6-Acetyl-3-methyl-2-quinoxalinecarboxamide 1,4-Dioxide (1) and 7-Acetyl-3-methyl-2-quinoxalinecarboxamide 1,4-Dioxide (2). A mixture of the 6- and 7-acetyl-3-methyl-2-quinoxalinecarboxamide 1,4-dioxide ethylene ketals (4, 27 g, 0.089 mol) was dissolved in 2.5 L of acetone and 150 mL of 1 N hydrochloric acid, and the solution was refluxed for 5 h. During this time yellow crystals precipitated that were collected by suction filtration upon termination of the reaction. The crystals were washed thoroughly with acetone to afford 11.5 g (50%) of **2**: mp 229–230 °C; NMR (CH_3CO_2D) δ 2.97, 3.03 (6, two overlapping singlets, CH_3, $COCH_3$), 8.60–9.10 (2, m, H-5, H-6), 9.40 (1, d, J = 2 Hz, H-8); IR (KBr) 1680 ($CONH_2$), 1700 cm^{-1} ($COCH_3$); UV λ_{max} (MeOH) 238 nm (ϵ 24200), 280 (23300), 385 (8390); mass spectrum m/e 261 (M^+). Based on spectral data less than 10% of 1 was present in this sample of **2**. Anal. ($C_{12}H_{11}N_3O_4$) H, N; C: calcd, 55.22; found, 54.80.

The mother liquor was concentrated to 0.5 vol in vacuo and 10.4 g (45%) of 1 crystallized from the solution: mp 216–217 °C; NMR (CF_3CO_2D) δ 3.00 (6, s, CH_3, $COCH_3$), 8.60–9.10 (2, m, H-7, H-8), 9.47 (1, d, J = 2 Hz, H-5); IR (KBr) 1695 cm^{-1} (shoulder at 1690, $COCH_3$, $CONH_2$); UV λ_{max} (MeOH) 237 nm (ϵ 21500), 278 (22100), 380 (6330); mass spectrum m/e 261 (M^+). Based on spectral data, less than 10% of **2** was present in this sample of 1.

5(6)-Acetylbenzofurazan 1-oxide (**3**, 1.78 g, 0.01 mol) and acetoacetamide (1.01 g, 0.01 mol) were dissolved in 25 mL of tetrahydrofuran. A solution of methylamine in methanol (1.0 mL of a 4.56 M solution) was added to the reaction mixture, which was then stirred at room temperature for 18 h. The dark reaction mixture was filtered under suction, and 0.50 g (19%) of 1 was obtained as yellow crystals which melted at 216–217 °C after Darco treatment and recrystallization from methanol. The reaction mother liquor contained tars. None of **2** was found to be present (<10%) in this sample of 1 based on spectral data. The mixture melting point with material (1) from above was 216–217 °C. Anal. ($C_{12}H_{11}N_3O_4$) C, H, N.

Quinoxaline Mono-*N*-oxides 6–9. These compounds were prepared solely for the structural elucidation of 1 and **2** and were used without purification in order to prevent fractionalization of 6- and 7-acetyl isomers. Selective monodeoxygenation of 1 and **2** to afford **7** and **9**, respectively, was accomplished in refluxing 1-propanol containing trimethyl phosphite in the manner described previously.[12] Acetic anhydride–acetic acid rearrangement of 1 and **2** to the corresponding 3-acetoxymethyl-2-quinoxalinecarboxamide 1-oxides **6** and **8**, respectively, was carried out according to a literature procedure.[11] Compounds **6–9** were characterized by NMR, IR, UV, and mass spectral analyses.

Acknowledgment. We are indebted to Dr. James W. McFarland for stimulating our interest in this problem, and we wish to thank Dr. Robert F. Myers for advice regarding this work. We thank Richard Pezzullo and Jules Aimetti for their technical assistance.

References and Notes

(1) (a) J. Francis, J. K. Landquist, A. A. Levi, J. S. Silk, and J. M. Thorp, *Biochem. J.*, **63**, 455 (1956); (b) J. R. Valenta, J. R. E. Hoover, and J. F. Pagano, *Antimicrob. Agents Chemother.*, 453 (1966); (c) E. N. Padeiskaya, G. N. Pershin, and T. P. Radkevich, *Int. Congr. Chemother., Proc., 5th*, 1, 825 (1967); *Chem. Abstr.*, **70**, 18594b (1969).

(2) Carbadox, a QNO, is highly effective as a growth promotant for swine: G. W. Thrasher, J. E. Shively, C. E. Askelson, W. E. Babcock, and R. R. Chalquest, *J. Anim. Sci.*, **31**, 333 (1970).

