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Characterization of Two Substances Isolated from an Indian Shrub

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Two high melting compounds isolated from the root bark of an Indian shrub, provisionally designated compounds A and B, are tentatively assigned the formulas $C_{30}H_{48}O_3$ (A) and $C_{30}H_{46}O_3$ (B). Compound B has been characterized as a 1,3-diketone having a methylene group between the two carbonyl functions; one of the carbonyl groups is hindered and the other is reactive. The third oxygen atom appears to be present as an oxide bridge in a pentacarbocyclic system. Compound A is also a 1,3-diketone; the third oxygen atom seems to be present as an isolated keto group.

Two plant principles that in this paper will be designated compounds A and B have been isolated from the phellem (root bark) of the large straggling shrub *Salacia prinoides* (DeCondolle), *Celastraceae* (*Hippocrateaceae*). The shrub is widely distributed in India; it is found in Silhet, the Khasia mountains, and the East-West Peninsula, particularly along the Western Ghats in the Kanara districts. Locally it is used as a tonic and blood purifier. Extraction with petroleum ether affords a mixture of compounds A and B that is readily separated by processing with acetone, in which A is readily soluble and B is practically insoluble.

The substances are colorless, crystalline solids of relatively high and not well defined melting points. The extended melting range apparently is due to polymorphism. Though no definite transformation could be observed in the melting of compound A, the substance appeared in differently shaped crystals on recrystallization. Furthermore all the derivatives of the two compounds showed similar tendency to polymorphism.

Most of the experiments were performed with the weakly levorotatory compound B. The material appeared homogeneous by the criterion of chromatography, since no differentiation was observed in the infrared spectra of the fractions. The analytical results agree slightly better with the formula $C_{30}H_{46}O_3$ than with the formula $C_{29}H_{44}O_3$, and the higher-carbon composition is supported by analyses of dibromo-B, which is readily formed by the action of two moles of bromine in chloroform–acetic acid. The homologous formulations differ in carbon content by 0.6% and the analyses indicate the formula $C_{30}H_{44}O_3Br_2$. B gives no color in the Liebermann–Burchard test, with ferric chloride or with tetranitromethane. Evidence cited below characterizes two of the three oxygen atoms as ketonic. The infrared spectrum (Fig. 1B) contains no hydroxyl band, and a negative alkoxyl determination indicated the absence of an alkoxyl group. Thus the analytical results suggest a saturated hexacyclic structure with oxygen as a hetero atom in one of the six rings.

The most characteristic features of the infrared spectrum (Fig. 1, No. 1B) are the carbonyl bands at 5.79 and 5.87 μ and the large band system centered around 9.10 μ, probably associated with the cyclic oxide structure. In neutral alcoholic solution B shows an absorption maximum of 261 mμ (*E* 4700), and addition of alkali causes a bathochromic shift to 290 mμ with accompanying increase in intensity (*E* 19,900); acidification reverses the change. Further evidence of the presence of an acidic function is that B dissolves in warm alcoholic alkali and is reprecipitated on acidification. Moreover, B reacts with diazomethane to give two isomeric methylated derivatives, m.p. 358 and 275°, exhibiting characteristic maxima at 6.05, 6.18 μ and 6.06, 6.21 μ, respectively (Fig. 1, Nos. 2, 3). The disappearance of the two bands in the 5.8–5.9 μ region coupled with the appearance of a band at 6.05–6.06 μ points to the conversion of a diketone system to a conjugated carbonyl system; the strong band at 6.18–6.21 μ is attributable to the stretching of the olefinic link of the system, and its high intensity indicates the presence of an alkoxyl substituent.[2] The lower melting derivative showed maximal ultraviolet absorption at 256.5 mμ (13,250).

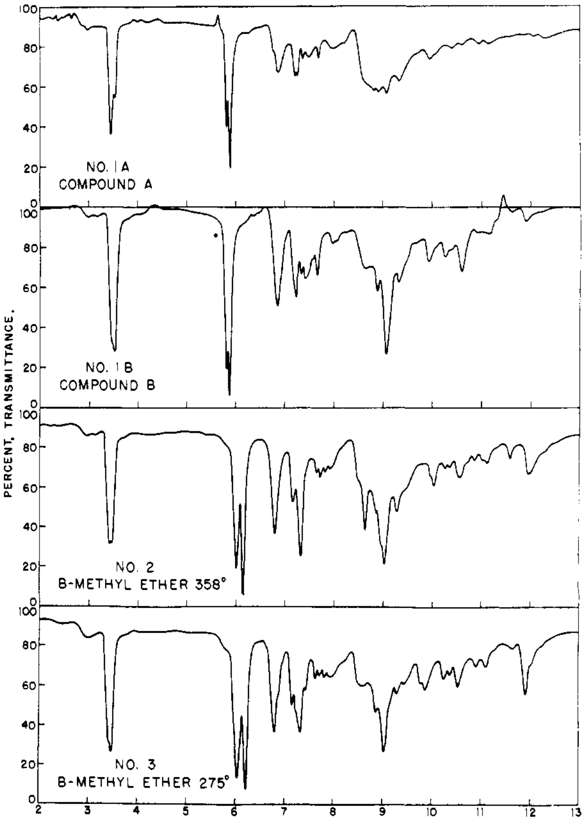

Fig. 1.—Infrared spectra (in chloroform).

