slow rate as the host aggregates. The larger 2-methylnaphthalene is also taken up in about a 2:1 ratio, and the cmr spectrum (Figure 12c) shows that the resonances of the CH carbons are more broadened relative to those of the quaternary carbons than for *p*-xylene. Indeed, some additional broadening of the carbon resonances of the salt of **2** seems evident from the spectrum. With either *p*-xylene or 2-methylnaphthalene, the methyl resonances of the included materials are sharp. This is expected on the basis that spin rotation is the important relaxation mechanism with rapidly rotating methyl groups as those of toluene[21] and duene.[22] Apparently, the rates of the methyl rotations are not reduced in the included molecules and the reduced rate of tumbling, as of 2-methylnaphthalene, does not affect the relaxation rate of the methyl carbons.

It seems that the cmr spectra of choleic acids formed with properly sized molecules could be useful in assigning resonances to particular carbons as well as providing a rapid method of differentiating between various relaxation mechanisms. The relatively narrow groupings of the resonances of **2** should be helpful in these respects.

Acknowledgment. We are pleased to acknowledge the courtesy of Varian Associates in providing the use of a FT-equipped XL-100 spectrometer in their Applications Laboratory for taking some of the early spectra and measurements of relaxation times.

(21) C. F. Schmidt, Jr., and S. I. Chan, *J. Chem. Phys.*, in press.
(22) K. F. Kuhlmann and D. M. Grant, *ibid.*, **55**, 2998 (1971).

Nybomycin. VII. Preparative Routes to Nybomycin and Deoxynybomycin[1,2]

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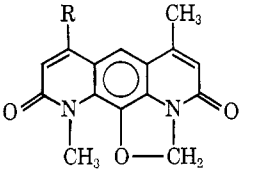
Abstract: Syntheses of the antibiotics nybomycin (**1**) and deoxynybomycin (**2**) from *o*-anisidine, in twelve and eight steps, respectively, are described.

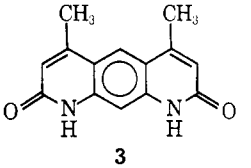
The antibiotic nybomycin was isolated several years ago in two laboratories from streptomycete cultures;[4,5] it was found to be quite active against Gram-positive and some Gram-negative bacteria, but its very limited solubility restricts its *in vivo* activity.

The molecular structure of nybomycin has recently been assigned as **1**.[6] One of the key intermediates in establishing structure **1**, deoxynybomycin (**2**), was initially obtained from nybomycin by hydriodic acid reduction,[7] but it has very recently been reported by Umezawa, *et al.*, as an antibiotic in its own right, being produced by *Streptomyces hyalinum* n. sp. Hamada et Yakayama.[8] The biological activity of deoxynybomycin and the observation that nybomycin acetate and dichloroacetate are more active than the parent compound, especially against staphylococci,[9] lend interest to the development of synthetic methods which might be employed in preparing compounds of this type for investigations of structure–activity relationships. The present paper describes in detail preparative studies culminating in the total synthesis of deoxynybomycin and nybomycin and leading to a number of related heterocyclic compounds.

Formation of a Model Oxazoline. The ring system of nybomycin provides the first naturally occurring example of a pyridoquinolone (diazaanthracenedione), and a reduction product (**3**) from deoxynybomycin con-



1, R = CH_2OH
2, R = CH_3



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taining this ring system was synthesized earlier[10] from *m*-xylene. However, the most striking structural feature in the nybomycin ring system is the fused 4-oxazoline nucleus; this heterocyclic system, with a saturated linkage between nitrogen and oxygen, appears not to have been reported before in natural products, although its oxygen analog, the methylenedioxy group, is found in many natural products, including casimiroin,[11] a methylenedioxy-*N*-methylquinolone, and the streptovaricin antibiotics.[12] In contrast to the numerous

(1) This work has been the subject of two preliminary reports: (a) R. M. Forbis and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **92**, 6995 (1970); (b) *J. Antibiot.*, **24**, 326 (1971).
(2) Taken from the Ph.D. Thesis of R. M. Forbis, University of Illinois, February 1971.
(3) National Science Foundation Predoctoral Fellow.
(4) F. Strelitz, H. Flon, and D. N. Asheshov, *Proc. Nat. Acad. Sci. U. S.*, **41**, 620 (1955).
(5) T. E. Eble, G. A. Boyack, C. M. Large, and W. H. DeVries, *Antibiot. Chemother.*, **8**, 627 (1958).
(6) K. L. Rinehart, Jr., G. Leadbetter, R. A. Larson, and R. M. Forbis, *J. Amer. Chem. Soc.*, **92**, 6994 (1970).
(7) K. L. Rinehart, Jr., and H. B. Renfroe, *J. Amer. Chem. Soc.*, **83**, 3729 (1961).
(8) H. Naganawa, T. Wakashiro, A. Yagi, S. Kondo, T. Takida, M. Hamada, K. Maeda, and H. Umezawa, *J. Antibiot.*, **23**, 365 (1970).
(9) T. D. Brock and W. T. Sokolski, *Antibiot. Chemother.*, **8**, 631 (1958).
(10) G. Leadbetter and K. L. Rinehart, Jr., *Can. J. Chem.*, **43**, 1625 (1965).
(11) B. Weinstein and T. A. Hylton, *Tetrahedron*, **20**, 1725 (1964).
(12) A review: K. L. Rinehart, Jr., *Accounts Chem. Res.*, **5**, 57 (1972).

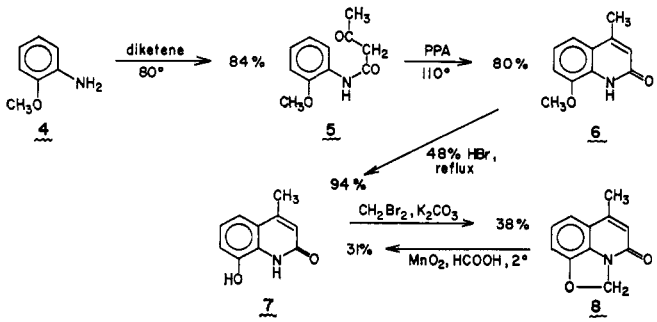


Figure 1. Preparation and reactions of 6-methyl-2*H*,4*H*-oxazolo-[5,4,3-*ij*]quinolin-4-one (**8**); PPA = polyphosphoric acid.

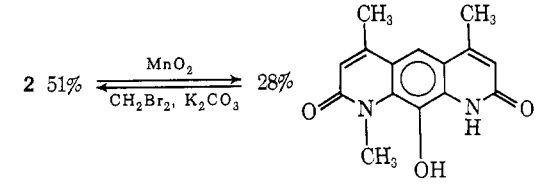
methods reported for the introduction of a methylenedioxy group into catechol systems,[13] there has been only one report of the synthesis of a 4-oxazoline unsubstituted in the 2 position, the reaction of *N*-benzoyl-*o*-aminophenol with methylene bromide to give 3-benzoylbenzoxazoline in 1% yield.[14]

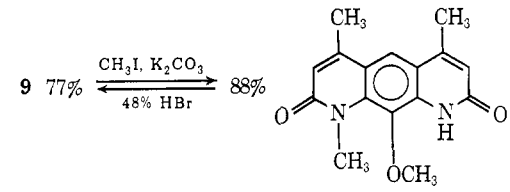
We considered a reliable method for preparation of a fused oxazoline–quinolone ring system to be the key to successful synthesis of nybomycin, and a study of a suitable sequence for the preparation of the model compound **8** (Figure 1) was initiated. A suitable model substrate for a methylenation reaction was the 8-hydroxyquinolone **7**. The preparation of **7** proceeded from *o*-anisidine (**4**), as shown in Figure 1. Treatment of **7** with methylene bromide and potassium carbonate gave **8**, in 24% overall yield (from **4**).

The properties of **8**, with its unique ring system, were of special interest for comparison to the properties of nybomycin and deoxynybomycin. The nmr spectrum (trifluoroacetic acid) of **8** shows a methylene singlet at δ 6.66 which corresponds reasonably well with the methylene absorptions at δ 6.84 and 6.82 in the spectra of deoxynybomycin and nybomycin, respectively. The methylene protons in **8** are observed as a singlet at δ 6.21 in deuteriochloroform, while the methylene signal occurs at δ 6.36 in the corresponding spectrum of nybomycin *n*-butyrate.[6]

The stability in acid of the methylene bridge in the fused 4-oxazoline of deoxynybomycin and nybomycin is remarkable: while the methylenedioxy group in safrole is readily hydrolyzed in dilute acid,[15] the methylene bridge in nybomycin is unaffected by refluxing 47% hydriodic acid. The model compound **8** was subjected to these conditions and was recovered unchanged after 3 hr. Oxidation of the methylene bridge in deoxynybomycin (**2**) by manganese dioxide, to give the phenol **9**, was instrumental in the structural assignment of nybomycin.[6] The synthetic bridged quinolone **8** was found to be similarly reactive (Figure 1); treatment with activated manganese dioxide in formic acid at 2° effected a 31% conversion back to **7**. The synthesis of a model compound having chemical and spectral properties similar to those of deoxynybomycin provided strong supporting evidence for the existence of this unique structural feature, the *N*,*O*-methylene bridge, in deoxynybomycin.

Attempted Synthesis of *O*-Methyldemethylenedeoxynybomycin (10). As noted above, a key reaction in

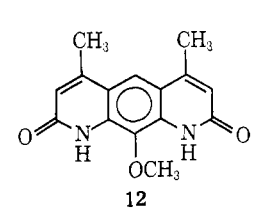




assigning the structure of nybomycin was the oxidation of deoxynybomycin (**2**) with manganese dioxide to give demethylenedeoxynybomycin (**9**). Moreover, treatment of the latter compound (**9**) with methylene bromide and potassium carbonate regenerated **2** in the structural studies.[6]

Since demethylenedeoxynybomycin (**9**) could be reconverted to deoxynybomycin, the former compound occupied a central position; a total synthesis of **9** would constitute a total synthesis of deoxynybomycin and that goal was first attempted. In the projected synthesis of **9** protection of the phenolic hydroxyl was deemed requisite to prevent cyclization at the hydroxyl; thus, a reasonable semifinal step was felt to be the demethylation of *O*-methyldemethylenedeoxynybomycin (**10**). Accordingly, **10** was prepared from **9** by methylation with methyl iodide and potassium carbonate. Demethylation of **10** in 48% hydrobromic acid at reflux was then accomplished in 77% yield to regenerate **9**, shown by its nmr, infrared, and mass spectra to be identical with the compound obtained from controlled oxidation of deoxynybomycin.

Since a synthesis of deoxynybomycin (**2**) had thus been effected from **10**, it only remained to prepare the latter compound to complete the total synthesis of the antibiotic. Of the methods available for synthesis of the 2-quinolone ring system[16] present in **10**, the acetoacetamido pathway[17] appeared promising. In view of the nearly symmetrical substitution of the central benzenoid ring in **9**, both heterocyclic rings of the diazaanthracene nucleus might be formed in the same reaction, **12** arising from the diacetoacetamide **11** (Figure 2).



