The Carboxylation and Formylation of Certain 2-Tetralones[1,2]

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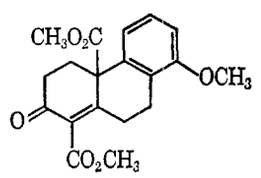
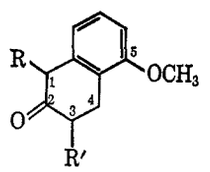
Treatment of 5-methoxy-2-tetralone (II) and 2-tetralone (XVIII) with magnesium methyl carbonate has been shown to lead to 3-carboxy-substituted products V and XX, respectively. Similarly, formylation of 5-methoxy-2-tetralone under the conditions described leads to the 3-hydroxymethylene derivative XXXII. In each case the assigned structures were demonstrated by conversion of the products to known naphthalene derivatives. This study demonstrates that carboxylation and formylation of simple 2-tetralones, like oxalylation, occurs preferentially at the 3-position.

In connection with work directed toward the total synthesis of diterpene alkaloids we were interested in constructing the tricyclic keto diester I (Chart I),

CHART I



I



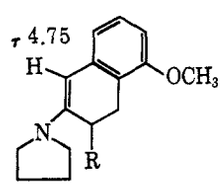
II, R = R′ = H
III, R = CO_2H; R′ = H
IV, R = CO_2CH_3; R′ = H
V, R = H; R′ = CO_2H
VI, R = H; R′ = CO_2CH_3

as a potential intermediate. After failure to carboxylate 5-methoxy-2-tetralone[3] (II) by conventional procedures,[4] we tried the elegant procedure of Stiles,[5,6] utilizing magnesium methyl carbonate. This paper summarizes the results of carboxylation and formylation studies on β-tetralones which were reported in part in our preliminary communications.[7,8]

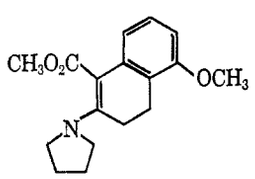
Treatment of 5-methoxy-2-tetralone (II) with magnesium methyl carbonate gave a β-keto acid in 45% yield, mp 153–155°; methyl ester, mp 123–125°. By analogy with several base-catalyzed alkylation reactions of β-tetralones which lead to 1-substituted derivatives,[9] we initially expected the β-keto acid and its methyl ester to have structures III and IV, respectively, and that the β-keto ester IV might serve as a suitable starting material for the synthesis of the tricyclic ketodiester I. However, since it is known that acylation can occur at either the 1- or 3-position depending on the nature of the acyl group and of the solvent system employed,[10,11] detailed studies were undertaken to determine the position of carboxylation. These studies lead to the assignment of structures V and VI to the β-keto acid and its methyl ester, respectively.

The β-keto ester in question, VI, reacted smoothly with pyrrolidine[12] in refluxing benzene to give a crystalline enamine, mp 104–105°. In the nmr spectrum this enamine exhibited a singlet of one proton intensity at τ 4.75 which is consistent with structure VII (Chart II) for the enamine and therefore structure VI for the

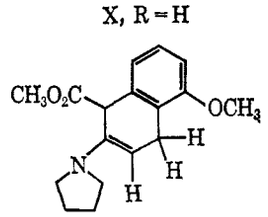
CHART II



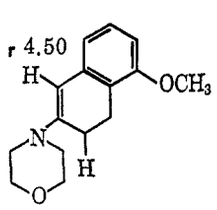
VII, R = CO_2CH_3
X, R = H



VIII



IX



XI

β-keto ester. The enamine VIII, derived from the alternate structure IV, has no vinyl proton and the less likely structure IX would not be expected to exhibit an unsplit vinyl proton signal. It is relevant to note that the pyrrolidine and morpholine enamines (X, mp 77–79, and XI, 126.5°, respectively) of 5-methoxy-2-tetralone exhibited sharp one-proton singlets at τ 4.82 and 4.50, respectively. While the nmr evidence suggested that carboxylation, like oxalylation,[10] had occurred at the 3-position, independent evidence in favor of the course of the carboxylation reaction is provided in the sequel.

The β-keto ester VI has been converted to the acetoxycarbomethoxynaphthalene XIII and the corresponding hydroxynaphthoic acid XIV *via* the enol acetate XII (Chart III). Thus treatment of VI with acetic anhydride and a trace of *p*-toluenesulfonic acid[13] under

(1) This investigation was supported in part by Grants RG 5807 and GM 10921 from the National Institutes of Health, U. S. Public Health Service.

(2) Preliminary phases of this work were carried out at the Rockefeller Institute, New York, N. Y.

(3) J. W. Cornforth, R. H. Cornforth, and R. Robinson, *J. Chem. Soc.*, 689 (1942).

(4) *E.g.*, treatment of the sodioderivative of 5-methoxy-2-tetralone (II) either with ethyl chloroformate or diethyl oxalate failed to afford any desirable products.

(5) M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959); M. Stiles, *Ann. N. Y. Acad. Sci.*, **88**, 332 (1960).

(6) H. L. Finkbeiner and M. Stiles, *J. Am. Chem. Soc.*, **85**, 616 (1963).

(7) S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, **No. 2**, 103 (1964).

(8) S. W. Pelletier, R. L. Chappell, and P. C. Parthasarathy, *ibid.*, **No. 1**, 41 (1965).

(9) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 676 (1946); C. A. Grob and W. Jundt, *Helv. Chim. Acta*, **35**, 2111 (1952); J. W. Cornforth, O. Kauder, J. E. Pike, and R. Robinson, *J. Chem. Soc.*, 3348 (1955); W. S. Johnson, W. A. Vredenburgh, and J. E. Pike, *J. Am. Chem. Soc.*, **82**, 3409 (1960).

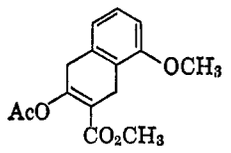
(10) M. D. Soffer, R. A. Stewart, and G. L. Smith, *ibid.*, **74**, 1556 (1952).

(11) L. M. Roch, *Ann. Chim. Paris*, **6**, 105 (1961); K. Wiedhaup, A. J. H. Nollet, J. G. Korsloot, and H. O. Huisman, *Tetrahedron Letters*, **No. 21**, 1599 (1965).

