Acylanthranils. 4. The Effect of Steric Hindrance on Selectivity in the Reaction of Amines with Acetylanthranil[1]

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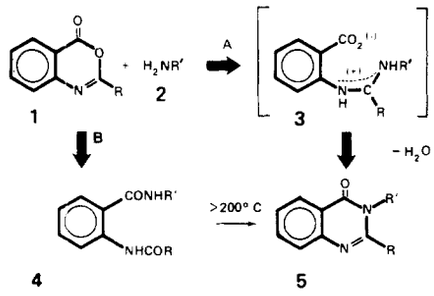
Acetylanthranil (1) was made to react with a set of 17 amines to give acetamidines, **3**, via pathway A, and/or *o*-acetamidobenzamides, **4**, via pathway B as shown in Scheme I. Simple primary amines, such as ethylamine and aniline, follow pathway A, whereas secondary amines and those primary amines with substituents on the α-carbon atom, such as *tert*-butylamine or isopropylamine, follow pathway B. The rate of conversion to products **3** and/or **4** varies directly with pK_a, but inversely with the bulk of the amine substituents. These results show that both the steric and electronic contributions are important factors that determine overall reactivity via either pathway, but only the steric factor has a significant effect on selectivity.

In our previous publications[2-4] concerned with the reinvestigation of the reaction of acylanthranils, **1**, with amines, **2**, we reported that the products, ortho-substituted benzamides (**4**) and/or quinazolones (**5**), are not formed sequentially (**5** from **4**) as was assumed by the early investigators, but rather are formed competitively via alternative pathways A and B as illustrated in Scheme I. We showed that the precursors of **5** are in fact novel amidine salt intermediates, **3**, which undergo cyclodehydration in solution even at room temperature. In contrast to this facile conversion, temperatures in excess of 200 °C are required to effect cyclodehydration of **4** to give **5**.

Scheme I



We observed[3,4] that the product distribution obtained with a given amine is markedly dependent upon the substituent R at the 2 position of the benzoxazone, **1**. The selectivity ratio for reaction via pathway A to pathway B, i.e., k_A/k_B = (**3** and/or **5**)/**4**, as well as the rate of conversion to products, decreases with increase in bulk of R, showing that steric hindrance on the part of the acylanthranil is a major factor that determines selectivity. Thus, the selectivity ratio with reference to aniline is >50/1 for acetylanthranil (**1a**, R = CH_3), whereas at the other extreme it is <1/25 for benzoylanthranil (**1b**, R = Ph). We noted that substituents at other positions on the aromatic ring increase or decrease only the overall rate of reaction with the given amine, depending upon their respective electronic contribution to the electrophilic centers at the 2 and 4 positions, but do not alter significantly the selectivity manifested by the parent acylanthranil.[4] Thus, all reported reactions of benzoylanthranils with an amine follow pathway B, whereas all but two reported reactions of acetylanthranils with an amine followed pathway A. The exceptions are (1) the reaction of 7-acetamidoacetylanthranil with 2-aminobutane to give in good yield the corresponding 2,4-diacetamidobenzamide as reported by Bogert,[5] and (2) the reaction of acetylanthranil with anthranilic acid to give in good yield *o*-(*o*-acetamidobenzamido)benzoic acid as reported by us.[3]

We suggested[4] that perhaps both exceptions are due to steric hindrance on the part of the coreactant amine. We now report results obtained with acetylanthranil and a large set of aliphatic amines, which show that steric hindrance on the part of the amine is indeed a major factor that influences reaction selectivity.