(3) (a) M. J. Haddadin, G. Agopian, and C. H. Issidorides, *J. Org. Chem.*, **36**, 514 (1971); (b) E. Abushanab and N. D. Alteri, Jr., *ibid.*, **40**, 157 (1975).

(4) (a) W. Dürckheimer, *Justus Liebigs Ann. Chem.*, **756**, 145 (1972); (b) N. A. Mufarrij, M. H. Haddadin, C. H. Issidorides, J. W. McFarland, and J. D. Johnston, *J. Chem. Soc., Perkin Trans. 1*, 965 (1972).

(5) It has generally been assumed, although not determined, that the antibacterial activity of both isomers would be similar: T. H. Cronin and K. Richardson, U.S. Patent 3818007 (1974).

(6) Subsequent to completion of our work a patent describing some of this work has been issued from these laboratories: U.S. Patent 3948911 (1976).

(7) P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.*, 11, 305 (1968).

(8) (a) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965); (b) *Heterocycles*, 4, 767 (1976).

(9) A mixture of 6- and 7-substituted QNO isomers is expected when 5(6)-substituted BFO's are used (ref 3 and 4). However, the major isomer in this reaction is predicted to be the 6-acetyl QNO isomer 1, as observed, based on previous studies with BFO's containing electron-withdrawing substituents (ref 3b).

(10) This technique has been used previously for the structural determination of other 6- and 7-substituted QNO isomers (ref 4a).

(11) M. J. Haddadin and A. S. Salameh, *J. Org. Chem.*, **33**, 2127 (1968).

(12) Our recent study of the reduction of some 2,3-disubstituted QNO's with trimethyl phosphite in refluxing alcohol solvent has shown that deoxygenation occurs exclusively at the nitrogen adjacent to the carbon bearing an electron-withdrawing group: J. P. Dirlam and J. W. McFarland, *J. Org. Chem.*, **42**, 1360 (1977).

(13) H. E. Batson, "An Introduction to Statistics in the Medical Sciences", Burgess Publishing Co., Minneapolis, Minn., 1957, pp 64–69.

(14) E. Steers, E. L. Foltz, and B. S. Graves, *Antibiot. Chemother.*, **9**, 307 (1959).

Quinolone Antimicrobial Agents. 1. Versatile New Synthesis of 1-Alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids

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A flexible reaction sequence has been developed which starts with readily available anthranilic acids or isatoic anhydrides and leads regiospecifically to 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids after reaction with 1,3-dicarbonyl compounds. The sequence is superior to earlier published methods by allowing electron-releasing and -withdrawing groups in any position on the aromatic ring, by allowing convenient substitution at C_2, and better overall yield. A number of new and known antimicrobial agents were prepared and tested in vitro, demonstrating, inter alia, that substitution of the H at C_2 abolishes antibacterial activity.

Synthetic antimicrobial agents descended from nalidixic acid (**1**),[1] including oxolinic acid (**2**),[2] piromidic acid (**3**),[3] and pipemidic acid (**4**)[4] have found clinical acceptance in the treatment of human urinary tract infections. Closely

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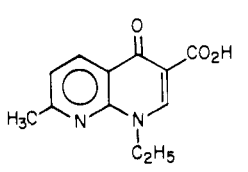

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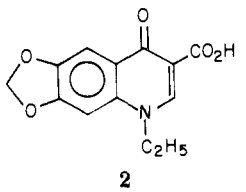

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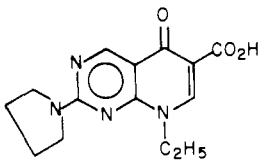

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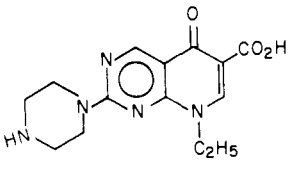


4

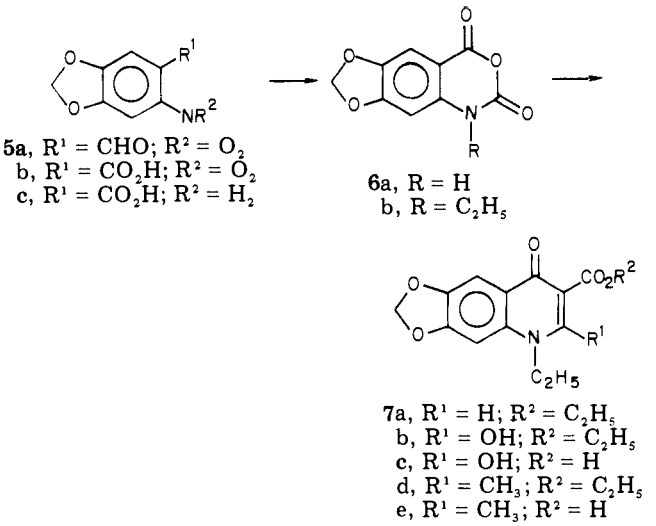
related molecules are currently being investigated as antibiotics, antitumor agents,[5-8] and potent diuretics.[9] Extensive study of the antibacterial mode of action of these agents has led to much useful information but has failed to uncover a suitable rationale for drug design. In absence of such a rationale, bioassay-directed molecular manipulation retains its value.