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(13) (a) With methylene iodide: R. Fittig and I. Remsen, *Justus Liebigs Ann. Chem.*, **168**, 94 (1873); A. Meisels and F. Sondheimer, *J. Amer. Chem. Soc.*, **79**, 6328 (1957); (b) with methylene bromide: K. N. Campbell, P. F. Hopper, and B. K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951); (c) with methylene chloride: W. Bonthrone and J. W. Cornforth, *J. Chem. Soc. C*, 1202 (1969); (d) with methylene sulfate: W. Baker, *J. Chem. Soc.*, 1765 (1931).

(14) W. Weigel, *J. Prakt. Chem.*, [4] **4**, 79 (1956).

(15) K. Ono and S. Kirayama, *J. Chem. Soc. Jap., Pure Chem. Sect.*, **58**, 926 (1937); *Chem. Abstr.*, **32**, 528 (1938).

(16) For a comprehensive review, see R. C. Elderfield in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1952, pp 1–343.

(17) (a) L. Knorr, *Justus Liebigs Ann. Chem.*, **236**, 83 (1886); (b) A. K. Mallams and S. S. Israelstam, *J. Org. Chem.*, **29**, 3548 (1964).

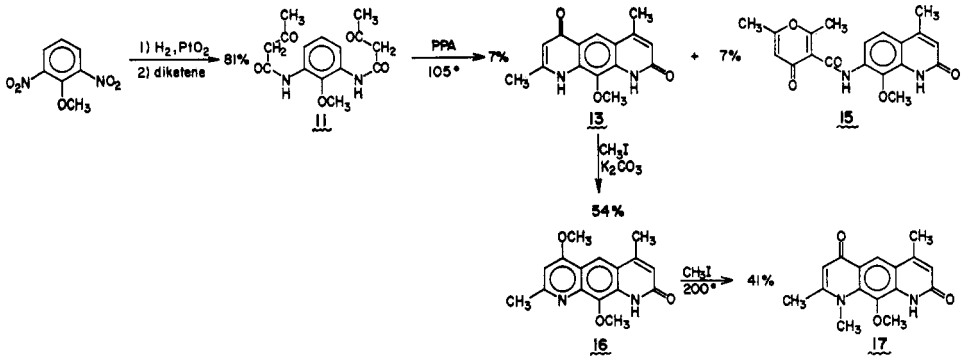
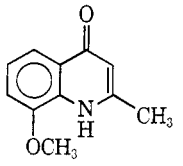


Figure 2. Compounds derived from 2,6-diacetoacetamidoanisole (**11**).

The symmetrical diacetoacetamide (**11**) was prepared by hydrogenation (98%) of 2,6-dinitroanisole, followed by condensation of the diamine with diketene (83%). Cyclization of **11** with polyphosphoric acid at 105° produced, instead of **12**, the isomeric product, 4,8-dimethyl-10-methoxypyrido[3,2-*g*]quinoline-2,6(1*H*,9*H*)-dione (**13**) in 7% yield, together with a 4-pyrone, **15**, in 7% yield. The unsymmetrical structural assignment for **13** was made on the basis of the nmr spectrum (TFA), which reveals nonequivalent aromatic methyl groups at δ 2.93 and 3.06 and nonequivalent pyridone ring hydrogens at δ 7.12 and 7.30. The signal at δ 2.93 was assigned to the 4-methyl and that at δ 3.06 to the 8-methyl, by comparison to spectra of model 2- and 4-quinolones (δ 2.89 for the aryl CH_3 group in **6**; δ 3.00 for the aryl CH_3 group in **14**, prepared from *o*-



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anisidine and ethyl acetoacetate). The 4-pyrone derivative, **15**, was identified by its nmr and mass spectra. Products of this type [3-(*N*-arylcarboxamido)-2,6-dimethyl-4-pyrones, like **15**] were suggested by Mallams[18] to be the result of heterolytic cleavage of an acetoacetamide linkage in polyphosphoric acid to give an acylium ion which could react with an uncyclized molecule. The use of different cyclization conditions (polyphosphoric acid at 75 or 150°; sulfuric acid at 80 or 120°) also failed to give **12**, yielding mainly **15**.

Although this route (Figure 2) had failed to provide a suitable intermediate for the preparation of **2**, it might provide an isomer of the methylated degradation product **10** for conversion to a potentially biologically interesting isomer of deoxynybomycin. Accordingly, the unsymmetrical diazaanthracene **13** was treated with methyl iodide and potassium carbonate in acetone. Only one major component, a monomethylated derivative, was isolable from the resulting mixture of methylation products; assignment of its structure as **16** was supported by its nmr spectrum (TFA), which shows singlet absorptions at δ 2.87 (4-methyl), 3.11 (8-methyl), 4.24 (10-methoxy), and 4.51 (6-methoxy).

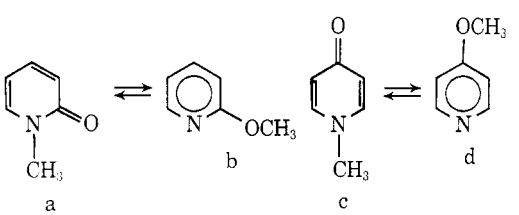
Of the other possible structures for this monomethylation product, the two *N*-methyl isomers were eliminated by the ability of **16** to undergo thermal isomerization.[19] A solution of **16** in chloroform was heated in a sealed tube with a trace of methyl iodide at 200° to afford a new monomethylated product (**17**), as evidenced by the product's altered nmr spectrum (TFA), which shows singlet methyl signals at δ 2.94 (4-methyl), 3.06 (8-methyl), 4.17 (10-methoxy), and 4.71 (9-methyl). The alternative *O*-methyl formulation (2-*O*-methyl isomer) was eliminated by nmr absorption (in TFA) of model compounds, which indicates that O-methylation of the 2-quinolone **6** results in a substantial downfield shift of the 4-methyl group on the heterocyclic ring (δ 2.89 to 3.04) while O-methylation of the 4-quinolone **14** is accompanied by only a small shift of the 2-methyl group (δ 3.00 to 3.01). Since the original methylation product (**16**) shows the 4-methyl absorption at δ 2.87, O-methylation could not have occurred on the 2-quinolone ring; thus, the structure of the methylation product is assigned as **16**, and the rearrangement product as 4,8,9-trimethyl-10-methoxypyrido[3,2-*g*]quinoline-2,6[1*H*,9*H*]-dione (**17**).

In view of the failure of the double ring closure route an alternative pathway was investigated, one involving the introduction of nitrogen functionality at the 7 position of a previously cyclized 2-quinolone (Figure 3). The compound initially sought in this route was 8-methoxy-4-methyl-7-nitro-2-quinolone (**18**). Nitration in acetic anhydride[20a] has been widely reported to give increased ratios of *o*- to *p*-nitro isomers in substrates such as anisole.[20b] In the present study, however, treatment of **6** with this reagent mixture at ice bath temperatures afforded only the 5- and 6-nitro isomers, **19** and **20**.

Identification of **20** was obvious from its nmr spectrum (TFA), which revealed two low-field doublets (δ 8.12 and 8.64) with a coupling constant, 2 Hz, char-

(18) A. K. Mallams, *J. Org. Chem.*, **29**, 3555 (1964).

(19) Beak and coworkers [*J. Amer. Chem. Soc.*, **90**, 1569 (1968)] have reported equilibrium of the amide–imidate pairs a–b and c–d under the



a b c d

catalytic action of an alkylating agent. The equilibrium was determined to lie far on the side of the amides a and c, with reaction observed only in experiments starting with imidates b and d.

(20) (a) J. H. Ridd in "Studies on Chemical Structure and Reactivity," J. H. Ridd, Ed., Methuen, London, 1966, p 140; (b) P. H. Griffiths, W. A. Walkey, and H. B. Watson, *J. Chem. Soc.*, 631 (1934).

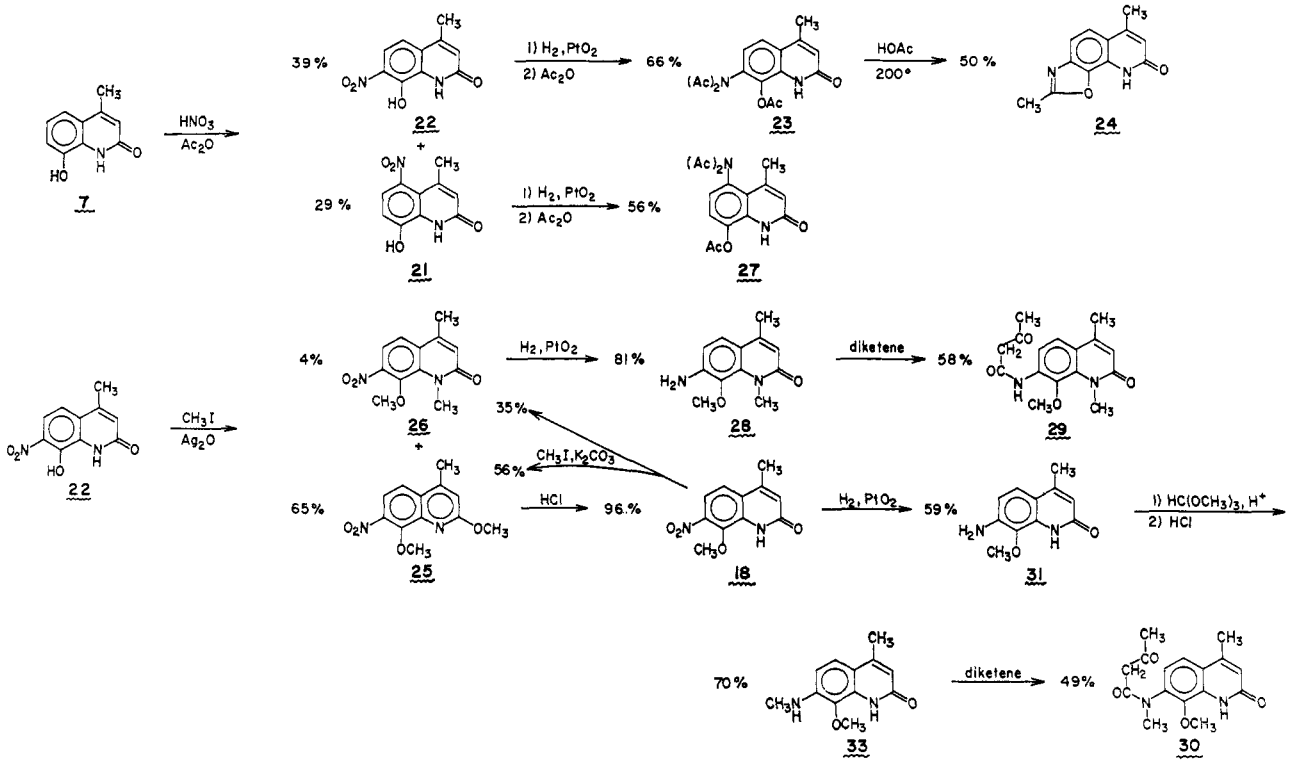
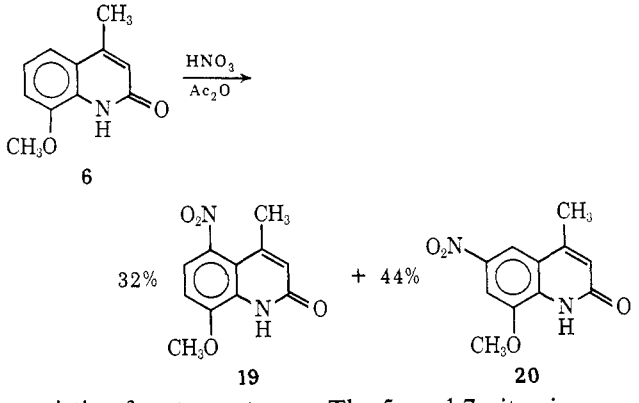


Figure 3. Preparation of 7-acetoacetamido-2-quinolones (**29** and **30**).



acteristic of meta protons. The 5- and 7-nitro isomers would not be immediately distinguishable by nmr alone, for both compounds would exhibit ortho coupling of 6–9 Hz; the nmr spectrum of the nitro isomer **19** did show aromatic coupling of 8.5 Hz. Structure **19** was assigned from evidence presented below. The high yield of 6-nitro product (**20**), substituted meta to the methoxyl, was unexpected and is presumably a result of the activating influence of the quinolone amide group for electrophilic substitution in the 6 position, together with steric hindrance by the 4-methyl and 8-methoxyl groups toward substitution in the 5 and 7 positions.

