comparison of its n.m.r. and infrared spectra with those of the authentic material.

Attempted Reduction of N-Methyl-2β,3β-iminocholestane (IX) with Lithium Aluminum Hydride.—A solution of 92 mg. of the N-methylaziridine IX in 20 ml. of anhydrous tetrahydrofuran was treated with 100 mg. of lithium aluminum hydride. The suspension was refluxed for 13 hr. Excess hydride was destroyed with ethyl acetate, followed by 20% aqueous sodium hydroxide solution. This solution was then extracted with ether. The ether extracts were washed well with water, then dried over anhydrous magnesium sulfate. Removal of solvent gave 86 mg. of unchanged starting material, m.p. 71–79°, identified by comparison of its infrared spectrum with that of the authentic material.

In a similar experiment 2β,3β-iminocholestane (IV) was recovered unchanged after 12 hr. heating with lithium aluminum hydride in ether.

An attempted reaction of N-methyl-2β,3β-iminocholestane with methylmagnesium bromide in ether for 3 hr. led to recovery of unchanged starting material.

2β-Acetamidocholestan-3α-ol Acetate (VIII). A. From 2α,3α-Oxidocholestane (V).—Epoxide V (128 mg.) was suspended in a mixture of 20 ml. of ethanol and 20 ml. of 15 *M* ammonium hydroxide solution. The suspension was placed in a Pyrex tube of 100-ml. capacity and sealed. The sealed tube was placed in an oil bath and heated at 120° for 14 hr. During this time there was always some insoluble oil at the bottom of the tube. At the end of the reaction, the tube was cooled and opened, and the contents were poured into an excess of water. The resulting white solid was filtered off and air dried. This material was acetylated with 5 ml. of acetic anhydride and 5 ml. of pyridine on a steam bath for 30 min. The solution was then poured into ice–water and let stand for 1 hr., then extracted with ether. The ether extracts were washed with water, saturated sodium bicarbonate solution, and dilute hydrochloric acid, then dried over anhydrous magnesium sulfate. Removal of solvent gave 112 mg. of clear oil. On adding hexane and warming briefly on a steam bath, the product separated as white needles, 23 mg. (14%), m.p. 186–188°. This material was identical by infrared and mixture melting point with the diacetate prepared by the following procedure.

B. From 2β,3β-Iminocholestane (IV).—A solution of 340 mg. of the aziridine IV in 10 ml. of glacial acetic acid was heated on a steam bath for 10 min. At this time 2 ml. of acetic anhydride and 6 drops of pyridine were added and the solution was heated for 5 min. longer. The solution was poured into ice–water and worked up as in the preceding preparation. The product was 426 mg. of clear oil. On trituration with hexane, there was obtained 260 mg. of the diacetate VIII (60%): m.p. 188–190°; ν_{max}^{KBr} 3300, 3090, 1730, 1645, 1555, 1240, 1040, and 1025 cm.$^{-1}$.

The n.m.r. spectrum, in deuteriochloroform, has bands at τ 4.3 (N–H), 5.12 (C-3 H, half-width 6 c.p.s.), 5.92 (C-2 H, half-width 15 c.p.s.), 7.97 and 8.07 (acetoxy and acetamido methyls), 9.10 (C-19 H_3, singlet), 9.15 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.36 (C-18 H_3, singlet).

An analytical sample was prepared by two recrystallizations from benzene–hexane, m.p. 191–192° (lit.[22] m.p. 186°).

Anal. Calcd. for $C_{31}H_{53}NO_2$: C, 76.33; H, 10.95; N, 2.87. Found: C, 76.66; H, 11.07; N, 2.93.

2β-Acetamidocholestan-3α-ol (VII).—2β-Acetamidocholestan-3α-ol acetate (VIII, 188 mg.) was dissolved in a mixture of 30 ml. of methanol and 7 ml. of water containing 2.3 g. of potassium hydroxide (*ca.* 1.1 *N* in KOH). The solution was refluxed for 2 hr. and filtered while still hot. This initial crop of white needles weighed 90 mg. (52%) and had m.p. 214–217°. On cooling, the mother liquor deposited a second crop of needles weighing 77 mg. (45%): m.p. 212–213°; ν_{max}^{KBr} 3225, 3080, 1640, 1555, 1040, and 1018 cm.$^{-1}$.

The combined product was recrystallized from methanol–water to give 136 mg. of pure product (79%), m.p. 217° (lit.[22] m.p. 211–212°).

Anal. Calcd. for $C_{29}H_{51}NO_2$: C, 78.14; H, 11.53; N, 3.14. Found: C, 78.09; H, 11.35; N, 2.89.

2β-Aminocholestan-3α-ol (VI).—Diacetate VIII (387 mg.) was dissolved in a mixture of 18 ml. of methanol and 2 ml. of water containing 8 g. of potassium hydroxide (*ca.* 6.5 *M* in KOH). The solution was refluxed for 48 hr., poured into water, and filtered. The product weighed 300 mg. (94%) and had m.p. 212–214°; ν_{max}^{KBr} 3500–3100, 1610, 1063, 1050, 1018, 842, and 763 cm.$^{-1}$.

The n.m.r. spectrum, in deuteriochloroform, had bands at τ 6.38 (C-3 H, half-width 10 c.p.s.), 7.00 (C-2 H, half-width 10 c.p.s.), 9.05 (C-19 H_3, singlet), 9.13 (C-26 and C-27 H_6, doublet, J = 6.5 c.p.s.), and 9.36 (C-18 H, singlet).

An analytical sample was prepared by two recrystallizations from methanol, m.p. 212–214° (lit. m.p. 184–187°,[16] m.p. 206–207°[22]). After the first recrystallization the material melted at 215–216°.

Anal. Calcd. for $C_{27}H_{49}NO$: C, 80.33; H, 12.24; N, 3.47. Found: C, 79.94; H, 12.06; N, 3.32.

(22) K. Ponsold, *Ber.*, **96**, 1411 (1963).

A New Synthesis of Desacetamidocolchiceine*,[1]

JACQUES MARTEL, EDMOND TOROMANOFF, AND CHANH HUYNH

Centre de Recherches Roussel-Uclaf, Romainville, Seine, France

Received November 18, 1964

The synthesis of desacetamidocolchiceine (I) *via* a seven-membered ring closure of the dissymmetrical intermediate II (X = CN), accessible by two methods, is reported. The shorter and the easier method involves a selective monocyclization of the keto ester VII (R = CH_3) into bicyclic VIII followed by vinylogous formylation of the latter into XXII.

Although at the inception of our work several syntheses had already been published,[2] we still felt the need for a short and flexible route to desacetamidocolchiceine (I), the precursor of the physiologically interesting desacetamidocolchicine[3] and of natural colchicine.[2,4]

In the synthesis of I a main difficulty lies in the elaboration of the tropolonic ring and, more precisely, in the direct introduction of the α-diketone system in the right position of the C ring. A simple solution to this problem has already been given by Van Tamelen and his group[2b] who used the acyloin condensation to obtain a ketol whose oxidation afforded the desired diketone. We looked for a more satisfactory synthetic route and we report here our results.

From the beginning a Dieckmann-type cyclization of a bicyclic carboxylic diester like II (X = CO_2CH_3)

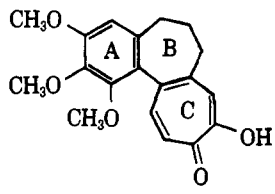
* To Professor Louis F. Fieser.

(1) Part of the work was reported in a preliminary form in *Compt. rend.*, **258**, 243 (1964).

(2) (a) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961); (b) E. E. Van Tamelen, T. A. Spencer, Jr., D. S. Allen, Jr., and R. L. Orvis, *Tetrahedron*, **14**, 8 (1961); (c) A. I. Scott, F. McCapra, J. Nabney, D. W. Young, A. J. Baker, T. A. Davidson, and A. C. Day, *J. Am. Chem. Soc.*, **85**, 3041 (1963). This simulated biogenetic synthesis of colchicine was published after the completion of our work.

