Some Anomalous Reactions of 4-Quinolone-5-diazonium Salts

Judit Frank* and Piroska Rákóczy

Chinoin Pharmaceutical and Chemical Works Ltd., H-1325 Budapest, Pf. 110., Hungary

Lajos Radics and Eszter Gács-Baitz

NMR Laboratory, Central Research Institute for Chemistry, H-1525 Budapest, Pf. 17., Hungary

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Diazotisation of the 5-amino function in 6,7-alkoxy-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids led to various products. Dediazoniation was always accompanied by fission of the 6-alkoxy substituent; 6,7-methylenedioxy groups gave formaldehyde which could form a *m*-dioxino ring. Hydrolysis of the diazonium chlorides resulted in halo-dediazoniation.

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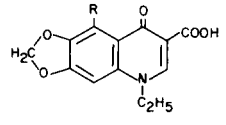
The search for active analogues of oxolinic acid (**1**) [an efficient antibacterial agent (1) for gram-negative pathogens] led to 5-nitro and 5-amino substituted 1-ethyl-4-oxoquinoline-3-carboxylic acids (2). 5-Aminooxolinic acid (**2**), with antibacterial activity comparable to that of oxolinic acid, seemed a good starting material for further derivatives. Its diazotisation was studied closely; 5-hydroxyoxolinic acid (**3**) could not be prepared, but we now report several unusual reactions and unexpected products. ^{13}C-nmr spectroscopy is a useful diagnostic tool in this series and was frequently used throughout this work. The detailed study of the spectra of a variety of these compounds will be published separately (3).



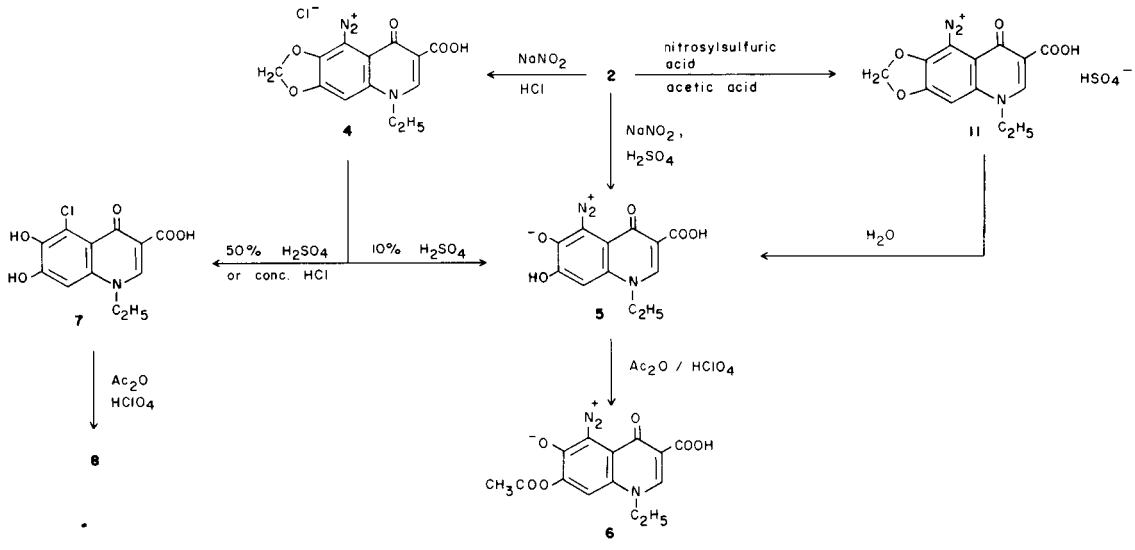
1 R = H
2 R = NH_2
3 R = OH

5-Aminooxolinic acid (**2**) being a weak base could only be diazotised in a strong acid at ambient temperature. Most of the diazonium compounds studied could be isolated, dried and even recrystallised from hot solvents. They were not explosive.

The reaction of **2** with sodium nitrite in hydrochloric acid yielded the expected diazonium chloride (**4**) with characteristic ir absorption at 2120 cm^{-1}. It coupled with phloroglucinol in ethanolic sodium ethoxide; the azo dye absorbed at 535 nm.

On heating **4** in diluted sulfuric acid, no nitrogen evolution was observed, but a new product was formed lacking the methylenedioxy peak in the nmr and retaining diazo absorption now at 2160 cm^{-1}. It was assumed to be stabilized in a zwitterionic form, yielding the diazo-oxide **5**. On acetylating **5** to improve its solubility (4), the monoacetyl derivative **6** was obtained. This result further confirms the diazo-oxide structure of **5**.

Scheme I



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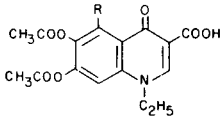
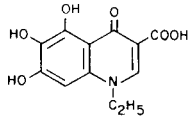
Use of hot sulfuric acid or concentrated hydrochloric acid resulted in nitrogen evolution leading to the 5-chloro-6,7-dihydroxy compound **7** identified as the diacetyl derivative **8** (Scheme 1). Halo-dediazoniation is usually only a side reaction (5) during hydrolysis. In this case, **7** is the main product and probably due to a close ion-pair coordination. This hypothesis is supported by the fact that the diazo-oxide **5** with hydrochloric acid did not yield the 5-chloro derivative **7**.

