Synthetic Intermediates Related to the Diterpene Alkaloids[1,2]

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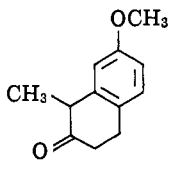
Abstract: The preparation of various intermediates obtained in connection with a study of synthetic routes to the diterpene alkaloids is described.

Some time ago an investigation of synthetic routes to diterpene alkaloids of the atisine–garryine type was undertaken in this laboratory. The work was interrupted, and although we have been anticipated in our ultimate objective by three groups of investigators,[3-5] we wish at this time to record our experimental results. In preliminary work 1-methyl-7-methoxy-2-tetralone (**1**), obtained by enamine methylation[6] of 7-methoxy-2-tetralone,[7] served as starting material. Alkylation of this substance with ω-bromovaleronitrile in the presence of potassium *t*-butoxide afforded a mixture of amorphous cyano ketone **2**, cyanohydrin **3**, and the unsaturated nitrile **4**, which could be separated chromatographically. For preparative purposes the mixture was



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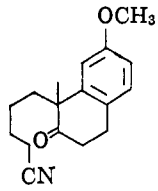

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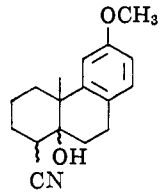

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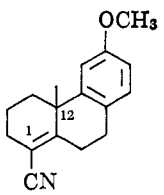

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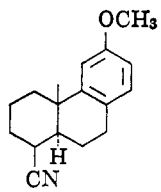

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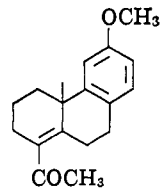

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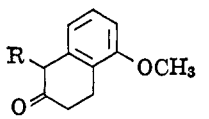
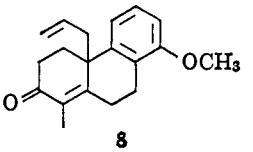
normally treated further with potassium *t*-butoxide at elevated temperature which converted intermediates **2** and **3** to **4**. The latter substance was obtained in crystalline form in about 60% yield by this procedure. Catalytic hydrogenation (Pd–C) of **4** furnished the corresponding saturated nitrile as a single epimer, for which structure **5** is suggested. Smooth conversion of **4** to methyl ketone **6** was accomplished by reaction with the Grignard reagent. The hope that nitriles **4** and **5** might undergo stereospecific methylation at C-1 was not realized, since all attempts at alkylation including the use of sodium hydride in toluene and in dimethyl sulfoxide, triphenylmethylsodium, potassium *t*-butoxide in dimethyl sulfoxide, potassium amide, sodamide, and lithium hydride in combination with methyl iodide, allyl bromide, and the highly reactive methyl chloromethyl sulfide ended routinely in the isolation of starting material.[7a] No useful application of ketone **6** was forthcoming, and the approach through these intermediates was therefore abandoned.

We turned next to a consideration of aldol cyclization as a method for introducing the required bridge element between carbon atoms 1 and 12 of the tricyclic nucleus (*cf.* structures **18** and **24**). For this purpose 6-methoxy-2-tetralone was alkylated[6] with allyl bromide, and the resulting allyl ketone **7a** was further condensed



7a, R = $CH_2CH{=}CH_2$
b, R = CH_2COOH



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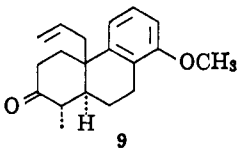

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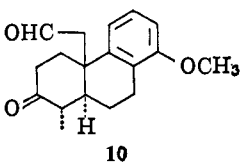
with diethylaminopentanone methiodide by the standard procedure[8] to yield tricyclic ketone **8**. Lithium–ammonia reduction of the conjugated double bond in **8** proceeded without incident and gave ketone **9**, convertible to keto aldehyde **10**, and thence into keto acid **11a**[9,10] by ozonization and oxidation with the Jones reagent.[11]



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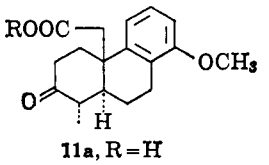


11a, R = H
b, R = CH_3

(1) The financial support of the Robert A. Welch Foundation is gratefully acknowledged.

(2) Taken in part from the Ph.D. Theses of Guy D. Diana, Rice University, 1961, and G. E. Fodor, Rice University, 1965.

(3) W. Nagata, T. Sugsawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963).

(4) S. Masamune, *ibid.*, **86**, 288, 289, 290, 291 (1964).

(5) (a) J. A. Finlay, W. A. Henry, T. C. Jain, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 869 (1962); (b) Z. Valenta, K. Wiesner, and C. M. Wong, *ibid.*, 2437 (1964).

(6) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954); G. Stork and H. K. Landesman, *ibid.*, **78**, 5128, 5129 (1956).

(7) *Cf.* M. E. Kuehne, *ibid.*, **83**, 1492 (1961).

(7a) NOTE ADDED IN PROOF. *Cf.* E. Wenkert and B. G. Jackson, *ibid.*, **81**, 5601 (1959).

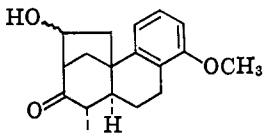
(8) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

(9) The stereochemistry assigned to derivatives in this series is established by correlations outlined in a later section.

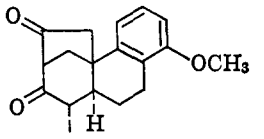
(10) Keto acid **11a** is an intermediate in the Wiesner garryine–veatchine synthesis[5] and was obtained by the New Brunswick group by an alternate procedure, also explored independently by us. In our experience the route through allyl ketone **7a** is the more satisfactory.

