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Quinolone Antimicrobial Agents. 2. Methylenedioxy Positional Isomers of Oxolinic Acid

Lester A. Mitscher,* Daniel L. Flynn, H. Eugene Gracey, and Steven D. Drake

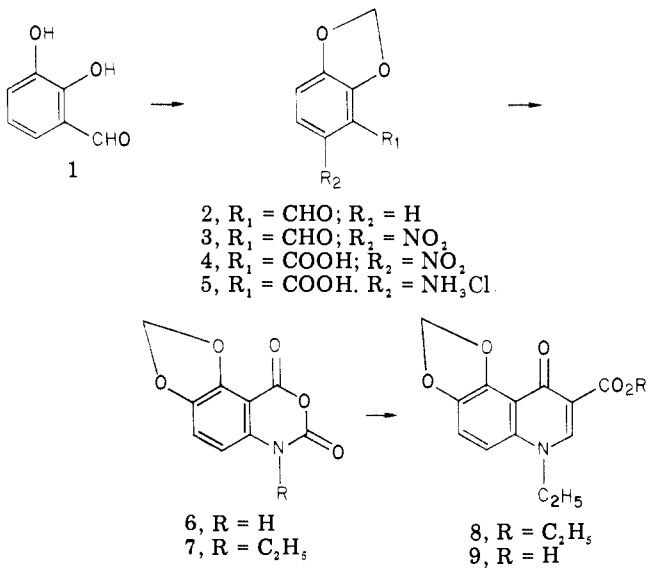
Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045. *Received April 13, 1979*

The synthesis and antimicrobial activity of the methylenedioxy positional isomers, 1-ethyl-1,4-dihydro-5,6-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**9**) and 1-ethyl-1,4-dihydro-7,8-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**17**), of oxolinic acid (**18**) have been accomplished. Isomer **9** was prepared by the reaction of *N*-ethyl-6,7-methylenedioxyisatoic anhydride with sodioethyl formylacetate [L. A. Mitscher, H. E. Gracey, G. W. Clark III, and T. Suzuki, *J. Med. Chem.*, **21**, 485 (1978)], while isomer **17** was prepared by thermal cyclization of diethyl 2-[(2,3-methylenedioxyanilino)methylene]malonate [D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, 11, 160 (1968)]. Both of the new isomers are less active in vitro when compared to oxolinic acid (**18**) itself.

Oxolinic acid (**18**) has found widespread clinical use in the treatment of urinary tract infections. Recent findings that nalidixic acid and oxolinic acid act by inhibiting the DNA gyrase[3,4] necessary for bacterial,[5,6] plasmid,[7,8] and bacteriophage[9-11] replication, as well as phage recombination[12] and phage-promotor-dependent transcription,[13] have heightened interest in the properties of these antimicrobial agents. The mechanistic details of their interactions with DNA gyrase are unavailable as yet. Our previous work[1] and that of others have shown that substitution at C-2 in this therapeutic group abolishes activity.

Continuing our systematic SAR study, we decided to synthesize the methylenedioxy positional isomers of oxolinic acid, compounds which, surprisingly, have not been reported. This also, circumstantially, allowed a side by side comparison of the newer[1] vs. the classical[2] methods available for synthesis of these agents.

The desired 1-ethyl-1,4-dihydro-5,6-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**9**) cannot be made by the classical Gould–Jacobs-dependent route because thermal cyclization of the requisite diethyl 2-[(2,3-methylenedioxyanilino)methylene]malonate leads exclusively to oxolinic acid (**18**). The known 2,3-methylenedioxy-6-nitrobenoic acid (**4**) was prepared from commercially available 2,3-dihydroxybenzaldehyde (**1**) by catechol methylenation employing dibromomethane with cupric oxide as catalyst to give **2**, nitration of **2** to **3**, followed by permanganate oxidation essentially as reported.[14] Catalytic reduction gave an 83% yield of the anthranilic acid salt **5**. Condensation with phosgene[15] led to 6,7-methylenedioxyisatoic anhydride (**6**) in 78% yield, and N-ethylation with NaH and iodoethane afforded **7** in 80% yield. Condensation of **7** with sodioethyl formylacetate[1] gave exclusively **8** in 86% yield. Alkaline hydrolysis of **8** then gave a 91% yield of the desired positional isomer **9**.