(3) R. Schindler, *Nature*, **196**, 73 (1962).

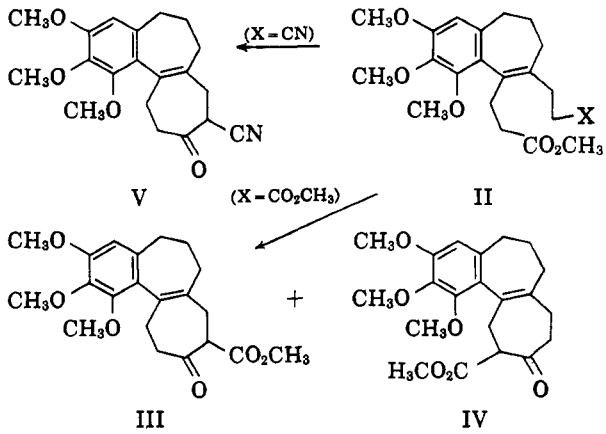
(4) J. Nakamura, *et al.*, *Chem. Pharm. Bull.* (Tokyo), **8**, 843 (1960); **9**, 81 (1961); **10**, 281 (1962). In these papers colchicine is obtained without using desacetamidocolchiceine as a precursor.



I

looked very promising, taking into account the fair yields reported in the literature for such seven-membered ring closures[5] and the presumably easy oxidation of the β-keto ester into an α-diketone (*via* an oximino ketone, for example).

To avoid the possible mixture of isomers III and IV to be expected from compound II (X = CO_2CH_3) bearing two identical propionic side chains, we decided to make use of the dissymmetrical intermediate II (X = CN). Despite the scarcity of information concerning the course of such ring closures in the literature, we were fairly confident[6] that the presence of the cyano group in the chain of II (X = CN) would force the cyclization in the desired direction giving mainly the cyano ketone V. A selective hydroxylation of the activated methyne group of V should then give the cyanohydrin of a diketone which could be oxidized into the desired tropolone by Van Tamelen's method.[2b]

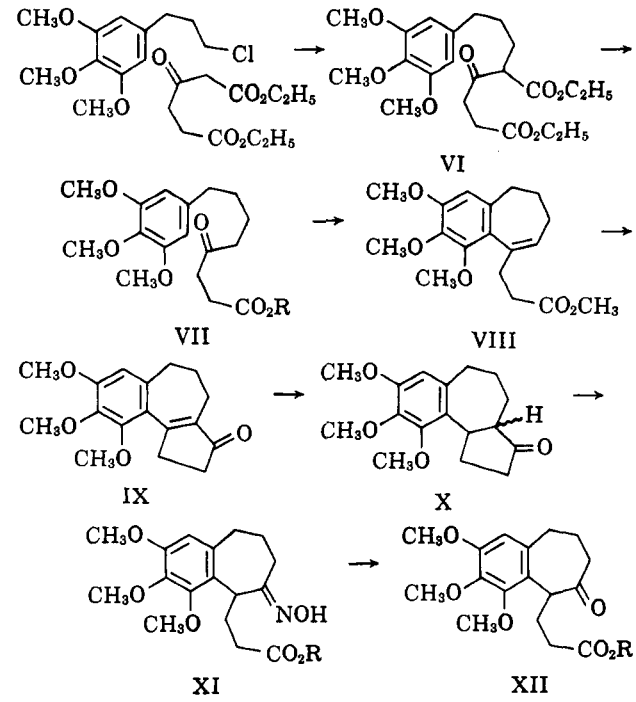


V (X = CN) II (X = CO_2CH_3) III + IV

Our first goal was therefore to prepare II (X = CN) which could be obtained from the simpler bicyclic intermediate VIII. In the latter, the reactive end of the styrenic double bond could be either employed to attach a substituent or it could be turned into a ketone adjacent to the propionic side chain by conventional methods.

We set out to prepare VIII by a series of classical steps: the alcoylation of the sodioenolate of ethyl β-oxoadipate by 3-(3,4,5-trimethoxyphenyl)propyl chloride[7] yielded VI[8] which was saponified. Subsequent decarboxylation and re-esterification of the remaining carboxyl group gave VII (R = CH_3). While conditions which led to VIII were found only later and after extensive experimentation, preliminary trials with ordinary cyclizing agents (sulfuric and phosphoric acids of various concentrations) afforded only the crystalline tricyclic ketone IX. Clearly, the first ring closure is rapidly followed by a second intramolecular acylation of the end of the styrenic double bond by the carboxylic ester group. We decided to use this compound after establishing its structure as indicated below (Chart I). Catalytic hydrogenation or, better, selective Birch reduction of the conjugated olefinic bond of IX followed by nitrosation on the tertiary carbon of the resulting saturated tricyclic ketone X led, *via* the expected opening of the cyclopentanone ring, to the oximino acid XI (R = H). The latter was hydrolyzed to the crystalline keto acid XII (R = H) whose ethyl ester was identical with that obtained by Crabb and Schofield using another method.[9]

CHART I



VI VII VIII IX X XI XII

Taking advantage of the keto group of XII, we planned to introduce the cyanoethyl chain of the desired compound II (X = CN) by an allylic rearrangement, subsequent replacement of allylic halide by cyanide, and isomerization of the exocyclic olefinic bond. Notwithstanding the apparent simplicity of this series of reactions, this scheme met with experimental difficulties at nearly every step. As formulated below (Chart II) the sodium salt of acetylene reacted stereoselectively with the sodium salt of keto acid XII (R = H) in liquid ammonia to give only XIII. Selective hydrogenation of the triple bond of the latter gave the vinylcarbinol XIV (R = H) whose carboxyl was methylated with diazomethane. Allylic rearrangement of the tertiary vinylcarbinol XIV (R = CH_3) worked fairly well only when using phosphorus tribromide in hexane and led to a mixture of isomeric bromides XVa and b. The great lability of the halogens in both allylic isomers prevented any exchange with cyanide ion under ordinary conditions. Only

(5) See, for instance, the following references: H. Rapoport, A. R. Williams, and M. E. Cisney, *J. Am. Chem. Soc.*, **73**, 1414 (1951); G. A. Page and D. S. Tarbell, *ibid.*, **75**, 2053 (1953); N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

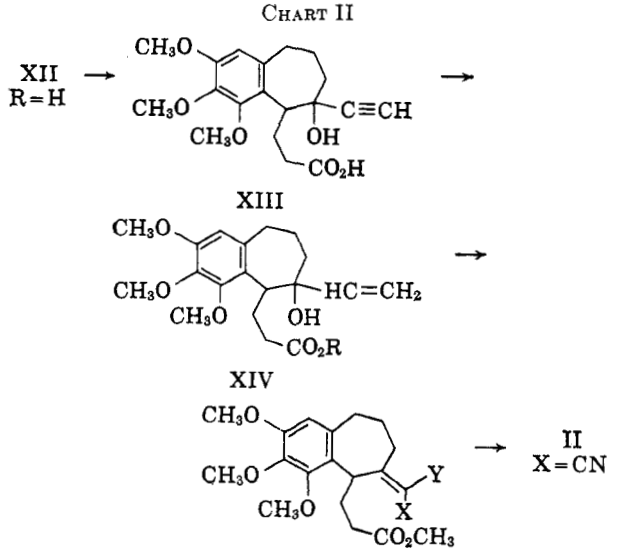
(6) *Cf.* the successful acylation of aliphatic nitriles into β-ketonitriles by aliphatic carboxylic esters. H. Lettré, G. Meiners, and H. Wichmann, *Naturwissenschaften*, **33**, 157 (1946); R. Levine and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 760 (1946).

(7) 3,4,5-Trimethoxyphenylpropyl chloride was prepared according to the method of H. Rapoport and J. E. Campion [*ibid.*, **73**, 2239 (1951)]; in our hands this compound was a crystalline solid of instantaneous m.p. 45° (from hexane).

(8) This compound was a nonisolated intermediate in the work of D. Nasipuri, R. Roy, and U. Rakshit [*J. Indian Chem. Soc.*, **37**, 369 (1960)].