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Aldol cyclization of keto aldehyde **10** was explored under conditions of both acid and base catalysis. In the presence of hydrochloric acid cyclization afforded a hydroxy ketone (**12a**), mp 232–233°, which was clearly not identical with a product of similar constitution (**12b**), mp 204–205° obtained by cyclization with potassium hydroxide. Base treatment of **12a** resulted in its transformation into **12b**, and the fact that these



12a, mp 233°
12b, mp 205°



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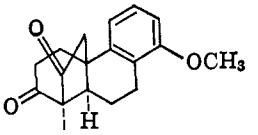

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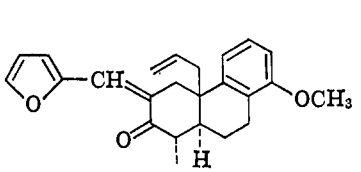
substances differ only in the configuration of the hydroxy group was established by oxidation of each compound to the same diketone **13**. Aldol **12b** is unaffected by acid treatment. Formation of **12a** is ascribed to the failure of this substance to equilibrate with keto aldehyde **10** under the *acidic* conditions employed for cyclization. Compound **12a** is hence regarded as the product of kinetic control.

The presence of a methyl doublet in the nmr spectra of these derivatives indicated that cyclization had occurred at C-3 instead of at C-1 and implied that a blocking group would be required to direct the condensation to the desired position.[12] Tricyclic ketone **9** was accordingly condensed with furfuraldehyde, and the resulting furfurylidene derivative (**15**) was then treated with osmium tetroxide in the presence of pyridine. Glycol **16** was obtained in this way as a single



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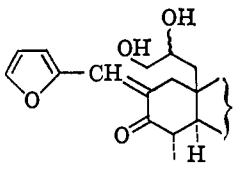

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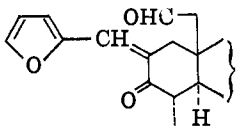

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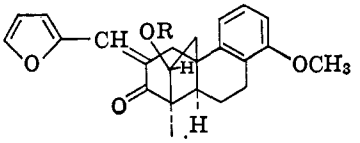
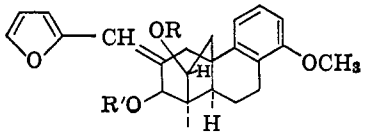


18a, R = H
18b, R = Ac



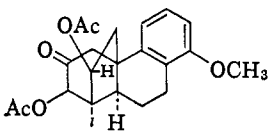
19a, R = Ac; R′ = H
19b, R = H; R′ = H
19c, R = Ac; R′ = Ac

(12) In accepting this view we lost the opportunity of encountering the interesting equilibration reaction whereby **13** is converted to **14**. This transformation constitutes the key step in the Wiesner synthesis.[5]

stereoisomer. Cleavage with lead tetraacetate afforded an amorphous aldehyde (**17**), which was cyclized directly with potassium hydroxide to the desired aldol product (**18a**). The substance yielded an acetyl derivative (**18b**), convertible into hydroxy acetate **19a** by reduction with sodium borohydride. Acetylation of the latter substance gave diacetate **19c**. The orientation assigned to the bridged-ring oxygen function in these derivatives, and in those described immediately below, *i.e.*, *trans* to the aromatic ring, is based on an argument given in a later section.

With the C-1–C-12 bridge thus established, attention was next directed to removal of the blocking group and ring A acetoxyl function.

Ozonolysis of **19c** in chloroform–methanol solution was carried out without difficulty, and the keto diacetate **20** was obtained in 70% yield. Although Wolff–Kishner reduction of **20** might have led directly to olefin with simultaneous elimination of both ring A



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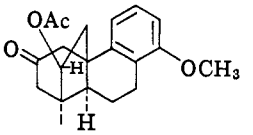

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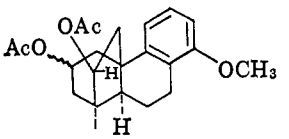

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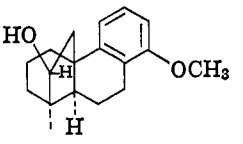

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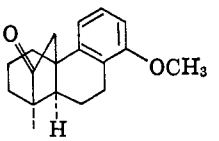

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oxygen functions,[13] the formation of mixtures in such treatment of certain α-ketols,[14] coupled with incomplete elimination of the hydroxyl group when equatorially oriented[15] and the obvious possibility of hydrolysis, ketol rearrangement, and bridge cleavage, precluded application of this method in the present instance. Compound **20** was therefore reduced with calcium in ammonia,[16] and keto acetate **21**, accompanied by the corresponding hydroxy ketone, was obtained in this way. When methanol[17] was substituted for the bromobenzene normally employed to destroy the excess calcium, complete reduction of the keto group resulted, and a hydroxy acetate, characterized as the corresponding diacetate **22**, was isolated.

Wolff–Kishner reduction of **21** proceeded smoothly and furnished the hydroxy derivative **23**, mp 173–174°, in good yield. A substance of the same constitution, but melting at 146–149°, has been reported by the Wiesner group[5a] as a product of Raney nickel desulfurization of the C-2 monothioketal of diketone **14**. The

(13) *Cf.* D. H. R. Barton, N. J. Holness, and W. Klyne, *J. Chem. Soc.*, 2456 (1949), and references cited therein.

(14) O. Wintersteiner, M. Moore, and K. Reinhardt, *J. Biol. Chem.*, **162**, 707 (1946).

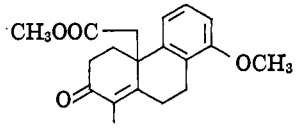
(15) R. B. Turner, R. Anliker, R. Helbling, J. Meier, and H. Heusser, *Helv. Chim. Acta*, 38, 411 (1955).

(16) J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956); see also C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 76, 4092 (1954).

(17) J. S. Mills, H. J. Ringold, and C. Djerassi, *ibid.*, **80**, 6118 (1958).

discrepancy in melting point undoubtedly reflects a difference in the stereochemistry of the hydroxyl group, which is differently introduced in the two procedures. Since it is unlikely that catalytic hydrogenation can give an alcohol other than the one with the hydroxyl group *cis* to the aromatic ring, structures **18** through **23** would appear to be correctly formulated. Oxidation with the chromium trioxide–pyridine complex[18] finally gave the tetracyclic ketone **24**. Expansion of the five-membered bridged ring with incorporation of nitrogen is described in a subsequent communication.

At the time when this work was carried out the stereochemistry at the A–B ring fusion in **9**, and in the substances derived from it, including ketone **24**, was not rigorously defined. The availability of derivatives **25**, **26**, and **27**, which had been prepared for other purposes, made possible correlation of **9** with substances of known stereochemistry.



