Phosgenation of Methyl Anthranilate

Norton P. Peet* and Shyam Sunder

Dow Interdisciplinary Group, Chemical Biology Research, Dow Chemical Company, Midland, Michigan 48640

Received December 6, 1973

The reaction of methyl anthranilate (**1a**) with phosgene in EtOAc produces 2-carbomethoxyanilinecarbonyl chloride (**2a**), 2-carbomethoxyphenyl isocyanate (**3a**), dimethyl 2,2′-[carbonylbis(imino)]benzoate (**4a**), methyl 2-[1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoate (**5a**), and isatoic anhydride (**6**), with distribution dependent upon reaction conditions. Product **2a**, **3a**, **4a**, or **6** can be obtained as the major product in excellent yield. Alternate syntheses of **5a** (and **4a**) are reported. In preparing **5a** from **4a** with polyphosphoric acid, conditions were developed which led to the exclusive formation of methyl 2-[(4-oxo-4*H*-3,1-benzoxazin-2-yl)amino]benzoate (**11**). The mechanism of isatoic anhydride formation is shown to involve the direct displacement of an ester alkyl group by chloride ion.

The reaction of methyl anthranilate (**1a**) with phosgene to produce 2-carbomethoxyphenyl isocyanate (**3a**) is well documented in the literature.[1] Although these preparations indicate the presence of at least one additional product,[2] no attempt was made to establish its identity. In a reinvestigation of the phosgenation of **1a** we have isolated and identified five products. The distribution of these products is altered rather markedly by changes in the reaction conditions.

When **1a** was treated with excess phosgene in EtOAc, the initial product was carbamoyl chloride **2a**. Carbamoyl chloride **2a** can be dehydrochlorinated to **3a** either thermally or by base treatment. When a benzene solution of carbamoyl chloride **2a** was treated with saturated K_2CO_3, distillation of the concentrated organic phase gave a good yield of isocyanate **3a**. Modest amounts of diester urea **4a**[3] and quinazolinedione **5a** were isolated from the distillation pot. Product **4a** could arise from the hydrolysis of some **2a** or **3a** to **1a** (during the base extraction) which could then react with either **2a** or **3a**. Product **5a** could have been formed from **4a** in the distillation pot by acid catalysis. Thermal elimination of HCl from **2a** also afforded **3a** in good yield, when a solution of **2a** in EtOAc was heated for 70 hr without interruption. See Scheme I.

Diester urea **4a** is a known compound[4] and its structure was readily established. This material could be prepared either by treating methyl anthranilate (**1a**) with isocyanate **3a**, or by treating **3a** with water using DME as a cosolvent.

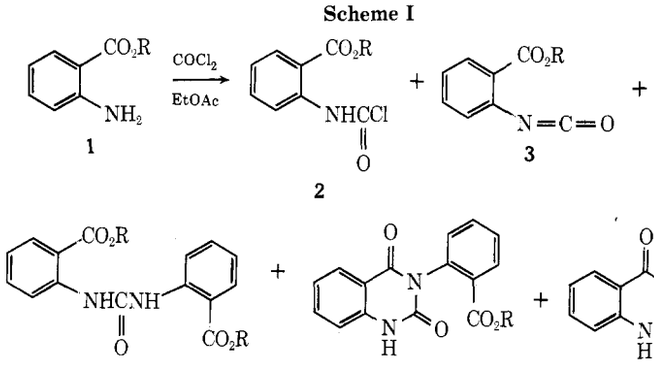
In devising an alternate route to quinazolinedione **5a**, for structural confirmation, we initially chose the route depicted in Scheme II. Several synthetic schemes for 3-substituted quinazolinediones are outlined in the literature.[5-8]

Perhaps the most obvious precursor of **5a** was the diester urea **4a**. *o*-Carboalkyoxyphenylureas have been converted, under acid-catalyzed conditions, to quinazoline-2,4-diones.[1b,9] Although we did pursue this route to **5a** (*vide infra*), it was not our first choice, since we felt that formation of the benz-3,1-oxazin-4-one ring system might be competitive.

Anthraniloylanthranilic acid (**7a**) was prepared[10] and esterified using 1-methyl-3-*p*-tolyltriazine (TMT),[11] since attempted esterification of **7a** with methanolic HCl led mainly to **7a** HCl. We found that, although ester **7b** would react with ethyl chloroformate in pyridine at reflux to give the corresponding carbamate, a nonbasic solvent with added triethylamine would not suffice. Cyclization of the carbamate to **5a** was effected with *p*-toluenesulfonic acid (HOTs) in toluene at reflux.

o-Aminobenzamides are important starting materials for the synthesis of quinazolin-4-ones and dihydroquinazo-