(9) T. A. Crabb and K. Schofield, *J. Chem. Soc.*, 643 (1960).

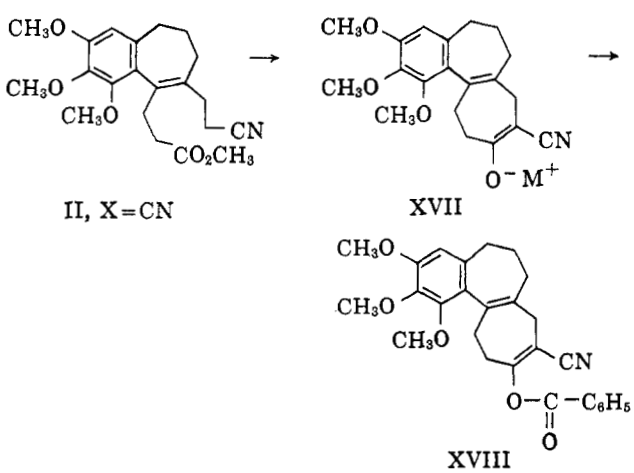
CHART II



XVa, X = H; Y = CH_2Br XVIa, X = H; Y = CH_2CN
b, X = CH_2Br; Y = H b, X = CH_2CN; Y = H

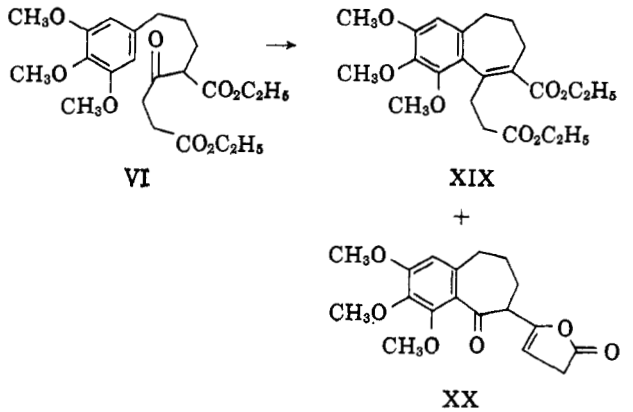
with dimethyl sulfoxide as solvent and under mild experimental conditions was it possible to isolate two isomeric nitriles XVIa and b in acceptable yields. These very sensitive nitriles could finally be converted into the desired II (X = CN) through isomerization of the exocyclic double bond by 2,4-dinitrobenzenesulfonic acid in anhydrous benzene.

With II (X = CN) at our disposal we could, at last, test the value of our hypotheses. In agreement with our expectations it was found that under the influence of metallic potassium in toluene the bicyclic cyano ester II (X = CN) gave selectively the tricyclic cyano ketone V, isolated as the crystalline enol benzoate XVIII.



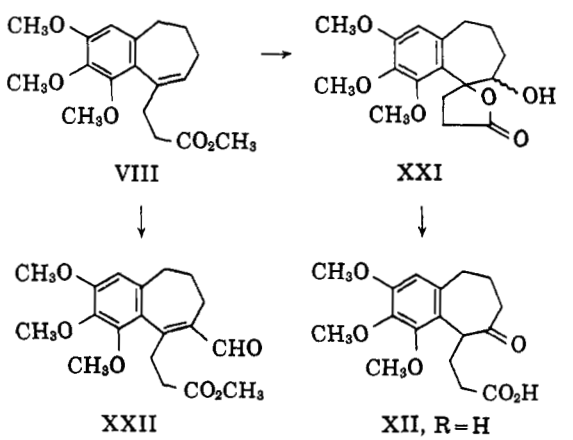
At this stage of the synthesis, we resumed our investigations on the cyclization of the keto esters VI and VII (R = CH_3) trying in the latter case to stop the reaction after the first cyclization; trapping the intermediate VIII meant an appreciable shortening of the whole synthesis.

Brief treatment of the keto diester VI with concentrated sulfuric acid gave only a small percentage of the expected product XIX; the main component of the mixture was the ketoenol lactone XX, resulting from the condensation of the carboxylic ester group on the aromatic ring. We next tried more moderate conditions using milder cyclizing agents.



A thorough investigation using *p*-toluenesulfonic acid monohydrate revealed that short treatment of the keto ester VII (R = CH_3) with this reagent yielded a mixture of the tricyclic ketone IX accompanied by VIII (the product of monocyclization). It was easy to guess that under these conditions the ester group of VIII undergoes an acidolysis to the free carboxyl which then performs the additional ring closure. In order to prevent this undesirable second step, it was logical to try an anhydrous reagent. Indeed, using anhydrous *p*-toluenesulfonic acid, we were able to get smoothly the bicyclic ester VIII in more than 80% yield.

From the acid corresponding to VIII, we could secure a readily available supply of the keto acid XII (R = H) since perphthalic acid oxidation of the olefinic bond followed by acid treatment of the resulting hydroxy lactone XXI, which need not be isolated, gives the crystalline keto acid XII (R = H) in excellent over-all yield.

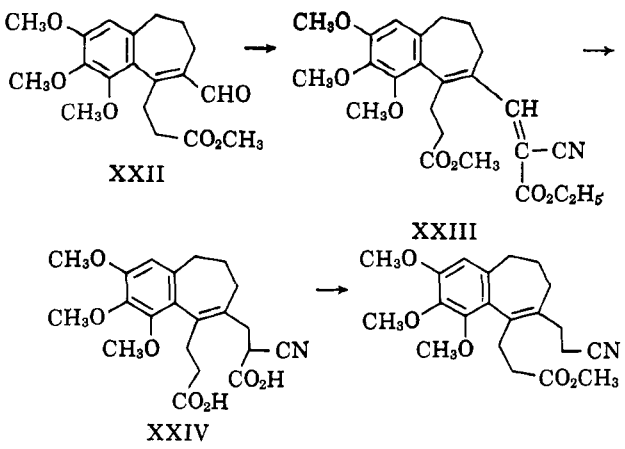


The ready availability of the bicyclic unsaturated ester VIII encouraged us to try one more shortening of the synthetic path. The troublesome occurrence of intramolecular acylation at the end of the olefinic bond during ring closure of VII suggested the possibility of an intermolecular acylation at the same position. Direct formylation with N-methylformanilide and phosphoryl chloride[10] was attempted on VIII and, after

(10) Analogous formylations of this general type[11] are not scarce in the literature, but in all the cases reported so far the styrenic bond is coplanar or nearly so with the aromatic ring. In our case, models show clearly that the olefinic bond is definitely not coplanar with the trimethoxyphenylated ring. Hence, one could not be sure in advance whether the vinylogous effect of the methoxyl groups was effectively transmitted through the olefinic bond.

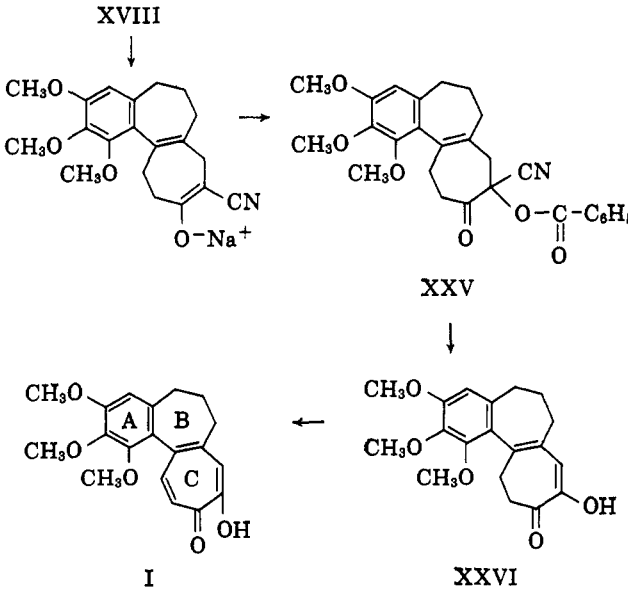
(11) For examples of vinylogous formylations, see R. Wizinger and P. Kolliker, *Helv. Chim. Acta*, **38**, 377 (1955); C. J. Schmidle and P. G. Barnett, *J. Am. Chem. Soc.*, **78**, 3209 (1956); F. Dallacker, K. W. Glombitza, and M. Lipp, *Ann.*, **643**, 67 (1961).

