**, 1529 (1938).



(as shown by formation of lactam VII) proves the structure to be XIV.



(a) $R = R' = COOH$
(b) $R = CH_2OH$ $R' = CH=CH_2$
(c) $R = CHO$ $R' = CH=CH_2$
(d) $R = CH_2OH$ $R' = C_2H_5$
(e) $R = CHO$ $R' = COOCH_3$

Various attempts to prepare the methiodide of caranine anhydromethine failed until its sensitive nature was realized.[8] The best procedure was to allow a methyl iodide solution of the methine to stand at room temperature until a crystalline precipitate slowly settled. This proved to be the product XVIII of reaction of two molecules of methyl iodide with the anhydromethine. Undoubtedly the first reaction was the formation of the normal methiodide XVI which then underwent nucleophilic attack by the iodide ion at the benzylic carbon.[9] The resulting iodo-tertiary amine XVII was quaternized by another molecule of methyl iodide to give XVIII. When this methiodide was subjected to the Hofmann reaction with two equivalents of silver oxide, the vinyl benzyl alcohol XVb was formed.[10] The other product of the reaction, trimethylamine, was isolated as its picrate when the quaternary salt XVIII was heated with aqueous base.

The presence of a vinyl group in XVb was shown by the strong infrared absorption at 10.98 μ[11] which disappeared on hydrogenation with the absorption of one equivalent of hydrogen. The

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(8) The strain introduced into the biphenyl system of XIV by the four-atom bridge renders the anhydromethine extremely sensitive to nucleophilic attack at the benzylic carbon bonded to the nitrogen atom when this nitrogen is quaternized by a proton or an alkyl group. This will be elaborated in a later publication.

(9) *Cf.* the formation of 6-phenylpiperonyl iodide from tazettine methine (6-phenylpiperonyl dimethylglycinate) on heating in acetone with methyl iodide at 100°. *Cf.* (a) G. R. Clemo and M. Hoggarth, *Chemistry & Industry*, 1046 (1954); (b) G. R. Clemo and R. Robinson, *ibid.*, 1086 (1955); (c) W. I. Taylor, S. Uyeo and H. Yajima, *J. Chem. Soc.*, 2962 (1955).

(10) A second, crystalline compound, $C_{32}H_{26}O_5$, was isolated from the Hofmann reaction on oily anhydromethine methiodide prepared in acetone at 95°. This was apparently the ether of two molecules of XVb.

(11) R. S. Hampton, *Anal. Chem.*, **21**, 923 (1949). See also references cited in L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 42–43.

hydroxyl of XVb was shown to be benzylic by its oxidation to an aldehyde XVc with active manganese dioxide. Finally, the isolation of 4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid from the permanganate oxidation of the vinyl aldehyde XVc excludes the possibility of a rearrangement in the second Hofmann reaction.

An authentic sample of 3,4-methylenedioxy-2,3′-biphenyldicarboxylic acid was prepared by an Ullmann reaction. Methyl *m*-iodobenzoate and 6-bromopiperonal were condensed in the presence of copper powder to give 14% of methyl 2-formyl-4,5-methylenedioxy-3′-biphenylcarboxylate (XVe) which was saponified and oxidized to the diacid XVa by heating with hydrogen peroxide in basic ethanol solution. In addition to the desired Ullmann product, there were isolated two fluorenones, formed by dehydrogenative coupling of the formyl group of XVe with the unsubstituted *o*-positions of the aromatic ring containing the carbomethoxyl group.[12] The isolation of two fluorenones is possible only if the carbomethoxyl group of XVe is in the 3′-position.

The degradation of the Hofmann product to XVa means that the remaining two carbon atoms forming the D-ring of caranine are joined to the nitrogen atom and either C_2 or C_{3a} (formula I). Attachment at C_2 was eliminated both by (a) the preparation of a hydroxymethylene α-dihydrocaranone (XIX) which had the same ultraviolet absorption peak at 275 mμ, after subtraction of the methylenedioxyphenyl contribution, as a simple α-hydroxymethylene ketone[13] and by (b) Takeda and Kotera's conversion of dihydrolycorine to α-dihydrocaranine.[14,14a]

The position of the double bond in caranine is as yet fixed only by negative evidence. The double bond is not conjugated with the aromatic ring. The failure of caranine to yield an α,β-unsaturated ketone on stirring with manganese dioxide[15] and, more important, the formation of two dihydrocaranines preclude the 2,3-position for the double bond. Nor is the double bond α,β to the nitrogen atom since (a) caranine is not reduced by lithium aluminum hydride, (b) neither the perchlorate of caranine nor of acetylcaranine shows strong infrared absorption in the 6 μ region[16] and (c) the pK_a of α-dihydrocaranine is higher than that of caranine.[17] The double bond must be at least trisubstituted since two isomers were obtained on hydrogenation of caranine. Of the two possible positions 3,3a or 3a,4 for the double bond, the 3,3a-isomer more readily accommodates the oxidation of caranine to II.

The stereochemistry of caranine, α-dihydrocaranine and β-dihydrocaranine as indicated in I, IV and V, respectively, follows from the work of Takeda and Kotera[14] who have produced convincing evidence that monodesoxydihydrolycorine, identical with α-dihydrocaranine,[18] has the stereochemistry shown in IV. If no double bond migration has taken place during any of the hydrogenations, β-dihydrocaranine must be the C_{3a} epimer of α-dihydrocaranine.

Experimental[19]

Preliminary Tests.—Caranine was recovered unchanged after (a) 2-hour reflux in 10% hydrochloric acid, (b) 1-hour reflux in 10% ethanolic potassium hydroxide and (c) 4-hour reflux with 90% formic acid.

Anal. Calcd. for $C_{16}H_{17}NO_3$: (1) OCH_3, 11.43; (1) (N)–CH_3, 5.54; (1) (C)–CH_3, 5.54; mol. wt., 271. Found: OCH_3, none; (N)–CH_3, 0.53; (C)–CH_3, none; mol. wt. (Rast), 277.

