The Synthesis of Ismine[1]

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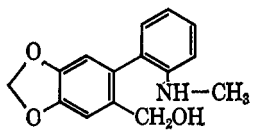
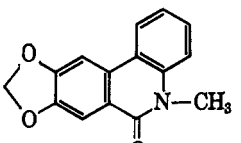
The synthesis of the alkaloid ismine, employing a new method of construction of unsymmetrical biphenyls, is described.

Highet has recently reported[4] the isolation from an *Ismene* species and the proof of structure of an alkaloid, ismine (I), an aromatized relative of many of the more common *Amaryllidaceae* alkaloids. Its structure was assigned on the basis of spectroscopic methods and conversion to the known phenanthridone II.

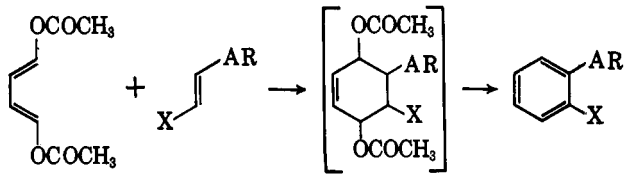


I



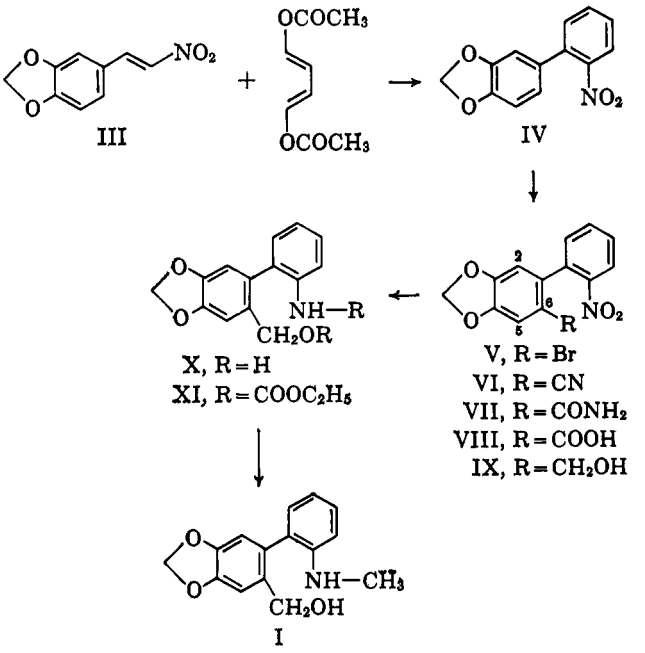
II

The synthesis of even such an apparently simple aromatic structure as I presents certain difficulties. The few methods available for the preparation of unsymmetrical biphenyls, such as the Bachman–Gomberg arylation[5] or the mixed Ullman coupling, suffer either from lack of control of orientation in linking the two rings[5] or from low yields and tedious separation of mixed products.[6] We have therefore developed a new method for the preparation of unsymmetrical biphenyls and used it to synthesize ismine. The method involves the Diels–Alder addition of 1,4-diacetoxybutadiene to aromatic dienophiles. At temperatures above 110°, the adduct (not isolated) is generally aromatized by elimination of acetic acid.[7]



In applying this method to the synthesis of ismine (Scheme I), 3,4-methylenedioxy-β-nitrostyrene (III) was heated with diacetoxybutadiene to afford the biphenyl IV in 45% yield. Several approaches to the introduction of the hydroxymethyl group were investigated. Bromination of IV gave the bromide V, which was converted to the nitrile VI by cuprous cyanide. Hydrolysis of the nitrile occurred to a slight extent during work-up to give a low yield of the amide VII. Complete hydrolysis to the nitro acid VIII required several days refluxing with concentrated hydrochloric acid, but the yield was impractically low.

SCHEME I



6-Cyanopiperonal (XII) was prepared from 6-bromopiperonal by cuprous cyanide treatment of the ethylene ketal, but condensation of XII with nitromethane could not be effected. Friedel–Crafts acetylation of IV was also unsuccessful.