CHART III



hydrolyzing the intermediate immonium salt, we were able to isolate the crystalline aldehyde ester derivative XXII. From the latter, the series of reactions shown in Chart III, including the selective hydrogenation of a conjugated double bond, gave in satisfactory over-all yield the bicyclic cyano ester II (X = CN).

We turn now to the completion of our work. Saponification of the tricyclic cyanoenol benzoate XVIII gave readily the crystalline cyano ketone V whose sodioenolate XVII (M = Na) was treated with benzoyl peroxide by the method of Lawesson.[12] The resulting ketocyanohydrin benzoate XXV was converted with exceptional ease (sodium bicarbonate in refluxing water–methanol) to the crystalline enol of the free α-diketone XXVI which was oxidized into desacetamidocolchiceine (I) as described earlier.[2b]



Experimental[13]

Preparation of VII (R = CH_3). A. Benzene Solution of 1-Iodo-3-(3′,4′,5′-trimethoxyphenyl)propane.—Anhydrous sodium iodide (64.5 g., 0.43 mole) was added to a solution of 1-chloro-3-(3,4,5-trimethoxyphenyl)propane[7] (69.7 g., 0.28 mole) in acetone, 430 ml. After refluxing for 18 hr., the deposited sodium chloride was separated and washed with anhydrous acetone and the filtrate was evaporated *in vacuo*. Addition of anhydrous benzene (100 ml.) to the residue precipitated the sodium iodide in excess which was separated and washed twice with 30-ml. portions of benzene. The benzene solution was used directly in the following alkylation.

B. Alkylation of Ethyl β-Oxoadipate with the Iodo Derivative.—Under nitrogen, to a solution of 100 ml. of ethyl β-oxoadipate in 130 ml. of anhydrous benzene was added 8.8 g. of sodium in small portions, so as to keep the solution boiling. To the suspension of the sodium enolate resulting from complete reaction of the metal with ethyl β-oxoadipate was quickly added the benzene solution of the iodo derivative prepared above. The mixture was refluxed for 6 hr. and kept overnight at room temperature. The inorganic salt was filtered and the solution was received into aqueous hydrochloric acid (52 ml. of concentrated hydrochloric acid in 250 ml. of water). The benzene layer was decanted, washed with 1 *N* hydrochloric acid and then with water to neutrality, and dried. The solvent and the ethyl β-oxoadipate in excess were wholly removed by distillation on heating to 160° (metal bath) under reduced pressure (1 mm.).

C. Saponification and Decarboxylation of VI[8] to VII (R = H).—The residue (VI) from the preceding distillation was saponified by refluxing with 250 ml. of methanol, 65 ml. of water, and 65 ml. of concentrated sodium hydroxide for 1.5 hr. The methanol was removed *in vacuo* and the solution was diluted with water and extracted twice with ether. The ethereal extracts were washed with water. The combined alkaline phase and aqueous washings were acidified with hydrochloric acid and the acid solution was extracted twice with methylene chloride. The organic layer, washed with brine, was dried and evaporated to dryness. The residual gum, taken up in ether and isopropyl ether (1:1) and kept for 1 hr. in ice, crystallized. The solid was filtered, drained, and dried giving 64 g. (70% based on the chloro derivative), m.p. 90°. From the mother liquors a second crop (1.8 g., m.p. 87°) was recovered.

Anal. Calcd. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46; O, 29.6. Found: C, 62.9; H, 7.4; O, 29.3.

D. Esterification to VII (R = CH_3).—Methylation of the above acid with a methylene chloride solution of diazomethane or with methanol containing 1% concentrated sulfuric acid gave quantitatively the ester VII (R = CH_3). Titration of the methyl ester with 0.1 *N* NaOH solution gave the theoretical value (165.8).

Cyclization of VII (R = CH_3) to the Tricyclic Ketone IX.—The ester VII (R = CH_3, 63 g.) and 85% polyphosphoric acid (520 g.) were stirred with a glass rod under an atmosphere of nitrogen until the mixture became homogeneous and was then allowed to stand for 16 hr. at 50°. After addition of ice and dilution with water, the solution was extracted twice with methylene chloride. The organic layer was washed with aqueous sodium bicarbonate and water and then dried. Evaporation of the solvent left a residue which was crystallized from 100 ml. of isopropyl ether. After keeping in ice for 1 hr., the crystals were filtered, washed with a small amount of isopropyl ether, and dried; 37.43 g. (70%), m.p. 110°. The second crop weighed 1.8 g. (3%), m.p. 108°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 71.1; H, 6.8.

The oxime prepared in the usual manner with hydroxylamine hydrochloride in pyridine–ethanol had m.p. 202–204°.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.5; H, 6.9; N, 4.8.

Birch Reduction of IX.—A solution of 17.22 g. of IX in 170 ml. of anhydrous tetrahydrofuran was quickly added to a solution of 0.920 g. (2.22 g.-atoms) of lithium in 520 ml. of liquid ammonia maintained at −70° and the whole was stirred for 1.6 hr. Powdered ammonium chloride (52 g.) and then 170 ml. of water were added cautiously. The ammonia was allowed to evaporate at room temperature and the tetrahydrofuran was removed under

(12) S. O. Lawesson, C. Frisell, D. Z. Denney, and D. B. Denney, *Tetrahedron*, **19**, 1229 (1963).

(13) All instantaneous melting points (taken on a Kofler hot stage) and boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra with Cary Models 11 and 14 spectrophotometers. Proton magnetic resonance spectra were determined with a Varian spectrometer 4300C at 56.4 Mc., using tetramethylsilane as internal standard. Chloroform, ethanol, and deuteriochloroform were used, respectively, for infrared, ultraviolet, and n.m.r. spectra unless noted otherwise. All solvents are reagent grade unless otherwise stated. Ligroin had a 60–80° boiling range. The drying of organic liquids was effected over anhydrous magnesium sulfate unless otherwise specified. We are indebted to Mrs. Bartos and her associates for microanalysis and to Dr. Legrand, Mr. Delaroff, Miss Fabian, and their associates for spectral determinations and for interpretations.

vacuum (water pump). The residual solution was extracted with methylene chloride; the organic layer was washed with water, dried, and filtered. The yellow filtrate was decolorized by shaking with a small amount (3 g.) of commercial alumina and the solvent was removed *in vacuo*. The residue was crystallized from ether; 13.69 g. (79%), m.p. 104°.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.5; H, 7.5.

Overreduction occurred when an excess of lithium (10 equiv.) was used yielding a mixture of cyclopentanone XI and the corresponding cyclopentanol, m.p. *ca.* 70° (from isopropyl ether), which could be separated by treatment with Girard reagent T.

Catalytic Hydrogenation of IX.—A suspension of 2 g. of 5% palladium on carbon (Baker-Premetal) in 50 ml. of absolute ethanol containing 1.1 g. of KOH pellets was saturated with hydrogen at atmospheric pressure and room temperature. To this was added 5 g. of the pentenone IX. The hydrogen uptake at 19° was slow and stopped after 32 hr. (uptake, 400 ml. of hydrogen). After separation of the catalyst, the filtrate was made acidic with 2 *N* hydrochloric acid, diluted with water, and extracted with methylene chloride. The extracts were dried, the solvent was removed, and the residual oil was treated with Girard reagent T gave, besides a nonketonic fraction (1.056 g.), another fraction which was treated with 2 *N* hydrochloric acid, extracted with methylene chloride, and dried. The residue crystallized easily into a mixture of needles and prisms corresponding to both possible isomers (*cis* and *trans* X). Fractional crystallization from alcohol yielded 0.873 g. of prisms, m.p. 128–130°, of one pure isomer, 1.8 g. of a mixture of isomers, and 0.235 g. of the other pure isomer, m.p. 102°. This last compound does not depress the melting point (104°) of the tricyclic pentanone obtained above by Birch reduction of IX.