In dimethylformamide-water (3:7) these pK_a's were obtained: caranine, 7.60; α-dihydrocaranine, 9.00; lycorine, 6.90; dihydrolycorine, 8.67.

The addition of a few drops of 70% perchloric acid to a solution of 100 mg. of acetylcaranine in 5 ml. of ether gave 123 mg. (93%) of **acetylcaranine perchlorate** which was recrystallized three times from 99% ethanol to give colorless prisms, m.p. 259.5–261.5°, λ_{max}^{Nujol} 2.91, 5.77, 9.72 and 10.80 μ with no strong absorption in the 6 μ region.

Anal. Calcd. for $C_{18}H_{19}NO_4 \cdot HClO_4$: C, 52.24; H, 4.87; N, 3.38. Found: C, 52.58; H, 4.98; N, 3.50.

Action of Lithium Aluminum Hydride on Caranine.—A solution of 150 mg. of caranine in 10 ml. of dry tetrahydrofuran was refluxed with 150 mg. of lithium aluminum hydride for 25 hours. The excess hydride was destroyed with ethyl acetate and concentrated aqueous sodium hydroxide was added until the precipitated aluminum hydroxide dissolved. Extraction with ether gave 138 mg. of colorless oil which was crystallized from ethyl acetate to yield 111 mg. of caranine, m.p. 178.5–181°, undepressed on admixture with starting material. The infrared spectrum in chloroform was identical with that of caranine.

Reaction of Caranine with Manganese Dioxide.—Caranine (200 mg.) was stirred with 1.00 g. of manganese dioxide[20] in 10 ml. of chloroform. The infrared spectrum of the solution at the end of 1 and 2 hours showed no carbonyl band. The reaction mixture was filtered and the emerald-green solution evaporated to give 146 mg. of brown glass. Sublimation at 145° (2 μ) gave 106 mg. of crude caranine and 40 mg. of unsublimed brown residue which was insoluble in organic solvents and dilute hydrochloric acid. Two recrystallizations of the sublimate from ethyl acetate gave 62 mg. of pure caranine, m.p. 179–181°, undepressed on admixture with starting material. The infrared spectrum in chloroform was identical with that of caranine.

Permanganate Oxidation of Caranine.—A solution of 1.00 g. of caranine dissolved in 50 ml. of water containing 6 ml. of 10% hydrochloric acid was made just basic by the addition of 10% aqueous potassium hydroxide. This solution was stirred with a Vibro-mischer[21] while a solution of 5.00

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[12] For other examples of this reaction see S. Uyeo, *Ber.*, **73**, 661 (1940).

[13] For example, hydroxymethylene taraxerone, λ_{max} 275 mμ, E. Koller, A. Hiestand, P. Dietrich and O. Jeger, *Helv. Chim. Acta*, **33**, 1050 (1950).

[14] K. Takeda and K. Kotera, *Chemistry & Industry*, 347 (1956).

[14a] Added in Proof.—A third and most convincing argument for the lycorine ring system in caranine is the conversion of lycorine to caranine with sodium and amyl alcohol (W. C. Wildman and H. M. Fales, unpublished observation).

[15] (a) B. C. L. Weedon, *Ann. Repts.*, **49**, 142 (1952); **50**, 169 (1953); (b) F. Sondheimer, E. Amendolla and G. Rosenkranz, This Journal, **75**, 5932 (1953).

[16] N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954).

[17] R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

[18] For a comparison of physical properties see the Experimental section.

[19] All melting points are corrected and were taken on a Kofler microscope hot-stage equipped with a polarizer unless otherwise specified. Optical rotations were taken in a 2-dm. tube on chloroform solutions unless otherwise specified. Analyses were performed by J. F. Alicino, Metuchen, New Jersey; W. Manser, Zurich, Switzerland; and W. C. Alford, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra were recorded with a Cary Model 11MS spectrophotometer by F. Byers, F. C. Bateman, C. Monaghan and C. Smith. Unless otherwise noted the ultraviolet spectra were run in Pharmco absolute ethanol. Molar extinction coefficients are given in parentheses after the wave length. Merck reagent grade chromatographic alumina (pH 10) was used. The pK_a measurements were made by Mrs. L. E. Giuffrida.

[20] J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

[21] AG für Chemie Apparatebau, Zurich, Switzerland.

g. of potassium permanganate in 250 ml. of water was added dropwise during 45 minutes. After an additional 15-minute stirring period the reaction mixture was treated with sulfur dioxide until solution of the manganese dioxide was effected. A few milliliters of dilute sulfuric acid was added and the yellow solution was extracted with ethyl acetate to give 413 mg. of yellow solid. The solid was triturated with 10% potassium bicarbonate solution and filtered. Acidification of the filtrate followed by ethyl acetate extraction gave 178 mg. of solid which was refluxed with 8 ml. of 20% aqueous sodium hydroxide under nitrogen for 3.5 hours. A yellow gum (84 mg.) was obtained on acidification and extraction with ethyl acetate. This was sublimed at 160° (0.3 mm.) to give 12.5 mg. of crude **hydrastic anhydride** (III), m.p. 168–175°.

Continuous ether extraction of the original aqueous layer from the oxidation gave 83 mg. of brown oil which was sublimed at 160° (0.3 mm.) to give 8.5 mg. more of crude hydrastic anhydride, m.p. 140–155°, bringing the total yield to 3%.

A sample of the sublimate (4.5 mg.) was recrystallized from cyclohexane–acetone to give 3.0 mg. of pure **hydrastic anhydride**, m.p. 179–180.5°, undepressed on admixture with an authentic specimen[22] of m.p. 179.5–180.5°. The infrared spectra of the two samples in chloroform were identical, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.40, 5.49, 5.65, 6.28, 9.70 and 10.69 μ.

