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Synthesis and Antibacterial Activity of Some Substituted 4-Quinolone-3-carboxylic Acids

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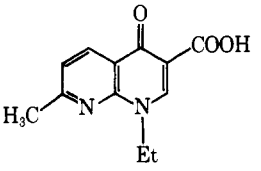
The activity of nalidixic[1,2] (**1**) and oxolinic[3,4] (**2**) acids against gram-negative pathogens in refractory urinary tract infections[5] suggested the synthesis and study of related compounds. Although a number of substituted *N*-alkyl-4-quinolone-3-carboxylic acids have been prepared and claimed to have antibacterial activity,[6] only few 8-substituted representatives have been studied thus far. The present note deals with this type (**3a–h**) and with *N*-ethylbenzo[*h*]-4-quinolone-3-carboxylic acid (**4**). In an attempt to improve upon the considerable antibacterial activity of the latter, we also synthesized 6- and 7-methoxybenzo[*h*]-4-quinolone-3-carboxylic acid (**5** and **6**), since it seemed possible that methoxy groups so placed might simulate the methylenedioxy ring of oxolinic acid.



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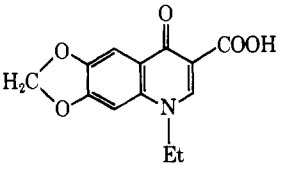

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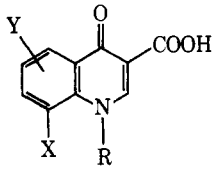
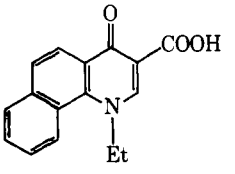


	R	X	Y
3a	H	MeO	H
b	Et	MeO	H
c	Et	EtO	H
d	H	Cl	5-Me
e	H	Cl	H
f	Et	Cl	H
g	Et	Cl	6-Cl
h	Me	Me	H



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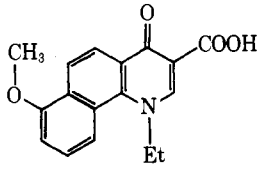

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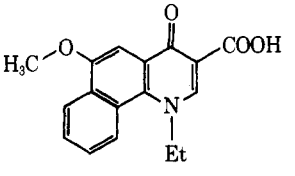

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The acids were obtained by modifications of the Gould-Jacobs synthesis. The required alkylanilines were prepared by reductive alkylation of the corresponding anilines with Raney nickel catalyst. The methoxynaphthylethylamines were obtained by reduction of the acetamido compounds with sodium bis(2-methoxyethoxy)aluminum hydride ("Red-Al," Aldrich). Condensations of the secondary amines with diethyl ethoxymethylenemalonate (EMME) require higher temperatures and longer times than those of primary amines[7,8] (Table I). Cyclization to the acids was effected by P_2O_5 in nitrobenzene;[7] polyphosphoric acid[8] was used to cyclize less reactive malonates (Table II).

† This note is dedicated to Dr. Alfred Burger, with whom I had the pleasure to be associated some years ago and whose continued friendship I consider a privilege.

Table I. Arylethylamines (ArNHEt) and Their Reaction with EMME

Ar	Bp or mp, °C	Yield, %	Condensation with EMME: Time, hr	Condensation with EMME: Temp, °C
2-MeO-C_6H_4	111–115 (9 mm)[a]	54	0.3	160
2-EtO-C_6H_4	114–117 (10 mm)[b]	48	0.3	160
2-Cl-C_6H_4	98–100 (10 mm)[c]	68	18	100
2,4-$(Cl)_2$-C_6H_3[d]	96–97 (1 mm)	55	18	100
5-MeO-$C_{10}H_7$-α	70–72[e]	25	18	100
4-MeO-$C_{10}H_7$-α[f]	71–72.5	26	18	100

[a]Lit. 117° (31 mm): M. Förster, *J. Prakt. Chem.*, [2] **21**, 341 (1880). [b]Lit. 234–236° (751 mm): E. Diepolder, *Ber.*, **31**, 495 (1898). [c]Lit. 219° (726 mm): C. M. Suter and F. B. Dains, *J. Amer. Chem. Soc.*, **50**, 2733 (1928). [d]*Anal.* ($C_8H_9NCl_2$) N. [e]Lit.[12] 74.5–75°. [f]*Anal.* ($C_{13}H_{15}NO$) C, H, N.