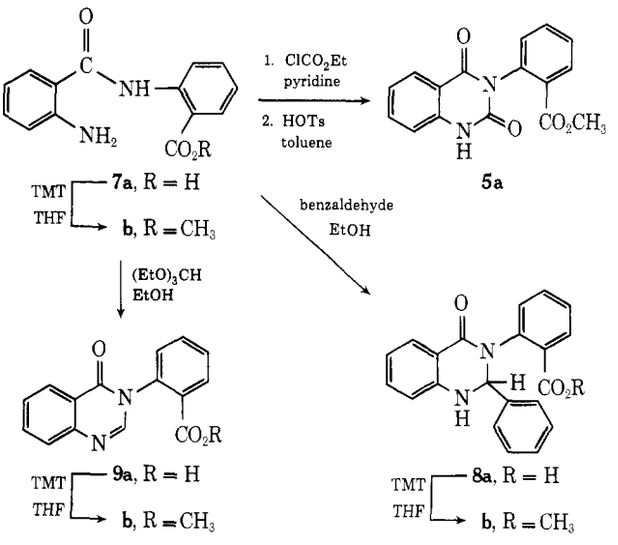
Scheme I



1 2 3 4 5 6

	Reaction conditions	Product yields, % 2	3	4	5	6	RCl
a series, R = CH_3	stir or heat briefly	100					
	heat briefly; wash with K_2CO_3		67	3.3	11		
	heat at reflux for 70 hr		70			18	
	heat for 2 hr; stir for 15 hr; heat for 2 hr		46			34	
	45–55° for 28 days		7			91	
	isolate **2**; thermolyze (neat) 100°		~20			73	?
b series, R = *n*-butyl	isolate **2**; thermolyze (neat) 100°		54			35	37

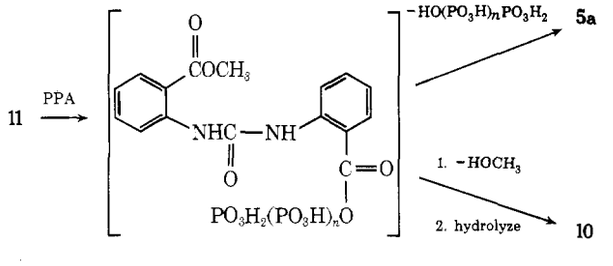
Scheme II



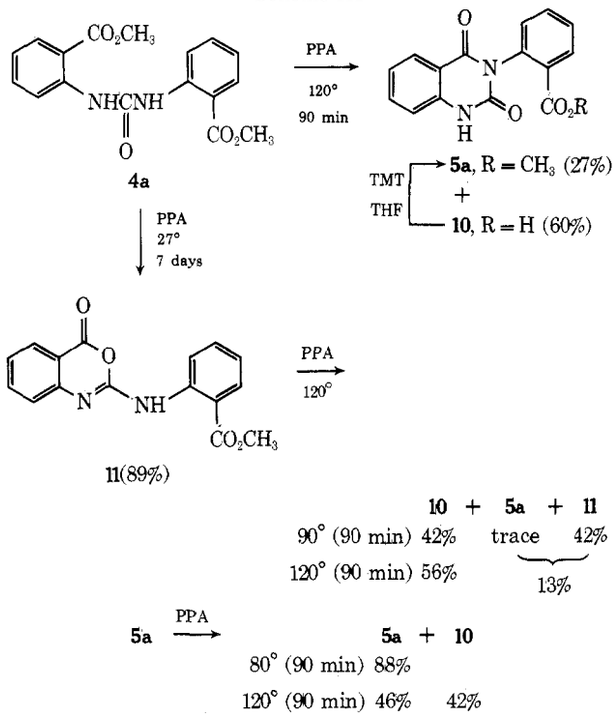
lin-4-ones. These two classes of heterocycles can be prepared by treating *o*-aminobenzamides with ortho esters[12] and aldehydes[13] or ketones,[14] respectively. Compounds **7a** and **7b** reacted readily with benzaldehyde and triethyl orthoformate to give cyclic products **8a,b** and **9a,b**, respectively, as shown in Scheme II. It should be recognized that isomeric with structures **8a** and **8b** are acyclic, Schiff base structures which are possible products of the condensation reactions. Some authors[13a] have failed to discount this possibility when making structural assignments. Our nmr data for compounds **8a** and **8b** clearly establish their structures. The methine protons for these compounds appear as sharp singlets[15] at δ 6.31 and 6.20, respectively. Aldimine protons would necessarily appear at lower field.[16]

In attempting to prepare quinazolinedione **5a** from diester urea **4a** with polyphosphoric acid (PPA), it became apparent that reaction temperature was a critical factor. When **4a** was stirred with PPA at room temperature for 7 days, benzoxazinone **11** was isolated in 89% yield. However, when **4a** was treated with PPA at 120° for 90 min, quinazolinediones **5a** and **10** were the products isolated in 27 and 60% yields, respectively. Intermediate reaction temperatures resulted in mixtures of **5a**, **10**, and **11**. These results indicate that **11** is the kinetically favored product while **5a** is favored thermodynamically.