The observations cited are compatible with an unsymmetrically substituted 1,3-diketone system

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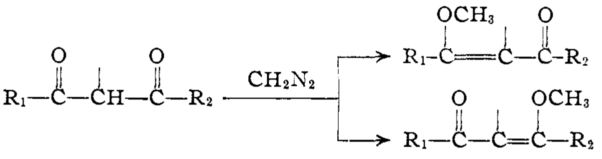
[1] Ciba Pharmaceutical Products, Inc., Summit, N. J.

[2] *Cf.* H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953).



$$R_1-\overset{O}{\overset{\|}{C}}-\overset{|}{C}H-\overset{O}{\overset{\|}{C}}-R_2 \xrightarrow{CH_2N_2} \begin{cases} R_1-\overset{OCH_3}{\overset{|}{C}}=\overset{|}{C}-\overset{O}{\overset{\|}{C}}-R_2 \\ R_1-\overset{O}{\overset{\|}{C}}-\overset{|}{C}=\overset{OCH_3}{\overset{|}{C}}-R_2 \end{cases}$$

The structure postulated is supported further by spectral comparison with dimedon (5,5-dimethylcyclohexane-1,3-dione), which as the free diketone possesses absorption bands at 5.75 and 5.83 μ (a broad band with a shoulder at 6.08 μ may be due to partial enolization). Absorption characteristics found for dimedon methyl ether (Fig. 2, Nos. 4, 5) are: λ^{Chf} 6.06, 6.18 μ, λ^{EtOH} 250.5 mμ (19,900). Comparison of the ultraviolet absorption with that of B-methyl ether (256.5 mμ) does not reveal whether or not the latter substance carries an alkyl substituent on the central carbon atom. Attempts to settle the point by preparation of a benzylidene or isonitroso derivative failed. A dicarboxylic acid resulting from hypochlorite oxidation of B will be described below; here it is significant to state that careful examination of the oxidation mixture failed to disclose the presence of a volatile acid such as would be expected if the central carbon had an alkyl substituent.

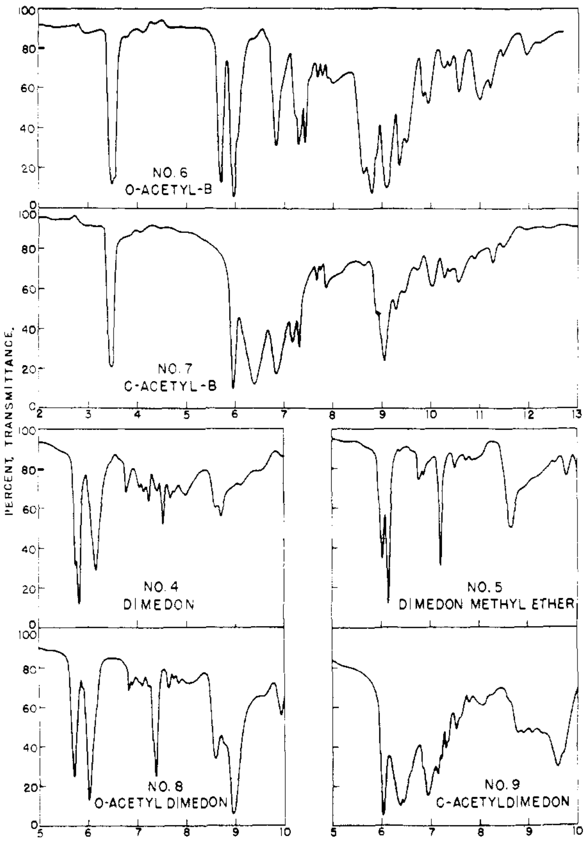


Fig. 2.—Infrared spectra (in chloroform).

Further evidence was obtained from acetylation experiments. With pyridine and acetic anhydride in the cold, B yields preponderantly an O-acetyl derivative, so characterized by ready saponification to B and by an infrared spectrum (Fig. 2, No. 6), with bands at 5.69 and 5.95 μ, comparable to that of O-acetyl dimedon (Fig. 2, No. 8): with both enol acetates the band at 8.0 μ characteristic of ordinary acetates is absent and a new band appears at 8.8–9 μ. Acetylation of B in the presence of pyridine and acetic acid at steam-bath temperature affords an isomer that must be a C-acetyl derivative, since it is non-saponifiable, resistant to acid hydrolysis and contains an acidic function, as demonstrated by reversible spectral changes on successive addition of base and acid. The infrared spectrum (Fig. 2, No. 7) shows characteristic bands at 5.97 and 6.4 μ and parallels that of C-acetyl dimedon (Fig. 2, No. 9). The acidity of C-acetyl-B leaves no doubt that the central carbon atom of the 1,3-diketone system of B carries no alkyl substituent.

