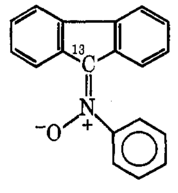
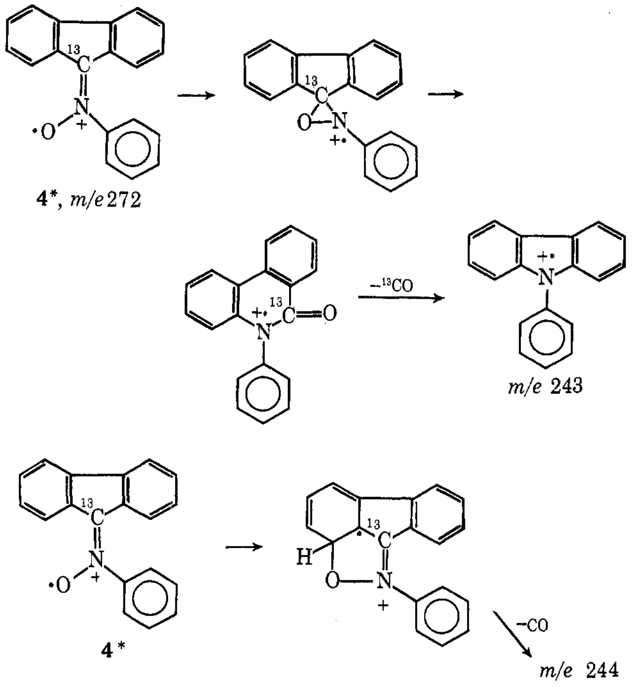


4*

While the mass spectra of 1 and 4 are quite normal and in accord with results reported in an earlier study,[2] the mass spectral fragmentation of 2 is remarkably similar to that of 1 but significantly unlike that of 4 (see Table I).



Experimental Section

Fluorenone anil was prepared according to the procedure described by Reddelien.[10]

Fluorenone Anil *N*-Oxide (4).—To a solution of 5.0 g of fluorenone anil in 200 ml of chloroform was added 7.2 g of *m*-chloroperoxybenzoic acid (85% pure). The yellow solution, which turned pale yellow after 45 min, was kept at room temperature for 3 days. The solution was poured through a column of neutral alumina and then evaporated on the Rotovac. The resulting material was crystallized from 95% ethanol affording yellowish needles of 4, 3.4 g (64%), mp 189–190° (lit.[7] mp 191–193°).

***N*-Phenylphenanthridone (2). A.**—A 4×10^{-3} *M* solution of 4 (500 ml) in cyclohexane was irradiated for 8 hr in a water-cooled chamber with a 450-W medium-pressure total immersion lamp (quartz filter). After irradiation, examination of the solution by thin layer chromatography gave evidence that most of the starting material had been unaffected by the irradiation. Evaporation of solvent gave an oil which was passed through a column of silica gel with chloroform. The first eluted fraction, after removal of solvent, was an oil which had an infrared spectrum similar to that of an authentic sample of *N*-phenylphenanthridone.

B.—A 10^{-4} *M* solution of 4 (500 ml) in 95% ethanol was irradiated for 3 hr in a Rayonet reaction chamber with 2537-Å lamps and then the solvent was evaporated. The solid residue (8.5 mg, mp 218°) was recrystallized from 95% ethanol to give colorless crystals of 2, 2.8 mg (21%), mp 227° (lit.[11] mp 225°). The infrared spectrum, identical with that of an authentic sample of 2, exhibited characteristic peaks at 2920, 1650, 1450, 1370, and 745 cm^{-1}.

Biphenyl-2-carboxylic Acid-α-^{13}*C*.—2-Iodobiphenyl was converted to the Grignard reagent which was carbonated using the vacuum line technique at −20° with 100 ml of $^{13}CO_2$[12] (54% enrichment, Bio-Rad Laboratories). Crystallization yielded 574.3 mg of colorless crystals (81.2% based on CO_2), mp 113.5–114°. The infrared spectrum exhibited a carbonyl peak at 1680 cm^{-1}; nmr (in CCl_4) showed peaks at δ 11.6 (s, H of acid) and 7.2–8.0 (m, 9 H).

