crystals, m.p. 125–126°, λ_{max}^{EtOH} 234 mμ (E 13,800), assumed to be Δ^5-cholestene-7-one.

Anal. Calcd. for $C_{27}H_{44}O$: C, 84.37; H, 11.46. Found: C, 83.97; H, 11.44.

Dehydrobromination of 7-Keto-8-bromocholesteryl Acetate (IX).—A solution of 1 g. of IX and 30 cc. of pyridine was refluxed for 7 hours and the reaction mixture was treated in the usual manner; the reddish-brown oily product was chromatographed through a column of 50 g. of alumina (Brockmann Grade II) with a petroleum ether–benzene (1:1) solution (200 cc.). The eluate was fractionated into 40 cc. each.

Fractions 3 and 4 afforded a solid which after crystallization from alcohol gave 80 mg. of colorless crystals, m.p. 119–120°, identical with V.

Development of the column with a benzene–ether (1:1) mixture afforded 90 mg. of III, m.p. 152–153°.

Preparation of 7-Keto-$\Delta^{3,5,8(9)}$-cholestatriene (V) from 7-Keto-$\Delta^{3,5}$-cholestadiene (XI).—To a solution of 4 g. of XI in 25 cc. of carbon tetrachloride, 2 g. of NBS and 150 mg. of dibenzoyl peroxide were added, and the mixture was refluxed on a water-bath, with protection from moisture, with irradiation of a 375-watt infrared lamp at a distance of 40 cm. Most of the NBS was converted to succinimide within 30 minutes, and the reaction was complete in about 50 minutes. The cooled reaction mixture was filtered, and the filtrate was evaporated to a brown, oily residue which could not be crystallized. Therefore, 2 g. of this bromide was dissolved in 30 cc. of pyridine, the mixture was refluxed for 6 hours, and the cooled mixture was poured into ice-cooled dilute hydrochloric acid. This was extracted with ether, the ether layer was washed consecutively with 10% hydrochloric acid and water, dried, and the solvent was removed under reduced pressure.

The brown oily residue (1.2 g.) was dissolved in 200 cc. of petroleum ether–benzene (1:1) and passed through a column containing 40 g. of alumina (Brockmann Grade I/II). The column was eluted with 200 cc. of petroleum ether–benzene and the eluate was fractionated into 40 cc. each. The oily residue obtained from fractions 2 and 3 was recrystallized from ethanol; colorless needles (XV), m.p. 150–151°, λ_{max}^{EtOH} 294 mμ (E 10,700), yield 250 mg.

Anal. Calcd. for $C_{27}H_{40}O$: C, 85.20; H, 10.59. Found: C, 85.36; H, 10.49.

Fractions 5–8 afforded an oil which crystallized from ethanol as colorless needles (V), 600 mg., m.p. 119–120°, λ_{max}^{EtOH} 281 mμ (E 25,100).

Anal. Calcd. for $C_{27}H_{40}O$: C, 85.20; H, 10.59. Found: C, 85.48; H, 10.73.

Hydrogenation of 7-Keto-$\Delta^{5,8(9)}$-cholesteryl Acetate (III) with Raney Nickel.—A solution of 500 mg. of III dissolved in 20 cc. of ethyl acetate, with Raney nickel as catalyst, was hydrogenated until about 1 mole of H_2 had been absorbed. After removal of the catalyst, the filtrate was evaporated under reduced pressure; 400 mg. of a colorless solid, m.p. 135–145°, was obtained. This was purified by chromatography through 30 g. of acid-treated alumina by dissolving 450 mg. of the crude crystals in 400 cc. of a 1:4 mixture of petroleum ether and benzene. Development with the same solvent and fractionation of the eluate into 40-cc. portions gave, from fractions 4–5, crystals, m.p. 138–146°, λ_{max}^{EtOH} 250–251 and 258–260 mμ. From the results of ultraviolet absorption data, the crude crystals are the mixture of about 15% of a product showing maximal absorption at 250–251 mμ and 85% of a substance with λ_{max} at 258–260 mμ. Recrystallization from methyl alcohol failed to provide a pure substance but a solution of the crystals in 80% methyl alcohol afforded after standing plate crystals which were recrystallized three times from methyl alcohol; colorless plates, m.p. 154.5–155.5°, λ_{max}^{EtOH} 253 mμ (E 15,000), yield 25 mg.