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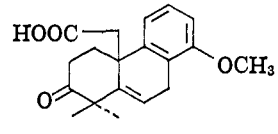

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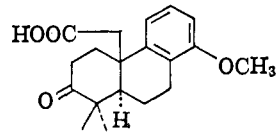

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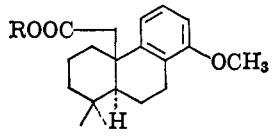
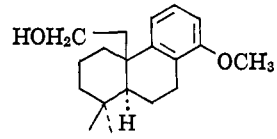
Assignment of configuration to the A–B ring fusion in **27** is based on the following considerations. Wolff–Kishner reduction of **27** yielded the expected desoxo derivative **28a** which was further reduced, as the methyl ester **28b**, with lithium aluminum hydride. The resulting alcohol (**29**) was then oxidized with chromium



28a, R = H
28b, R = CH_3



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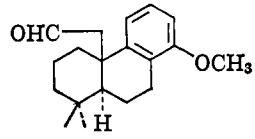

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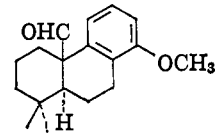

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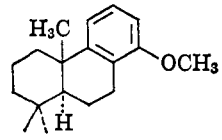

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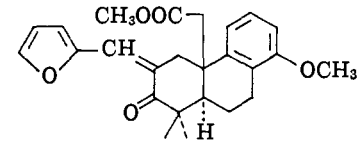
trioxide–pyridine to the corresponding aldehyde (**30**), which was converted by transformation into the enol acetate and ozonolysis of the latter substance into aldehyde **31**. Wolff–Kishner reduction then gave the tricyclic compound **32**, which had previously been converted into phyllocladene,[19] a substance of known stereochemistry. The configuration (A–B) of compounds **27** through **31** is thereby established.

Keto acid **27** was next transformed by condensation with furfuraldehyde and subsequent treatment with diazomethane into furfurylidene derivative **33**. Reduction of the latter substance with lithium aluminum



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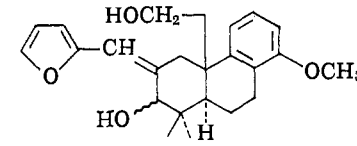

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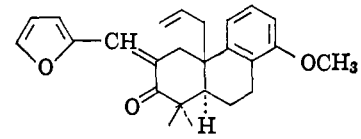
hydride afforded the furfurylidene glycol **34** which served as the correlation compound for members of the allyl series. In particular, furfurylidene ketone **15**, derived from the key intermediate **9**, afforded a dimethyl derivative **35**, and the latter product was converted successively into an amorphous glycol (OsO_4), a keto aldehyde (**36**), and thence by lithium aluminum hydride reduction into a product identical in all respects with glycol **34**. Attempts to purify the keto aldehyde **36** by chromatography on alumina afforded an isomer whose spectral characteristics are consistent with the tentatively suggested structure **37** (see the Experimental Section).



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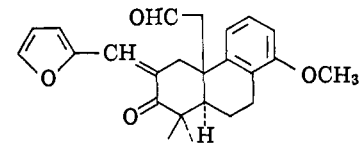

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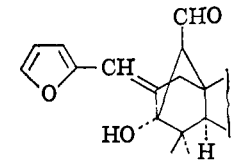

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This work, coupled with Wiesner's conversion of the hydroxy epimer of **23** to garryine and veatchine[5b] constitutes a further connective link between the diterpenes and the diterpenoid alkaloids.[4,20]

Experimental Section

Alkylation of 1-Methyl-7-methoxy-2-tetralone (1) with ω-Bromovaleronitrile. Potassium (11.3 g) was dissolved (nitrogen atmosphere) in 200 ml of *t*-butyl alcohol that had been previously distilled from calcium hydride. A solution of 22.6 g of 1-methyl-7-methoxy-2-tetralone (**1**)[21] in 10 ml of anhydrous benzene was then added, and the reaction mixture was stirred for 20 min at room temperature. At the end of this period, a solution of 25.0 g of ω-bromovaleronitrile[22] was introduced by dropwise addition, and

(18) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 422 (1953). Oxidation with chromium trioxide in acetic acid resulted in extensive attack on the benzyl position. This difficulty is not encountered with chromium trioxide–pyridine nor with the Jones reagent.

(19) R. B. Turner and P. Shaw, *Tetrahedron Letters*, No. 18, 24 (1960); R. B. Turner and K. H. Gänshirt, *ibid.*, No. 7, 231 (1961).

(20) *Cf.* W. A. Ayer, C. E. McDonald, and G. G. Iverach, *ibid.*, No. 17, 1095 (1963).

(21) F. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 1248 (1958).

(22) Aldrich Chemical Co., Milwaukee, Wis.

stirring was continued for 15 hr. The mixture was then neutralized with dilute hydrochloric acid, the bulk of the solvent was removed under reduced pressure, and the product was extracted with ether. The organic phase was washed thoroughly with water and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the ether was evaporated leaving 26.7 g of residual oil. Chromatography of a small sample on alumina furnished homogeneous, but amorphous, keto nitrile **2**, a crystalline specimen of conjugated nitrile **4**, more conveniently prepared as described below, and the hydroxy nitrile **3**. Recrystallization of the latter compound from methanol afforded the analytical sample: mp 158.5–159.5°, λ_{max}^{Nujol} 2.9 and 4.46 μ.

Anal. Calcd for $C_{17}H_{21}O_2N$: C, 75.25; H, 7.80; N, 5.16. Found: C, 74.80; H, 7.79; N, 4.83.

In order to effect conversion of intermediates **2** and **3** into the desired product **4**, the total crude material in 80 ml of dry benzene was added to a solution of potassium (30.0 g) in 600 ml of dry *t*-butyl alcohol, and the resulting mixture was heated under nitrogen for 2 hr at 90° and for 3 hr at 65–70°. After standing overnight at room temperature, the product **4** was isolated as described above, yielding 17.6 g. Recrystallization from methanol gave the analytical sample: mp 85–86°, $\lambda_{max}^{CH_2Cl_2}$ 4.52 μ.

Anal. Calcd for $C_{17}H_{19}ON$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.30; H, 7.53; N, 5.71.