The steric hindrance argument suggested the 8-hydroxyquinolone as a better substrate for nitration; **7** was then nitrated with acetic anhydride–nitric acid to yield the 5- and 7-nitro isomers **21** and **22**, in 29 and 39% yields, respectively. Although the nmr spectra of both isomers indicate ortho aromatic protons (J = 8.5 Hz for **21**, J = 9 Hz for **22**), the aromatic proton (H-5) in the peri position of **22** is significantly deshielded by the adjacent ring, appearing at δ 8.34. Additional confirmation of the structural assignment was obtained from the chemical shifts of the pyridone methyl group, which appears at δ 2.91 for **22** and 2.89 for **6**, but is shifted upfield to δ 2.70 in the spectrum of **21** due to anisotropic shielding by the *peri*-nitro group. In addition to the nmr arguments, the two nitro isomers were distinguished by chemical means, by formation of a benzoxazole derivative[21] from **22** (Figure 3). Compound **22** was reduced and the product was treated with acetic anhydride to afford its triacetyl derivative **23**, which on ring closure gave the oxazoloquinolone **24**. The structure **24** was in accord with its infrared, nmr, and mass spectra. Similar treatment of **21** yielded the corresponding triacetate **27**, which did not give isolable products upon sealed tube reaction.

The nitroquinolone **22** was subsequently subjected to methylation conditions with the goal of reprotecting the phenolic hydroxyl group and N-methylating the amide nitrogen. Methylation using methyl iodide and silver oxide[22] in chloroform gave only a 4% yield of the desired *N*-methyl isomer, **26**, and a 65% yield of **25**, whose structures were assigned from their infrared spectra and their relative ease of hydrolysis. The favored compound (**25**) was then hydrolyzed almost quantitatively to 8-methoxy-4-methyl-7-nitro-2-quinolone (**18**) upon vigorous treatment with hydrochloric acid.[23] Subsequent reaction of **18** with methyl iodide and potassium carbonate in acetone (reagents favoring the formation of *N*-methylquinolones)[24] afforded a more satisfactory ratio of the two isomers (**26** in 35%

(21) (a) M. A. Phillips, *J. Soc. Chem. Ind., London, Trans. Commun.*, **56**, 747 (1937); (b) W. Theilacker, *J. Prakt. Chem.*, [2] **153**, 54 (1930).

(22) (a) P. Friedlander and A. Weinberg, *Chem. Ber.*, **15**, 1421 (1882). (b) Other standard techniques, dimethyl sulfate and aqueous base or methyl iodide and potassium carbonate, failed to give methylated products even upon prolonged treatment, either from the insolubility of the sodium and potassium salts of **22** or from reduced nucleophilicity caused by the *o*-nitro group.

(23) (a) H. N. McCoy, *Amer. Chem. J.*, **21**, 122 (1899); (b) P. Friedlander and H. Ostermaier, *Chem. Ber.*, **15**, 332 (1882).

(24) P. Friedlander and F. Muller, *Chem. Ber.*, **20**, 2009 (1887).

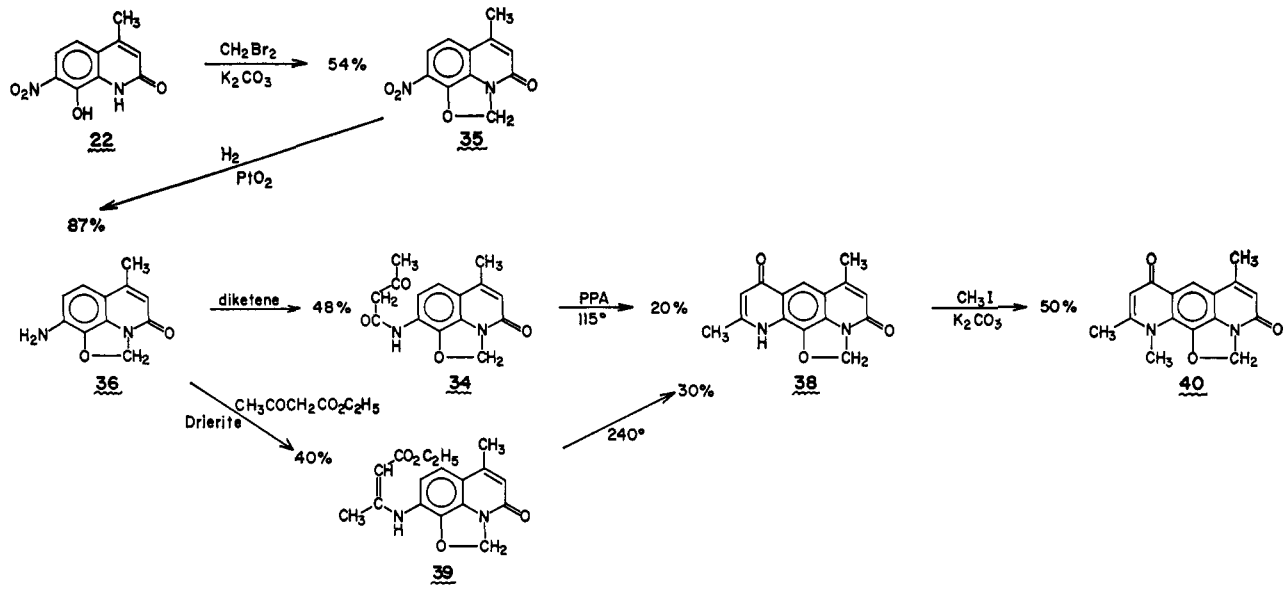


Figure 4. Preparation of isodeoxynybomycin (**40**).

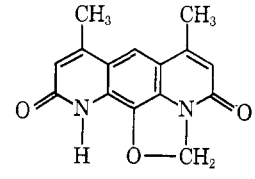
yield and **25** in 56% yield). The dimethoxyquinoline could be separated by chromatography and recycled through the demethylation–methylation reactions to increase significantly the effective yield of **26**.

Atmospheric hydrogenation of **26** afforded an 81% yield of the corresponding amine (**28**), which was condensed with diketene in refluxing benzene to give a 58% yield of 7-acetoacetamido-1,4-dimethyl-8-methoxy-2-quinolone (**29**). Attempts to effect cyclization of **29** to the diazaanthracene **10** required for the relay synthesis of deoxynybomycin were singularly unsuccessful even though polyphosphoric acid (ambident, 85, 100, 120, and 140°), sulfuric acid (ambident, 100°), aluminum chloride (in carbon disulfide and nitrobenzene), and liquid hydrogen fluoride were all tried. The product isolated in most cases was **28**, resulting from hydrolysis of the amide linkage, or a pyrone similar to **15**.[2]

An alternative route to the desired intermediate **10** would entail cyclization of the isomeric acetoacetamidoquinolone **30**. Preparation of **30** proceeded from **18**, whose atmospheric hydrogenation gave the amine **31** in 59% yield. Using trimethyl orthoformate and acidic catalysis, the amine was then converted to its *N*-methyl-*N*-formyl intermediate (**32**), which was hydrolyzed without isolation to afford the *N*-methylaminoquinolone **33** (70%). Finally, condensation of **33** with diketene gave 8-methoxy-4-methyl-7-(*N*-methylacetoacetamido)-2-quinolone (**30**). As with **29**, attempts to effect ring closure of **30** with polyphosphoric acid and sulfuric acid were unsuccessful.

The disappointing failure of ring-closure reactions with **29** and **30** appeared to be a consequence of competing reactions, in which heterolysis of the acetoacetamido linkage predominated over the anticipated cyclization process. If, during the cyclization process, the diprotonated acetoacetanilide must assume a conformation essentially coplanar with the benzene ring in order to facilitate electrophilic attack by the protonated carbonyl group onto the benzenoid nucleus,[25] interaction between the 8-methoxyl group and the acetoacetamide may be sufficient to make this conformation sterically unfavorable. Since ring closure of the related **5** went very smoothly, a buttressing interaction between the methoxyl and the already formed quinolone is implicated, an interaction forcing the methoxyl into the sphere of the acetoacetamide.

6,10,11-Trimethyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinoline-4,8(11*H*)-dione (40). Since attempts to synthesize the key intermediate (**10**) for the relay route failed, an alternative route not involving **10** was explored. This route proposed to *N*-methylate **37** as a



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final step, hoping to alleviate the steric problems encountered in the cyclization of **11**, **29**, and **30** by employing an acetoacetamido derivative of a compound with a preformed methylene bridge (**34**, Figure 4). The synthetic approach to **34** involved methylenation of the 7-nitroquinolone **22**, to give **35**, followed by catalytic hydrogenation to **36** and diketene condensation.

Treatment of **34** with polyphosphoric acid at 115° afforded a small amount of a light-colored solid whose spectral properties (see Experimental Section) were consistent with those expected for the desired **37**. In spite of the spectral evidence the isomeric 4-quinolone product **38** could not be ruled out, and the preparation of an authentic sample of **38** was undertaken *via* the Conrad–Limpach synthesis.[26] Following the procedure of Hauser and Reynolds,[27] condensation of **36** with ethyl acetoacetate gave the crotonate ester derivative **39**, whose cyclization in mineral oil at 240° afforded 6,10-dimethyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]-quinoline-4,8(11*H*)-dione (**38**). The compound prepared by this route had spectral characteristics identical with those of the product obtained upon cyclization of

(25) B. Staskun, *J. Org. Chem.*, **29**, 1153 (1964).

(26) M. Conrad and L. Limpach, *Chem. Ber.*, **20**, 988 (1887).

(27) C. R. Hauser and G. A. Reynolds, *J. Amer. Chem. Soc.*, **70**, 2402 (1948).