The diazo-oxide **5** was found to be stable. It did not give the characteristic diazonium reactions. However, on heating in sodium hydroxide, followed by acetylation, the hydro-dediazoniation product **9** was formed.



8 R = Cl
9 R = H
10 R = OH



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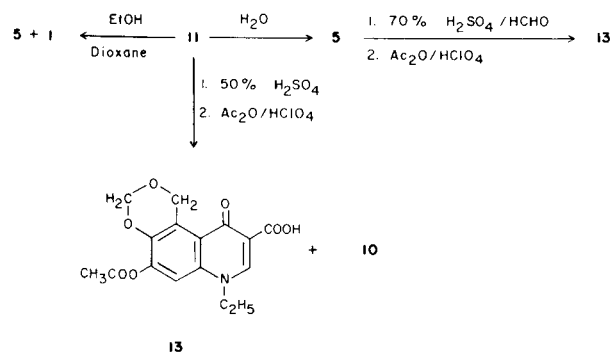
In an attempt to prepare the diazonium sulfate **11**, aminooxolinic acid (**2**) was treated with sodium nitrite in sulfuric acid. It led under different conditions to various compounds (among others **5** and **12**, along with oxolinic acid (**1**) the result of hydro-dediazoniation), but no **11** could be isolated. It was obtained by reacting **2** with nitrosyl sulfuric acid in acetic acid (Scheme 1). Salt **11**, (ν N≡N, 2230 cm^{-1}) coupled with phloroglucinol, and also with α-naphthylamine, the azo dye absorbing at 580 nm. Salt **11** was used to study the unusually easy opening of the methylenedioxy ring. For the preparation of the 6,7-dihydroxy analogue (1) of oxolinic acid hot hydrobromic acid was needed. Although the quaternary salt of the 4-amino-3-ethoxycarbonyl-1-ethyl-6,7-methylenedioxyquinoline undergoes displacement at the 6,7-methylenedioxy substituent by ethoxide to yield the 7-ethoxy-6-hydroxy derivative (6), oxolinic acid (**1**) and its 5-nitro and 5-amino (**2**) derivatives show no 6,7-methylenedioxy ring opening upon heating in the acids used for the diazotisations. Only a few examples are known in which alkoxy groups in *o*- and *p*-positions of benzenediazonium salts are substituted by hydroxyl groups. For the transformation the presence of another electron-withdrawing substituent is needed to support the effect of the diazonium group (preferably *m*-dinitro substituent) (7). In our case this is attributed to the quinoline nitrogen.

The solvolysis of **11** was studied in water and in other solvents of known effect on diazonium salts, such as alcohols that form ether in an S_N1 reaction along with some hydro-dediazoniation product, resulting from a radical process (5). In water **11** gave the diazo-oxide **5** without nucleophilic substitution at the diazonium group

Scheme 2



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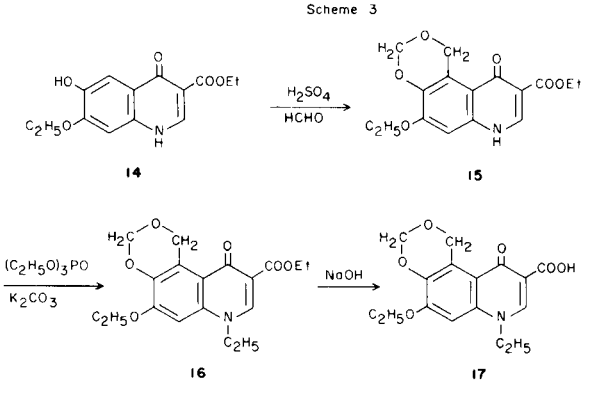
(Scheme 2). Refluxing **11** in ethanol again gave **5** together with **1** but no alkoxy substitution was observed. The by-products formed in the reaction mixture were examined by gc-ms: in dry ethanol, diethyl formal and diethyl acetal were detected. Diethyl acetal results from hydro-dediazoniation reaction leading to **1**, whereas diethyl formal arises from the opening of the methylenedioxy ring to give **5**. Paraformaldehyde was isolated from the same reaction carried out in dioxan, the effect of which on diazonium salts has also been studied (8). This clearly demonstrates that the solvolysis of the methylenedioxy group is accompanied by formaldehyde elimination.

Heating **11** in sulfuric acid (Scheme 2) gave after acetylation the unexpected **13** and **10**. (Compare this result with the hydrolysis of the diazonium chloride **4** that in diluted acid gave diazo-oxide **5** and in strong acid the 5-chloro derivative **7**). In the ^{1}H nmr spectrum of **13**, two 2H singlets were found at δ 5.3 and 5.6 ppm. The precise structures, particularly orientation of the dioxino ring and acetoxy group in **13** and of the hydroxy substituent in **10**, were established (3) by ^{13}C nmr spectroscopy.

