Addition of a drop of aqueous ferric chloride to a methanol solution of colchicide gave a characteristic red color which disappeared on dilution.

Colchicide Hydrochloride.—A solution of colchicide hydrate (200 mg., 0.52 mmole) in benzene (2 ml.) and ether (10 ml.) was treated dropwise with ethereal hydrogen chloride (*ca.* 2 ml.) until no more orange gum formed. On rubbing, this gum solidified, and it was centrifuged, washed with benzene (3 × 4 ml.) and dried *in vacuo* over magnesium perchlorate to give 246 mg. of yellow solid. This material was dissolved in ethyl acetate (40 ml.) by warming at 75° for 3 to 4 minutes, and on cooling overnight 146 mg., 67% yield, of colchicide hydrochloride hydrate, m.p. 119–121°, crystallized as long, yellow needles.

Anal. Calcd. for $C_{21}H_{23}O_5N\cdot HCl\cdot H_2O$: C, 59.5; H, 6.2; Cl, 8.3. Found: C, 59.9; H, 6.1; Cl, 8.0.

A solution of colchicide hydrochloride hydrate in benzene was heated on the steam-bath for 10 min. and then chromatographed on an alumina column. Successive elution with benzene and 0.5% absolute ethanol in benzene allowed the quantitative recovery of colchicide, $[\alpha]^{23}D$ −256° (*c* 0.6, ethanol).

Hydrogenation of Colchicide (III) to Tetrahydrodemethoxycolchicine (IV).—Hydrogenation of 200 mg. (0.52 mmole) of colchicide hydrate in 20 ml. of ethanol at atmospheric pressure and room temperature in the presence of 80 mg. of 5% palladized barium sulfate proceeded rapidly with the absorption of two moles of hydrogen in 40 min., after which hydrogen absorption ceased. Filtration, evaporation of the filtrate and chromatographing on alumina using 0.5 % absolute ethanol in benzene for elution gave 154 mg. of crude material. On crystallization from a mixture of ethyl acetate and *n*-butyl ether, 81 mg. (42% yield) of tetrahydrodemethoxycolchicine was obtained, m.p. 142–143° (reported[1] m.p. 143–144°).

BERKELEY, CALIFORNIA

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

The Synthesis of Isocolchinol Methyl Ether

BY HENRY RAPOPORT, ROBERT H. ALLEN[1] AND MERLE E. CISNEY

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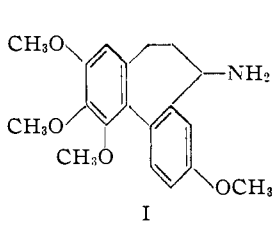
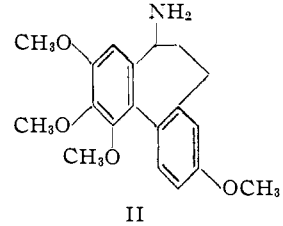
Application of the method previously devised for the synthesis of unsymmetrical biphenyls,[2] consisting in ring-opening of a phenanthrene, has led to a synthesis of isocolchinol methyl ether (II). The Perkin reaction, notoriously poor with *p*-methoxybenzaldehydes and *o*-nitrophenylacetic acids, gave a 50% yield with intermediates substituted in this fashion when allowed to proceed at room temperature. Ring-closure to the phenanthrene was carried out in dimethylformamide, and the phenanthroic acid was then converted to the phenanthrol, treatment of which with nitrous acid gave either the monoxime or quinone. Subsequent reactions of the monoxime paralleled those which afforded colchinol methyl ether (I), and isocolchinol methyl ether (II) resulted.

Recently[2] the synthesis of colchinol methyl ether (I) was realized through a method which had as its salient feature the preparation of a highly substituted, unsymmetrical biphenyl by ring-opening of the corresponding phenanthrene. This method led not only to a single isomer of unambiguous structure, but also to the presence of functional groups which then could be employed to construct the desired, bridging, seven-membered ring. In an effort to examine the versatility of this procedure, we have considered the synthesis of isocolchinol methyl ether (II) and pseudocolchinol methyl ether.[3] These isomers also may be of interest in regard to their relative activity as mitotic poisons for which the presence of a β-phenylethylamine skeleton has been postulated as requisite.[4] This report is concerned with the synthesis of isocolchinol methyl ether [5-amino-1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene].



I



II

Of the possible combinations[5] of intermediates which could be employed for the synthesis of the required 2,3,4,7-tetramethoxy-9-phenanthroic acid (VII), the most attractive pair appeared to be 3,4,5-trimethoxybenzaldehyde and 5-methoxy-2-nitrophenylacetic acid. Both the aldehyde[2] and the phenylacetic acid[6] are easily prepared in quantity, and the only phenanthroic acid possible on subsequent ring-closure is the desired isomer.

However, a serious deterrent to the use of this pair of intermediates is the history[7] of very poor yields in the condensation to cinnamic acids when an *o*- or *p*-nitro group is on the phenylacetic acid portion or when the aldehyde bears a *p*-methoxy group.[8] In a recent study[7i] of the Perkin reaction, using triethylamine as the catalyst,[9] the best yield (79%) was obtained in the condensation of *p*-nitrobenzaldehyde and phenylacetic acid. By contrast, only an 8% yield was obtained from *p*-methoxy-

(1) National Science Foundation Fellow, 1952-1953.

(2) H. Rapoport, A. R. Williams and M. E. Cisney, THIS JOURNAL, **73**, 1414 (1951).

(3) Isocolchinol methyl ether is the name assigned to the isomer with the amino group at position 5, and pseudocolchinol methyl ether refers to the 6-isomer.