Preparation of 1-Cyano-6-methoxy-12-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene (5). A solution of 603 mg of unsaturated nitrile **4** in 30 ml of methanol was shaken with 312 mg of 10% palladium on charcoal in a hydrogen atmosphere. After 60 hr, 1 molar equiv of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was concentrated to dryness under reduced pressure. Chromatography on alumina and crystallization from methanol gave 553 mg of saturated nitrile **5**; mp 114–115°, $\lambda_{max}^{CS_2}$ 4.46 μ.

Anal. Calcd for $C_{17}H_{21}ON$: C, 79.96; H, 8.29. Found: C, 79.80; H, 8.40.

Preparation of 1-Acetyl-6-methoxy-12-methyl-2,3,4,9,10,12-hexahydrophenanthrene (6). Methyl bromide was passed over silica gel and into a flask containing 60 ml of anhydrous ether and 2.45 g of magnesium turnings. After 30 min the magnesium had dissolved, and the excess methyl bromide together with some ether was removed with a dry nitrogen purge. The volume was made up with additional dry ether, and 847 mg of unsaturated nitrile **4** in 20 ml of ether was introduced by dropwise addition. The reaction mixture was then heated under reflux for 33 hr, at the end of which time 30 ml of glacial acetic acid and 30 ml of water were added. The ether was removed, and the residual mixture was heated under reflux for 30 min. The product was isolated by ether extraction and, after washing and drying, furnished 875 mg of conjugated ketone **6**: mp 73–74° (from ether–petroleum ether), $\lambda_{max}^{CS_2}$ 5.90 μ.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.02; H, 8.34.

Preparation of 1-Allyl-5-methoxy-2-tetralone (7a). A solution of 130 g of 5-methoxy-2-tetralone[8] in 700 ml of benzene was treated with 200 ml of freshly distilled pyrrolidine, and the mixture was heated under a reflux condenser in a nitrogen atmospnere for 1.5 hr.[6] The solvent was then removed under reduced pressure at 50° The residue was taken up in 700 ml of dry methanol, 75 ml of allyl bromide was added, and the solution was refluxed for 30 min. An additional 150 ml of allyl bromide was added and heating was continued for 1 hr. After removal of the excess allyl bromide by distillation, 150 ml of glacial acetic acid and 150 g of sodium acetate in 300 ml of water were added. After a reflux period of 45 min, the bulk of the solvent was removed under reduced pressure, and the residue was taken up in ether. The organic phase was washed successively with water, dilute sodium hydroxide, dilute hydrochloric acid, water, and saturated sodium chloride solution. The resulting solution was finally dried over anhydrous magnesium sulfate, the solvent was evaporated, and the residue was distilled through a spinning-band column: yield 100 g, bp 99–101° (0.05 mm), $\lambda_{max}^{CS_2}$ 5.82 and 10.85 μ. The semicarbazone, prepared as a derivative, melted at 156–157°.

Anal. Calcd for $C_{15}H_{19}O_2N_3$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.91; H, 7.03; N, 15.40.

Preparation of Keto Acid 7b. A solution of 5 g of 5-methoxy-2-tetralone in 60 ml of benzene containing 15 ml of pyrrolidine was heated to reflux temperature under a water separator until removal of water was complete. The mixture was concentrated *in vacuo*, and the resulting oil was taken up in 60 ml of alcohol. Freshly distilled methyl bromoacetate (50 g) was added, and, after a reflux period of 1 hr, 8 ml of acetic acid and 8 g of sodium acetate in 16 ml of water were introduced, and refluxing was continued for an additional 45 min.

The product was isolated by the usual procedure: yield 3.8 g, bp 153–156° (0.02 mm). Hydrolysis furnished the keto acid **7b**, which was obtained *as the corresponding lactol:* mp 176.5–179.5°, $\lambda_{max}^{CH_2Cl_2}$ 2.85 and 5.60 μ.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.44; H, 6.12.

Preparation of 2,3,4,9,10,12-Hexahydro-1-methyl-8-methoxy-12-allyl-2-oxophenanthrene (8). A solution of 25 g of **7a** in 150 ml of anhydrous benzene was treated with diethylaminopentanone methiodide, obtained from 16 g of diethylaminopentanone[23] and 6.8 g of sodium in 200 ml of ethanol according to the general procedure of Cornforth and Robinson.[8] The crude, oily reaction product was crystallized first from methylene chloride–petroleum ether (bp 30–60°) and then from methanol: yield 13 g, mp 88–89°, λ_{max}^{MeOH} 228 mμ (ϵ 19,500),[24] $\lambda_{max}^{CS_2}$ 5.99 and 10.95 μ.

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.81; H, 7.83.

Lithium–Ammonia Reduction of Compound 8. A sample of compound **8** (8.5 g) was dissolved in 800 ml of anhydrous ether and 1.5 l. of liquid ammonia. Small pieces of lithium wire (total, 5 g) were added rapidly to the stirred solution. After 45 min, the blue color was discharged by the addition of ammonium chloride, the ammonia was allowed to evaporate, and a small amount of ethanol was finally added to decompose any remaining traces of lithium.

The product was taken up in ether–methylene chloride and was washed with water and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate the solvent was removed, and the residue was crystallized from methanol to give 6.4 g of compound **9**, mp 110–115°. The analytical sample, mp 115.5–116°, $\lambda_{max}^{CS_2}$ 5.82 and 10.95 μ, was obtained by recrystallization from methanol.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.02; H, 8.79.

Preparation of Keto Aldehyde 10. Ozone was passed into a solution of 200 mg of allyl ketone **9** in 4 ml of chloroform and 1 ml of methanol (cooled to −10° in a salt–ice bath) for 10 min at the rate of 0.32 mmole of ozone per min. The reaction mixture was allowed to stand in the cooling bath for an additional 20 min, at the end of which time 300 mg of zinc dust and 3 ml of acetic acid were added. The mixture was stirred until a negative starch–iodide test was obtained, and the product was then isolated in the normal way. After crystallization from methanol and from methylene chloride–petroleum ether, a 125-mg sample of **10** was obtained: mp 121–122°, $\lambda_{max}^{CS_2}$ 3.7 and 5.82 μ.

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.23; H, 7.69.

