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The preparation of 2-indolyl alkyl ketones by reductive cleavage of a β-keto sulfone or by the reaction of 1-chloro-2-propanone (chloroacetone) with a 2-aminobenzoic acid derivative is described. The β-keto sulfone intermediates are prepared by condensation of the carbanion of dimethyl sulfone and indole-2-carboxylic acid esters. Lack of reactivity of several 2-aminobenzoic acids in the 1-chloro-2-propanone process is related to the presence of electron-withdrawing substituents in the aromatic ring.

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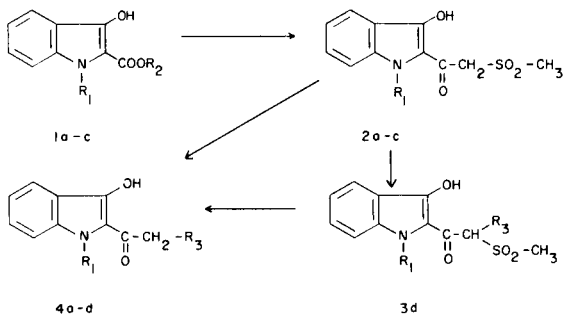
In connection with additional work underway in our laboratories, we required a convenient synthetic procedure suitable for large-scale preparation of certain 3-hydroxy-2-indolyl alkyl ketones. Although the simplest compound of this type **4a** is well known (4,5), additional examples are rare in the literature.

The preparation of alkyl ketones by the reductive cleavage of β-keto sulfones is a versatile synthetic method (6,7). The intermediate β-keto sulfones are usually prepared by the addition of an alkyl sulfone carbanion to a carboxylic acid ester. We have employed this sequence of reactions as one method for the preparation of several 2-indolyl alkyl ketones (Scheme I).

Scheme I



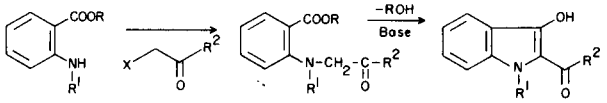
| Compound | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 1,2,4a | H | $C_2H_5$ | H |
| 1,2,4b | $CH_3$ | $C_2H_5$ | H |
| 1,2,4c | $C_6H_5$ | $CH_3$ | H |
| 3,4d | $CH_3$ | ---- | $CH_3$ |

The indole-2-carboxylic acid esters **1a-c** were prepared by known (8,9,10) procedures. The esters were then converted to the β-keto sulfones **2a-c** by condensation with the carbanion of dimethyl sulfone in dimethyl sulfoxide-tetrahydrofuran solvent. A 3:1 stoichiometric ratio of the generated sulfone carbanion to ester was employed to account for reaction with the base-labile hydroxyl and methylene protons in the products. Ester **1a** required an additional molar equivalent of carbanion due to the presence of the indole NH moiety. Acidic work-up led to recovery of the products in their fully protonated form.

Further elaboration of the β-keto sulfone intermediates **2** is possible by alkylation at the reactive α-methylene position before reduction to the corresponding ketone (6,11). The α-methyl sulfone **3d** was obtained in this manner by treating the carbanion derived from **2b** in dimethyl sulfoxide with one equivalent of iodomethane. Additional products resulting from dialkylation at the α-carbon or alkylation at the enolic hydroxyl group of **2b** were not observed.

The intermediate sulfones (Table I) were then reductively cleaved with zinc and acetic acid in ethanol to obtain the 2-indolyl ketones **4a-d**. Representative synthetic procedures for Scheme I are given in the Experimental.

An alternate preparative method for 2-indolyl ketones involves the Claisen-type cyclization of a 2-amino-*N*-(2-oxopropyl)benzoic acid ester (5,12).



The required keto-ester intermediates are usually prepared by alkylation of a 2-aminobenzoic acid ester with an α-haloketone. Cyclization with strong base then yields the indole product.

We have found that 2-indolyl ketones of this type can be prepared in moderate yield directly from the free 2-amino benzoic acids (referred to hereafter for convenience as "anthranilic acids"), with no isolation of the intermediate esters needed (Scheme II).