(4) H. Lettré, *Angew. Chem.*, **63**, 421 (1951); H. Lettré and M. Albrecht, *Hoppe-Seyler's Z. physiol. Chem.*, **287**, 58 (1951); T. F. Dankova, *et al.*, *J. Gen. Chem.*, **21**, 787 (1951).

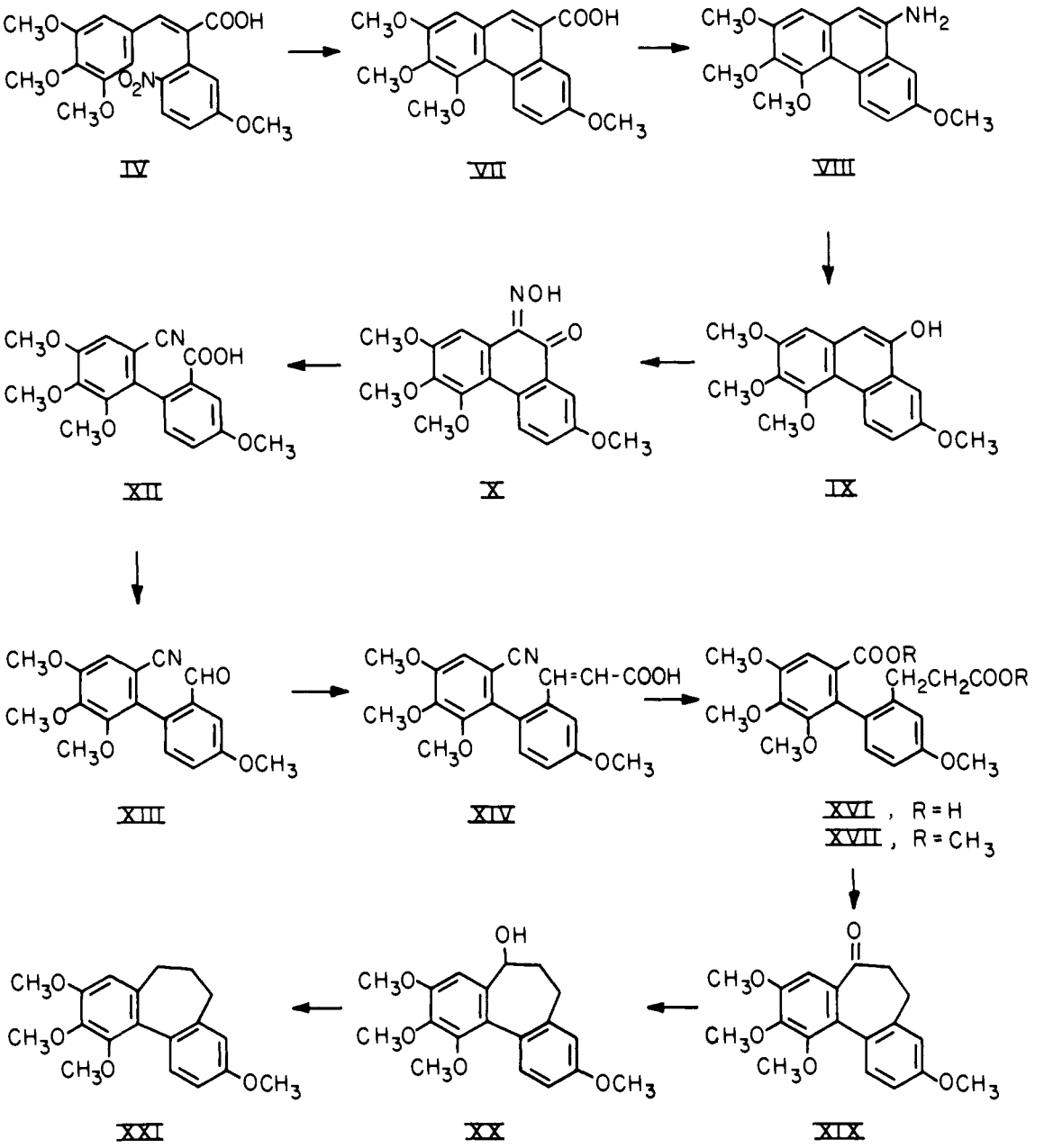
(5) (a) G. L. Buchanan, J. W. Cook and J. D. Loudon, *J. Chem. Soc.*, 325 (1944); (b) N. Barton, J. W. Cook and J. D. Loudon, *ibid.*, 176 (1945).

(6) C. F. Koelsch, THIS JOURNAL, **66**, 2019 (1944).

(7) (a) R. v. Walther and A. Wetzlich, *J. prakt. Chem.*, **61**, 169 (1900); (b) W. Borsche, *Ber.*, **42**, 3596 (1909); (c) F. Mayer and G. Balle, *Ann.*, **403**, 167 (1914); (d) P. W. Neber and E. Röcker, *Ber.*, **56**, 1710 (1923); (e) P. Ruggli and F. Lang, *Helv. Chim. Acta*, **21**, 38 (1938); (f) W. Cocker and D. G. Turner, *J. Chem. Soc.*, 57 (1940); (g) F. Bergmann and Z. Weinberg, *J. Org. Chem.*, **6**, 134 (1941); (h) E. L. May and E. Mosettig, *ibid.*, **11**, 435 (1946); (i) R. E. Buckles, M. P. Bellis and W. D. Coder, THIS JOURNAL, **73**, 4972 (1951).

(8) J. R. Johnson in "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 218.