Preparation of Keto Acid 11a and Keto Ester 11b. A sample of keto aldehyde **10** (1.0 g) in 75 ml of acetone was treated with 1.75 ml of Jones reagent[11] for 12 min, followed by further reaction with 0.86 ml of oxidizing agent for 8 min and 0.5 ml for 5 min. The excess reagent was then destroyed with isopropyl alcohol, and, after dilution with water, the product was taken into ether and isolated by base extraction. Acidification followed by extraction with ether, washing and drying, furnished 740 mg of keto acid **11a**, mp 201–202° (from methanol) (lit[5] mp 205–210°).

Esterification of the keto acid with diazomethane afforded the corresponding keto ester **11b** which, after recrystallization from methylene chloride–petroleum ether, melted at 127–129°, $\lambda_{max}^{CS_2}$ 5.78 and 5.82 μ.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.58; H, 7.56.

Preparation of Aldol 12a. A solution of 269 mg of keto aldehyde **10** in 10 ml of 80% methanol, to which 2 ml of concentrated hydrochloric acid had been added, was allowed to stand under nitrogen at room temperature for 17 hr. Dilution of the reaction mixture with water and extraction with ether gave an organic phase that was washed with water, dilute sodium hydroxide, and saturated sodium chloride solution. Removal of the ether yielded crude material which was crystallized from methylene chloride–methanol: yield 103 mg, mp 228–232°. The sample for analysis melted at 232–233°, $\lambda_{max}^{CH_2Cl_2}$ 2.80 and 5.85 μ.

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.54; H, 7.31.

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(23) Unpublished procedure of A. L. Wilds, K. E. McCaleb, and G. E. Inglett.

(24) *Cf.* R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riebel, and J. M. Sanders, *J. Am. Chem. Soc.*, 88, 1766 (1966), footnote 19.

Preparation of Aldol 12b. A sample of keto aldehyde **10**, 370 mg, was dissolved in 20 ml of 80% methanol containing 10% of potassium hydroxide. The mixture was allowed to stand at room temperature for 17 hr under a nitrogen atmosphere and was then diluted with water and extracted with ether. After washing and drying, the solvent was removed under reduced pressure, and the residue was crystallized from methylene chloride–petroleum ether: yield 128 mg, mp 199–201°. Recrystallization from the same solvent mixture afforded the analytical sample: mp 204–205°, $\lambda_{max}^{CH_2Cl_2}$ 2.80 and 5.85 μ.

Anal. Found: C, 75.46; H, 7.69.

Treatment of ketol **12a** under these conditions furnished material identical with ketol **12b**. The reaction of **12b** with methanolic hydrochloric acid gave back unaltered starting material.

Preparation of Diketone 13 from 12a. Aldol **12a** (60 mg) was dissolved in 1 ml of pyridine and treated with 25 mg of chromium trioxide in 1 ml of pyridine. The mixture was allowed to stand overnight at room temperature, and the product was isolated in the usual manner. Chromatography on Florisil afforded 22 mg of diketone **13**, mp 182–187°. Several recrystallizations from methylene chloride–petroleum ether furnished the analytical sample as needles: mp 192–192.5°, $\lambda_{max}^{CS_2}$ 5.70 and 5.82 μ.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.10; H, 7.25.

From 12b. A 320-mg sample of aldol **12b** was oxidized by the procedure of the preceding experiment. Chromatography on Florisil gave as the major crystalline fraction 182 mg of material which, after recrystallization from methylene chloride–petroleum ether, melted at 190–192°. A mixture melting point with diketone derived from **12a** was undepressed, and the infrared spectra of the two samples were identical.

Preparation of Furfurylidene Ketone 15. Compound **9** (2 g) in 80 ml of methanol was treated (nitrogen atmosphere) with 10 ml of freshly distilled furfuraldehyde and 30 ml of 33% aqueous sodium hydroxide solution. Methanol was then added until a clear solution was obtained. The reaction mixture was seeded with a crystal of furfurylidene ketone obtained in a separate experiment and was allowed to stand in the dark at room temperature for 12 hr. During this period the product separated as a crystalline mass. Addition of water followed by cooling to 0° and filtration gave 2.2 g of **15** melting at 90–92°. The analytical sample was obtained by recrystallization from methanol: mp 90–91°, λ_{max}^{EtOH} 320 mμ (ϵ 19,000), $\lambda_{max}^{CS_2}$ 6.00 and 10.95 μ.

Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.51; H, 7.20.

Preparation of Glycol 16. Osmium tetroxide (4.5 g) and dry pyridine (6 ml) were added to a solution of 6 g of furfurylidene ketone (**15**) in 150 ml of dry ether, and the mixture was allowed to stand at room temperature for 12 hr.[25] The ether was then removed under reduced pressure, and the residue was taken up in 250 ml of ethanol and 150 ml of water containing 45 g of sodium sulfite. The resulting mixture was heated under reflux for 3 hr and was finally cooled and filtered.

After removal of the bulk of the solvent, the product was dissolved in methylene chloride–ether and was washed successively with water, dilute sodium hydroxide, water, dilute hydrochloric acid, water, and saturated sodium chloride solution. After drying over anhydrous sodium sulfate the solvent was evaporated, and the residue was crystallized from a small volume of ether: yield 4.8 g, mp 173–176°.

Recrystallization from methylene chloride–petroleum ether furnished a pure sample of glycol **16**: mp 186.5–188°, $\lambda_{max}^{CS_2}$ 2.85 and 6.00 μ.

Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.96; H, 7.34.

Preparation of Compound 18a. A 1-g sample of glycol **16** in 30 ml of dry benzene was treated with 1.6 g of lead tetraacetate. After 15 min at room temperature the reaction mixture was diluted with ether and was washed with water and saturated sodium chloride solution. Drying over anhydrous magnesium sulfate followed by solvent evaporation yielded 1 g of oily aldehyde **17**, $\lambda_{max}^{CS_2}$ 3.70, 5.85, and 6.00 μ, suitable for further processing.

The crude aldehyde was dissolved in 60 ml of 80% aqueous methanol containing 10% of potassium hydroxide. This solution was allowed to stand under nitrogen for 12 hr at room temperature, at the end of which time ether and methylene chloride were added, and the reaction mixture was acidified with dilute hydrochloric acid. The product was isolated by the customary procedure and furnished 591 mg of **18a**, mp 196–198°.