Results and Discussion

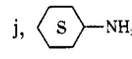
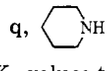
Acetylanthranil (**1a**, R = CH_3) was made to react with the set of amines, **2a–q**, either neat or in a nonpolar solvent. The product mixtures were separated according to the material balance procedure described previously,[3] and usually accounted for more than 95% of the starting materials added in equivalent amounts. The percent acetylanthranil units isolated as **3**, **4**, and **5** were then used to calculate the corresponding selectivity ratio for reaction via pathway A relative to pathway B (i.e., k_A/k_B). The data are collected in Table I and the supporting characterization data are collected in Table II. Unreacted acetylanthranil was either recovered per se (example **d**) or isolated as *o*-acetamidobenzoic acid, which was produced by reaction with water as part of the postreaction separation procedure (examples **g, i, j, k, p,** and **q**). The reaction conditions list the solvent, temperature, and elapsed time before beginning the separation procedure, which was sometimes longer than the minimum time required for total conversion of **1** to **3** or **5** (examples **a, b, c, e, f, h, l, m,** and **n**).

The data show that the rate of reaction with amines that manifest the same selectivity is markedly dependent upon the pK_a of the amine. Thus, reaction with primary aromatic amines, such as aniline (**2a**) and *p*-toluidine (**2b**), which have pK_a values of about 5, required about 2–3 h for completion, whereas reaction with simple primary aliphatic amines, such as methylamine (**2c**) and ethylamine (**2h**), which have pK_a values of about 11, required only 5–10 min for completion. The reaction rate was significantly slower, however, with primary aliphatic amines with more bulky substituents, such as a neopenthyl group, **2n**, presumably owing to the effect of steric hindrance. Similarly, reaction with secondary aliphatic amines, such as dimethylamine (**2f**) and pyrrolidine (**2p**), is considerably faster than that with *N*-methylaniline (**2o**), which did not interact significantly even after several days in refluxing benzene.

Although the reaction rate is a function of the amine basicity, the reaction selectivity appears to be independent of this parameter. Thus, the set of amines that follow pathway A exclusively (amines **a–e, h, l**) have pK_a values that range from 5 to 11, and the same is true of the set of amines that follow pathway B exclusively (amines **f, k, o, p,** and **q**).

Selectivity appears to be more associated with the combined bulk of the substituents about the nucleophilic center, rather

Table I. Product Distribution in the Reaction of Acetylanthranil (1a) with Amines 2

Amine 2	pK_a,[a] 25 °C	Reaction conditions: Solv[b]	Temp, °C	Time[c]	% 1a units Isolated as: 4	3	5	Selectivity k_A/k_B = (3 + 5)/4
a, $PhNH_2$	4.63	a, b	RT	4 h	0	75	25	>50/1
b, p-CH_3PhNH_2	5.08	a, b	RT	4 h	0	70	25	>50/1
c, $CH_2{=}CHCH_2NH_2$	9.49	c	RT	1 h	0	0	91	>50/1
d, NH_3	9.26	a, b	RT	2 days[f]	0	0	0	>50/1[d]
e, CH_3NH_2	10.7	a	RT	1 h	0	100	32	>50/1
		d	RT	1 h	20	43	32	4/1
f, $(CH_3)_2NH$	10.8	c	0	1 h	100	0	0	>1/25
g, $(CH_3)_3N$	9.9	c	Reflux	1 day	0	0	0	*d*
h, $CH_3CH_2NH_2$	10.8	a	RT	1 h	0	100	0	>50/1[e]
i, $(CH_3)_2CHNH_2$	10.6	a	RT	18 h	8	40	0	5/1[e]
		c	RT	18 h	43	0	0	>1/25[e]
j, 	10.7	a	RT	18 h	9	79	0	9/1[e]
k, $(CH_3)_3CNH_2$	10.7	a	Reflux	4 h	65	0	0	>1/25[e]
		c	RT	1 day	59	0	0	>1/25[e]
l, $CH_3CH_2CH_2NH_2$	10.71	c	0	1 h	0	90	0	>50/1
m, $(CH_3)_2CHCH_2NH_2$	10.5	b	RT	18 h	4	95	0	23/1
n, $(CH_3)_3CCH_2NH_2$	10.2	b	RT	18 h	8	92	0	12/1
o, $PhNHCH_3$	4.84	a	Reflux	4 days	0	0	0	*e*
p, 	11.3	b	RT	4 h	56	0	0	>1/25[e]
q, 	11.1	b	RT	4 h	65	0	0	>1/25[e]