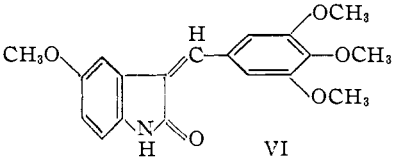
(9) M. Bakunin and D. Peccerillo, *Gazz. chim. ital.*, **65**, 1145 (1935).



benzaldehyde (and 0% from *m*-methoxybenzaldehyde) and *p*-nitrophenylacetic acid.

Notwithstanding these discouraging prospects, the very ready availability of the starting materials induced us to examine the condensation of 3,4,5-trimethoxybenzaldehyde with 5-methoxy-2-nitrophenylacetic acid. Since it was observed that considerable carbon dioxide was evolved at around 90°, the condensation was allowed to proceed at room temperature for 65 hours (instead of 90° for 12 hours[9] or on the steam-bath or in refluxing acetic anhydride[7i]) and these milder conditions reproducibly gave 45–50% yields of the nitrocinnamic acid (IV).

Ferrous sulfate was used to reduce the nitrocinnamic acid (IV) to the aminocinnamic acid (V), and although the latter easily lactamized to form the oxindole (VI) on heating or crystallization from ethanol,[7h] it could be purified by repeated solution in ammonia and precipitation by acid. To effect



VI

ring-closure to the phenanthroic acid (VII) the previously[2] applied procedure of Cassaday and Bogert,[10] diazotization in dioxane, was inapplicable because the diazonium salt precipitated as a hard, unworkable cake. Substitution of dimethylformamide as solvent kept everything in solution during the diazotization, and addition of this solution to a

(10) J. T. Cassaday and M. T. Bogert, THIS JOURNAL, **61**, 2461 (1939).

suspension of finely-divided copper, also in dimethylformamide, led to a 65% yield of the phenanthroic acid.

The phenanthrylamine (VIII) was prepared by Curtius degradation of VII and on heating with sulfur dioxide in dioxane formed the phenanthrol[11] (IX), a reaction which was found to be extremely sensitive to temperature. Good yields were obtained at 93°, but if the temperature was allowed to increase as little as two degrees, the product consisted to a large extent of highly insoluble material.

Reaction of the phenanthrol with nitrous acid produced the monoxime X. However, a serious side reaction was quinone formation resulting from the further action of nitrous acid on the monoxime. To prevent this destruction of monoxime, aqueous ethanol was employed as the solvent, the amount of water being such that the phenanthrol just remained in solution whereas the much less soluble monoxime precipitated as formed. If, conversely, a solvent such as dioxane was chosen, in which the monoxime is readily soluble, the reaction could be used to prepare quinone (XI) directly from phenanthrol in good yield.

From the monoxime X to the cyanocinnamic acid (XIV) the synthesis proceeded exactly as in the isomeric series previously reported.[12] Difficulty was encountered, however, in converting the latter to the saturated dibasic acid XVI. With the isomeric compound (cyano and acrylic acid groups interchanged) it had been found most expeditious to hydrogenate the acrylic double bond to obtain the cyanopropionic acid and then hydrolyze to the saturated dibasic acid, thus avoiding the extremely slow hydrolysis of the cyanocinnamic acid.[13] With the present isomer XIV the relative rates of hydrogenation were reversed, and the cyano group was found to be reduced much more readily than the acrylic double bond. Therefore hydrolysis had to be performed first, and it required an eleven-day reflux in 6 *N* aqueous potassium hydroxide for completion. The resulting carboxycinnamic acid (XV) was easily hydrogenated to the carboxypropionic acid (XVI), the dimethyl ester of which was then cyclized by the excellent high-dilution procedure recently described[14] and the crystalline β-ketoester XVIII isolated.

The β-ketoester could be converted to ketone XIX either directly by carbonate cleavage[15] (reverse Claisen ester condensation) or by saponification followed by decarboxylation. The former route, which gave the better yield, was the result of the action of hot aqueous methanolic potassium hydroxide, whereas saponification of the ester was the predominate reaction at room temperature.

(11) This phenanthrol (IX) was methylated to 2,3,4,7,9-pentamethoxyphenanthrene, m.p. 125–127°. Previously,[2] 2,3,4,7,10-pentamethoxyphenanthrene, m.p. 111–112°, had been prepared in an analogous manner. In view of these data, the pentamethoxyphenanthrene prepared[12] by treating 2,3,4,7-fluorenone with diazomethane and reported to melt at 115–117° appears to be a mixture of the 9- and 10-isomers.

(12) N. Barton, J. W. Cook, J. D. Loudon and J. MacMillan, *J. Chem. Soc.*, 1079 (1949).

(13) H. Rapoport, A. R. Williams, O. G. Lowe and W. W. Spooncer, THIS JOURNAL, **75**, 1125 (1953).

(14) N. J. Leonard and R. C. Sentz, *ibid.*, **74**, 1704 (1952).

(15) A. Fry and M. Calvin, *J. Org. Chem.*, **17**, 1308 (1952).

The ketone XIX, 1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene-5-one, was reduced to the alcohol XX and hydrogenolysis of the alcohol gave 1,2,3,9 - tetramethoxydibenzo[a,c][1,3]cycloheptadiene, identical with dihydrodeaminocolchinol methyl ether. Hydrogenation of the oxime of the ketone gave the amine, thus completing the synthesis of isocolchinol methyl ether (II) (5-amino-1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene). As was expected, the ultraviolet absorption spectrum of N-acetylisocolchinol methyl ether (λ_{max}^{MeOH} 262 mμ, log ε 4.31; λ_{min}^{MeOH} 242 mμ, log ε 3.97) was identical with that of N-acetylcolchinol methyl ether.[16] The infrared spectra[2] of these two compounds in chloroform were essentially identical except in the region 8.6–9.2 μ where N-acetylisocolchinol methyl ether showed additional absorption peaks.