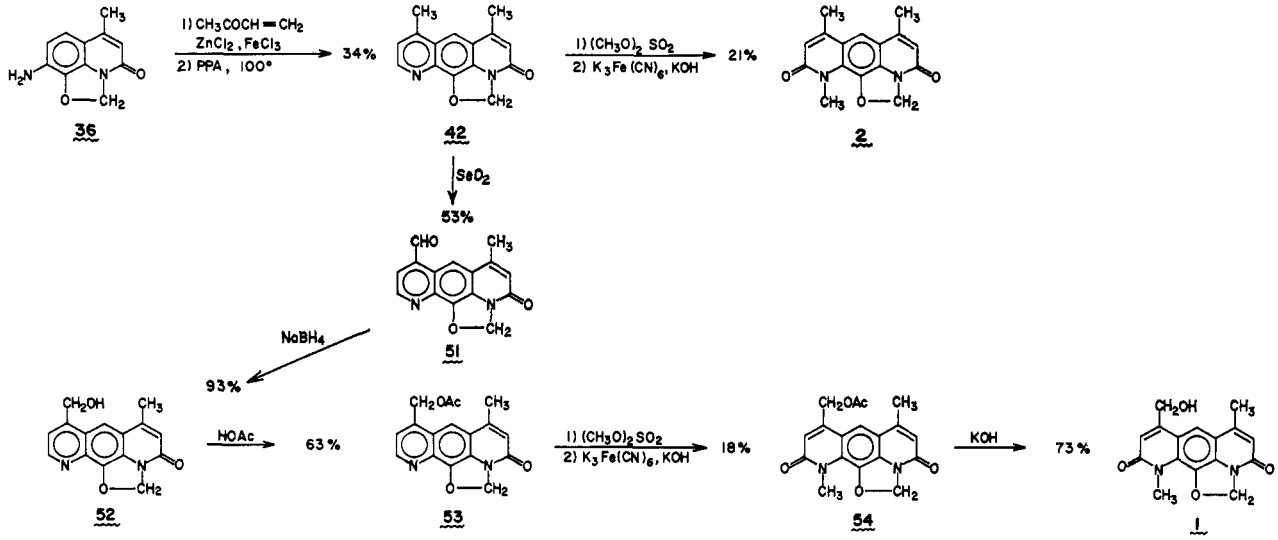
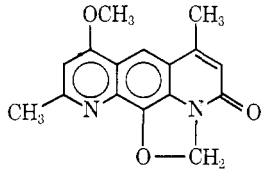


Figure 5. Syntheses of deoxynybomycin (**2**) and nybomycin (**1**).

34; thus, once again, cyclization of the acetoacetamido moiety had failed to construct the desired ring system.

With the 4-quinolone in hand, however, it was decided to complete the reaction sequence required to prepare an isomer of deoxynybomycin for biological testing. Methylation of **38** with methyl iodide and potassium carbonate in dimethylformamide afforded the methylated derivative (**40**). The *O*-methyl isomer (**41**) was eliminated by the fact that the methylation



41

product was inert to refluxing 48% hydrobromic acid, a reagent which readily cleaves aromatic methyl ethers but is ineffective in cleaving an *N*-methyl linkage.

Synthesis of Deoxynybomycin (2). Of the methods reported for synthesis of the 2-quinolone nucleus that we had not already investigated, oxidation of the methosulfate salt of a quinoline unsubstituted in the 2 position seemed to afford an excellent alternative route, combining the oxidation and N-methylation steps.[28] The quinoline derivative **42** was regarded as a logical intermediate in this reaction pathway (Figure 5) for the preparation of deoxynybomycin.

The synthesis of **42** was carried out using a modification of the Doebner–von Miller sequence[29] for the preparation of quinolines. Treatment of the hydrochloride salt of **36** with a limiting amount of methyl vinyl ketone in the presence of zinc chloride and ferric chloride,[30] followed by reaction with polyphosphoric acid at 100°, resulted in a 34% yield of the strongly fluorescent tetracyclic product **42**. Nmr signals (TFA) at δ 2.89 and 7.16 were assigned to the aryl CH_3 and aryl protons on the methylene bridge side of the molecule, an assignment of consequence in the revision of the structure of nybomycin.[6]

Oxidation of **42** was carried out by treatment of its methosulfate salt with potassium hydroxide and potassium ferricyanide at 3°,[31] giving the dioxo compound **2**, which was found to be identical with authentic deoxynybomycin prepared from nybomycin, in melting point (> 350°) and tlc behavior, and in nmr, infrared, and mass spectra. The overall yield of deoxynybomycin from *o*-anisidine (**4**) *via* **5**, **6**, **7**, **22**, **35**, **36**, and **42** was 0.83%.

Synthesis of Nybomycin (1). In view of the successful route to **2**, it was decided to modify that route to prepare **1**. The most promising approach appeared to involve selective oxygenation of the 7-methyl group of **42**, taking advantage of the enhanced reactivity of alkyl groups situated ortho or para to the ring nitrogen atom in substituted pyridines.[16] In particular, Cook, Heilbron, and Steger[32] have reported that, of various methods for obtaining quinoline aldehydes, oxidation of the methyl groups in quinaldine and lepidine with selenium dioxide was the most convenient route to 2- and 4-formylquinolines, respectively. It was hoped the quinolone methyl would be less reactive.

Before attempting to prepare **1** from **42** model studies were carried out to develop a sequence for conversion of lepidine (**43**) to the hydroxymethylquinolone **49**. Oxidation of **43** with freshly prepared selenium dioxide[33] in refluxing dioxane gave **44** in 48% yield. Under the same conditions the methylquinolone **47** was unaffected; oxidation of the methyl group in **47**, to give **48**, required fusion with selenium dioxide at 175° for 1.25 hr.[34]

Reduction of **44** with sodium borohydride[35] in ethanol gave the hydroxymethyl derivative **45**; but

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(34) D. J. Cook and M. Stamper, *J. Amer. Chem. Soc.*, **69**, 1467 (1947).

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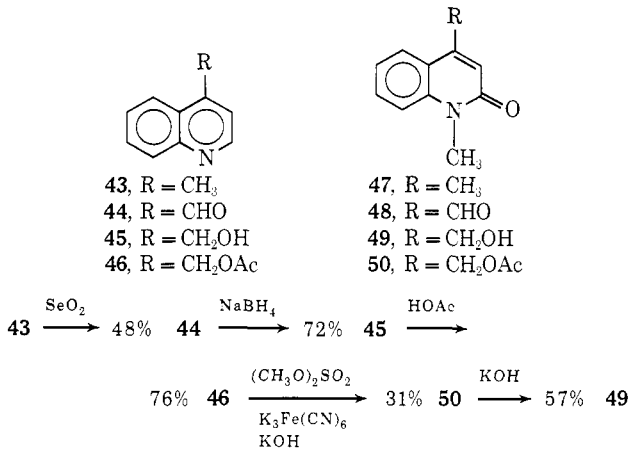
attempts to oxidize **45** to the quinolone **49** by conversion of **45** to its methosulfate followed by reaction with potassium hydroxide and potassium ferricyanide gave aldehyde products, necessitating protection of the hydroxyl group. Treatment of **45** with glacial acetic acid and a trace of sulfuric acid afforded the ester **46**, which was subsequently methylated with dimethyl sulfate and oxidized with a stoichiometric amount of hydroxide and ferricyanide to give the protected quinolone **50**. The



overall yield of **50** from **43** was 8.1%. Conversion of **50** to the hydroxymethylquinolone **49** with potassium hydroxide completed the model studies.

Using the same conditions that were successful in the model sequence, the 7-methyl group of the synthetic intermediate **42** was selectively oxidized in 53% yield with excess selenium dioxide (Figure 5). The aldehyde **51** was subsequently reduced with sodium borohydride to afford **52** in 93% yield and converted to the acetate **53** with glacial acetic acid. Methylation of **53** with dimethyl sulfate and oxidation afforded an 18% conversion to **54**.

The nmr spectrum of **54** is superimposable on that of authentic nybomycin acetate prepared by the method of Eble and coworkers[5] from natural nybomycin; the infrared and mass spectra of the two samples are also superimposable. An intimate mixture of the two preparations did not cause a depression of the melting point, 233–235°.

The hydrolysis of **54** to **1** was carried out in 73% yield with 0.5 *N* ethanolic potassium hydroxide. The product, after recrystallization from dimethylformamide, was identical with authentic nybomycin in melting point (> 350°) and tlc behavior, and in nmr, infrared, and mass spectra. The overall yield of nybomycin from *o*-anisidine (**4**) was 0.16%.

Experimental Section[36]

2-Methoxyacetoacetanilide (5). The procedure of Williams and Krynitsky[37a] provided 2-methoxyacetoacetanilide (**5**) in 92% yield, mp 83–84° (lit.[37b] mp 87°).

8-Methoxy-4-methyl-2-quinolone (6). 2-Methoxyacetoacetanilide (**5**, 55.00 g) was added in five portions to 250 ml of stirred polyphosphoric acid (85%) at 100°. After being heated and stirred for 20 hr, the acidic reaction mixture was poured onto crushed ice. Following hydrolysis, the mixture was stirred, then an insoluble residue was filtered and the acidic filtrate was carefully neutralized with 6 *N* sodium hydroxide. The white, crystalline precipitate, recrystallizable from 95% ethanol, weighed 46.5 g (93%); mp 187–189° (lit.[17b] 188–190°).

8-Hydroxy-4-methyl-2-quinolone (7). A mixture of 75.0 g of **6** in 750 ml of 48% hydrobromic acid was heated at reflux for 20 hr, cooled, diluted with water, and filtered. The precipitate was dissolved in dilute sodium hydroxide and, after filtration, reprecipitated with concentrated hydrochloric acid. The white precipitate was filtered, washed well with water, and dried to yield 68.0 g (98%) of **7**: mp 248–250°; nmr (basic deuterium oxide with DSS) δ 2.20 (3 H, d, *J* = 1 Hz), 6.32 (1 H, q, *J* = 1 Hz), 7.20–6.55 (3 H, m). A ferric chloride test (methanol) gave a dark green coloration.

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.52; H, 5.18; N, 8.01.

6-Methyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]quinolin-4-one (8). A slurry of 500 mg of **7**, 4.0 g of dibromomethane, and 1.5 g of powdered potassium carbonate in 100 ml of acetone was heated at reflux for 65 hr, cooled, and evaporated under reduced pressure. The solid residue was washed well with water, then dried, and extracted thoroughly with chloroform. Evaporation of the chloroform extract yielded 204 mg (38%) of a white solid, recrystallizable from 2-propanol: mp 193–195°; ir (KBr) 1660, 1620 cm^{-1}; nmr (TFA) δ 2.90 (3 H, s), 6.66 (2 H, s), 7.77–7.20 (4 H, m).

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48; mol wt, 187. Found: C, 70.67; H, 4.63; N, 7.56; mol wt (mass spec), 187.

A mixture of 0.5 g of **8** and 0.44 g of activated manganese dioxide (Winthrop Laboratories) in 55 ml of 98% formic acid was stirred for 2.5 hr in an ice bath, then filtered. On standing in a refrigerator cream colored crystals precipitated which were dissolved in sodium hydroxide and reprecipitated with acid to give 40 mg (9%) of **7**, identical in physical properties with an authentic sample.

10-*O*-Methyldemethylenedeoxynybomycin (10). A suspension of 1.040 g of demethylenedeoxynybomycin (**9**)[6] and 3.0 g of powdered potassium carbonate in a mixture of 60 ml of acetone and 20 ml of water containing 4 ml of dimethyl sulfate[38] was heated at reflux for 3 hr and evaporated to dryness under reduced pressure. The residue was extracted into chloroform and chromatographed over silica gel using 5% methanol in chloroform to give 948 mg (88%) of white solid, recrystallizable from ethanol: mp 319–321°; nmr (TFA) δ 2.95 (6 H, s), 4.10 (3 H, s), 4.51 (3 H, s), 6.93 (1 H, s), 7.20 (1 H, s), 7.37 (1 H, s), 8.60 (1 H, s).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85; mol wt, 284. Found: C, 67.41; H, 5.58; N, 9.69; mol wt (mass spec), 284.