A series of *N*-substituted anthranilic acids **8a-c,e,f** were combined with approximately one equivalent of potassium carbonate and two equivalents of twice-distilled 1-chloro-2-propanone in water or aqueous ethanol solvent. After heating at reflux for one to three hours, the crude 2-indolyl ketones **4b, 9b,c,e,f** separated from the warm

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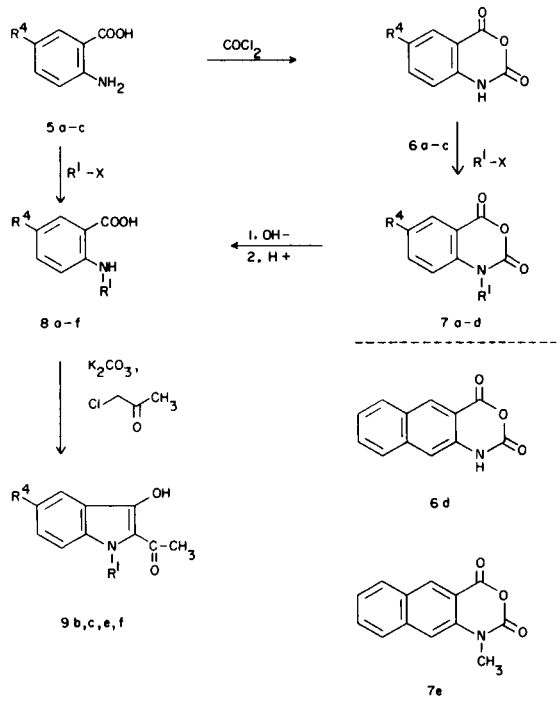
Scheme II

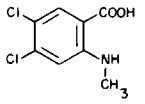


| Compound | $R^1$ | $R^4$ |
|---|---|---|
| **5,6a** | | H |
| **5,6b** | | Cl |
| **5,6c** | | $CH_3$ |
| **7,8a** | $CH_3$ | H |
| **7,8b** | $CH_3$ | Cl |
| **7,8c** | $CH_3$ | $CH_3$ |
| **7,8d** | $CH_3$ | $NO_2$ |
| **8e** | $C_2H_5$ | H |
| **8f** | $CH_2C_6H_5$ | H |
| **9b** | $CH_3$ | Cl |
| **9c** | $CH_3$ | $CH_3$ |
| **9e** | $C_2H_5$ | $CH_3$ |
| **9f** | $CH_2C_6H_5$ | H |

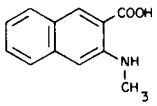
reaction mixtures. The enolic indole products were purified by dissolving in aqueous sodium hydroxide and reprecipitating with acid.

Precursor anthranilic acid derivatives **8a-f** were prepared either by direct alkylation (13) of anthranilic acid itself **5a**, or by base hydrolysis (14) of an *N*-substituted-2*H*-3,1-benzoxazine-2,4(1*H*)dione (an "isatoic anhydride" derivative), **7a-d**. The *N*-substituted isatoic anhydrides resulted from treatment of the appropriate anthranilic acid **5a-c** with phosgene, followed by alkylation of the resulting anhydride **6a-c**. The phosgene-alkylation-hydrolysis procedure was generally performed with only limited purification of intermediates required. Table II summarizes the 2-indolyl ketones prepared by the sulfone reduction and 1-chloro-2-propanone methods.

In addition, several related *N*-substituted amino acids **8d,10,11** were prepared, but could not be successfully converted to the analogous 2-indolyl ketones.

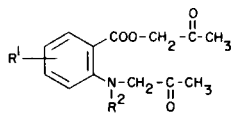


10

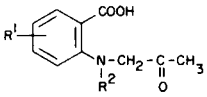


11

Formation of an intermediate of type **12** is probably a prerequisite to 2-indoyl ketone formation. Shorter heating times, and the use of ≥1 molar equivalent of haloketone to amino acid substrate, has been shown (5,15) to generally yield *N*-alkylated acids **13** as the major product of similar haloketone-anthranilic acid reactions.