It might be propitious at this time to consider the question of the stereochemistry of this biphenyl system[17] bridged by three carbon atoms as it occurs in colchinol and isocolchinol methyl ether. Taking for comparison 4,4'-dimethoxybiphenyl (λ_{max}^{hexane} 263 mμ, log ε 4.34)[18] in which there is little or no resistance to co-planarity and methyl and phenyldihydrothebaine (λ_{max} 281 mμ, log ε 3.75)[19] in which the benzene rings have been proved not to be co-planar by the isolation of optical isomers,[20] the ultraviolet spectrum of N-acetylisocolchinol methyl ether supports the suggestion[21] that the three carbon bridge introduces no major hindrance to co-planarity of the benzene rings.

Experimental[22]

5-Methoxy-2-nitrophenylacetic Acid (III).—Modifications of the procedures of Blaikie and Perkin[23] and Koelsch[6] led to consistent and improved yields in large-scale preparations of 5-methoxy-2-nitrophenylacetic acid. To a suspension of 149 g. (2.62 moles) of commercial sodium methoxide in 400 ml. of absolute ether with stirring, cooling and in a nitrogen atmosphere was added 382 g. (2.61 moles) of diethyl oxalate. The mixture rapidly set to a yellow mush to which was added, at room temperature, a solution of 400 g. (2.40 moles) of 3-methyl-4-nitroanisole (prepared as directed by Koelsch[6] and purified by distillation, b.p. 162° (18 mm.)) in 600 ml. of absolute ether. After about four hours of stirring and heating at 45°, the reaction mixture became quite firm, and solvent was then removed at reduced pressure until the distillate was water soluble. Addition of two liters of ice-water resulted in a deep red solution to which alternate portions of 10% hydrogen peroxide solution and 25 ml. of 10 *N* sodium hydroxide were added. The hydrogen peroxide was added until the red color was discharged, then the sodium hydroxide was added. When the sodium hydroxide failed to restore the red color (after addition of about one liter of hydrogen peroxide and 100 ml. of sodium

(16) H. T. Huang, D. S. Tarbell and H. R. V. Arnstein, THIS JOURNAL, **70**, 4181 (1948).

(17) For a detailed discussion of this subject see G. H. Beaven, D. M. Hall, M. S. Lesslie, E. E. Turner and G. R. Bird, *J. Chem. Soc.*, 131 (1954) and preceding publications.

(18) B. Williamson and W. H. Rodebush, THIS JOURNAL, **63**, 3018 (1941).

(19) L. F. Small, L. J. Sargent and J. A. Brailey, *J. Org. Chem.*, **12**, 839 (1947).

(20) K. W. Bentley and R. Robinson, *J. Chem. Soc.*, 947 (1952).

(21) R. Horowitz, G. E. Ullyot, E. C. Horning, M. G. Horning, J. Koo, M. S. Fish, J. A. Parker and G. N. Walker, THIS JOURNAL, **72**, 4330 (1950).

(22) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California.

(23) K. G. Blaikie and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 296 (1924).

hydroxide solution), the mixture was filtered to recover 3-methyl-4-nitroanisole (44.1 g., 0.26 mole) and the filtrate acidified to precipitate the phenylacetic acid. Crystallization from methanol gave 346 g. of material, m.p. 175–177° and from the mother liquors, by evaporation of the methanol, solution of the residue in aqueous sodium bicarbonate, washing with benzene, decolorizing with carbon, and crystallizing again from methanol after precipitating by acidification was obtained an additional 33 g. of 5-methoxy-2-nitrophenylacetic acid, m.p. 174–176° (reported[23] m.p. 176°); total yield 379 g. (1.80 moles, 84%), based on unrecovered 3-methyl-4-nitroanisole.

3,4,5-Trimethoxy-α-(5′-methoxy-2′-nitrophenyl)-cinnamic Acid (IV).—With stirring and cooling, 47.5 g. (0.47 mole) of dry triethylamine was added to a mixture of 120 g. (0.61 mole) of 3,4,5-trimethoxybenzaldehyde,[2] 100 g. (0.48 mole) of 5-methoxy-2-nitrophenylacetic acid and 151 g. (1.48 moles) of acetic anhydride cooled in an ice-bath. Without removing the bath, the solution was allowed to warm up to room temperature and after 65 hours was heated to 50° for 2 hours, 80° for 1.5 hours, and then 1.5 liters of water was added and the mixture warmed for one hour. Slowly and in portions 10 *N* sodium hydroxide was now added until the *p*H remained above 9, and the mixture was filtered and extracted with two 500-ml. portions of benzene. From the combined benzene extracts, by washing with 40% aqueous bisulfite, was recovered 46.9 g. of 3,4,5-trimethoxybenzaldehyde. To the aqueous phase was added 1 kg. of sodium chloride and the solution stirred overnight. The precipitated sodium salt of the cinnamic acid was then removed by filtration, dissolved in 2 liters of water, and acidified to precipitate the acid. Crystallization from methanol gave 91.6 g. (49.5% yield based on 5-methoxy-2-nitrophenylacetic acid and 63.1% yield based on unrecovered 3,4,5-trimethoxybenzaldehyde) of 3,4,5-trimethoxy-α-(5′-methoxy-2′-nitrophenyl)-cinnamic acid, m.p. 173–174°.

Anal. Calcd. for $C_{19}H_{19}O_8N$: C, 58.6; H, 4.9; equiv. wt., 389. Found: C, 58.7; H, 4.9; equiv. wt., 390.

The **methyl ester** was prepared in methanol with sulfuric acid and crystallized from methanol, m.p. 130–131°.