The isomeric ketones have quite different infrared spectra: the ketonic bond is at 1735 cm.$^{-1}$ for the isomer of m.p. 128–130° and at 1729 cm.$^{-1}$ for the other (m.p. 102–104°). The mode of formation, the infrared data, and the properties of each isomer are in agreement with the lower melting ketone being of the B/C *trans* series and the higher melting ketone being of the *cis* series. These assignments are only tentative. For the stability of such systems see ref. 14.

Oximino Acid XI (R = H) from the Opening of X and Saponification of the Intermediate Ester.—The tricyclic pentanone X (3.9 g., m.p. 104°) was treated at 0° under nitrogen with a solution of 0.34 g. of sodium in 78 ml. of ethanol. The temperature being kept between 0 and 2°, 3.9 ml. of isoamyl nitrite was added dropwise to the enolate thus prepared. The mixture was allowed to stand 1 hr. at 0° with stirring and then 20 hr. in an icebox. After adding 5 ml. of acetic acid, the acidic solution, diluted with water, was extracted with ether. The ethereal layer was washed twice with 25-ml. portions of Claisen alkali,[15] made acid with 15 ml. of acetic acid, and extracted with ether. The ethereal extracts were washed with water and dried. The solvent was removed and the residue (4.6 g.) crystallized. The paste obtained by adding isopropyl ether was filtered; the resulting crystals were drained and dried yielding 2.86 g. (63%), m.p. 166°, of crude XI (R = H). The analytical sample (2.13 g.) obtained from successive recrystallizations from methanol–methylene chloride had m.p. 191°.

Anal. Calcd. for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.6; H, 7.0; N, 4.3.

Keto Acid XII (R = H). A. By Hydrolysis of the Oximino Group of XI (R = H).—The oximino acid XI (R = H, 5.68 g.) was introduced into 114 ml. of 1:1 acetic acid–water containing 7.3 ml. of pyruvic acid. The solution was kept on the steam bath for 2 hr., cooled, diluted with water, and extracted with methylene chloride. The extract, washed with water, was dried and the solvent was removed *in vacuo*. The residual gum was crystallized from isopropyl ether; 4.89 g. (90% yield), m.p. 86°. Two crystallizations from the same solvent raised the melting point to 88–90° (rectangular plates).

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.2; H, 6.9.

XII, an unisolated intermediate in Van Tamelen's synthesis,[2b] was converted into the corresponding enol lactone as described earlier.[2b] The yield was improved by shortening the time of the reaction as follows.

Enol Lactone.—XII (2 g.), sodium acetate (0.14 g.), and acetic anhydride (10 ml.) were heated at 100° for 4 hr. After the usual treatment 1.66 g. (86%) of the enol lactone, m.p. 106°, was obtained, identical in every respect with the formerly described compound.[2b]

B. From Bicyclic Unsaturated VIII through Hydroxy Lactone XXI.—The unsaturated bicyclic acid corresponding to ester VIII (25.6 g., m.p. 68°) was dissolved in 100 ml. of ether. After cooling in ice, a solution of 37% perphthalic acid in ether (*ca.* 2 mole equiv.) was added with stirring. The mixture was kept overnight in an icebox, and then the ether was removed under vacuum (water pump). The residue was taken up in methylene chloride and washed with aqueous sodium bicarbonate to complete dissolution and the organic layer was decanted. The aqueous layer was re-extracted twice with methylene chloride. The organic extracts were washed with aqueous sodium bicarbonate and water and dried; the solvent was removed to dryness. Ether was added to the crystalline residue and the crystals of hydroxy lactone XXI were drained and washed with ether; 17.72 g. (66%), m.p. 201°. Recrystallization from methanol–acetone raised the melting point to 206°; ν 1780 (C=O) and 3610 cm.$^{-1}$ (OH); λ_{max} 273 mμ (ϵ 700), inflection around 229 mμ (ϵ 11,000) and 280 mμ (ϵ 600).

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.5; H, 6.8.

The mother liquors contained an additional amount of lactone which could be converted directly to the keto acid XII (R = H).

Acid Conversion of XXI to XII (R = H).—The hydroxy lactone XXI (20 g., m.p. 201°) in acetic acid (100 ml.) and 5 *N* sulfuric acid (100 ml.) was warmed at 75–80° with stirring. Dissolution was complete within 10 min. and the mixture was kept for one more hour at 80°. The cooled solution was diluted with ice water and extracted twice with methylene chloride. The extracts were washed three times with water, dried, and evaporated to dryness to a gum which was crystallized from isopropyl ether: 17.17 g. (86%), m.p. 92°; second crop, 0.77 g. (3.8%), m.p. 92°.

The keto acid was identical in every respect with a sample prepared by the method A. In practice it is advantageous not to isolate the intermediate hydroxy lactone XXI but to rearrange it by acids. In this way the keto acid XII can be obtained from VII in more than 50% yield.

Keto Ester XII (R = CH_3).—Esterification of acid XII (R = H) with diazomethane in methylene chloride yields the methyl ester; 94%, m.p. 86°, ν^{CS_2} 1711 (C=O) and 1741 cm.$^{-1}$ (CO_2Me).

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.5; H, 7.2.

Ethynylation of XII.—A stream of purified acetylene was passed at −70° through 1.2 l. of liquid ammonia. After 15 min. 5.13 g. (6 g.-atoms) of sodium was added gradually with stirring; the current of acetylene was maintained to complete dissolution of the metal (2.5 hr.). The keto acid XII (R = H; 12 g.) in anhydrous tetrahydrofuran (50 ml.) was introduced dropwise into the above solution while passing acetylene through the solution at −40° for 5.5 hr. more. The ammonia was allowed to evaporate slowly during the night. To the residue, freed from acetylene at the water pump, acetic acid (50 ml.), water (100 ml.), and ice (100 g.) were added and the solution was extracted three times with methylene chloride; the organic layer was washed with water, dried, and distilled at the water pump. The residue was crystallized from ether; 7.58 g. (58%), m.p. 148°. Recrystallization from chloroform gave plates, m.p. 150°.

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.5; H, 6.9.

From the mother liquors treated with diazomethane in methylene chloride, a small amount (0.3 g.) of ethynylated ester compound (methyl ester of XIII) was recovered besides much of the methyl ester of the starting keto acid (2 g., m.p. 86°).

Selective Hydrogenation of the Ethynyl Group of XIII.—The acid XIII (8.27 g.) in 10% pyridine in dimethylformamide (82 ml.) was hydrogenated in the presence of a 5% palladium on calcium carbonate catalyst (0.83 g) at atmospheric pressure and room temperature. The reaction was stopped after an uptake of 570 ml. of hydrogen (theoretical amount, 535 ml.) and the catalyst was removed by filtration. The filtrate was diluted with water and extracted with methylene chloride. The extracts were washed with 2 *N* hydrochloric acid and with water and dried; the solvent was removed. The residual gum was crystallized from ether and isopropyl ether; 7.4 g. (90%), m.p.

(14) D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958); A. M. Islam and R. A. Raphael, *ibid.*, 3151 (1955).

(15) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 310.

142°. A further crystallization from methylene chloride–ether raised the melting point to 144° (platelets).

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.1; H, 7.4.

The methyl ester XIV (R = CH_3) was prepared by treatment of the acid XIV (R = H) with diazomethane; m.p. 58° (from hexane).

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 66.1; H, 7.8.

Allylic Rearrangement of XIV (R = CH_3) to XV.—The vinylcarbinol XIV (R = CH_3, 4.37 g., 12 mmoles) was dissolved in 10 ml. of $CHCl_3$ and 24 ml. of ligroin. To the solution cooled at −30° was added very slowly 13.2 ml. of a freshly prepared solution of 1 ml. of phosphorus tribromide in 9 ml. of ligroin. The temperature of the stirred solution was maintained between −20 and −10° for 5 hr.; an orange oil appeared after 1 hr. The whole was then poured into ice–water and extracted three times with ether. The extracts were washed with water to neutrality and dried; the solvent was removed *in vacuo* below 50°. The residual yellow oil was crystallized from ligroin; 3.8 g. (74%), m.p. *ca.* 70° dec. This unsharp melting point is suggestive of a mixture of isomeric bromides which we did not try to separate.