The dicarboxylic acid resulting from oxidation of B when melted or when warmed with acetic anhydride formed an anhydride that appears, from the infrared absorption bands at 5.55 and 5.67 μ, to be a glutaric rather than a succinic anhydride. Alkaline hydrolysis and careful acidification gave the free acid, which reacted with diazomethane to give the dimethyl ester. Saponification of this dimethyl nor-B-dicarboxylate removed only one ester group and gave a monoester, m.p. 264°. An isomeric monomethyl ester, m.p. 290°, resulted from treatment of the anhydride with methanol–sulfuric acid or with 0.1 *N* alkali in 90% methanol; diazomethane converts this monoester to the diester described above. These observations show that one of the two carboxyl groups is strongly hindered, and most of the reactions of compound B bear evidence that one of the keto groups is subject to considerable steric hindrance. Esterification with diazomethane is not subject to much steric impediment, and this reaction gives products involving both carbonyl groups. However, only one of the two possible O-acetyl derivatives appears to be formed, and B reacted with only one molecule of 2,4-dinitrophenylhydrazine and formed a monoöxime. The reaction with ethanedithiol was not smooth but the sole product, isolated after extensive purification, proved to be a monoethylenethioketal.

Attempts to reduce B with sodium borohydride or lithium aluminum hydride were unsuccessful; apparently the salt formed from enol-B and the reagent was too insoluble or unusually resistant to reduction. With platinum in acetic acid B readily consumed one equivalent of hydrogen but the product was a complex mixture. However, O-acetyl-B reacts smoothly in ethyl acetate over platinum with uptake of two equivalents of hydrogen and formation of a saturated monoketone, desoxo-B; presumably the less hindered carbonyl group of B has been eliminated. When the monoketone was subjected to drastic Wolff–Kishner reduction the sole product was not the expected deoxygenated compound but an alcohol, dihydrodesoxo-B, which was acylable, although with some difficulty.

Preliminary data suggest for compound A (Fig. 1, 1A) the formula $C_{30}H_{48}O_3$. The three oxygen atoms are all ketonic; two of them constitute a 1,3-diketone system as in B, and the third one is located at an isolated position since on treatment with diazomethane it gives two isomeric enol methyl ethers which still possess a pronounced band at 5.85 μ ascribable to the isolated carbonyl function. The composition tentatively ascribed to A implies that this substance possesses one carbocyclic ring less than B, but we do not consider the analytical evidence sufficiently secure to attach great weight to this conclusion. Further details about oxime and 2,4-dinitrophenylhydrazine derivatives of A are recorded in the Experimental section.

Experimental[3]

Isolation of Compounds A and B.—Air-dried scrapings of the root bark described in the introduction were extracted exhaustively with petroleum ether (b.p. 45–65°) at room temperature. The solvent was removed at reduced pressure and the residue dissolved in the minimum amount of boiling chloroform. Addition to the solution of excess ligroin (b.p. 80–90°) precipitated a mixture of compounds A and B as a brittle cake; the mixture was let stand for 30 min. to allow resinous products and pigments to dissolve and then the precipitate was collected. Two or three repetitions of the precipitation from chloroform solution gave a microcrystalline mixture of compounds A and B. The two components were then separated by treatment with acetone, in which A is highly soluble and B practically insoluble. The mixture was extracted repeatedly with small quantities of hot acetone until the residue (compound B) gave a negative Liebermann–Burchard color test. The acetone extract was allowed to stand for an hour at room temperature, when the small amount of B that had been extracted separated in rectangular crystals. The acetone mother liquor was then concentrated and treated with ligroin to precipitate compound A, which was purified further by repeated crystallization from benzene–ligroin. Compound B was purified by crystallization from chloroform–ligroin and then from benzene–ligroin.

The combined yield of compound A and B ranged 0.48 to 0.54; the higher yields were obtained from material collected in October, November and December. The average ratio of A:B is 2:3.

Characterization of Compound A.—The substance as received from Col. Bhatnagar was recrystallized from benzene–ligroin, from chloroform solution by addition of methanol, or from ethanol (by preparation of a hot saturated solution in a sealed tube at 100°). The compound forms shiny, colorless needles, plates or prisms.

The melting behavior of A is not very characteristic; on the microscope hot-stage, the needles begin to "sweat" near 240°, soften from 255–270°; sometimes all of the material is melted at 270°, and at other times the last crystals do not disappear until 280°. The melt is slightly discolored. No doubt the large melting range is due to allotropism, evidence for which is also seen in the crystallization behavior of the compound.

The compound gives a positive Liebermann–Burchard test; no color is given with tetranitromethane, and a ferric chloride test in aqueous ethanol solution was negative.