The crystals that precipitated from the solution in later stages melted at 143–147°; after three crystallizations from methyl alcohol the colorless scaly crystals melted at 143–144°, λ_{max}^{EtOH} 261 mμ (E 9,400), yield 165 mg.

The material of m.p. 143–144° is probably 7-keto-$\Delta^{8(14)}$-cholestenyl acetate, and that of m.p. 154.5–155.5° is probably 7-keto-$\Delta^{8(9)}$-cholestenyl acetate. Recrystallization of fraction 10–12 from ethyl alcohol gave colorless prismatic crystals, m.p. 153–154°, λ_{max}^{EtOH} 239.5 mμ (E 26,500), yield 70 mg. This substance is 7-keto-$\Delta^{5,8(9)}$-cholestenyl acetate (III).

HAKATA, FUKUOKA, JAPAN

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

The Preparation of Colchicide[1] (Demethoxycolchicine)

BY HENRY RAPOPORT AND JOE B. LAVIGNE[2]

RECEIVED JUNE 28, 1954

The reaction of colchicine (I) with methyl mercaptan in the presence of zinc chloride resulted in replacement of the methoxyl group by methyl thio to give methylthiocolchicide (II). Partial desulfurization with nickel afforded the tropone, colchicide (III), which formed a hydrochloride and was hydrogenated to tetrahydrodemethoxycolchicine (IV).

Although colchicine has a dramatic activity as a mitotic poison, its use chemotherapeutically has been severely limited by its marked toxicity, and much effort has been expended in attempts to prepare less toxic derivatives which still are mitotic poisons. Within the group of derivatives in which ring C has remained tropoloid, the structural variations have for the most part consisted in replacement of the methoxy group by various alkoxyls, replacement of the methoxyl group by various aminos, and variations in the substituents on the amino group at C_7.[3] The preparation of two further derivatives of this type, methylthiocolchicide[1] (II) and colchicide (III), is described in the present report.

Alkylthiotropones have been prepared by several methods,[4] none of which appeared particularly attractive for the preparation of methylthiocolchi-

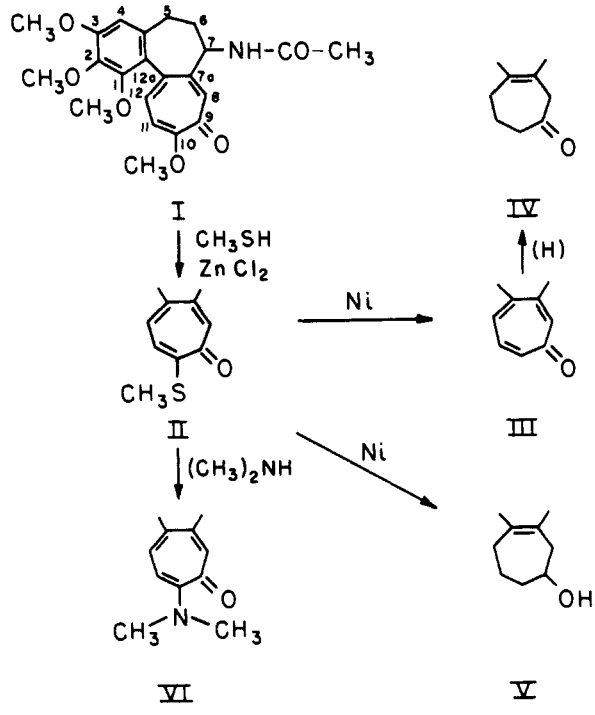
(1) H. Rapoport, A. R. Williams, J. E. Campion and D. E. Pack, THIS JOURNAL, **76**, 3693 (1954). A rational basis for this nomenclature has been proposed in footnote 13. Colchicide serves as the name for the compound in which the methoxyl (C_{10}) has been replaced by hydrogen, and as the root name for those compounds in which replacement has been by groups other than hydrogen.

