peaks of *E* and *Z* epoxy alcohols. But it was estimated that, by comparison of the NMR spectra with those of *E* epoxy alcohols, *E* isomers were the main products.

AIBN Autoxidation of 1,3-Cyclooctadiene (6) and 1,4-Cyclooctadiene (7) and Na_2SO_3 Reduction. Dried oxygen was slowly bubbled into a mixture of **6** (54 g, 500 mmol) and AIBN (0.11 g, 0.67 mmol) with stirring at 60 °C. After 7 h, absorption of oxygen reached 15% based on the olefin used, and then unreacted olefin was removed under reduced pressure to give an oily residue (13.5 g, 60% active oxygen). The methanol solution of aliquots (1 g) was reduced by Na_2SO_3 aqueous solution at 0 °C. The resulting solution was extracted with ether, and distillation gave 2,4-cyclooctadienol (**6c**, 0.38 g). Other aliquots (1 g) were treated with $LiAlH_4$/ether under reflux. The GLC analysis showed four isomers of enediols, cyclooct-2-ene-*cis*-1,4-diol (15%), cyclooct-2-ene-*trans*-1,4-diol (5%), cyclooct-3-ene-*cis*-1,2-diol (8%), cyclooct-3-ene-*trans*-1,2-diol (7%), which were assigned by comparison of GLC retention time with authentic samples.[19]

1,4-Cyclooctadiene (**7**) (10.8 g, 100 mmol) was oxidized by the same procedure as **6**. After 40 min, absorption of oxygen reached 28% on the basis of olefin used, and unreacted olefin was removed. The oily residue was extracted twice with 100 mL of *n*-hexane. The hexane solution was evaporated at 60 °C (0.1 mmHg) to give colorless cycloocta-2,4-dienyl hydroperoxide (**6e**, 2.1 g): NMR ($CDCl_3$) τ 1.85 (br s, 1 H, OOH), 4.1–4.4 (m, 4 H, CH=CH), 5.43 (m, 1 H, CH–O), 7.6–8.7 (m, 6 H, CH_2); IR (film) cm^{-1} 3360, 3040, 1627, 1064, 1027, 950, 860, 807, 780, 677. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.62; H, 8.67.

The hydroperoxide (**6e**, 0.6 g) was treated with Na_2SO_3, and the GLC analysis showed 2,4-cyclooctadienol (**6c**, 98.3%) and 2,7-cyclooctadienol (**7c**, 1.7%): IR (film) cm^{-1} 3380, 3040, 1057 813, 795.

Reaction of Cycloocta-2,4-dienyl Hydroperoxide (6e) with $VO(acac)_2$ Catalyst. The reactant peroxide **6e** (1.40 g, 10 mmol) was added to 5 mL of a benzene solution of $VO(acac)_2$ (26.5 mg, 0.1 mmol). The mixture was stirred at 40 °C for 4 h under a nitrogen atmosphere. GLC analysis showed a mixture of 9-oxabicyclo[3.3.1]non-3-en-*exo*-2-ol (**6a**, 42%), cycloocta-2,4-dien-1-ol (**6c**, 27%), cycloocta-2,4-dien-1-one (**6d**, 15%), and *trans*-2,3-epoxycyclooct-4-en-1-ol (**7a**, 4%).[8b]

Oxidation of 3-Deuterio-1,4-cyclooctadiene (8) with $VO(acac)_2$ Catalyst. 3-Deuterio-1,4-cyclooctadiene (**8**) (1.7 g, 15.6 mmol) was oxidized by the same procedure as **6**. The reaction rate, compared with that of **7**, was slow and absorption of oxygen reached 35%, on the basis of olefin consumed, after 7.5 h. Unreacted **8** was evaporated under reduced pressure. To the oily residue was added a benzene solution of $VO(acac)_2$ (4.5 mg, 0.017 mmol). The mixture was stirred at room temperature for 24 h. 3-Deuterio-9-oxabicyclo[3.3.1]non-3-en-*exo*-2-ol (**8a**) was isolated by preparative GLC: NMR ($CDCl_3$) τ 3.82 (d of d, 0.21 H), 4.08 (d, J = 3.8 Hz, and with further fine structures, 1 H), 5.66 (m, 1 H), 5.85 (d, J = 4.0 Hz, and with further fine structures, 1 H), 6.26 (br s, 1 H), 7.65 (br s, 0.79 H), 8.0–8.7 (m, 6 H); IR (film) cm^{-1} 3300, 2215 (=CD), 1200, 1075–1057 (doublet), 1033–1020–1009 (triplet), 990–974 (doublet), 912, 878, 840, 800; mass spectrum m/e 140, 141 ($M^{+\cdot}$).