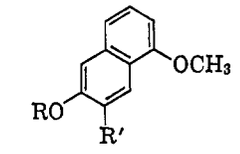
(12) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(13) P. Z. Bedoukian, *ibid.*, **67**, 1430 (1945).

CHART III



XII



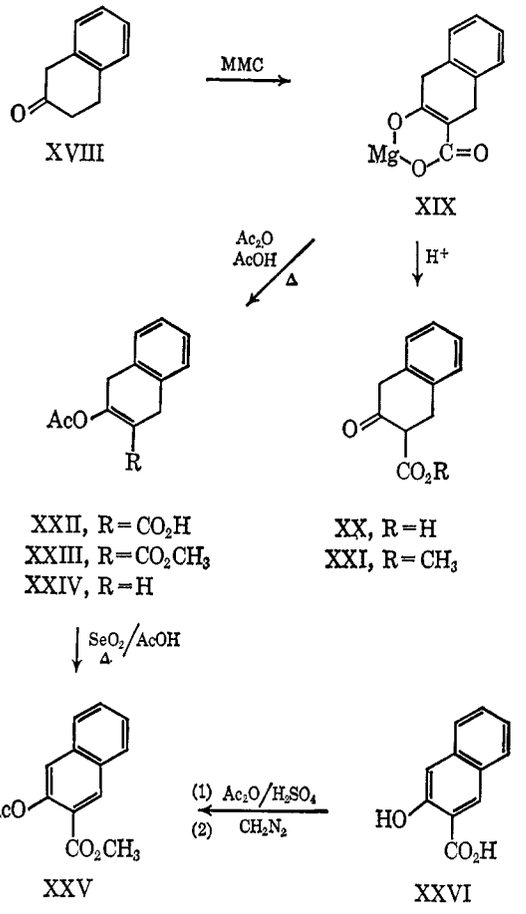
XIII, R = Ac; R′ = CO_2CH_3
XIV, R = H; R′ = CO_2H
XV, R = H; R′ = $-CHOH-CO_2CH_3$
XVa, R = Ac; R′ = $-CHOAc-CO_2CH_3$
XVI, R = H; R′ = $-CHOH-CH_2OH$
XVII, R = H; R′ = CHO
XVIIa, R = Ac; R′ = CHO
XVIIb, R = H; R′ = CH = NOH

reflux gave the enol acetate (XII), mp 97.5°, showing no vinyl proton in the nmr spectrum. Dehydrogenation of enol acetate XII with freshly sublimed selenium dioxide[14,15] in glacial acetic acid gave pale yellow plates of the naphthalene derivative, XIII, mp 123–124°. Hydrolysis of XIII with 5% methanolic sodium hydroxide gave a hydroxynaphthoic acid as pale yellow needles, mp 228.5–230.5°. The ultraviolet spectrum of the product was characteristic of a 2-hydroxy-3-naphthoic acid[16] and it proved to be identical with an authentic sample of 2-hydroxy-5-methoxy-3-naphthoic acid (XIV) obtained from 5-methoxy-2-tetralone (II).

Soffer,[10] has demonstrated that oxalylation of 2-tetralone leads to substitution at position 3. Treatment of 5-methoxy-2-tetralone (II) with dimethyl oxalate–sodium methoxide gave the glycolate XV, mp 126–127°, and diacetate XVa, mp 128–129°, in excellent yield. On reduction of XV with lithium aluminum hydride, triol XVI, mp 123.5–124.5°, was obtained which was cleaved with periodic acid to furnish the aldehyde XVII, mp 148.5–149.5°. This compound was characterized as the acetate XVIIa, mp 77–78°, and the oxime XVIIb, mp 199–201°. Finally aldehyde XVII underwent smooth oxidation with freshly prepared silver oxide in methanol to afford an acid, mp 228.5–230.5°, identical in all respects with the naphthoic acid XIV described above.

With a view to confirm the generality of the course of carboxylation of 2-tetralones with magnesium methyl carbonate, the reaction was applied to 2-tetralone (XVIII) (Chart IV), itself. The reaction appeared to proceed normally but in only a single experiment was it possible to isolate the crude β-keto acid XX, mp 113–115° (methyl ester XXI, mp 45–46°), which had been prepared previously by electrolytic reduction of 3-

CHART IV



hydroxy-2-naphthoic acid.[17] The keto acid XX appeared to undergo decarboxylation during hydrolysis of the magnesium complex XIX with cold, aqueous hydrochloric acid (acetic acid and sodium dihydrogen phosphate gave similar results).[18] However, when the dry, solid magnesium complex from β-tetralone was heated with acetic anhydride–acetic acid, it was possible to isolate a mixture of the enol acetates XXII and XXIV. Treatment of this mixture with diazomethane gave a product which was separated by chromatography over Florisil and silicic acid into the enol acetate of β-tetralone XXIV and the enol acetate methyl ester XXIII, mp 76–76.5°, of keto ester XXI. The dehydrogenation of XXIII was effected in low yield by refluxing with selenium dioxide in glacial acetic acid. The product, XXV, mp 96–97°, showed the expected spectral characteristics and was identical with an authentic sample of methyl-2-acetoxy-3-naphthoate prepared by successive acetylation and methylation of commercially available 2-hydroxy-3-naphthoic acid (XXVI).[19]

It has been pointed out that, under the conditions employed, the carboxylation process is reversible, and the magnesium salt that results is the one formed at equilibrium.[18] Thus, the steric requirement of the chelate salt causes XXVII and XXVIII (Chart V) to be favored over XXXIX and XXX, respectively.

(14) S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4531 (1950).

(15) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *ibid.*, **72**, 4534 (1950).

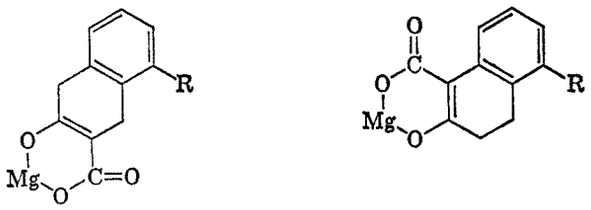
(16) E. D. Bergmann, Y. Hirshberg, and S. Pinchas, *J. Chem. Soc.*, 2351 (1950); M. R. Padhye, N. R. Rao, and K. Venkataraman, *Proc. Indian Acad. Sci.*, **A38**, 297 (1953). The greater bathochromic shift of the longest wavelength band of 2,3-disubstituted naphthalenes compared with 1,2-disubstituted naphthalenes and the added bathochromic shift due to the intramolecular hydrogen bonding of 2-hydroxy-3-naphthoic acids afford a simple means of distinguishing the latter from other position isomers. The longest wavelength band of 2-hydroxy-3-naphthoic acids occurs in the region from 370 to 380 mμ; the other known isomers have the corresponding band from 300 to 340 mμ, depending on the position of the two substituents and the possibility of chelation.