Fluorenone-9-^{13}*C*.—Ring closure was carried out with 574.3 mg (2.92 mmol) of biphenyl-2-carboxylic acid-α-^{13}*C* dissolved in 2.6 ml of 80% sulfuric acid.[13] The mixture was heated at 85° for 0.5 hr and poured onto crushed ice. The greenish-yellow product was extracted with ether and the ether extract was washed with 3 *N* sodium hydroxide. Ether was removed and crystallization from water yielded 419.9 mg (2.32 mmol, 79.5%) of yellow-green product, mp 82° (lit.[13] 84–86°). Ir and nmr spectra were identical with those of unlabeled fluorenone.

9-Fluorenone hydrazone-α-^{13}*C* was prepared according to the procedure described by Wieland and Roseau.[14]

9-Diazofluorene-α-^{13}*C* was prepared by following the procedure of Closs, *et al.*[15]

Fluorenone anil *N*-oxide-α-^{13}*C* (4*) was prepared according to the procedure for the synthesis of 4 as described by Johnson.[16] A slurry of 383.2 mg of 9-diazofluorene-α-^{13}*C* (1.98 mmol) and 212 mg (1.98 mmol) of nitrosobenzene in 10 ml of dry ether was stirred for 1 hr. The mixture was filtered and the yellow crystals were recrystallized from 95% ethanol, mp 198–199° (lit.[16] mp 200°). Ir (CCl_4) exhibited a peak at 1270 cm^{-1} (N→O). The mass spectrum at 20 eV showed 52.6% excess ^{13}C.

Registry No.—**1**, 15263-58-8; **2**, 13355-65-2; **4**, 4535-09-5; biphenyl-2-carboxylic acid-α-^{13}*C*, 31504-46-8.

Acknowledgment.—We are grateful to Professor Edward C. Taylor for generous supplies of compounds 1 and 2.

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[10] G. Reddelien, *Ber.*, **43**, 2476 (1910).

[11] D. H. Hey and T. M. Moynehan, *J. Chem. Soc.*, 1563 (1959).

[12] A. Murray and D. H. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958, p 78.

[13] C. Heidelberger and H. Reike, *Cancer Res.*, **11**, 640 (1951).

[14] H. Wieland and A. Roseau, *Justus Liebigs Ann. Chem.*, **381**, 231 (1911).

[15] G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964).

[16] A. W. Johnson, *J. Org. Chem.*, **28**, 2153 (1963).

Nitration of Antibiotic X-537A and Facile Conversion to 6-Hydroxy-2,7-dimethyl-5-nitroquinoline

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The structure[1] and biosynthesis[2] of antibiotic X-537A (**1a**) have been reported recently. As part of a chemical study on this antibiotic, we have investigated the nitration of **1a** in glacial acetic acid. Treatment with 5 molar equiv of concentrated nitric acid gave the expected 5-nitro derivative **1b**. However, the major product was shown by base degradation to be dinitrophenol **1c**. This result was consistent with the observation[3] that nitration of highly substituted benzene

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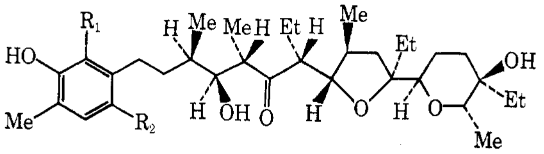
[1] (a) J. W. Westley, R. H. Evans, Jr., T. Williams, and A. Stempel, *Chem. Commun.*, 71 (1970); (b) S. M. Johnson, J. Herrin, S. J. Liu, and I. C. Paul, *ibid.*, 72 (1970).

[2] J. W. Westley, R. H. Evans, Jr., D. L. Pruess, and A. Stempel, *ibid.*, 1467 (1970).

[3] H. Barbier, *Helv. Chim. Acta*, **11**, 157 (1928).