Another sample of the crude anhydride (8.0 mg.) was triturated in a sublimation tube with 2 drops of 30% aqueous ethylamine. The tube was heated to drive off the water and the residue was sublimed at 160° (0.3 mm.) to give 8.0 mg. of **N-ethylhydrastimide**, m.p. 150–164°. Recrystallization from ethanol gave 5 mg. of colorless blades, m.p. 168.5–169.5°, undepressed on admixture with an authentic specimen[23] of m.p. 169–170°. The ultraviolet and infrared spectra of the two specimens were identical, $\lambda_{\max}$ 245 (41,100), 302 (1860), 313 (1810) and 341 mμ (1010); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.64, 5.85, 6.23, 9.66 and 10.66 μ.

Hydrogenation of Caranine in Acetic Acid with Platinum.—A solution of 5.000 g. of caranine in 30 ml. of glacial acetic acid was added to a suspension of 400 mg. of reduced platinum oxide in 5 ml. of glacial acetic acid. The reduction stopped in two hours after 0.96 equivalent of hydrogen was absorbed at atmospheric pressure and room temperature. Most of the acetic acid was evaporated from the solution after filtration and the residue was basified with 10% aqueous potassium hydroxide before extraction with ethyl acetate. Concentration of the dried solution gave 3.626 g. (72%) of **α-dihydrocaranine** (IV), m.p. 169–172°. A second crop of 0.300 g. (6%), m.p. 168–172°, brought the total yield to 78%. Three recrystallizations from ethyl acetate gave colorless prisms, m.p. 170.5–172°, $[\alpha]^{26}\mathrm{D}$ $-126°$ (c 0.441), λ_{inf} 233 mμ (4400) and $\lambda_{\max}$ 291 mμ (4700); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.77, 9.65 and 10.70 μ.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.44; H, 6.95; H, 5.27.

The picrate was prepared with ethanolic picric acid and recrystallized three times from acetone–ethanol to give clusters of yellow needles, m.p. 149–150° and 172–173° dec.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot C_6H_3N_3O_7$: C, 52.59; H, 4.41; N, 11.15. Found: C, 52.65; H, 4.60; N, 11.23.

A sample of **monodesoxydihydrolycorine** kindly supplied by Dr. Takeda[14] had m.p. 170.5–172.5°, $[\alpha]^{24}\mathrm{D}$ $-126°$ (c 0.610). The mixture melting point with α-dihydrocaranine was 170.5–172.5°. The infrared spectra of the two compounds in chloroform were identical. The mixture melting point of the monodesoxydihydrolycorine and β-dihydrocaranine was depressed to 141–160°.

Hydrogenation of Caranine in Ethanol with Palladium.—A solution of 300 mg. of caranine in 9 ml. of ethanol in the presence of 100 mg. of 10% palladium-on-carbon catalyst took up one mole of hydrogen at room temperature and atmospheric pressure. Filtration of the solution and evaporation of the solvent gave 290 mg. of colorless glass. This was crystallized from ethyl acetate to give 96 mg. (32%) of β-dihydrocaranine (V), m.p. 157–163°. A second crop of 41 mg. (14%), m.p. 156–162°, brought the total yield to 46%. Five recrystallizations from ethyl acetate–cyclohexane gave colorless prisms, m.p. 166.5–168° (depressed to 142–164° on admixture with α-dihydrocaranine), $[\alpha]^{25}\mathrm{D}$ $-191°$ (c 0.520), λ_{inf} 233 mμ (3720), $\lambda_{\max}$ 292 mμ (4650); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.75, 9.65 and 10.69 μ.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.64; H, 7.00; N, 5.08.

The picrate was prepared with ethanolic picric acid and recrystallized twice from chloroform–ethanol to give yellow spherulites, m.p. 174–175° dec., depressed to 163–171° on admixture with α-dihydrocaranine picrate.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot C_6H_3N_3O_7$: C, 52.59; H, 4.41. Found: C, 52.65; H, 4.35.

Hydrogenation of Acetylcaranine.—A solution of 230 mg. of acetylcaranine in 8 ml. of glacial acetic acid was stirred under hydrogen with 72 mg. of platinum oxide catalyst. The reduction stopped in 20 minutes after the absorption of 20 ml. (108% of one equivalent) of hydrogen. The catalyst was removed by filtration and most of the acetic acid evaporated at reduced pressure. The residue was dissolved in 2% hydrochloric acid, washed with ethyl acetate, basified and extracted with ethyl acetate to give 220 mg. (95%) of colorless oil which crystallized. Five recrystallizations from ethyl acetate–cyclohexane gave colorless felted needles of **α-dihydroacetylcaranine** (VI), m.p. 193.5–195°, $[\alpha]^{23.5}\mathrm{D}$ $-121°$ (c 0.332), $\lambda_{\max}$ 235 (3950) and 293 mμ (4770); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.77, 9.64 and 10.67 μ.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.65; H, 6.81; N, 4.46.

The picrate was prepared in ethanol solution and when crystallized rapidly from chloroform–ethanol gave feathery needles, m.p. 182–184°, but when crystallized slowly from the same solvent gave micaceous yellow plates, m.p. 188–189°.

Acetylation of α-Dihydrocaranine (IV).—A solution of 200 mg. of α-dihydrocaranine in 3 ml. of dry pyridine and 1 ml. of acetic anhydride was refluxed for 3 hours. Most of the acetylation mixture was removed at reduced pressure. The residue was taken up in chloroform, washed with aqueous potassium carbonate solution, dried and evaporated to give 225 mg. of yellow oil which was chromatographed on 7 g. of alumina. Benzene and benzene–ethyl acetate (49:1) eluted 183 mg. (80%) of α-dihydroacetylcaranine (VI) which crystallized.

A solution of 50 mg. of the acetate in ethanol gave 79 mg. (92%) of **picrate**, m.p. 183–192°, on treatment with ethanolic picric acid. Four recrystallizations from chloroform–ethanol gave yellow micaceous plates, m.p. 188–189°, $\lambda_{\max}$ 237 (15,200), 292.5 (6450) and 359 mμ (15,700).