Random molecular manipulation has shown that antimicrobial potency is optimized when the N-substituent is ethyl[1,3,10-12] or methoxy,[13] that the 2,3 double bond cannot be reduced,[11,14] that esters and amides are active to the extent that they hydrolyze in vivo,[2,15] and that carboxy replacement by methylsulfinyl and methylsulfonyl groups,[15] or sulfonamides and phosphoric acids,[16] leads to inactive products. Considerably more flexibility is permissible in the aromatic moiety as may be inferred from formulas 1–4. Further investigation has shown that, regardless of the precise ring system, substitution at C_5 generally results in inactivity[11,17] with the amino function being a unique exception.[17-19] The most fruitful position for monofunctional modification of activity is C_7. Primarily due to synthetic difficulties, knowledge of the effect of substituents at C_6 and C_8 and of electron-withdrawing groups has been limited. Until very recently little information was available on the effect of substitution at C_2.[13]

The most common synthetic entry to this series is the reaction of an arylamine with methoxymethylenemalonic esters to yield anilinomethylenemalonates which may be cyclized by heating (the Gould–Jacobs reaction) or by the use of a Friedel–Crafts catalyst to yield the desired quinoline. This sequence works well when the arylamine is activated, particularly by electron-releasing substituents meta to the nitrogen. Low yields result, however, when electron-withdrawing substituents are present. Product formation can be further complicated by ring-closure isomers.

Upon examining the utility of the reaction between isatoic anhydrides and carbanions for the syntheses of dihydrofuroquinoline alkaloids[20,21] and the related work of others,[22,23] it appeared that a relatively simple modification of the sequence would lead to a convenient synthesis of the oxolinic acid class which would overcome the above difficulties.

This concept was first applied to the synthesis of oxolinic acid (2). The necessary substituted isatoic anhydride was readily prepared. 6-Nitropiperonal (**5a**) was oxidized with permanganate to 6-nitropiperonylic acid (**5b**), followed by catalytic reduction in an acidic medium to give **5c**. This procedure is an alternative to the published method for this compound.[24] Treatment of **5c** with phosgene[25] led to **6a**, whose acidic NH proton was ethylated to produce the desired isatoic anhydride **6b**. Reaction of **6b** with sodioethyl formylacetate[26] led efficiently to **7a**[2,27] which, upon hydrolysis with aqueous HCl, was converted in almost



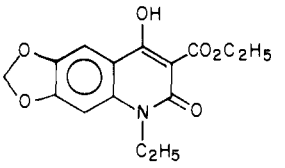
5a, $R^1 = CHO$; $R^2 = O_2$
b, $R^1 = CO_2H$; $R^2 = O_2$
c, $R^1 = CO_2H$; $R^2 = H_2$

6a, R = H
b, $R = C_2H_5$

7a, $R^1 = H$; $R^2 = C_2H_5$
b, $R^1 = OH$; $R^2 = C_2H_5$
c, $R^1 = OH$; $R^2 = H$
d, $R^1 = CH_3$; $R^2 = C_2H_5$
e, $R^1 = CH_3$; $R^2 = H$

quantitative yield to oxolinic acid (2), identical with an authentic specimen. This sequence provides a convenient and flexible new synthesis for this clinically useful antimicrobial agent.

Attention was next turned to use of this sequence to prepare a series of the previously unknown C_2-substituted analogues of oxolinic acid for biological evaluation. Thus, **6b** was reacted with sodioethyl malonate to produce **7b** whose solid-state IR spectral characteristics are more in accord with a tautomeric depiction such as that of **8a**, while the ^1H NMR deshielding of the C_5 proton (7.43 ppm) in $CDCl_3$ suggests tautomer **7b**. An IR in $CHCl_3$ resulted



8a

in a shift of CO frequencies to 1675 and 1620 cm^{-1} in accord with formula **7b**. Clearly, the substance tautomerizes freely and the nature of the solvent, as expected, plays an important role. Saponification with aqueous KOH resulted in decarboxylation on acidic workup.[22] Careful hydrolysis of **7b** with BBr_3 produced the desired analogue, **7c**. Repetition of the sequence using **6b** and sodioethyl acetoacetate produced intermediate **7d** which was saponified easily to **7e**. The IR and UV spectra of **7e** are very similar to those of oxolinic acid which suggests that the C_2 methyl group does very little to interfere with planarity of the C_4 ketone and the C_3 carboxy group and their normal interaction.