From these spectral data, it was confirmed that this epoxy alcohol (**8a**) was a mixture of 3-deuterio and 3-protio derivatives (79:21).

One-Pot Synthesis of Oxabicycloenol 6a from the Reaction of 1,4-Cyclooctadiene (7) and Molecular Oxygen. The oxidation of **7** (2.8 g, 26 mmol) with the $VO(acac)_2$ (3.5 mg, 0.013 mmol) and AIBN (10.7 mg, 0.065 mmol) catalyst system in 1,2-dichloroethane (6 mL) was performed under an oxygen atmosphere at 50 °C. After 10 h, an equimolar amount of oxygen was absorbed. Then the GLC analysis showed that **7** gave **6a** (43%), **7a** (10%), **7b** (23%), **6c** (15%), and **6d** (9%) among volatile products. 1,2-Dichloroethane was removed from the reaction solution under reduced pressure and the residue was chromatographed on a Florisil column. The eluate from petroleum ether–ether (1:1) was concentrated and evaporated. The residue was sublimed at 100 °C (0.2 mmHg). Crystallized **6a** was obtained (655 mg, isolated yield 18%).

Registry No. **1**, 110-83-8; **1a**, 26828-72-8; **1b**, 286-20-4; **1c**, 822-67-3; **1d**, 930-68-7; **2**, 591-49-1; **2a**-1, 38309-50-1; **2a**-2, 38309-43-2; **2a**-3, 56595-76-7; **2b**, 1713-33-3; **3**, 628-92-2; **3a**, 65697-35-0; **3b**, 286-45-3; **3c**, 4096-38-2; **3d**, 1121-66-0; **4**, 931-88-4; **4b**, 286-62-4; (*E*)-**5**, 1486-75-5; (*Z*)-**5**, 1129-89-1; **5a**, 69798-84-1; (*E*)-**5b**, 4683-60-7; (*Z*)-**5b**, 1502-29-0; **5d**, 42858-38-8; **6**, 1700-10-3; **6a**, 61686-85-9; **6c**, 29234-93-3; **6d**, 10095-80-4; **6e**, 73908-47-1; **7**, 1073-07-0; **7a**, 61686-86-0; **7c**, 73908-48-2; **8**, 73908-49-3; **8a**, 73908-50-6; cyclooct-3-ene-*cis*-1,4-diol, 37996-40-0; cyclooct-2-ene-*trans*-1,4-diol, 37996-39-7; cyclooct-3-ene-*cis*-1,2-diol, 37989-33-6; cyclooct-3-ene-*trans*-1,2-diol, 21491-46-3; 1-methylcyclohex-2-en-1-ol, 23758-27-2; 3-methylcyclohex-2-en-1-ol, 21378-21-2; 2-methylcyclohex-2-en-1-ol, 20461-30-7; 3-methylcyclohex-2-en-1-one, 1193-18-6; 2-methylcyclohex-2-en-1-one, 1121-18-2; $VO(acac)_2$, 3153-26-2; AIBN, 78-67-1.

(19) Barrelle, M.; Apparu, M. *Bull. Soc. Chim. Fr.* **1972**, 2016.