Synthesis of the positional isomer **17** was effected fundamentally by the established method of Kaminsky and Meltzer.[2] In this case, thermal cyclization of the appropriate diethyl 2-[(2,3-methylenedioxyanilino)-methylene]malonate (**14**) can only proceed in one direction. The known 2,3-methylenedioxyaniline (**13**)[16] was prepared from 2,3-methylenedioxybenzaldehyde (**2**). Oxidation of **2** to **10** with permanganate,[17] conversion to the acid chloride **11**,[17] ammonolysis to the benzamide **12**,[17] and Hofmann rearrangement afforded the requisite aniline **13**.[16] An addition–elimination reaction with diethyl ethoxymethylenemalonate afforded **14** in 81% yield. Thermal cyclization gave **15** in 76% yield, and N-ethylation with

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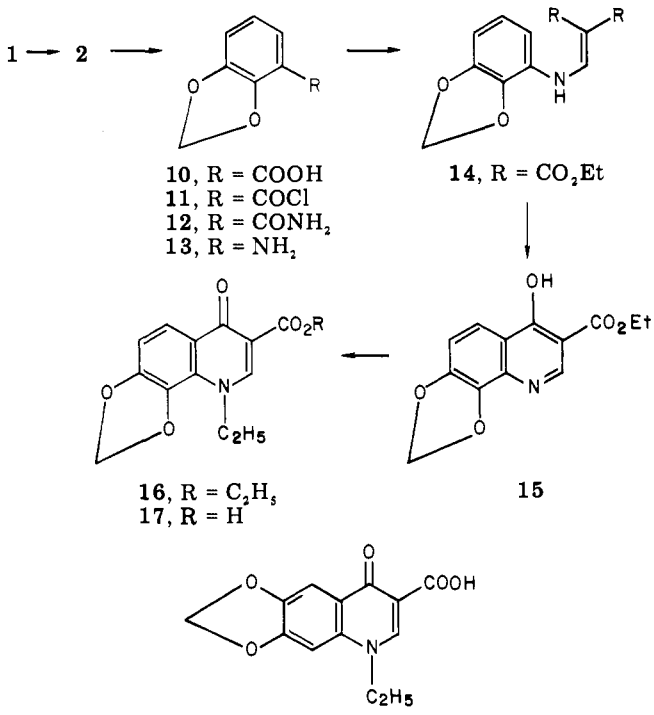

iodoethane afforded **16** in 73% yield. Saponification with aqueous base gave a 93% yield of the desired isomer **17**.

Starting with commercially available materials, both syntheses required eight steps and proceeded in comparable (8.6% of **7** and 10.0% of **17**) yields.

Both positional isomers were found to be less active than oxolinic acid (**18**) in vitro (Table I). Noteworthy, however, is the observation that the 5,6-methylenedioxy isomer **9** is substantially less active than the 7,8-methylenedioxy isomer **17** against all microorganisms tested. This is not totally unexpected, as previous molecular manipulations have revealed that substitution at C-5 generally results in inactivity.[18,19]

This study demonstrates that the methylenedioxy aromatic substituent must reside at C-6, C-7 in the quinolone nucleus (oxolinic acid) for optimal antimicrobial activity.

Experimental Section

Melting points were obtained on a calibrated Thomas-Hoover Unimelt apparatus. Infrared spectra were recorded on a Beckman 33 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer. Me_4Si was used as internal standard in all ^{1}H NMR spectra. Ultraviolet spectra were recorded on a Cary 219 UV-vis spectrophotometer. Mass spectra were conducted on a Hitachi Perkin-Elmer RMS-4 mass spectrometer. Microanalyses were performed on a Hewlett-Packard 185B at the University of Kansas and are within 0.4% of theory unless otherwise noted.

2,3-Methylenedioxybenzaldehyde (2). Following the procedure of Chen and Cheng,[14] a mixture of 60.7 g (0.44 mol) of 2,3-dihydroxybenzaldehyde, 92.0 g (0.53 mol) of dibromomethane, 62.0 g (0.45 mol) of potassium carbonate, and 4.0 g cupric oxide in 400 mL of DMF was heated under an inert atmosphere at 130 °C for 2.5 h. After cooling to room temperature, the mixture was diluted with 1.3 L of water and extracted with four portions of benzene. The benzene extract was washed with water and dried over potassium carbonate. Concentration under reduced pressure afforded 61.0 g of a black residue which, on distillation, afforded 51.5 g (78%) of a light-yellow oil [bp 84–90.5 °C (0.25 mm Hg)] which crystallized in the receiver, mp 35–36 °C (lit.[14] mp 34 °C). Anal. ($C_8H_6O_3$) C, H, N.