The analytical sample was obtained by dissolving the crystalline product in boiling ether, filtering the solution on carbon black, adding ligroin to the cooled solution to slight turbidity, and allowing to crystallize slowly; the product had m.p. 75–78°.

Anal. Calcd. for $C_{20}H_{27}BrO_5$: C, 56.21; H, 6.37; Br, 18.70. Found: C, 56.2; H, 6.2; Br, 18.6.

The infrared and n.m.r. spectra are in agreement with the proposed structure.

Isomeric Nitriles XVIa and b from XV.—Under an atmosphere of nitrogen, 3 g. of cuprous cyanide previously dried at 120° for 24 hr. was placed in 80 ml. of rectified dimethyl sulfoxide which gave a grey greenish solution after 15 min. at 50°. To this was added 3 g. of the preceding mixture of allylic bromide XV (m.p. *ca.* 70°). The stirred mixture which turned limpid yellow after the first 15 min. was kept for 25 hr. at 50° under nitrogen. After cooling, 170 ml. of methylene chloride was added. The organic layer was washed with 2 *N* HCl and then with water and dried. The solvent was removed and the residual orange oil was taken up in the minimum amount of isopropyl ether so as to make a fluid paste which was then diluted with ligroin. The resulting crystals were drained and dried; 1.55 g. (59%), m.p. 70–75°.

Purification of the crude product was effected by chromatography on Florisil. The main isomer, m.p. 93°, crystallized from isopropyl ether in rods; from the n.m.r. data it corresponds to XVIa. The minor isomer was obtained from the mother liquors either by chromatography on alumina or by slow crystallization. It formed irregular platelets, m.p. 102°, from ligroin; the n.m.r. spectrum agrees with the structure XVIb. Both isomers have very similar infrared spectra.

Anal. Calcd. for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found for isomer of m.p. 93°: C, 67.8; H, 7.2; N, 3.8. Found for isomer of m.p. 102°: C, 67.7; H, 7.2; N, 3.8.

II (X = CN) by Acid Isomerization of the Exocyclic Bond of XVI.—2,4-Dinitrobenzenesulfonic acid (1.2 g.) was dried[16] by refluxing for 2 hr. with anhydrous benzene and by removing the water which was azeotropically separated over a desiccant (Drierite). This dry benzene solution, after rapid addition of the cyano derivatives XVI (2.5 g., m.p. 70–75°), was refluxed for 2 hr., cooled, and washed with water, aqueous sodium bicarbonate, and water. The aqueous washings were extracted with ether. The combined organic layers were dried and evaporated to dryness *in vacuo*. The gummy residue crystallized slowly from isopropyl ether after having been kept for 16 hr. at 0°. The crystals were drained and washed with cold isopropyl ether; 0.886 g. (35%), m.p. 68° (prisms). The low yield is attributed to the difficult isolation of the compound II (X = CN). From the ultraviolet absorption, the conversion of XVI to II amounted to 66%; λ_{max} 220 mμ (ε 28,800), 252 (12,200), and inflection around 283 (1400). The infrared and n.m.r. spectra agree with the proposed structure (>C=C< tertiary conjugated).

Anal. Calcd. for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.5; H, 7.5; N, 4.0.

(16) The presence of even small amounts of water favors the intramolecular addition of the carboxyl group on the olefinic bond to the γ-lactone and hydration of the cyano group to the amide.

II (X = CN) from VIII. A. VIII by Cyclization of VII (R = CH_3).—*p*-Toluenesulfonic acid hydrate (56 g.) and anhydrous benzene (900 ml.) were heated under reflux with removal of the azeotropically separated water over Drierite. A solution of keto ester VII (R = CH_3, 50 g.) in anhydrous benzene (100 ml.) was then added to the solution of anhydrous tosylic acid and the whole was refluxed for 16 hr. with removal of the azeotropically separated water over Drierite. The cooled solution was poured into ice–water. After decantation, the aqueous layer was extracted with benzene. The organic layer was washed successively once with water, once with aqueous sodium bicarbonate, and twice with water and dried; the solvent was distilled at the water pump. Treatment of the residual oil (50 g.) with Girard reagent T removed the ketonic fraction containing the tricyclic pentenone IX, leaving after the usual work-up 40.4 g. (80%) of bicyclic ester VIII; b.p. 170–172° (0.5 mm.); λ_{max} 218 mμ (ε 28,000), 250 (9600), inflection at *ca.* 280 (1450). In a series of preparations the yields were between 80 and 85%.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 68.0; H, 7.4.

The Free Acid of VIII.—Saponification of the ester VIII with methanolic sodium hydroxide readily gave the free acid (VIII, COOH instead of $COOCH_3$), m.p. 69°. Two further recrystallizations from ligroin raised the melting point to 72°; λ_{max} 218 mμ (ε 27,200), 250 (9600), inflection at *ca.* 282 (1200). This acid was described as an oil by Acker.[17]

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.5; H, 7.4.

The crude acid from the saponification was treated directly with perphthalic acid in ether to give the hydroxy lactone XXI.

The thiouronium salt of the acid melts instantaneously at 193° and in a soft glass capillary tube at 175–178° (lit.[17] m.p. 162–163°).

Anal. Calcd. for $C_{25}H_{32}N_2O_5S$: C, 63.53; H, 6.83; N, 5.93; S, 6.78. Found: C, 63.6; H, 6.6; N, 6.1; S, 6.8.

B. XXII by Formylation of VIII.—Working under nitrogen and excluding any moisture, freshly distilled phosphoryl chloride (2 ml.) was added dropwise to N-methylformanilide (3.2 ml.). The stirred mixture yielded after 0.5–1 hr. a yellow solid complex. At this stage, 4.3 g. of VIII was introduced and the mixture was warmed at 55–60° (internal temperature) for 4 hr. The yellow complex gave way gradually to a deep brown solution which was cooled down to room temperature and diluted with anhydrous benzene. The solution was transferred to a separatory funnel containing 20 g. of sodium acetate dissolved in 20 ml. of water and shaken vigorously. After decantation, the aqueous layer was extracted twice with benzene. The benzene layer was washed five times with 2 *N* HCl and then with water and dried. The solvent was evaporated to dryness *in vacuo*, leaving a blackish gum which was percolated through a small column of alumina with benzene (1 l.). The solvent was again evaporated to dryness *in vacuo* and the residual resin was purified by chromatography on acid-washed alumina. The first eluate with benzene (250 ml.) contained mainly the starting compound VIII and little of the aldehyde XXII. The second eluate, using 500 ml. of methylene chloride, contains 2.56 g. of a resin which was crystallized from ligroin; 2 g. (43%), m.p. 90°. A further crystallization from ether and isopropyl ether gave long prisms with m.p. 92°; λ_{max} 252 mμ (ε 10,800), 308–309 (10,700), inflection at *ca.* 223 (10,400).

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.7; H, 7.0.

The crude aldehyde could be also purified *via* the semicarbazone which was chromatographed on alumina. The pure crystalline semicarbazone (possibly a mixture of the *syn* and *anti* isomers) melted at 100–110° (from CH_2Cl_2–ether).

Anal. Calcd. for $C_{20}H_{27}N_3O_6$: C, 59.24; H, 6.71; N, 10.37. Found: C, 59.3; H, 6.9; N, 10.3.

The semicarbazone can be hydrolyzed back to the free aldehyde XXII in the usual manner.

The 2,4-dinitrophenylhydrazone of XXII melted at 184°.

Anal. Calcd. for $C_{25}H_{28}N_4O_9$: C, 56.81; H, 5.34; N, 10.60. Found: C, 56.7; H, 5.4; N, 10.6.