(17) M. M. Przhujalgovskaya, L. N. Lavrishcheva, and V. N. Belov, *J. Gen. Chem. USSR*, **27**, 1349 (1957); **30**, 1617 (1960).

(18) M. Stiles, personal communication, 1963. Dr. Stiles has kindly informed us that in their laboratory preliminary carboxylation experiments on 2-tetralone led to a complex mixture from which only derivatives of 2-tetralone-3-carboxylic acid could be isolated.

(19) Eastman Organic Chemicals, No. T 392.

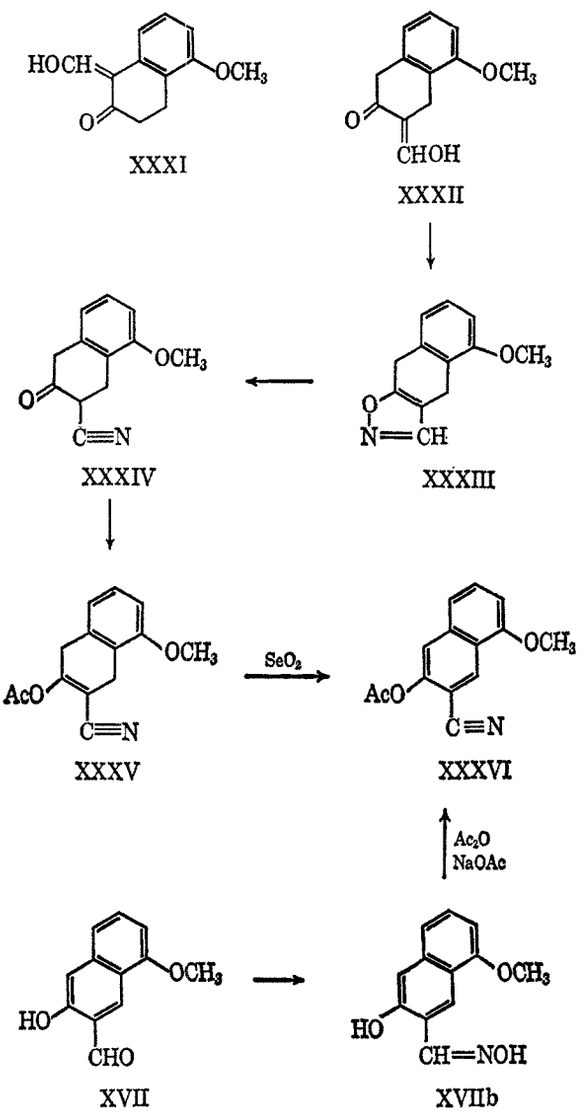
CHART V



XXVII, R=H
XXVIII, R=OCH$_3$

XXIX, R=H
XXX, R=OCH$_3$

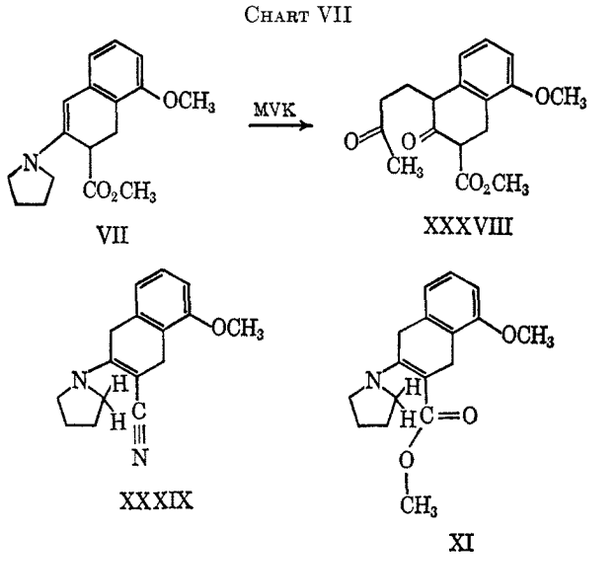
CHART VI



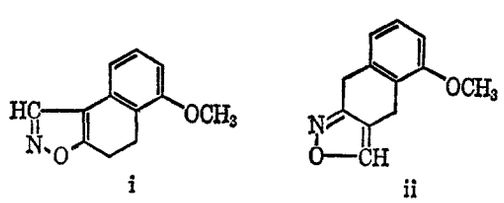
Since carboxylation and oxalylation[10] of 2-tetralones were shown to occur preferentially at the 3-position under the conditions described, we were prompted to study the course of formylation of 5-methoxy-2-tetralone (II). The latter reacted smoothly with ethyl formate–sodium methoxide to yield a hydroxylmethylene derivative, mp 102–103°, for which we originally suggested structure XXXI[7] (Chart VI). More recent work has required revision of the structure to that of a 3-hydroxymethylene derivative (XXXII) since the compound could be converted to cyano ketone XXXIV *via* the isoxazole XXXIII[20] prepared by a conventional procedure.[21,22] The structure of the cyano ketone XXXIV was confirmed by transformation to the cyanonaphthalene XXXVI by selenium dioxide dehydrogenation of the corresponding enol acetate XXXV. The cyanonaphthalene XXXVI synthesized by this procedure was found to be identical with an authentic sample obtainable by the following method. The aldehyde XVII was converted to the corresponding oxime XVIIb, dehydration of which with acetic anhydride–sodium acetate[23] afforded the cyanonaphthalene XXXVI identical in all respects with a sample obtained from the hydroxymethylene derivative. Thus, it follows that formylation,[24] under the conditions described, occurs preferentially at the 3-position of 2-tetralones.