Several recrystallizations from methylene chloride–petroleum ether gave the analytical sample: mp 199–201°, $\lambda_{max}^{CH_2Cl_2}$ 2.82 and 6.00 μ.

Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.84; H, 6.72.

Acetylation of the aldol (*1* g) with acetic anhydride and pyridine gave 981 mg of keto acetate **18b**, melting at 212–216°. After several recrystallizations from methylene chloride–petroleum ether the sample melted at 222–224°, $\lambda_{max}^{CS_2}$ 5.80 and 6.00 μ.

Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 73.66; H, 6.24.

Sodium Borohydride Reduction of 18b. A solution of 400 mg of keto acetate **18b** in 2 ml of tetrahydrofuran was treated with 200 mg of sodium borohydride in 25 ml of methanol. After 15 min at room temperature, water and methylene chloride were added, and the aqueous layer was extracted three times with methylene chloride. The combined organic fractions were washed, dried, and evaporated. Crystallization of the residue from methylene chloride–petroleum ether gave 320 mg of hydroxy acetate **19a**: mp 145–146°, $\lambda_{max}^{CS_2}$ 2.83 and 5.75 μ.

Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.60; H, 6.81.

In addition to the hydroxy acetate, 49 mg of diol **19b**, mp 229.5–230°, $\lambda_{max}^{CH_2Cl_2}$ 2.83 μ, was obtained.

Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.04; H, 7.18.

Preparation of Diacetate 19c. The total crude product from sodium borohydride reduction of 4.7 g of keto acetate **18b** was acetylated directly with 60 ml of acetic anhydride and 24 ml of pyridine. The product was isolated in the usual way and was crystallized from methylene chloride–petroleum ether yielding 4.8 g of diacetate **19c**, mp 170–173°. Recrystallization from methanol furnished the analytical sample: mp 172–173°, $\lambda_{max}^{CS_2}$ 5.75 μ.

Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.86; H, 6.86.

Ozonolysis of 19c to Keto Diacetate 20. A 200-mg sample of compound **19c** was dissolved in 6 ml of chloroform and 1.5 ml of methanol, and the resulting solution was cooled to −10° in a salt–ice bath. Ozone was then passed into the solution until 4 equiv had been added (8 min). After an additional 20 min at −10°, 400 mg of zinc dust and 3.5 ml of acetic acid were added, and the mixture was stirred until a negative starch–iodide test was obtained (15 min). Routine processing gave 100 mg of keto diacetate **20**, mp 207–215° (from methylene chloride–petroleum ether). The analytical sample, obtained after several recrystallizations from methanol, melted at 235.5–237.5°, $\lambda_{max}^{CS_2}$ 5.75 μ.

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.39; H, 6.74.

Preparation of Keto Acetate 21. A solution of 159 mg of keto diacetate **20** in 7 ml of dry toluene was added slowly to a solution of 200 mg of calcium in 75 ml of liquid ammonia. The reaction mixture was stirred for 1 hr, during which time an additional 100 mg of calcium was added to maintain a blue coloration. The excess calcium was then destroyed by addition of bromobenzene,[16] the ammonia was evaporated, and the residue was taken up in methylene chloride. The solution was washed with dilute hydrochloric acid and water and was finally dried and evaporated.

Chromatography furnished 21 mg of keto acetate **21** and 56 mg of the corresponding ketol which was reacetylated to give a total of 87 mg of **21**, mp 145–150°. The analytical sample prepared by recrystallization from methylene chloride–petroleum ether melted at 157–158°, $\lambda_{max}^{CS_2}$ 5.73 and 5.80 μ.

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.02; H, 7.35.

In a run in which methanol was used in place of bromobenzene to remove excess calcium,[17] the product after reacetylation was the diacetate **22**: mp 134–135° (from methylene chloride–petroleum ether), $\lambda_{max}^{CS_2}$ 5.73 μ.

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58.Found: C, 70.68; H, 7.61.

Wolff–Kishner Reduction of Keto Acetate 21. A solution of 30 mg of **21** and 600 mg of potassium hydroxide in 2.5 ml of ethanol, 0.6 ml of water, and 0.6 ml of ethylene glycol was treated with 0.6 ml of 85% hydrazine hydrate. The mixture was heated under reflux (122°) in a nitrogen atmosphere for 2 hr, at the end of which time the condenser was removed, and the temperature was raised to 200°. After 2 hr at the higher temperature the reaction mixture was cooled and ice was added, followed by dilute hydrochloric acid

(25) *Cf.* L. H. Sarett, *J. Biol. Chem.*, 162, 625 (1946).

and methylene chloride. After the conventional washing and drying operations the solvent was removed, and the crude product was chromatographed on alumina. In this way 21 mg of alcohol **23**, mp 170–175°, was obtained. Recrystallization from methylene chloride–petroleum ether furnished a pure sample: mp 173–174°, $\lambda_{max}^{CS_2}$ 2.80 μ.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.17; H, 8.92.

Preparation of Ketone 24. Oxidation of 25 mg of alcohol **23** was carried out in 0.8 ml of pyridine to which 20 mg of chromium trioxide had been added. After standing at room temperature for 12 hr the reaction mixture was diluted with water and extracted with methylene chloride and ether. Washing, drying, and evaporation of the solvent afforded 20 mg of ketone **24**, melting at 145–150°. Recrystallization from methylene chloride–petroleum ether furnished a pure specimen: mp 152–152.5°, $\lambda_{max}^{CS_2}$ 5.75 μ.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.10; H, 8.21.

Preparation of Keto Ester 25. Diethylaminopentanone methiodide obtained from 3.5 g of diethylaminopentanone, and 6.0 g of keto acid (lactol) **7b** were suspended in 100 ml of benzene, and a solution of 2.5 g of potassium in 50 ml of ethanol was added over a period of 5 min with stirring and ice cooling. Stirring was continued for 1.5 hr at 0–5° and for 30 min at room temperature, and the mixture was finally heated under reflux for 45 min. The reaction mixture was then poured onto ice, neutralized with dilute sulfuric acid, and extracted with ether. The ethereal layer was washed with water and was treated immediately with excess diazomethane.