Acylanthranils. 9. Influence of Hydrogen Bonding on the Reaction of Acetylanthranil with Ammonia[1]

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It was shown that hydrogen bonding has a marked influence on the reaction of acetylanthranil (**1**) with ammonia. The product of the reaction in anhydrous benzene is 2-methylquinazolin-4-one (**5**, R = H) which is formed via pathway A as shown in Scheme I, but the rate of formation is unusually slow. The rate of this conversion is about 6 times faster in pyridine than in benzene. If water is added to the benzene system, the rate of reaction is increased by orders of magnitude, but the product is *o*-acetamidobenzamide (**4**, R = H) and not **5**. In contrast to this result, the addition of water to the pyridine system causes a small decrease in rate and only a slight change in selectivity. These results are consistent with postulated mechanisms whereby **1** reacts with molecular clusters of ammonia, i.e., with $(NH_3)_n$ in benzene, with $N(H{\cdot}S)_3$ in strong proton acceptor solvents S, and with $(NH_3)_n{\cdot}H_2O$ in benzene plus added water. It was verified that cyclodehydration of **4** to give **5** occurs at an appreciable rate in aqueous solution at elevated temperatures and that this rate is accelerated considerably by the presence of strong base even at room temperature. It was also observed that *o*-acetamidobenzamide exists in at least two crystalline forms, α and β, which have different physical properties.

We have shown[2] that primary amines react with acetylanthranil (**1**) via alternate pathways, A and B, as outlined in Scheme I. Reactions with small amines are complete within minutes to give the corresponding acet-

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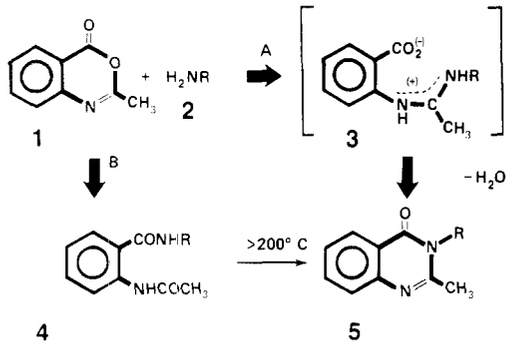
Table I. Reaction of Acetylanthranil (1) with Ammonia in Various Solvents

expt no.	reaction conditions: solvent	presence of H_2O[g]	temp[h]	duration of expt	k, L/(mol min)	product distribution[i]: 4	5	6	7	selectivity, 5/4
1	benzene	A[a]	rt	>3 days	0.009		100[a]			>50/1
2	benzene	B	rt	<1 h		89				<1/25
4	benzene	C	rt	>3 days			70[b]		28[b]	>50/1
4	water, 30% NH_3	D	rt	<2 min		83			13	<1/25
5	liquid NH_3	E	rt	20 min		95[c]	5[c]			1/19
6	liquid NH_3	F	rfx	<2 min		100				<1/25
7	pyridine	E	rfx	3 h		18	67		12	3.7/1
8	pyridine	E	rt	30 h (Figure 2)	0.053	9	82		5	9/1
8′	pyridine	D	rt	70 h	0.028[d]		78[d]		20[d]	[e]
9	pyridine	D	rt	26 h (Figure 3)	0.018		86		14	[e]
10	methanol	A	rt	1 h				95		
11	methanol	G	rt	10 min		85			5	<1/25
12	ethanol	A	rt	1 h				90		
13	ethanol	G	rt	10 min		80			5	<1/25
14	none	A[a,f]	rt	>10 days	Figure 1	50[c]	50[c]			1/1
15	none	B	rt	8 h	Figure 1	95			5	<1/25

[a] Water of reaction via 3 → 5 + H_2O removed by stream of anhydrous NH_3 gas. [b] Product 7 formed via 1 + H_2O → 7. Subsequent addition of NH_3 caused immediate precipitation of the corresponding ammonium salt, which was removed by filtration. [c] The product distribution changed with percent conversion as discussed in the text. The data shown are those established at 100% conversion. [d] After the data for expt 8 were established, additional NH_3 in the form of concentrated NH_4OH was added at t = 30 h. The reaction was allowed to occur for an additional 70 h to establish the data recorded for expt 8′. [e] The presence of NH_3 and H_2O in pyridine was observed to cause conversion of 4 to 5. Therefore, the selectivity ratio is suspect. [f] Some retention of water of reaction via surface adsorption onto powdered acetylanthranil. [g] A, anhydrous; B, added as air stream saturated with NH_3 and H_2O vapor; C, benzene saturated with water vapor prior to addition of anhydrous ammonia vapor; D, concentrated NH_4OH (i.e., 30% NH_3); E, accumulation of water via 1 + NH_3 → [3] → 5 + H_2O; F, liquid water added to an equivalent weight of 1 in liquid NH_3; G, 5–10% water in alcohol. [h] Abbreviations: rt = room temperature; rfx = reflux. [i] 4 = *o*-acetamidobenzamide; 5 = 2-methylquinazolin-4-one; 6 = ester of *o*-acetamidobenzoic acid; 7 = *o*-acetamidobenzoic acid.