2,3-Methylenedioxy-6-nitrobenzaldehyde (3). Following the procedure of Chen and Cheng,[14] 2.0 g (13.33 mmol) of **2** was gradually added to 18 mL of concentrated nitric acid at −5 °C over a period of 10 min. Stirring was continued for 10 additional min, after which time the reaction was quenched with 85 mL of ice–water to afford a floculent yellow precipitate. Recrystallization three times from acetone afforded 0.97 g (37%) of the 6-nitro isomer **3**, mp 142–143 °C (lit.[14] mp 144–145 °C). Anal. ($C_8H_5NO_5$) C, H, N.

2,3-Methylenedioxy-6-nitrobenzoic Acid (4). Following the procedure of Chen and Cheng,[14] a hot solution of 10.8 g (68.4 mmol) of $KMnO_4$ in 270 mL of water was added dropwise to a solution of 8.0 g (41.0 mmol) of **3** in 200 mL of acetone over a period of 40 min. Acetone was removed by distillation, and the aqueous mixture was filtered through Celite to remove MnO_2. The MnO_2 cake was washed with 100 mL of water. The filtrate was acidified to pH 1 with concentrated HCl, resulting in 6.3 g (73%) of yellow crystals, mp 185–186 °C (lit. mp 188–189 °C). Anal. ($C_8H_5NO_6$) C, H, N.

2,3-Methylenedioxy-6-aminobenzoic Acid Hydrochloride (5). To 100 mL of ethanol in a Parr pressure bottle was added 4.9 g (23 mmol) of **4**, 4.0 mL of concentrated HCl, and 500 mg of 5% Pd/C. The reaction was charged on a Parr apparatus at 40 psi at 25 °C and allowed to proceed until the required volume of H_2 had been taken up. The catalyst was filtered, and the ethanol solution was concentrated under reduced pressure. The catalyst was repeatedly boiled in 150 mL of ethanol plus 7 mL of concentrated HCl until no further increase in residue weight was noted. Recrystallization from ethanol afforded 4.21 g (83%) of **5**, decomposition point 199–201 °C; UV (ETOH) λ_{max} 204 nm (ϵ 19500), 229 (16900), 236 (10900); IR (KBr) 1710 (C=O), 1260 and 1035 cm^{-1} (C-O); ^{1}H NMR (D_2O) δ 6.10 (s, 2, methylenedioxy), 6.92–7.05 (m, 2, aromatic).

6,7-Methylenedioxyisatoic Anhydride (6). Following the procedure of Wagner and Fegley,[18] 9.1 g (41.8 mmol) of **5** was dissolved in 500 mL of distilled water and filtered into a three-neck round-bottom flask fitted with a mechanical stirrer, a gas-inlet dispersion tube, and a gas-outlet tube. Trapping bottles and an ammonium hydroxide scrubber were connected from the gas-outlet tube to an aspirator. Another trapping bottle was placed between the phosgene cylinder and the gas-inlet tube. Phosgene gas was introduced into the reaction solution under slight negative pressure at such a rate that gas bubbles appeared in the ammonium hydroxide trap at a rate of three per second. After 1 h, the reaction mixture was aerated and filtered to give 5.93 g of light-tan crystals. After an additional 45 min, a second crop (0.84 g) of crystals was collected: total product 6.77 g (78%); mp 261 °C (dec); IR (KBr) 1770 and 1720 (C=O), 1280, 1240, and 1060 cm^{-1} (C-O); ^{1}H NMR (Me_2SO-d_6) δ 6.20 (s, 2, methylenedioxy), 6.44–6.57 (d, 1, J = 8 Hz, aromatic), 7.16–7.30 (d, 1, J = 8 Hz, aromatic); EIMS M$^+$ 207. Anal. ($C_9H_5NO_5$) H, N; C: calcd, 52.20; found, 50.39.