Table II. Physical Properties and Preliminary Screening of 4-Quinolone-3-carboxylic Acids

No.	Method	Yield, % (based on amine)	Mp, °C[a]	MIC, μg/ml: *P. vulgaris*	MIC, μg/ml: *S. aureus*
3a	A	62	282–283[b]	>100	>100
3b	A	51	255–258[c,d]	100	>100
3c	A	58	199–202[e]	>100	>100
3d	*f*	76	290–292[g]	>100	>100
3e	A	83	239–242[c,h]	>100	>100
3f	A, B	16, 43	161–163[i]	50	>100
3g	B	12	207–208.5[j]	25	>100
3h	A	85	259–261[k]	>100	>100
4	A	76	242–243[k]	6.3	50
5	B	19	257.5–258.5[l]	12.5	25
6	B	74	249–251[m]	*n*	
1	Nalidixic acid			6.3	>100
2	Oxolinic acid[o]			0.39	3.13–12.5

[a]Recrystallized from EtOH unless otherwise noted. [b]Lit. 280° dec: W. M. Lauer, R. T. Arnold, B. Tiffany, and J. Tinker, *J. Amer. Chem. Soc.*, **68**, 1268 (1946). [c]Recrystallized from MeCN. [d]Lit.[8] 261–262.5°. [e]Lit.[8] 199–200°. [f]Method of R. G. Gould and W. A. Jacobs, *J. Amer. Chem. Soc.*, **61**, 2890 (1939). [g]Lit. 285–286° dec: B. R. Baker and R. R. Bramhall, *J. Med. Chem.*, **15**, 230 (1972). [h]Lit. 248–250° dec: D. S. Tarbell, *J. Amer. Chem. Soc.*, **68**, 1277 (1946). [i]*Anal.* ($C_{12}H_{10}NO_3Cl$) C, H, N. [j]*Anal.* ($C_{12}H_9NO_3Cl_2$) C, H, N, Cl. [k]Reference 7. [l]*Anal.* ($C_{17}H_{13}NO_4$) C, H, N. [m]*Anal.* ($C_{17}H_{13}NO_4$) C, H, N. [n]Too insoluble to test adequately by the method used. [o]Data from ref 4a.

Results and Discussion

The only compounds with significant antibacterial activity were acids **3f**, **3g**, **4**, and **5** (Table II). Their mini-

Table III. MIC (μg/ml) of Selected 4-Quinolone-3-carboxylic Acids

No.	*A. aerogenes*	*E. coli*	*E. coli B*	*N. catarrhalis*	*P. mirabilis*	*Ps. fluorescens*
3f	>50	50	50	>50	50	>50
3g	>50	>50	25	>50	12.5	>50
4	50	12.5	6.3	3.1	3.1	>50
5	>50	25	6.3	1.6	1.6	>50
1	25	12.5	6.3	12.5	6.3	>50
2[a]	0.19	0.098–1.56		1.56	0.39–0.78	

[a] Data from ref 4a.

mal inhibitory concentrations against a wider range of organisms are contained in Table III and compared with the activity of nalidixic and oxolinic acids. Acids **3f** and **3g** are consistently less effective than nalidixic and oxolinic acids, whereas **4** and **5** are approximately as active as nalidixic but inferior to oxolinic acid.