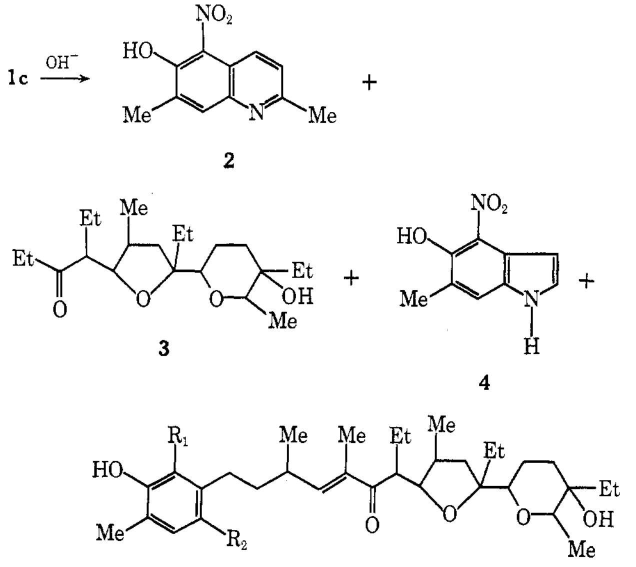
derivatives often results in the displacement of substituents meta to the entering group by additional nitro groups. In addition, salicylic acid is known to readily decarboxylate probably *via* a β-keto acid tautomer.



1a, $R_1 = CO_2H$; $R_2 = H$
b, $R_1 = CO_2H$; $R_2 = NO_2$
c, $R_1 = R_2 = NO_2$

To confirm the structure of **1c**, the derivative was treated under conditions known to cause retroaldol cleavage[1a] of the antibiotic. Four compounds were isolated from the reaction (Scheme I).

SCHEME I



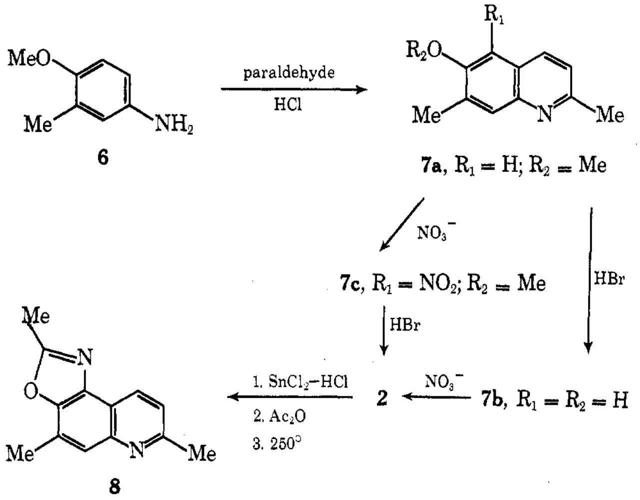
5a, $R_1 = R_2 = NO_2$
b, $R_1 = CO_2H; R_2 = H$

One product was identical with the ketone **3** previously isolated[1a] from **1a** under identical conditions. The other major cleavage product was tentatively identified by microanalysis and spectroscopic methods as 6-hydroxy-2,7-dimethyl-5-nitroquinoline (**2**). A third compound isolated in very low yield was identified as 5-hydroxy-6-methyl-4-nitroindole (**4**) by comparison with material prepared by nitration of 5-hydroxy-6-methylindole.[4]

The structure of the three cleavage products was consistent with the dinitrophenol structure **1c**, proposed for the major nitration product of antibiotic X-537A. The fourth compound isolated was the α,β-unsaturated ketone **5a**, which arose from dehydration of the β-ketol system in **1c**. The analogous compound **5b** has been isolated[5] from base treatment of the antibiotic.

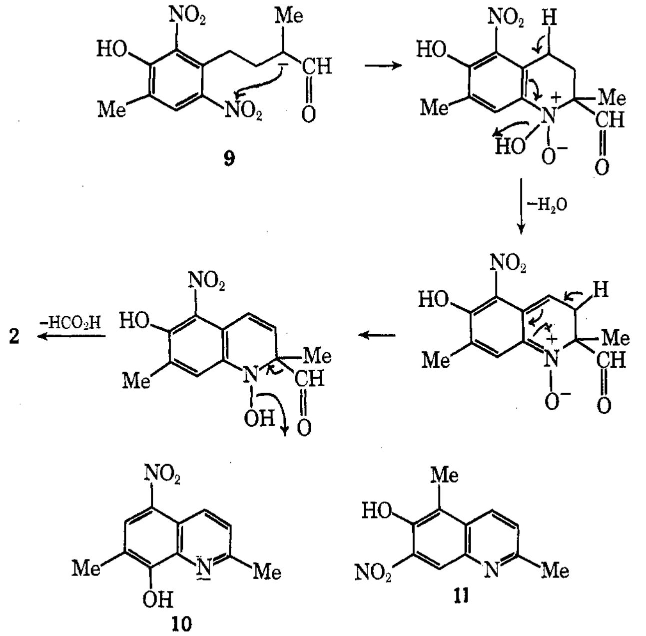
Confirmation of structure **2** was provided by an alternative synthesis (Scheme II). Conversion of **2** in three steps[6] to the oxazoquinoline **8** was further evidence of an *o*-nitrophenol structure for **2**.