***N*-Ethyl-6,7-methylenedioxyisatoic Anhydride (7).** Under an inert atmosphere, 2.96 g (14.3 mmol) of **6** in 100 mL of DMF

Table I. Minimum Inhibitory Concentrations[a]

microorganism	9	17	18
Acinetobacter sp. 2437	>100	6.25	0.4
Escherichia coli ATCC 26	>100	6.25	0.1
Klebsiella pneumoniae ATCC 8045	25	1.56	>0.05
Proteus mirabilis Finland no. 9	>100	50	0.78
Proteus vulgaris ATCC 6897	100	3.13	>0.05
Pseudomonas aeruginosa BMH no. 1	>100	>100	12.5
Salmonella typhi ATCC 9992	>100	12.5	0.2
Serratia marcescens ATCC 4003	>100	3.13	0.1
Shigella sonnei ATCC 9290	>100	3.13	0.2
Staphylococcus aureus ATCC 6538P	>100	25	0.78
Streptococcus faecalis ATCC 8043	>100	>100	25

[a] Potency data are in micrograms per milliliter. Tests were performed by an agar dilution-streak method.

was added dropwise to a stirring suspension of 0.344 g (14.3 mmol) of NaH (hexane-washed) in 25 mL of DMF. After 15 min, 4.46 g (28.6 mmol) of iodoethane in 20 mL of DMF was added dropwise, and the resulting solution was allowed to stir at room temperature overnight. DMF was removed in vacuo to one-third of the original volume. The concentrated DMF solution was poured over 250 mL of ice–water, resulting in a light-tan precipitate. The solid was collected and recrystallized from THF to yield 2.69 g (80%) of **7**: mp 199 °C; UV (CH_3CN) λ_{max} 242 nm (ϵ 23 950), 260 (8890), 363 (6100); IR (KBr) 1750 and 1700 (C=O), 1275, 1235, and 1010 cm^{-1} (C-O); ^1H NMR (Me_2SO-d_6) δ 1.06–1.30 (t, 3, J = 7 Hz, N-CH_2CH_3), 3.84–4.20 (q, 2, J = 7 Hz, N-CH_2), 6.30 (s, 2 methylenedioxy), 6.76–6.92 (d, 1, J = 9 Hz, aromatic), 7.29–7.45 (d, 1, J = 9 Hz, aromatic); EIMS M^+ 235. Anal. ($C_{11}H_9NO_5$) C, H, N.

Ethyl 1-Ethyl-1,4-dihydro-5,6-methylenedioxy-4-oxo-3-quinolinecarboxylate (8). Under an inert atmosphere, 200 mg (0.851 mmol) of **7** in 20 mL of DMF was added to a stirring solution of 353 mg (2.553 mmol) of sodioethyl formylacetate in 30 mL of DMF. The resulting solution was stirred at 110 °C for 3.5 h, after which time TLC showed total consumption of starting material. The reaction mixture was cooled to room temperature and DMF removed in vacuo, followed by benzene azeotrope to remove trace DMF. The brownish residue was taken up in water, and the aqueous solution was extracted with three portions of ether, then acidified to pH 2 with concentrated HCl, and extracted with four portions of chloroform. The chloroform extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 211 mg (86%) of **8**. Recrystallization from ethyl acetate afforded white crystals: mp 170–172 °C; IR (KBr) 1680 and 1640 cm^{-1} (C=O); ^1H NMR (TFA) δ 0.94–1.3 (t, 3, J = 6 Hz, O-CH_2CH_3), 1.3–1.64 (t, 3, J = 7 Hz, N-CH_2CH_3), 3.85–4.30 (q, 2, J = 6 Hz, O-CH_2), 4.30–4.75 (q, 2, J = 7 Hz, N-CH_2), 6.12 (s, 2, methylenedioxy), 7.42 (s, 2, aromatic), 8.86 (s, 1, H-2); EIMS M^+ 289. ($C_{15}H_{15}NO_5$) C, H, N.