(2) Supported in part from a generous grant by Smith, Kline and French Laboratories.

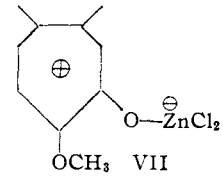
(3) An excellent review of the physiological activity of colchicine and its derivatives is provided by J. W. Cook and J. D. Loudon in Manske and Holmes, "The Alkaloids," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 291. See also (a) R. M. Horowitz and G. E. Ullyot, THIS JOURNAL, **74**, 587 (1952); (b) J. L. Hartwell, M. V. Nadkarni and J. Leiter, *ibid.*, **74**, 3180 (1952); (c) R. F. Rauffauf, A. L. Farren and G. E. Ullyot, *ibid.*, **75**, 2576 (1953); (d) F. Šantavý, *Chem. Listy*, **46**, 280 (1952); (e) A. Uffer, *Helv. Chim. Acta*, **35**, 2135 (1952); (f) A. Uffer, O. Schindler, F. Šantavý and T. Reichstein, *ibid.*, **37**, 18 (1954).

(4) (a) B. D. Abadir, J. K. Cook, J. D. Loudon and D. K. V. Steel, *J. Chem. Soc.*, 2350 (1952); (b) T. Nozoe, M. Sato and K. Matsui, *Proc. Japan Acad.*, **28**, 407, 410 (1952); *ibid.*, **29**, 22 (1953).

cide. In every case, the halotropone was an intermediate and it either was heated directly with a sodium mercaptide in ethanol, or converted first to the mercaptotropone with sodium hydrosulfide and then methylated with diazomethane. The halotropone in turn was prepared directly from the tropolone with phosphorus trihalide or thionyl chloride or from the hydrazinotropone. Both the number of steps involved, and a tropolone intermediate with its resulting isomer problem argued against the application of these procedures, and a process was sought which might convert colchicine directly to methylthiocolchicide.



When heated with methyl mercaptan or sodium methylmercaptide, colchicine was recovered unchanged. However, when the heating was carried out in the presence of zinc chloride a 72% yield of methylthiocolchicide was obtained.[4c] This catalysis by zinc chloride can be adequately explained in terms of the generalized mechanism for acid-catalyzed displacement reactions of tropolone derivatives.[3a,5] Direct evidence for the initial formation of a colchicine–zinc chloride complex (VII) was obtained by evaporation of a solution of colchicine and zinc chloride in methyl mercaptan before subjecting it to heat. The residue was exhaustively digested with benzene, chloroform and ethyl acetate, and the remaining material (equal in weight to the colchicine and zinc chloride that had been added) had the composition $C_{22}H_{25}NO_6 \cdot ZnCl_2$.



VII

That II is the structure of methylthiocolchicide is indicated by its conversion to dimethylaminocolchicide (VI)[1] on heating with dimethylamine, and the formation of hexahydrodemethoxycolchicine (V)[1] on desulfurization with nickel. The infrared spectrum[5c] exhibits absorption bands in the 7 μ region characteristic of colchicine rather than isocolchicine derivatives[3a] and the ultraviolet spectrum displays the shift to longer wave lengths expected upon substitution of $-SCH_3$ for $-OCH_3$.[6] Also, there is an additional maximum at 290 mμ (log ϵ 4.01) not present in the spectrum of colchicine. Methylthiotropone has a similar absorption (λ_{max}^{EtOH} 282, log ϵ 3.91)[4b] not present in tropolone methyl ether.[5a]

The conversion of methylthiocolchicide (II) to the tropone, colchicide (III), finally was accomplished successfully by the controlled action of Raney nickel. Initially, the prospect of preparing a compound as susceptible to reduction as is colchicide by nickel desulfurization seemed quite dim in view of the numerous examples wherein desulfurization is accompanied by hydrogenation of easily reduced groups.[7] However, by deactivating Raney nickel by heating with acetone[8] or ammoniacal acetone[9] this difficulty has been overcome to some extent and aldehydes[8] and aldimines[8] have been prepared by desulfurization.