Anal. Calcd. for $C_{18}H_{21}NO_4 \cdot C_6H_3N_3O_7$: C, 52.94; H, 4.44; N, 10.29. Found: C, 52.73; H, 4.51; N, 10.15.

This picrate exhibited the same polymorphic behavior as the picrate in the preceding experiment and the mixture melting point of the two was undepressed. The infrared spectra of the two picrates in chloroform were identical.

Oxidation of α-Dihydroacetylcaranine.—A solution of 290 mg. (0.92 mmole) of α-dihydroacetylcaranine in 8 ml. of reagent-grade acetone was cooled to 1–2° in an ice–salt bath. A solution of 194 mg. (1.23 mmoles) of potassium permanganate in 19 ml. of water was cooled to 5° and added dropwise over a period of 20 minutes to the stirred acetone solution. At the end of the addition period all permanganate had been reduced. The reaction mixture was filtered through Celite and the manganese dioxide washed with acetone. The filtrates were evaporated to dryness and taken up in ether–chloroform before washing with dilute hydrochloric acid. Concentration of the dried organic layer gave 135 mg. (44% crude yield) of oily **α-dihydroacetylcaranine lactam** (VII) which crystallized on trituration with ethyl acetate, m.p. 180°. Four recrystallizations from ethyl acetate–cyclohexane gave irregular prisms, m.p. 192–194°; $[\alpha]^{23}\mathrm{D}$ $-171°$ (c 0.595); $\lambda_{\max}$ 222 (29,900), 251 (5150), 265 (4600) and 305 mμ (6940); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.80, 6.11, 6.25, 9.67 and 10.70 μ.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.39; H, 5.63; N, 4.21.

Reduction of α-Dihydroacetylcaranine Lactam.—A solution of 30 mg. of the lactam VII, m.p. 189–193°, in 10 ml. of ether was refluxed with lithium aluminum hydride for 22 hours. The excess hydride was decomposed with dilute hydrochloric acid and the aqueous solution was washed with ether. Basification of the acid solution followed by extrac-

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(22) M. Freund, *Ann.*, **271**, 375 (1892).

(23) E. Späth and F. Kuffner, *Ber.*, **64**, 370, 1123 (1931).

tion with ether gave 19 mg. of crystals, m.p. 168°. Recrystallization from ethyl acetate gave 5 mg. of **α-dihydrocaranine** (IV), m.p. 170–172.5°, undepressed on admixture with an authentic sample of m.p. 170.5–172°. The infrared spectra of the two samples in chloroform were identical.

Modified Oppenauer Oxidation of α-Dihydrocaranine (IV).—Potassium *t*-butoxide was prepared from 2.30 g. of potassium and 75 ml. of dry *t*-butyl alcohol. The excess alcohol was evaporated at reduced pressure. To the dry alkoxide were added a magnetic stirring bar, 65 ml. of benzene, 5.00 g. of fluorenone and 3.000 g. (11.0 mmoles) of α-dihydrocaranine, m.p. 169–172°. The reaction mixture was put under nitrogen and stirred at room temperature. The color changed from orange to a dark brown within the first few seconds after mixing. At the end of 1.5 hours water was added to the brown mixture whereupon the color lightened to an orange-yellow. The aqueous layer was separated and washed twice with ether. The combined organic layers were washed once with water and extracted with three portions of 5% hydrochloric acid. The combined acid layers were washed with ether and basified with concentrated sodium hydroxide solution. The oil which precipitated was extracted with ether to give 2.873 g. (96% crude yield) of crystalline α-dihydrocaranone (VIII). Recrystallization from methanol gave 1.945 g. (65%) of long colorless prisms, m.p. 140–149°. The analytical sample after three more recrystallizations from methanol had m.p. 141–148°, unchanged when taken in a nitrogen atmosphere, $[\alpha]^{25}_{\mathrm{D}}$ 0°, $[\alpha]^{25}_{436}$ +24° (*c* 0.849); λ_{inf} 226 mμ (5660), $\lambda_{\max}$ 289 mμ (4600); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.87, 9.68 and 10.70 μ.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70·83; H, 6.32; N, 5.16. Found: C, 70.97; H, 6.44; N, 5.25.

A solution of 40 mg. of the ketone and 50 mg. of 2,4-dinitrophenylhydrazine in 4 ml. of glacial acetic acid was warmed on a steam-bath and allowed to stand at room temperature overnight. Dilution of the solution with water and neutralization of the acid precipitated 71 mg. of 2,4-dinitrophenylhydrazone which was recrystallized twice from chloroform–ethanol to give felted orange needles which decomposed with a yellow flash at *ca.* 270° on a Kofler Heizbank, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 3.01, 6.19, 6.28, 9.67 and 10.70 μ.

Anal. Calcd. for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69; N, 15.52. Found: C, 58.90; H, 4.46; N, 16.04.

The material in the mother liquor from recrystallization of the ketone was taken up in ether–ethyl acetate and washed with three portions of 5% hydrochloric acid, dried and evaporated to give 100 mg. (3%) of neutral keto-lactam (IX), m.p. 220–250°, which was recrystallized three times from chloroform–methanol to give small felted needles, m.p. 251.5-253°, $[\alpha]^{26}_{\mathrm{D}}$ −21.5° $[\alpha]^{26}_{436}$ −92° (*c* 1.01), $\lambda_{\max}$ 214 (12,600), 247 (30,900), 265 (28,000), 303 (7140), 330 (9480) and 344 mμ (9480); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.09, 6.18, 6.30, 9.65 and 10.65 μ. The model compound X[3] had $\lambda_{\max}$ 216 (11,700), 246 (30,500), 265, (27,400), 316 (8380), 331 (9600) and 345 mμ (8200).

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.95. Found: C, 67.84; H, 4.70; N, 4.88.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized twice from dimethylformamide as felted red needles, m.p. 299–302° dec.