[a] pK_a values taken from D. D. Perrin, "Dissociation Constant of Organic Bases in Aqueous Solutions," Butterworth, London, 1965. [b] a = benzene; b = ether; c = neat; d = pyridine. [c] Interval to reaction termination by initiation of separation procedure. [d] 1a units not isolated as 5 were recovered as unreacted 1a. [e] 1a units not isolated as 4, 3, or 5 isolated as *o*-acetamidobenzoic acid, owing to reaction with water in postreaction separation. [f] $T_{1/2}$ = 1.3 days.

Table II. Characterization Data for Products as Noted in Table I

Product	Mp, °C	Key IR absorption bands, μ
Acetamidines, 3		
from amine **a**	115–116	3.2–4.4 6.3
b	119–120	3.2–4.4 6.3
c	136–137	3.0–4.0 6.3
h	109–110	3.0–4.4 6.3
i	167–168	3.4–4.1 6.3
j	184–185	3.3–4.3 6.3
l	117–119	3.2–4.3 6.3
m	150–151	3.2–4.3 6.3
n	170–171	3.2–4.3 6.3
2-Methylquinazolones, 5		
from amine **a**	147–148	6.0 6.3
b	151–152	5.9 6.3
c	78–79	6.0 6.3
d	240–241	6.0 6.2
e	70–71	6.0 6.2
h	79–80	6.0 6.2
l	81–82	6.0 6.3
m	71–72	6.0 6.3
o-Acetamidobenzamide, 4		
from amine **a**	180–181	3.1, 6.0, 6.1, 6.2, 6.3, 6.5
f	83–86	2.9, 6.0, 6.2, 6.5
l	140–141	3.0, 5.9, 6.2, 6.3, 6.6
j	147–149	3.0, 6.0, 6.2, 6.3, 6.6
k	158–159	3.0, 3.1, 6.0, 6.2, 6.3, 6.6
m	158–159	3.0, 6.0, 6.2, 6.3, 6.5
n	164–165	3.0, 3.2, 6.0, 6.2, 6.3, 6.5
p	90–93	2.9, 6.1, 6.3, 6.6
q	86–88	2.9, 3.1, 6.0, 6.2, 6.6

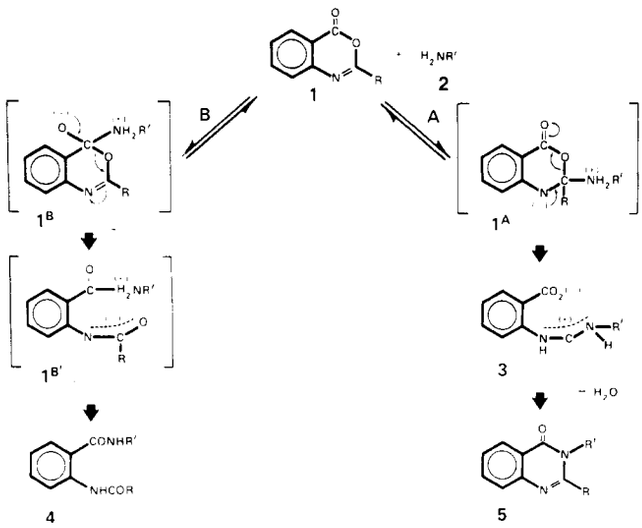
than the resultant electronic contribution to this site. The effect of steric hindrance on selectivity is particularly striking when the observed k_A/k_B values within the sets $H_{(3-n)}N(CH_3)_n$, $H_2NCH_{(3-n)}(CH_3)_n$, and $H_2NCH_2CH_{(3-n)}(CH_3)_n$ are examined as a function of n. Table I shows that crossover in selectivity from pathway A (i.e., k_A/k_B >50/1) to pathway B (i.e., k_A/k_B <1/25) within the first two sets of amines (**d, e, f,** and **g** and **e, h, i,** and **k**) occurs when n = 2 (i.e., with amines **f** and **i**). This is exactly where one would expect the effect of steric hindrance to manifest itself in both sets, according to the well-known results of Brown[6] and others,[7] who developed the now classical theories regarding steric effects in the reaction of amines with electrophilic reagents. The data in Table I also show that within the third set (amines **h, l, m,** and **n**), k_A/k_B decreases from >50/1 for **2h** to 12/1 for **2n,** but does not exhibit the crossover in selectivity noted in sets 1 and 2. This demonstrates that the effect due to the branching in an isopropyl or *tert*-butyl group is substantially reduced when this branched group is separated from the nucleophilic center by only one methylene unit. This is as would be expected if steric hindrance were the important factor that determines selectivity.