Scheme 3

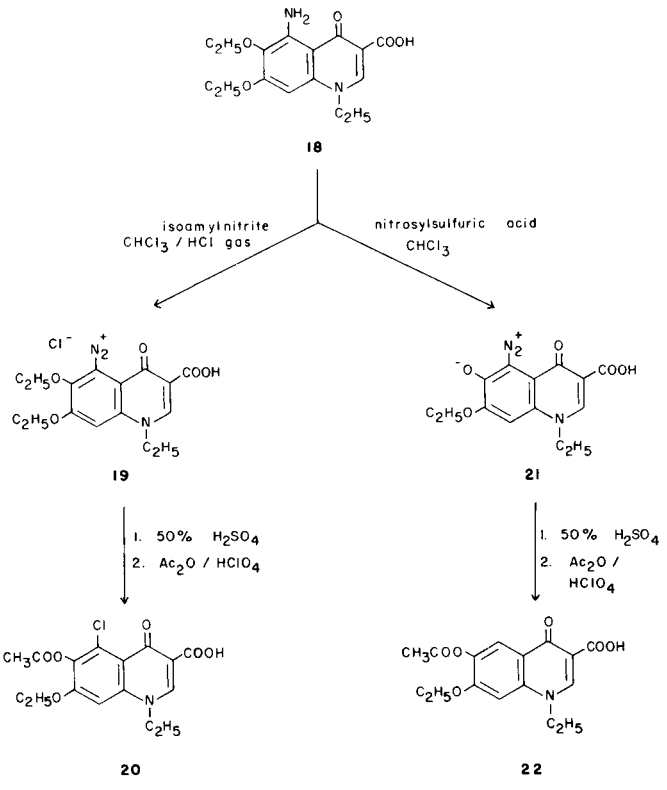


14 **15** **16** **17**

The corresponding 7-ethoxy derivative **17** (9) was synthesized as a model from formaldehyde and ethyl 7-ethoxy-6-hydroxy-4-quinolone-3-carboxylate (**14**), that was described earlier by one of us (10) (Scheme 3). Hydroxyquinolines react with formaldehyde in sulfuric acid solution to form *m*-dioxinoquinolines (11). This formation of **13** from **11** involves loss of the methylenedioxy groups as

formaldehyde (12) (giving **10** on hydroxy-dediazoniation), which reacts with another ring-opened molecule of **11** to form the dioxino ring. Reaction of **5** with formaldehyde followed by acetylation, did indeed give **13** (Scheme 2), thus confirming the structure assigned by ^{13}C nmr spectroscopy. The presence of *m*-dioxino-fusion at positions-5,6 was further proved by X-ray crystallography.

Scheme 4



The 5-diazonium neighbouring group effect in 6-alkoxy-4-quinolones is also shown in the diazotisation of a 6,7-diethoxy derivative **18**, the preparation of which is described in the experimental section (Scheme 4). None of the 6,7-diethoxy-5-diazonium salt (type **19**) could be isolated, instead the 6-ethyl group was lost to give the diazo-oxide **21** (ν N≡N 2110 cm^{-1}). Heating in sulfuric acid caused hydro-dediazoniation and on acetylation **22** was isolated. In the reaction of **18** with isoamyl nitrite, the intermediate **19** was trapped by coupling with phloroglucinol to yield an azo dye which absorbed at 500 nm. Heating the diazotisation product **19** in sulfuric acid followed by acetylation as for **21** yielded the 5-chloro compound **20** by halo-dediazoniation.

EXPERIMENTAL

Melting points all occured with decomposition. They were measured on a Boetius hot plate and are uncorrected. Uv and ir spectra were obtained with Unicam SP 8000 and Perkin Elmer 225 spectrometers, respectively. Nmr spectra were recorded on Varian XL 100-15 and EM 360 spectrometers, using TMS as an internal or an external standard. Mass spectra were determined with MS 902/70 eV apparatus, gc-ms measurements were made with Pye-104 GC connected to VG-MM-12/F I.A instrument. For tlc Merck Silicagel-60 or 60F-254 plates with layer thickness 0.25 mm were used. The spots were detected in iodine vapour and/or with Dragendorff reagent.

3-Carboxy-1,4-dihydro-1-ethyl-6,7-methylenedioxy-4-oxoquinoline-5-diazonium Chloride (**4**).

Aminooxolinic acid (**2**) 5.52 g (0.02 mole) in 25 ml of concentrated hydrochloric acid was stirred at ambient temperature and 1.8 g (0.026 mole) of sodium nitrite in 10 ml of water was added dropwise with such a rate that the temperature would not exceed 45°. Stirring was then continued for 5 hours. The solution was poured into 60 ml water and allowed to stand overnight in the refrigerator. The precipitate was filtered off, washed with water and dried *in vacuo* over phosphorus pentoxide to yield 5.3 g (82%) of yellow diazonium chloride **4**, mp 263-266°. A sample was purified by recrystallization from a 10:1 DMF:acetic acid solvent mixture to give mp 268-270°; uv (acetone) λ max: 404, 412 nm; ir (potassium bromide): ν 2120 (N_2), 1720 (CO acid), 1630 (CO), 1240, 1050, 980 (COC) cm^{-1}; nmr (deuteriochloroform + deuteriotrifluoroacetic acid): δ 8.80 (s, 1H, C_2H), 7.40 (s, 1H, C_8H), 6.10 (s, 2H, OCH_2O), 4.45 (q, 2H, CH_2C), 1.70 ppm (t, 3H, CCH_3).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_5$: C, 48.2; H, 3.1; Cl, 10.9, N, 13.0. Found: C, 48.5; H, 3.2; Cl, 10.9; N, 12.8.