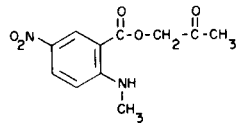
12



13

The three substituted amino acids **8d, 10,** and **11** which did not yield indole products in the 1-chloro-2-propanone reaction have substituents (nitro, dichloro, and phenyl, respectively) which deactivate the amine moiety in relation to nucleophilic displacement of the chlorine of 1-chloro-2-propanone (16,17). Formation of an ester **12** suitable for cyclization to the indole product is thus restricted in these specific cases.

The major product from reaction of the nitro acid **8d** and 1-chloro-2-propanone was the 2-oxopropyl ester **14**, thus demonstrating the decreased reactivity of the amino moiety. Analogous results were observed with substituted acids **10** and **11**.



14

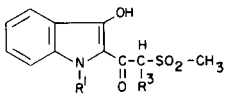
The structure of **14** is discernable from the 90 MHz nmr spectrum. The spectrum of the precursor nitro-acid **8d** (*cf.* Experimental) in deuteriochloroform/DMSO-$d_6$ contains a doublet at δ 3.00, representing the amino methyl group being split by the proton on nitrogen (18) (The amino proton appears as a broad singlet in the aromatic region).

The nmr spectrum of **14** in deuteriochloroform also contains a doublet at δ 3.00 and a broad singlet in the aromatic region, indicating that replacement of the amino proton has not occurred.

Representative spectral data for the 2-indolyl ketones

Table I

2-Indolyl(methylsulfonyl) Ketones

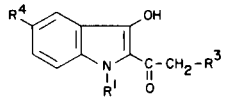


| Compound (a) No. | Formula | M.p. °C | % Yield (b) | | Analyses C | H | N | S |
|---|---|---|---|---|---|---|---|---|
| **2a** | $C_{11}H_{11}NO_4S$ | 225 dec. | 61 | Calcd. | 52.17 | 4.38 | 5.53 | 12.66 |
| | | | | Found | 52.09 | 4.39 | 5.48 | 12.66 |
| **2b** | $C_{12}H_{13}NO_4S$ | 168-170 | 83 | Calcd. | 53.92 | 4.90 | 5.24 | 12.00 |
| | | | | Found | 53.75 | 4.99 | 5.11 | 12.04 |
| **2c** | $C_{17}H_{15}NO_4S$ | 163-166 | 85 | Calcd. | 61.99 | 4.59 | 4.25 | 9.74 |
| | | | | Found | 61.98 | 4.69 | 4.23 | 9.74 |
| **3d** | $C_{13}H_{15}NO_4S$ | 183-185 | 56 (c) | Calcd. | 55.50 | 5.37 | 4.98 | 11.40 |
| | | | | Found | 55.51 | 5.37 | 4.82 | 11.22 |

(a) Substituents are given in Scheme I. (b) Yields represent recrystallized products. (c) Yield of product before recrystallization.

Table II

2-Indolyl Ketones



| Compound (a) No. | Method (b) | Formula | M.p. °C | % Yield (c) | | Analyses C | H | N | Halogen |
|---|---|---|---|---|---|---|---|---|---|
| **4a** | A | $C_{10}H_9NO_2$ | 154-157 (d) | 72 | | | | | |
| **4b** | A,B | $C_{11}H_{11}NO_2$ | 119-121 | 88,70 | Calcd. | 69.82 | 5.86 | 7.40 | |
| | | | | | Found | 69.56 | 5.85 | 7.24 | |
| **4c** | A | $C_{16}H_{13}NO_2$ | 127-130 | 77 | Calcd. | 76.47 | 5.22 | 5.57 | |
| | | | | | Found | 76.37 | 5.41 | 5.32 | |
| **4d** | A | $C_{12}H_{13}NO_2$ | 127-129.5 | 86 | Calcd. | 70.91 | 6.45 | 6.89 | |
| | | | | | Found | 70.78 | 6.53 | 6.83 | |
| **9b** | B | $C_{11}H_{10}ClNo_2$ | 177 dec. | 57 | Calcd. | 59.07 | 4.51 | 6.26 | 15.85 |
| | | | | | Found | 58.95 | 4.59 | 6.09 | 15.78 |
| **9c** | B | $C_{12}H_{13}NO_2$ | 120-122 | 63 | Calcd. | 70.91 | 6.45 | 6.89 | |
| | | | | | Found | 70.87 | 6.43 | 7.02 | |
| **9e** | B | $C_{12}H_{13}NO_2$ | 119.5-121 | 40 | Calcd. | 70.91 | 6.45 | 6.89 | |
| | | | | | Found | 70.70 | 6.53 | 6.86 | |
| **9f** | B | $C_{17}H_{15}NO_2$ | 149.5-151.5 | 26 | Calcd. | 76.96 | 5.70 | 5.28 | |
| | | | | | | 76.81 | 5.80 | 5.27 | |