Anal. Calcd. for $C_{22}H_{17}N_5O_7$: C, 57.02; H, 3.70; N, 15.11. Found: C, 56.89; H, 3.77; N, 15.34.

Reaction of Acetic Anhydride with α-Dihydrocaranone.—A solution of 400 mg. of α-dihydrocaranone (VIII) and three drops of triethylamine in 2 ml. of acetic anhydride was kept under nitrogen at 90° for 2 hours. The clear brown solution was evaporated to dryness *in vacuo*. The infrared spectrum of the crude material in chloroform showed carbonyl absorption at 5.73, 5.99, and 6.10 μ which indicated a mixture of enol acetate XI and keto amide XII. The brown glass was dissolved in ethyl acetate, washed with 5% hydrochloric acid and 5% potassium hydroxide solution, dried and evaporated to give 252 mg. (55%) of oily keto-amide XII which crystallized on trituration with ethyl acetate. Three recrystallizations from ethyl acetate–cyclohexane gave colorless prisms, m.p. 182.5–184.5°, $[\alpha]^{27}_{\mathrm{D}}$ +242° (*c* 0.565); $\lambda_{\max}$ 245 mμ (10,300), λ_{inf} 260 (7350) and 292 mμ (3910); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.99, 6.12, 9.66 and 10.72 μ.

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47; (N)-$COCH_3$, 13.73. Found: C, 68.89; H, 6.22; N, 4.44; (N)-$COCH_3$, 14.52.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized twice from dimethylformamide to give small red needles, m.p. 300–301° dec., in amount insufficient for analysis.

Attempts to isolate the pure enol acetate XI from acetylations under milder conditions by fractional sublimation, crystallization and rapid chromatography failed because of the sensitivity of the compound to oxidation and hydrolysis. A sample of the crude enol acetate containing very little XII had $\lambda_{\max}$ 263 (12,000) and $\lambda_{\max}$ 304 mμ (5720) compared to $\lambda_{\max}$ 260 (11,800) and 305 mμ (5200) for isosafrole. The infrared spectrum in chloroform had $\lambda_{\max}$ 5.72, 9.65 and 10.70 μ with weaker peaks at 6.00 and 6.11 μ.

Caranine α- and β-Methiodides (XIII).—To a refluxing solution of 6.00 g. (22.1 mmoles) of caranine, m.p. 178.5–180.5°, in 130 ml. of benzene was added 20 ml. of redistilled methyl iodide. A white precipitate formed immediately. The reaction mixture was cooled and filtered to give 9.15 g. (100%) of crude methiodide, m.p. 270–275° dec., $[\alpha]^{28}_{\mathrm{D}}$ −60° (*c* 0.34, 1:1 water–dimethylformamide).

A 200-mg. sample was recrystallized from water–ethanol to give 76 mg. (38%) of colorless blades, m.p. 305–308° dec. Two more recrystallizations from water–ethanol gave pure **caranine β-methiodide**, m.p. 312–314° dec. (reported[2] 316–318° dec.), $[\alpha]^{28}_{\mathrm{D}}$ +62° (*c* 0.28, 1:1 water–dimethylformamide); $\lambda_{\max}$ 291 mμ (4740); $\lambda_{\max}^{\mathrm{KBr}}$ 2.90, 9.69 and 10.75 μ.

The filtrates from the first recrystallization of the methiodide were evaporated to dryness and the resulting glass triturated with ethanol whereupon it crystallized. Recrystallization from 99% ethanol gave 98 mg. (49%) of **caranine α-methiodide**, m.p. 255–256° dec. Three more recrystallizations from 99% ethanol gave colorless felted needles, m.p. 254–255° dec., $[\alpha]^{25}_{\mathrm{D}}$ −111° (*c* 0.459, 1:1 water–dimethylformamide); $\lambda_{\max}$ 293 mμ (4600); $\lambda_{\max}^{\mathrm{KBr}}$ 2.92, 9.70 and 10.72 μ.

Anal. Calcd. for $C_{17}H_{20}NO_3I$: C, 49.40; H, 4.88; N, 3.39. Found: C, 49.68; H, 5.17; N, 3.49.

The proportion of α- to β-methiodide calculated from rotation data is 70:30 whereas that calculated from the fractional crystallization is 62:38.

The Hofmann Reaction on Caranine Methiodide.—To a suspension of 8.95 g. (21.6 mmoles) of a mixture of caranine α- and β-methiodides in 80 ml. of water was added neutral silver oxide prepared from 3.900 g. (22.9 mmoles) of silver nitrate. The formation of the methohydroxide was shown to be complete within a few minutes when a centrifuged sample of the mixture gave no precipitate with silver nitrate–nitric acid solution. The silver salts were removed by filtration through Celite. The clear filtrate was evaporated under reduced pressure at 50°. The flask containing the greenish residual oil was put under nitrogen and immersed in an oil-bath at 120° for 40 minutes. The water given off was removed at reduced pressure, and the brown glass dried in a desiccator to give 5.76 g. (99%).

The product was partitioned between ether and 5% hydrochloric acid. The acid solution was washed with ether, cooled in an ice-bath and basified with concentrated sodium hydroxide solution. Ether extraction gave 4.80 g. of brown oil which was dissolved in cyclohexane and chromatographed on a column of 120 g. of alumina. Elution with cyclohexane:benzene (49:1) gave 2.22 g. of colorless oil which solidified. Recrystallization from methanol gave 1.95 g. (33%) of **caranine anhydromethine** (XIV), m.p. 91–92.5°.

The material eluted with cyclohexane:benzene (3:1) was rechromatographed to give an additional 208 mg., m.p. 91–92.5° after recrystallization from methanol, bringing the total yield to 37%.

Three additional recrystallizations from methanol gave white flakes, m.p. 92–92.5°, $[\alpha]^{24}_{\mathrm{D}}$ 0°, $[\alpha]^{24}_{436}$ 0° (*c* 0.835); $\lambda_{\max}$ 255 (8460) and 302 mμ (7080); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 6.25, 6.37, 9.67 and 10.76 μ.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; (N)–CH_3, 5.62. Found: C, 76.25; H, 6.36; N, 5.11; (N)–CH_3, 4.07; (C)–CH_3, none.