3-Carboxy-1,4-dihydro-1-ethyl-6,7-methylenedioxy-4-oxoquinoline-5-diazonium Sulfate (**11**).

To a stirred mixture of 4.14 g (0.015 mole) of **2** and 30 ml of glacial acetic acid, 7.4 ml (0.016 mole) of nitrosylsulfuric acid was added dropwise in about 30 minutes. The solution was stirred at ambient temperature for 2 hours, while a precipitate began to separate. Ether, 50 ml, was added and the precipitate was filtered and washed thoroughly with dry acetone. It was dried and stored in a desiccator over phosphorus pentoxide, yielding 4.05 g (70%) of yellow diazonium sulfate **11**, mp 143-147°; ir (potassium bromide): ν 2230 (N_2), 1720 (CO acid), 1640 (CO), 1285, 1040 (COC) cm^{-1}; nmr (deuteriotrifluoroacetic acid + acetone): δ 9.30 (s, 1H, C_2H), 8.0 (s, 1H, C_8H), 6.90 (s, 2H, OCH_2O), 4.70 (q, 2H, CH_2C), 1.70 ppm (t, 3H, CCH_3).

Anal. Calcd. for $C_{13}H_{11}N_3O_9S$: C, 40.5; H, 2.9; N, 10.9; S, 8.3. Found: C, 40.2; H, 2.8; N, 11.1; S, 8.3.

Coupling of **4** and **11**.

With Phloroglucinol

Compound **4** (0.32 g, 0.001 mole) was coupled with 0.20 g (0.0015 mole) phloroglucinol in 20 ml of dry ethanol in the presence of sodium ethoxide. The dark purple mixture was stirred for 2 hours, 10 ml of water was added and the mixture was acidified with concentrated hydrochloric acid. The dark red precipitate was filtered off. Its uv absorption at λ max 535 nm (0.01N sodium hydroxide) was characteristic.

To 0.39 g (0.001 mole) of **11** in 20 ml of dry acetone, 0.13 g (0.001 mole) of phloroglucinol in 10 ml ethanol, containing sodium ethoxide, was added dropwise. The colour turned dark red. After stirring for 15 minutes and acidification with hydrochloric acid the precipitate was filtered to give 0.46 g of azo-dye with characteristic uv peak at 460 nm in 0.01N sodium hydroxide.

With α-Naphthylamine.

To a solution of 0.19 g (0.0005 mole) of **11** in 30 ml of dry nitromethane 0.14 g (0.001 mole) of α-naphthylamine was added. The colour changed from dark green to deep lilac. Stirring was continued for 2 hours, then the mixture was concentrated *in vacuo* and the azo-dye (0.2 g) crystallized on cooling; uv (methanol) λ max 580 nm.

Diazo-Oxide **5**.

From Diazonium Chloride **4**.

Compound **4** 3.23 g (0.01 mole) was added in portions to 5 ml of 10% sulfuric acid solution at ambient temperature. Stirring was continued at 90-95° for 12 hours, the mixture was cooled and 30 ml of water was added. The precipitate was separated by suction, washed with water to *p*H 4 and dried *in vacuo* to yield 2.31 g (84%) of yellow diazo-oxide **5**, mp 260-264.° On recrystallization from pyridine, mp 268-270°; uv (acetone) λ max 400, 420 nm; ir (potassium bromide): ν 3200 (OH), 2160 (N_2), 1720 (CO acid), 1630 (CO), 1250 (COC) cm^{-1}; nmr (DMSO-d_6): δ 10.80 (b, 1H, COOH), 8.75 (s, 1H, C_2H), 7.20 (s, 1H, C_8H), 4.45 (q, 2H, CH_2C), 3.40 (b, 1H, OH), 1.40 ppm (t, 3H, CCH_3).

Anal. Calcd. for $C_{12}H_9N_3O_5$: C, 52.4; H, 3.3; N, 15.3. Found: C, 52.4; H, 3.3; N, 14.9.

By Diazotization of **2**.

To a well stirred mixture of 2.76 g (0.01 mole) of **2** in 40 ml of dioxane and 2 ml of 70% sulfuric acid, 1.34 g (0.02 mole) of sodium nitrite was added in portions. Stirring was continued at room temperature for 15 minutes. After cooling the precipitate was filtered off (1.2 g) and refluxed in excess dioxane. The undissolved yellow material proved to be **5**, mp 257-260°.

By Solvolysis of Diazonium Sulfate **11**.