Anal. Calcd. for $C_{20}H_{21}O_8N$: OCH_3, 38.5. Found: OCH_3, 38.3.

3,4,5-Trimethoxy-α-(2′-amino-5′-methoxyphenyl)-cinnamic Acid (V).—Reduction of the nitrocinnamic acid (IV) to the aminocinnamic acid (V) was conveniently carried out using ferrous sulfate following the same procedure as in the case of the isomeric compound,[2] except that centrifugation was employed to separate the sludge of precipitated iron hydroxide. All attempts at crystallizing the aminocinnamic acid led only to progressively increasing proportions of oxindole (see below). An analytical sample was prepared by repeated solution in aqueous ammonia, treatment with carbon, and acidification, and dried to constant weight at 50° *in vacuo*. It changed from white to orange-red at 150–170° and melted at 218–220°, the m.p. of the oxindole VI.

Anal. Calcd. for $C_{19}H_{21}O_6N$: C, 63.5; H, 5.9. Found: C, 63.3; H, 6.2.

5-Methoxy-3-(3′,4′,5′-trimethoxybenzylidene)-oxindole (VI) was obtained from the aminocinnamic acid merely by crystallizing several times from absolute ethanol, m.p. 218–220°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.9; H, 5.6; OCH_3, 36.4. Found: C, 66.7; H, 5.6; OCH_3, 36.8.

2,3,4,7-Tetramethoxy-9-phenanthroic Acid (VII).—To 50.6 g. (0.14 mole) of the aminocinnamic acid (V) in 125 ml. of dimethylformamide was added, with stirring and at a temperature below 0°, 10.5 ml. of 36 *N* sulfuric acid. Then 18.2 g. (0.16 mole) of isoamyl nitrite was added at 10° and the reaction mixture maintained at this temperature for 30 min. after which it was pipetted in 5-ml. portions over a period of 15 min. into a stirred suspension of 7.5 g. of Gattermann paste[24] in 60 ml. of dimethylformamide maintained at 65–70°. When the addition was complete, the solution was heated to 80°, poured into 3 liters of 0.5 *N* aqueous ammonia, filter aid was added, and the suspension was filtered and the filtrate rapidly acidified. The resulting precipitate was washed free of acid and crystallized from either absolute ethanol or methyl isobutyl ketone; yield 31.5 g. (65.4%), m.p. 238–239° (reported[5a] m.p. 236°).

(24) L. Gattermann, *Ber.*, **23**, 1218 (1890).

Methyl 2,3,4,7-tetramethoxy-9-phenanthroate was prepared in methanol with sulfuric acid and crystallized from methanol, m.p. 101–102° (reported[5a] m.p. 103°).

2,3,4,7-Tetramethoxy-9-phenanthrylamine (VIII).—The phenanthroic acid (VII) was converted to the corresponding amine by essentially the same procedure as had been used for the previous isomer.[2] No attempt was made to isolate the intermediate acid chloride, and 2,3,4,7-tetramethoxy-9-phenanthrylamine, m.p. 151–152°, was obtained in 84.5% yield from the phenanthroic acid.

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 69.0; H, 6.1; N, 4.5. Found: C, 68.8; H, 6.2; N, 4.9.

N-Acetyl-2,3,4,7-tetramethoxy-9-phenanthrylamine was prepared in the same fashion as the analogous 10-isomer, m.p. 202–203°.

Anal. Calcd. for $C_{20}H_{21}O_5N$: C, 67.6; H, 6.0; N, 3.9. Found: C, 67.7; H, 5.9; N, 3.8.

2,3,4,7-Tetramethoxy-9-phenanthrol (IX).—Into each of five heavy-walled Pyrex bomb tubes of 300-ml. capacity was placed a solution of 5 g. (0.016 moles) of 2,3,4,7-tetramethoxy-9-phenanthrylamine in 50 ml. of pure dioxane, followed by 50 ml. of water. Sulfur dioxide was then passed into each tube until 120 g. had been absorbed, and the tubes were sealed and heated, totally immersed, in an oil-bath at 93° for 48 hours. The contents were then poured into 6 liters of water, nitrogen was bubbled through the mixture overnight, and the mixture was filtered. After washing free of sulfur dioxide, the solid was digested with 950 ml. of 1 *N* potassium hydroxide, the solution was filtered, and carbon dioxide was passed into the filtrate until the *p*H reached about 7. The precipitate was removed, digested with 150 ml. of absolute ethanol, filtered hot, and 250 ml. of hot water added to the filtrate. On cooling, 18.6 g. (74% yield) of 2,3,4,7-tetramethoxy-9-phenanthrol resulted, m.p. 156–158°.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8. Found: C, 68.5; H, 5.9.

When the phenanthrol (IX) in 3 *N* sodium hydroxide was shaken with dimethyl sulfate, **2,3,4,7,9-pentamethoxyphenanthrene** was formed and was crystallized from methanol, m.p. 125–127°.

Anal. Calcd. for $C_{19}H_{20}O_5$: OCH_3, 47.3. Found: OCH_3, 46.8.

2,3,4,7-Tetramethoxyphenanthrenequinone-10-oxime (X).—A solution of 18.0 g. (0.057 mole) of 2,3,4,7-tetramethoxy-9-phenanthrol in 600 ml. of 95% ethanol and 225 ml. of water was cooled to room temperature, filtered free from any insoluble material, and then cooled (2–10°) until the phenanthrol just began to separate whereupon a solution of 5.6 g. (0.08 mole) of sodium nitrite in 20 ml. of water was added followed by 21.6 ml. of 12 *N* hydrochloric acid. After 1 hour at 10°, the solution was filtered and the precipitate was digested with 900 ml. of 0.5 *N* potassium hydroxide. The alkaline solution was then filtered and the filtrate acidified to *p*H 7. Crystallization of the resulting red solid from about 2 liters of absolute ethanol gave 14.5 g. (74% yield) of 2.3,4,7-phenanthrenequinone-10-oxime, m.p. 183–184°.