Scheme I



amidine, 3, and/or the quinazolinone 5 via pathway A, whereas reactions with bulky amines require days for completion and give the corresponding *o*-acetamidobenzamide 4 via pathway B. It was observed, however,[2,3] that the reaction of acetylanthranil (1) with anhydrous ammonia (2, R = H) in a nonpolar solvent, such as benzene or ether, is somewhat anomalous; i.e., the selectivity is "normal" for an amine that does not exhibit steric hindrance, but the reactivity is unusually low, even for an amine that exhibits considerable steric hindrance. The reaction with anhydrous ammonia follows pathway A to give 2-methylquinazolin-4-one (5, R = H) and water as outlined in Scheme I, but it requires days for completion instead of just minutes, which is normal for reaction with a nucleophile, such as methyl- or ethylamine, that exhibits no steric hindrance.[2]

The exact opposite results were observed by others,[4,5] who caused 1 to react with ammonia in polar solvents, such as water and ethanol. They reported that *o*-acetamidobenzamide (4, R = H) is the only product and that reaction is complete within minutes, indicating that reaction in these solvents follows pathway B at an unusually fast rate. We decided, therefore, to investigate this reaction further to clarify how the solvent can influence the reactivity and selectivity so markedly.

Effect of Solvent and Added Water on Reactivity and Selectivity

The results of this investigation (expt 1–15) are collected in Table I. We verified that acetylanthranil (1) is converted within seconds in concentrated aqueous ammonium hydroxide (i.e., 30% NH_3) at room temperature to give 4 in a very good yield (expt 4, Table I), as was reported by Anschutz et al.,[4] but we did not obtain 4 when anhydrous ammonia was made to react with 1 in anhydrous methanol or ethanol, as was reported by Zentmyer and Wagner.[5] We obtained instead the corresponding esters, 6, of o-acetamidobenzoic acid (7) in good yield (expt 10 and 12) despite the fact that esterification occurred more slowly relative to the very rapid formation of 4 in aqueous ammonia. Apparently ammonia in anhydrous alcohol acts better as a catalyst for esterification of 1 than it does as a nucelophilic reagent per se.[6] The expected diamide, 4, is indeed obtained, however, if 5–10% water in alcohol is used as solvent (expt 11 and 13) instead of anhydrous alcohol.

The above observations imply that the sharp change in selectivity and reactivity may not be caused by a change

(1) Presented in part before the American Chemical Society/Chemical Society of Japan Chemical Congress, Honolulu, HI, Apr 3, 1979, No-ORGN 227

(2) Part 4: L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.*, **42**, 656 (1977).

(3) Part 6: L. A. Errede, *J. Org. Chem.*, **43**, 1880 (1978).

(4) R. Anschutz, O. Schmidt, and A. Griffenberg, *Ber. Dtsch. Chem. Ges.*, **35**, 3483 (1901).

(5) D. O. Zentmyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949).

(6) We have shown that esterification in the presence of base is a general reaction for acylanthranils that usually is complete at room temperature within 0.5 h. In the absence of base, however, little or no conversion occurs. In fact, ethyl alcohol can be used as a good recrystallization solvent for these compounds (unpublished results).

from a nonpolar to a polar solvent, as described at the beginning of the paper, but rather appears to be attributable specifically to the presence or absence of water. We decided to check this possibility by comparing the rates of reaction and the product distributions obtained by reaction of 1 with NH_3 in benzene with and without added water vapor.