Compound **11** (7.7 g, 0.02 mole) was stirred in 300 ml of water at ambient temperature for 8 hours. Upon cooling, a yellow precipitate separated to yield 4.67 g (85%) diazo-oxide **5**, mp 259-262°.

Compound **11** (1.9 g, 0.005 mole) in 10 ml of absolute ethanol was heated at 80° under nitrogen gas for 20 hours. The solvent was evaporated, the residue was treated with acetone and filtered to give 1 g of a mixture of **5** and **1**. Their ratio according to nmr measurement was 2:1. In the ethanolic solution diethyl formal and diethyl acetal were detected by gc-ms measurement.

Preparation of **6** by Acetylation of Diazo-Oxide **5**.

With Acetylchloride.

To a mixture of 2.75 g (0.01 mole) of diazo-oxide **5** in 40 ml of dry pyridine, 2.35 g (0.03 mole) acetylchloride was added dropwise with stirring so as to keep the temperature below 30°. Stirring was continued at room temperature for 2 hours, then the chilled reaction mixture was filtered. The precipitate was washed with pyridine, yielding 1.3 g (41%) of the monoacetoxy derivative **6**, mp 182-185°. Crystallization from dry acetone gave mp 188-190°.

With Acetic Anhydride.

Diazo-oxide **5** (0.55 g, 0.002 mole) was stirred in 7 ml acetic anhydride in the presence of a few drops of perchloric acid at room temperature for 10 hours. The solvent was evaporated off and the residue crystallized from dry acetone to yield 0.4 g (63%) **6**, mp 187-190°; ir (potassium bromide): ν 2105 (N_2), 1780 (CO acyl), 1715 (CO acid), 1640 (CO), 1235 and 1010 (COC) cm^{-1}; nmr (DMSO-d_6 + acetone): δ 8.95 (s, 1H, C_2H), 8.10 (s, 1H, C_8H), 4.60 (q, 2H, CH_2C), 2.35 (s, 3H, CH_3CO), 1.45 ppm (t, 3H, CCH_3); ms: m/e 317 (M^+).

Anal. Calcd. for $C_{13}H_{11}N_3O_6$: C, 53.0; H, 3.5; N, 13.2. Found: C, 52.7; H, 3.2; N, 13.1.

5-Chloro-6,7-dihydroxy- and 6,7-Diacetoxy-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic Acids (**7** and **8**).

Preparation in 50% Sulfuric Acid.

Diazonium chloride **4** (3.23 g, 0.01 mole) in 25 ml of 50% sulfuric acid solution was heated at 95° for 12 hours. Meanwhile, nitrogen evolution ceased. The reaction mixture was poured into 200 ml of water and the precipitate filtered. The 5-chloro-6,7-dihydroxy (2.81 g, 99%) compound **7** was obtained, mp 264-266°; nmr (DMSO-d_6 + deuteriochloroform): δ 8.66 (s, 1H, C_2H), 7.10 (s, 1H, C_8H), 4.32 (q, 2H, CH_2C), 2.50 (b, 2H, OH), 1.52 ppm (t, 3H, CCH_3).

This compound was purified and identified as the **8** diacetoxy derivative prepared by heating **7** in 40 ml of acetic acid in the presence of 0. 75 g dried sodium acetate at 95° for 10 hours. It was poured into 60 ml of water, the precipitate was filtered off and washed with water to *p*H 5, yielding 3 g (81.7%) of white diacetoxy derivative **8**, mp 238-240°. Recrystallization from acetone gave mp 246-248°; ir (potassium bromide): ν 1800 (CH_3CO), 1715 (CO acid), 1620 infl. (CO), 1260 (COC) cm^{-1}; nmr (DMSO-d_6): δ 14.95 (b, 1H, COOH), 9.05 (s, 1H, C_2H), 8.05 (s, 1H, C_8H), 4.55 (q, 2H, CH_2C), 2.42 (s, 3H, CH_3CO), 2.38 (s, 3H, CH_3CO), 1.40 ppm (t, 3H, CCH_3).

Anal. Calcd. for $C_{16}H_{14}NO_7Cl$: C, 52.3; H, 3.8; N, 3.8; Cl 9.6. Found: C, 52.5; H, 4.0; N, 3.7; Cl, 9.5.

In Concentrated Hydrochloric Acid.

Compound **4** (3.23 g, 0.01 mole) in 30 ml concentrated hydrochloric acid was heated at 110° for 5 hours. Nitrogen evolution was observed. After cooling it was poured into 100 ml of water, made neutral with 50% sodium hydroxide solution and filtered to give 2.5 g (68.1%) of **7**, mp 263-266°, identical with the compound described above.

6,7-Diacetoxy-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic Acid (**9**).