In attempting to determine whether **11** was in intermediate in the conversion of **4a** to **5a** and to delineate the origin of **10**, benzoxazinone **11** was treated with PPA. After 90 min at 90°, equal amounts of **11** and **10** were isolated, while only the presence of **5a** in trace amounts was indicated by ir. Treatment of **11** with PPA for 90 min at 120° yielded acid **10** in 56% yield and a mixture of **5a** and **11** (indicated by ir) in 13% yield. Ester **5a** was shown to be stable in PPA at 80°, but at 120° 46% of **5a** was recovered and 42% of acid **10** was produced. These results (Scheme III) indicate that **11** is not necessarily an intermediate in the conversion of **4a** to **5a**. Although **10** can



Scheme III



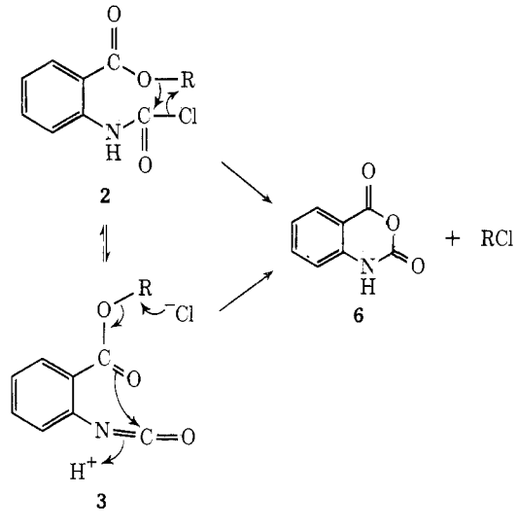
arise from **5a** as demonstrated, it might also be produced from an intermediate polyphosphoric ester originating from **11**. Cyclization of this intermediate could give both **5a** and **10**. Although none of the three possible tetracyclic products which might have arisen from **4a** and PPA by the loss of two molecules of methanol was observed, the possibility of their intermediacy (*i.e.*, in the conversion of either **11** or **5a** to **10**) cannot be excluded. One of these products has been isolated and characterized by Doleschall and Lempert[18] from the treatment of **10** with phosphoryl chloride.

Turning back to our consideration of the products obtained from the phosgenation of methyl anthranilate (**1a**), the product yet to be discussed is the most intriguing from a mechanistic standpoint. In Scheme I are shown the reactions in which isatoic anydride (**6**) was produced. Notably, when **1a** was treated with excess phosgene in EtOAc for 4 weeks, a 91% yield of **6** was obtained. These experiments indicated to us that the formation of **6** was favored either when **3a** was constrained in a chloride-rich environment for a long period of time or when **2a** was allowed to decompose at a solution temperature lower than required for its dehydrochlorination, or both.[19]

To explore the above possibilities, we isolated a sample of carbamoyl chloride **2a** and thermolyzed it (neat) at 100°. The result was a 73% yield of isatoic anhydride (**6**), with the remainder of material being mostly isocyanate **3a**. We next resubjected a sample of isocyanate **3a** to a solution of phosgene in EtOAc for 3 days at room temperature. The result was a 26% yield of **6**. In light of these results, the dual mechanistic pathway illustrated below seems reasonable.[20] However, since **2a** and **3a** are interconvertible, the possibility of **6** arising solely from **2a** or **3a** is not excluded. Imidate hydrohalides have been shown to decompose in chloroform and *tert*-butyl alcohol solutions at 60°, following first-order kinetics with respect to the disappearance of halide ion, to yield amides and haloalkanes.[21] *N*-Carboalkoxy-α-amino acid chlorides also decompose thermally to yield chloroalkanes and 2,5-oxazolidinediones.[22]

To test this mechanism, it was imperative to prove that

choloroalkane was being produced. Picking chlorobutane as our target chloroalkane for isolation, we synthesized and thermolyzed carbamoyl chloride **2b** (Scheme I). Although the ratio of isatoic anhydride (**6**) to isocyanate **3b** was different from the ratio of **6** to **3a** in the thermolysis of **2a**, **6** was isolated in 35% yield. To our satisfaction, a stoichiometric amount of chlorobutane was also isolated.



The work reported herein had its inception with the seemingly routine preparation of 2-carbomethoxyphenyl isocyanate (**3a**). The use of **3a** in the preparation of novel heterocyclic compounds will be the subject of future papers.

Experimental Section

Phosgenation of Methyl Anthranilate (1a) Followed by Treatment with K_2CO_3. A 200-g (1.32 mol) quantity of **1a** (Aldrich) in 400 ml of EtOAc was added, *via* syringe, over a period of 40 min to 400 ml of $COCl_2$ (Matheson) in 400 ml of EtOAc under a nitrogen atmosphere with ice-bath cooling and mechanical stirring. After 1 hr at reflux, the solution was concentrated, the resulting solid was dissolved in benzene, and the benzene solution was washed with saturated K_2CO_3, dried ($MgSO_4$), concentrated, and distilled to yield 156 g (67%) of **3a**, bp 99° (0.50 mm), mp 46–46.5° [lit.[1] bp 145–146° (10 mm)].

The distillation pot residue was lixiviated with benzene to remove, after concentration, 9.26 g of material which was recrystallized (heptane) to yield 7.24 g (3.3%) of dimethyl 2,2′-[carbonylbis(imino)]bisbenzoate (**4a**): mp 140–142° (lit.[4] mp 144°; ir (Nujol) 3270 (NH), 1695 (ester C=O), 1675 cm^{-1} (urea C=O); nmr ($CDCl_3$) δ 10.80 (s, 2, NH), 8.70–8.46 (m, 4, aromatic), 8.08–7.87 (m, 4, aromatic), 3.90 (s, 6, CH_3); mass spectrum (70 eV) *m/e* 177, 151.

Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.90; H, 4.91; N, 8.66.

The benzene-insoluble pot residue weighed 23.4 g and was recrystallized (EtOH) to yield 21.2 g (11%) of methyl 2-[1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoate (**5a**): mp 248–250° (lit.[18] mp 248–249°); ir (Nujol) 3280 (NH), 1720 (ester C=O), 1670 (amide C=O), 1645 cm^{-1} (urea C=O); nmr (DMSO) δ 8.20–7.01 (m, 9, aromatic and NH), 3.65 (s, 3, CH_3); mass spectrum (70 eV) *m/e* 296 (molecular ion).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.70; H, 4.38; N, 9.31.

Preparations of 2-Carbomethoxyphenyl Isocyanate (3a) and Isatoic Anhydride (6) from 1a. A 181-g (1.20 mol) quantity of **1a** was treated with 400 ml of $COCl_2$ as described above and the solution was heated at reflux for 70 hr. The cooled reaction mixture was filtered and the filtrate was concentrated, slurried with benzene, and again filtered. The combined precipitates yielded 34.6 g (18%) of **6**,[23] mp 243–247° dec (methyl ethyl ketone) (lit.[24] mp 240–243° dec). The filtrate was concentrated and distilled to yield 148 g (70%) of **3a**, bp 80° (0.05 mm).

A 181-g (1.20 mol) quantity of **1a** was treated with 400 ml of $COCl_2$ in the same manner, heated at reflux for 2 hr, stirred at room temperature for 15 hr, and heated at reflux for 2 hr. Work-up as above gave 67.1 g (34%) of **6** and 101 g (46%) of **3a**.

Preparation and Thermolysis of 2-Carbomethoxyanilinecarbonyl Chloride (2a). A 181-g (1.20 mol) quantity of **1a** was treated with 400 ml of $COCl_2$ as described above. A needle-like precipitate was present which dissolved with slight warming and formed again with cooling. Removal of an aliquot of the mixture and filtration separated **2a** as white needles, which were unstable in air: mp 80–82.5°; ir (Nujol) 3200 (NH), 1780 (carbamoyl C=O), 1675 cm^{-1} (ester C=O). Reaction of **2a** with excess morpholine afforded methyl 2-(3,3-oxydiethyleneuramido)benzoate,[23] mp 105–106° (hexane) (lit.[25] mp 110–112°). An ir of a concentrated aliquot of the reaction mixture showed it to be pure **2a**. A 15-ml aliquot of the solution was withdrawn and concentrated to leave 2.93 g (13.7 mmol) of **2a**, which was heated neat, under a nitrogen atmosphere, at 100° for 2.5 hr. The benzene-insoluble portion of the resulting mixture yielded 1.64 g (73%) of isatoic anhydride. The concentrated benzene filtrate yielded 550 mg of material which was shown (ir) to be mainly **3a**.

Re-treatment of 3a with Phosgene. A 15.0-g (89.6 mmol) quantity of **3a** was treated with 100 ml of $COCl_2$ as described above and stirred at room temperature for 3 days, and the mixture was heated at reflux for 22 hr. The mixture was concentrated to dryness and the semisolid was washed with benzene to leave 3.65 g (26%) of isatoic anhydride (**6**).

Preparation and Thermolysis of 2-(Carbo-*n*-butoxy)anilinecarbonyl Chloride (2b). A 29.0-g (15.0 mmol) quantity of *n*-butyl anthranilate[26] was treated with 50 ml of $COCl_2$ as described above to yield a clear solution. Evaporative crystallization of an aliquot yielded **2b** as white needles: mp 85–88°; ir (Nujol) 3200 (NH), 1780 (carbamoyl C=O), 1690 cm^{-1} (ester C=O). Reaction of **2b** with excess morpholine afforded *n*-butyl 2-(3,3-oxydiethyleneuramido)benzoate,[23] mp 54–59° (hexane) (lit.[25] mp 67–67.5°). A 50-ml aliquot of the solution was concentrated to yield 21.6 g (84.5 mmol) of pure **2b**, which was heated neat, under a nitrogen atmosphere, at 100° for 2 hr. The resulting mixture was slurried with pentane and filtered to yield 4.00 g of **6**. The filtrate was distilled (760 mm) in fractions, which were mixtures of pentane, chlorobutane, EtOAc, and EtOCOCl. Response factors for these components on a glpc system which separated them were determined as 3.58, 1.00, 1.05, and 1.07, respectively.[29] The yield of chlorobutane in the fractions was 2.88 g (37%). The material remaining in the distillation pot was again slurried with pentane and filtered to remove an additional 0.77 g of **6**. Total yield of **6** was 4.77 g (35%). The filtrate was concentrated to leave 10.1 g (54%) of *n*-butyl 2-isocyanatobenzoate (**3b**): bp 121° (0.6 mm); ir 2270 (NCO), 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.33–7.12 (m, 4, aromatic), 4.45 (t, J = 6.5 Hz, 2, OCH_3), 2.10–1.78 (m, 7, $CH_2CH_2CH_3$).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.90; H, 5.73; N, 6.25.