We reported[2] that the conversion of 1 to 5 in benzene saturated with a stream of anhydrous ammonia gas (expt 1) is pseudo first order and that this conversion is half complete after 32 h. It was determined[7] subsequently that the solubility of ammonia in benzene is 0.7 g/L, which enabled us to calculate that the approximate second-order rate constant for the reaction of 1 with 0.041 M NH_3 in benzene is $k = 0.009$ L/(mol min). We repeated this study using a stream of air that was bubbled through concentrated aqueous ammonium hydroxide (expt 2). We observed that conversion was already complete within 1 h and that the product was 4 and not 5 as was noted with anhydrous NH_3 in expt 1. This result indicates that the rate of interaction with "NH_4OH" in benzene is at least 2 orders of magnitude faster than that with NH_3.

In contrast to the results of expt 2, with "wet" ammonia and "dry" benzene, which gives 4, the addition of anhydrous ammonia gas to a solution of 1 in "wet" benzene (i.e., benzene that was saturated with water vapor at room temperature before contact with 1) gives the ammonium salt of *o*-acetamidobenzoic acid, which precipitates instantly (expt 3), showing that the slow rate of reaction with 1 is not due to the limited solubility of ammonia gas in benzene. Conversion of residual 1 thereafter occurs very slowly via first-order kinetics, as noted in expt 1, and again the product is 5 and not 4. Apparently the "wet" benzene was "dried" chemically by reaction with 1 to give *o*-acetamidobenzoic acid (7) which in turn formed the insoluble ammonium salt when anhydrous ammonia gas was metered to the system. These results show clearly that in an anhydrous nonpolar solvent, reaction of 1 with ammonia occurs very slowly to give 5, whereas in the presence of water it occurs very rapidly to give 4.

One might still argue that the above results are attributable to solvent effects that limit physically the interaction of 1 with NH_3 rather than to the change in chemistry of the reactants. To be certain that this is not the case, we decided to study the interaction of powdered 1 with anhydrous NH_3 gas (expt 14). The conversion to products was monitored by IR and by proton NMR spectroscopy, which showed that 4 and 5 were being produced as products of the gas–solid reaction and that the ratio of 4 to 5 was increasing monotonically with time from 1/9 at 10% conversion after 8 h to 1/3 at 40% conversion after 76 h and finally to 1/1 at 95% conversion after 296 h. This progressive increase in the ratio of products 4 to 5 reflects the corresponding change in selectivity caused by the liberation of H_2O as a side product of the formation of 5 via pathway A, as shown in Scheme I, which dominated initially. The conversion of 1 to products 4 and 5 in expt 14 was first order as shown in Figure 1. About 90 h was required to achieve 50% conversion of 1 to 4 and/or 5 via this heterogeneous gas–solid phase interaction whereas only 32 h was required via the gas–liquid phase interaction in expt 1.

Experiment 14 was repeated by using a stream of air saturated with NH_3 and H_2O vapors instead of a stream of anhydrous NH_3. Under these conditions (expt 15) only 2 h was required to attain 50% completion. Again the

(7) We are indebted to Dr. J. S. Marhevka of 3M Co. for this experimental result.

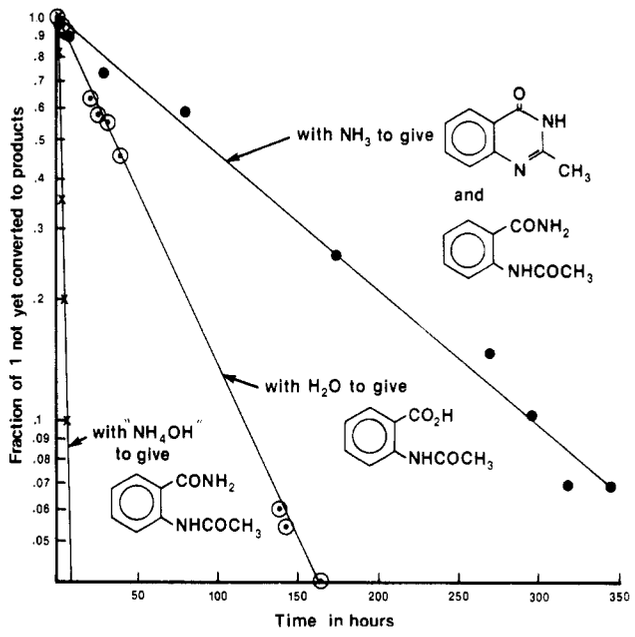


Figure 1. Reaction of powdered acetylanthranil with NH_3, H_2O, and "NH_4OH" vapors.