1-Ethyl-1,4-dihydro-5,6-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid (9). **8** (181 mg, 0.63 mmol) was dissolved into 25 mL of 10% NaOH and heated to reflux for 2.5 h. After this time, the reaction mixture was cooled to room temperature and washed with ether. The aqueous phase was then acidified to pH 1 with concentrated HCl, whereupon 132 mg (81%) of **9** immediately precipitated from solution. Recrystallization from aqueous DMF afforded light-yellow crystals: mp 292 °C; UV (1% KOH/H_2O) λ_{max} 249 nm (ϵ 30 040), 318 (8770), 364 (8580); IR (KBr) 1715 and 1640 (C=O), 1270 and 1020 cm^{-1} (C-O); ^1H NMR (TFA) δ 1.50–1.86 (t, 3, J = 7 Hz, N-CH_2CH_3), 4.46–4.92 (q, 2, J = 7 Hz, N-CH_2), 6.30 (s, 2, methylenedioxy), 7.58 (s, 2, aromatic), 9.04 (s, 1, H-2); EIMS M^+ 261. Anal. ($C_{13}H_{11}NO_5$) C, H, N.

2,3-Methylenedioxybenzoic Acid (10). Following the procedure outlined above for **4**, 20.0 g (0.133 mol) of **2** yielded 13.35 g (61%) of **10**, mp 227–228 °C (lit.[17] mp 227 °C). Anal. ($C_8H_6O_4$) C, H, N.

2,3-Methylenedioxybenzoic Acid Chloride (11). Following the procedure of Perkin and Trikojus,[17] 1.58 g (9.51 mmol) of **10** was suspended in 25 mL of thionyl chloride that had been freshly distilled.[20] DMF, 1.0 mL, was added for dissolution and catalytic purposes. The temperature was heated to reflux and stirred overnight. Thionyl chloride was removed under reduced pressure, and trace DMF was removed by benzene azeotrope, leaving 1.848 g (97%) of **11**, mp 112–114 °C (lit.[17] mp 116 °C).

2,3-Methylenedioxybenzamide (12). **11** (1.848 g, 9.22 mmol) was dissolved into 150 mL of benzene in a 250-mL three-neck flask fitted with a gas-inlet dispersion tube, condenser, and a gas-outlet tube. At room temperature while stirring, ammonia gas was introduced under slight negative pressure at such a rate that gas bubbles escaped through the outlet tube at a rate of four per second. The reaction was allowed to run for 4 h, after which time the system was aerated and poured onto 200 mL of 10% NaOH. There immediately separated a white solid, which was collected and dried in vacuo to yield 2.294 g (77%) of **12**, mp 174–175 °C (lit.[17] mp 176 °C). Anal. ($C_8H_7NO_3$) C, H, N.

2,3-Methylenedioxyaniline (13). Following the procedure of Pai et al.,[16] 6.0 g (36.4 mmol) of **12** was added, at room temperature, to a rapidly stirred solution of sodium hypochlorite [prepared by passing chloride gas onto an ice–water solution of sodium hydroxide (4.77 g), crushed ice (18.3 g), and water (32 mL) until the weight of the solution had increased by 1.8 g]. The temperature was raised to 50 °C, dioxane (4.2 mL) was added, and the mixture was stirred at 70 °C for 1 h. After this time, a solution of sodium hydroxide (4.77 g) in water (4.8 mL) was added, and the mixture was stirred at 85 °C for an additional hour. The deep-brown solution was cooled to 0 °C and extracted with four portions of ether. The ether extract was washed with water and dried over potassium carbonate. Concentration of the ether solution under reduced pressure afforded 5.23 g of a brown oil. Distillation afforded 3.237 g (65%) of **13** as a colorless oil, bp 135–140 °C (10 mmHg) [lit.[16] bp 140 °C (10 mmHg)]. Anal. ($C_7H_7NO_2$) C, H, N.

Diethyl 2-[(2,3-Methylenedioxyanilino)methylene]-malonate (14). Following the method of Kaminsky and Meltzer,[2] a mixture of 1.0 g (7.3 mmol) of **13** and 1.58 g (7.3 mmol) of diethyl ethoxymethylenemalonate was heated at 95–100 °C for 3 h. The residue was recrystallized from Skelly B to yield 1.815 g (81%) of **14** as a white solid: mp 95 °C; UV (EtOH) λ_{max} 207 nm (ϵ 29 160), 323 (23 350); IR (KBr) 1680 and 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.04–1.50 (m, 6, N- and O-CH_2CH_3), 4.00–4.42 (m, 4, N- and O-CH_2), 5.96 (s, 2, methylenedioxy), 6.48–6.68 (m, 3, aromatic), 8.66 (s, 1, olefinic); EIMS M^+ 307. Anal. ($C_{15}H_{17}NO_6$) C, H, N.