When methylthiocolchicide was heated with Raney nickel in aqueous ethanol, the expected further reduction of the intermediate colchicide occurred and a 40% yield of hexahydrodemethoxycolchicine (V) was isolated. Deactivation of the nickel by either procedure mentioned above resulted in a decreased yield of V, but again it was the only isolable product. Ultimately, by using nickel deactivated by long reflux in acetone and deliberately discontinuing the reaction when 20 to 30% of the methylthiocolchicide still remained unchanged, it was possible to obtain a 61% yield of colchicide. Although separation of unreacted methylthiocolchicide and colchicide required long and careful chromatography, this method of partial desulfurization is quite feasible for the preparation of colchicide and may have application in other easily reduced systems.

(4c) NOTE ADDED IN PROOF.—While this paper was in press, two reports on the preparation of methylthiocolchicide appeared. L. Velluz and G. Muller [*Bull. soc. chim. France*, 755 (1954)] treated colchicine with methyl mercaptan and *p*-toluenesulfonic acid and obtained a compound of m.p. 192°, $[\alpha]_D$ −221° (*c* 0.5, chloroform). T. Nozoe, T. Ikemi and S. Itô [*Proc. Japan Acad.*, **30**, 609 (1954)], from the action of diazomethane on thiocolchiceine, obtained a non-crystalline substance of m.p. *ca.* 130° to which structure II was assigned. Our material has m.p. 189—190°, $[\alpha]^{28}D$ −191° (*c* 0.94, chloroform).

(5) (a) W. E. Doering and L. H. Knox, THIS JOURNAL, **73**, 828 (1951); **74**, 5683 (1952); (b) W. E. Doering and C. F. Hiskey, *ibid.*, **74**, 5688 (1952).

(5c) We are indebted to Dr. N. K. Freeman of the Radiation Laboratory, University of California, for the infrared spectra.

(6) E. A. Braude, *Ann. Repts. Progress Chem.*, **42**, 105 (1945).

(7) See, among others, R. Mozingo, C. Spencer and K. Folkers THIS JOURNAL, **66**, 1859 (1944); V. Prelog, J. Norymberski, and O. Jeger, *Helv. Chim. Acta*, **29**, 360 (1946); J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, THIS JOURNAL, **73**, 1528 (1951); G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, *ibid.*, **75**, 384 (1953); C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).

(8) G. B. Spero, A. V. McIntosh, Jr., and R. H. Levin, *ibid.*, **70**, 1907 (1948).

(9) M. W. Cronyn and J. E. Goodrich, *ibid.*, **74**, 3936 (1952).

Colchicide (III) is very hygroscopic and is best handled as the hydrate. It was homogeneous to further chromatography, gives a characteristic red color with ferric chloride, and readily forms a yellow, crystalline hydrochloride which is unstable toward heat (losing hydrogen chloride) and from which colchicide is recovered unchanged. The formation of a hydrochloride is a reaction typical of tropones, and its stability varies with the structure of the tropone.[5b,10,11] Although reaction did occur between colchicide and 2,4-dinitrophenylhydrazine, a pure, crystalline derivative could not be isolated. This is not surprising in view of the fact that the carbonyl of colchicide is not a normal carbonyl (see below). Hydrogenation of colchicide proceeded readily in the presence of palladized barium sulfate and gave the known tetrahydrodemethoxycolchicine (IV).[1]

As is typical of tropones,[5b,10] the infrared spectrum of colchicide exhibits the absence of normal carbonyl absorption, and is similar to that reported[10,12] for tropone itself. The ultraviolet spectrum (λ_{max}^{EtOH} 236, 328 mμ; log ϵ 4.35, 4.01) shows the shift toward shorter wave lengths expected on replacement of the methoxyl of colchicine by hydrogen.