Anal. Calcd. for $C_{18}H_{17}O_6N$: C, 63.0; H, 5.0; N, 4.1. Found: C, 63.1; H, 5.1; N, 3.9.

2,3,4,7-Tetramethoxyphenanthrenequinone (XI).—In 40 ml. of dioxane was dissolved 3.14 g. (0.01 mole) of 2,3,4,7-tetramethoxy-9-phenanthrol and at room temperature was added a solution of 1.75 g. (0.025 mole) of sodium nitrite in 5 ml. of water followed by 3 ml. of 12 *N* hydrochloric acid. After one hour, the reaction mixture was poured into 300 ml. of water, the mixture was extracted with two 100-ml. portions of chloroform, and the chloroform was washed with four 100-ml. portions of 1 *N* potassium hydroxide. The residue resulting from evaporation of the combined, dried chloroform extracts was crystallized from absolute ethanol; yield 1.7 g. (52%) of 2,3,4,7-tetramethoxyphenanthrenequinone, m.p. 191–192° (reported[2] m.p. 195–196°).

2-(6′-Cyano-2′,3′,4′-trimethoxyphenyl)-5-methoxybenzoic Acid (XII).—Rearrangement of the monoxime X to the cyano acid was carried out as described[2] for the previous isomer except that the initial reflux in pyridine was shortened to 0.5 hour and the hydrolysis with aqueous methanolic potassium carbonate was extended to eight hours. After evaporation of the methanol, additional water was added,

the *p*H adjusted to 8, and the solution filtered to recover unrearranged oxime. Continued acidification to *p*H 1 then precipitated the cyano acid which was crystallized from benzene–hexane (10:1). The yield was 86.5% based on unrecovered oxime, and the m.p. was 201–202°.

Anal. Calcd. for $C_{18}H_{17}O_6N$: C, 63.0; H, 5.0; equiv. wt., 343. Found: C, 63.1; H, 5.0; equiv. wt., 345.

The dibasic acid, **4,4′,5,6-tetramethoxydiphenic acid**, prepared by hydrolysis of the cyano acid XII with 1 *N* aqueous potassium hydroxide was crystallized from aqueous methanol and melted at 239–241° (reported[2] m.p. 240–241°).

The same acid was obtained when the quinone (XI) in glacial acetic acid was oxidized with 30% aqueous hydrogen peroxide, m.p. 238–239°.

2-(6′-Cyano-2′,3′,4′-trimethoxyphenyl)-5-methoxybenzaldehyde (XIII).—Conversion of the cyano acid XII to acid chloride and reduction of the latter to aldehyde followed in detail the procedure used with the previous isomer,[2] except that the product was isolated by complete evaporation of the xylene and crystallization of the residue from methylcyclohexane. A 92% yield of aldehyde, m.p. 118–120°, resulted, from which an analytical sample was prepared through the bisulfite addition compound and two crystallizations from methylcyclohexane, m.p. 122–123°.

Anal. Calcd. for $C_{18}H_{17}O_5N$: C, 66.1; H, 5.2. Found: C, 66.2; H, 5.3.

The **semicarbazone** was prepared with semicarbazide hydrochloride and sodium acetate, and was crystallized from aqueous ethanol, m.p. 185–187°.

Anal. Calcd. for $C_{19}H_{20}O_5N_4$: C, 59.4; H, 5.2; N, 14.6. Found: C, 58.9; H, 5.2; N, 14.5.

2-(6′-Cyano-2′,3′,4′-trimethoxyphenyl)-5-methoxycinnamic Acid (XIV).—Condensation of the aldehyde XIII with malonic acid, as in the case of the previous isomer,[2] gave an 86% yield of the cyano cinnamic acid, m.p. 205–206° after crystallization from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{19}O_6N$: C, 65.0; H, 5.2; equiv. wt., 369. Found: C, 65.3; H, 5.4; equiv. wt., 372.

2-(6′-Carboxy-2′,3′,4′-trimethoxyphenyl)-5-methoxycinnamic Acid (XV).—A solution of 4.54 g. (0.0123 mole) of the cyanocinnamic acid (XIV) in 300 ml. of 6 *N* potassium hydroxide was heated under reflux in a nitrogen atmosphere for 11 days at which time the ammonia evolution had reached 91% of the theoretical. After adding acid to *p*H 8, the solution was filtered and the filtrate made strongly acid. The resulting precipitate was re-methylated by dissolving in 12 ml. of 5 *N* potassium hydroxide and shaking with 4 ml. of dimethyl sulfate, repeating the addition of dimethyl sulfate and alkaline (when necessary) three times. Finally, a solution of 24.4 g. of potassium hydroxide in 50 ml. of water was added, and the solution was diluted to 125 ml. and heated under reflux for 10 hours. Acidification gave the carboxycinnamic acid (XV) which was crystallized from 50% aqueous methanol; yield 3.95 g. (83%), m.p. 196–197°.

Anal. Calcd. for $C_{20}H_{20}O_8$: C, 61.8; H, 5.2; OCH_3, 32.0; equiv. wt., 194. Found: C, 61.6; H, 5.3; OCH_3, 32.1; equiv. wt., 194.