The compound is soluble in alcoholic alkali, particularly in the heat, and is regenerated from such solutions by acid. No reaction takes place with alkali under conditions as drastic as those of the Huang-Minlon Wolff–Kishner reduction: λ^{Chf} 5.77, 5.84, 6.9, 7.20, 7.25, 7.35, 7.50, 7.70, 8.00, 8.6–9.1 (broad) 9.35, 9.95; λ^{Alc} 261 mμ 4700); λ in 0.01 *N* NaOH in 70% alcohol 289–290 mμ (19,900). Upon acidification of the neutral solution the absorption maximum underwent no shift: α_D +6.6° (*c* 3.3, Chf).

Anal. Calcd. for $C_{30}H_{48}O_3$ (456.68): C, 78.89; H, 10.59. Found: C, 78.78, 78.89; H, 10.24, 10.36.

Monoxime of A.—A solution of hydroxylamine was prepared by dissolving 1 g. of sodium acetate and 0.5 g. of hydroxylamine hydrochloride in 1 ml. of water and adding absolute ethanol to a total volume of 10 ml. The solution was filtered from sodium chloride and 1 ml. was added to 53 mg. of A in a small test-tube, which was subsequently sealed. On brief warming on the steam-bath the solid dissolved and crystals began to appear after 2 minutes; 41 mg. of colorless leaflets was collected. The solid may be recrystallized from a large volume of ethanol which require concentration until crystals appear, or from acetic acid the solid melts at 290–295° dec., λ^{Chf} 2.77, 3.00 (broad), 5.82, 6.03 (weak) μ.

Anal. Calcd. for $C_{30}H_{49}O_3N$: C, 76.38; H, 10.47; N, 2.97. Found: C, 76.28; H, 10.28; N, 3.40.

2,4-Dinitrophenylhydrazone of A.—The material prepared at the Caius laboratory was recrystallized from benzene, which yielded flat, yellow needles, m.p. 280–285° dec. The analytical data agree best with the assumption that one molecule of benzene of crystallization is present: λ^{Chf} 3.03, 5.79, 6.14, 6.24 μ; λ^{Alc} 265 mμ (13,000), 355 mμ (15,200).

Anal. Calcd. for $C_{42}H_{58}O_6N_4$ (714.92): C, 70.56; H, 8.18; N, 7.84. Found: C, 70.68; H, 8.32; N, 9.04.

Isomeric Monomethyl Ethers of A.—To a suspension of 36 mg. of A in a small amount of ether–methanol was added excess ethereal diazomethane. Gas was evolved, the solid dissolved and soon a product began to separate. The unused diazomethane was destroyed with a drop of acetic acid and the solvent was evaporated. The residue was collected and rinsed with ether; it amounted to 22 mg., m.p. 250–310°. The solid was recrystallized twice by dissolution in chloroform and precipitation with hot methanol. Lozenge-shaped plates resulted that changed to rectangular crystals at 280°, which melted at 315–317°.

The ether washings and mother liquors were combined and chromatographed on acid-washed alumina. The fractions eluted by 100% benzene were combined and recrystallized three times from alcohol, yielding needles, m.p. 223–229°, α_D +2.6° (*c* 1.56, Chf). *315°-Isomer:* λ^{Alc} 253 mμ (14,200); λ^{Chf} 5.85, 6.06, 6.18, 6.80, 7.20, 7.35 (strong), 7.75, 8.65, 9.00, 9.25, 10.10, 11.10, 11.80, 11.95 μ.

Anal. Calcd. for $C_{31}H_{50}O_3$ (470.71): C, 79.10; H, 10.71; CH_3O, 6.58. Found: C, 79.09; H, 10.53; CH_3O, 6.50.

223°-Isomer: λ^{Chf} 5.85, 6.06, 6.23, 6.80, 7.18, 7.27 μ.

Anal. Calcd. for $C_{31}H_{50}O_3$ (470.71): C, 79.10; H, 10.71. Found: C, 78.75; H, 10.38.

Dimedon methyl ether was prepared with diazomethane for comparison purposes, λ^{Alc} 250–251 mμ (19,900); λ^{Chf} 6.06, 6.18, 6.78, 6.85, 7.22 μ. Dimedon itself exhibited λ^{Chf} 5.75, 5.83, 6.18–6.19 μ.

Characterization of Compound B.—The material is best recrystallized by precipitation with methanol from chloroform solution; it appears in the form of flat needles. The samples supplied from Caius laboratory often contained such needles admixed with heavier prismatic crystals. The needles change to rectangular plates at 270°, which melt at 290–295°. The compound gives no color in the Liebermann–Burchard test, nor with ferric chloride in aqueous alcoholic solution, nor with tetranitromethane. The compound is soluble in alcoholic alkali, particularly in the heat, and is regenerated from such solutions by acid, λ^{Alc} 260–261 mμ (5300); λ in 0.01 *N* NaOH in 70% aqueous alcohol, 289 mμ (24,700). The maximum returns to 260 mμ upon acidification of the solution, λ^{Chf} 5.79, 5.87, 6.85, 7.21, 7.32, 7.40, 7.65, 8.00 (weak), 8.90, 9.08, 9.35, 9.90, 10.25, 10.60 μ; α_D −0.5° (*c* 3.4, Chf).