It is interesting to note that the pyrrolidine enamine VII (Chart VII) of VI reacts smoothly with methyl vinyl ketone in dioxane to afford the diketone XXVIII. Under the same conditions the enamine XXXIX, derived from cyano ketone XXXIV, was recovered unchanged. It is not clear why the cyano enamine XXXIX contains a tetrasubstituted double bond

CHART VII



compound isomeric with the isoxazole XXXIII. Initially we thought that this isomer would have structure i, derived possibly from the 1-hydroxymethylene derivative (XXXI), and had undergone isomerization with acid to give XXXIII when treated with hydroxylamine hydrochloride. However, this was disproved since the isomer was recovered unchanged either on refluxing with acetic acid containing hydrogen chloride or on treatment with sodium ethoxide. It is likely that the isomer possesses the structure ii.



i ii

(20) The hydroxymethylene derivative of 5-methoxy-2-tetralone on treatment with hydroxylamine acetate in acetic acid furnished a crystalline

(21) W. S. Johnson, J. W. Petersen, and C. D. Guitsche, *J. Am. Chem. Soc.*, **67**, 2274 (1945); **69**, 2942 (1947).

(22) R. T. Rapala, B. W. Roberts, W. L. Truett, and W. S. Johnson, *J. Org. Chem.*, **27**, 3814 (1962).

(23) M. N. Browne and R. L. Shriner, *J. Org. Chem.*, **22**, 1320 (1957).

(24) Professor Turner has informed us that, in repeating the sequence of reactions, they have been able to isolate an isomeric isoxazole from the mother liquors which can be converted to 1-methyl-5-methoxy-2-tetralone. This would suggest that either a small amount of the 1-hydroxymethylene derivative is formed when 5-methoxy-2-tetralone is treated with ethyl formate or some rearrangement occurs during the formation of the isoxazole. Moreover, they have synthesized 1-cyano-5-methoxy-2-tetralone and shown it to be different from our 3-cyano derivative.[25] We thank Professor Turner for informing us of these results prior to publication.

(25) P. Grafen and R. B. Turner, *Tetrahedron Letters*, **No. 52**, 3935 (1964).

whereas the corresponding carbomethoxy enamine VII has a trisubstituted double bond. A study of molecular models does not indicate a clear preference between the possible double-bond structures.[26] Perhaps the greater electron-withdrawing power of the cyano group compared with the carbomethoxy group accounts for the double bond in XXXIX conjugating with the -CN rather than with the aromatic ring.

Experimental Section

General Procedures.—Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Finely powdered samples were placed on the stage 15° below the melting point and the temperature was raised at a rate of about 4°/min. Ultraviolet spectra were determined in 95% ethanol on a Perkin-Elmer Model 202 spectrophotometer and infrared spectra on Perkin-Elmer Model 137 and 237 spectrophotometers. Infrared spectra are in Nujol unless otherwise indicated. Proton magnetic resonance (pmr) spectra were taken on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The removal of solvents *in vacuo* was accomplished with a Craig-type rotating flash evaporator at 15–20 mm and with the water bath usually at 35–50°.

3-Carbomethoxy-5-methoxy-2-tetralone (VI).—Magnesium methyl carbonate[5,6] (from 40 g of pure magnesium) was dissolved in 400 ml of dry dimethyl formamide followed by slow addition of 36 g of 5-methoxy-2-tetralone (II). The clear solution was then heated in an atmosphere of nitrogen at 130° for 4 hr and the methanol formed during the reaction was allowed to distill. The reaction mixture was then cooled in an ice bath and added slowly, with vigorous stirring, to 1500 ml of ice-cold 10% hydrochloric acid. The solid which separated was collected, washed well with water and then with small quantities of cold acetone, and finally allowed to dry in the air. A small portion of the crude acid (20 g) was crystallized thrice from acetone to give iridescent cubes of V: mp 153–155°; ν_{max} 2632, 1661, 1608, and 1404 cm^{-1}. The ultraviolet spectrum showed maxima at 214 mμ (ε 11,750), 264 mμ (6,500), and 279 mμ (3,900).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.36; H, 5.55.

The acidic filtrate and washings furnished 15 g of the recovered tetralone upon extraction with ether followed by removal of the solvent and distillation of the residue at 135° (0.5 mm).

The above crude acid (19.5 g) was suspended in 600 ml of dry ether to which 25 ml of methanol had been added and treated slowly with a cold ethereal solution of diazomethane (prepared from 33 g of "Diazald") with stirring. After addition of diazomethane was complete, the stirring was continued for 1 hr, and then the bulk of the solvent was removed under reduced pressure whereupon the keto ester VI separated from the solution as colorless, slender needles. The product was collected, washed with a small quantity of cold alcohol, and pressed dry. The air-dried material weighed 15 g. On recrystallization from acetone, it was obtained as clusters of long colorless needles VI: mp 123°, yield 12 g. An analytical specimen on crystallization twice from acetone had mp 123–125°; ν_{max} 1672, 1634, and 1404 cm^{-1} (-$COCH_2$); λ_{max} 214 mμ (ε 12,900), 262 mμ (6,460), and 278 mμ (3,890); in base, λ_{max} 225 mμ (7,660), 279 mμ (11,220), and 288 mμ (11,480).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.41; H, 5.95.

The above keto ester readily furnished an ethylene ketal which crystallized from methanol as cubes: mp 93.5; ν_{max} 1727 (-$COOCH_3$) and 1081 cm^{-1} (ketal).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.68; H, 6.54.

Pyrrolidine Enamine of 3-Carbomethoxy-5-methoxy-2-tetralone (VII).—The keto ester (500 mg) in benzene (30 ml) was heated to reflux under nitrogen and treated dropwise with freshly distilled pyrrolidine (0.8 ml). The mixture was refluxed for 12 hr with an attached Bidwell–Sterling trap to remove water. The pale yellow solution was diluted with benzene (50 ml), washed with water, dried, and the solvent was evaporated *in vacuo*. The resulting yellow gum (320 mg) was triturated with ether when a crystalline solid (280 mg) soon separated. Recrystallization from acetone–ether (1:1) afforded colorless crystals of the enamine VII: mp 104–105°; ν_{max} 1730 (-$COOCH_3$), 1613 and 1592 cm^{-1}; λ_{max} 225 mμ (ε 8,230), 245 mμ (8,500), 314 mμ (11,230), and 327 mμ (11,480); τ 6.20, 3 H singlet (OCH_3), τ 6.40, 3 H singlet ($COOCH_3$), τ 4.75, 1 H singlet (vinyl proton).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37. Found: C, 71.18; H, 7.32.