Morphological examination of cultures of *Escherichia coli* and *P. vulgaris* which had been exposed to compound **4** revealed filamentous forms similar to those observed when these organisms were treated with nalidixic[2b] or oxolinic acid.[4d] This observation supports the view that all these compounds act by a similar mechanism.

The limited data permit only few and mostly tentative conclusions regarding structure–activity correlations. Our results are consistent with the observation by Turner, *et al.*,[4a] that the *N*-ethyl group on the quinoline ring is essential for significant activity (acids **3a, 3d,** 3e, and 3h are inactive). The nature of the 8 substituent in the quinoline ring seems to be important. Substituents activating the benzene ring (alkoxy **3b, 3c,** and possibly methyl **3h**‡) reduce antibacterial activity, but a deactivating chlorine atom (**3f** and **3g**) favors it. Thus, the Cl-substituted acids might be considered nonclassical bioisosteres[9] of nalidixic acid, but this view is open to question, since the high activity of acids **4** and **5** could not be explained on this basis. The low solubility of the last two compounds in water suggests that a favorable lipid–water distribution coefficient or a permeability effect may account for the relative activities of all these compounds rather than electronic effects due to a polar substituent in position 8.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected; ir spectra were obtained on a Beckman IR-8 spectrometer and transmittance measurements on a Bausch and Lomb Spectronic 20 colorimeter. An Orion Research Model 801 digital pH meter was used for pH measurements. Mr. J. F. Alicino (Metuchen, N. J.) and Dr. Harry Agahigian (Orange, Conn.) performed the analyses.

Cultures were obtained from Carolina Biological Supply and were maintained on Trypticase Soy Agar (BBL); the assay broth was from Difco Laboratories. Nalidixic acid was a product of K&K Laboratories, Inc.

Starting Materials. Diethyl ethoxymethylenemalonate, all primary amines, *N*-ethyl-1-naphthylamine, and *N*-methyl-*o*-toluidine were commercial products.

Other required *N*-ethylanilines were prepared by the method of Emerson and Walters.[10] In all cases 10–15 g of Raney nickel catalyst per 0.1–0.2 mol of amine was sufficient. Infrared spectra were consistent with the postulated structures; preparative details are in Table I.

***N*-Ethyl-5-methoxy-1-naphthylamine.**[11] To a mechanically stirred solution of 23 ml of Red-Al (70% in benzene) was added 7.5 g of *N*-acetyl-5-methoxy-1-naphthylamine[12] suspended in 100 ml of dry benzene. When addition was complete, the mixture was refluxed for 3 hr. After decomposition with 10 ml of 20% H_2SO_4, benzene was removed by steam distillation; the residue was made alkaline (10% NaOH) and extracted with several portions of Et_2O (200 ml total). The ethereal solution was dried (Na_2SO_4), the Et_2O removed, and the residue distilled at reduced pressure. The fraction boiling at 155–165° (0.8–0.9 mm) solidified and was recrystallized from cyclohexane (Table I).

***N*-Ethyl-4-methoxy-1-naphthylamine.** *N*-Acetyl-4-methoxy-1-naphthylamine obtained by reduction of 4-nitro-1-methoxynaphthalene[13] with iron in AcOH[14] was reduced with Red-Al under the same conditions as the 5-methoxy analog. Distillation gave a fraction boiling over 150–160° (0.5 mm) which solidified and was recrystallized from cyclohexane (Table I).

Condensations with Diethyl Ethoxymethylenemalonate (EMME). Equimolecular amounts of the primary amines and EMME were mixed and heated at reduced pressure on the steam bath until EtOH evolution ceased. Reaction conditions for condensations of secondary amines are recorded in Table I; in these reactions also, residual EtOH was removed as above. The viscous oils and low-melting solids which resulted were used directly and not further purified.