The anhydromethine (42 mg.) gave 75 mg. (96%) of **picrate**, m.p. 134–148°, when treated with ethanolic picric acid. The derivative was recrystallized twice by solution in a small volume of acetone at room temperature followed by addition of ethanol and chilling to −20° to give the pure picrate, m.p. 130–152°, λ_{max} 304 (10,200) and 358 mμ (16,100).

Anal. Calcd. for $C_{17}H_{17}NO_2 \cdot C_6H_3N_3O_7$: C, 55.64; H, 4.06; N, 11.29. Found: C, 55.68; H, 4.02; N, 11.20.

When the salt was warmed above *ca.* 50° in aqueous or alcoholic solution, an acid-catalyzed rearrangement occurred. Presumably the low and wide melting point of the picrate is also due to this rearrangement taking place.

A solution of 100 mg. of the anhydromethine in 8 ml. of 99% ethanol with 100 mg. of 10% palladium-on-carbon did not absorb any hydrogen in two hours. The anhydromethine was recovered unchanged on evaporation of the alcohol.

Oxidation of Caranine Anhydromethine.—To a solution of 400 mg. (1.50 mmoles) of caranine anhydromethine (XIV) in 50 ml. of water containing 3 ml. of 10% hydrochloric acid was added 10% aqueous potassium hydroxide until the solution was neutral and there was only a faint turbidity. This solution was warmed to 70°, and a solution of 1.895 g. (12.0 mmoles) of potassium permanganate in 100 ml. of water was added dropwise during 0.5 hour with stirring by a Vibro-mischer.[21] A few minutes after addition was over all the permanganate had been reduced. The reaction mixture was cooled and sulfur dioxide bubbled in until solution of the manganese dioxide was effected. The solution was extracted continuously with ethyl acetate after the addition of 5 ml. of 10% sulfuric acid. Evaporation of the ethyl acetate gave 233 mg. of brown gum which after trituration with chloroform left 53 mg. of insoluble acid. The chloroform solution containing 180 mg. was chromatographed on 15 g. of Mallinckrodt silicic acid. Chloroform–methanol (99:1) eluted 69 mg. of the same crude acid which had not dissolved in chloroform. This material could not be completely purified by recrystallization from ethyl acetate. Some of the purer crops of crystals were combined (44 mg.) in ethyl acetate and converted to the methyl ester with ethereal diazomethane. Evaporation of the solvent and chromatography of the residue on 2.5 g. of alumina gave 24 mg. of crystalline ester eluted with benzene. The ester was dissolved in 3 ml. of methanol and refluxed for 1 hour with 2 ml. of water containing 0.8 g. of sodium hydroxide. The methanol was boiled off and the cooled aqueous solution acidified with dilute sulfuric acid. The resulting white precipitate was filtered, washed and dried to give 19 mg. of **4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid** (XVa) which was recrystallized from ethyl acetate–benzene to give 17 mg. (4%) of small white prisms, m.p. 262.5–263.5°. The mixture melting point with an authentic specimen, m.p. 262.5–263.5°, prepared as described below, was 261–263.5°. The infrared and ultraviolet spectra of the two compounds were identical, λ_{max} 226 (37,200), 267.5 (6750) and 295 mμ (5950); λ_{max}^{KBr} 3.70–3.95, 5.92, 6.20, 9.72 and 10.81 μ.

Anal. Calcd. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52. Found: C, 62.84; H, 3.61.

Caranine Anhydromethine Bis-methiodide (XVIII).—Caranine anhydromethine (1.000 g., 3.74 mmoles) was dissolved in 13 ml. of redistilled methyl iodide and allowed to stand at room temperature protected from light. After 17 hours 600 mg. (29%) of tan solid was removed by filtration. After another 8 hours 157 mg. (7.6%) of almost colorless matted needles separated. Further crops collected over a period of several days gave 1.181 g. (57%) more bis-methiodide for a total yield of 93% of XVIII. The salt decomposed on warming with solvents. A sample prepared for analysis by washing a colorless crop of the matted needles several times with benzene before drying at room temperature *in vacuo* had m.p. 199–201° dec., λ_{max} 295 mμ (6700).

Anal. Calcd. for $C_{19}H_{23}NO_2I_2$: C, 41.39; H, 4.20; N, 2.54; I, 46.05; (3) (N)–CH_3, 8.18. Found: C, 41.01; H, 4.12; N, 2.67; I, 44.83; (N)–CH_3, 8.18.

Isolation of Trimethylamine from Caranine Anhydromethine Bis-methiodide.—A mixture of 135 mg. of the bis-methiodide XVIII and 10 ml. of 10% potassium hydroxide solution was heated to reflux in an oil-bath. Nitrogen was passed through the solution and the effluent gas bubbled through an ethanolic solution of picric acid. A slow precipitation of trimethylamine picrate occurred. The picrate was recrystallized twice from ethanol to give long yellow prisms, m.p. 213–216° (sealed capillary), undepressed on admixture with an authentic specimen of trimethylamine picrate, m.p. 214–217° (sealed capillary). The infrared spectra of the two picrates in chloroform were identical. The organic material in the potassium hydroxide solution was an intractable brown gum.