Anal. Calcd. for $C_{30}H_{46}O_3$ (454.67): C, 79.24; H, 10.20. Found: C, 78.93, 79.20; H, 10.06, 10.43.

An alkoxyl determination failed to give evidence of the presence of such a grouping.

Monoxime of B.—A hydroxylamine solution resulting from the mixture of 690 mg. of hydroxylamine hydrochloride, 820 mg. of sodium acetate, 2 ml. of water and alcohol to a volume of 50 ml. was decanted from the sodium chloride, and 2 ml. was added to 33 mg. of B. Alcohol (3 ml.) was added and the mixture was boiled for 2 hr. Water was added to permanent turbidity and on cooling 25 mg. of the oxime separated; dilution of the filtrate furnished another 6 mg. The oximation proceeds also within 10 minutes in a sealed tube on the steam-bath. The product was recrystallized from benzene and forms needles that begin to sublime at 260° and melt at 276–284° dec. When recrystallized from chloroform–methanol, the oxime retains one-half molecule of methanol of crystallization, which is recognized analytically and by a strong absorption at 9.83 μ, associated with methyl alcohol.

Anal. Calcd. for $C_{30}H_{47}O_3N$ (469.68): C, 76.71; H, 10.09. Found: C, 76.76; H, 10.24. Calcd. for $C_{30}H_{47}O_3N\cdot{}^1/_2CH_3OH$ (485.71): C, 75.42; H, 10.17; N, 2.88;

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[3] Unless otherwise indicated, melting points were determined on a microscope hot-stage and are uncorrected. Microanalyses were performed in the laboratory of Mr. S. M. Nagy at the Massachusetts Institute of Technology.

CH_3O, 3.2. Found: C, 75.56; H, 10.40; N, 2.92; CH_3O, 3.59.

The same monoxime results when the O-acetate of B is treated with hydroxylamine.

2,4-Dinitrophenylhydrazone of B.—To the solution of 57 mg. of B and 50 mg. of 2,4-dinitrophenylhydrazine in 0.75 ml. of benzene was added 1.25 ml. of 2.8% alcoholic hydrochloric acid (2.8 ml. of concd. acid to 100 ml. of abs. ethanol). The mixture was warmed, finally for 5 minutes on the steam-bath in a sealed vessel, and the resulting yellow solid (80 mg.) was collected and washed with methanol. The product was dissolved in benzene, passed over a column of alumina and recovered by concentration; 42 mg. of bright yellow needles resulted, m.p. 322–324° dec.

A sample was recrystallized from chloroform–methanol and dried at 80°, 0.5 mm., for 20 hr.; it appeared to be solvent free; λ^{Chf} 3.05, 5.85, 6.17, 6.25, 6.65, 7.00, 7.25, 7.35, 7.50, 7.60, 7.87, 8.90, 9.10, 9.60, 9.65, 10.2, 10.63, 10.90, 12.00 μ.

Anal. Calcd. for $C_{36}H_{50}O_6N_4$ (634.79): C, 68.11, H, 7.94; N, 8.83. Found: C, 67.46; H, 7.69; N, 9.41.

Bromination of B.—A sample of B (58 mg.) was dissolved in the minimum amount of chloroform and cooled in ice. Now 0.43 cc. of 0.603 *M* bromine in acetic acid was added. The color was discharged rapidly and after the mixture had stood in the dark for three minutes crystals had separated. The pale yellow supernatant was diluted with methanol and 58 mg. of product was collected. It was recrystallized by solution in chloroform followed by reprecipitation with methanol. The material forms feathery needles or small cubes that become discolored and decompose between 220–250°. The carbonyl bands are displaced toward shorter wave lengths, λ^{Chf} 5.74, 5.79. (The last pair of C/H analyses and the second Br determination were carried out with a separate sample.)

Anal. Calcd. for $C_{30}H_{44}O_3Br_2$ (612.49): C, 58.82; H, 7.24; Br, 26.10. Found: C, 58.90, 58.93, 58.94; H, 7.11, 7.22, 7.45; Br, 26.49, 26.33.

Acetylation of B. (a) C-Acetate.—A solution of 39 mg. of B in 1 ml. of acetic acid, 0.5 ml. of pyridine and 0.5 ml. of acetic anhydride was warmed for one hour on the steam-bath. On cooling, 22 mg. of the C-acetate separated. Dilution of the mother liquor yielded 15 mg. of solid whose infrared spectrum disclosed the presence of unchanged B; by reacetylation for 2 hours on the steam-bath 13 mg. consisting largely of the C-acetate was obtained. The product is recrystallized by addition of methanol to a chloroform solution; it forms needles, m.p. 271–273°. No color was produced when ferric chloride was added to a solution of the C-acetate in aqueous alcohol or aqueous dioxane. The compound is soluble in alcoholic alkali and is regenerated unchanged by acidification. Heating on the steam-bath with 1 ml. of acetic acid containing 0.1 ml. of concentrated hydrochloric acid for 10 minutes led to recovery without change.