Cyclizations. Method A is described elsewhere.[7]

Method B. Cyclization with polyphosphoric acid as reported by Nakagome, *et al.*,[8] was employed and the reaction mixture worked up as follows. After the reactants had been heated with PPA at 110–120° for 15 min, the resulting gum was mixed with ice–water and made strongly basic (2.5 *M* NaOH). The alkaline mixture was boiled for 30 min, filtered with diatomaceous earth to remove oily material if necessary, acidified (3 *M* HCl), and cooled, and the product was collected (Table II).

Biological Tests. Before screening the acids were dried at 78° (1.5 mm) for several hours. The twofold dilution method used by Turner, *et al.*,[4a] was employed for determination of the MIC; the highest concentration tested in the preliminary screening was 100 μg/ml (Table II) and 50 μg/ml in subsequent tests (Table III). The low water solubility of these acids required that the tryptose–phosphate broth be adjusted to pH 7.8 by addition of solid NaOH. The lowest concentration not showing visible growth (in 13 × 100 mm test tubes) was recorded as the MIC; in doubtful cases, the higher concentration was recorded. Values represent a minimum of four trials.

For morphological examination, cultures of *E. coli* B and *P. mirabilis* which had been exposed to an inhibitory concentration of **4** for over 20 hr were compared with controls of the same species. The organisms were stained with Crystal Violet and examined under oil at 1000× magnification.

Acknowledgment. The authors wish to thank Dr. Norman G. Brink of Merck, Sharpe and Dohme for kindly donating the sample of nalidixic acid.

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‡ The lack of activity of acid **3h** may be owing to 8 substitution by a methyl group or to the presence of methyl on the ring nitrogen, or both.

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Oral Gold. Synthesis and Antiarthritic Properties of Some Large-Ring Gold Chelates

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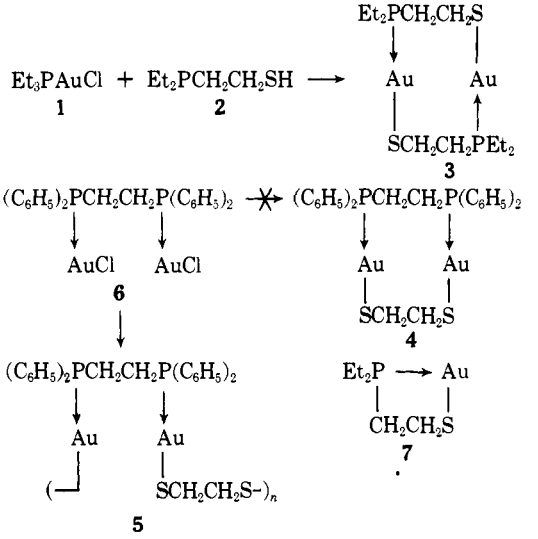
The antiadjuvant arthritic properties of several alkylphosphinegold coordination complexes were discussed in a previous report from this laboratory.[1] We now describe the antiarthritic properties of gold chelates.

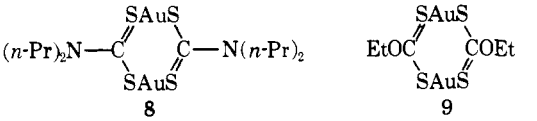
A typical orally active aurous complex, previously reported, was [(tetra-*O*-acetyl-β-D-glucopyranosyl)thio](triethylphosphine)gold which contains both phosphorus and sulfur ligands. Metabolism studies in animals‡ indicated that this complex extensively dissociated after absorption. This suggested that chelates of gold with the sulfur and phosphorus in one molecule, which should be chemically and possibly metabolically more stable, might have interesting biological profiles and led us to attempt preparation of a simple chelate **7**.

Chemistry. Treatment of AuCl with diethyl(2-thioethyl)phosphine (**2**)[2] in the presence of 1 mol of alkali did not result in the desired product. However, an exchange reaction, using the anion of **2** and chloro(triethylphosphine)-gold (**1**) gave a white solid in 77% yield whose elemental analysis indicated a one-to-one complex of the thiophosphine and gold. The mass spectrum and osmometric molecular weight clearly indicated that the compound was the dimer **3**.