SCHEME II



Compound **2** probably arose in the base degradation reaction *via* cyclization of the carbanion **9** followed by dehydration, tantomerization, and elimination of formic acid (Scheme III).

SCHEME III



It should be noted that, whereas cyclization of **9** could have given the 8-hydroxy isomer **10**, the other possible isomer from the Doebner–Miller reaction on 3-methyl-4-methoxyaniline[7] (**6**, Scheme II) would have led to the 2,5-dimethyl isomer **11**. Therefore, only **2** could have arisen from *both* syntheses.

The base-catalyzed cyclization of **9** to **2** is a novel type of quinoline synthesis. However, the aromatic substituents necessary to cause the base-catalyzed cyclization of *o*-nitrophenylbutyraldehyde to quinoline have not been determined.

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[4] F. Troxler, G. Bormann, and F. Seemann, *Helv. Chim. Acta.*, **51**, 1203 (1968).

[5] J. W. Westley and R. H. Evans, Jr., unpublished results.

[6] R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, Wiley, New York, N. Y., 1957, p 420.

[7] M. Heidelberger and W. A. Jacobs, *J. Amer. Chem. Soc.*, **41**, 1450 (1919).

Experimental Section[8]

Conversion of Antibiotic X-537A (1a) into the 5-Nitro Derivative of X-537A (1b) and 2-Methyl-4,6-dinitro-5-(7-ethyl-4-hydroxy-3,5-dimethyl-6-oxo-7-[5-ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]heptyl)phenol (1c).—To a stirred solution of 2.0 g (3.39 mmol) of **1a** in 75 ml of glacial acetic acid was added 1 ml of concentrated nitric acid at room temperature. After 0.5 hr, 75 ml of water was added and the mixture was extracted with two 100-ml portions of ether. The combined extracts were washed with three 100-ml portions of saturated aqueous sodium carbonate solution, dried (Na_2SO_4), and evaporated to give 2.4 g of a yellow solid. Treatment with methylene chloride gave 840 mg (47%) of **1c** as the sodium salt which, on recrystallization from benzene, gave yellow needles: mp 165–170°; $[\alpha]_D$ +19.6° (*c* 1, DMSO); ir (KBr) 1710 and 1605 cm^{-1}; uv max (2-propanol) 413 mμ (ϵ 19,600); nmr (DMSO-d_6) δ 1.92 (s, 3, aromatic CH_3), 3.81 (s, 1, OH), 4.02 (d, 1, CHO, J = 6 Hz), 7.86 (s, 1, aromatic). *Anal.* Calcd for $C_{33}H_{51}N_2O_{10}Na$: C, 60.16; H, 7.80; N, 4.25. Found: C, 59.79; H, 8.07; N, 4.20.

The methylene chloride filtrate was concentrated under reduced pressure and chromatographed on 20 g of silica using methylene chloride–methanol (1%) as the eluent. The first fraction eluted gave 660 mg (37%) of **1b** sodium salt, which, on recrystallization from methylene chloride–hexane, gave pale yellow plates: mp 214–215°; $[\alpha]_D$ −98° (*c* 1, DMSO); ir ($CHCl_3$) 1710, 1605 cm^{-1}; uv max (2-propanol) 262 mμ (ϵ 5800) and 317 (5400); nmr (DMSO-d_6) δ 2.12 (s, 3, aromatic CH_3), 7.60 (s, 1, aromatic). *Anal.* Calcd for $C_{34}H_{52}NO_{10}Na$: C, 62.18; H, 7.98; N, 2.13; Na, 3.49. Found: C, 62.02; H, 8.25; N, 2.11; Na, 3.27.

