C. 3-(2′-Pyridyl)-, 3-(3′-Pyridyl)-, and 3-(4′-Pyridyl)thiophene (IV, V, and VI).—Over a period of 15 min a solution of 10 g (0.063 mol) of bromopyridine in 25 ml of dry ether was added to a well-stirred solution of 0.063 mol of *n*-butyllithium in 32 ml of hexane diluted with 100 ml of dry ether under a nitrogen atmosphere. During the addition the temperature was maintained between −75 and −60°. After a second 15-min period of stirring, a solution of 6.4 g (0.063 mol) of 3-ketotetrahydrothiophene[15] in 25 ml of dry ether was added in 15 min. The stirring of the gray suspension was continued for another 15-min period raising the temperature to −40°. The reaction mixture was poured into 100 ml of water and the aqueous layer was extracted with ether (in the case of the 4-pyridyl compound chloroform must be used). The combined organic layers were dried ($CaCl_2$) and the solvent was evaporated. Removal of unused ketone through distillation at the water pump [up to 85° (20 mm)] left 6.0–8.0 g (0.033–0.044 mol, 52–70%) of a viscous oil (for the 4-pyridyl compound a solid), mainly the tertiary carbinol.

This oil was heated with 2.5 g of sulfur and 2.0 g of $KHSO_4$. At 160° water began to distil from the reaction mixture and hydrogen sulfide was evolved. The heating was continued for 30 min and the temperature was slowly raised to 225°. Steam distillation of the reaction mixture yielded crystalline plates of 3-(3′-pyridyl)- and 3-(4′-pyridyl)thiophene (V and VI). With the 2-pyridyl compound an oil was obtained, which was further purified through preparative tlc on silica gel (Merck PF-254) with chloroform as eluent to remove some unchanged carbinol. Distillation furnished an analytical sample of 3-(2′-pyridyl)-thiophene (IV), bp 93–95° (0.45 mm). See Table III for analytical data.

TABLE III

Compd	Mp, °C	Overall yield, %	Analysis, % Found C	H	N	S
IV	27–28	10	67.16	4.50	8.59	19.71
V	75–76.5	10	66.70	4.39	8.59	19.94
VI	138.5–139	2	66.99	4.41	8.62	19.75
			Calcd for C_9H_7NS			
			67.12	4.38	8.68	19.92

(15) F. A. Buiter, J. H. Sperna Weiland, and H. Wynberg, *Rec. Trav. Chim.*, **83**, 1160 (1964).

Bromopyridines.—The 2- and 3-bromopyridines were commercially available. The unstable[16] 4-brompyridine was obtained from the commercially available hydrogen chloride salt through addition of an equimolar amount of concentrated sodium hydroxide solution at 0°. Extraction with ether, drying of the organic layers (Na_2SO_4), and evaporation of the solvent below 30° yielded almost pure 4-bromopyridine. Because of its instability, it was used immediately for further reactions.

Desulfurizations.—The desulfurizations were accomplished by refluxing the individual highly purified pyridylthiophenes (I, II, III, and V) with 10 times their weight of Raney nickel W-5[17] in absolute ethanol for 30 min. The Raney nickel was removed by filtration through a glass filter and was washed carefully with absolute ethanol. The concentrated filtrates were dissolved in ether and dried ($CaCl_2$). Evaporation of the solvent yielded a crude oil giving pmr spectra (Table IV) consistent with butylpyridines (25–70%).

TABLE IV

Desulfurization product of	Pmr spectra Aromatic	Alkyl
I	1.7 (t–t) (1), 2.2–3.2 (m) (3)	7.2 (t) (2), 8.0–8.9 (m) (4), 9.0 (t) (3)
II	1.7 (s) (2), 2.5–3.2 (m) (2)	7.5 (t) (2), 8.2–8.9 (m) (4), 9.1 (t) (3)
III	1.7 (d) (2), 3.1 (d) (2)	7.6 (t) (2), 8.1–8.8 (m) (4), 9.1 (t) (3)
V	1.7 (s) (2), 2.4–3.1 (m) (2)	7.2 (m) (1), 8.0–8.8 (m) (5), 9.0 (t) (3)

Registry No.—I, 3319-99-1; II, 21298-53-3; III, 21298-54-4; IV, 21298-55-5; V, 21308-81-6; VI, 21308-82-7; 2-phenylpyridine, 1008-89-5; 3-phenylpyridine, 1008-88-4; 4-phenylpyridine, 939-23-1.