(a) Substituents are given in Schemes I and II; Compound **4d**, $R^3 = CH_3$; all others, $R^3 = H$. (b) Method A: Zinc reduction of β-ketosulfone. Method B: 1-Chloro-2-propanone-anthranilic acid reaction. (c) Yields represent materials purified but not recrystallized. (d) Literature (5) m.p. 157-159.°

and sulfones are presented in Tables III and IV. The enolic hydroxyl group absorption appears in the infrared spectra of the sulfones as a slightly broadened peak in the region 3325-3380 $cm^{-1}$. A corresponding absorption in the highly-conjugated 2-indolyl ketones is observed only as a very broad shoulder. The conjugated carbonyl absorption appears at 1620-1640 $cm^{-1}$ for the sulfones and at 1600-1630 $cm^{-1}$ for the ketones.

In the nmr spectra, the enolic hydroxyl of the sulfones appears as a broad exchangeable singlet in the region δ

Table III

Spectra of 2-Indolyl(methylsulfonyl) Ketones

| Compound No. | Infrared (Nujol Mulls) ν, Cm⁻¹ | | | Nmr (δ) Solvent | $SO_2CH_3$ | $COCH_2$ | Aromatic H | OH | Other |
|---|---|---|---|---|---|---|---|---|---|
| **2a** | 3327, | 1622, | | DMSO-$d_6$ | 3.18 (s) | 4.93 (s) | 6.75-7.50 (m) | 10.87 (b) | |
| | 1582, | 1282, | 1127 | | | | 7.75-8.0 (m) | (broad s) | |
| **2b** | 3328, | 1640 | | DMSO-$d_6$ | 3.25 (s) | 5.00 (s) | 6.75-7.59 (m) | 11.20 | 3.84 (s, $NCH_3$) |
| | 1619, | 1288, | 1117 | | | | 7.65-8.10 (m) | (broad s) | |
| **2c** | 1626, | 1600, | | DMSO-$d_6$ | 3.15 (s) | 5.04 (s) | 6.93-7.67 (m) | 11.62 | |
| | 1532, | 1326, | 1161 (a) | | | | 7.96-8.17 (m) | (broad s) | |
| **3d** | 3380, | 1640 | | DMSO-$d_6$ | 3.00 (s) | | 6.80-7.55 (m) | 11.19 | 2.57 (d, J = 7.0 Hz, $CHCH_3$), |
| | 1619, | 1290, | 1125 | | | | 7.72-8.02 (m) | (broad s) | 5.52 (q, J = 7.0 Hz, $COCH$). |

(a) Spectrum recorded in chloroform solution. (b) May also represent NH.