The Hofmann Reaction on Caranine Anhydromethine Bis-methiodide.—To a suspension of 1.246 g. (2.26 mmoles) of the crystalline bis-methiodide XVIII in 15 ml. of water was added the neutral silver oxide from 800 mg. (4.71 mmoles) of silver nitrate. The mixture was stirred until a sample of the supernatant liquid gave no precipitate with silver nitrate–nitric acid solution. The silver salts were separated by centrifugation and the opalescent solution of quaternary amine hydroxide decanted and evaporated to dryness *in vacuo* at 60°. An aspirator was attached to the flask which was immersed in an oil-bath at 120° for 30 minutes. The dark brown residue was taken up in benzene, washed twice with dilute hydrochloric acid, dried and evaporated to give 280 mg. (48%) of neutral yellow oil. This was combined with 47 mg. of oil from a smaller scale reaction, dissolved in benzene and chromatographed on 10 g. of alumina. Elution with benzene–ethyl acetate (1:1) gave 270 mg. of colorless **2-hydroxymethyl-4,5-methylenedioxy-3′-vinylbiphenyl** (XVb) which did not crystallize on trituration with various solvents. A sample was evaporatively distilled at 140° (0.025 mm.); λ_{max} 251 (22,100) and 293 mμ (5900); $\lambda_{max}^{CHCl_3}$ 2.76, 2.90, 6.19, 6.26, 6.31, 9.66, 10.73 and 10.98 μ.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.69; H, 5.52.

From a Hofmann reaction on the crude bis-methiodide prepared by heating crude, non-crystalline caranine anhydromethine with methyl iodide in acetone at 95° was obtained by chromatography on alumina a neutral, nitrogen-free compound which was apparently the ether derived from two molecules of XVb, m.p. 111–113° after three recrystallizations from 99% ethanol, λ_{max} 252 (41,400) and 293 mμ (11,400); $\lambda_{max}^{CHCl_3}$ 6.18; 6.25; 6.35, 9.65, 10.72 and 11.00 μ.

Anal. Calcd. for $C_{32}H_{26}O_5$: C, 78.35; H, 5.34. Found: C, 78.27; H, 5.44; N, 0.0.

Hydrogenation of 2-Hydroxymethyl-4,5-methylenedioxy-3′-vinylbiphenyl.—A solution of 71 mg. of XVb in 5 ml. of 99% ethanol absorbed 7.0 ml. (92% of one equivalent) of hydrogen over 40 mg. of 10% palladium-on-carbon catalyst in 8 minutes at room temperature and atmospheric pressure. Filtration of the solution and evaporation of the solvent gave 62 mg. of **2-hydroxymethyl-4,5-methylenedioxy-3′-ethylbiphenyl** (XVd), a colorless liquid, which was evaporatively distilled at 140° (0.03 mm.); λ_{max} 257 (7210) and 293 mμ (5400); $\lambda_{max}^{CHCl_3}$ 2.76, 2.90, 6.19, 6.25, 6.33, 9.65 and 10.72 μ.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.53; H, 6.25.

The ultraviolet spectrum of 6-phenylpiperonyl alcohol has λ_{max} 257.5 (7150) and 293 mμ (5410) for comparison.

An attempt to prepare a 3,5-dinitrobenzoate of the alcohol by allowing the alcohol in pyridine to react with 3,5-dinitrobenzoyl chloride at room temperature for 4 days gave recovered starting material.

2-Formyl-4,5-methylenedioxy-3′-vinylbiphenyl (XVc).—Manganese dioxide[20] (700 mg.) was added to a solution of 146 mg. of the benzyl alcohol XVb in 10 ml. of chloroform. The mixture was stirred for three hours at the end of which time the solution showed strong carbonyl absorption at 5.95 μ and no hydroxyl absorption. The solution was filtered and evaporated to give 137 mg. of colorless oil. Chromatography over 4 g. of alumina gave 116 mg. (80%) of XVc in the benzene eluate. The aldehyde crystallized from ethanol at −78° but after separation from solvent liquefied at room temperature. Evaporative distillation at 140° (0.025 mm.) gave a colorless glass, λ_{max} 247 (40,000) and 325 mμ (6630); $\lambda_{max}^{CHCl_3}$ 5.97, 6.20, 9.66, 10.70 and 10.96 μ.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.38; H, 5.04.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized four times from chloroform–ethanol to give small felted orange needles, m.p. 215.5–216.5°, $\lambda_{max}^{CHCl_3}$ 396 mμ (30,400); $\lambda_{max}^{CHCl_3}$ 3.04, 6.21, 6.28, 9.67, and 10.72 μ.

Anal. Calcd. for $C_{22}H_{16}N_4O_6$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.95; H. 3.94; N, 12.95.

Oxidation of 2-Formyl-4,5-methylenedioxy-3′-vinylbiphenyl.—To a solution of 48 mg. of the aldehyde XVc in 6 ml. of reagent-grade acetone stirred with a magnetic stirring bar was added a solution of 90 mg. of potassium permanganate in 3 ml. of water. After the 2-minute addition period the brown reaction mixture was allowed to stir for 30 minutes. Sulfur dioxide was added until solution of the manganese dioxide. Most of the acetone was blown off in an air jet and the residual aqueous solution was extracted continuously with ethyl acetate. The ethyl acetate was evaporated and to the residue was added 3 ml. of ethanol, 3 ml. of water and 1 g. of sodium hydroxide. This mixture was warmed for 45 minutes on the steam-bath during the dropwise addition of 12 ml. of 30% hydrogen peroxide. Acidification of the cooled solution gave 33 mg. of white precipitate, m.p. 240–252°. This acid was converted to the methyl ester with ethereal diazomethane and chromatographed on 2 g. of alumina. The benzene eluate (24.5 mg.) was saponified with methanolic sodium hydroxide. Acidification of the solution and recrystallization of the white precipitate from ethyl acetate–benzene gave 12.5 mg. (23%) of **4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid** XVa, m.p. 262.5–263.5°, undepressed on admixture with an authentic specimen of m.p. 262.5–263.5°, prepared as described below. The infrared spectra of the two acids were identical, $\lambda_{\max}^{\mathrm{KBr}}$ 3.70–3.95, 5.93, 6.22, 9.73 and 10.83 μ.