The infrared spectrum contains a carbonyl band at 5.97 μ and a strong broad band at 6.4 μ associated with the 1,3,3′-triketone system as demonstrated by inspection of the spectrum of C-acetyl dimedon. The ultraviolet spectrum exhibits maxima at 235 and 280 mμ in neutral medium, and a single, strong maximum at 274 mμ in basic medium. On acidification of the alkaline solution the original spectrum reappears. Similar effects are observed with C-acetyl dimedon; α_D −3.6° (*c* 3.28, Chf); λ^{Chf} 5.97, 6.40, 6.82, 7.15, 7.30, 7.65, 7.85, 8.90, 9.05, 9.30, 9.45, 9.73, 10.05, 10.28, 10.70, 10.90, 11.25 μ; λ^{Alc} 235 mμ (9660); 280 mμ (10,990); λ^{Alc} (in alkaline medium) 274 mμ (22,300).

Anal. Calcd. for $C_{32}H_{48}O_4$ (496.70): C, 77.37; H, 9.74. Found: C, 77.41; H, 9.77.

In an attempted acetyl determination using *p*-toluenesulfonic acid as the catalyst for the hydrolysis, no volatile acid was produced.

Data on C-acetyl dimedon: λ^{Chf} 6.03, 6.40 μ; λ^{Alc} 234 mμ (10,820), 274 mμ (11,190); λ^{Alc} (in alkaline medium) 266 mμ (26,900).

(b) O-Acetate.—Compound B (30 mg.) was dissolved in 0.7 ml. of warm pyridine, and the solution was cooled in ice. Before crystallization occurred, 0.6 ml. of acetic anhydride was added and the solution was kept at 0–4° for 20 hr. Long needles (23 mg.) had separated which were collected. The material in the mother liquor (9 mg.) consisted, on the basis of its infrared absorption, of unchanged B and of the C-acetate described above. The main crop was recrystallized from ethanol and from chloroform–methanol; the compound forms needles, m.p. 275–278°.

The compound gives no color with ferric chloride in aqueous alcoholic solution. Brief treatment with base regenerates the original B. Micro-acetyl determinations using *p*-toluenesulfonic acid as a catalyst yielded unsatisfactory results, indicating resistance to acid hydrolysis.

The spectrum exhibits bands at 5.69 and 5.95 μ characteristic of the β-keto enol acetate system, and analogous to the behavior of O-acetyl dimedon. In both substances a marked enhancement of the 7.3 μ band associated with the C-methyl group is seen. There is no band in the usual position of ester absorption near 8 μ. In the ultraviolet the O-acetate absorbs at 237 mμ; upon addition of a little base the spectrum changes to that of the anion of B itself, and such a solution upon acidification exhibits the spectrum of B; λ^{Chf} 5.69, 5.95, 6.82, 7.30, 7.42, 7.70, 7.78, 7.90, 8.00, 8.60, 8.80, 9.10, 9.35, 9.50, 9.85, 9.95, 10.25, 10.40, 10.60, 11.00, 11.20, 11.46, 11.95 μ; λ^{Alc} 237 mμ (9090), λ^{Alc} (alkaline) 289 mμ (19,800).

Anal. Calcd. for $C_{32}H_{48}O_4$ (496.70): C, 77.37; H, 9.74; CH_3CO, 8.46. Found: C, 77.20; H, 9.80; CH_3CO, 5.40, 3.58, 5.22.

Data on O-acetyl dimedon: λ^{Chf} 5.70, 6.01, 7.28 μ.

Enol Ethers of B.—A suspension of 22 mg. of B in methanol was treated with ethereal diazomethane. Gas was evolved and the solid was brought into homogeneous solution by addition of chloroform. The excess reagent was destroyed with acetic acid and the solvents were removed. The residual solid (23 mg.) was recrystallized twice from chloroform–methanol, yielding 8 mg. of leaflets that change to square plates at 260° (marked sublimation), which melt at 358°.

The mother liquors were concentrated and by recrystallization from methanol–chloroform yielded 7 mg. of needles, m.p. 271–275°.

358°-Ether: λ^{Chf} 6.05, 6.18, 6.80, 7.15, 7.30, 7.65, 7.72, 7.83, 8.65, 9.05, 9.30, 10.05, 10.55, 11.6, 11.95 μ.

Anal. Calcd. for $C_{31}H_{48}O_3$ (468.69): C, 79.44; H, 10.32. Found: C, 79.28; H, 10.48.

275°-Ether: λ^{Chf} 6.06, 6.21, 6.80, 7.15, 7.30, 7.45, 7.65, 7.70, 7.82, 8.85, 9.05, 9.30, 9.90, 10.25, 10.38, 10.55, 10.90, 11.10, 11.95 μ; λ^{Alc} 256.5 mμ (13,250).

Anal. Calcd. for $C_{31}H_{48}O_3$ (468.69): C, 79.44; H, 10.32. Found: C, 78.87; H, 10.30.