Neither **7c** nor **7e** could have been prepared readily by Gould–Jacobs-like methods because the requisite alkylidenemalonic esters are difficult to prepare. During the preparation of this paper, an alternative approach to the 2-methyl derivative (**7e**) was published.[13] The overall yield of **7e** via the isatoic anhydride is 27% based on 6-nitropiperonal compared to 4% based on 6-nitropiperonylic acid.[13] Compared to previous methods, the condensation of isatoic anhydrides with β-dicarbonyl compounds not only increases yields but also flexibility in altering the C_2 substituent. While it is obvious that a wide range of substituents could be added to the C_2 position in this way, our efforts ceased when in vitro antibacterial testing (Table I) showed that the C_2-OH and C_2-methyl analogues are inactive despite the high potency of **2**. This finding is consistent with the more limited findings of Agui et al.[13] A molecular theory of the mode of action of this antibiotic

Table I. Minimum Inhibitory Concentrations[a]

	2	11a	11b	11c	11d	7c	7e
Staph. aureus Smith (ATCC 130709)	5	40	40	>100	100	>100	>100
E. coli (9637)	1.25	20	2.5	>100	20	>100	>100
S. gallinarum (9184)	1.25	20	1.25	>100	20	>100	>100
K. pneumoniae (10031)	<0.625	>100	10	>100	10	>100	>100
M. smegmatis (607)	>40	>100	>100	>100	±100	>100	>100
C. albicans (10231)	>40	>100	>100	>100	>40	>100	>100

[a] Potency data are in micrograms per milliliter. Tests were preformed by an agar dilution–streak method.[31]

class will have to rationalize this finding. The IR, UV, and ^{1}H NMR properties of **7c** and **7e** make it unlikely that the explanation for this inactivity lies in steric inhibition of resonance.

In order to explore the presumed generality of this synthesis, the method was used to prepare several *N*-ethyl monosubstituted isatoic anhydrides and each was reacted with sodioethyl formylacetate to produce the desired analogues **11a–d**, after saponification, in an average 67% yield. In each case, only one final product was obtained and no chromatography was necessary for purification. The 6-chloro analogue **11d** is especially interesting. It was obtained in 59% overall yield while the Gould–Jacobs procedure gives only a 27% yield because of ring deactivation.[27] Using 3-chloroaniline, the Gould–Jacobs reaction yields 5% of 7-chloro and 2% of ethyl 5-chloro-4-hydroxy-3-quinolinecarboxylate.[28]

The C_7-substituted analogue **11d** was found to be the most potent of these agents in vitro. None of these agents was as potent as **2** itself.

These studies are sufficient to demonstrate major elements of the versatility of this synthesis and some significant new features relating to structure–activity relations. Future work will explore in a systematic way the influence of aromatic ring substitution on biopotency.

Experimental Section

Melting points were obtained on a calibrated Thomas-Hoover Unimelt apparatus. Infrared data were recorded on a Perkin-Elmer 727 and a Beckman 33 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 spectrometer with a Nicolet Technology TT-7 Fourier transform attachment. Tetramethylsilane or DSS was used as internal standard. Ultraviolet data were recorded on a Perkin-Elmer UV–visible Model 25 spectrophotometer. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMS-4 mass spectrometer. Thin-layer chromatography was performed on 0.25-mm silica gel 60 F-254 plates (Merck) using chloroform–ethanol (95:5). Visualization was done by UV or $KMnO_4$ spray. Microanalyses were performed on a Hewlett-Packard 185B, at the University of Kansas, and are within 0.4% of theory unless noted otherwise.

2-Nitro-4,5-methylenedioxybenzoic Acid (5b). To a solution of 300 mL of H_2O and 200 mL of acetone was added 25.7 g (0.132 mol) of 6-nitropiperonal (Aldrich Chemical Corp.) and 41.6 g (0.264 mol) of potassium permanganate. The mixture was mechanically stirred and heated to reflux for 4 h. Following distillation of the acetone, the flask was cooled and the MnO_2 precipitate filtered and washed with 2 × 50 mL of hot water. The filtrate was cooled in an ice bath and acidified to produce a yellow precipitate. Filtration yielded 22.8 g (82%) of the desired carboxylic acid: mp 166–167 °C dec (lit.[24] mp 165–166 °C dec). Anal. ($C_8H_5NO_6$) C, H, N.