Compound **5** diazo-oxide (2.75 g, 0.01 mole) was heated in 8 ml of 50% sodium hydroxide at 90° until nitrogen evolution ceased (*ca.* 2 hours). The cooled solution was made neutral by concentrated hydrochloric acid and the precipitate was filtered. The crude product, 1.65 g (66%), was obtained (presumably the 6,7-dihydroxy derivative) and was acetylated in 15 ml of acetic anhydride in the presence of perchloric acid at ambient temperature for 4 hours. The reaction mixture was poured in 50 ml of water, allowed to stand overnight in the refrigerator and was filtered to give 1.64 g (74.5%) of **9**, mp 243-246° (from acetone); ir (potassium bromide): ν 1775 (CH_3CO), 1735 (CO acid), 1635 (CO), 1205 (COC) cm^{-1}; nmr (deuteriochloroform): δ 9.80 (b, 1H, COOH), 8.80 (s, 1H, C_2H), 8.35 (s, 1H, C_5H), 7.60 (s, 1H, C_8H), 4.30 (q, 2H, CH_2C), 2.35 (s, 6H, CH_3CO), 1.60 ppm (t, 3H, CCH_3).

Anal. Calcd. for $C_{16}H_{15}NO_7$: C, 57.7; H, 4.5; N, 4.2. Found: C, 57.9; H, 4.6; N, 4.2.

4-Acetoxy-6,9-dihydro-6-ethyl-9-oxo-10*H*-1,3-dioxino[4,5-*f*]quinoline-8-carboxylic Acid (**13**).

From Diazonium Sulfate **11**, Along with **10**.

Compound **11** (38.5 g, 0.1 mole) was stirred in 30 ml of 50% sulfuric acid solution at 90° for 3 hours, until nitrogen evolution ceased. With 250 ml of acetone added, it was allowed to stand overnight. The precipitate which formed was filtered and washed with acetone to yield 19.2 g of yellow product. It was acetylated in 60 ml of acetic anhydride in the presence of a few drops of perchloric acid for 5 hours at room temperature. The solvent was evaporated and from the residue (1:1 mixture of **13**:**10**), the components were separated by subsequent recrystallization from acetone and chloroform.

Compound **13**.

This compound had mp 287-290°; ir (potassium bromide): ν 1780 (CH_3CO), 1705 (CO acid), 1625 (CO), 1190, 1080 (COC) cm^{-1}; nmr (DMSO-d_6 + deuteriochloroform): δ 14.90 (b, 1H, COOH), 8.90 (s, 1H, C_2H), 7.70 (s, 1H, C_8H), 5.60 (s, 2H, CH_2O), 5.30 (s, 2H, CH_2O), 4.55 (q, 2H, CH_2C), 2.35 (s, 3H, CH_3CO), 1.50 ppm (t, 3H, CCH_3); ms m/e 333 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_7$: C, 57.7; H, 4.5; N, 4.2. Found: C, 58.0 H, 4.6; N, 4.3.

Compound **10**.

This compound had mp 219-223°; ir (potassium bromide): ν 1790, 1770 (CH_3CO), 1720 (CO acid), 1650 (CO), 1280, 1200 (COC) cm^{-1}; nmr (deuteriochloroform): δ 13.3 (s, 1H, OH), 13.20 (s, 1H, COOH), 8.75 (s, 1H, C_2H), 6.95 (s, 1H, C_8H), 4.33 (q, 2H, CH_2C), 2.38 (s, 6H, $COCH_3$), 1.60 ppm (t, 3H, CCH_3); ms: m/e 349 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_8$: C, 55.0; H, 4.3; N, 4.0. Found: C, 54.8; H, 4.0; N, 4.1.

From Diazo-Oxide **5**.

To 2.75 g (0.01 mole) of **5** in 15 ml of 70% sulfuric acid solution, 3.33 g (36%, 0.04 mole) of aqueous formaldehyde was added and stirred at 90° for 3 hours. Nitrogen evolution was observed. It was poured into 100 ml

of water to precipitate 2.4 g of crude product which was separated by filtration, mp 247-250°, nmr (DMSO-d_6 + deuteriochloroform): δ 8.80 (s, 1H, C_2H), 7.20 (s, 1H, C_8H), 5.50 (s, 2H, CH_2O), 5.40 ppm (s, 2H, CH_2O). The above product (1.45 g) was acetylated in 15 ml of acetic anhydride in the presence of perchloric acid at room temperature for 5 hours. It was poured into 50 ml of water, allowed to stand overnight and filtered off to yield 1.2 g (72%) of white **13**, mp 285-287° (from acetone). It was identical with the above sample.

6,9-Dihydro-4-ethoxy-6-ethyl-9-oxo-10*H*-1,3-dioxino-[4,5-*f*]quinoline-8-carboxylic Acid. (**17**).

Hydrolysis of the Ester.

Ethyl 1,4-dihydro-5,6-dioxino-7-ethoxy-1-ethyl-4-oxoquinoline-3-carboxylate (**16**) (0.35 g 0.001 mole) was hydrolysed in 3 ml of 0.1*N* sodium hydroxide solution at 80°. It was made acidic by 0.2*N* hydrochloric acid, and the precipitate was filtered and washed with water. Compound **17** (0.3 g, 94%) was obtained, mp 256-258° [lit. (9) mp 259-260°].

N-Ethylation.