The k_A/k_B for cyclohexylamine (**2j**) in benzene (9/1) is somewhat higher than that for isopropylamine (**2i**) in benzene (5/1) and considerably higher than that of isopropylamine neat (<1/25), which is consistent with the expectation that steric hindrance should be less when the rotational freedom of the interfering components on the α-carbon atom is restrained by the ring structure. Such a change of selectivity does not occur, however, when the interfering groups are attached directly to the nucleophilic nitrogen atom instead of the α-carbon atom. Reaction with a secondary amine (**f, p,** and **q**) appears always to follow pathway B exclusively even when the secondary amine is a small heterocyclic compound such as pyrrolidine, **p,** or piperidine, **q.**

The observation that the rate of reaction of an amine with a given acylanthranil is a function of both the electronic and steric factors on the part of the amine whereas the selectivity is determined only by steric differences parallels the observations noted earlier regarding the reactions of acylanthranils with a given amine as described in the introduction. Both sets

of results can be rationalized on the basis that the transition states **1A** and **1B**, produced by addition of the amine to the 2 and 4 positions, respectively, of the acylanthranil, **1**, are in equilibrium with each other as illustrated in Scheme II. Al-

Scheme II



though addition to the more electrophilic center at the 4 position may occur faster than to the less electrophilic center at the 2 position, nothing fruitful occurs until either cyclic transition state **1A** or **1B** rearranges to give the more stable product **4** or **3**, respectively. These are the rate-determining steps to product formation.

It should be easier to transfer negative charge from N to O of **1A** via pathway A than from O to N of **1B** via pathway B, because O is more electronegative than N. Accordingly, pathway A occurs more readily than B, and we obtain the amidine product **3** preferentially. When the formation of **1A** is strongly inhibited or precluded by steric factors, owing to bulky substituents either on the amine or at the 2 position of the acylanthranil, then reaction is limited to the alternative pathway B which occurs more slowly. The overall rate of reaction via pathways A and/or B is of course affected by ring substituents that influence the electrophilicity at the 2 and 4 positions of the acylanthranil and by substituents that influence the nucleophilicity of the amine. These electronic rate considerations are modified in turn by steric factors that interfere with the approach of these mutually attractive centers. The selectivity, however, is determined by the competitive rate-limiting pathways to stable products. In the absence of steric hindrance, this occurs faster via the more electronically favored pathway A, whereas in the presence of steric hindrance it is limited to the less favored pathway B.

This sensitivity to steric hindrance, resulting in a readily detected selectivity in product distribution, makes available a useful "chemical" method to complement existing "physical" methods for detecting and measuring the influence of steric hindrance in the reactions of amines with electrophiles. The isolation of a quinazolone, **5** (or its precursor, **3**), as the major product indicates that the coreactant is a primary amine with no branching on the α-carbon atom, whereas the isolation of a *o*-acetamidobenzamide, **3**, as the major product indicates that the coreactant is either a secondary amine or a primary amine exhibiting steric hindrance.