Base Transformation of 1c into 4-[5-Ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]-3-hexanone (3), 5-Hydroxy-6-methyl-4-nitroindole (4), 6-Hydroxy-2,7-dimethyl-5-nitroquinoline (2), and 2-Methyl-4,6-dinitro-5-(7-ethyl-3,5-dimethyl-6-oxo-7-[5-ethyl-3-methyl-5-(5-ethyl-5-hydroxy-6-methyl-2-tetrahydropyranyl)-2-tetrahydrofuryl]-4-heptenyl)phenol (5a).—A solution of 10 g of the dinitrophenol **1c** in 700 ml of 1:1 aqueous dioxane containing 50 g of sodium hydroxide was stirred for 20 hr at room temperature. The solution separated into two phases, and the upper phase was treated with 200 ml of water and 200 ml of ethyl acetate. The organic layer was separated and concentrated to 6.13 g of a viscous oil. The oil was chromatographed on 350 g of silica using a linear gradient from 4 l. of methylene chloride to 4 l. of 1:1 methylene chloride–ether. The first fraction was concentrated and crystallized by the addition of hexane to give 8 mg (0.3%) of 5-hydroxy-6-methyl-4-nitroindole (**4**) as orange needles: mp 185–187°; uv max (methanol) 210 mμ (ϵ 21,300), 247 (10,200), 274 infl (2890), 398 (9300); ir ($CHCl_3$) 3485, 1630, 1580, 1480 cm^{-1}; nmr ($CDCl_3$) δ 2.38 (s, 3, aromatic CH_3), 7.23 (s, 1, NH), 7.23 (t, 1, J = 2 Hz, CH=CHN), 7.32 (t, 1, J = 2 Hz, CH=CH—N), 7.51 (s, 1, aromatic), 12.01 (s, 1, aromatic OH); mass spectrum (70 eV) m/e 193 (M$^+$), 175 (loss of OH from *o*-nitrophenol system). *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.19; N, 14.57. Found: C, 56.71; H, 3.97; N, 14.22.

The second fraction gave, on evaporation, 4.07 g (76%) of the ketone **3**, which was identical with the compound isolated[1] from retroaldol cleavage of **1a** by uv max (2-propanol) 283 mμ (ϵ 57); ir ($CHCl_3$) 3600, 1710 cm^{-1}; and mass spectrum m/e 354 (M$^+$). *Anal.* Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.37; H, 10.61.

The third fraction was concentrated and, after addition of hexane, gave 501 mg of the sodium salt of the α,β-unsaturated ketone **5a** as yellow needles: mp 222–223°; $[\alpha]_D$ +66° (*c* 1, $CHCl_3$); ir ($CHCl_3$) 1615 and 1605 cm^{-1}; uv max (2-propanol) 232 mμ (ϵ 21,700), 388 (10,850); nmr ($CDCl_3$) δ 1.76 (s, 3, CH_3C=), 2.20 (s, 3, aromatic CH_3), 6.53 (d, 1, J = 10 Hz, C = CHCH), 7.95 (s, 1, aromatic); mass spectrum m/e 640 (M$^+$). *Anal.* Calcd for $C_{33}H_{49}N_2O_9Na$: C, 61.86; H, 7.71; N, 4.37; Na, 3.59. Found: C, 62.09; H, 7.84; N, 4.28; Na, 3.29.

The aqueous phase was acidified with hydrochloric acid to pH 2.0 and extracted twice with ethyl acetate. The extracts were combined and concentrated to 1.8 g of crude solid. Chromatography on 200 g of silica gave a further 360 mg of **5a** for a total yield of 861 mg (9%).

An earlier fraction gave 366 mg (11%) of 6-hydroxy-2,7-dimethyl-5-nitroquinoline (**2**) which crystallized as yellow needles mp 175–176°, from methylene chloride–hexane; ir ($CHCl_3$) 3250, 1660, 1620, 1570, 1520 cm^{-1}; uv max (2-propanol) 221 mμ (ϵ 38,690), 296 sh (4580), 330 (6760), 370 sh (4100); nmr ($CDCl_3$) δ 2.50 (s, 3, aromatic CH_3), 2.72, (s, 3, aromatic CH_3), 7.42, 9.00 (AB, 2, J_{ortho} = 8 Hz, aromatic), 8.02 (s, 1, aromatic), 12.46 (s, 1, aromatic OH); mass spectrum m/e 218 (M$^+$), 201 (loss of OH from *o*-nitrophenol). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.53; H, 4.61; N, 12.89.