(16) J. P. Wibaut, J. Overhoff, and H. Geldof, *ibid.*, **54**, 807 (1935).

(17) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., p 176.

An Unusually Facile Anilide Ethanolysis

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Received April 7, 1969

Refluxing ethanol promptly converts the 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilides (Ia–e) into ethyl 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxylate (II) in good yields. The facility with which this ethanolysis occurs appears to be related to the higher energy state of I relative to II. Lack of enol character of I, presumably due to steric hindrance, and the hydrogen-bonded stabilization of its enolate anion (V) impart substantial acidic character to this molecule, and this property provides the proton which is believed to catalyze the ethanolysis.

Treatment of carboxylic acid esters with amines is generally a convenient method for the preparation of amides.[1] Alcohols, which often facilitate this reaction,[2,3] are generally considered to be sufficiently poor nucleophiles as to allow the intermediate tetrahedral complex formed by nucleophilic attack of an amine on carbonyl carbon to lead, irreversibly, to amide formation.[4] Furthermore, the inertness of alcohols toward amides and anilides frequently suggests their use as recrystallization solvents.[5]

Quite unexpectedly, therefore, in the course of purifying 2′-chloro-2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ib) it was discovered that refluxing ethanol converted this substance into ethyl 2-methyl-1,3-(2H,4H)-dioxoisoquinoline-4-carboxylate (II) in a yield of better than 90% and this unusual alcoholysis was subsequently found to be characteristic for related anilides (Table I). To gain insight into the mechanism of this uncommon and extraordinarily facile reaction, the physical properties of these anilides and related substances were investigated.

The 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-car-

(1) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1953, p 568.

(2) R. L. Betts and L. P. Hammett, *J. Amer. Chem. Soc.*, **59**, 1568 (1937).

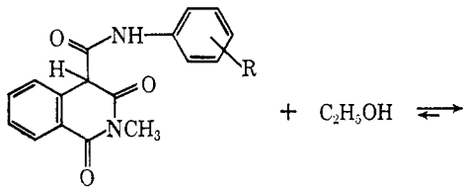
(3) R. Baltzly, I. M. Berger, and A. A. Rothstein, *ibid.*, **72**, 4149 (1950).

(4) J. F. Bunnett and G. T. Davis, *ibid.*, **82**, 665 (1960).

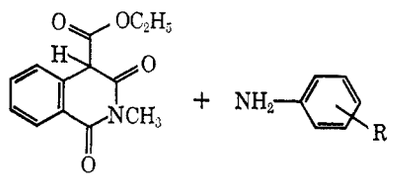
(5) S. M. McElvain, "The Characterization of Organic Compounds," Rev. Ed., The Macmillan Co., New York, N. Y., 1945, pp 141, 189.

TABLE I

pK_a' VALUES AND ETHANOLYSIS RESULTS OF SUBSTITUTED 2-METHYL-1,3(2H,4H)-DIOXOISOQUINOLINE-4-CARBOXANILIDES



I



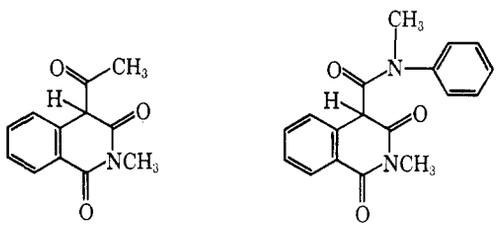
II

Compound	R	pK_a' [a]	Yield of II, %
Ia	H	5.68	42
Ib	2-Cl	4.38	94
Ic	2-OCH_3	5.49	71
Id	2-CH_3	5.36	64
Ie	4-NO_2	insoluble	81