Table IV

Spectra of 2-Indolyl Ketones

| Compound No. | Infrared (Nujol Mulls) ν, Cm⁻¹ | | | Nmr (δ) Solvent | $COCH_3$ | $NCH_3$ | Aromatic H | OH | Other |
|---|---|---|---|---|---|---|---|---|---|
| **4a** | 3350, | 3250, | | DMSO-$d_6$ | 2.58 (s) | | 6.52-7.50 (m) | 10.63 (a) | |
| | 1623, | 1550, | | | | | 7.50-8.13 (m) | (broad s) | |
| | 1350, | | | | | | | | |
| **4b** | 1621, | 1600, | | deuterio- | 2.61 (s) | 3.81 (s) | 6.80-7.60 (m) | 11.15 | |
| | 1351, | 1265, | 735 | chloroform | | | 7.60-7.93 (m) | (broad s) | |
| **4c** | 1615, | 1602, | | deuterio- | 1.95 (s) | | 6.87-7.74 (m) | 11.23 | |
| | 1497, | 1292, | 735 | chloroform | | | 7.74-8.00 (m) | (broad s) | |
| **4d** | 1623, | 1600, | | deuterio- | | 3.81 (s) | 6.82-7.60 (m) | 11.28 (b) | 1.26 (t, J = 7.0 Hz, $CH_2CH_3$), |
| | 1532, | 1243, | 740 | chloroform-deuterium-oxide | | | 7.60-7.88 (m) | (broad s) | 2.93 (q, J = 7.0 Hz, $CH_2$-$CH_3$) |
| **9b** | 1615, | 1581, | | DMSO-$d_6$ | 2.61 (s) | 3.85 (s) | 7.15-7.65 (m) | | |
| | 1332, | 960, | 779 | | | | 8.00-8.15 (m) | | |
| **9c** | 1630, | 1600, | | deuterio- | 2.61 (s) | 3.80 (s) | 6.92-7.45 (m) | 11.18 (b) | 2.41 (s, $ArCH_3$) |
| | 1340, | 1262, | 968 | chloroform-deuterium-oxide | | | 7.45-7.72 (m) | (broad s) | |
| **9e** | 1612, | 1592, | | deuterio- | 2.65 (s) | | 6.82-7.60 (m) | 11.38 (b) | 1.35 (t, J = 7.0 Hz, $CH_2CH_3$), |
| | 1340, | 1224, | 968 | chloroform-deuterium-oxide | | | 7.60-8.02 (m) | (broad s) | 4.32 (q, J = 7.0 Hz, $CH_2CH_3$) |
| **9f** | 1612, | 1590, | | deuterio | 2.45 (s) | | 6.80-7.55 (m) | 11.49 (b) | 5.52 (s, $NCH_2Ar$) |
| | 1342, | 1191, | 951 | chloroform-deuterium-oxide | | | 7.72-8.03 (m) | (broad s) | |

(a) May also represent N*H*. (b) Chemical shift in deuteriochloroform only.

10-12 in DMSO-$d_6$ solution. The spectra of the ketones contain a corresponding peak at δ 11.1-11.5.

The magnetic environment of the number 4 aromatic proton in the ketones and sulfones is influenced by the 3-position enolic hydroxyl group (5). The number 4 proton resonance is therefore observed as a one proton multiplet appearing between δ 7.5-8.5, usually distinct from the remaining aromatic proton resonance.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary

apparatus and are uncorrected. NMR spectra were recorded on a Perkin-Elmer R-12B spectrometer at 60 MHz, or on a Varian EM-390 spectrometer at 90 MHz. Tetramethylsilane was employed as an internal standard in both instances. Infrared spectra were recorded on a Beckmann DK-I spectrophotometer or a Digilab FTS-14 pulsed Fourier-transform spectrophotometer as Nujol mulls or potassium bromide disks, as indicated.

1-(3-Hydroxy-1-methyl-1*H*-indol-2-yl)-2-(methylsulfonyl)ethanone (**2b**).

A solution of 56.4 g. (0.60 mole) of dimethyl sulfone in 300 ml. of dimethylsulfoxide was added over 10 minutes to a nitrogen filled flask containing 30.0 g. (0.62 mole) of sodium hydride (previously washed with hexane). After stirring and heating at 65-75° for 75 minutes, the mixture was cooled to room temperature, and 100 ml. of tetrahydrofuran was added, followed by a solution of 43.8 g. (0.20 mole) ethyl 3-hydroxy-1-methyl-1*H*-indole-2-carboxylate (8) in 250 ml. of tetrahydrofuran, added over 10 minutes. The mixture was heated at 65-75° for 2 hours, cooled, and added to 2.2 liters of cold 0.55*N* hydrochloric acid. The product was filtered, washed with cold water, and recrystallized from methanol to yield yellow needles of **2b**, m.p. 168-170° (44.4 g., 83% yield).

The above procedure was also employed to prepare **2c** from methyl 3-hydroxy-1-phenyl-1*H*-indole-2-carboxylate (9), and **2a** from methyl 3-hydroxy-1*H*-indole-2-carboxylate (10).