Ethyl 4-Hydroxy-7,8-methylenedioxy-3-quinolinecarboxylate (15). Following the method of Kaminsky and Meltzer,[2] a mixture of 0.918 g (2.99 mmol) of **14** and 15 mL of Dowtherm A was heated to reflux over a period of 1 h and maintained at reflux for an additional hour. After this time, the reaction mixture was cooled to room temperature, whereupon a light-tan solid precipitated. The solid was filtered and washed liberally with ether to yield 0.591 g (76%) of **15**: mp 256–257 °C (dec); IR (KBr) 3400–2700 (O-H), 1710 cm^{-1} (C=O); ^1H NMR (TFA) δ 0.94–1.26 (t, 3, J = 6 Hz, O-CH_2CH_3), 4.00–4.54 (q, 2, J = 6 Hz, O-CH_2), 5.95 (s, 2, methylenedioxy), 6.96–7.12 (d, 1, J = 9 Hz, aromatic), 7.78–7.94 (d, 1, J = 9 Hz, aromatic); EIMS M^+ 261. Anal. ($C_{13}H_{11}NO_5$) C, H, N.

Ethyl 1-Ethyl-1,4-dihydro-7,8-methylenedioxy-4-oxo-3-quinolinecarboxylate (16). A mixture of 0.50 g (1.91 mmol) of **15** in 20 mL of DMF and 0.09 g (3.75 mmol) of NaH (hexane washed) was heated, with stirring under an inert atmosphere, to 80–90 °C for 30 min. Iodoethane (0.50 g, 3.18 mmol) was then added dropwise over a period of 5 min, and then the temperature was maintained at 80 °C for 2 h. After this time, an additional 0.25 g (1.59 mmol) of iodoethane was added, and the temperature maintained at 70 °C for 2 h. The reaction was then allowed to stir at room temperature overnight. DMF was removed in vacuo, followed by benzene azeotrope to remove trace DMF. The residue was dissolved in boiling chloroform, decolorized with charcoal, filtered, and concentrated under reduced pressure to yield a yellow residue. Recrystallization from ethyl acetate afforded 0.403 g (73%) of **16** as a white solid: mp 162 °C; IR (KBr) 1675 and 1610 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.20–1.60 (m, 6, N- and O-CH_2CH_3), 4.04–4.52 (m, 4, N- and O-CH_2), 6.14 (s, 2, methylenedioxy), 6.80–6.94 (d, 1, J = 9 Hz, aromatic), 7.80–7.94 (d, 1, J = 9 Hz, aromatic), 8.44 (s, 1, H-2); EIMS M^+ 289. Anal. ($C_{15}H_{15}NO_5$) C, H, N.

1-Ethyl-1,4-dihydro-7,8-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid (17). **16** (0.15 g, 0.52 mmol) was dissolved into 15 mL of 10% NaOH and heated to reflux for 2.5 h. The reaction mixture was cooled to room temperature and washed with ether. The aqueous phase was then acidified to pH 1 with concentrated HCl, whereupon a white solid immediately precipitated, yielding 0.126 g (93%) of **17**. Recrystallization from aqueous DMF afforded white crystals: mp 320–321 °C; UV (1% KOH/H_2O) λ_{max} 233 nm (ϵ 23 490), 280 (25 100), 324 (8230); IR (KBr) 1710, 1610 cm^{-1} (C=O); ^1H NMR (TFA) δ 1.52–1.84 (t, 3, J = 7 Hz, N-CH_2CH_3), 4.70–5.14 (q, 2, J = 7 Hz, N-CH_2), 6.36 (s, 2, methylenedioxy), 7.44–7.58 (d, 1, J = 9 Hz, aromatic), 8.30–8.44 (d, 1, J = 9 Hz, aromatic), 9.10 (s, 1, H-2); EIMS M^+ 261. Anal. ($C_{13}H_{11}NO_5$) C, H, N.