Pyrrolidine Enamine of 5-Methoxy-2-tetralone (X).[27]—This enamine prepared in the usual way[27] from 2-tetralone (5.0 g) crystallized as large, rectangluar plates (4.0 g): mp 77–79°; ν_{max} 1618, 1597, and 1563 cm^{-1}; λ_{max} 205 mμ (ε 10,700), 223 mμ (12,000), 245 (10,500), and 316 mμ (14,500); τ 6.15, 3 H singlet (OCH_3), τ 4.82, 1 H singlet (vinyl proton).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.62; H, 8.51.

Morpholine Enamine of 5-Methoxy-2-tetralone (XI).—5-Methoxy-2-tetralone (1.76 g) in benzene (20 ml) containing *p*-toluenesulphonic acid (5 mg) and morpholine (2 ml) was refluxed for 24 hr. The morpholine enamine was obtained as colorless needles: mp 126.5°; τ 6.20, 3 H singlet (OCH_3), τ 4.50, 1 H singlet (vinyl proton).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.52; H, 7.88.

Condensation of the Pyrrolidine Enamine (VII) of 3-Carbomethoxy-5-methoxy-2-tetralone with Methyl Vinyl Ketone to Give Diketone XXXVIII.—The enamine VII of keto ester VI (500 mg) was dissolved in dry dioxane (10 ml) and cooled to 5°. Methyl vinyl ketone (0.32 g) in dioxane (5 ml) was added dropwise to the enamine solution with occasional shaking. After leaving the reaction mixture overnight in a nitrogen atmosphere at room temperature, benzene (40 ml) was added and the solvents were removed *in vacuo*. The brown resin was suspended in 10 ml of 10% hydrochloric acid and left at room temperature for several hours. On extraction with ether, a diketone XXXVIII (285 mg) was obtained as slender needles, mp 111.5–112.5°. An analytical sample crystallized from methanol: mp 114°; it gave violet color with alcoholic ferric chloride; ν_{max} 1706 (>C=O), 1667, and 1626 cm^{-1}; λ_{max} 260 mμ (ε 5,570), λ_{sh} 278 mμ (3,040) and 282 mμ (2,030); τ 6.15, 6 H singlet (OCH_3 and $COOCH_3$), τ 7.97, 3 H singlet (-C-$COCH_3$).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.36; H, 6.46.

Enol Acetate of 3-Carbomethoxy-5-methoxy-2-tetralone (XII).—3-Carbomethoxy-5-methoxy-2-tetralone VI (400 mg) was dissolved in acetic anhydride (5 ml) containing 5 mg of *p*-toluenesulfonic acid. After refluxing for 3 hr at 140° (bath temperature), the reaction mixture was poured over ice and left at room temperatue overnight. Next morning, the solid that separated was collected and washed with 5% sodium bicarbonate and finally with water. On crystallization from ether, the enol acetate (XII, 320 mg) was obtained as colorless prisms: mp 97.5°; ν_{max} 1760 (enol acetate carbonyl), 1712 (>C=C-CO_2CH_3), and 1686 (>C=C<); λ_{max} 203 mμ (ε 47,000), 273 mμ (2,400), 280 mμ (2,400); τ 6.15, 6.20, 3 H singlets (OCH_3 and $COOCH_3$), τ 7.75, 3 H singlets ($OCOCH_3$), τ 6.30, 4 H singlet (cyclic methylene protons), no vinyl proton.

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.50; H, 5.74.

2-Acetoxy-3-carbomethoxy-5-methoxynaphthalene (XIII).—A mixture of the foregoing enol acetate XII (300 mg), selenium dioxide (76 mg), and glacial acetic acid (5 ml) was refluxed for 5 min in a nitrogen atmosphere. After removal of acetic acid *in vacuo*, the residue was dissolved in benzene and washed with 5% sodium bicarbonate solution and finally with water. After drying, the benzene solution was concentrated *in vacuo* and chromatographed over Florisil (5 g) covered with a layer of dry silver oxide (3 g). On elution of the column with benzene, the naphthalene derivative XIII was obtained as pale yellow plates (220 mg): mp 119–121°. Recrystallization from methanol gave an analytical specimen: mp 123–124°; ν_{max} 1754 (acetate carbonyl) and 1730 cm^{-1} (ester); λ_{max} 214 mμ (ε 40,000), 249 mμ (48,000), 288 mμ (4,900), 297 mμ (5,600), 307 mμ (4,600) and 347 mμ (6,400); τ 6.07, 6.00, 3 H singlets (OCH_3 and $COOCH_3$), τ 7.62, 3 H singlet (aromatic $OCOCH_3$).

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.51; H, 5.31.

(26) A referee suggests that there may be steric inhibition of resonance for a structure such as XL, but not for XXXIX.

(27) We thank Mr. Burton Hawley for performing this experiment. *Cf.* T. Matsumoto and A. Suzuki, *Bull. Chem. Soc. Japan*, **34**, 374 (1961).

2-Hydroxy-5-methoxy-3-naphthoic Acid (XIV).—Compound XIII (50 mg) was refluxed in 5% methanolic potassium hydroxide under nitrogen for 4 hr. Work-up gave 45 mg of the acid, which crystallized as pale yellow needles from benzene: mp 228.5–230.5° dec; ν_{max} 3300 (OH) and 1661 cm^{-1} (–CO_2H); λ_{max} 227 mμ (ε 34,200), 235 mμ (40,700), 260 mμ (20,600), 301 mμ (5,600), 309 mμ (4,650), and 370 mμ (2,900). There was no depression in melting point on admixture with an authentic sample of the acid described below, prepared from glycolate XV.

Glycoate (XV).—The procedure used parallels that of Soffer.[10] 5-Methoxy-2-tetralone (II, 15.96 g) was added to a mixture of sodium methoxide (5.56 g), dry benzene (50 ml), and dimethyl oxalate (10.08 g). After allowing the reaction mixture to stand at room temperature for 2.5 hr, it was refluxed for 1 min and worked up in the usual manner. There was obtained 10.32 g of crude glyoxalate XV, which on crystallization from benzene melted at 126–127°: ν_{max} 3570 (–OH), 3320 (hydrogen-bonded OH), and 1748 cm^{-1} (ester); λ_{max} 223 mμ (ε 49,000), 250 mμ (32,000), 279 mμ (3,800), 288 mμ (4,300), 298 mμ (3,500), 326 mμ (1,850), and 336 mμ (2,100).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.31; H, 6.44.