5-Hydroxy-6-methyl-4-nitroindole (4).—To 588 mg (4.0 mmol) of 5-hydroxy-6-methylindole[5] dissolved in 25 ml of concentrated sulfuric acid at 5° was added an ice-cold solution of 350 mg (4.1 mmol) of sodium nitrate in 10 ml of concentrated sulfuric acid while maintaining the reaction temperature at 2–5°. After an additional 5 min, the amber-black solution was poured onto 500 ml of ice water. The resulting suspension was extracted with three 200-ml portions of methylene chloride–ethyl acetate (1:1) and the organic phases were backwashed with 100 ml of 5% sodium bicarbonate solution. The combined organic phases were dried (Na_2SO_4), filtered, evaporated under reduced pressure to give a brown solid which was dissolved in 100 ml of methylene chloride, and filtered through a column of 5 g of silica gel prepared in hexane. The column was eluted with chloroform until no residue was obtained on evaporation of the solvent. The red solid (585 mg) thus obtained was crystallized from ether to give 450 mg (59%) of 5-hydroxy-6-methyl-4-nitroindole (**4**) as orange needles, mp 186–187°. This material was identical by mixture melting point, tlc, ir, uv, nmr, and mass spectrum with the compound isolated from the base treatment of **1c**.

6-Methoxy-2,7-dimethylquinoline (7a).—To a solution of 145 g (1.06 mol) of 3-methyl-4-methoxyaniline[7] (**6**) in 500 ml of concentrated hydrochloric acid was added 200 g of paraldehyde. The stirred mixture was warmed in an oil bath to 60°. Another 50 g of paraldehyde was added and the reaction mixture heated to reflux (oil bath 130°) within 1 hr. Heating and stirring were continued for 3.5 hr at 140°. The mixture was allowed to cool to 80° and then was poured into an aqueous solution of excess potassium carbonate. The alkaline solution and its precipitates were extracted with 1 l. of chloroform. The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The remaining black oil was distilled at reduced pressure to yield 77.5 g (29%) of approximately 75% pure **7a** (by nmr), bp 122–27° (0.250 mm). The compound formed a picrate, mp 243–244.5°, which crystallized from methanol. *Anal.* Calcd for $C_{18}H_{16}N_4O_8$ (416.34): C, 51.92; H, 3.87; N, 13.46. Found: C, 51.95; H, 4.06; N, 13.19.

6-Hydroxy-2,7-dimethylquinoline (7b).—A solution of 70 g of crude (75%) **7a** (0.28 mol) in 400 ml of 48% hydrobromic acid was stirred and heated at reflux (oil bath 130°) for 4 hr. Then 100 ml of 48% hydrobromic acid was added and the reaction mixture was heated at 150° for another 4 hr. The mixture was poured over ice. Concentrated ammonia was added until the solution was slightly alkaline. The white precipitate was separated by filtration, washed with water followed by 50% ethanol, and dried *in vacuo* giving 47.0 g of crude material, mp 269–272°. This was extracted with 500 ml of methanol under reflux, cooled, and filtered to yield 32.0 g of **7b**, mp 273–275°, and from the mother liquor an additional 4.8 g, mp 270–273°, was obtained. Total yield was 36.8 g (76%) of **7b**: ir (KBr) 3160–2400, 1950, 1800 cm^{-1}; uv max (2-propanol) 213 mμ (ϵ 43,600), 234 (37,600), 273 (2950), 283 (2800), sh 327 (5000), 337 (5400); nmr (DMSO) δ 2.35 (s, 3, 7-CH_3), 2.57 (s, 3, 2-CH_3) 7.13 (s, 1, H_5), 7.21, 7.95 (AB, 2, J = 8.5 Hz, $H_{3,4}$) 7.68 (s, 1, H_8); mass spectrum m/e 173 (M$^+$). *Anal.* Calcd for $C_{11}H_{11}NO$(173.20): C, 76.27; H, 6.40; N, 8.09. Found: C, 76.27; H, 6.73; N, 8.04.