4,5-Methylenedioxyanthranilic Acid Hydrochloride (5c). 6-Nitropiperonylic acid (**5b**, 1.0 g, 4.73 mmol) was dissolved in a solution of 100 mL of EtOH and 1 mL of concentrated HCl. To this solution was added 0.1 g of 10% Pd/C. The hydrogenation resulted in a 15-psi drop from an initial 50 psi. After filtration of the catalyst, evaporation of the solution resulted in 0.831 g (4.59 mmol, 97%) of the acid hydrochloride **5c**. For characterization, a portion was converted to the free amine by dissolving **5c** in water and neutralizing the acidic solution to pH 7.0 with 2% aqueous KOH, followed by extraction with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallized from THF: mp 175–176 °C dec (lit.[29] mp 175–176 °C dec). Anal. ($C_8H_7NO_4$) C, H, N.

5,6-Methylenedioxyisatoic Anhydride (6a). The general method of Wagner and Fegley,[25] utilizing the amine hydrochloride **5c** (7.09 g, 0.0386 mol) and phosgene, was used to prepare the isatoic anhydride. Crops were combined and recrystallized from THF to yield 4.4 g (55%) of **6a**: mp 258–259 °C; IR (KBr) 1800, 1720 (C=O), 1320, 1280 cm^{-1} (CO). Anal. ($C_9H_5NO_5$) C, H, N.

***N*-Ethyl-5,6-methylenedioxyisatoic Anhydride (6b).** Under an inert atmosphere, 3.8 g (0.0184 mol) of 5,6-methylenedioxyisatoic anhydride (**6a**) in 30 mL of DMF was added dropwise to a stirring solution of 0.73 g (0.0184 mol, hexane washed) of sodium hydride. Next, 5.73 g (0.0364 mol) of iodoethane was added to the solution which was then stirred overnight at room temperature. The solution was then concentrated to $^2/_3$ vol in vacuo. Ice was added to the concentrate resulting in 3.32 g (77.2%) of **6b**. Recrystallization from THF gave mp 205–206 °C (lit.[15] mp 207 °C); IR (KBr) 1790, 1730, 1660 cm^{-1} (C=O). Anal. ($C_{11}H_9NO_5$) C, H, N.

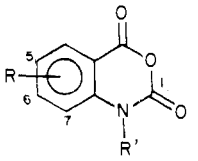
Ethyl 1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (7a). In an inert atmosphere, 100 mg (0.426 mmol) of *N*-ethyl-5,6-methylenedioxyisatoic anhydride (**6b**) and 176 mg (1.28 mmol) of sodioethyl formylacetate were combined in DMF for 15 min and then heated to 110 °C for 2 h. The DMF was evaporated to dryness in vacuo, followed by benzene azeotrope to remove residual DMF. The residue was then dissolved in water and acidified with 6 N HCl to produce a white precipitate which gave a single spot on TLC (R_f 0.74). Filtration, followed by recrystallization from acetonitrile, produced 82.3 mg (0.283 mmol, 66%) of **7a**: mp 179–180 °C (lit. mp 179–180,[27] 178–179 °C[2]); IR (KBr) 1685, 1640 cm^{-1} (C=O). Anal. ($C_{15}H_{15}NO_5$) C, H, N.

1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid (Oxolinic Acid, 2). In 20 mL of 10% aqueous HCl was suspended 70 mg (0.242 mmol) of the ester **7a**. The suspension was heated to reflux for 1 h to result in a white precipitate which was filtered and dried to yield 64 mg (0.241 mmol, 99%) of the acid. Acid **2** was recrystallized twice from aqueous DMF: mp 317 °C dec (lit.[2] mp 318 °C dec); IR (KBr) 1710, 1640 cm^{-1} (C=O); UV λ max (1% KOH–H_2O) 257 nm (ε 36 850), 265 (38 200), 296 (7200), 310 (9400), 324 (12 134), 338 (13 032); EIMS M$^+$ 261. Anal. ($C_{13}H_{11}NO_5$) C, H, N.

Ethyl 1-Ethyl-1,2-dihydro-4-hydroxy-6,7-methylenedioxy-2-oxo-3-quinolinecarboxylate (7b). Utilizing the method outlined for the preparation of **7a**, 27.2 mg (1.70 mmol) of diethyl malonate and 200 mg (0.851 mmol) of **6b** were condensed to yield (77%) 200 mg of the desired ester **7b** which upon recrystallization from $CHCl_3$–heptane gave mp 173–174 °C; IR (KBr) 1645, 1620 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.16–1.56 (m, 6, N- and O-CH_2CH_3), 3.67 (s, 2, –OH, exchangeable), 5.67–6.34 (m, 4, N- and O-CH_2), 6.00 (s, 2, CH_2O_2–), 6.67 (s, 1, H-8), 7.40 (s, 1, H-5); EIMS M$^+$ 305. Anal. ($C_{15}H_{15}NO_6$) C, H, N.