1-(3-Hydroxy-1-methyl-1*H*-indol-2-yl)-2-(methylsulfonyl)-1-propanone (**3d**).

A mixture of 6.15 g. (0.13 mole) 50% sodium hydride (previously washed free of mineral oil with hexane) in 150 ml. of dimethyl sulfoxide was treated over 30 minutes with a solution of 17.0 g. (0.064 mole) of the sulfone **2b** in 180 ml. of dimethyl sulfoxide. The reaction was carried out under nitrogen, and the reaction mixture temperature was maintained at 20-25°. The mixture was stirred an additional one hour, and 4.0 ml. (9.11 g., 0.064 mole) of iodomethane was then added dropwise over 10 minutes. After a final one hour of stirring, the reaction mixture was added to 850 g. of ice-water containing 32 ml. of concentrated hydrochloric acid. The mixture was stirred overnight, and the crude sulfone **3d** was filtered and washed with cold water. The yield was 9.9 g. (56%). Several recrystallizations from methanol/water, followed by ethyl acetate/hexane, yielded yellow needles of **3d**, m.p. 183-185°.

The indol-2-yl ketones described in Table II were prepared by one or both of the following general procedures.

Method A. 1-(3-Hydroxy-1-methyl-1*H*-indol-2-yl)ethanone (**4b**).

A mixture of 17.0 g. (0.064 mole) of **2b**, 21.0 g. (0.32 mole) of zinc dust, 40 ml. of glacial acetic acid and 80 ml. of absolute ethanol was stirred vigorously and heated at 45-50° for 1 hour. After stirring an additional hour at room temperature, the mixture was filtered through diatomaceous earth and the filter cake washed several times with fresh ethanol. The combined filtrates were condensed to 150 ml., and 50 ml. of hot water was added. Cooling yielded a green solid which was filtered, washed with cold water, and recrystallized from 70% aqueous methanol to yield **4b**, green needles of m.p. 119-121° (10.7 g., 88% yield).

Method B. 1-(5-Chloro-3-hydroxy-1-methyl-1*H*-indol-2-yl)ethanone (**9b**).

To a solution of 74.1 g. (0.54 mole) potassium carbonate in 1.9 l. of water, was added 97.0 g. (0.52 mole) of 5-chloro-2-(methylamino)benzoic acid, followed by 106 g. (1.15 mole) of 1-chloro-2-propanone. The mixture was stirred at reflux for 2.0 hours, cooled, and the tan solid was filtered and washed with cold water. The crude product was stirred for 3.0 hours in 1.25 l. of 0.5*N* aqueous sodium hydroxide, the mixture was filtered by gravity, and the product re-precipitated with 4.0*N* hydrochloric acid. The tan solid was filtered, washed with cold water, and air-dried for several days. Residual water was removed by suspending the purified product in 1.2 l. of ethyl acetate and then distilling the mixture for ~30 minutes. The mixture was cooled in ice, and the product filtered and washed with cold hexane to yield a tan solid **9b** of m.p. 177° dec (66.3 g., 57% yield). An analytically pure sample of the same melting point was obtained by recrystallization from methanol.

A sample of **4b** prepared by the above 1-chloro-2-propanone procedure (Method B) was identical in all respects to a sample prepared by Method A.

1,6-Dimethyl-2*H*-3,1-benzoxazine-2,4(1*H*)dione (**7c**).

A mixture of 16.0 g. (0.09 mole) of 6-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)dione ("5-methylisatoic anhydride") and 10.0 g. (0.09 mole) of anhydrous sodium carbonate in 100 ml. of *N,N*-dimethylformamide, was treated with 14.3 g. (0.10 mole) iodomethane. After stirring at room temperature for 24 hours, the reaction mixture was added to 700 g. of ice-water. The product was filtered, washed with water, and air-dried to yield the off-white solid **7c** of m.p. 165-169° (16.1 g., crude yield 93%).