6-Methoxy-2,7-dimethyl-5-nitroquinoline (7c).—To a stirred solution of 19.5 g (0.078 mol) of approximately 75% (purity) **7a** in 50 ml of concentrated sulfuric acid, 11.0 g (0.108 mol) of potassium nitrate was added at room temperature in small portions over a period of 1 hr. The mixture was then warmed

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(8) The ultraviolet spectra were measured with a Cary recording spectrophotometer Model 14M. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 or HA-100 spectrophotometer. Chemical shifts are reported in δ with the following abbreviations: s, singlet; m, multiplet; t, triplet; b, broad. Optical rotations were measured with a Perkin-Elmer polarimeter Model 141 using a 1% solution at 25°. The mass spectra were taken with a CEC-21-110 mass spectrometer at 70 eV.

to 40° for 3 hr and poured over ice. After neutralization with ammonium hydroxide, the organic material was extracted twice with 200 ml of chloroform. The organic layer was washed twice with 200 ml of water, dried (Na_2SO_4), evaporated, and taken up in 100 ml of ether. This solution was treated with charcoal, heated, and washed thoroughly with ether through 40 g of Florisil. On concentration at reduced pressure and crystallization, 7.37 g (41%) of tan needles, mp 88–89.5°, was obtained. The mother liquor yielded another 1.05 g of less pure material. Recrystallization of the first crop from ether afforded **7c**: mp 88.5–90°; ir ($CHCl_3$) 1526, 1345 cm^{-1}; uv max (2-propanol) 228 mμ (ϵ 51400), 277 (4450), sh 311–314 (5000), 324–325 (6400); nmr (DMSO) 2.52 (s, 3, 7-CH_3), 2.67 (s, 3, 2-CH_3), 3.94 (s, 3-OCH_3), 7.55, 7.96 (AB, 2, J = 8.5 Hz, $H_{3,4}$), 8.06 (s, 1, H_8); mass spectrum *m/e* 232 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$ (232.23): C, 62.06; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.34; N, 11.97.

6-Hydroxy-2,7-dimethyl-5-nitroquinoline (**2**). **Method A.**—To a solution of 32.0 g (184.8 mmol) of **7b** in 100 ml of concentrated sulfuric acid, stirred in an ice bath, a solution of 20.4 g (200 mmol) of potassium nitrate in 50 ml of concentrated sulfuric acid was added dropwise within 30 min. The reaction mixture was stirred for 2 hr in an ice bath and then for 2 hr at room temperature. The reaction mixture was poured over ice, neutralized with ammonium hydroxide, and extracted with 1.5 l. of chloroform. The organic layer was washed twice with 500 ml of water, dried (Na_2SO_4), washed thoroughly with chloroform through 100 g of Florisil, and finally concentrated to 300 ml to yield 33.8 g of **2**, mp 177–178.5°, as small plates. From the mother liquor another 2.95 g, mp 178°, was obtained; the total yield was 36.75 g (91.5%). This material was identical by mixture melting point, tlc, and spectra with the material isolated from the base treatment of **1c**.

Method B.—A mixture of 0.5 g (2.15 mmol) of **7c** and 15 ml of 40% hydrobromic acid was heated at reflux for 3 hr (oil bath temperature 150°), then was poured over ice, neutralized with ammonium hydroxide, and extracted twice with 200 ml of chloroform. The combined chloroform layers were washed with 100 ml of water, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from ethanol and gave 0.39 g (83%) of **2**, yellow needles, mp 177–178.5°.

5-Amino-6-hydroxy-2,7-dimethylquinoline.—A solution of 4.36 g (2.0 mmol) of **2**, in 50 ml of concentrated hydrochloric acid was warmed together with 20 g of stannous chloride dihydrate on a steam bath until the solution became colorless. This mixture was neutralized with sodium carbonate and extracted with 500 ml of chloroform. The emulsion which formed was filtered through Celite. The chloroform layer was separated, dried (Na_2SO_4), and concentrated to yield 250 mg (6.6%) of a brownish powder: mp 231–233°; ir (KBr) 3400, 3350, 3260, 2700–2500 cm^{-1}; mass spectrum *m/e* 188 (M^+). *Anal.* Calcd for $C_{11}H_{12}N_2O$ (188.22): C, 70.18; H, 6.43; N, 14.88. Found: C, 70.23; H, 6.45; N, 15.02.