Demethylenedeoxynybomycin (9) from 10. A 36-mg sample of **10** was demethylated as described for the preparation of **7** to afford **9** in 77% yield; the infrared spectrum (KBr) is superimposable on that of **9** obtained from manganese dioxide oxidation of deoxynybomycin.[6]

2,6-Diacetoacetamidoanisole (11). 2,6-Dinitroanisole [15.36 g, mp 114–115° (lit.[39] mp 116°)], prepared in 84% yield from 2,6-dinitrophenol, was dissolved in absolute ethanol and hydrogenated at atmospheric pressure over 500 mg of platinum oxide. After quantitative hydrogen uptake (10,400 ml), the catalyst was filtered, and the solvent was removed under reduced pressure to leave 10.48 g (98%) of an orange oil which darkened rapidly. The crude diamine was treated with 13.00 g of freshly distilled diketene in dry benzene containing 1 ml of pyridine. The reaction mixture was heated at reflux for 17 hr, after which the solvent was evaporated under reduced pressure. One recrystallization from 2-propanol, using activated charcoal, yielded 18.98 g (80% overall yield) of a light yellow solid: mp 126–128°; nmr ($CDCl_3$) δ 2.32 (6 H, s),

(36) Melting points were taken on a Thomas-Hoover capillary melting point apparatus or a Kofler micro hot stage; all are uncorrected and given in degrees Centigrade. Infrared spectra were recorded with a Perkin-Elmer spectrophotometer, Model 521; nuclear magnetic resonance (nmr) spectra were obtained with Varian spectrometers, Models T-60, A-60A, or HA-100 using tetramethylsilane as internal standard except where noted. Low resolution mass spectra were taken with Varian MAT mass spectrometers, Models CH4 and CH5; high resolution data were obtained on a Varian MAT SM1B spectrometer. The assistance of Messrs. J. C. Cook, Jr., J. Wrona, R. Thrift, J. Nemeth, and their associates in obtaining spectral data and microanalyses is appreciated.

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(38) R. E. Buckles and M. P. Bellis, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 722.

(39) H. Salkowski, *Justus Liebigs Ann. Chem.*, **174**, 272 (1874).

3.63 (4 H, s), 3.87 (3 H, s), 7.93 (1 H, t, J = 8 Hz), 7.97 (2 H, d, J = 8 Hz), 9.46 (2 H, broad s).

Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.72; H, 6.00; N, 8.99.

4,8-Dimethyl-10-methoxypyrido[3,2-*g*]quinoline-2,6(1*H*,9*H*)-dione (13). A stirred solution of 5.0 g of **11** in 150 ml of polyphosphoric acid was heated at 105° for 3.5 hr; the acidic mixture was poured into 200 g of cracked ice and neutralized with 6 *N* sodium hydroxide. After the mixture was cooled, the white precipitate was filtered and redissolved in 50 ml of hot 3 *N* sodium hydroxide. The basic solution was treated with activated charcoal and filtered while hot; the filtrate was cooled to precipitate 320 mg (7%) of **13**, a white solid recrystallizable from dimethylformamide: mp 320–325° dec; ir (KBr) 1650 cm^{-1}; nmr (TFA) δ 2.93 (3 H, s), 3.06 (3 H, s), 4.26 (3 H, s), 7.12 (1 H, s), 7.30 (1 H, s), 8.96 (1 H, s).

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 66.66; H, 5.22; N, 10.36; mol wt, 270. Found: C, 66.89; H, 5.14; N, 10.11; mol wt (mass spec), 270.

Acidification of the basic filtrate from the initial recrystallization gave 393 mg (7%) of light tan solid, identified as the 4-pyrone **15**: mp >300°; nmr (TFA) δ 2.61 (3 H, s), 2.88 (3 H, s), 3.03 (3 H, s), 4.16 (3 H, s), 6.93 (1 H, s), 7.20 (1 H, s), 7.97 (1 H, d, J = 9 Hz), 8.47 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{19}H_{18}N_2O_5$: mol wt, 354. Found: mol wt (mass spec), 354.

8-Methoxy-2-methyl-4-quinolone (14). *o*-Anisidine (24.60 g) was treated with ethyl acetoacetate (26.00 g, 0.20 mol) according to the procedure of Hauser and Reynolds[27] to give 11.08 g (24%) of ethyl 3-(2′-methoxyanilino)-2-butenoate, bp 133° (0.20 mm).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 65.99; H, 7.54; N, 6.29.

A portion (5.45 g) of this intermediate was thermally cyclized to afford 2.53 g (58%) of **14**, recrystallizable from 2-propanol–water: mp 229–231° (lit.[40] mp 229°); nmr (TFA) δ 2.93 (3 H, s), 4.20 (3 H, s), 7.2–8.1 (4 H, m).

6,10-Dimethoxy-4,8-dimethylpyrido[3,2-*g*]quinolin-2(1*H*)-one (16). A suspension of 90 mg of **13** and 90 mg of powdered potassium carbonate in 50 ml of acetone containing 4.0 g of methyl iodide was heated at reflux for 16 hr. The solvent was evaporated, and the residue was washed with water and filtered. The crude methylation product was chromatographed on a silica gel preparative plate using 10% methanol in chloroform as eluent; the major fraction afforded 51 mg (54%) of yellow crystalline material: mp 250–253°; ir (KBr) 1650 cm^{-1}; nmr (TFA) δ 2.87 (3 H, s), 3.11 (3 H, s), 4.24 (3 H, s), 4.51 (3 H, s), 7.10 (1 H, s), 7.23 (1 H, s), 8.88 (1 H, s).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.87; H, 5.79; N, 9.61.

4,8,9-Trimethyl-10-methoxypyrido[3,2-*g*]quinoline-2,6(1*H*,9*H*)-dione (17). A solution of 82 mg of **16** in 5 ml of chloroform containing a trace of methyl iodide was heated in a sealed Pyrex tube at 200° for 12 hr. After being cooled, the tube was carefully opened and the chloroform solution was evaporated. The brown residue was chromatographed on a preparative tlc plate (silica gel) with 10% methanol in chloroform. The major band afforded 34 mg (41%) of white solid: mp 286–290°; nmr δ 2.94 (3 H, s), 3.06 (3 H, s), 4.17 (3 H, s), 4.71 (3 H, s), 7.18 (1 H, s), 7.36 (1 H, s), 9.04 (1 H, s).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.49; H, 5.58; N, 10.01.

8-Methoxy-4-methyl-5-nitro-2-quinolone (19) and 8-Methoxy-4-methyl-6-nitro-2-quinolone (20). A slurry of 2.00 g of 8-methoxy-4-methyl-2-quinolone (**6**) in 15 ml of acetic anhydride was cooled in an ice–salt mixture at 0–5° while a solution of 0.6 ml of concentrated nitric acid in 5 ml of glacial acetic acid was added dropwise. After the addition was complete, the mixture was stirred in a water bath for 10 hr, then stoppered and left to stand for an additional 35 hr. The reaction mixture was carefully hydrolyzed with 3 *N* hydrochloric acid and the yellow solid was filtered, washed with glacial acetic acid and water, and recrystallized from methanol to give 1.09 g (44%) of the 6-nitro isomer (**20**), a yellow solid: mp 286–287°; nmr (TFA) δ 2.92 (3 H, s), 4.29 (3 H, s), 7.29 (1 H, s), 8.19 (1 H, d, J = 2 Hz), 8.67 (1 H, d, J = 2 Hz).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.27; H, 4.28; N, 12.27.

The acetic acid filtrate was then diluted with 150 ml of water and and yellow precipitate was filtered and recrystallized from 2-propanol to give 0.80 g (32%) of the 5-nitro isomer (**19**) as yellow needles: mp 193–195°; nmr ($CDCl_3$) δ 2.36 (3 H, d, J = 1.3 Hz), 4.11 (3 H, s), 6.64 (1 H, q, J = 1.3 Hz), 6.94 (1 H, d, J = 8.5 Hz), 7.37 (1 H, d, J = 8.5 Hz).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.59; H, 4.20; N, 11.82.

8-Hydroxy-4-methyl-7-nitro (and -5-nitro-) -2-quinolones (22 and 21). A procedure modified from that of Buckles and Bellis[38] was employed. A stirred suspension of 26.50 g of 8-hydroxy-4-methyl-2-quinolone (**7**) in 220 ml of acetic anhydride, cooled to ice bath temperature, was treated dropwise with a mixture of 8.4 ml of 70% nitric acid and 27 ml of glacial acetic acid, then held at 5° for 6.5 hr. The acetic anhydride mixture was carefully hydrolyzed during 2 hr with external cooling with 25 ml of 3 *N* hydrochloric acid and diluted with water. The yellow precipitate was found by nmr assay to contain a mixture of 5- and 7-nitroquinolones, in addition to a small amount of dinitro product. The 7-nitro isomer was isolated by dissolving the crude precipitate in 3 *N* sodium hydroxide, solubilizing the 5-nitro and dinitro compounds but leaving the 7-nitro isomer as an insoluble sodium salt. The phenolic salt was filtered, washed well with dilute base, and reacidified to afford 13.08 g (**39**) of the yellow 7-nitro isomer (**22**), recrystallizable from chloroform: mp 284° dec; ir (KBr) 1650 cm^{-1}; nmr (TFA) δ 2.91 (3 H, d, J = 0.75 Hz), 7.40 (1 H, q, J = 0.75 Hz), 7.77 (1 H, d, J = 9 Hz), 8.34 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72; mol wt, 220. Found: C, 54.02; H, 3.57; N, 12.84; mol wt (mass spec), 220.

The 5-nitro isomer (**21**) was isolated by treatment of the basic solution of the phenolic salts with charcoal, filtration, and acidification with concentrated hydrochloric acid to yield 9.74 g (29%) of a tan solid: mp 205–207°; nmr (TFA) δ 2.70 (3 H, s), 7.34 (1 H, s), 7.40 (1 H, d, J = 8.5 Hz), 7.82 (1 H, d, J = 8.5 Hz).

In a second run, on a doubled scale, the yield of the 7-nitro isomer (**22**) was 34.0 g (51%).

2,6-Dimethyloxazolo[4,5-*h*]quinolin-8(9*H*)-one (24). A solution of 1.00 g of **22** in glacial acetic acid containing 50 mg of platinum oxide was subjected to atmospheric hydrogenation. After uptake of the theoretical amount of hydrogen (306 ml), the catalyst was filtered and solvent was removed under reduced pressure to give 0.80 g (93%) of a yellow solid which darkened rapidly upon standing: nmr (TFA) δ 2.89 (3 H, s), 7.30 (1 H, s), 7.81(1 H, d, J = 9 Hz), 7.95 (1 H, d, J = 9 Hz); mass spectrum *m/e* 190 (molecular ion).