Preparations of Dimethyl 2,2′-[Carbonylbis(imino)]bisbenzoate (4a). A 17.7-g (10.0 mmol) quantity of **3a** and 15.1 g (10.0 mmol) of **1a** in 60 ml of benzene were heated at reflux for 15 hr, and the solution was diluted with an equal volume of hexane. Cooling resulted in the formation of large, white prisms, which were collected by filtration to yield 27.9 g (85%) of **4a**, mp 142–145° (lit.[4] mp 144°). Diester urea **4a** could also be prepared in nearly quantitative yield by treating **4a** with a mixture of water and dimethoxyethane at room temperature.

Preparation of Methyl Anthraniloylanthranilate (7b). Anthranilic acid and **6** were condensed to give anthraniloylanthranilic acid (**7a**) in 62% yield as described in the literature.[10a] Since treatment of **7a** with methanolic HCl afforded mainly **7a** HCl in our hands, **7a** was esterified with 1-methyl-3-*p*-tolyltriazine (TMT, Eastman) to afford **7b**. Thus, 6.41 g (25.0 mmol) of **7a** and 4.03 g (27.0 mmol) of TMT in 50 ml of THF were allowed to react at room temperature for 3 hr. The reaction solution was concentrated, washed with ether–hexane, and recrystallized (EtOH) to give 4.30 g (64%) of **7b** as white needles: mp 109–111°; ir (Nujol) 3495 (NH), 1695 (ester C=O), 1660 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 11.87–11.70 (broad s, 1, NH), 9.00–6.56 (m, 10, aromatic and NH_2), 3.93 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.60; H, 5.32; N, 10.41.

Preparation and Cyclization of Methyl 2-{[2-(Ethoxycarbonylamino)benzoyl]amino}benzoate. A 3.30-g (12.1 mmol) quantity of **7b** and 1.31 g (12.1 mmol) of EtOCOCl (Aldrich) in 50 ml of pyridine were heated at reflux for 4 hr. The dark solution was concentrated and the residue was taken up in CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and concentrated to leave 1.20 g (28%) of the carbamate: mp 154.5–155° (EtOH); ir (Nujol)

3270 (NH), 1730 (carbamate C=O), 1690 (ester C=O), 1650 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 9.00–6.83 (m, 8, aromatic), 4.21 (q, J = 7.2 Hz, 2, CH_2), 3.95 (s, 3, OCH_3), 1.32 (t, J = 7.2 Hz, 3, CH_2CH_3).

Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.30; H, 5.05; N, 8.50.

A 550-mg (16.0 mmol) quantity of the carbamate and 0.1 g of *p*-toluenesulfonic acid in 50 ml of benzene were heated at reflux for 15 hr. The solution was washed with H_2O, dried (Na_2SO_4), and concentrated to leave a mixture of **5a** and the carbamate, in a ratio of *ca.* 1:4, respectively. The recovered material was subjected to the same reaction conditions and work-up, substituting toluene for benzene, to give a mixture of **5a** and the carbamate, in a ratio of *ca.* 3:2, respectively. Fractional crystallization of the mixture from EtOH afforded 100 mg of the carbamate as a first crop and 150 mg of compound **5a**, mp 245–250°, as the second crop.

Preparation of 2-[1,4-Dihydro-4-oxo-2-phenyl-3(2*H*)-quinazolinyl]benzoic Acid (8a). A 12.8-g (50.0 mmol) quantity of amino acid **7a** and 5.41 g (51.0 mmol) of benzaldehyde in 100 ml of EtOH were heated at reflux for 4 hr. Cooling caused a precipitate to form which was collected to yield 15.1 g (86%) of **8a**: mp 171–173°; ir (Nujol) 3300–2400 (OH), 3280 (NH), 1690 (acid C=O), 1625 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 10.04 (s, 1, OH, D_2O exchangeable), 8.92–6.56 (m, 13, aromatic), 6.31 (s, 1, methine), 5.67–5.33 (broad s, 1, NH, D_2O exchangeable).

Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.64; H, 5.07.

Acid **8a** was converted into ester **8b** in 58% yield with TMT using the procedure described in the preparation of **7b.**

Preparation of Methyl 2-[1,4-Dihydro-4-oxo-2-phenyl-3(2*H*)-quinazolinyl]benzoate (8b). A 3.00-g (11.1 mmol) quantity of amino ester **7b** and 1.27 g (12.0 mmol) of benzaldehyde in 25 ml of EtOH were heated at reflux for 6 hr. The solution was concentrated and the resulting solid was recrystallized (EtOH) to give 2.40 g (63%) of **8b**: mp 169–171°; ir (Nujol) 3280 (NH), 1720 (ester C=O), 1635 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.06–6.36 (m, 8, aromatic), 6.20 (s, 1, methine), 5.18–4.80 (broad s, 1, NH, D_2O exchangeable), 3.73 (s, 3, CH_3).

Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06, N, 7.82. Found: C, 74.00; H, 5.09; N, 7.90.