conversion was pseudo first order as shown in Figure 1, but the major product was 4 instead of 5, and the only minor product was the ammonium salt of *o*-acetamidobenzoic acid (7). It was concluded, therefore, that the unusually slow reaction rate of anhydrous NH_3 with acetylanthranil in benzene or ether is not due to unusual solvent effects that suppress interaction but rather is characteristic of the reactants per se.

It was of interest to compare the above results with the corresponding conversion to *o*-acetamidobenzoic acid (7) by reaction of powdered acetylanthranil (1) with air saturated with water vapor at room temperature. This conversion was monitored both by gravimetric means and by proton NMR spectroscopy. The two experiments were carried out in parallel under the same conditions. Both studies showed that this heterogeneous conversion of 1 to 7 is first order, as indicated by the gravimetric data plotted in Figure 1, and that about 35 h is required to achieve 50% conversion. The results of the three studies plotted in Figure 1 show clearly that conversion of 1 to 4 by reaction with NH_3 and H_2O vapors is faster than conversion of 1 to 7 by H_2O vapor, which in turn is faster than the conversion of 1 to 5 by anhydrous NH_3 gas despite the fact that ammonia is more nucleophilic than water.

The autocatalytic increase in reactivity and the associated change in selectivity of powdered acetylanthranil (1) with ammonia gas were also noted in the reaction of 1 in liquid ammonia at reflux, which occurred homogeneously (expt 5). The ratio of products 4 to 5 changed monotonically from 1/3 at 4% conversion after 3 min to 14/1 at 75% conversion after 10 min and finally to 19/1 at 100% conversion in less than 20 min. When this reaction was made to occur in liquid ammonia containing 1 drop of water, conversion was complete within seconds, and the product was 4 (expt 6). Again these results are consistent with the point of view that the initial reaction of 1 with ammonia occurred via pathway A at a relatively slow rate to give 5 and H_2O, as shown in Scheme I, and that the accumulation of this water of reaction is responsible for the corresponding increase in reactivity and associated change in selectivity that favors pathway B, so that 4 accumulates as the major product of reaction of 100% conversion. On the basis of these results, it was

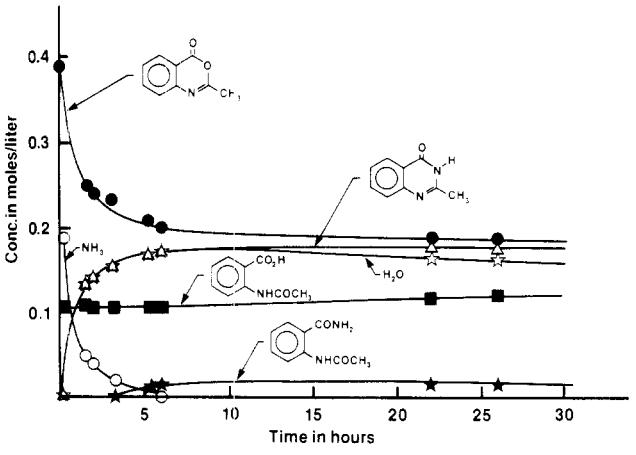


Figure 2. Time study of the reaction of NH_3 with excess acetylanthranil in pyridine at room temperature.

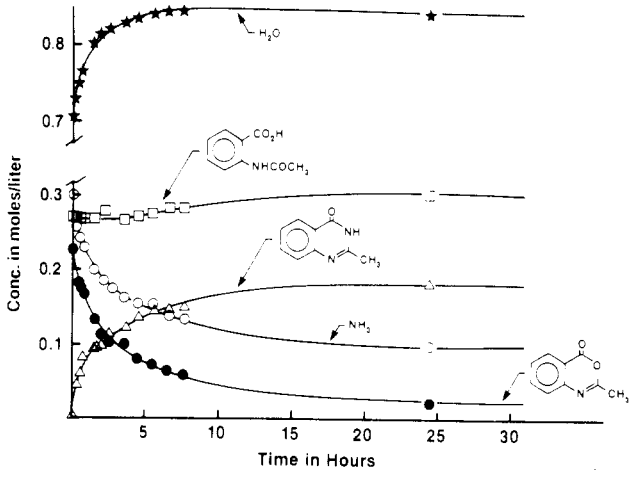


Figure 3. Time study of the reaction of acetylanthranil with excess NH_3 and H_2O in pyridine at room temperature.