The above evidence demonstrates that colchicide (III) is the tropone congeneric with colchicine (I), and its method of preparation through methylthiocolchicide (II) and partial desulfurization suggests a procedure which may be applicable for other tropones when the tropolone is readily available.

Preliminary biological testing with colchicide indicates it acts as a mitotic poison in the same manner as colchicine on the isolated mitotic apparatus of the sea urchin egg[13] and is markedly less toxic to mice than is colchicine.[14]

Experimental[15]

Methylthiocolchicide (II).—A mixture of purified colchicine[16] (6.0 g., 0.015 mole) and fused zinc chloride (0.42 g., 0.003 mole) contained in a 200-ml. Pyrex tube was heated at 135° *in vacuo* for 0.5 hour after which methyl mercaptan (75 g., 1.56 moles) was added at 0°, and the tube was sealed and heated in a steam-bath for 5.5 hours. Evaporation of the reaction mixture at room temperature (water pump) gave a residue which was treated with 10 ml. of water and then extracted with two 100-ml. portions of chloroform. After being washed with 2 *N* sodium hydroxide (two 25-ml. portions) and water (10 ml.), the chloroform solutions were combined, dried and concentrated *in vacuo*. The residue, which still contained some methyl mercaptan, was dissolved in ethyl acetate and this solution then evaporated, finally heating at 95° (2 mm.) for 12 hours, to give 5.53 g. of yellow residue. This material, dissolved in 55 ml. of benzene, was applied to a column (2.5 cm. × 18 cm.) of alumina (90 g.) and followed by benzene (500 ml.), 0.5% absolute ethanol–benzene (250 ml.) and 1% absolute ethanol–benzene (1400 ml.). The methylthiocolchicide obtained on evaporation of the 1% absolute ethanol–benzene solution was crystallized from ethyl acetate and dried at 135° *in vacuo;* 4.48 g. (72% yield), m.p. 189–190°, $[\alpha]^{28}D$ −191° (*c* 0.94, chloroform).

Anal. Calcd. for $C_{22}H_{25}NO_5S$: C, 63.6; H, 6.1; S, 7.7; OCH_3, 22.4. Found: C, 63.6; H, 6.2; S, 7.7; OCH_3, 22.1.

Continuation of the elution with acetone (120 ml.) gave 0.11 g. of recovered colchicine, m.p. 152–154° after crystallization from ethyl acetate.

N,N-Dimethylaminocolchicide (VI) from Methylthiocolchicide (II).—Heating a solution of 500 mg. (1.2 mmoles) of methylthiocolchicide in 1.5 ml. of 15% methanolic dimethylamine in a sealed tube at 100° for 24 hr. followed by evaporation of the solution left a residue which was dissolved in benzene and extracted thoroughly with 2 *N* hydrochloric acid. Basification of the combined aqueous extracts, extraction with benzene, evaporation of the dried benzene solutions and crystallization of the residue from ethyl acetate gave 230 mg. (46% yield) of N,N-dimethylaminocolchicide, m.p. 174–176° (reported[1] m.p. 178–179°).

Desulfurization of Methylthiocolchicide (II). A. Hexahydrodemethoxycolchicine (V).—A solution of 500 mg. (1.2 mmoles) of methylthiocolchicide in 100 ml. of 90% aqueous ethanol to which 10 g. of Raney nickel[17] had been added was heated under reflux and stirred in a nitrogen atmosphere for 18 hours. The mixture was then filtered, the insoluble portion was digested with two 50-ml. portions of boiling benzene, and the combined filtrate and digests evaporated. Crystallization of the residue from benzene gave 180 mg. (40% yield) of hexahydrodemethoxycolchicine (V), m.p. 170–171°, which showed no depression in m.p. when mixed with an authentic sample (m.p. 168–170°[1]).