Monoethylenethioketal of B.—A sample of B (63 mg.) was mixed with 0.2 ml. of ethanedithiol and 0.3 ml. of boron fluoride etherate. The mixture was allowed to react at room temperature for 19 hr., cooled in ice and diluted with methanol. The white solid that separated was collected, washed with methanol and reprecipitated from chloroform with methanol, yielding 22 mg. of crude crystalline product. After two recrystallizations from benzene 9 mg. of long rectangular needles resulted, subliming markedly near 300° and melting 324–329°. The combined mother liquors were recognized by their infrared absorption to contain a bad mixture of starting material, ethers and unknown bodies, and no attempt at separation was made. In one experiment, when one-half hour was allowed for reaction, the starting material was recovered unchanged: λ^{Chf} 5.84, 6.80, 7.20, 7.30, 7.40, 7.55, 7.68, 7.80, 8.72, 8.85, 9.07, 9.25, 9.90, 10.35, 10.60, 11.10, 11.45, 11.65 μ. (Note the complete disappearance of the band at 5.78 μ.)

Anal. Calcd. for $C_{32}H_{50}O_2S_2$ (530.72): C, 72.41; H, 9.50. Found: C, 72.47; H, 9.61.

Desoxo-B.—A solution of 192 mg. of the O-acetate of B in 175 ml. of ethyl acetate was shaken with hydrogen and platinum resulting from the separate reduction of 52 mg. of Adams catalyst. After 13 min., 2.04 molecular equivalents of hydrogen had been consumed and no further uptake was observable. The solid was recovered by evaporation and recrystallized from chloroform–methanol and from ethanol, yielding 163 mg. of pure product in two crops of needles. The crystals change to lozenge-shaped plates near 270°, melt partially at 288–290° and resolidify to bundles of spears that sublime markedly at 315° and melt 320–322°. For one experiment a further change was noted to hexagons, m.p. 337°: λ^{Chf} 5.86, 6.82, 7.23, 7.35, 7.48, 7.70, 7.78, 8.00, 8.53, 8.65, 8.90, 9.10, 9.30, 9.95, 10.22, 10.30, 10.40, 10.60, 10.90, 11.05, 11.55, 11.95 μ.

Anal. Calcd. for $C_{30}H_{48}O_2$ (440.68): C, 81.76; H, 10.98. Found: C, 81.38; H, 10.95.

The material is resistant to sodium dichromate in acetic acid at 100°, and to boiling methanolic alkali.

Dihydro-desoxo-B.—Whereas desoxo-B is recovered essentially unchanged from the Huang-Minlon modification of the Kishner–Wolff reduction, treatment of 148 mg. with 1 g. of sodium in 12 ml. of ethanol and 1.25 ml. of hydrazine ("free base, 94%") for 16 hr. at 217–240° led to the isolation of a carbonyl-free *hydroxy compound.* The crude solid obtained by dilution of the contents of the bomb tube was recrystallized, yielding 112 mg. of needles (from chloroform–methanol, and from ethanol) that undergo a transformation below 260° and melt 288–290°, λ^{Chf} 2.80 (sharp), 2.95 (broad), 6.80, 7.22, 7.35, 7.70, 7.75, 7.85, 8.80 8.93, 9.12, 9.50, 10.00, 10.30, 10.60, 10.90, 11.05, 11.18, 11.45 μ.

Anal. Calcd. for $C_{30}H_{50}O_2$ (442.70): C, 81.39; H, 11.38. Found: C, 81.70; H, 11.52.

Dihydrodesoxo-B Acetate.—Acetylation of 56 mg. of dihydrodesoxo-B with 1.0 ml. of pyridine and 0.5 ml. of acetic anhydride for 7 minutes on the steam-bath led to only partial acetylation, but repetition of this treatment for 4 hours yielded 56 mg. of hydroxyl-free material that was recrystallized from absolute ethanol, yielding silky needles that begin to sublime near 236° and melt 241–242°, α_D −21.6° (*c* 2.03 Chf); λ^{Chf} 5.82, 6.83, 7.25, 7.35, 7.55, 7.70, 8.0 (broad), 8.65, 8.90, 9.12, 9.80, 10.10, 10.35, 10.60, 10.90, 11.35 μ.

Nor-B-dicarboxylic Acid and Anhydride.—A mixture of 528 mg. of B, 30 ml. of purified dioxane, 15 ml. of 0.1 *N* NaOH and 30 ml. of 0.618 *N* sodium hypochlorite solution was warmed to 64° (reflux temperature of methanol) for 1.5 hr. The solution was diluted with 100 ml. of distilled water and treated with ferrous sulfate solution until the potassium iodide–starch test became negative. The small quantity of ferric hydroxide formed was filtered and the filtrate acidified with phosphoric acid.

The precipitated organic acid was collected. The filtrate (240 ml.) was subjected to steam distillation in an apparatus with dephlegmator, the volume being maintained constant. Fifty-ml. portions of distillate were collected and examined acidimetrically for volatile acid. The results of these titrations were compared with those obtained in a blank run and it was found (a) that 0.04 ml. of acetic acid could be detected with certainty by the technique employed and (b) no volatile acid was formed in the oxidation of B.