A solution of 500 mg of the amine in 50 ml of acetic anhydride was heated at reflux for 15 hr. After hydrolysis, the solvent was removed under reduced pressure, and the brown residue was dissolved in chloroform and filtered. The filtrate was washed with saturated sodium bicarbonate solution, treated with charcoal, dried over magnesium sulfate, and evaporated to give 590 mg (71%) of the triacetate **23**, a white solid: mp 278–280° dec; nmr (TFA) δ 2.57 (6 H, s), 2.63 (3 H, s), 2.81 (3 H, s), 7.13 (1 H, s), 7.58 (1 H, d, J = 8.5 Hz), 8.12 (1 H, d, J = 8.5 Hz) mass spectrum *m/e* 316 (molecular ion).

A solution of 200 mg of the triacetate in 5 ml of glacial acetic acid was heated for 12 hr at 210° in a sealed tube. After evaporation of the solvent, the residue was dissolved in chloroform, which was washed with saturated sodium bicarbonate, dried with magnesium sulfate, and evaporated to give 67 mg (50%) of **24**, a tan solid, sublimable and recrystallizable from acetone: mp 236–238°; ir 1650 cm^{-1}; nmr (TFA) δ 2.97 (3 H, s), 3.34 (3 H, s), 7.30 (1 H, s), 8.06 (1 H, d, J = 9 Hz), 8.39 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 67.28; H, 4.71; N, 13.08; mol wt, 214. Found: C, 67.45; H, 4.84; N, 13.06; mol wt (mass spec), 214.

8-Acetoxy-5-diacetylamino-4-methyl-2-quinolone (27). Using a procedure similar to that employed for the preparation of **23**, 120 mg of **21** was catalytically reduced, and the intermediate amine was subsequently treated with acetic anhydride to yield 95 mg (56%) of **27**: mp 241–243° dec; nmr ($CDCl_3$) δ 2.30 (6 H, s), 2.40 (3 H, s), 2.56 (3 H, s), 6.61 (1 H, s), 7.00 (1 H, d, J = 8.5 Hz), 7.48 (1 H, d, J = 8.5 Hz).

Anal. Calcd for $C_{16}H_{16}N_2O_5$: mol wt, 316.1059. Found: mol wt, 316.1062 (mass spec).

Treatment of **27** in acetic acid solution at 200° in a sealed tube for 12 hr did not yield isolable products.

2,8-Dimethoxy-4-methyl-7-nitroquinoline (25) and 1,4-Dimethyl-8-methoxy-7-nitro-2-quinolone (26). A. From 8-Hydroxy-4-methyl-7-nitro-2-quinolone (22). A mixture of 3.00 g of **22**, 6.0 g of silver oxide, and 60 g of methyl iodide in 250 ml of chloroform was heated at reflux for 96 hr; the reaction mixture was cooled and

(40) M. Conrad and L. Limpach, *Chem. Ber.*, **21**, 1654 (1888).

filtered, and the methylated product was chromatographed over silica gel (chloroform) to yield two fractions. The faster moving fraction contained 2.19 g (65%) of **25**, a white solid recrystallizable from cyclohexane: mp 134–135°; nmr ($CDCl_3$) δ 2.60 (3 H, d, J = 1 Hz), 4.08 (3 H, s), 4.32 (3 H, s), 6.85 (1 H, q, J = 1 Hz), 7.63 (2 H, s). In trifluoroacetic acid, the aromatic protons were seen as two one-proton doublets, J = 9 Hz, at δ 8.16 and 8.22. The infrared spectrum shows no amide carbonyl absorption near 1650 cm^{-1}.

Anal. Calcd for $C_{12}N_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28; mol wt, 248. Found: C, 58.10; H, 4.86; 'N, 11.52; mol wt (mass spec), 248.

The slower moving fraction contained only 0.12 g (4%) of the *N*-methyl isomer **26**, a yellow solid, recrystallizable from 2-propanol: mp 174–176°; ir (KBr) 1655 cm^{-1}; nmr (TFA) δ 2.88 (3 H, s), 4.08 (3 H, s), 4.47 (3 H, s), 7.51 (1 H, s), 8.08 (2 H, s).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28; mol wt, 248. Found: C, 58.33; H, 4.88; N, 11.19; mol wt (mass spec), 248.

B. From 8-Methoxy-4-methyl-7-nitro-2-quinolone (18). A slurry of 2.99 g of **18** (see next section) and 5.0 g of powdered potassium carbonate in 150 ml of acetone containing 30 g of methyl iodide was heated at reflux for 107 hr; the solvent was evaporated and the residue was partially dissolved in chloroform. The chloroform solution was washed twice with water, with dilute base, and with water again, dried with magnesium sulfate, and evaporated. Chromatographic separation of the residue over silica gel (chloroform) yielded 1.77 g (56%) of **25** and 1.10 g (35%) of **26**, which were identical with the two products characterized in section A.

8-Methoxy-4-methyl-7-nitro-2-quinolone (18). A mixture of 2.31 g of **25** in 120 ml of 12% hydrochloric acid was heated at reflux for 3.5 hr, cooled, and diluted with water. The copious precipitate was filtered, washed with water, and dried to give 2.09 g (96%) of a yellow solid, recrystallizable from 2-propanol: mp 261–263°; ir (KBr) 1680 cm^{-1}; nmr (TFA) δ 2.86 (3 H, d, J = 1 Hz), 4.23 (3 H, s), 7.27 (1 H, q, J = 1 Hz), 7.92 (1 H, d, J = 9 Hz), 8.14 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.38; H, 4.23; N, 12.06.

7-Amino-1,4-dimethyl-8-methoxy-2-quinolone (28). 1,4-Dimethyl-8-methoxy-7-nitro-2-quinolone (**26**, 1.006 g) was subjected to atmospheric hydrogenation in ethanolic solution over 300 mg of platinum oxide. After uptake of the theoretical amount of hydrogen (272 ml), the mixture was filtered, the filtrate was evaporated to dryness, and the residue was dissolved in chloroform and extracted with 1 *N* hydrochloric acid. The acidic extract was washed with chloroform, neutralized with bicarbonate, and extracted with chloroform. The chloroform extracts were then washed with water, dried with magnesium sulfate, and evaporated to give 470 mg (53%) of white solid from which an analytically pure sample was obtained by sublimation: mp 167–168°; ir (KBr) 3430, 3320, 1655 cm^{-1}; nmr ($CDCl_3$) δ 2.35 (3 H, d, J = 1 Hz), 3.67 (3 H, s), 3.90 (3 H, s), 4.18 (2 H, broad s), 6.36 (1 H, q, J = 1 Hz), 6.70 (1 H, d, J = 9 Hz), 7.28 (1 H, d, J = 9 Hz). An additional 245 mg (81% total yield) of crude amine was obtained by extracting the initial chloroform solution again with 1 *N* hydrochloric acid and repeating the subsequent purification steps.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84; mol wt, 218. Found: C, 66.28; H, 6.43; N, 13.00; mol wt (mass spec), 218.

7-Acetoacetamido-1,4-dimethyl-8-methoxy-2-quinolone (29). A solution of 319 mg of **28** in 170 ml of dry benzene was heated at reflux for 100 hr with 2.0 g of diketene. The reaction mixture was evaporated under reduced pressure and the solid residue was recrystallized from 2-propanol to yield 258 mg (58%) of tan solid: mp 177–179°; ir (KBr) 1697, 1679, 1655 cm^{-1}; nmr ($CDCl_3$) δ 2.38 (3 H, s), 2.41 (3H, d, J = 1 Hz), 3.74 (5 H, s), 3.90 (3 H, s), 6.51 (1 H, q, J = 1 Hz), 7.43 (1 H, d, J = 9 Hz), 8.27 (1 H, d, J = 9 Hz), 9.91 (1 H, broad s).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27; mol wt, 302. Found: C, 63.81; H, 6.04; N, 9.18; mol wt (mass spec), 302.

Numerous attempts to effect cyclization of this product to the diazaanthracene system were unsuccessful.

7-Amino-8-methoxy-4-methyl-2-quinolone (31). A solution of 7.51 g of 8-methoxy-4-methyl-7-nitro-2-quinolone (**18**) in 250 ml of absolute ethanol was subjected to atmospheric hydrogenation (2160 ml) over 800 mg of platinum oxide. Work-up, following that for the preparation of **28**, gave 3.88 g (59%) of amine, sublimable and recrystallizable from chloroform: mp 134–136°; ir ($CHCl_3$) 3450, 3360, 1650 cm^{-1}; nmr (TFA) δ 2.84 (3 H, broad s), 4.22 (3 H, s), 7.21 (1 H, broad s), 7.77 (1 H, d, J = 9 Hz), 8.07 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.58; H, 5.81; N, 13.48.

7-*N*-Methylamino-8-methoxy-4-methyl-2-quinolone (33). A mixture of 2.60 g of **31**, 50 ml of trimethyl orthoformate, and *ca.* 0.07 g of concentrated sulfuric acid was heated for 6 hr at 120° in a 100-ml flask equipped with a heated column filled with glass helices, then cooled, and evaporated. The brown semisolid residue was hydrolyzed for 2 hr with 75 ml of refluxing 12% hydrochloric acid. Upon cooling, the solution was made basic with 3 *N* sodium hydroxide and extracted with chloroform; the extracts were washed with water, dried with magnesium sulfate, treated with charcoal, and evaporated to give 1.94 g (70%, overall yield) of tan solid, recrystallizable from 2-propanol: mp 154–157°; nmr ($CDCl_3$) δ 2.37 (3 H, d, J = 1 Hz), 2.93 (3 H, s), 3.77 (3 H, s), 4.49 (1 H, broad s), 6.63 (1 H, q, J = 1 Hz), 6.55 (1 H, d, J = 8.5 Hz), 7.28 (1 H, d, J = 8.5 Hz), 9.60 (1 H, broad s).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.75; H, 6.75; N, 13.00.

8-Methoxy-4-methyl-7-*N*-methylacetoacetamido-2-quinolone (30). The *N*-methylamine **33** (1.00 g) was treated with diketene (3.00 g) in benzene as described for **29** to yield, after chromatography (silica gel, 5% methanol in chloroform), 640 mg (49%) of light tan solid, recrystallizable from 2-propanol: mp 199–202°; nmr ($CDCl_3$) δ 2.13 (3 H, s), 2.48 (3 H, s), 3.29 (2 H, s), 3.35 (3 H, s), 3.90 (3 H, s), 6.56 (1 H, s), 6.95 (1 H, d, J = 8 Hz), 7.41 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.41; H, 5.83; N, 9.48.

Cyclization attempts with sulfuric acid and polyphosphoric acid at 80, 110, and 130° were unsuccessful, with only amine products being detected.

6-Methyl-9-nitro-2*H*,4*H*-oxazolo[5,4,3-*ij*]quinolin-4-one (35). A mixture of 10.00 g of 8-hydroxy-4-methyl-7-nitro-2-quinolone (**22**), 10.0 g of powdered potassium carbonate, and 250 g of dibromomethane in 1000 ml of dimethylformamide was stirred at 100° for 48 hr. After the mixture was cooled, most of the solvent was evaporated under reduced pressure, and the residue was diluted with water; the solid which settled out was repeatedly filtered and triturated with 2 *N* sodium hydroxide. The dark red filtrates were collected and acidified to recover unreacted starting material. The crude product was dissolved in boiling glacial acetic acid, and the solution was treated with activated charcoal, filtered, reheated, and diluted with water until the solution was turbid. Cooling gave 4.52 (54%, based on the recovery of 2.10 g of starting material) of dark yellow crystals: mp 293–295° dec; ir (KBr) 1665 cm^{-1}; nmr (TFA) δ 2.82 (3 H, d, J = 1 Hz), 6.83 (2 H, s), 7.26 (1 H, q, J = 1 Hz), 7.62 (1 H, d, J = 9 Hz), 8.20 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.06; mol wt, 232. Found: C, 56.66; H, 3.40; N, 12.09; mol wt (mass spec), 232.