Finally, however, it proved possible to hydroxymethylate IV in good yield by treating with formaldehyde and hydrochloric acid in acetic acid, and by hydrolyzing the mixture of chloride and acetate to the alcohol IX. Three possible positions of attack, at carbons 2, 5, and 6, are available to the entering hydroxymethyl group. Since electrophilic substitution of 3,4-methylenedioxybenzenes invariably occurs at C-6, structure IX appeared most probable. This was confirmed in several ways. (a) The infrared spectrum of IX, taken in dilute (1 mg./ml.) carbon tetrachloride solution, showed only a free hydroxyl stretching band, at 3620 cm.$^{-1}$, and no indication whatever of intramolecular hydrogen bonding.[8] Had substitution occurred at positions 2 or 6, intramolecular hydrogen bonding between the hydroxyl and one of the ether oxygens would have been observed; 1-(2,4-dimethoxyphenyl)propanol-1, for example,[8] exhibits such a bonded peak at 3584 cm.$^{-1}$. Since IX probably exists, on a time average, primarily in the *trans* conformation IXa, the failure to observe hydrogen bonding between the hydroxyl and nitro groups is understandable, and studies from this laboratory[9] have shown the absence of intramolecular bonding in a 2-nitro-2′-hydroxymethylbi-

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(2) Alfred P. Sloan Foundation Research Fellow.

(3) National Institutes of Health Predoctoral Fellow, 1963–1964.

(4) R. J. Highet, *J. Org. Chem.*, **26**, 4767 (1961).

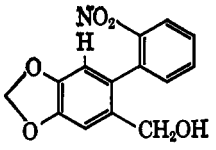
(5) W. E. Bachman and R. A. Hoffman, *Org. Reactions*, **2**, 224 (1944).

(6) See, *e.g.*, H. Erdtman, F. Haglid, and N. E. Stjernström, *Acta Chem. Scand.*, **15**, 1761 (1961).

(7) A preliminary communication describing this method has appeared: R. K. Hill and R. M. Carlson, *Tetrahedron Letters*, 1157 (1964).

(8) We are indebted to Mr. Louis Joris for obtaining this spectrum.

(9) W. F. Baitinger, Jr., P. v. R. Schleyer, and K. Mislow, *J. Am. Chem. Soc.*, in press.



IXa

phenyl even when the conformation is favorable. (b) The n.m.r. spectrum of IV in $CDCl_3$ shows two distinct sets of aromatic protons: a broad group of four from the nitrophenyl ring centered at τ 2.5 and a sharp band of three, from the methylenedioxyphenyl ring, at τ 3.25. In the spectrum of IX, this latter singlet appears instead as two widely separated singlets, at τ 3.06 and 3.48. The lack of *ortho* coupling between these two protons rules out substitution of the hydroxymethyl at C-2, and it appears to us that only structure IXa, in which the nitro group strongly influences the chemical shift of the C-2 proton, offers a reasonable explanation for the separation of the two aromatic protons.

The bromo compound V shows exactly the same pattern in the aromatic region of its n.m.r. spectrum, and so is also a 6-substituted compound. That electrophilic substitution has occurred in the same position in these two series is confirmed by oxidation of IX to the acid VIII.

In any case, conversion of IX to ismine substantiated these conclusions. Catalytic reduction of IX gave the amino alcohol X. The N-methyl group was introduced smoothly by lithium aluminum hydride reduction of the O,N-dicarbethoxy derivative XI, to afford crystalline ismine. Its identity was established by comparison of infrared spectra and by mixture melting point comparison of the alkaloid and its picrate with authentic samples.[10]

Through the courtesy of Dr. A. Brossi of Hoffmann-La Roche, Inc., Nutley, N. J., ismine was tested for analgesic activity, but proved inactive in mice at a dose of 200 mg./kg.

Experimental

3,4-Methylenedioxy-2′-nitrobiphenyl (IV).—A mixture of 3,4-methylenedioxy-β-nitrostyrene[11] (8.0 g.), *trans,trans*-1,4-diacetoxybutadiene[12] (8.5 g.), and hydroquinone (0.1 g.) was sealed in a Pyrex tube and heated at 110–120° in a metal bath for 3 days. The tube was cooled in ice and opened, and the dark oil was chromatographed on alumina. Elution with benzene gave a yellow solid (4.59 g., 45.5%), m.p. 79–85°. Recrystallization from acetone gave yellow plates of the pure material, m.p. 84–85°. The infrared spectrum showed no absorption in the carbonyl region. The n.m.r. spectrum (in carbon tetrachloride, with tetramethylsilane as an internal standard) showed singlets at τ 3.98 (2H, methylenedioxy), 3.2 (3H, ether-substituted aromatic ring), and a multiplet at 2.5 (4H, nitro-substituted aromatic ring).