Glycolate Diacetate XVa.—The glyoxalate diacetate, prepared in acetic anhydride–pyridine, melted at 128–129°, after crystallization from methanol.

Anal. Calcd for $C_{15}H_{18}O_7$: C, 62.42; H, 5.24. Found: C, 62.63; H, 5.20.

Triol XVI.—The foregoing methyl glycolate (XV, 1.85 g) on reduction with lithium aluminum hydride (1 g) in ether (15 ml) at room temperature, overnight gave 995 mg of the triol XVI which crystallized as needles from benzene: mp 123.5–124.5°; ν_{max} 3546 (free OH) and 3268 cm^{-1} (hydrogen-bonded OH); λ_{max} 222 mμ (ε 38,700), 244 mμ (25,600), 248 mμ (24,700), 279 mμ (3,100), 287 mμ (3,660), 296 mμ (3,020), 318 mμ (1,460), and 332 mμ (1,520).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.84; H, 6.10.

Cleavage of Triol XVI to Aldehyde XVII.—The above triol XVI (196 mg) in 15 ml of methanol was treated with sodium metaperiodate (261 mg) dissolved in the minimum of water. After addition of 5 ml of water the reaction mixture was allowed to stand overnight. After work-up in the usual manner, the product was crystallized from methanol to give 117 mg of yellow needles of aldehyde XVII. An analytical sample melted at 148.5–149.5°: ν_{max} 3300 (OH) and 1664 cm^{-1} (>C=O stretch for aldehyde); λ_{max} 223 mμ (ε 29,900), 257 mμ (30,300), 270 mμ (20,600), 315 mμ (6,850), 323 mμ (7,600), and 398 mμ (2,460).

Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.10; H, 4.97.

Aldehyde Acetate XVIIa.—The acetate prepared by heating XVII in acetic anhydride–pyridine for 30 min on a steam bath melted at 77–78°: ν_{max} 2740, 1757, 1698 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 69.04; H, 4.83.

Oxime (XVIIb).—The acetate XVIIa dissolved in a solution of 2 ml of pyridine and 1 ml of water was treated with 200 mg of hydroxylamine hydrochloride and allowed to stand overnight. Work-up gave the oxime: mp 199–201°; ν_{max} 3472 (OH), 1639 (>C=N–); no absorption for an acetate group. This product was identical with that prepared by treatment of XVII with hydroxylamine hydrochloride (see below).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10. Found: C, 66.24; H, 5.02.

Oxidation of Aldehyde XVII to 2-Hydroxy-5-methoxy-3-naphthoic Acid (XIV).—A solution of 47 mg of aldehyde XVII in a mixture of ethanol, 57 mg of silver nitrate, and 6 ml of water was treated dropwise (under nitrogen) over 2 hr with a solution of 55 mg of sodium hydroxide in 15 ml of water. After the addition of alkali the reaction mixture was allowed to stand at room temperature for 4 hr. Excess silver oxide was collected and most of the ethanol was removed *in vacuo*. Water was added and the brown solution was extracted with ether. Acidification of the aqueous extract with cold 10% sulphuric acid gave the crude naphthoic acid. The products from this run and from another in which 208 mg of aldehyde XVII was oxidized, were combined and chromatographed in benzene over silicic acid to give naphthoic acid XIV. After crystallization from benzene (105 mg), it melted at 228.5–230.5° dec: ν_{max} 3330 (free OH stretch) and 1667 cm^{-1} (acid >C=O stretch); λ_{max} 228 mμ (ε 33,000), 236 mμ (37,500), 260 mμ (20,100), 302 mμ (5,170), 310 mμ (4,280), and 370 mμ (2,760). This acid was identical in all respects with the sample prepared by saponification of XIII (see above).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.87; H, 4.76.

2-Tetralone-3-carboxylic Acid (XX).—Magnesium methyl carbonate[5,6] prepared from 14 g of pure magnesium was dissolved in 100 ml of dry dimethyl formamide (DMF) followed by slow addition of 13 g of 2-tetralone[28] in 40 ml of DMF. The reaction mixture was heated in an oil bath at 115–120° for 4 hr under nitrogen and the methanol which was formed was allowed to distill. The cold reaction mixture was poured into 300 ml of ice-cold 20% hydrochloric acid with vigorous stirring. The white powder which separated was collected. The yield of very crude acid from two such runs was 4.18 g. Crystallization from methanol gave a product melting at 113–115° (lit.[17] 110–113° dec): ν_{max} 2625, 2688, 1667, 1600, and 1580 cm^{-1}.

3-Carbomethoxy-2-tetralone (XXI).—Methylation of XX with diazomethane gave the methyl ester XXI, mp 45–46° (lit.[17] mp 49°), ν_{max} 1664 cm^{-1}.

3-Carbomethoxy-2-tetralone Enol Acetate (XXIII) and 2-Tetralone Enol Acetate (XXIV).—Magnesium methyl carbonate,[5,6] prepared from 14 g of magnesium was treated with 13 g of 2-tetralone as previously described. After refluxing for 4 hr, the reaction mixture was evaporated to dryness *in vacuo* and treated with an excess of acetic anhydride. The mixture was allowed to stand at room temperature overnight and was then evaporated to dryness. The infrared spectrum indicated the presence of a carboxylic acid salt or complex. The dry complex was dissolved in 100 ml of acetic anhydride and 100 ml of acetic acid and heated on a steam bath overnight. After removal of excess acid and anhydride *in vacuo*, the resulting dark red oil was taken up in benzene, treated wih water, washed with sodium bicarbonate solution, and dried. Evaporation of the benzene gave 3.0 g of yellow oil. The infrared spectrum and tlc (four spots) suggested this consisted of a mixture of enolactates XXII and XXIV: ν_{max} (neat) 1724 (CO_2H), 1761, 1675, and 1205 cm^{-1} (enol acetate).

The 3.0 g of yellow oil was methylated immediately with etherial diazomethane. Chromatography over 110 g of Florisil gave a product showing two spots by tlc. All fractions were combined (2.5 g) and rechromatographed in benzene over 100 g of silicic acid. Benzene eluted 0.82 g of enolactate XXIII: mp 76.0–76.5°; ν_{max} 1757, 1669, 1236 (enol acetate), 1718 cm^{-1} (>C=C–CO_2CH_3). Chloroform–hexane (1:1) eluted 0.95 g of the enol acetate of 2-tetralone (XXIV) as an oil: ν_{max} 1761, 1667, 1205 cm^{-1} (enol acetate). Enol acetate XXIII was identical with a sample prepared by treatment of 3-carbomethoxy-2-tetralone (XXI) with acetic anhydride and *p*-toluenesulfonic acid (see below).