B. Colchicide (III).—After being washed with five 15-ml. portions of acetone, a 10-g. portion of Raney nickel was heated in 50 ml. of refluxing acetone with stirring in a nitrogen atmosphere for 10.5 hours, following which a solution of 500 mg. (1.2 mmoles) of methylthiocolchicide in 50 ml. of acetone was added and refluxing and stirring continued for an additional 17 hours. The mixture was then filtered, the insoluble material washed with acetone, and the combined filtrate and washings evaporated *in vacuo* to 460 mg. of pale yellow residue which contained 30% of unreacted methylthiocolchicide as indicated by sulfur analysis. Repetition of the above procedure on a larger scale using 5.71 g. (13.7 mmoles) of methylthiocolchicide gave 5.31 g. of residual material containing 20% of methylthiocolchicide, based on sulfur analysis.

The combined residues (5.77 g., containing approximately 21% methylthiocolchicide) were dissolved in 65 ml. of benzene and chromatographed on an alumina (1100 g.) column (5.6 cm. × 42.5 cm.) with a flow rate of 1 l. per hour. Development with benzene (2 l.), and elution with 0.5% absolute ethanol in benzene (22 l.) removed a thin orange band and spread a yellow band over the entire column. When viewed under ultraviolet light the latter was seen to consist of an upper band fluorescing golden yellow, and a lower dark green-yellow band, which was removed using the above solvent (10 l.) followed by 1% absolute ethanol in benzene (4 l.). Concentration *in vacuo* gave 1.66 g. of yellow solid from which 0.88 g. of methylthiocolchicide was obtained on crystallization from ethyl acetate.

Collection of the next fraction was continued (8 l.) as long as the characteristic fluorescence appeared in the eluate. Concentration *in vacuo* gave 3.03 g. of colchicide hydrate as a light yellow glass (yield 61%, based on unrecovered methylthiocolchicide) which was dried overnight *in vacuo* over magnesium perchlorate prior to analysis. Water was determined using the Karl Fischer reagent.

Anal. Calcd. for $C_{21}H_{23}O_5N \cdot H_2O$: C, 65.1; H, 6.5; H_2O, 4.7. Found: C, 65.5; H, 6.5; H_2O, 5.0.

A sample dried overnight at 60° and 0.03 mm. had m.p. 105–120° and $[\alpha]^{25}D$ −87° (*c* 1.01, benzene); $[\alpha]^{27}D$ −260° (*c* 0.42, ethanol); $[\alpha]^{27}D$ −196° (*c* 0.47, chloroform).

Anal. Calcd. for $C_{21}H_{23}O_5N$: C, 68.3; H, 6.3. Found: C, 68.0; H, 6.2.

(10) H. J. Dauben, Jr., and H. J. Ringold, THIS JOURNAL, **73**, 876 (1951); W. E. Doering and F. L. Detert, *ibid.*, **73**, 877 (1951).

(11) T. Nozoe, T. Mukai and J. Minegishi, *Proc. Japan. Acad.*, **27**, 419 (1951).

(12) T. Nozoe, T. Mukai, K. Takase and T. Nagase, *ibid.*, **28**, 477 (1952).

(13) Observations by Dr. Roslansky of the Zoology Department, University of California, Berkeley.

(14) We are indebted to Dr. F. C. Turner, Laboratory for Research on the Treatment of Cancer, Boulder Creek, California, for these tests.

(15) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California; alumina used for chromatography was Merck reagent grade.

(16) G. A. Nicholls and D. S. Tarbell, THIS JOURNAL, **75**, 1104 (1953).

(17) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941)

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]

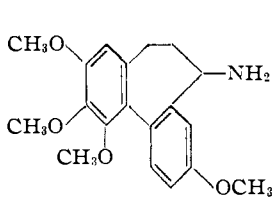
The Synthesis of Isocolchinol Methyl Ether

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

RECEIVED AUGUST 9, 1954

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].



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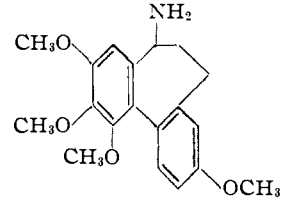

II

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).

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