2-Hydroxymethylene-α-dihydrocaranone (XIX).—A solution of 654 mg. of α-dihydrocaranone in 6 ml. of benzene and 3 ml. of redistilled ethyl formate was refluxed under nitrogen with 335 mg. of sodium methoxide for 3 hours. The reaction mixture was diluted with water and benzene. The benzene solution was separated and washed with two portions of 10% aqueous potassium hydroxide. The combined basic aqueous solutions were washed with benzene, acidified to *p*H 7 with dilute hydrochloric acid and extracted with three portions of ethyl acetate. Evaporation of the dried ethyl acetate solution gave 461 mg. (64%) of hydroxymethylene ketone (XIX). A portion was recrystallized thrice from absolute ethanol to give almost colorless prisms, m.p. 131–133°, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.98, 6.24, 9.60 and 10.70 μ, which gave a deep violet ferric chloride test.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73. Found: C, 68.59; H, 5.95.

In absolute ethanol containing 2 drops of 10% hydrochloric acid per 10 ml. the derivative had $\lambda_{\max}$ 280 mμ (16,600). Subtraction of the spectrum of α-dihydrocaranone gave $\lambda_{\max}$ 275 mμ (13,700). The absorption peak of XIX was shifted to 304 mμ (24,700) in absolute ethanol containing 2 drops of 10% aqueous potassium hydroxide per 10 ml.

Methyl 2-Formyl-4,5-methylenedioxy-3′-biphenylcarboxylate (XVe).—In a 50-ml. pear-shaped flask equipped with a stirrer and nitrogen inlet were placed 26.2 g. (0.10 mole) of methyl *m*-iodobenzoate, m.p. 45.5–48.5°, and 22.9 g. (0.10 mole) of 6-bromopiperonal,[24] m.p. 122–128°. A small flask containing 50 g. of copper powder was attached to the third neck of the flask by a piece of rubber tubing and the whole apparatus was flushed with nitrogen. The flask was heated to 230–250° in a Woods metal-bath while the copper powder was added in small portions to the stirred liquid during one-half hour. The reaction was kept at 230–250° for another hour. The contents of the cooled flask were dissolved in benzene and filtered. Benzene was removed by distillation and 5.5 g. of recovered methyl *m*-iodobenzoate was distilled at 150° (0.8 mm.). The 22.1 g. of residue in the flask was taken up in benzene and chromatographed on 500 g. of alumina. Benzene eluted 4.0 g. of methyl *m*-iodobenzoate and 1.0 g. of impure 6-bromopiperonal. Benzene-ethyl acetate (49:1) eluted 3.62 g. of yellow oil which crystallized on trituration with ether. Further elution with the same solvent gave 1.04 g. of an orange fluorenone (a) while elution with pure ethyl acetate gave a different orange fluorenone (b).

The 3.62 g. of partially crystalline material was triturated with benzene and filtered to remove some insoluble fluorenone. The benzene of the filtrate was replaced by methanol and the solution concentrated to give 1.66 g. of **methyl 2-formyl-4,5-methylenedioxy-3′-carboxylate** (XVe), m.p., 129.5–131°. A second crop of 0.93 g., m.p. 126–131°, brought the yield to 14% based on recovered methyl *m*-iodobenzoate. A sample was recrystallized twice more from methanol to give colorless prisms, m.p. 130–131°, $\lambda_{\max}$ 242.5 (30,900), 281 (6580) and 324 mμ (6670); $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.82, 5.98, 6.21, 9.66 and 10.71 μ.

Anal. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.42; H, 4.39.

A sample of the orange fluorenone (a) was recrystallized three times from dimethylformamide and sublimed at 200° (0.05 mm.) to give bright orange prisms of **2,3-methylenedioxy-6(or 8)-carbomethoxyfluorenone**, m.p. 287–288° with sublimation, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 277 (46,100), 331 (2780) and 437 mμ (610); $\lambda_{\mathrm{inf}}^{\mathrm{CHCl_3}}$ 316 (3960) and 344 mμ (1180); $\lambda_{\max}^{\mathrm{Nujol}}$ 5.82, 5.86, 6.26, 9.70 and 10.88 μ.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found: C, 67.90; H, 3.81.

A specimen of the orange fluorenone (b) was recrystallized three times from chloroform–ethanol to give pale orange felted needles of **2,3-methylenedioxy-8(or 6)-carbomethoxyfluorenone**, m.p. 247–249° and 272.5–275° with sublimation, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 282 (64,500), 340 (4550), 356 (3550) and 448 mμ (590); $\lambda_{\mathrm{inf}}^{\mathrm{CHCl_3}}$ 275 (45,500) and 313 mμ (8970); $\lambda_{\max}^{\mathrm{Nujol}}$ 5.80, 5.85, 6.25, 9.63 and 10.80 μ.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found: C, 67.89; H, 3.52.

4,5-Methylenedioxy-2,3′-biphenyldicarboxylic Acid (XVa).—A solution of 91 mg. of the Ullmann product XVe, m.p. 129–131°, from the above reaction in 10 ml. of ethanol and 2 ml. of water containing five potassium hydroxide pellets was warmed on a steam-bath. The addition of 5 ml. of 30% hydrogen peroxide caused a vigorous reaction. After subsidence of gas evolution another 5 ml. of peroxide was added. The solution was heated for another 30 minutes, concentrated to one-third its original volume, cooled and acidified with 10% hydrochloric acid. The white precipitate was collected on a filter, washed with water and dried to give 78 mg. (85%) of 4,5-methylenedioxy-2,3′-biphenyldicarboxylic acid (XVa), m.p. 248–263°. Three recrystallizations from ethyl acetate–benzene gave small colorless prisms, m.p. 262.5–263.5°, $\lambda_{\max}$ 226 (36,800), 268 (6750) and 295 mμ (5970); $\lambda_{\max}^{\mathrm{KBr}}$ 3.70–3.95, 5.92, 6.20, 9.70 and 10.81 μ.

Anal. Calcd. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52. Found: C, 62.97; H, 3.46.

BETHESDA, MARYLAND

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[24] R. G. Naik and T. S. Wheeler, *J. Chem. Soc.*, 1780 (1938).