Conversion of XXI to the Enol Acetate (XXIII).—A solution of 200 mg of keto ester XXI in 5 ml of acetic anhydride and 5 mg of *p*-toluenesulfonic acid was refluxed for 4 hr under nitrogen. Work-up in the usual manner followed by chromatography over acid-washed alumina afforded 95 mg of enol acetate XXIII. Recrystallizatin from methanol gave an analytical sample melting at 75.76.0°: ν_{max} 1715 (>C=C–CO_2CH_3), 1761, 1675, 1236 cm^{-1} (enol acetate). This material was identical with material prepared by treatment of the carboxylation complex from β-tetralone with acetic anhydride–acetic acid, followed by methylation (see above).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.55; H, 5.64.

Dehydrogenation of Enol Acetate (XXIII) to 2-Acetoxy-3-carbomethoxynaphthalene (XXV).—A solution of 177 mg of XXIII in 20 ml of glacial acetic acid was treated with 86 mg of freshly sublimed selenium dioxide and boiled under reflux for 2 hr. After removing the solvent *in vacuo*, the residue was taken up in benzene and washed with 10% sodium bicarbonate solution. Chromatography over a column of silicic acid covered with a layer of silver oxide gave 18 mg of needles of the naphthalene derivative XXV: mp 96–97°; ν_{max} 1754, 1220 (OAc), 1718 (CO_2CH_3), 1631 cm^{-1} (aromatic C=C); λ_{max} 236 mμ (ε 57,700), 271 mμ (5,400), 280 mμ (6,320), λ_{sh} 291 mμ (3,930), λ_{max} 325–340 mμ (1190). This material had an infrared and ultraviolet spec-

(28) Columbia Organic Chemicals Co.; *cf.* J. G. Stork and E. L. Foreman, *J. Am. Chem. Soc.*, **68**, 2172 (1946); M. D. Soffer, M. P. Bellis, H. E. Gellerson, and R. A. Stewart, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., p 903, 1963.

trum identical with that of an authentic sample prepared from 2-hydroxy-3-naphthoic acid (see below).

2-Acetoxy-3-carbomethoxynaphthalene (XXV) from XXVI.—A sample of 2-hydroxy-3-naphthoic acid (XXVI) was refluxed for 10 min in acetic anhydride containing a trace of sulfuric acid. The mixture was treated with water, acetic acid and anhydride were removed *in vacuo*, and the residue was taken up in ether. The ether solution was washed, dried, and treated with diazomethane. The product XXV was obtained as needles in 90% yield: mp 97.0–97.5°; ν_{max} 1754, 1218 (OAc), 1715 (CO_2CH_3), 1629 cm^{-1} (aromatic C=C); λ_{max} 236 mμ (ε 57,400), 271 mμ (5,150), 281 mμ (6,110), λ_{sh} 292 mμ (3,290), λ_{max} 325–340 mμ (1,140).

3-Hydroxymethylene-5-methoxy-2-tetralone (XXXII).—5-Methoxy-2-tetralone (II) (1.54 g) dissolved in dry ether (30 ml) was stirred with freshly distilled ethyl formate (2.2 ml) and cooled to 0°. Freshly prepared sodium methoxide (645 mg) was added very slowly during a period of 1 hr and the reaction was conducted in an atmospere of dry nitrogen. After 6 hr, 30 ml of water was added and the mixture was quickly extracted with ether. The aqueous layer was cooled to 5° and acidified with 25 ml of 2 *M* sodium dihydrogen phosphate solution. The yellow solid that separated was quickly extracted with ether and the ether solution was washed and dried. After evaporation of the solvent, the residue (825 mg) was crystallized from dry ether to give 535 mg of yellow needles, mp 97–99°. Tlc of this sample in the system benzene–methanol (4:1) showed one strong spot and one weak spot. Recrystallization gave one-spot material: mp 102–103°; ν_{max} 1661 and 1608 cm^{-1} (–CO–C=CHOH); λ_{max} 205 mμ (ε 9,330), 280 mμ (3,980), and 308 mμ (3,390); τ 6.13, 3 H singlet (OCH_3), τ 6.37, singlet (methylene protons).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.79; H, 5.74.

Tlc of the mother liquor gave a strong spot for XXXII and a weak one indicating another component in the reaction mixture.

Isoxazole (XXXIII).—The above hydroxymethylene derivative (XXXII, 150 mg) dissolved in glacial acetic acid (1.4 ml) was treated with hydroxylamine hydrochloride (76 mg). The reaction mixture was heated under reflux for 5 min in an atmosphere of dry nitrogen and worked up as usual. The crude residue was passed through a column of neutral alumina (10 g) using benzene as the eluent. The first 25-ml portion of the eluate, on evaporation of the solvent *in vacuo*, gave white needles of the isoxazole XXXIII, mp 127–131°. Recrystallization from acetone gave 35 mg: mp 130–132°; ν_{max} 1658, and 1605 cm^{-1}; λ_{max} 274 mμ (ε 1,740) and 280 mμ (1,950); τ 6.17, 3 H singlet (OCH_3), τ 1.80, singlet (–N=C*H*–), τ 6.10 multiplet (cyclic methylene protons). An analytical sample melted at 133–134°.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51. Found: C, 71.60; H, 5.63.

Treatment of XXXII with Hydroxylamine Acetate.[20]—The hydroxymethylene compound XXXII (90 mg), hydroxylamine acetate (109 mg), and glacial acetic acid (2 ml) were refluxed for 10 min and the reaction mixture was worked up as described earlier. The crude residue dissolved in benzene was chromatographed over neutral alumina (10 g) using benzene as the eluent. The first 50-ml fraction, on evaporation *in vacuo*, gave a small amount of a colorless residue which could not be induced to crystallize. Further elution of the column with benzene containing 5% methanol afforded a yellow residue which when crystallized from ether melted at 92–95°. Recrystallization from the same solvent afforded needles (47.2 mg): mp 95.5–96.5°; ν_{max} 1653 cm^{-1}; τ 6.10, 3 H singlet (OCH_3), τ 1.73, singlet (–O–C*H*=C), τ 5.90 broad peak (cyclic methylene protons).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51. Found: C, 71.80, 71.97; H, 5.78, 5.69%.