1-Ethyl-1,2-dihydro-4-hydroxy-6,7-methylenedioxy-2-oxo-3-quinolinecarboxylic Acid (7c). A solution of 100 mg (0.328 mmol) of ester **7b** in CH_2Cl_2 was cooled to −78 °C and slowly added, under inert atmosphere, to a −78 °C stirring solution of 0.24 g (0.983 mmol) of boron tribromide in CH_2Cl_2. A solution of 100 mg (0.328 mmol) of ester **7b** in CH_2Cl_2 was cooled to −78 °C and slowly added, under inert atmosphere, to a −78 °C stirring solution of 0.24 g (0.983 mmol) of boron tribromide in CH_2Cl_2. After 2 h, ice was added to the stirring solution which was allowed to come to room temperature. The precipitated boric acid was filtered. The CH_2Cl_2 layer of the biphasic filtrate was collected,

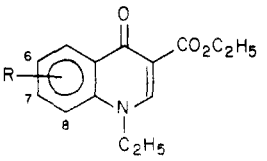
Table II. N-Substituted Isatoic Anhydrides[e]



Compd no.	Substituent R	Substituent R'	Mp, °C	Recrystn solvent	Yield,[a] %	Mol formula[b]
9a	5-CH_3	C_2H_5	184–185 dec	THF	92	$C_{11}H_{11}NO_3$
9b	6-CH_3	H	228 dec[c]	Aq DMF	67	$C_9H_7NO_3$
9c	6-CH_3	C_2H_5	178–179	Aq DMF	62	$C_{11}H_{11}NO_3$
9d	7-CH_3	H	277 dec[c]	THF	92	$C_9H_7NO_3$
9e	7-CH_3	C_2H_5	208 dec	THF	89	$C_{11}H_7NO_3$
9f	5-Cl	C_2H_5	147 dec[d]	THF	91	$C_{10}H_8ClNO_3$

[a] Yields are of purified product and are not maximal. [b] All compounds were analyzed for C, H, and N; analytical results were within ±0.4% of the theoretical values. [c] Reference 32. [d] Reference 33. [e] Reference 34.

Table III. Ethyl 1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylates



Compd no.	Substituent R	Mp, °C	Recrystn solvent	Yield,[a] %	Mol formula[b]
10a	6-CH_3	189–190[c]	MeCN	65	$C_{15}H_{17}NO_3$
10b	7-CH_3	218–219	MeCN	68	$C_{15}H_{17}NO_3$
10c	8-CH_3	129–130[c]	MeCN	76	$C_{15}H_{17}NO_3$
10d	6-Cl	184–185	MeCN	69	$C_{14}H_4ClNO_3$

[a,b] See corresponding footnotes in Table II. [c] Reference 27.

Table IV. 1-Ethyl-1,4-dihydro-4-oxo-3-quinolincarboxylic Acids

Compd no.	Substituent R[c]	Mp, °C	Recrystn solvent	Yield,[a] %	Mol formula[b]	Ref
11a	6-CH_3	218–219	Aq DMF	96	$C_{13}H_{13}NO_3$	27
11b	7-CH_3	283–284	Aq DMF	98	$C_{13}H_{13}NO_3$	28
11c	8-CH_3	203–204	DMF	86	$C_{13}H_{13}NO_3$	27
11d	6-Cl	226–227	DMF	93	$C_{10}H_{10}ClNO_3$	30

[a,b] See corresponding footnotes in Table II. [c] Numbering identical with that in Table III.

dried ($MgSO_4$), and evaporated to yield 0.394 g (89%) of the carboxylic acid **7c**. Recrystallization from THF gave mp 204–205 °C; IR (KBr) 1675, 1635 cm^{-1} (C=O); UV (1% KOH–H_2O) λ max 226 nm (ε 40 440), 302 (11 600), 322 (14 680), 336 (12 190); EIMS M^+ 277. Anal. ($C_{13}H_{11}NO_6$) C, H, N.

Ethyl 1-Ethyl-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (7d). Following the procedure detailed for **7a**, 218 mg (1.70 mol) of ethyl acetoacetate and 200 mg (0.851 mmol) of anhydride **6b** were condensed to yield, after recrystallization, 180 mg (70%) of the desired ester **7d**: mp 205 °C dec; IR (KBr) 1711, 1620 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.30 (t, 6, J = 7 Hz, N- and O-CH_2CH_3), 2.47 (s, 3, C-2 CH_3), 4.30 (m, 4, N- and O-CH_2), 6.10 (s, 2, CH_2O_2), 6.88 (s, 1, H-8), 7.75 (s, H-5); EIMS M^+ 303. Anal. ($C_{16}H_{17}NO_5$) C, H, N.