Anal. Calcd. for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.19; H, 3.67; N, 5.85.

2-Bromo-4,5-methylenedioxy-2′-nitrobiphenyl (V).—To a solution of 3.24 g. of 3,4-methylenedioxy-2′-nitrobiphenyl in 50 ml. of warm glacial acetic acid was added a freshly prepared solution of 4.40 g. of pyridinium bromide perbromide in 25 ml. of glacial acetic acid. The solution was warmed on the steam bath for about 1 min., cooled to room temperature, and poured into water, precipitating a yellow solid. After drying in a vacuum desiccator overnight, the bromide weighed 4.18 g. (97.8%), m.p. 130–145°. Recrystallization from acetone–heptane gave pale yellow crystals, m.p. 157–160°, sensitive to light.

Anal. Calcd. for $C_{13}H_8BrNO_4$: N, 4.35. Found: N, 4.42.

2-Cyano-4,5-methylenedioxy-2′-nitrobiphenyl (VI).—A mixture of 2-bromo-4,5-methylenedioxy-2′-nitrobiphenyl (0.36 g.), cuprous cyanide (0.11 g.), and dry pyridine (0.5 ml.) was heated at 220° for 16 hr. The reaction mixture was triturated with 50 ml. of benzene and 50 ml. of ammonium hydroxide, then washed successively with dilute ammonium hydroxide (four 5-ml. portions), 6 *N* hydrochloric acid (two 5-ml. portions), water (two 5-ml. portions), and saturated salt solution (two 5-ml. portions). Evaporation of the dried benzene solution left an oil (0.2 g.), which crystallized from benzene–heptane (charcoal) to afford 0.10 g. (33%), m.p. 187–190°. Recrystallization from acetone–heptane gave yellow crystals, m.p. 188–190°, with an infrared band at 4.48 μ (–CN).

Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.45. Found: C, 62.48; H, 3.25; N, 10.48.

In repeating the preparation of the nitrile on a larger scale (3.9 g. of the bromide VI), the solid residue from the reaction was warmed with the benzene–ammonia mixture to speed decomposition of the complex. From the first fraction of the benzene extract was obtained a small amount (0.14 g., 4%) of **2-(2-nitrophenyl)-4,5-methylenedioxybenzamide** (VII), m.p. 174–179°, in addition to a difficultly separable mixture of the nitrile and amide (1.11 g.). The amide was recrystallized from acetone–heptane; m.p. 179–181°, yellow crystals, infrared absorption at 2.83, 2.93, and 5.95 μ.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; N, 9.79. Found: C, 58.85; H, 3.48; N, 10.03.

2-(2-Nitrophenyl)-4,5-methylenedioxybenzoic Acid (VIII). A.—The above mixture (1.11 g.) of nitrile and amide obtained from the cuprous cyanide reaction was dissolved in a 4:3 mixture of ethanol–dioxane and refluxed for 24 hr. with 25 ml. of concentrated hydrochloric acid. The dark reaction mixture was made basic with sodium carbonate and evaporated to dryness. The solid residue was distributed between water and ether, and the aqueous layer was acidified to congo red with 30% sulfuric acid. The precipitate was collected and dried, affording 20 mg. of the solid acid. An additional 25 mg. was obtained by refluxing the recovered neutral solids with 1:1 dioxane–concentrated hydrochloric acid for 60 hr. and working up as before. Recrystallized from acetone–heptane, the colorless acid melted at 235–240°.

Anal. Calcd. for $C_{14}H_9NO_6$: C, 58.54; H, 3.16; N, 4.88. Found: C, 58.20; H, 3.30; N, 4.87.

B.—To a cooled and mechanically stirred solution of 2-(2-nitrophenyl)-4,5-methylenedioxybenzyl alcohol (0.11 g.) in 8 ml. of a 4:1 acetone–water mixture was added potassium permanganate (0.16 g.). The mixture was stirred at 40–45° for an additional 1.75 hr. and filtered, and the filtrate was diluted with 50 ml. of water and acidified with concentrated sulfuric acid. Cooling and scratching effected crystallization of the acid (0.09 g., 78%), m.p. 225–240°, with an infrared spectrum identical with that of the acid from part A.