Ethyl 5,6-dioxino-7-ethoxy-4-quinolone-3-carboxylate (**15**) (0.64 g, 0.002 mole) was refluxed in 3 ml (0.01 mole) of triethyl phosphate in the presence of 0.27 g (0.002 mole) of potassium carbonate for 30 minutes. Having cooled it down and diluted with 10 ml of water, the precipitate was filtered off and washed with water to yield 0.5 g (72%) of white ethyl 1-ethyl-5,6-dioxino-7-ethoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate (**16**), purified by recrystallization from acetone, mp 162-164°; ir (nujol): ν 1680 (CO ester), 1630 (CO), 1280, 1200, 1125 (COC) cm^{-1}; nmr (DMSO-d_6 + *deuteriochloroform*): δ 8.50 (s, 1H, C_2H), 7.0 (s, 1H, C_8H), 5.45 (s, 2H, CH_2O), 5.30 (s, 2H, CH_2O), 4.5-4.1 (3 x q, 6H, CH_2C), 1.5-1.2 ppm (3 x t, 9H, CCH_3).

Anal. Calcd. for $C_{18}H_{21}NO_6$: C, 62.2; H, 6.1; N, 4.0. Found: C, 61.9; H, 6.3; N, 4.3.

Formylation.

To a solution of 5.45 g (0.02 mole) of ethyl 6-hydroxy-7-ethoxy-4-quinolone-3-carboxylate (**14**) in 4 ml of water and 14 ml of concentrated sulfuric acid, 3.75 ml of aqueous formaldehyde solution (36%, 0.05 mole) was added. It was allowed to stand for 3 days at ambient temperature. A precipitate was formed which was separated by adding 50 ml of water to the reaction mixture, followed by filtration. It was washed with water to yield 5.3 g (83%) of crude product. It was purified by stirring it in 15 ml of 40% hydrobromic acid solution for 3 hours at ambient temperature. Following neutralization with 50% sodium hydroxide solution, the precipitate was filtered and washed with water giving 4.8 g (75.1%) of ethyl 5,6-dioxino-7-ethoxy-4-quinolone-3-carboxylate (**15**), mp 296-298°; ir (nujol): ν 1700 (CO ester), 1620 (CO), 1280, 1195, 1120 (COC), cm^{-1}; nmr (DMSO-d_6): δ 8.30 (s, 1H, C_2H), 7.0 (s, 1H, C_8H), 5.50 (s, 2H, CH_2O), 5.30 (s, 2H, CH_2O), 4.28, 4.23, (2 x q, 4H, CH_2C), 1.48, 1.33 ppm (2 x t, 6H, CCH_3).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.2; H, 5.4; N, 4.4. Found: C, 60.1; H, 5.4; N, 4.2.

5-Amino-6,7-diethoxy-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic Acid (**18**).

By Reduction of the 5-Nitro Group.

6,7-Diethoxy-1,4-dihydro-1-ethyl-5-nitro-4-oxoquinoline-3-carboxylic acid (3.5 g, 0.01 mole) in 50 ml of acetic acid and 16 ml of concentrated hydrochloric acid was hydrogenated in the presence of 1 g of palladium on charcoal catalyst. The catalyst was removed by filtration and the reaction mixture was poured in 100 ml of water. The yellowish precipitate was filtered off and washed with water to yield 2.56 g (80%) of the 5-amino derivative **18**, mp 217-219°; ir (nujol): ν 3480, 3320 (NH_2), 1700 (CO acid), 1610 (CO), 1290, 1140 (COC) cm^{-1}; nmr (deuteriochloroform): δ 15.0 (s, 1H, COOH), 8.53 (s, 1H, C_2H), 6.60 (bs, 2H, NH_2), 6.13 (s, 1H, C_8H), 4.35-4.0 (3 x q, 6H, CH_2C), 1.65-1.35 ppm (3 x t, 9H, CCH_3).

Anal. Calcd. for $C_{16}H_{20}N_2O_5$: C, 60.0; H, 6.3; N, 8.8. Found: C, 59.7; H, 6.4; N, 9.0.

Nitration of 6,7-Diethoxy-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic Acid.

To a solution of 3.1 g (0.01 mole) of 6,7-diethoxy-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic acid in 7 ml of concentrated sulfuric acid, 1.52 g (0.015 mole) of potassium nitrate was added in portions below 10°. It was stirred at 10° for 1 hour and then at ambient temperature for an additional 8 hours. The reaction mixture was poured in 200 ml of water and the yellow precipitate filtered and washed with water giving 2.97 g (85%) of the 5-nitro compound, mp 260-263°; ir (nujol): 1730 (CO acid), 1615 (CO), 1545 (NO_2), 1280, 1040 (COC); nmr (DMSO-d_6): δ 8.98 (s, 1H, C_2H), 7.46 (s, 1H, C_8H), 4.64, 4.44, 4.22 (3 x q, 6H, CH_2C), 1.47, 1.43, 1.26 ppm (3 x t, 9H, CCH_3).

Anal. Calcd. for $C_{16}H_{18}N_2O_7$: C, 54.9; H, 5.2; N, 8.0. Found: C, 55.0; H, 5.3; N, 7.9.