β-[2-(6′-Carboxy-2′,3′,4′-trimethoxyphenyl)-5-methoxyphenyl]-propionic Acid (XVI).—When 3.95 g. of the carboxycinnamic acid (XV) was hydrogenated in 25 ml. of 95% ethanol at room temperature and atmospheric pressure in the presence of 0.7 g. of 5% palladized carbon, hydrogen absorption ceased after the uptake of one mole in 1.5 hours. Filtration, evaporation of the filtrate and crystallization of the residue from aqueous methanol gave 3.67 g. (93% yield) of the carboxypropionic acid (XVI), m.p. 147–148°.

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.5; H, 5.7; OCH_3, 31.8; equiv. wt., 195. Found: C, 61.2; H, 5.9; OCH_3, 31.9; equiv. wt., 195.

Methyl β-[2-(6′-Carbomethoxy-2′,3′,4′-trimethoxyphenyl)-5-methoxyphenyl]-propionate (XVII).—Esterification of 9.37 g. (0.024 mole) of the carboxypropionic acid (XVI) in 100 ml. of methanol was effected by adding ethereal diazomethane until the solution remained distinctly yellow and no further evolution of nitrogen occurred. After standing for an additional 0.5 hour, the solution was concentrated and a total of 9.83 g. (98%) of crystalline dimethyl ester was obtained, m.p. 84–85° after crystallization from methanol.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.2; H, 6.3; OCH_3, 44.5. Found: C, 63.2; H, 6.4; OCH_3, 44.6.

6-Carbomethoxy-1,2,3,9-tetramethoxydibenzo[a,c][1,3]-cycloheptadiene-5-one (XVIII).—Using the high-dilution apparatus recently described[14] and conducting the entire reaction in a nitrogen atmosphere, 1.82 g. of potassium was added to a solution of 15 ml. of *t*-butyl alcohol in 2 liters of xylene. The solution was heated to just below its boiling point and when all the potassium had dissolved (*ca.* 18 hr.), 125 ml. of solvent was distilled from the solution. To the briskly refluxing solution was then added a solution of 9.86 g. (0.0236 mole) of the dimethyl ester XVII in 60 ml. of xylene at a rate of about 3 ml. per hour. Periodically (9 hr., 13 hr., end of addition), addition of the diester was discontinued and 100-ml. portions of solvent were slowly distilled from the reaction mixture. After removal of the last portion, reflux was continued for 3 hours more and then 550 ml. of 0.1 *N* aqueous acetic acid was added to the cooled solution. The aqueous phase was separated, washed with three 75-ml. portions of benzene and the combined benzene and xylene solutions, after washing with water (500 ml.) and 2 *N* potassium carbonate solution (500 ml.) and drying, were evaporated to dryness *in vacuo*. The residue was crystallized from methanol to give 6.08 g. (67% yield) of β-ketoester XVIII, m.p. 108–113°, which was again crystallized from methanol for analysis; m.p. 115–117°.

Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.3; H, 5.7; OCH_3, 40.2. Found: C, 65.0; H, 5.7; OCH_3, 40.1.

1,2,3,9-Tetramethoxydibenzo[a,c][1,3]cycloheptadiene-5-one (XIX).—After adding 2 ml. of 12 *N* aqueous potassium hydroxide to a hot solution of 200 mg. (0.52 mmole) of β-ketoester XVIII in 15 ml. of methanol and heating under reflux for 2 hours, 10 ml. of water was added and the methanol evaporated with a nitrogen stream. Water (10 ml.) and benzene (30 ml.) were added, the layers were separated, and the aqueous phase washed with two 30-ml. portions of benzene. The combined benzene solutions were washed, dried (sodium sulfate) and evaporated, and the residue, dissolved in hexane, was chromatographed on alumina (Merck, 8 g.). Progress of the ketone on the column could be followed by its fluorescence in ultraviolet light. After development with hexane, the ketone was eluted with 50% hexane–benzene; 110 mg. (65% yield), m.p. 105–107° after crystallization from methanol.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1; OCH_3, 37.8. Found: C, 69.5; H, 6.3; OCH_3, 37.5.

The oxime was prepared by heating under reflux for 24 hours a solution of ketone, hydroxylamine hydrochloride and pyridine in absolute ethanol. The ethanol was evaporated, the residue was distributed between benzene and water, and the benzene was evaporated after washing with aqueous acid and drying. Crystallization of the residue from methanol gave a 78% yield of oxime, m.p. 174–175°.

Anal. Calcd. for $C_{19}H_{21}O_5N$: C, 66.5; H, 6.2; N, 4.1. Found: C, 66.4; H, 6.3; N, 4.0.

1,2,3,9-Tetramethoxydibenzo[a,c][1,3]cycloheptadiene-5-ol (XX).—Hydrogenation of 150 mg. (0.44 mmole) of the ketone XIX in 10 ml. of absolute ethanol at 25° and atmospheric pressure in the presence of 100 mg. of 5% palladized carbon and 1 ml. of 60% aqueous perchloric acid stopped after the absorption of 102 mole % of hydrogen. The solution was filtered, neutralized with sodium bicarbonate, the ethanol evaporated, 20 ml. of water added, and the aqueous phase extracted with three 20-ml. portions of chloroform. Evaporation of the chloroform and crystallization of the residue from methanol resulted in 80 mg. (53% yield) of the carbinol, m.p. 162–163°.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.1; H, 6.7; OCH_3, 37.6. Found: C, 68.9; H, 6.7; OCH_3, 37.3.