1-Ethyl-1,4-dihydro-2-methyl-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid (7e). In 30 mL of 10% aqueous KOH was suspended 50 mg (1.65 mmol) of ester **7d**. The mixture was refluxed for 1 h, cooled, and slowly acidified to pH 5 resulting in a precipitate. The mixture was extracted with $CHCl_3$ which dissolved the precipitate. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to yield 44.3 mg (1.63 mmol, 98%) of the carboxylic acid **7e**. A portion was recrystallized from THF: mp 304 °C dec (lit.[13] mp 305 °C); IR (KBr) 1690 cm^{-1} (C=O); UV λ max (1% KOH–H_2O) 229 nm (ε 22 000), 255 (48 500), 309 (14 578), 324 (15 950), 338 (15 400); EIMS M^+ 275. Anal. ($C_{14}H_{13}NO_5$) C, H, N.

Monosubstituted Isatoic Anhydrides 9a–f. Anhydrides **9b** and **9d** were prepared, according to the general procedure of Wagner and Fegley,[25] from the corresponding anthranilic acids. The isatoic anhydrides were then N-alkylated as detailed in the preparation of **6b**. Table II reports reaction yields and physical data.

Ethyl 1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylates 10a–d. Esters **10a–d** were prepared via the general procedure for the preparation of **7a**. Table III reports reaction yields and conditions.

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids 11a–d. Esters **10a–d** were saponified as detailed for **7c**. Table IV reports reaction yields and conditions.

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References and Notes

(1) G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey, and R. P. Brundage, *J. Med. Pharm. Chem.*, 5, 1063 (1962).
(2) D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, 11, 160 (1968).
(3) J. Matsumoto and S. Minami, *J. Med. Chem.*, 18, 74 (1975).
(4) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.*, 19, 1426 (1971).
(5) B. R. Baker and R. R. Bramhall, *J. Med. Chem.*, 15, 230 (1972).
(6) B. R. Baker and R. R. Bramhall, *J. Med. Chem.*, 15, 233 (1972).

(7) B. R. Baker and R. R. Bramhall, *J. Med. Chem.*, **15**, 937 (1972).
(8) M. Yoshimoto and C. Hansch, *J. Med. Chem.*, **19**, 71 (1976).
(9) J. Van Dijk, J. Hartog, and T. A. C. Boschman, *J. Med. Chem.*, **19**, 982 (1976).
(10) F. J. Turner, S. M. Ringel, J. T. Martin, P. J. Storino, J. M. Daley, and B. S. Schwartz, *Antimicrob. Agents Chemother.*, 475 (1968).
(11) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.*, **19**, 1482 (1971).
(12) H. Nakao, M. Fukushima, H. Yanagisawa, and S. Sugawara, *Chem. Pharm. Bull.*, **22**, 1864 (1974).
(13) H. Agui, T. Mitani, A. Izawa, T. Komatsu, and T. Nakagome, *J. Med. Chem.*, **20**, 791 (1977).
(14) A. A. Santilli, A. C. Scotese, and J. A. Yurchenco, *J. Med. Chem.*, 18, 1038 (1975).
(15) R. Albrecht, *Chim. Ther.*, 8, 45 (1973).
(16) H. Yanagisawa, H. Nakao, and A. Ando, *Chem. Pharm. Bull.*, 21, 1080 (1973).
(17) H. Agui, T. Mitani, M. Nakashita, T. Nakagome, T. Komatsu, A. Izawa, and Y. Eda, Japanese Patent 97 879 (1973); *Chem. Abstr.*, **80**, 82 714 (1974).
(18) Y. Nagano and M. Murakami, Japanese Patent 88 882 (1974); *Chem. Abstr.*, **82**, 43 195c (1975).
(19) H. Agui, T. Mitani, M. Nakashita, T. Nakagome, T. Komatsu, Y. Eda, Japanese Patent 97 880 (1973); *Chem. Abstr.*, **80**, 95 764r (1974).
(20) L. A. Mitscher, G. W. Clark, T. Suzuki, and M. S. Bathala, *Heterocycles*, **3**, 913 (1975).
(21) L. A. Mitscher, G. W. Clark, T. Suzuki, and M. S. Bathala, *Heterocycles*, **5**, 565 (1976).
(22) G. M. Coppola, G. E. Hardtmann, and O. R. Pfister, *J. Org. Chem.*, 41, 825 (1976).
(23) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959).
(24) S. Biniecki, Z. Kabzinska, and M. Szypulska, *Acta Pol. Pharm.*, **20**, 243 (1963); *Chem. Abstr.*, **62**, 466c (1965).
(25) E. C. Wagner and M. F. Fegley, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1975, p 488.
(26) W. Deuchel, *Helv. Chim. Acta*, **35**, 1587 (1952).
(27) H. Agui, T. Mitani, M. Nakashita, and T. Nakagome, *J. Heterocycl. Chem.*, 8, 357 (1971).
(28) H. Agui, T. Komatsu, and T. Nakagome, *J. Heterocycl. Chem.*, 12, 557 (1975).
(29) H. J. Hess, T. H. Cronin, and A. Scriabine, *J. Med. Chem.*, 11, 130 (1968).
(30) N. Barton, A. F. Crowther, W. Hepworth, D. N. Richardson, and G. W. Driver, British Patent 830 832 (1960); *Chem. Abstr.*, **55**, 7442e (1961).
(31) L. A. Mitscher, R.-P. Leu, M. S. Bathala, W. Wu, J. L. Beal, and R. White, *Lloydia*, **35**, 157 (1972).
(32) D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2916 (1957).
(33) G. E. Hardtmann, G. Koletar, and O. R. Pfister, *J. Heterocycl. Chem.*, 12, 565 (1977).
(34) Although Chemical Abstracts uses "2*H*-3,1-benzoxazine-2,4(1*H*)-dione", the authors prefer to use the more common trivial name of "N-substituted isatoic anhydride". We have adopted the anhydride numbering system as well.