Preparation of 2-[4-Oxo-3(4*H*)-quinazolinyl]benzoic Acid (9a). A 7.00-g (27.3 mmol) quantity of amino acid **7a** in 15 g of triethyl orthoformate (Aldrich) was heated at reflux for 20 hr. The mixture was cooled and filtered to remove 6.80 g (98%) of amino acid **9a**: mp 279–281° (lit.[30] mp 273–274°); ir (Nujol) 2700–2200 and 2000–1800 (protonated imine), 1690 cm^{-1} (C=O groups).

Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.90; H, 3.88; N, 10.39.

Acid **9a** was converted into ester **9b** in 92% yield with TMT using the procedure described in the preparation of **7b.**

Preparation of Methyl 2-[4-Oxo-3(4*H*)-quinazolinyl]benzoate (9b). A 3.00-g (11.7 mmol) quantity of amino ester **7b** in 7 ml of triethyl orthoformate was heated at reflux for 16 hr. The reaction solution was concentrated and recrystallized (EtOH) to yield 2.35 g (73%) of **9b**: mp 173–174° (lit.[30] mp 171–172°); ir (Nujol) 1720 (ester C=O), 1685 (amide C=O), 1615 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{21}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.30; H, 4.51; N, 10.21.

Preparation of 5a and 2-[1,4-Dihydro-2,4-dioxo-3(2*H*)-quinazolinyl]benzoic Acid (10) from 4a. A 5.00-g (15.2 mmol) quantity of diester urea **4a** was mixed with 50 g of polyphosphoric acid (PPA) and stirred at 110–120° for 90 min. The yellow reaction solution was poured into aqueous Na_2CO_3 and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The extracts were dried (Na_2SO_4) and concentrated to a small volume, and the crystalline solid which formed was collected to give 1.25 g (27%) of pure **5a**, mp 174–175°.

The aqueous phase was acidified (concentrated HCl) and the precipitated solid was removed by filtration to yield 2.60 g (60%) of **10**: mp 303–305° (EtOH) (lit.[31] mp 298–300°); ir (Nujol) 3400–2300 (OH), 1710 (acid C=O), 1675 (amide C=O), 1650 cm^{-1} (urea C=O).

Acid **10** was converted into ester **5a** in 95% yield with TMT using the procedure described in the preparation of **7b.**

Preparation of Methyl 2-[(4-Oxo-4*H*-3,1-benzoxazin-2-yl)-amino]benzoate (11). A 5.00-g (15.2 mmol) quantity of diester urea **4a** was mixed with 50 g of PPA in a stoppered reaction vessel and stirred at room temperature for 7 days. The clear reaction solution was poured into aqueous Na_2CO_3 and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 ml). The extracts were dried (Na_2SO_4) and concentrated to leave 4.00 g (89%) of pure **11**: mp 174–175° (EtOH); ir (Nujol) 3250–3000 (NH), 1765 (benzoxazinone C=O), 1695 (ester C=O), 1645 cm^{-1} (C=N); nmr ($CDCl_3$) δ 10.96 (broad s, 1, NH), 9.06–6.90 (m, 8, aromatic), 3.93 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 65.20; H, 4.25; N, 9.45.

Reactions of 11 with PPA. A 2.00-g (6.75 mmol) quantity of benzoxazinone **11** was mixed with 35 g of PPA and heated at 90° for 90 min. Work-up of the clear solution as above afforded 850 g (42%) of recovered **11** from the CH_2Cl_2 extract and 800 mg (42%) of acid **10** from the acidified aqueous phase.

A 700-mg (2.36 mmol) quantity of **11** was mixed with 20 g of PPA and heated at 120° for 90 min. Work-up of the clear solution as above afforded 100 mg (13%) of a mixture of **11** and **5a** from the CH_2Cl_2 extract and 39.5 mg (56%) of acid **10** from the acidified aqueous phase.

Reactions of 5a with PPA. A 5.00-g (16.8 mmol) quantity of ester **5a** was mixed with 50 g of PPA and heated at 80° for 90 min. The clear solution was poured into aqueous Na_2CO_3 and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The extracts were dried (Na_2SO_4) and concentrated to leave 4.40 g (88%) of pure **5a.**

When a 5.00-g (16.8 mmol) quantity of ester **5a** was treated with 50 g of PPA at 120° for 90 min, work-up of the clear solution as above yielded 2.29 g (46%) of recovered **5a.** Acidification of the aqueous phase precipitated a white solid which was collected and dried to yield 1.99 g (42%) of acid **10.**

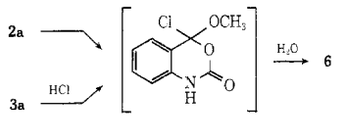
Acknowledgment. The authors are grateful to Dr. D. L. Trepanier and Professor E. C. Campaigne for helpful discussions, and T. McGowan and W. Braun for spectral data.

Registry No.—**1a,** 134-20-3; **1b,** 7756-96-9; **2a,** 51310-17-9; **2b,** 51310-18-0; **3a,** 1793-07-3; **3b,** 51310-19-1; **4a,** 51364-45-5; **5a,** 13905-97-0; **6,** 188-48-9; **7a,** 612-34-0; **7b,** 49854-16-2; **8a,** 51310-20-4; **8b,** 51364-46-6; **9a,** 25380-15-8; **9b,** 51310-21-5; **10,** 1701-95-7; **11,** 51310-22-6; methyl 2-{[2-(ethoxycarbonylamino)benzoyl]amino}-benzoate, 51310-23-7.