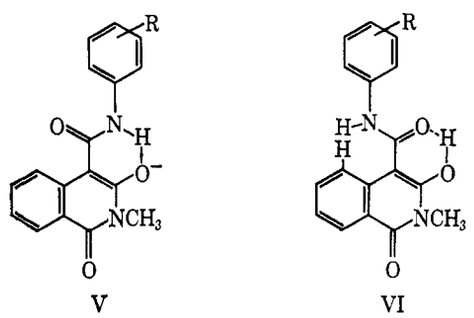
[a] See Experimental Section.

boxanilides are unexpectedly strong acids (Table I). Specifically, they are substantially more acidic than II (pK_a' = 7.15) or 4-acetyl-2-methylisoquinoline-1,3-(2H,4H)-dione (III) (pK_a' = 6.60). Since a carbamoyl moiety is inferior to an acetyl or a carbethoxy function in its electron-withdrawing properties,[6,7] it appeared that the reasons for the acidity of compounds of type I might be related directly to the facility with which they undergo ethanolysis.

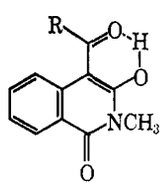
The nmr spectra of the carboxanilides are consistent with a keto rather than an enol configuration. For example, the spectrum of Ia exhibits a singlet at τ 6.75 (N-methyl), a singlet at 4.5 (methine hydrogen), an aromatic multiplet, and a signal at −0.5 (amide hydrogen). That the assignments of the methine and amide hydrogens are as indicated was confirmed by the nmr spectrum of N,2-dimethyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (IV) which is quite similar to that of Ia except that there is no signal downfield from the aromatic multiplet. Although the spectra were generally obtained, for solubility purposes, in deuterated dimethyl sulfoxide, a solvent which, in comparison with less polar solvents, is not expected to favor an intramolecularly hydrogen-bonded enolic configuration,[8] a few compounds were sufficiently soluble to be examined in deuterated chloroform in which case the nmr spectra showed little change from those obtained in the former solvent. Contrary to those of the carboxanilides, the nmr spectra of II and III exhibit chemical shifts which are expected for compounds having strongly bonded enolic configurations. The enolic proton of the former appears at τ −5.9 (CCl_4) and that of the latter at −6.8 (CCl_4). Evidently, part of the reason for the enhanced acidity of I compared with that of II and III is that ionization of I results in the formation of a planar, conjugated anion (V) in which π-orbital overlap is maximal. This contrasts with the nonplanar keto configuration of I which, because of the steric effect which would be engendered between the hydrogen on the anilide nitrogen and the hydrogen at position 5 of the isoquinolinedione moiety, cannot assume the low energy, resonance-stabilized enol configuration (VI) similar to that which occurs in II and III (VII).



III IV



V VI



VII, R = CH_3, OC_2H_5

Therefore, in the case of I, but not of II and III, ionization is probably enhanced by the formation of an anion which is configurationally more stable than its conjugate acid.

When II was refluxed with aniline or *o*-chloroaniline in ethanol, the corresponding carboxanilides were detected (tlc) in trace amounts although the ester was recovered almost quantitatively. Thus, II is the favored product under equilibrating conditions despite the greater nucleophilicity of aniline compared with that of ethanol,[9,10] lending additional credence to the postulated energy differences between I and II. As anticipated, conventional aminolysis of II in xylene proved to be a successful route to the synthesis of compounds of type I provided that ethanol was removed from the reaction mixture.