Microbiological Activity Assays. Compounds **9**, **17**, and **18** were dissolved in 0.04 N NaOH and tested by an agar-dilution streak method. The composition of the medium employed was cerelose (1 g), yeast extract (1 g), beef extract (2.5 g), tryptone (3 g), KH_2PO_4 (1 g), K_2HPO_4 (3 g), agar (20 g), and deionized water. The resulting pH was 7.2.

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Dibenzotropone- and Dibenzosuberonecarboxylic Acids with Bronchodilator Activity[1]

James P. Dunn, Dallas M. Green, Ian T. Harrison, Peter H. Nelson,* Jürg R. Pfister, Adolph P. Roszkowski, and Karl G. Untch

Institutes of Organic Chemistry and Pharmacology and Metabolism, Syntex Research, Palo Alto, California 94304.
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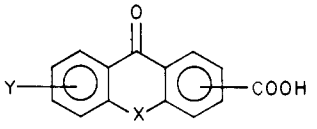
The syntheses of 44 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one derivatives bearing a carboxyl group at the 1, 2, 3, or 10 position and various substituents at the 7, 8, or 9 position are described. Some of the compounds showed significant bronchodilator activity in guinea pigs and protected the animals against a histamine challenge administered either by aerosol or intravenously. The most active compounds were 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-2-carboxylic acids bearing a methyl or halogen substituent at the 9 position. These compounds were approximately as active as aminophylline by intraperitoneal administration.

Recent studies in these laboratories[2,3] have shown that a number of xanthonecarboxylic acids (**1a**) show useful



1a, X = O
b, X = CH=CH
c, X = CH_2CH_2

antiallergic activity. 7-(Methylsulfinyl)xanthone-2-carboxylic acid (tixanox, USAN) has been shown to be orally active against exercise-induced asthma in man.[4] Compounds **1a** show activity in the rat passive cutaneous anaphylaxis (PCA) assay.[5] We have synthesized a number of tricyclic carboxylic acids, including the dibenzotropone and dibenzosuberone derivatives **1b** and **1c**. Many of these compounds showed significant bronchodilator activity, potentially useful for the treatment of asthma and related diseases.

Chemistry. The compounds were synthesized by five basic routes, with a number of variations, shown in the accompanying schemes. The first reaction in Schemes I, a and b, and II is the same; the routes differ in the stage at which separation of the isomeric products was accomplished. The first reaction is the condensation, catalyzed by potassium acetate, of a substituted phenylacetic acid and trimellitic anhydride **2a**. The analogous condensation between phenylacetic acid and phthalic anhydride to give benzylidine phthalide (**3**, X = R = H) was first reported by Gabriel.[6] The reaction proceeds satisfactorily with trimellitic anhydride; however, approximately equal amounts of the two phthalides **3a** and **3b** are produced. Separation of these products was accomplished by fractional crystallization (Scheme Ia) or, when this was not possible, the mixture was reduced to the diphenylethanes **4a** and **4b**, which were then separated by crystallization (Scheme Ib). The products from condensation with *p*-methoxyphenylacetic acid were not separable either at the stage of the phthalides **3** or the reduction products **4**. In this case, partial reduction followed by base-catalyzed elimination gave the *trans*-stilbenes **7a** and **7b**, which were separable by crystallization (Scheme Ic) (phosphorus/hydroiodic acid reduction of the methoxyphthalides **3**, X = OCH_3, gave products of partial reduction and demethylation). The final reduction products **4** were cyclized to the corresponding 10,11-dihydrodibenzo[*a*,*d*]cycloheptenonecarboxylic acids **5**, using polyphosphoric acid in most cases. The relative orientation of the carboxyl groups in the reduction products **4** was determined from their NMR spectra. The meta dicarboxylic acids **4b** showed a 1-proton doublet ($J \approx 2$ Hz) at low field (ca. 8.40 ppm, dimethyl-d_6 sulfoxide) due to the 2 hydrogen, deshielded by two ortho carboxyl groups. The 1,4-diacids **4a**, on the other hand, showed a broad 3-proton singlet at ca. 7.82 ppm, due to the 2, 3, and 5 hydrogens, each of which is ortho to a carboxyl group.

In order to avoid the separations necessary for Scheme Ia–c, some specific routes to the desired tricyclic compounds were developed. The first (Scheme II) involved base-catalyzed condensation of phthalide-6-carboxylic acid (**8a**) or its methyl ester **8b** with a substituted benzaldehyde.

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