References and Notes

(1) (a) D. L. Hunter, K. Kitasaki, R. F. Crawford, and C. W. Le Fevre, French Patent 1,542,354; *Chem. Abstr.*, **71**, 81196j (1969); (b) R. H. Rish, British Patent 1,139,627; *Chem. Abstr.*, **70**, 68420n (1969); (c) Netherlands Patent 6,407,857; *Chem. Abstr.*, **63**, 538*d* (1965).
(2) The preparations in ref 1 specify a filtration step prior to concentration of the isocyanate solution. The material being removed is undoubtedly isatoic anhydride.
(3) Diester urea **4a** can be made directly (as the major reaction product) by treating phosgene with methyl anthranilate in a 1:2 stoichiometric ratio, respectively. See ref 4.
(4) J. A. Murray and F. B. Dains, *J. Amer. Chem. Soc.*, **56**, 144 (1934).
(5) (a) R. P. Staiger, C. L. Moyer, and G. R. Pitcher, *J. Chem. Eng. Data*, **8**, 454 (1963); (b) K. Srivastava, *Indian J. Appl. Chem.*, **34**, 113 (1971).
(6) T. Kappe, W. Steiger, and E. Ziegler, *Monatsh. Chem.*, **98**, 214 (1967).
(7) British Patent 1,059,271 (1967).
(8) B. Loev, U. S. Patent 3,149,106; *Chem. Abstr.*, **61**, 14684*g* (1964).
(9) (a) R. H. Fish, British Patent 1,139,627; *Chem. Abstr.*, **70**, 68420n (1969). (b) French Patent 1,516,600; *Chem. Abstr.*, **70**, 96819t (1968). (c) *o*-Carboxyphenylureas have been used in this conversion as well. See S. Tohyama, M. Kurihara, and N. Yoda, *Bull. Chem. Soc. Jap.*, **43**, 1246 (1970).
(10) (a) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959); (b) A. Mohr, *J. Prakt. Chem.*, **79**, 295, 320 (1909).
(11) E. H. White, A. A. Baum, and D. E. Eitel, *Org. Syn.*, **48**, 102 (1968).
(12) (a) J. Bernstein and E. R. Spitzmiller, U. S. Patent 3,271,400; *Chem. Abstr.*, **65**, 18601*c* (1966); (b) B. V. Shetty, U. S. Patent 3,557,111; *Chem. Abstr.*, **74**, 141846v (1971); (c) U. S. Patent 3,637,681 (1972).
(13) (a) R. Alaimo and H. Russel, *J. Med. Chem.*, **15**, 335 (1972); (b) Belgian Patent 767,290 (1971); (c) E. Cohen and B. Klarberg, U. S. Patent 3,065,235; *Chem. Abstr.*, **58**, 6843*e* (1962); (d) H. Gurien and T. P. Gordon, U. S. Patent 3,162,636; *Chem. Abstr.*, **62**, 5285*f* (1964); (e) J. L. Rodgers and J. P. Milionis, U. S. Patent 3,169,129; *Chem. Abstr.*, **62**, 14696*a* (1965); (f) J. L. Rodgers and J. P. Milionis, U. S. Patent 3,269,955; *Chem. Abstr.*, **65**, 13735*d* (1966).

(14) J. W. Bolger, U. S. Patent 3,257,397; *Chem. Abstr.*, **65**, 8933*b* (1966).
(15) The NH protons in **8a** and **8b** are readily exchanged with D_2O, and are apparently exchanging too rapidly in solution for splitting of the methine protons to be observed.
(16) It is interesting to note that imino acid **9a** exists as a zwitterion. The infrared spectrum (Nujol) of **9a** shows two broad bands at 2700–2200 and 2000–1800 cm, characteristic of the protonated imine moiety.[17]
(17) (a) B. Witkop, *Experientia*, **10**, 420 (1954); (b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 260.
(18) G. Doleschall and K. Lempert, *Acta Chim. Acad. Sci. Hung.*, **48**, 77 (1966).
(19) Mechanisms which require water were necessarily excluded because of the anhydrous reaction conditions. Isatoic anhydride (**6**) was formed *in situ*, which eliminated the possibility of an intermediate such as i being converted to **6** on exposure to moisture during work-up.