Chromatography of the resulting keto ester on alumina furnished 2.5 g of **25** melting at 95–98°. The analytical sample melted at 100–101°, $\lambda_{max}^{CS_2}$ 5.77, 5.94 μ.

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.66; H, 7.03.

Preparation of Keto Acid 26. Keto ester **25** (2.5 g) was dissolved in 100 ml of *t*-butyl alcohol, and a solution of 1.1 g of potassium in 120 ml of *t*-butyl alcohol was added at room temperature. Methyl iodide (4 ml) was then added with stirring. After standing at room temperature for 1.5 hr, the mixture was heated to boiling for 10 min. Sodium hydroxide (6 g) in 120 ml of water was then added to the hot solution, and refluxing was continued for 2.5 hr. The reaction mixture was finally cooled, diluted with water, washed with benzene, and acidified. The material that separated was taken up in chloroform. After washing with water and drying, the solvent was removed, and the residue was crystallized from chloroform–petroleum ether: yield 1.25 g, mp 151–154°. The analytical sample melted at 154–155°, λ_{max}^{EtOH} 278 mμ (ε 1830).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.59; H, 7.01.

Catalytic Hydrogenation of Keto Acid 26. A 502-mg sample of keto acid **26** was hydrogenated over palladium on barium sulfate in ethanol as the solvent. After the absorption of 1 molar equiv of hydrogen (3.25 hr), the catalyst was removed by filtration, and the filtrate was concentrated to dryness. Crystallization of the residue from ether–petroleum ether furnished 372 mg of keto acid **27**, mp 192–198°. Several recrystallizations from the same solvent gave the analytical sample, mp 205–207°.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 71.79; H, 7.56.

Preparation of Acid 28a. To a solution of 600 mg of keto acid **27** in 55 ml of ethylene glycol there was added 9 g of potassium hydroxide in 9 ml of water and 15 ml of 85% hydrazine hydrate. The mixture was heated under reflux for 2 hr (bath temperature 122°). The reflux condenser was then removed, and the temperature was raised to 200° where it was maintained for an additional 2 hr. The reaction mixture was then cooled and poured into ice and dilute hydrochloric acid. The product was isolated by extraction with methylene chloride–ether: yield 576 mg, mp 198–200°. Several recrystallizations from methanol–ether gave the analytical sample, mp 203–204°.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.61; H, 8.53.

Esterification with diazomethane furnished the corresponding methyl ester **28b**, mp 75–76° (from ether–petroleum ether).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.85; H, 8.90.

Preparation of Alcohol 29. A solution of 330 mg of methyl ester **28b** in 10 ml of ether was reduced with excess lithium aluminum hydride at reflux temperature. The product **29** was isolated in the usual way and after crystallization from ether–petroleum ether yielded 270 mg of pure material, mp 132°.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.21; H, 9.75.

Chromium Trioxide–Pyridine Oxidation of Alcohol 29. A mixture of 300 mg of chromium trioxide and 3 ml of pyridine was treated with a solution of 300 mg of alcohol **29** in 3 ml of pyridine. After 15 hr at room temperature, water was added, and the mixture was extracted with methylene chloride and ether. The organic phase was washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide, water, and saturated sodium chloride solution, and was dried over anhydrous sodium sulfate. Removal of the solvent afforded 205 mg of aldehyde **30** which, after recrystallization from ether–petroleum ether, melted at 79.5–80°.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.66; H, 9.21.

Preparation of Aldehyde 31. A sample of aldehyde **30**, 250 mg, prepared as described in the previous experiment, was dissolved in 8 ml of acetic anhydride containing 250 mg of potassium acetate. The mixture was heated (nitrogen atmosphere) to 135° for 6 hr, at the end of which time water was added, and the product was taken into ether. Removal of the solvent after conventional washing and drying yielded 219 mg of amorphous enol acetate, which was employed directly in the next step without further purification.

The crude enol acetate was dissolved in 4 ml of chloroform and 1 ml of methanol, and ozone (0.170 mmole) was passed into the solution at −10°. After standing at −10° for 30 min, the ozonization mixture was treated with 300 mg of zinc dust and 3 ml of acetic acid, and was stirred at room temperature until a negative starch–iodide test was obtained. The product (170 mg) was isolated by routine extraction with methylene chloride–ether and after chromatography yielded 87 mg of pure aldehyde **31**, mp 133–134° (from ether–petroleum ether).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.34; H, 9.09.

Wolff–Kishner Reduction of Aldehyde 31. Reduction of 81 mg of aldehyde **31** was carried out for 3 hr at 200–210° by the procedure employed for the conversion of **21** to **23**. Chromatography of the crude reaction product afforded 51 mg of compound **32**, mp 117–118°, identical in all respects with an authentic sample.[19]

Preparation of Compound 33. A solution of 600 mg of keto acid **27** in 25 ml of methanol was treated with 10 ml of 33% aqueous potassium hydroxide solution and 3 ml of freshly distilled furfuraldehyde. The mixture was allowed to stand (nitrogen atmosphere) in the dark at room temperature for 16 hr. The solution was then diluted with water and thoroughly washed with ether. Acidification and ether extraction furnished a crude acidic fraction as a dark oil which was esterified directly with ethereal diazomethane. Chromatography (alumina) of the furfurylidene keto ester thus formed yielded 480 mg of **33**, mp 162–163° (from methylene chloride–petroleum ether).

Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.26; H, 6.91.

Lithium Aluminum Hydride Reduction of Keto Ester 33. A 320-mg sample of keto ester **33** in 8 ml of dry ether was added to a slurry of excess lithium aluminum hydride and ether. The reaction mixture was stirred at room temperature for 3 hr and was then heated under reflux for 1 hr. The excess hydride was destroyed by cautious addition of water followed by dilute sulfuric acid, and the organic layer was washed successively with water, sodium bicarbonate solution, and saturated sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was evaporated, and the residue was purified by chromatography and crystallization from ethyl acetate–petroleum ether: yield 229 mg, mp 209.5–210.5°.

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.25; H, 7.89.