5-Acetamido-6-acetoxy-2,7-dimethylquinoline.—A solution of 150 mg (0.8 mmol) of 5-amino-6-hydroxy-2,7-dimethylquinoline and 5 ml of acetic anhydride was warmed on the steam bath for 10 min. After cooling, ether was added and the crystals, which were separated by filtration, were washed with ether to yield 180 mg (83%): mp 239.5–240°; ir (KBr) 3275, 1750, 1658 cm^{-1}; nmr (DMSO) 2.16 (s, 3, 7-CH_3), 2.33 (s, 6, 2$CH_3C{=}O$), 2.66 (s, 3, 2-CH_3), 7.37, 8.07 (AB, 2, J_{ortho} = 8 Hz, $H_{3,4}$) 7.80 (s, 1, H_8), 9.80 (s, 1, NH); mass spectrum *m/e* 272 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$ (272.29): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.11; H, 5.99; N, 10.29.

2,4,7-Trimethoxyloxazolo[4,5-*f*]quinoline (**8**).—Pyrolysis of 100 mg (0.37 mmol) of 5-acetamido-6-acetoxy-2,7-dimethylquinoline in a metal bath at 250° resulted in the evolution of acetic acid. After 5 min, the reaction was finished and the crude semicrystalline oil was dissolved in an ether–methylene chloride mixture and washed with methylene chloride through 0.5 g of Florisil. The almost colorless solution was concentrated under reduced pressure. The crude residue crystallized from ether to give 35 mg (45%) of **8**: mp 134–134.5°; nmr ($CDCl_3$) δ 2.64, 2.70, 2.71 (s, 9, 3CH_3) 7.32, 8.55 (AB, 2, J_{ortho} = 8.5 Hz, $H_{3,4}$), 7.71 (s, 1, H_8); mass spectrum *m/e* 212 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O$ (212.24): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.76; H, 5.72; H, 13.27.

Registry No.—**1a,** 25999-31-9; **1b** sodium salt, 31478-24-7; **1c** sodium salt, 31478-25-8; **2,** 31504-47-9; **3,** 31478-26-9; **4,** 31478-27-0; **5a** sodium salt, 31478-28-1; **7a,** 31478-29-2; **7a** picrate, 31478-30-5; **7b,** 31478-31-6; **7c,** 31478-32-7; **8,** 31478-33-8; 5-amino-6-hydroxy-2,7-dimethylquinoline, 31478-34-9; 5-acetamido-6-acetoxy-2,7-dimethylquinoline, 31478-35-0.

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The Decahydro-1*H*-dibenzo[*a*,*h*]quinolizine System

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Having obtained the four isomers of the inside yohimbane system,[1] we turned our attention to their benzene analogs. When 3,4-dimethoxyphenethylamine and 2-formylcyclohexaneacetic acid were heated in acetic acid for a short time the open unsaturated lactam **1** was obtained. Longer heating of either the starting materials or lactam **1** resulted in cyclization to give lactam **2** as the predominant product, lactam **3** as the secondary product, and lactam **4** in trace yield. The lactams were reduced to the corresponding bases **8**, **10**, and **6**, respectively.

In the indole series the main product of the condensation had been the trans-anti isomer. However, the indole lactams may have been formed by a Pictet–Spengler cyclization followed by lactamization thus favoring a different isomer than in this case, where lactamization is the first step.

The uncyclized lactam **1** was reduced to the enamine **5** which on acid treatment undergoes hydrolysis of one methoxyl group and cyclization to the base **12**. The three dimethoxy bases **6**, **8**, and **10** were hydrolyzed to their corresponding dihydroxy derivatives **7**, **9**, and **11**. Further hydrolysis of **12** afforded the dihydroxy compound **11**, whose stereochemistry corresponds to the secondary product of the condensation reaction.

Having three isomers in hand we attempted to obtain the final one by the scheme which had produced the two isomers not obtained from the condensation in the indole series. Base **8** was oxidized to the dehydro compound **13**. Hydrogenation of **13** with platinum in alcohol gave back isomer **8** as the principal product along with isomer **6** and a small amount of isomer **10**. Sodium borohydride reduction gave essentially the same result. Zinc–acid reduction afforded a mixture containing a larger amount of isomer **10** (Scheme I).

The main difference between the indole and benzene series, other than the electronic nature of the two aromatic systems, is the steric relation of the hydrogens at C-1 to the adjacent hydrogen of the aromatic system. In the indole cis series we have shown that the syn

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(1) G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2768 (1967).