i

(20) The 28-day reaction in Scheme I was monitored by ir. During the first half of the reaction, the concentration of **2a** was greater than that of **3a**, and the converse was true during the latter half. Therefore, it is conceivable that both **2a** and **3a** contributed to the formation of **6**.
(21) (a) S. M. McElvain and B. E. Tate, *J. Amer. Chem. Soc.*, **73**, 2233 (1951); (b) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).
(22) (a) H. Leuchs, *Ber.*, **39**, 857 (1906); (b) H. Leuchs and W. Manasse, *ibid.*, **40**, 3235 (1907); (c) H. Leuchs and W. Gieger, *ibid.*, **41**, 1721 (1908).
(23) A satisfactory elemental analysis was obtained.
(24) (a) R. H. Clark and E. C. Wagner, *J. Org. Chem.*, **9**, 55 (1944); (b) E. C. Wagner and M. F. Fegley, *Org. Syn.*, **27**, 45 (1947).
(25) D. L. Hunter, K. Kitasaki, and C. W. Hunter, French Patent 1,509,718; *Chem. Abstr.*, **70**, 37822*r* (1969).
(26) *n*-Butyl anthranilate was prepared from anthranilic acid in the usual manner[27] in 44% yield, bp 135° (1.3 mm) [lit.[28] bp 182° (760 mm)].
(27) A. J. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1956, p 1000.
(28) H. C. Brill, *J. Amer. Chem. Soc.*, **43**, 1320 (1921).
(29) The glpc system of choice was 5% Carbowax 20M, 8 ft × 0.125 in., 50°, 30 cc/min of He.
(30) C. Runti, C. Nisi, and L. Sindellari, *Ann. Chim. (Rome)*, **51**, 719 (1961).
(31) G. Doleschall and K. Lempert, *Monatsh. Chem.*, **95**, 1083 (1964).

Carbon Magnetic Resonance Spectra of 2-Pyrones

W. V. Turner and W. H. Pirkle*

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received January 14, 1974

The cmr spectra of 21 2-pyrones or sulfur-containing analogs of 2-pyrones are assigned by selective proton decoupling, multiplicity, and uniformity of chemical shift or J_{CH} values. Cmr spectroscopy is a useful tool in establishing the structures of unknown 2-pyrones, complimenting pmr spectroscopy in this regard.

Substituted 2-pyrones occur commonly in nature, and this ring system has recently been found to have synthetic value and to undergo highly varied thermal and photochemical reactions. Our interest in 2-pyrones led to pmr studies[1] which we have now extended to cmr. Just as proton–proton coupling constants often allow unique assignment of 2-pyrone substitution patterns, carbon-13 chemical shifts and carbon-13 proton coupling constants prove to be especially informative, thus strongly complementing pmr as a tool for 2-pyrone characterization. Several sulfur-containing analogs of 2-pyrones have been included in this study for comparative purposes.

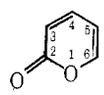
Experimental Section

Most of the 2-pyrones used in this study have been described previously. The thiones were prepared by action of P_2S_5 on the corresponding pyrones; thiapyran-2-ones were prepared by thermal isomerization of thiones.[2]

Cmr spectra were obtained with a Varian Associates Model XL-100-15 25.1-MHz spectrometer coupled with a Digilab NMR-3 Fourier transform system. The samples were quite concentrated (1.5–5.5 *M*) to minimize the time required to obtain selectively decoupled or undecoupled spectra. In several instances, solvents other than chloroform-*d* were used for increased solubility or for optimum separation of proton resonances for selective decoupling. Both 2-pyrone and 4,6-dimethyl-5-carbethoxy-2-pyrone were run almost neat (10% internal acetone-d_6 was used as a lock signal) to allow the recording of spectra in the continuous wave mode.

Results

Table I records chemical shifts for 2-pyrone ring carbons as parts per million downfield of TMS. The compounds in part A of the table are unsubstituted or monosubstituted pyrones (or sulfur analogs) for which each unsubstituted carbon resonance was identified by selective proton decoupling. Since the carbonyl carbon (C-2) chemical shift remains almost constant, the assignment of the substituted carbon is apparent.



2-pyrone

Like the corresponding proton resonances, the C-4 and C-6 resonances of 2-pyrone are downfield of those of C-3 and C-5. This order has also been observed in 2-pyridone.[3]

Single-bond carbon-13 proton coupling constants (J_{CH}, hertz) for most of the 2-pyrones appear in parentheses in Table I. They provide a means of identifying C-6 when it bears hydrogen. The ranges of values of J_{CH} for C-3 and C-5 are similar and larger than the usual values for C-4, although some overlapping occurs. The values for 2-pyrones may be compared with J_{CH} for 4-pyrone (200 Hz for C-2 and 169 Hz for C-3)[4] and furan (201 Hz for C-2 and 175 Hz for C-3).[5] A value of *ca.* 200 Hz is typical for J_{CH} of carbon atoms attached to oxygen in aromatic heterocycles.[6] J_{CH} values for sulfur analogs of 2-pyrones are similar to those of 2-pyrone, except that J_{CH} for C-6 of the thiapyran derivatives is *ca.* 180 Hz. (*Cf.* J_{CH} of 185 Hz for the α carbons of thiophene.[6]) Two exceptions to this pattern emerge from Table I. The unusually small J_{CH} of C-3 of 4-methylthiapyran-2-one and the unusually large J_{CH} for C-4 of coumalyl chloride are unexplained.

Significant longer range coupling is also observed, but this varies with the nature of the substituents. Thus, in 4-methyl-2-pyrone C-6 is coupled (J = 7 Hz) to some proton other than H-6, while in 4-methyl-6-chloro-2-pyrone the C-6 resonance is a singlet (J < 1 Hz). Because of