C. Condensation of XXII with Methyl Cyanoacetate.—XXII (0.525 g.), methyl cyanoacetate (0.150 g.), piperidine (52.5 mg.), acetic acid (91 mg.), and benzene (15 ml.) were heated for 20 hr. under reflux with removal of the water separated azeotropically

(17) T. E. Acker, Ph.D. Thesis, Columbia University, 1960; University Microfilms, Inc., Ann Arbor, Mich., Microfilm No. 61,243.

over Drierite. The cooled mixture, diluted with water, was extracted twice with ether. The extracts were washed with water, dried, and distilled *in vacuo*. The residual yellow resin (0.695 g.) was freed from the starting ketonic material by treatment with semicarbazide and then chromatography on alumina. The first eluate with methylene chloride yielded 0.525 g. (81%) of a yellow resin used directly in the next step, ν 2230 cm.$^{-1}$ (conjugated CN).

D. Selective Hydrogenation of the Conjugated Olefinic Bond of XXIII.—The preceding resin (0.525 g.) dissolved in absolute ethanol (2 ml.) was hydrogenated under normal pressure in the presence of platinum oxide (0.030 g.) at room temperature. After an uptake of 31 cc. of hydrogen (theory 27.5) in 1 hr. the catalyst was separated by filtration and washed with methylene chloride. The solvent was evaporated to dryness leaving a noncrystalline residue which, after being percolated through alumina with methylene chloride, yielded 0.5 g. of a yellow resin; ν 2260 cm.$^{-1}$ (very weak, nonconjugated CN).

E. XXIV by Saponification of XXIII.—The preceding resin (0.48 g.) was stirred with methanolic potassium hydroxide (14.5 ml. containing 9.7 mg./ml.) at room temperature for 17 hr. After removal of the methanol *in vacuo*, the residue was diluted with water and the aqueous solution was extracted with ether. The ether layer was washed twice with water. The aqueous layers collected were acidified with 2 *N* HCl and extracted twice with methylene chloride. The organic layer, washed with water, dried, and distilled *in vacuo*, yielded 0.416 g. of residue crystallizing from isopropyl ether; 0.208 g. (46.5%), m.p. 163°. The melting point did not change on further crystallization from methanol–ether.

Anal. Calcd. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.5; H, 6.4; N, 3.5.

Thermal decarboxylation at 180–200° of the preceding cyano diacid and methylation of the resulting cyano acid with diazomethane in methylene chloride yielded the cyano ester II (X = CN), m.p. 67°, identical in every respect with a sample from the other method.

The yields given in this series of reaction are those obtained in the first trials but we have indications suggesting that all the steps can be adjusted to proceed nearly quantitatively.

The O-Benzoyl Derivative of the Tricyclic Cyano Ketone V from the Cyclization of II (X = CN).—Under an atmosphere of nitrogen, 0.105 g. of potassium was added to 25 ml. of anhydrous toluene, and the stirred mixture was refluxed which produced a fine suspension of the melted metal in toluene. To this was added dropwise the cyano ester II (X = CN, 0.5 g.) dissolved in 20 ml. of anhydrous toluene. The stirred mixture was refluxed for 2 hr. under nitrogen. After cooling in ice the excess of potassium was cautiously destroyed with 2 ml. of anhydrous methanol. The solution was diluted cautiously with ice–water and extracted with ether. The ethereal extracts were washed with water to neutrality. The aqueous layer and the aqueous washings were combined, made acidic with 2 *N* HCl, and extracted three times with methylene chloride. The organic layer was washed with water and dried and the solvent was removed *in vacuo*. The residual orange resin (0.420 g.) in 4 ml. of anhydrous pyridine was benzoylated at 10° with benzoyl chloride (0.15 ml., *ca.* 0.182 g.); the stirred mixture was kept for 2 hr. at room temperature, added to ice–water, and extracted with methylene chloride. The organic extracts, washed successively with 2 *N* hydrochloric acid, aqueous sodium bicarbonate, and water, were dried and the solvent was eliminated *in vacuo*.

The purification of the residual resin (0.44 g.) was effected first by chromatography on silica gel and elution with methylene chloride and methylene chloride–methanol. The first eluate (200 ml.) with methylene chloride alone was discarded. The second elution with methylene chloride containing 10% methanol yielded, after removing the solvents *in vacuo*, 0.280 g. of a resin which was again submitted to chromatography on alumina (9 g.). Elution with 50 ml. of benzene yielded 0.160 g. of residue which was crystallized from isopropyl ether; 0.1 g. (17%), m.p. 124°. Two recrystallizations from acetone raised the melting point to 130° (needles). The infrared spectrum shows the presence of a conjugated CN (ν 2230 cm.$^{-1}$) and of an enol benzoate (ν 1735–1740 and 1260 cm.$^{-1}$); λ_{max} 220 mμ (ϵ 41,700), inflection around 255 mμ (ϵ 14,700).

Anal. Calcd. for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 73.0; H, 6.2; N, 3.4.

V from Debenzoylation of XVIII.—XVIII (800 mg.) dissolved in boiling methanol (20 ml.) was debenzoylated by addition of a solution of potassium hydroxide (0.116 g.), water (1 ml.), and methanol (11 ml.) and allowing the mixture to stand for 16 hr. at room temperature. The methanol was removed at the water pump; the residue, diluted with water, was extracted with methylene chloride three times. The organic layer was washed with brine, dried, and concentrated to dryness. The remaining methyl benzoate was removed by a stream of nitrogen with heating. The residue (0.627 g.) was crystallized from isopropyl ether; 0.556 g. (90%), m.p. 100°, ν 2260 (nonconjugated CN) and 1740 cm.$^{-1}$ (C=O). Recrystallization from ether raised the melting point to 104°.

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.2; H, 6.8; N, 4.1.

Cyanohydrin Benzoate XXV from the Benzoyloxylation of the Enolate of V.—Under an atmosphere of nitrogen to 0.150 g. of the preceding cyano ketone V, covered with 5 ml. of dry benzene, was added a small piece of freshly cut sodium. The mixture was heated under reflux for 15 hr. The formed enolate was freed from the metal in excess by removing the latter with a spatula. To the cooled suspension of the metallic derivative (XVII, M = Na) was added benzoyl peroxide, m.p. 110° (0.105 g., 1 mole equiv.). The whole was stirred overnight at room temperature and poured into ice–water containing an excess of 2 *N* hydrochloric acid. The solution was extracted with ether; the organic layer was washed with water, aqueous sodium bicarbonate, and twice again with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* leaving a residue which was crystallized from isopropyl ether. The crystals were drained and dried; 0.154 g. (76%), m.p. 135–140°. One recrystallization from alcohol raised the melting point to 142°.

Anal. Calcd. for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04. Found: C, 70.4; H, 5.9; N, 3.1.

Free Enol XXVI from the Hydrolysis of XXV.—Under an atmosphere of nitrogen, to 0.327 g. of the preceding cyanohydrin benzoate was added successively 1 ml. of a saturated aqueous solution of sodium bicarbonate, 2.5 ml. of water, and 2.5 ml. of alcohol. The whole was flushed with nitrogen to remove any oxygen and then allowed to reflux for 10 min. under nitrogen.

The warm yellow solution was not allowed to cool slowly but immediately ice–water and then brine were added and the whole was quickly extracted with ether by shaking energetically. The ethereal extracts were washed with water until neutral and dried over anhydrous sodium sulfate. Removal of the solvent by a stream of nitrogen gave a residue which crystallized from ether. The crystals were quickly filtered, washed with a few drops of isopropyl ether, and dried at 60–80° *in vacuo* yielding 0.161 g. (*ca.* 70%) of yellow crystals melting at 135° and giving a strong reaction with methanolic ferric chloride. Recrystallization from isopropyl ether gave yellow prisms, m.p. 135–137°.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.3; H, 7.0.

The ultraviolet absorption data agree well with the value given by Van Tamelen and his group[2b] who had only a solution of XXVI and did not isolate it: λ_{max} 258 mμ (ϵ 7800), 369–370 (10,500), and inflection at 220 (18,300).

The free enol XXVI is reasonably stable in the dry state but its solutions, especially in the presence of oxygen or in basic media, are rapidly altered.