Diazotization of **18** with Nitrosylsulfuric Acid Followed by Solvolysis. Preparation of **21**.

To 1.28 g (0.004 mole) of 5-amino-6,7-diethoxy-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic acid (**18**) in 12 ml of glacial acetic acid, 2.4 ml (0.006 mole) of nitrosylsulfuric acid was added drop by drop at ambient temperature. Stirring was continued for 2 hours. By adding ether, a brownish oil separated, which was treated with 50 ml of water to give a yellow precipitate, identified as **21** diazo-oxide. The yield was 0.81 g (67%), mp 190-192°; ir (potassium bromide): ν 2130, 2110 (N_2^+), 1720 (CO acid), 1620 (CO), 1240 (COC) cm^{-1}; nmr (deuteriochloroform): δ 14.40 (b, 1H, COOH), 8.50 (s, 1H, C_2H), 6.70 (s, 1H, C_8H), 4.30, 4.25 (2 x q, 4H, CH_2C), 1.58, 1.55 ppm (2 x t, 6H, CCH_3).

Anal. Calcd. for $C_{14}H_{13}N_3O_5$: C, 55.4; H, 4.3; N, 13.8. Found: C, 55.0; H, 4.5; N, 13.5.

6-Acetoxy-1,4-dihydro-7-ethoxy-1-ethyl-4-oxoquinoline-3-carboxylic Acid (**22**).

Compound **21** (3.03 g, 0.01 mole) was heated in 30 ml of 50% sulfuric acid at 90° until nitrogen evolution ceased (about 2 hours). The reaction mixture was poured in 150 ml of water and the precipitate was filtered to give 2.44 g (88%) of product, mp 290-292°, presumably the 6-hydroxy-7-ethoxy derivative.

It was acetylated in 10 ml of acetic anhydride in the presence of perchloric acid for 5 hours at ambient temperature, being allowed to stand for 12 hours, and extracted with 3 x 100 ml of chloroform. The organic layers were collected, concentrated *in vacuo*, and on cooling, **22** separated, giving 2 g (72%) of **22**, mp 230-235° (from chloroform); ir (nujol): ν 1780 (CH_3CO), 1720 (CO acid), 1620 (CO), 1290, 1210 (COC) cm^{-1}; nmr (deuteriochloroform): δ 14.76 (b, 1H, COOH), 8.70 (s, 1H, C_2H), 8.15 (s, 1H, C_5H), 6.90 (s, 1H, C_8H), 4.35, 4.22 (2 x q, 4H, CH_2C), 2.35 (s, 3H, CH_3CO), 1.57, 1.50 ppm (2 x t, 6H, CCH_3).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.2; H, 5.3; N, 4.4. Found: C, 59.9; H, 5.1; N, 4.1.

Diazotization of **18** with Isoamylnitrite Followed by Solvolysis. Preparation of **19** and **20**.

To the cooled mixture of 6.4 g (0.02 mole) of **18** in 250 ml of dry chloroform, saturated with hydrogen chloride gas, 8 ml (0.06 mole) of isoamylnitrite was added under cooling. Stirring was continued at 0° for 15 minutes, then at ambient temperature for 5 hours; meanwhile, a yellow precipitate separated. It was filtered to give 6 g (81.5%) of yellow product, presumably the **19** diazonium chloride, mp 198-200°. It coupled with phloroglucinol in ethanol/sodium ethoxide.

The above product (3.67 g, 0.01 mole) was heated in a mixture of 20 ml of water and 10 ml of concentrated sulfuric acid at 90° until nitrogen evolution ceased. The cold reaction mixture was poured in 50 ml of water and the precipitate was filtered to yield 2.2 g (70.7%) of beige product (presumably the 5-chloro-6-hydroxy-7-ethoxy derivative), mp 310-315°.

The above product (3.11 g, 0.01 mole) was acetylated in 30 ml of acetic anhydride in the presence of 0.5 ml of perchloric acid at ambient temperature for 5 hours. Ether was added and the precipitate was treated with ethyl acetate to yield 3.1 g (87.6%) of white 6-acetoxy-5-

chloro-1,4-dihydro-7-ethoxy-1-ethyl-4-oxoquinoline-3-carboxylic acid (**20**), mp 224-226° (from acetone); ir (nujol): ν 1780 (CH_3CO), 1710 (CO acid), 1600 (CO), 1270, 1200 (COC) cm^{-1}; nmr (deuteriochloroform + deuterionitromethane): δ 10.20 (b, 1H, COOH), 9.10 (s, 1H, C_2H), 7.30 (s, 1H, C_8H), 4.72, 4.40 (2 x q, 4H, CH_2C), 2.45 (s, 3H, CH_3CO), 1.70, 1.55 ppm (2 x t, 6H, CCH_3).

Anal. Calcd. for $C_{16}H_{16}ClNO_6$: C, 54.3; H, 4.5; Cl, 10.0; N, 4.0. Found: C, 54.6; H, 4.4; Cl, 10.2; N, 4.3.

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