2-(2-Nitrophenyl)-4,5-methylenedioxybenzyl Alcohol (IX).—A solution of 3,4-methylenedioxy-2′-nitrobiphenyl (3.0 g.), formaldehyde (10 ml. of 40% aqueous solution), and concentrated hydrochloric acid (12 ml.) in 50 ml. of glacial acetic acid was heated on the steam bath (80–85°) for 2 hr. The reaction mixture was poured into 300 ml. of water and extracted with two 100-ml. portions of ether. The extracts were washed with water (two 50-ml. portions), saturated aqueous sodium bicarbonate (until alkaline), water, and brine, dried, and concentrated. The crude residue appeared, from its infrared spectrum, to be a mixture of acetate, alcohol, and possibly chloride, and consequently was taken up in a 1:1 mixture of dioxane–saturated aqueous sodium bicarbonate and refluxed for 1 hr. After dilution with 500 ml. of water, the mixture was extracted with ether; the ether extracts were washed with water and brine, dried, and concentrated. Chromatography of the residue on alumina and elution with benzene gave first about 0.1 g. of recovered starting material, followed by the alcohol IX (2.53 g., 75%), m.p. 85–94°. Recrystallized from benzene, the alcohol melted at 103–104.5° and had infrared absorption at 2.96 μ.

Anal. Calcd. for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.31. Found: C, 61.57; H, 4.24; N, 5.10.

(10) We are indebted to Dr. Robert J. Highet of the National Heart Institute for supplying us with authentic samples.

(11) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1907).

(12) R. Criegee, W. Hörauf, and W. D. Schellenberg, *ibid.*, **86**, 126 (1953).

2-(2-Aminophenyl)-4,5-methylenedioxybenzyl Alcohol (X).—A solution of 2-(2-nitrophenyl)-4,5-methylenedioxybenzyl alcohol (1.0 g.) in 100 ml. of absolute alcohol was hydrogenated in a Parr shaker for 20 min. at 32 p.s.i. over platinum dioxide. The solution was filtered and the colorless filtrate was concentrated at reduced pressure, leaving an oily residue of the amino alcohol. The picrate, crystallized from ethanol, crystallized with 1 mole of solvent and melted at 150–154°.

Anal. Calcd. for $C_{14}H_{13}NO_3 \cdot C_6H_3N_3O_7 \cdot C_2H_6O$: C, 50.97; H, 4.28; N, 10.81. Found: C, 51.28; H, 4.67; N, 11.12.

Ismine (I).—To a solution of the 2-(2-aminophenyl)-4,5-methylenedioxybenzyl alcohol prepared above, in 10 ml. of pyridine, was added 6 ml. of ethyl chlorocarbonate, and the solution was kept overnight at room temperature. The red solution was poured into 150 ml. of water and extracted with three 50-ml. portions of ether. The ether extracts were washed with 2% hydrochloric acid, dried, and concentrated. The residual oil, showing broad carbonyl absorption at 5.7–5.8 μ, was taken up in 100 ml. of dry tetrahydrofuran and reduced with a threefold excess of lithium aluminum hydride at reflux for 20 hr. The mixture was cooled, diluted with 100 ml. of tetrahydrofuran, and treated cautiously with saturated aqueous sodium sulfate to destroy the excess hydride. The inorganic salts were filtered and the filtrate was concentrated. The colorless oily residue crystallized on the addition of a seed crystal of ismine, yielding 0.36 g. (38%), m.p. 76–87°. Recrystallization from 30% ethanol gave material of m.p. 93.5–95°, not depressed by admixture with an authentic sample,[8] m.p. 95–97.5°. The infrared spectra of the synthetic and authentic samples were superimposable. The picrate of the synthetic material melted at 157–159°, not depressed by mixing with a sample of authentic ismine picrate, m.p. 162–164°.

6-Cyanopiperonal (XII).—A mixture of 6-bromopiperonal[13] (54.4 g.), ethylene glycol (15.5 g.), and *p*-toluenesulfonic acid (2.0 g.) in benzene (450 ml.) was refluxed with a Dean–Stark trap for 4 hr., during which time 4.3 ml. of water (calcd. 4.5 ml.) was collected. After standing overnight, the benzene solution was washed with 10% sodium bicarbonate, dried, diluted with 200 ml. of heptane, and concentrated. On cooling, 45.2 g. of colorless acetal, m.p. 58–64°, was collected. The infrared spectrum showed only a trace of carbonyl absorption, and the acetal was used without further purification.