Preparation of Compound 35. A 1.09-g sample of the allyl furfurylidene ketone **15** was added to a solution of 273 mg of potassium in 25 ml of anhydrous *t*-butyl alcohol. The system was purged with nitrogen, 2.4 ml of methyl iodide was added, and the resulting mixture was stirred for 1.5 hr at 45° and for 1.5 hr at reflux temperature. The product was isolated by acidification and ether extraction. Chromatography of the crude material followed by recrystallization from ether–petroleum ether furnished a pure sample: 790 mg, mp 138–138.5°.

Anal. Calcd for $C_{25}H_{28}O_3$: C, 79.76; H, 7.50. Found: C, 79.48; H, 7.61.

Preparation of Glycol 34 from 35. A solution of 800 mg of allyl derivative **35** was treated with 590 mg of osmium tetroxide and 1 ml of dry pyridine according to the procedure outlined for the

preparation of glycol **16**. Hydrolysis of the intermediate osmate ester furnished 577 mg of crude material, which gave 243 mg of homogeneous, but amorphous, glycol on chromatography over Florisil. The glycol thus produced was dissolved in 5 ml of dry benzene and was treated directly with a solution of 384 mg of lead tetraacetate in 7 ml of anhydrous benzene. After 15 min at room temperature, the reaction mixture was worked up as previously described, yielding 214 mg of crystalline residue: $\lambda_{max}^{CS_2}$ 3.67, 5.80, and 5.94 μ.

Attempts to purify a small sample of the keto aldehyde **36** by chromatography (alumina) and subsequent crystallization from methylene chloride–petroleum ether gave an isomer, mp 215–216°, $\lambda_{max}^{CS_2}$ 2.81, 3.65, and 5.83 μ, for which structure **37** is suggested.

Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found: C, 76.23; H, 7.05.

In view of this difficulty the remainder of the crude keto aldehyde above was reduced directly with lithium aluminum hydride in ether as described for the reduction of keto ester **33**. Chromatography of the reduction product (Florisil) and crystallization from ethyl acetate–petroleum ether yielded a sample of glycol **34**, mp 210.5–211.5°, that was indistinguishable from the specimen derived from keto ester **33**.

Alkaloid Studies. LVI.[1] The Constitution of Vallesiachotamine[2]

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Abstract: Through a combination of chemical and spectroscopic techniques (notably nuclear magnetic resonance and mass spectrometry) it has been possible to show that vallesiachotamine, an alkaloid isolated from the Peruvian *Apocynaceae Vallesia dichotoma* Ruiz et Pav, possesses structure I. A likely biogenetic route to this unusual structure is discussed.

Extensive studies[3-6] in our laboratory on the constituents of the Peruvian plant *Vallesia dichotoma* Ruiz et Pav (family, *Apocynaceae*) have resulted in the isolation of 28 alkaloids, all but six of which have now been fully characterized. We should now like to report the structure elucidation of one of the remaining alkaloids, present to the extent of approximately 0.001%, which we have named vallesiachotamine.[7] As will be shown below, its structure (I) is of unusual biogenetic interest.

The very limited amount of material demanded great dependence upon physical measurements and establishment of empirical formulas principally through mass spectrometric measurements rather than combustion analyses. The alkaloid is relatively unstable to exposure to air and light, but this feature did not apply to some of its transformation products. The empirical formula $C_{21}H_{22}N_2O_3$ was established by high-resolution mass measurements and supported by the only combustion analysis[6] performed in this work. Its ultraviolet absorption spectrum (Figure 1), though strongly suggestive of an indole, exhibited abnormally high extinction in the 290-mμ region, which suggested the existence of a second chromophore absorbing in that region. The infrared spectrum exhibited bands at 2.89, 2.98, 6.02, and 6.25 μ typical of NH or OH and of α,β-unsaturated carbonyl groupings. The mass spectrum (Figure 2)[8] displayed a pattern, which was unlike that of any of the various indole alkaloids hitherto investigated,[9] but the high-resolution mass measurements did shed some light on the nature of the three oxygen atoms, which appeared to be incorporated in one carbonyl (see *m/e* 322 in Figure 2) and one methoxycarbonyl (see *m/e* 291 and 263 in Figure 2) group. These conclusions were verified by the 100-Mc nmr spectrum, whose most salient features are summarized in Table I. The spectrum was complicated by the fact that most of the signals appeared in pairs presumably due to restricted rotation of one or more groups,[5] but this did not preclude making the assignments summarized in Table I.

Table I. Nmr Spectrum of Vallesiachotamine (I)

Nmr signal,[a] δ (ppm)	No. of protons	Assignment
10.2/9.3	1	C(O)—*H*
8.6/8.55	1	N*H* (indole)
7.7/7.67	1	>C=C—*H*
7.6–7.1	4	Aromatic *H*
6.65/6.55 (two quartets, J = 7.5 cps)	1	CH_3CH=C<
2.18/2.07 (two doublets, J = 7.5 cps)	3	CH_3CH=C<
3.64	3	CO_2CH_3

[a] Doubling of signals presumed to be due to restricted rotation.

As will be shown below, these conclusions could be verified by nmr studies (see Figure 3) on derivatives, which did not exhibit these complicating features.

The analytical and spectral data cited so far can be summarized in terms of the following expression, which

(1) For paper LV see R. R. Arndt and C. Djerassi, *Experientia*, **21**, 566 (1965).

(2) Financial support from the National Institutes of Health (Grant No. GM-11309) of the U. S. Public Health Service is gratefully acknowledged. The purchase of the Atlas CH-4 mass spectrometer used in this investigation was made possible through NASA Grant NsG 81-60.

(3) J. S. E. Holker, M. Cais, F. A. Hochstein, and C. Djerassi, *J. Org. Chem.*, 24, 314 (1959).

(4) K. S. Brown, Jr., H. Budzikiewicz, and C. Djerassi, *Tetrahedron Letters*, 1731 (1963).

(5) A. Walser and C. Djerassi, *Helv. Chim. Acta*, **47**, 2073 (1964).

(6) A. Walser and C. Djerassi, *ibid.*, 48, 391 (1965).

(7) This was earlier[6] referred to as alkaloid number 20.

(8) Empirical formulas are marked for those peaks where the composition was established by high-resolution mass measurements.

(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964, Chapters 3–9.