1,2,3,9-Tetramethoxydibenzo[a,c][1,3]cycloheptadiene (XXI).—Hydrogenolysis of the carbinol XX was effected when 75 mg. (0.23 mmole), dissolved in 10 ml. of glacial acetic acid and 1 ml. of 60% aqueous perchloric acid and with 100 mg. of 5% palladized carbon as catalyst, slowly absorbed one molar equivalent of hydrogen during 19 hours at 25° and atmospheric pressure. After filtering, adding 25 ml. of water, and making alkaline with potassium hydroxide, the solution was extracted with three 50-ml. portions of benzene. Evaporating the benzene and chromatographing the residue on 8 g. of alumina (Merck) yielded 45 mg. of material eluted with benzene and crystallized from

methanol, m.p. 99–100°. This material was identical with that prepared from the 7-keto compound and with dihydrodeaminocolchinol methyl ether.[2]

5-Amino-1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene (Isocolchinol Methyl Ether) (II).—A solution of 845 mg. (2.46 mmoles) of 1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene-5-one oxime in 20 ml. of glacial acetic acid and 3 ml. of 60% aqueous perchloric acid was hydrogenated at 25° and atmospheric pressure in the presence of 440 mg. of 5% palladized carbon. When hydrogenation ceased after the absorption of slightly more than 200 mole % of hydrogen, the mixture was filtered and made alkaline with 10 *N* potassium hydroxide after adding 50 ml. of water. Chloroform (six 50-ml. portions) was used to extract the aqueous solution and the residue from evaporation of the combined chloroform extracts was distilled at 90° (0.1 mm.) onto a cold finger. Crystallization of the distillate from methylcyclohexane gave 770 mg. (95% yield) of isocolchinol methyl ether, m.p. 113–115°.

Anal. Calcd. for $C_{19}H_{23}O_4N$: C, 69.3; H, 7.0; N, 4.3. Found: C, 69.4; H, 7.0; N, 4.1.

By heating the amine (100 mg.) on the steam-bath for 5 min. with 0.4 ml. of acetic anhydride and adding 20 ml. of water, 110 mg. of crystalline **N-acetylisocolchinol methyl ether** was obtained, m.p. 213–214°, unchanged on recrystallization from benzene.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.9; H, 6.8. Found: C, 68.2; H, 7.0.

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[CONTRIBUTION FROM CHEMISTRY LABORATORY, UNIVERSITY OF NEW BRUNSWICK]

Synthesis of Dimethylapoerysopine and an Approach to the Total Synthesis of the Unrearranged Erythrina Bases

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Apoerysopine dimethyl ether II (R = CH_3) was synthesized and found identical with the methylation product of authentic apoerysopine. The reaction of 1,2-dialkyl-3,4-dihydroisoquinolinium bromides with Grignard reagents is described. By the use of this reaction the lactam diester XXXIII, which offers good possibilities for the elaboration of various erythrina alkaloids, was prepared.

Introduction

Carmack, MacKusick and Prelog[1] have proposed the structure II (R = H) for apoerysopine, which can be obtained by (*e.g.*) treatment of the alkaloid erythraline with refluxing hydrobromic acid. For erythraline itself the above authors proposed the structure I. It was the purpose of this investigation to confirm these proposals by an unambiguous synthesis of the structure II (R = CH_3) and identification of the synthetic product with dimethylapoerysopine obtained by methylation of apoerysopine. It was also intended to develop methods for the total synthesis of compounds of the general structure I.

The first part of this program has now been completed and has been reported in a preliminary communication.[2] In a preliminary communication[3] we have reported a general approach to the synthesis of compounds of the type XXX and we now describe the preparation of compound XXXIII. This or an analogous compound seems not only to be a suitable intermediate for the preparation of the erythrina skeleton, but might be useful in a total synthesis of the various erythrina alkaloids since the introduction of the necessary functional groups and double bonds would probably offer no insuperable difficulty. The synthesis by another method of a compound possessing the erythrina carbon and nitrogen skeleton has been subsequently reported by Belleau[4]; this compound could not however be connected with any derivative of the natural alkaloids.

Discussion of Results

The synthesis of dimethylapoerysopine was begun with the preparation of 2-carboxy-4,5-dimethoxy-2'-nitrobiphenyl (III). This compound was obtained by the Ullmann reaction between methyl 6-bromoveratrate and *o*-nitrobromobenzene. The reaction products were saponified and the compound III separated from the symmetrical 4,5,4',5'-tetramethoxy-2,2'-dicarboxy-biphenyl IV by a countercurrent distribution using three funnels. The acid III was then converted by an Arndt-Eistert reaction[5] into the homologous ester V. Hydrogenation of V with Raney nickel gave the corresponding aminoester with consumption of the theoretical volume of hydrogen. On heating this aminoester in an atmosphere of nitrogen to 200°, the lactam VI was quantitatively obtained. Lithium aluminum hydride reduction of this compound gave the secondary amine VII. The ultraviolet spectrum of VII taken in alcoholic hydrochloric acid is parallel with the spectrum of dimethylapoerysopine prepared by methylation of apoerysopine with diazomethane (Fig. 1). The fact that no rearrangement has taken place in the course of the Ullmann reaction was demonstrated by hydrogenation of compound III in alkaline solution with Raney nickel and oxidation of the crude product with potassium permanganate. A good yield of *m*-hemipic acid VIII was obtained and characterized as the methylimide.

In a model experiment 2-aminobiphenyl was chloroacetylated and the product was fused with aluminum chloride; a good yield of the 7-phenyloxindole IX resulted. This compound was smoothly reduced to 7-phenyldihydroindole by lithium aluminum hydride. The chloroacetyl derivative of VII was prepared in an analogous manner but treatment of this compound under a variety of conditions with aluminum chloride followed by treatment with diazomethane gave small amounts of starting material as the only detectable product.

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