In view of the foregoing discussion, the results obtained with ammonia (**2d**) are somewhat anomalous, since one would expect reaction to occur rapidly to give **3d** and/or **5d**, owing to the high pK_a and small size of the nucleophile. Although the product was **5d**, as expected, the rate of reaction in benzene and in ether saturated with anhydrous ammonia was so slow that conversion, which was first order with respect to acetylanthranil, was only half complete after 1.3 days. The product was removed periodically by filtration to follow the progress of reaction, and about a third of the starting material was recovered unchanged by evaporating the mother liquor to dryness after separation of the last product fraction at the end of the second day. Obviously more investigation is needed to understand why reaction with this nucleophile in nonpolar solvents is so unusually slow. This is particularly important, since some of the earlier investigators,[8] who used more polar solvents in their investigation, reported that *o*-acetamidobenzamide (**4d**) is the major product. Perhaps the solvent plays a more important role in determining reactivity with ammonia than with amines in general.

Experimental Section

The general procedure for reaction of acetylanthranil with an amine, the separation of the resultant product mixture into components, and the use of these data to calculate the corresponding reaction selectivity are described in earlier publications.[2-4] The percent acetylanthranil units isolated as the products **3**, **4**, and **5** for each of the amines in this investigation and the corresponding calculated reaction selectivity, k_A/k_B, are collected in Table I. The characterization data for the products listed in Table I are collected in Table II.

Registry No.—**1a**, 525-76-8; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 107-11-9; **2d**, 7664-41-7; **2e**, 74-89-5; **2f**, 124-40-3; **2g**, 75-50-3; **2h**, 75-04-7; **2i**, 75-31-0; **2j**, 108-91-8; **2k**, 75-64-9; **2l**, 107-10-8; **2m**, 78-81-9; **2n**, 5813-64-9; **2o**, 100-61-8; **2p**, 123-75-1; **2q**, 110-89-4; **3a**, 34264-61-4; **3b**, 58426-41-8; **3c**, 61041-27-6; **3h**, 61047-28-7; **3i**, 61047-29-8; **3j**, 61047-30-1; **3l**, 34242-12-1; **3m**, 34264-52-3; **3n**, 61047-31-2; **4a**, 54364-31-7; **4f**, 30367-86-3; **4i**, 61047-32-3; **4j**, 61047-33-4; **4k**, 61047-34-5; **4m**, 61047-35-6; **4n**, 61047-26-5; **4p**, 42103-90-2; **4q**, 42103-91-3; **5a**, 2385-23-1; **5b**, 22316-59-2; **5c**, 833-32-9; **5d**, 1769-24-0; **5e**, 1769-25-1; **5h**, 50677-59-3; **5l**, 50677-60-6; **5m**, 391-03-7.

Supplementary Material Available. More detailed procedures for reaction of **1** with the amines **2a–q**, and the characterization data of the products (12 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Presented before the 10th Great Lakes Regional Meeting of the American Chemical Society, Northwestern University, Evanston, Ill., June 1976, Abstract No. 276.
(2) Part 1: L. A. Errede, *J. Org. Chem.*, **41**, 1763 (1976).
(3) Part 2: L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.*, **41**, 1765 (1976).
(4) Part 3: L. A. Errede, H. T. Oien, and D. R. Yarian, *J. Org. Chem.*, **42**, 12 (1977).
(5) M. T. Bogert, C. G. Amend, and V. J. Chambers, *J. Am. Chem. Soc.*, **32**, 1297 (1910).
(6) H. C. Brown and G. K. Barbaras, *J. Am. Chem. Soc.*, **75**, 6 (1953).
(7) G. S. Hammond, "Steric Effect on Equilibrated Systems", and R. W. Taft, Jr., "Separation of Polar, Steric and Resonance Effects in Reactivity", in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956.
(8) A. Weddige, *J. Prakt. Chem.*, **36**, 141 (1887).