A mixture of the acetal (24.15 g.), cuprous cyanide (10.0 g.), and pyridine (5.0 ml.) was heated at 185° for 16 hr. Benzene (100 ml.) and ammonium hydroxide (100 ml.) were added to the still warm solution, the lumps were broken up, and the salts were filtered. The filtrate was diluted with 400 ml. of ether, the layers were separated, and the organic layer was washed successively with dilute ammonium hydroxide (30 ml.), 3 *N* hydrochloric acid (two 30-ml. portions), 5% sodium bicarbonate (two 30-ml. portions), water (two 30-ml. portions), and saturated salt solution. Concentration of the dried solution gave 7.55 g. (39%) of 6-cyanopiperonal ethylene acetal, m.p. 85–92°.

The cyano acetal (3.19 g.) was stirred for 5 min. with 20 ml. of 5% hydrochloric acid at 40–50°. The solid was collected, washed with water, and dried, giving 2.55 g. (100%) of cyanoaldehyde. After recrystallization from benzene, the pale yellow crystals melted at 162–164°, and showed infrared bands at 4.47 and 5.92 μ.

Anal. Calcd. for $C_9H_5NO_3$: C, 61.72; H, 2.88; N, 8.00. Found: C, 61.89; H, 2.98; N, 8.07.

(13) A. Oelker, *Ber.*, **24**, 2592 (1891).

Nuclear Magnetic Resonance Spectra and Stereochemistry of the Antibacterial Principle from *Haematoxylon braziletto*[1]

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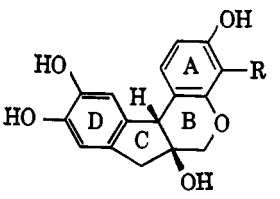
Aqueous extracts of the red heartwood of *Haematoxylon braziletto* gave brazilin (Ia), identified as its tetraacetate. N.m.r. spectroscopy confirmed its structure and that of the related haematoxylin (Ib) as containing an additional hydroxy group at C-4. The reactions of Ia indicate rings B and C to be *cis* fused, and optical rotatory dispersion shows the stereochemistry of Ia and Ib to be identical.

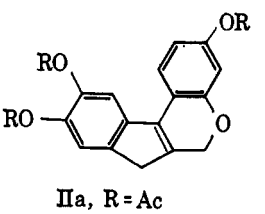
In Mexico and Lower California, sticks of the red heartwood of *Haematoxylon braziletto* have been employed for centuries for addition to drinking water for man and animals. The wood derives its name from the word *braza*, meaning fiery red, and has no geographic connection with Brazil or with the common brazilwood of the literature, *Caesalpinia echinata* or *Caesalpinia brasilensis*.

The antibacterial activity of the heartwood extracts has been previously reported.[2] The aqueous extracts, on isolation with ether, afforded a phenolic material which was acetylated at room temperature and gave an acetyl derivative shown by thin layer chromatography to consist of more than 60% of one compound, m.p. 149–151°. It was found to be identical by mixture melting point, infrared spectrum, and thin layer chromatography with a specimen of brazilin tetraacetate, m.p. 149–151°, prepared from brazilin (Ia) isolated from the South American tree *Caesalpinia echinata*.

It was of interest to examine the stereochemistry of brazilin and of the closely related haematoxylin (Ib), isolated from *Haematoxylon campechianum*. The



Ia, R=H
b, R=OH



IIa, R=Ac
b, R=Me

structures of both brazilin and haematoxylin as polyhydroxybenzindenopyrans are known from the work of Perkin and Robinson,[3] but the stereochemical cor-

(1) Supported in part by a grant (HE-5881) from the National Institutes of Health, U. S. Public Health Service.

(2) R. Pratt and Y. Yuzuriha, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 69 (1959).

(3) (a) W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **91**, 1073 (1907); (b) R. Robinson in "Chemistry of Carbon Compounds," Vol. IV, part B, E. H. Rodd, Ed., Elsevier Publishing Co., Inc., New York, N. Y., 1959, p. 1005; (c) R. Robinson, *Bull. soc. chim. France*, 125 (1958).