A second feature contributing to the enhanced acidity of I is noted when the pK_a' values of 23 anilides of structure I substituted in the *ortho*, *meta*, and *para* positions of the anilide moiety are plotted against the pK_a values of the correspondingly substituted anilines.[11] A straight line of slope 0.48 (correlation coefficient,

(6) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).
(7) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(8) M. T. Rogers and J. L. Burdett, *Can. J. Chem.*, **43**, 1516 (1965).
(9) C. G. Swain, D. C. Dittmer, and L. E. Kaiser, *J. Amer. Chem. Soc.*, **77**, 3737 (1955).
(10) Although Wepster and Verkade [*Rec. Trav. Chim.*, **67**, 425 (1948)] showed that 2′-nitroacetanilide undergoes methoxide ion catalyzed methanolysis, we have found that 2′-chloroacetoacetanilide [H. E. Fierz-David and E. Ziegler, *Helv. Chim. Acta*, **11**, 776 (1928)], a β-ketoanilide bearing some structural similarity to Ib, is recovered unchanged after refluxing in ethanol for 5 hr; no trace (tlc) of ethyl acetoacetate was detected.
(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 7.

0.97) is obtained. This indicates that the substituent effect upon the electron density about the aniline nitrogen is proportional to its effect upon the acidity of I, and that the latter effect is probably manifested by means of a hydrogen bond from the enolate anion oxygen to the hydrogen on the anilide nitrogen (V). A similar type of enolate anion stabilization has been proposed to explain the difference in acidity between N-salicoylmesitamide and salicylamide.[12] The fact that IV ($pK_a' = 7.57$) is much less acidic than Ia–d also emphasizes the acid-enhancing effect of the hydrogen on the anilide nitrogen.

In conclusion, the unusual ease with which compounds of type I undergo ethanolysis seems to be related to the substantially higher energy state in which they exist relative to the reaction product. The lack of enol character of I, presumably due to steric hindrance, and the relatively greater stability of the planar, conjugated anion (V) resulting upon ionization of I impart substantial acidic character to this molecule, and this intrinsic acidity provides the proton which is probably required to catalyze the ethanolysis.[13]

Experimental Section

Nmr spectra were recorded on a Varian A-60 spectrometer and are reported as τ values relative to tetramethylsilane as an internal standard. Melting points are uncorrected. pK_a' determinations were performed in 1:2 water–dioxane using a Metrohm Potentiograph. Isocyanates used were commercial materials. Each of the carboxanilides gave a positive ferric chloride test.

2-Methylisoquinoline-1,3(2H,4H)-dione.[14]—A solution of homophthalic acid in aqueous methylamine was evaporated to dryness under reduced pressure and the residue was heated for 1 hr in an oil bath at 180–190°. The melt was poured into ethanol from which crystals, mp 122–124°, were obtained (lit.[15] mp 123°).

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ia).—A refluxing solution of 35.0 g (0.2 mol) of 2-methylisoquinoline-1,3(2H,4H)-dione and 21.2 g (0.21 mol) of triethylamine in 250 ml of dry tetrahydrofuran was treated, dropwise, with a solution of 25.0 g (0.21 mol) of phenyl isocyanate in 10 ml of dry tetrahydrofuran. Refluxing was continued for 1.5 hr after addition of the isocyanate was complete. The red-brown solution was poured into a stirred ice–water mixture containing 28 ml of hydrochloric acid. The resulting precipitate was filtered, washed with water, dried, and recrystallized from acetonitrile to yield 32.0 g (55%) of white crystals, mp 243–244° dec.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.52; H, 4.81; N, 9.51.

2′-Chloro-2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ib).—Ib was prepared in 54% yield as described for Ia except that *o*-chlorophenyl isocyanate was employed: mp 212–213° dec (acetonitrile).

Anal. Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.10; H, 3.98; N, 8.52. Found: C, 61.99; H, 3.97; N, 8.47.

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carbox-*o*-anisidide (Ic).—Ic was prepared in 42% yield as described for Ia except that *o*-methoxyphenyl isocyanate was employed: mp 197–198° dec (acetonitrile).

Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.69; H, 5.02; N, 8.71.

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carbox-*o*-toluidide (Id).—A mixture of 4.4 g (0.025 mol) of 2-methylisoquinoline-1,3(2H,4H)-dione and 2.6 g (0.026 mol) of triethylamine in 20 ml of dry dimethyl sulfoxide was treated, dropwise, with 3.5 g (0.026 mol) of *o*-tolyl isocyanate. The resulting solution was stirred at room temperature for 3 hr and then poured into an ice–water mixture containing 5 ml of 6 *N* hydrochloric acid. The precipitate which formed was filtered, dried, and recrystallized from acetonitrile to yield 5.1 g (73%) of white crystals, mp 221–223° dec.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.45; H, 5.19; N, 9.17.