In an attempt to prepare the similar dimer **4**, μ-[1,2-bis(diphenylphosphino)ethane]-bis(chlorogold) (**6**)[3] was treated with the dianion of 1,2-ethanedithiol. This reaction gave a high melting white solid in 68% yield which, in contrast to **3**, was quite insoluble in all of the common organic solvents. After washing with $CHCl_3$, the crude product gave an excellent analysis for **4** (or **5**), but in contrast to **3**, its mass spectrum did not show a molecular ion. These properties led us to assign the polymeric structure **5** to the product.

Dimer **3** is reminiscent of the di-μ-(*N*,*N*-dialkyldithiocarbamato)-digold complexes such as **8**[4] which have been studied by X-ray crystallographic analysis.[5] In **8** the S-Au-S bonds are linear, and the Au-Au bond distance (2.76 Å) is shorter than that found in the metal (2.88 Å), which was ascribed to Au-Au attraction.



Mass spectral fragmentation patterns of the compounds, reported here, suggested that chelated gold complexes were more stable structures than coordination complexes and that there was Au-Au interaction in the cylic structures. Thus, the spectrum of **1**, a nonchelate complex, shows a small molecular ion at *m/e* 350 and a major peak at *m/e* 315 corresponding to the loss of Cl to give Et_3PAu^+. Successive cleavage of C-P and C-C bonds occurs to give finally CH_2PHAu^+. However, the mass spectrum of **3** shows a strong M^+ peak at *m/e* 692 and less intense peaks at *m/e* 664, 637, 636, and 608, arising from successive losses of 2-carbon fragments leaving the large ring intact. Interestingly, several small peaks at *m/e* 547, 515, and 483 contain Au_2 moieties. Similarly, the mass spectra of **8** and **9** have molecular ion peaks and peaks probably containing the Au_2 moiety. However, the highest molecular weight peak seen in the mass spectrum of polymer **5** is *m/e* 462, corresponding to bis[1,2-(diphenylphosphino)ethane] disulfide. This probably came from thermal decomposition of the polymer.

Formation of the dimeric chelate **3** rather than a monomeric chelate **7** is not surprising since gold forms linear complexes involving sp orbitals,[6] and the geometry of the PAuS array is such that P and S cannot be bridged by an ethylene group. However, two such arrays can be bridged by two ethylene groups. The formation of polymer **5** in preference to **4** can be rationalized in terms of intramolecular repulsive dipole interaction. In **4** similarly charged atoms would be adjacent while in **5** they could be at a distance. In **3** oppositely charged atoms are adjacent which contribute to the stability of the chelate.

Biology. Antiadjuvant arthritic properties of the Au compounds of this report were determined by previously described methods.[1,7] Chelate **3** was the only example which showed oral absorption properties. However, the magnitude of serum Au level attainment was less with **3** than with coordination complex **1** when the compounds were administered at doses equivalent in Au content. Compounds **5**, **8**, and **9** were ineffective when administered orally even though they exhibited markedly different solubility properties. The moderate Au levels obtained with **8** and **9** after intramuscular administration were ineffectual in preventing development of adjuvant arthritis in the rat. These data illustrate further that the nature of the Au complex markedly influences the biological fate of the antiarthritic species and suggest that a complex combination of physical and chemical factors is necessary for maximum biological efficacy. The increased stability per se of the chelates described in this paper related to **1** did not lead to higher serum gold levels (Table I).

Experimental Section

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting point apparatus. Mass spectra were obtained on a Hitachi Perkin-Elmer RMN-6E spectrometer. Nmr

†This article is dedicated to Professor Alfred Burger, our long-time friend and advisor.

‡B. Hwang, T. Flanagan, A. Intoccia, and S. Walkenstein, unpublished work, Smith Kline & French Laboratories.