A sample recrystallized from ethyl acetate/hexane had m.p. 168-170° (19); ir (Nujol): $\nu$ 1778, 1722 (C=O) $cm^{-1}$; nmr (DMSO-$d_6$): $\delta$ 2.39 (s, 3H, CC$H_3$), 3.43 (s, 3H, NC$H_3$), and 7.20-7.88 (m, 3H, Ar$H$).

*Anal.* Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.68; H, 4.56; N, 7.25.

5-Methyl-2-(methylamino)benzoic Acid (**8c**).

The anhydride (**7c**) (21.0 g., 0.11 mole) was added over 30 minutes to a stirred solution of 1*N* sodium hydroxide (340 ml.). Stirring was continued for an additional one hour, the mixture was filtered and the filtrate cooled in ice and acidified to *p*H 5 with acetic acid. The product was filtered, washed with cold water, and recrystallized from ethanol/water to yield the acid (**8c**), light yellow needles of m.p. 146-148.5° (lit. (20) m.p. 128°) (13.2 g., 73% yield); ir (Nujol): $\nu$ 3410 (N-H), 1668 (COOH) $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 2.23 (s, 3H, ArC$H_3$), 2.91 (s, 3H, NC$H_3$), 6.50-7.84 (m, 3H, Ar$H$), and 9.28 (broad s, 1H, N$H$).

*Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.65; H, 6.64; N, 8.40.

The combined alkylation-hydrolysis procedures described in the preparation of **7c** and **8c** were also employed to convert 6-chloro-2*H*-3,1-benzoxazine-2,4(1*H*)dione (**6b**) to 5-chloro-2-(methylamino)benzoic acid (**8b**) (m.p. 178-181°; lit. (21) m.p. 173-174.5°), and 1-methyl-6-nitro-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (**7d**) to 2-(methylamino)-5-nitrobenzoic acid (**8d**) (m.p. 258° dec; lit. (22,23) m.p. 263-264°, 258° dec); ir (potassium bromide): $\nu$ 3360 (N-H), 1665, 1319 $cm^{-1}$; nmr (deuteriochloroform plus DMSO-$d_6$): $\delta$ 3.00 (d, 3H, J = 4.5 Hz, NC$H_3$), 6.70 (d, 1H, J = 9.0 Hz, #3 Ar$H$), 8.11 (q, 1H, J = 9.0, 2.5 Hz, #4 Ar$H$), and 8.63 (d, 1H, J = 2.5 Hz, #6 Ar$H$, and broad s, 1H, N$H$).

4,5-Dichloro-2-(methylamino)benzoic Acid (**10**).

To a solution of 14.0 g. (0.10 mole) of potassium carbonate in 250 ml. of water, was added 41.2 g. (0.20 mole) of 2-amino-4,5-dichlorobenzoic acid, followed by 34.2 g. (0.24 mole) of iodomethane. The mixture was stirred at reflux for 2.5 hours, cooled, and the product filtered and washed with cold water.

Recrystallization from ethanol/water yielded **10**, yellow needles of m.p. 256° dec (22.5 g., 51% yield); ir (potassium bromide): $\nu$ 3390 (NH), 1670 (COOH) $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 2.82 (s, 3H, NC$H_3$), 6.80 (s, 1H, #3 Ar$H$), and 7.80 (s, 1H, #6 Ar$H$).

*Anal.* Calcd. for $C_8H_7Cl_2NO_2$: C, 43.66; H, 3.21; N, 6.37; Cl, 32.22. Found: C, 43.63; H, 3.29; N, 6.42; Cl, 32.12.

The above procedure was also employed in the preparation of 2-(ethylamino)benzoic acid **8e** (m.p. 152-155°; lit. (24) m.p. 150-152°), and 2-[(phenylmethyl)amino]benzoic acid **8f** (m.p. 170-173°; lit. (25) m.p. 175-176°) *via* alkylation with iodoethane and (chloromethyl)benzene, respectively.

2*H*-Napth[2,3-*d*][1,3]oxazine-2,4(1*H*)dione (**6d**) (26).