9-Amino-6-methyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]quinolin-4-one (36). A solution of 3.28 g of **35** in 97% acetic acid containing 400 mg of platinum oxide was subjected to atmospheric hydrogenation; uptake of hydrogen (950 ml) was complete after 3 hr. The catalyst was removed and solvent was evaporated to give a brownish liquid which solidified upon drying. The residue was washed with saturated bicarbonate and extracted into chloroform. The chloroform extract was washed with water, dried with magnesium sulfate, and evaporated to give 2.49 g (87%) of white solid, from which an analytical sample could be obtained by sublimation: mp 224–226°; ir (KBr) 3430, 3330, 1665 cm^{-1}; nmr (TFA) δ 2.81 (3 H, s), 6.72 (2 H, s), 7.21 (1 H, s), 7.66 (2 H, s).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85; mol wt, 202. Found: C, 65.12; H, 4.96; N, 13.79; mol wt (mass spec), 202.

9-Acetoacetamido-6-methyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]quinolin-4-one (34). A mixture of 1.920 g of **36**, 4.0 g of freshly distilled diketene, and 400 ml of dry benzene was maintained at reflux for 50 hr; solvent was evaporated, and the residue was dissolved in chloroform The chloroform solution was washed with 0.5 *N* hydrochloric acid and water, dried with magnesium sulfate, evaporated, and thoroughly dried to give 1.011 g (48%, based on the recovery of 450 mg of starting material from the acid wash) of white solid, recrystallizable from benzene: mp 185–187°; ir (KBr) 3430, 3340, 1670 cm^{-1}; nmr (TFA) δ 2.55 (3 H, s), 2.85 (3 H, s), 4.09 (2 H, s), 6.71 (2 H, s), 7.26 (1 H, s), 7.63 (1 H, d, J = 9 Hz), 7.93 (1 H, d, J = 9 Hz), 9.69 (1 H, broad s).

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78;

mol wt, 286. Found: C, 63.16; H, 4.91; N, 9.77; mol wt (mass spec), 286.

6,10-Dimethyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinoline-4,8-(11*H*)-dione (38). A. From 9-Acetoacetamido-6-methyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]quinolin-4-one (34). A mixture of 1.630 g of **34** and 250 ml of polyphosphoric acid was heated and stirred for 7.5 hr, then hydrolyzed with water and neutralized with 6 *N* sodium hydroxide, precipitating a white solid, which was filtered, dried, and washed with chloroform. The chloroform wash was dried with magnesium sulfate, treated with charcoal, and evaporated to give 505 mg (44%) of amine **36**. The chloroform-insoluble residue was recrystallized from dimethylformamide to yield 300 mg (20%) of light tan solid. An analytical sample, prepared by repeated recrystallization from dimethylformamide, darkened at 330° but did not melt below 370°: uv (95% C_2H_5OH) $\lambda\lambda_{max}$ 258, 287, 300, 355 nm, $\epsilon\epsilon_{max}$ 38,000, 35,000, 50,000, 13,000, respectively; ir 1670 cm^{-1}; nmr (TFA) δ 2.84 (3 H, s), 2.98 (3 H, s), 6.79 (2 H, s), 7.07 (1 H, s), 7.18 (1 H, s), 8.64 (1 H, s). The mass spectrum shows stepwise loss of two molecules of carbon monoxide from the molecular ion.

$$268 \xrightarrow{m^* 215} 240; \quad 240 \xrightarrow{m^* 187} 212$$

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44; mol wt, 268. Found: C, 66.89; H, 4.76; N, 10.21; mol wt (mass spec), 268.

B. From 9-(2′-Carbethoxy-1′-methylvinylamino)-6-methyl-2*H*,-4*H*-oxazolo[5,4,3-*ij*]quinolin-4-one (39). A solution of 150 mg of the butenoate derivative **39** (see next section) in 3 ml of chloroform was added dropwise to 10 ml of stirred mineral oil at 240°. The reaction mixture was heated at 240° for an additional 15 min, cooled, and poured into 50 ml of hexane. The precipitate was filtered, washed with hexane and benzene, and dried to yield 38 mg (30%) of light tan solid, recrystallizable from dimethylformamide; the nmr and infrared spectra were superimposable on those of the cyclization product in section A.

9-(2′-Carbethoxy-1′-methylvinylamino)-6-methyl-2*H*,4*H*-oxazolo-[5,4,3-*ij*]quinolin-4-one (39). Using the procedure of Hauser and Reynolds,[27] a mixture of 400 mg of **36**, 1.0 g of ethyl acetoacetate, and 5.0 g of Drierite was allowed to react in 100 ml of absolute ethanol containing 4 drops of glacial acetic acid. Column chromatography over silica gel with 2% methanol in chloroform, followed by recrystallization from cyclohexane–benzene (25:1), afforded 242 mg (40%) of white, crystalline product: mp 124–125°; ir 1680, 1660 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (3 H, t, J = 7 Hz), 2.07 (3 H, d, J = 1 Hz), 2.43 (3 H, d, J = 1 Hz), 4.15 (2 H, q, J = 7 Hz), 4.78 (1 H, d, J = 1 Hz), 6.27 (2 H, s), 6.36 (1 H, q, J = 1 Hz), 6.83 (1 H, d, J = 9 Hz), 7.08 (1 H, d, J = 9 Hz), 10.42 (1 H, broad s).

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91; mol wt, 314. Found: C, 65.05; H, 5.81; N, 9.09; mol wt (mass spec), 314.

6,10,11-Trimethyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinoline-4,8(11*H*)-dione (40). A slurry of 150 mg of **38**, 300 mg of powdered potassium carbonate, and 5.0 g of methyl iodide in 50 ml of dry dimethylformamide was heated at 80° and stirred for 48 hr, then cooled, and filtered. The filtered residue was washed with water, dried, and recrystallized from dimethylformamide to give 77 mg (50%) of light yellow solid: mp 311–313°; uv (95% C_2H_5OH) $\lambda\lambda_{max}$ 258, 289, 302, 363 nm, $\epsilon\epsilon_{max}$ 28,000, 24,000, 65,000, 8000, respectively; ir (KBr) 1685, 1665 cm^{-1}; nmr (TFA) δ 2.92 (3 H, s), 3.24 (3 H, s), 4.70 (3 H, s), 6.88 (2 H, s), 7.16 (1 H, s), 7.28 (1 H, s), 8.78 (1 H, s).

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92; mol wt, 282. Found: C, 67.88; H, 5.20; N, 9.74; mol wt (mass spec), 282.

6,8-Dimethyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinolin-4-one (42) was prepared by a modification of the procedure of Campbell and Schaffner.[30] A solution of 2.000 g of **36** in 400 ml of chloroform was treated with 10 ml of methanol saturated with hydrogen chloride, precipitating the white hydrochloride salt. After evaporation of the solvent, the salt, together with 4.280 g (15.8 mmol) of ferric chloride hexahydrate, 160 mg of anhydrous zinc chloride, and 100 ml of 95% ethanol, was stirred at 60°, while 554 mg (7.92 mmol, 0.64 ml) of methyl vinyl ketone was added in 0.05-ml aliquots during 1 hr. The mixture was then heated at reflux for 3 hr, stirred without heating for 4 hr, and evaporated under reduced pressure. The residue was heated with 50 ml of polyphosphoric acid at 100° for 2 hr, cooled, hydrolyzed with water, and made basic with 6 *N* sodium hydroxide. Repeated extractions with chloroform yielded, after treatment with decolorizing charcoal, drying with magnesium sulfate, and evaporation, a dark orange fluffy solid. The crude product was chromatographed over a silica gel column with 5% methanol in chloroform. The first fractions yielded pure product, while subsequent fractions contained a mixture of the desired product and starting material.

The combined impure fractions were heated at reflux with 2.0 g of 3-nitrophthalic anhydride[41] in 25 ml of dry benzene for 2.5 hr, cooled, and extracted with 3 *N* hydroxide. The slightly soluble yellow product was filtered, washed with water, and dried; extraction of the two-phase filtrate with chloroform afforded additional material. The combined product weighed 673 mg (34%) and was recrystallizable from benzene–cyclohexane (3:2): mp 235–238°; uv (95% C_2H_5OH) $\lambda\lambda_{max}$ 265 nm (sh), 275, 335, $\epsilon\epsilon_{max}$ 60,000, 72,000, 13,000, respectively; ir (KBr) 1685 cm^{-1}; nmr (TFA) δ 2.89 (3 H, d, J = 1 Hz), 3.28 (3 H, s), 6.90 (2 H, s), 7.16 (1 H, q, J = 1 Hz), 7.95 (1 H, d, J = 6 Hz), 8.54 (1 H, s), 9.03 (1 H, d, J = 6 Hz).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; mol wt, 252. Found: C, 71.30; H, 4.67; N, 10.92; mol wt (mass spec), 252.

Synthetic deoxynybomycin (6,8,11-trimethyl-2*H*,4*H*-oxazolo[5,4,-3-*ij*]pyrido[3,2-*g*]quinoline-4,10(11*H*)-dione (2) was prepared by a modification of the procedure of Prill and McElvain.[31] A mixture of 100 mg (0.4 mmol) of **42**, 40 ml of dry benzene, and 1.5 ml of dimethyl sulfate was heated at reflux for 6 hr, cooled, and filtered. The orange residue was repeatedly washed with ether to remove all traces of excess dimethyl sulfate and dried to afford 138 mg (98%) of methosulfate salt. A solution of the methosulfate salt (*ca.* 0.4 mmol) in 15 ml of water was stirred at 0° while separate solutions of 90 mg (1.6 mmol) of potassium hydroxide in 5 ml of water and 263 mg (0.8 mmol) of potassium ferricyanide in 10 ml of water were added dropwise at the same rate, the temperature being kept below 5°. After addition was complete, the reaction mixture was stirred at 3° for 2 hr and at room temperature for 5 hr. The precipitated solid was isolated by centrifugation, washed twice with water, and dried overnight *in vacuo*. Recrystallization of the dried residue three times from dimethylformamide (once using decolorizing charcoal) afforded 34 mg (21%) of a white solid, identical upon tlc analysis (5% methanol in chloroform; chloroform; ethyl acetate) with authentic deoxynybomycin: mp >350°; ir (KBr) 1660 cm^{-1}; nmr (TFA) δ 2.90 (3 H, s), 2.98 (3 H, s), 4.56 (3 H, s), 6.85 (2 H, s), 7.18 (1 H, s), 7.38 (1 H, s), 8.32 (1 H, s).

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92; mol wt, 282. Found: C, 68.09; H, 4.98; N, 10.18; mol wt (mass spec), 282.

4-Formylquinoline (44). Lepidine (15.0 g) was treated with 13.5 g of freshly prepared selenium dioxide[42] according to the procedure of Kaplan[33] to give, after chromatography over silica gel (5% methanol in chloroform), 7.9 g (48%) of light orange solid, recrystallizable from petroleum ether; mp 48–50° (lit.[43] mp 48–49°).