Desacetamidocolchiceine (I) from XXVI.—Oxidation of XXVI with N-bromosuccinimide according to ref. 2b yielded 40% of crystalline desacetamidocolchiceine, m.p. 166° (prisms from ethanol), identical in every respect with a sample, m.p. 169°, obtained from natural colchicine prepared according to ref. 2b. The spectral data are as follows: ν 3200 (tropolonic OH) and a doublet around 1600 and a strong, broad band around 1550 cm.$^{-1}$, both being characteristic features of the colchicinic motif; λ_{max} 243–244 mμ (ϵ 34,700), 350 (18,600), inflection at *ca.* 233 (30,500).

Cyclization of VI by Sulfuric Acid.—Concentrated sulfuric acid (30 ml.) was poured with stirring into 10 ml. (*ca.* 10 g.) of keto diester VI, cooled at −20°, at such a rate that the internal temperature did not rise above −10° (15 min.). The resulting orange paste was allowed to warm slowly to room temperature and was set aside overnight. The mixture was then poured over ice and extracted with methylene chloride. The organic layer was washed with water, sodium bicarbonate (the washings were kept), and water and dried; the solvent was removed by warming on the water bath leaving a neutral residue (8 g.) which was crystallized from ether; 2.3 g., m.p. 156°. This compound

(XX) is dimorphic and melted first at 130°. Recrystallization from isopropyl ether did not raise the melting point.

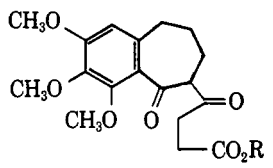
Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.9; H, 6.0.

The ultraviolet and infrared spectra and the chemical properties (*cf.* below) are in agreement with structure XX.

The aqueous bicarbonate washings, made acidic with 2 *N* hydrochloric acid, were extracted with methylene chloride. The organic layer was washed with water, dried, and distilled to dryness. The residue, crystallizing from ether, yielded 0.4 g., m.p. 165°, of the bicyclic diacid corresponding to the saponification of diester XIX. Recrystallization from isopropyl ether raised the melting point to 172°; λ_{max} 222 mμ (ε 19,600) and 271 mμ (ε 9300).

Anal. Calcd. for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33; O, 31.97. Found: C, 61.6; H, 6.3; O, 31.8.

Opening of the Enol Lactone Group of XX.—Opening of the enol lactone of XX can give rise either to the ester XXVII (R = CH_3) or to the corresponding acid XXVII (R = H) according to the amount of sodium hydroxide used in the reaction.



XXVII

A. Ester XXVII (R = CH_3).—To a solution of 1 g. of XX in 50 ml. of methanol containing 2 drops of phenolphthalein was added 3 ml. of 1 *N* sodium hydroxide which caused a change of the color of the indicator. Two more milliliters of 1 *N* sodium hydroxide was added and the stirred solution was kept for 30 min. at room temperature and then made acid with 1 *N* sulfuric acid. Water was added which precipitated crystals of the diketo ester XXVII (R = CH_3) which were filtered and dried; 0.8 g., m.p. 100° (prisms from ether).

Anal. Calcd. for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.7; H, 6.6.

Saponification of the preceding ester with aqueous methanolic potassium hydroxide (reflux for 30 min.) yielded the corresponding acid, m.p. 130°. The latter was obtained directly from the enol lactone as given below.

B. Acid XXVII (R = H).—Enol lactone XX (0.1 g.) was refluxed 0.5 hr. in a solution of methanol (2 ml.), water (0.1 ml.), and concentrated sodium hydroxide (0.1 ml.). After removing the methanol on the steam bath, the residue was diluted with water and extracted with methylene chloride. The alkaline aqueous layer, acidified with 7 *N* sulfuric acid, was extracted with ethyl acetate; the organic layer was washed with water, dried, and evaporated to dryness. The crystalline residue (needles) weighed 74 mg.; m.p. 130°; inflection at 240 mμ (ε 5900) and λ_{max} 319 mμ (ε 16,300). Titration of the acid with 0.1 *N* NaOH gave the theoretical value.

Anal. Calcd. for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33. Found: C, 61.6; H, 6.4.

Acknowledgment.—The authors gratefully acknowledge the encouragement given to them during this work by Professor L. Velluz, Director of Research at Roussel-Uclaf, to whom thanks are due for authorizing this publication.

Synthesis of Dehydrootobain*

DEREK BROWN AND ROBERT STEVENSON

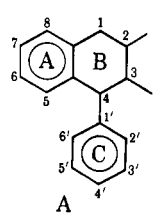
Department of Chemistry, Brandeis University, Waltham, Massachusetts

Received October 30, 1964

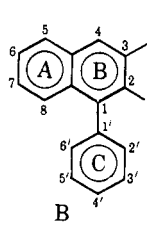
2,3-Dimethyl-7,8-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)naphthalene (**5**) has been synthesized from piperonal and is identical with dehydrootobain, a product obtained from the lignan otobain (**1**) by dehydrogenation with palladium–carbon. Dicyclohexylcarbodiimide is shown to be a useful reagent for conversion of phenylpropiolic acids to 1-phenylnaphthalene derivatives.

A natural product, first isolated in 1854 by Uricoechea[1] from the fruit of *Myristica otoba* and shown to have an empirical formula $C_{20}H_{20}O_4$ by Baughman and co-workers,[2] has since been characterized as a lignan and named otobain.[3] The constitution 5,6-methylenedioxy-2,3-dimethyl-4-(3′,4′-methylenedioxyphenyl)-1,-2,3,4-tetrahydronaphthalene (**1**) was proposed for otobain independently by two groups.[4,5] The proposed structure was based largely on interpretation of nuclear magnetic resonance spectra of otobain and derivatives, and the observation that the dehydrogenation product dehydrootobain, $C_{20}H_{16}O_4$, differed from the isomeric dehydroepigalbacin to which the structure 2,3-dimethyl-6,7-methylenedioxy-1-(3′,4′-methylenedioxyphenyl)naphthalene (**2**) had been assigned.[6] Dehydroepigalbacin (**2**) had been obtained both by acid isomerization of galbacin (**3**) followed by dehydrogenation,[4,7] and by oxidative cyclization[5] of dipiperonylidene succinic anhydride (**4**). Within the lignan class of natural products[8] of which about 60 members are known to date, the oxygenation pattern in ring A of otobain was considered sufficiently unusual to merit substantiation by a synthesis of dehydrootobain (**5**).

An attractive method for the preparation of 1-phenylnaphthalenes, particularly those where functional groups are required at C-2 and C-3, consists of treating suitably substituted phenylpropiolic acids with acetic anhydride. This reaction was first observed by



A



B

* Submitted in honor of Professor Louis F. Fieser by R. S. (Research Fellow, Harvard University, 1953).

(1) E. Uricoechea, *Ann.*, **91**, 369 (1854).

(2) W. F. Baughman, G. S. Jamieson, and D. H. Brauns, *J. Am. Chem. Soc.*, **43**, 199 (1921).

(3) R. Stevenson, *Chem. Ind.* (London), 270 (1962).

(4) N. S. Bhacca and R. Stevenson, *J. Org. Chem.*, **28**, 1638 (1963).

(5) T. Gilchrist, R. Hodges, and A. L. Porte, *J. Chem. Soc.*, 1780 (1962).

(6) The systematic name given to otobain, a phenyltetralin, is in accordance with lignan nomenclature in which the carbon atom bearing the C-ring phenyl group is regarded as C-4 [*i.e.*, as in A]. The lignan dehydrogenation products and synthetic phenylnaphthalenes herein described are named as 1-phenylnaphthalenes [*i.e.*, as in B].

(7) G. K. Hughes and E. Ritchie, *Australian J. Chem.*, **7**, 104 (1956).

(8) General reviews of lignans include (a) H. M. Hearon and W. S. MacGregor, *Chem. Rev.*, **55**, 957 (1955); (b) K. Freudenberg and K. Weinges, *Tetrahedron*, **15**, 115 (1961); (c) M. S. Adjangba, *Bull. soc. chim. France*, 2344 (1963).