The crude **diacid** on recrystallization from aqueous acetone gave 315 mg. of fine needles that change at 240–260° and melt 310–325° with decomposition. From the mother liquor 153 mg. of acid was isolated, which, by warming with 0.5 ml. of acetic acid and 1.0 ml. of acetic anhydride for 5 minutes, gave 96 mg. of the **anhydride**, which on recrystallization from benzene–petroleum ether gives needles and plates that at 290° change to hexagonal prisms of characteristic shape, melting 320–324°; λ^{Chf} 5.55, 5.67, 6.82, 7.20, 7.30, 7.65, 7.95, 9.00, 9.30, 9.45, 9.70, 9.90, 10.21, 10.55, 11.50 μ.

Anal. Calcd. for $C_{29}H_{44}O_4$ (456.64): C, 76.27; H, 9.71. Found: C, 76.32, 76.20; H, 9.64, 9.60.

Dimethyl Nor-B-dicarboxylate.—This ester is obtained by treatment of the C_{29}-acid with ethereal diazomethane and recrystallization from ethanol and from chloroform–methanol. The compound forms lozenge-shaped plates, m.p. 176.8–178.8° (cor.); λ^{Chf} 5.79, 6.80, 6.92, 7.20, 7.40, 7.65, 7.95, 8.70, 8.86, 9.10, 10.25, 10.60 μ.

Anal. Calcd. for $C_{31}H_{50}O_5$ (502.71): C, 74.06; H, 10.03; CH_3O, 12.36. Found: C, 73.68, 73.83; H, 10.12, 10.13; CH_3O, 12.25.

Unhindered Monomethyl Ester of Nor-B-dicarboxylic Acid.—A sample of crude nor-B-dicarboxylic acid (72 mg.) was treated with 1 ml. of methanol containing 0.05 ml. of concentrated sulfuric acid in a sealed tube for 8 hr. at 80°. A first crop of 45 mg. of needles was collected, and a second crop of 24 mg. Recrystallization from chloroform–methanol and from ethanol (under pressure) yielded well-formed needles, decomposing at 288–290° with gas evolution; the melt partially resolidifies and remelts near the m.p. of the anhydride. Treatment with diazomethane yields the diester, m.p. 178–179°, not depressed by admixture of authentic material. The monoester also results when the anhydride is boiled with 0.1 *N* sodium hydroxide in 90% methanol; the product was identified by its behavior on melting, by its spectrum and by conversion to the diester, m.p. 179°; λ^{Chf} 2.9–3.2 (broad shoulder), 5.82, 5.87, 6.85, 7.25, 7.35, 7.45, 7.50, 7.95, 8.70, 8.90, 9.10, 9.30, 10.0, 10.30, 10.60 μ.

Anal. Calcd. for $C_{30}H_{48}O_5$ (488.68): C, 73.73; H, 9.90; CH_3O, 6.35. Found: C, 73.86, 73.77; H, 10.08, 9.68; CH_3O, 5.72, 6.43.

Hindered Monomethyl Ester of Nor-B-dicarboxylic Acid.—A sample of dimethyl nor-B-dicarboxylate (11 mg.) was heated in a sealed vessel with 0.5 ml. of 20% methanolic potassium hydroxide on the steam-bath for 1.5 hr. The product (8 mg.) was precipitated by water and recrystallized from dilute methanol. The substance formed needles, m.p. 255–264°; no gas evolution was noted during rapid heating of a sample, and when mixed with the isomeric monomethyl ester described above the sample melted below 250°.

Anal. Calcd. for $C_{30}H_{48}O_5$ (488.68): CH_3O, 6.35. Found: CH_3O, 6.45.

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The Degradation of Colchicine to Octahydrodemethoxydesoxydesacetamidocolchicine[1]

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Although a complex mixture of difficultly separable products is formed on hydrogenation of colchicine (I), replacement of the methoxyl of ring C by dimethylamino and hydrogenation of the thus formed N,N-dimethylaminocolchicide (II) results in a good yield of easily purified tetrahydrodemethoxycolchicine (III). By conversion to the mercaptole and desulfurization, the carbonyl group is transformed to methylene giving hexahydrodemethoxydesoxycolchicine (V). Removal of the acetamido group is accomplished by heating with phosphorus pentoxide in xylene and hydrogenation yields octahydrodemethoxydesoxydesacetamidocolchicine (VI). This degradation sequence very reasonably takes place without rearrangement in the colchicine carbon skeleton and thus affords a degradation product whose synthesis would establish the nature of ring C.

With the synthesis of colchinol methyl ether,[3,4] the only remaining portion of the colchicine molecule (I) for which a definitive proof of structure is lacking is ring C. The features yet to be established by decisive chemical evidence are the seven-membered, tropoloid nature of the ring[5] and the relative positions of the carbonyl and methoxyl groups.

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[2] American Cancer Society Postdoctoral Fellow, 1951.

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

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[5] First proposed by M. J. S. Dewar, *Nature*, **155**, 141, 479 (1945).