4-Hydroxymethylquinoline (45). A mixture of 3.00 g of **44** and 3.0 g of sodium borohydride in 50 ml of ethanol was stirred for 4 hr, diluted with water, and extracted with chloroform. The chloroform extracts were washed with water, dried with magnesium sulfate, and evaporated to give an orange oil; chromatography over a silica gel column with 5% methanol in chloroform afforded 2.19 g (72%) of white solid, recrystallizable from benzene; mp 93–95° (lit.[43] mp 97–99°).

Attempts to oxidize the hydroxymethylquinoline to 4-hydroxymethyl-1-methyl-2-quinolone, using the procedure of Prill and McElvain,[31] were unsuccessful, giving aldehyde products.

4-Acetoxymethylquinoline (46). A solution of 1.00 g of **45** in 40 ml of glacial acetic acid containing 1 ml of sulfuric acid was heated at 100° for 4 hr, carefully poured into sodium bicarbonate, and extracted with chloroform. The extracts were dried with magnesium sulfate and evaporated to give 0.96 g (76%) of light tan solid: mp 55–57°; nmr ($CDCl_3$) δ 2.12 (3 H, s), 5.48 (2 H, s), 8.2–7.2 (6 H, m). An analytical sample was prepared by vacuum sublimation.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.74; H, 5.58; N, 7.04.

4-Acetoxymethyl-1-methyl-2-quinolone (50). A heated solution of 500 mg of **46** in 100 ml of dry benzene was treated with *ca.* 2 ml of dimethyl sulfate, precipitating a light yellow solid. After being heated at reflux for 4 hr, the reaction mixture was filtered,

(41) J. W. Alexander and S. M. McElvain, *J. Amer. Chem. Soc.*, **60**, 2285 (1938).
(42) R. H. Baker and R. N. Maxson, *Inorg. Syn.*, **1**, 119 (1939).
(43) S. F. MacDonald, *J. Amer. Chem. Soc.*, **69**, 1219 (1947).

and the methosulfate salt was washed thoroughly with ether. A solution of the salt in 45 ml of water was cooled to 0° while separate solutions of 420 mg (7.5 mmol) of potassium hydroxide in 15 ml of water and 1.645 g (5 mmol) of potassium ferricyanide in 30 ml of water were added, dropwise and at the same rate, to the stirred solution. The reaction mixture was stirred for 2 hr each at 3° and room temperature, and then thoroughly extracted with chloroform; the extracts were washed with 3 *N*, then 1 *N* hydrochloric acid, finally with water. The residue from evaporation of the solvent was chromatographed over silica gel (5% methanol in chloroform) to afford 186 mg (31%) of white solid: mp 157–159°; nmr (TFA) δ 2.40 (3 H, s), 4.39 (3 H, s), 5.83 (2 H, s), 7.42 (1 H, s), 8.40–7.67 (4 H, m).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.34; H, 5.51; N, 6.28.

4-Hydroxymethyl-1-methyl-2-quinolone (49). A solution of 150 mg of **50** in 50 ml of 0.5 *N* ethanolic potassium hydroxide was heated at reflux for 1.5 hr; after the solvent was evaporated, the crude residue was recrystallized twice from dilute (*ca.* 8%) hydrochloric acid to yield 69 mg (57%) of white solid: mp 178–181°; nmr (TFA) δ 4.36 (3 H, s), 5.60 (2 H, s), 7.60–8.30 (5 H, m).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.41. Found: C, 69.59; H, 5.71; N, 7.22.

4-Formyl-1-methyl-2-quinolone (48). Using the procedure of Cook and Stamper,[34] 3.10 g of 1,4-dimethyl-2-quinolone (**47**) was oxidized with selenium dioxide at 175° to yield 1.84 g (55%) of an orange solid, after recrystallization from benzene–petroleum ether; mp 180–182°; ir 1698, 1670 cm^{-1}.

Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.68; H, 4.83; N, 7.73.

4-Hydroxymethyl-1-methyl-2-quinolone (49). 4-Formyl-1-methyl-2-quinolone (**48,** 500 mg) was reduced with aluminum isopropoxide in 2-propanol according to the procedure of Cook and Stamper,[34] to yield 114 mg (23%) of white solid, mp 177–179°; spectral and tlc properties identical with those of a sample of **49** prepared above from **50**.

8-Formyl-6-methyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinolin-4-one (51). A modification of the procedure of Kaplan[33] was used. A stirred solution of 500 mg of the bridged diazaanthracene **42** in 75 ml of dioxane was heated to 60° then treated with a solution of 2.0 g of freshly prepared selenium dioxide[42] in 50 ml of dioxane containing 5 ml of water. The reaction mixture was heated at reflux for 6 hr, and the precipitated selenium was filtered from the hot solution. After evaporation of the solvent, the residue was thoroughly dried *in vacuo* and extracted with boiling chloroform until the extracts were colorless. Evaporation of the chloroform solution afforded the crude aldehyde product (mixed with starting material), which was chromatographed on preparative tlc plates (silica gel) using 5% methanol in chloroform. Isolation of the orange, slower moving major band afforded 282 mg (53%) of bright orange solid: mp 278–280°; ir (KBr) 1690, 1668 cm^{-1}; nmr (TFA) δ 2.91 (3 H, s), 6.91 (2 H, s), 7.19 (1 H, s), 8.50 (1 H, d, J = 5.5 Hz), 9.47 (1 H, s), 9.52 (1 H, d, J = 5.5 Hz), 10.82 (1 H, s).

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 67.67; H, 3.79; N, 10.52; mol wt, 266.0691. Found: C, 68.04; H, 3.91; N, 10.75; mol wt (high resolution mass spec), 266.0689.

Reaction of **51** with 2,4-dinitrophenylhydrazine gave a bright red precipitate, mp 285–292° dec.

7-Hydroxymethyl-6-methyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinolin-4-one (52). A large excess of sodium borohydride (1.0 g), 200 mg of **51**, and 100 mg of sodium carbonate in 100 ml of hot ethanol was stirred at room temperature for 2 hr. After addition of 10 ml of water, the solution was heated on a steam bath for 1 hr, cooled overnight, and filtered. The filtered residue was recrystallized from 2-propanol to give 80 mg of yellow product. The filtrate was evaporated, and the residue was partitioned between chloroform and water; the chloroform fraction was washed twice with water and evaporated. The residue was recrystallized from 2-propanol to afford an additional 108 mg (total 188 mg, 93%) of bright yellow solid: mp 224–226°; ir (KBr) 1668 cm^{-1}; nmr (TFA) δ 2.84 (3 H, s), 5.87 (2 H, s), 6.84 (2 H, s), 7.12 (1 H, s), 8.36 (1 H, d, J = 5.5 Hz), 8.37 (1 H, s), 9.16 (1 H, d, J = 5.5 Hz).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44; mol wt, 268.0848. Found: C, 67,11; H, 4.43; N, 10.28; mol wt (high resolution mass spec), 268.08502.

7-Acetoxymethyl-6-methyl-2*H*,4*H*-oxazolo[5,4,3-*ij*]pyrido[3,2-*g*]quinolin-4-one (53). A solution of 100 mg of **52** in 12 ml of glacial acetic acid containing a trace of sulfuric acid was heated at 100° for 3 hr, then the dark red reaction mixture was poured into water, neutralized with saturated bicarbonate, and extracted with chloroform. The extracts were washed with water and evaporated; preparative tlc (silica gel) using 5% methanol in chloroform afforded 72 mg (63%) of yellow solid: mp 248–250°; ir (KBr) 1730, 1670 cm^{-1}; nmr (TFA) δ 2.60 (3 H, s), 2.90 (3 H, s), 6.22 (2 H, s), 6.90 (2 H, s), 7.16 (1 H, s), 8.24 (1 H, d, J = 5.5 Hz), 8.51 (1 H, s), 9.22 (1 H, d, J = 5.5 Hz).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03; mol wt, 310.09535. Found: C, 65.91; H, 4.64; N, 8.92; mol wt (high resolution mass spec), 310.0952.

Nybomycin Acetate (54). A. From Nybomycin. Using the procedure outlined by Eble, *et al.*,[5] 1.20 g of nybomycin was treated with acetic acid to yield 0.99 g (72%) of **54**, after recrystallization from 30 ml of ethanol–chloroform (2:1). An analytical sample was obtained by preparative tlc (silica gel, 5% methanol in chloroform) followed by recrystallization: mp 232–234° (lit.[5] mp 236–237°); ir (KBr) 1740, 1660 cm^{-1}; nmr (TFA) δ 2.44 (3 H, s), 2.87 (3 H, s), 4.45 (3 H, s), 5.87 (2 H, s), 6.80 (2 H, s), 7.14 (1 H, s), 7.49 (1 H, s), 8.15 (1 H, s).

Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.53; H, 4.74; N, 8.23; mol wt, 340. Found: C, 63.38; H, 4.61; N, 8.39; mol wt (mass spec), 340.

B. From Oxidation of 53. The procedure of Prill and McElvain[31] was used with slight modification. A heated solution of 124 mg (0.4 mmol) of the acetate **53** in 50 ml of dry benzene was treated with *ca.* 2 ml of dimethyl sulfate, precipitating an orange solid. The reaction mixture was heated at reflux for 8 hr, cooled, and filtered; the orange salt was washed thoroughly with ether to remove all traces of excess dimethyl sulfate.

A solution of the salt in 15 ml of water was stirred at 0° while separate solutions of 68 mg (1.2 mmol) of potassium hydroxide in 5 ml of water and 263 mg (0.8 mmol) of potassium ferricyanide in 10 ml of water were added, dropwise and at the same rate. The reaction mixture was stirred at 3° for 2 hr and at room temperature for an additional 4 hr. The aqueous reaction mixture was extracted with chloroform; the extracts were washed with 3 *N* and 1 *N* hydrochloric acid, and with water. After evaporation of the solvent, the residue was chromatographed on a preparative tlc plate (silica gel) using 5% methanol in chloroform. The white solid isolated from the tlc plate weighed 24 mg (18%) and showed chromatographic behavior (5% methanol in chloroform; 2% methanol in chloroform; ethyl acetate) identical with that of nybomycin acetate (**54**) prepared from natural nybomycin; the nmr, infrared, and mass spectra were also identical with those of authentic nybomycin acetate. A mixture melting point was undepressed.

Anal. Calcd for $C_{18}H_{14}N_2O_5$: mol wt, 340.10581. Found: mol wt (high resolution mass spec), 340.1061.

Nybomycin (1). A solution of 50 mg of nybomycin acetate (**54**) in 50 ml of a 0.5 *N* ethanolic potassium hydroxide solution was heated at reflux for 30 min; the solvent was evaporated and the residue was recrystallized from dimethylformamide using activated charcoal. The white solid, after drying *in vacuo*, weighed 32 mg (73%): mp >350°; ir (KBr) 1655 cm^{-1}; nmr (TFA) δ 2.87 (3 H, s), 4.55 (3 H, s), 5.58 (2 H, s), 6.82 (2 H, s), 7.16 (1 H, s), 7.69 (1 H, s), 8.19 (1 H, s). Ultraviolet, infrared, nmr, and mass spectra were identical with those of the natural product.

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