A suspension of 9.36 g. (0.50 mole) of 3-amino-2-naphthalene carboxylic acid (Aldrich Technical Grade, 80%) in 125 ml. of dioxane was treated with 46.6 g. (0.059 mole) of 12.5% phosgene in benzene solution over 20 minutes. A cold water bath was employed to maintain the reaction temperature at 15-20° during addition. The mixture was stirred for 2 hours after addition was complete, warmed to 45-50° for an additional 2 hours, then stirred overnight at room temperature. The product was filtered and washed twice with ether to yield 5.90 g. (55% yield) of **6d** as a brown solid. A sample recrystallized from *N,N*-dimethylformamide/water yielded yellow plates of m.p. 265° dec; ir (potassium bromide): $\nu$ 1780, 1743 (C=O) $cm^{-1}$; nmr (DMSO-$d_6$): $\delta$ 7.2-8.0 (m, 4H, Ar$H$), 7.38 (s, 1H, #10 Ar$H$), 8.48 (s, 1H, #5 Ar$H$), and 11.58 (s, 1H, N$H$).

*Anal.* Calcd. for $C_{12}H_7NO_3$: C, 67.60; H, 3.31; N, 6.57. Found: C, 67.25; H, 3.49; N, 6.69.

1-Methyl-2*H*-naph[2,3-*d*][1,3]oxazine-2,4(1*H*)dione (**7e**) (26).

The dione **6d** was converted to the *N*-methyl derivative **7e** with iodomethane and sodium carbonate in *N,N*-dimethylformamide by a procedure analogous to that employed in the preparation of **7c**. A 5.0 g. (0.024 mole) sample of **6d** yielded 3.2 g. (60% yield) of **7e**. Recrystallization of the final product from acetone/water gave yellow needles of m.p. 235-238°; ir (potassium bromide): $\nu$ 1771, 1736 (C=O) $cm^{-1}$; nmr (DMSO-$d_6$): $\delta$ 3.38 (s, 3H, NC$H_3$), 7.18-7.98 (m, 4H, Ar$H$), 7.55 (s, 1H, #10 Ar$H$) and 8.48 (s, 1H, #5 Ar$H$).

*Anal.* Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.17. Found: C, 68.74; H, 4.20; N, 6.21.

3-(Methylamino)-2-naphthalenecarboxylic Acid (**11**).

The *N*-methyl dione **7e** was hydrolysed to the acid **11** by a procedure analogous to that employed in the preparation of **8c**. A 2.90 g. (0.013 mole) sample of **7e** yielded 1.40 g. (54% yield) of **11**. Recrystallization of the final product from ethanol/water gave yellow needles of m.p. 231-233°; ir (potassium bromide): $\nu$ 3420 (NH), 1668 (COOH) $cm^{-1}$; nmr (deuteriochloroform plus DMSO-$d_6$): $\delta$ 2.93 (s, 3H, NC$H_3$), 6.64 (s, 1H, #4 Ar$H$), 6.83-7.61 (m, 4H, Ar$H$), 8.35 (s, 1H, #1 Ar$H$), and 8.90 (broad s, 1H, N$H$).

*Anal.* Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.53; H, 5.36; N, 6.92.

2-Oxopropyl 2-(Methylamino)-5-nitrobenzoate (**14**).

A mixture of 1.67 g. (0.0085 mole) of **8d**, 1.20 g. (0.0087 mole) of potassium carbonate, and 1.70 g. (0.018 mole) of 1-chloro-2-propanone in 15 ml. water and 6 ml. ethanol was stirred at reflux for 18 hours. The yellow solid that precipitated upon cooling was filtered, washed with cold water, and recrystallized twice from methanol/water to yield yellow needles of ester **14**, m.p. 144-147° (1.20 g., 56% yield); ir (potassium bromide): $\nu$ 3365 (NH), 1742, 1697 $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 2.20 (s, 3H, COC$H_3$), 3.00 (d, 3H, J = 4.5 Hz, NC$H_3$), 4.87 (s, 2H, C$H_2$), 6.66 (d, 1H, J = 9.0 Hz, #3 Ar$H$), 8.22 (q, 1H, J = 9.0, 2.5 Hz, #4 Ar$H$), 8.32 (broad s, 1H, N$H$), and 8.89 (d, 1H, J = 2.5 Hz, #6 Ar$H$).

*Anal.* Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.16; H, 4.75; N, 10.82.

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