4′-Nitro-2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxanilide (Ie).—A solution of 4.94 g (0.02 mol) of ethyl 2-methyl-1,3-(2H,4H)-dioxoisoquinoline-4-carboxylate and 3.0 g (0.022 mol) of *p*-nitroaniline in 100 ml of xylene was refluxed for 4.5 hr during which time solvent was slowly removed by means of a still head. A precipitate began to form as the mixture approached reflux temperature and became heavier with time. When the mixture had cooled, the precipitate was filtered and dried to yield 6.0 g (88%), mp 235–236° dec. Attempted recrystallizations were unsuccessful.

Anal. Calcd for $C_{17}H_{13}N_3O_5$: C, 60.17; H, 3.86; N, 12.39. Found: C, 60.45; H, 3.88; N, 12.74.

2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carbox-N-methylanilide (IV).—A solution of 2.5 g (0.01 mol) of ethyl 2-methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxylate and 1.1 g (0.01 mol) of N-methylaniline in 25 ml of xylene was refluxed for 1 hr during which time solvent was slowly removed by means of a still head. The reaction mixture was chilled in an ice bath while 15 ml of hexane was added. The resulting precipitate was filtered, dried, and recrystallized from benzene–hexane to yield 1.8 g (58%) of white crystals, mp 160–162°.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.86; H, 5.22; N, 9.06.

Ethyl 2-Methyl-1,3(2H,4H)-dioxoisoquinoline-4-carboxylate (II).—A solution of 16.4 g (0.05 mol) of Ib in 125 ml of ethanol was refluxed for 4 hr after which time *ca.* half of the ethanol was allowed to evaporate. Cooling produced white needles which were recrystallized from ethanol to yield 11.5 g (94%) of material, mp 113–115° (positive ferric chloride test).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.07; H, 5.33; N, 5.65.

Ethanolyses of other compounds in Table I were effected by a similar procedure, using tlc to follow the course of the reaction.

A solution of 8.75 g (0.05 mol) of 2-methylisoquinoline-1,3-(2H,4H)-dione in 80 ml of dry tetrahydrofuran was added to a stirred suspension of 4.45 g of a 59.5% mineral oil dispersion of sodium hydride in 15 ml of dry tetrahydrofuran and the resulting suspension was treated over 45 min with a solution of 6.0 g (0.055 mol) of ethyl chloroformate in 10 ml of the same solvent. A tan suspension developed during 19 hr of stirring at room temperature after which time the reaction mixture was poured into an ice–water mixture containing 20 ml of 6 *N* hydrochloric acid. The resulting precipitate was filtered, dried, and recrystallized three times from ethanol to yield 2.0 g (16%) of white crystals, mp 111–113° (positive ferric chloride test) whose infrared spectrum was superimposable on that of the material obtained by anilide ethanolysis.

4-Acetyl-2-methylisoquinoline-1,3(2H,4H)-dione (III).—This compound was prepared by the method of Bailey and Swallow:[15] mp 115–117° (lit.[15] mp 115°).

Registry No.—Ia, 21389-75-3; Ib, 21389-76-4; Ic, 21389-77-5; Id, 21389-78-6; Ie, 21389-79-7; II, 21389-80-0; IV, 21389-81-1.

(12) R. M. Topping and D. E. Tutt, *J. Chem. Soc., B*, 1346 (1967).

(13) The possibility also exists that the ethanolysis proceeds through a ketene intermediate similar to that recently proposed by Bruice and Holmquist [*J. Amer. Chem. Soc.*, **90**, 7136 (1968)] for the hydrolysis of malonate and cyanoacetate esters.

(14) S. Gabriel, *Ber.*, **19**, 2363 (1886).

(15) A. S. Bailey and D. L. Swallow, *J. Chem. Soc.*, 2477 (1956).