Synthesis and Hypoglycemic Activity of Some Substituted 2-Arylthiazolo[3,2-*a*]pyridinium Salts

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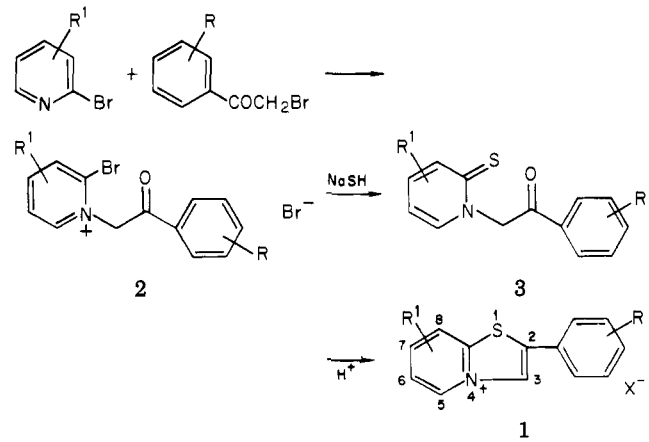
A series of substituted 2-arylthiazolo[3,2-*a*]pyridinium salts (**1a–q**) was prepared by known methods and tested for hypoglycemic activity in 48-h fasted rats. Two compounds, 2-phenylthiazolo- and 8-methyl-2-phenylthiazolo[3,2-*a*]pyridinium perchlorate (**1a** and **1q**), showed consistent hypoglycemic activity in this screen, demonstrating that a high degree of structural specificity was required for hypoglycemic activity. At higher doses the hypoglycemic activity of **1a** and **1q** was associated with elevated levels of hepatic triglycerides.

As part of a continuing program of screening novel structures, particularly pyridines, for hypoglycemic activity in the 48-h fasted rat, it was noted that 2-phenyloxazolo- and thiazolo[3,2-*a*]pyridinium salts had significant activity. These and several similar compounds have been described by Bradsher and co-workers.[1-5] Since the thiazolo compound seemed more potent, this system was chosen for further development. The 2-phenylthiazolo[3,2-*a*]-pyridinium compound **1a** was tested originally as the perchlorate. To obviate any problem that might have been attendant with this salt, three other salts (chloride, bisulfate, and trifluoroacetate) were prepared by modification of the ring closure procedure or by ion-exchange techniques and tested.

As a first approach to the selection of compounds for synthesis, use was made of a "best set of substituents" list authored by Dr. Richard Cramer of our laboratories. This list was based on proposals of Wootton et al.[6] The purpose of such choices was to search for a structure–activity trend (in terms of partition coefficients π, electronic effects σ, and steric factors) with the minimum number of compounds. The compounds prepared are listed in Table I. Their method of preparation paralleled that used by Bradsher and Boliek[5] (Scheme I).

Scheme I



2-Bromopyridines were quaternized in sulfolane (tetramethylene sulfone) with an arylacyl halide to produce the 2-bromopyridinium salts **2** (Table II). The salts were converted to pyridine-2-thiones **3** (Table III) by treatment

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