A solution of 40 mg of the foregoing compound in 2 ml of acetic acid and 3 drops of concentrated HCl was refluxed for 10 min. Work-up gave recovered starting material. Also treatment of the product with a solution of sodium methoxide in methanol did not cause any change.

3-Cyano-5-methoxy-2-tetralone (XXXIV).—The foregoing isoxazole XXXIII (616 mg) in 15 ml of dry benzene was treated with sodium methoxide (from 180 mg of sodium in 15 ml of methanol) at room temperature under nitrogen for 4 hr. Work-up gave 585 mg of residue which crystallized from acetone to give 402 mg of the crude cyano ketone XXXIV. Crystallization from acetone afforded colorless needles: mp 168–169°; ν_{max} 3205 (OH), 2212 (–CN), and 1672 cm^{-1} (carbonyl); λ_{max} 272 mμ (ε 8,320) and 278 mμ (7,590).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51. Found: C, 71.68; H, 5.32.

Ethylene Ketal of XXXIV.—A solution of 73 mg of XXXIV in 15 ml of dry benzene was refluxed with 0.2 ml of ethylene glycol and 5 mg of *p*-toluenesulfonic acid. After 20 hr, 0.3 ml of ethyl ene glycol and 5 mg of PTS were added and refluxing was continued for 2 days. Work-up in the usual way afforded 59 mg of product, mp 124–127°. Recrystallization gave the pure ethylene ketal of XXXIV: mp 125–126°; ν_{max} 2247 (–CN) and 1081 cm^{-1} (ketal).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16. Found: C, 68.56; H, 6.36.

Pyrrolidine Enamine XXXIX of 3-Cyano-5-methoxy-2-tetralone.—The cyano ketone (XXXIV, 100 mg) in benzene (5 ml) was heated to reflux under nitrogen and treated dropwise with pyrrolidine (500 mg) and 5 mg of *p*-toluenesulfonic acid. After 40 hr, the reaction mixture was worked up as usual and the product on crystallization from acetone gave 80 mg of enamine: mp 144.5–146.5°; ν_{max} 2174 (–CN), 1613, and 1582 cm^{-1}; λ_{max} 214 mμ (ε 11,750), 280 mμ (12,590), and 289 mμ (13,180); τ 6.18, 3 H singlet (OCH_3), no vinyl proton.

Anal. Calcd for $C_{16}H_{18}NO_2$: C, 75.56; H, 7.13. Found: C, 75.38; H, 7.08.

Enol Acetate of 3-Cyano-5-methoxy-2-tetralone (XXXV).—3-Cyano-5-methoxy-2-tetralone (XXXIV, 463 mg) was dissolved in acetic anhydride (10 ml) containing *p*-toluenesulfonic acid (5 mg) and refluxed gently for 6 hr in an atmosphere of nitrogen. The reaction mixture was worked up as before and the crude enol acetate (362 mg) was obtained as pale yellow needles. On recrystallization from methanol, it melted at 123–124°: ν_{max} 2230 (–CN), 1760 (enol acetate), and 1680 cm^{-1} (C=C stretch); λ_{max} 202 mμ (ε 28,600), 275 mμ (2,100), and 281 mμ (2,350); τ 6.17, 3 H singlet (OCH_3), τ 7.72, 3 H singlet ($OCOCH_3$), τ 6.37, triplet (cyclic methylene protons), no vinyl proton.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39. Found: C, 69.07; H, 5.51.

2-Acetoxy-3-cyano-5-methoxynaphthalene (XXXVI).—The above enol acetate (XXXV, 85 mg) was dissolved in glacial acetic acid (10 ml) containing selenium dioxide (50 mg) and refluxed for for 4 hr in a nitrogen atmosphere. Benzene was added and the solvents were evaporated *in vacuo*. The residue in benzene was washed with 5% sodium bicarbonate solution, dried, and chromatographed over Florisil (5 g) covered with a layer of dry silver oxide (3 g). Elution of the column with benzene gave naphthalene XXXVI which crystallized as cubes from ether: mp 118–119° (undepressed on admixture with an authentic sample); ν_{max} 2237 (–CN) and 1764 cm^{-1} (aromatic acetate); λ_{max} 215 mμ (ε 38,900), 252 mμ (40,600), 290 mμ (2,840), 299 mμ (3,430), 310 mμ (2,960), and 352 mμ (5,150).

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59. Found: C, 69.77; H, 4.53.

2-Hydroxy-5-methoxy-3-naphthaldehyde Oxime (XVIIb).—2-Hydroxy-5-methoxy-3-naphthaldehyde (XVII, 166 mg) was dissolved in a solution of pyridine (2 ml), water (1 ml), and hydroxylamine hydrochloride (200 mg), warmed to 50° for 1 hr and left at room temperature overnight. After work-up in the usual manner, oxime XVIIb was obtained as pale yellow needles (150 mg), mp 198–200°, on crystallization from benzene.

Anal. Calcd for $C_{12}H_{11}HO_3$: C, 66.35; H, 5.10. Found: C, 66.47; H, 5.33.

Dehydration of Oxime XVIIb to 2-Acetoxy-3-cyano-5-methoxynaphthalene (XXXVI).—A solution of 30 mg of oxime XVIIb in 10 ml of acetic anhydride was treated with 100 mg of freshly fused sodium acetate and refluxed for 4 hr. After removal of acetic anhydride *in vacuo*, the residue was treated with water and allowed to stand at room temperature for 4 hr. The residue, obtained after extraction with ether, was crystallized twice from ether to give colorless cubes: mp 116–117°; ν_{max} 2237 (–CN) and 1764 cm^{-1} (aromatic acetate); λ_{max} 215 mμ (ε 38,000), 252 mμ (40,300), 291 mμ (2,860), 300 mμ (3,300), 310 mμ (3,040), and 352 mμ (5,240); τ 6.03, 3 H singlet (OCH_3), τ 7.60, 3 H singlet ($OCOCH_3$).

Anal. Calcd for $C_{14}H_{11}HO_3$: C, 69.70; H, 4.59. Found: C, 69.96; H, 4.66.

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