postulated that reaction in anhydrous media to give **3** via pathway A is slowed considerably by steric hindrance, owing to formation of $(NH_3)_n$ by intramolecular hydrogen bonding that shields the nucleophilic centers in the ammonia clusters from the electrophilic centers of **1**. Although intermolecular association to form $1\cdot(HNH_2)_n$ is facile, subsequent conversion to products **3** and/or **4** is not, unless H_2O is added to form $1\cdot(NH_3)_n\cdot H_2O$, which undergoes immediate conversion to **4**.

In order to test the effect of a solvent, S, that would preclude intramolecular hydrogen bonding of the type $(NH_3)_n$ by favoring intermolecular hydrogen bonding of the type $(S\cdot H)_3N$, we reacted **1** homogeneously in pyridine saturated at reflux with a slow stream of anhydrous NH_3 gas (expt 7). The material balance data, which were established after the conversion to products was complete, indicated that 67% of reactant **1** was isolated as **5**, 18% as **4**, and 12% as *o*-acetamidobenzoic acid (**7**), which was actually isolated as an unusually stable salt of the weak acid **7** and weak base **5**. This product distribution shows that interaction of **1** with ammonia via pathways A and B occurs competitively with hydrolysis of **1** under the above experimental conditions.

In order to establish the sequence in which these reactions become competitive, we reacted 2 equiv of acetylanthranil (**1**) in pyridine at room temperature with 1 equiv of ammonia, neutralized in part by 0.5 equiv of *o*-acetamidobenzoic acid (expt 8). The conversion of **1** to products was monitored by proton NMR, and the results of this time study are plotted in Figure 2, which shows that reaction of NH_3 with excess **1** followed pathway A preferentially until conversion of NH_3 to **5** and H_2O was about 90% complete. Thereafter, the selectivity changed in favor of pathway B to give **4** preferentially instead of **5** so that the ratio of **5** to **4** in the final product mixture was about 6:1. The corresponding plot of log $[1]/[NH_3]$ as a function of time was linear during the first 3 h, indicating that the kinetics of this conversion to **5** via pathway A was second order. Accordingly, the rate constant during this interval was calculated to be $k = 0.053$ L/(mol min), which indicates that the initial rate of reaction in pyridine (i.e., **1** with $N(H\cdot S)_3$) is about 6 times faster than the rate of reaction in benzene ($k = 0.009$ L/(mol min)), i.e., **1** with $(NH_3)_n$. This rate of conversion in pyridine slowed significantly, however, after the first 3 h probably because of associations of the type $(S\cdot H)_3N\cdot HOH\cdot S$ and $S\cdot HOH\cdot S$ to give **4** and/or **7**.

An additional equivalent of ammonia in the form of concentrated ammonium hydroxide (29%) was added at $t = 30$ h so that the concentrations of NH_3 and H_2O were 0.14 and 0.52 M, respectively at this point in time when [1] was 0.18 M (expt 8′). The second-order rate constant for conversion of **1** to **5** thereafter was 0.028, which is slower than that calculated from the data plotted in Figure 2. The addition of concentrated NH_4OH caused rapid conversion of **4** to **5**, presumably owing to the combined presence of NH_3 and excess H_2O as described later in this report. No additional **4** accumulated, however, until most of the NH_3 was consumed by conversion to product.

Acetylanthranil was also made to react in pyridine with excess ammonia, added in the form of concentrated aqueous ammonium hydroxide (expt 9). Again the major product isolated was **5** not **4** as shown by the data plotted in Figure 3. The second-order rate constant at room temperature calculated from these data is 0.018 L/(mol min) (i.e., for reaction of **1** with $(S\cdot H)_3N\cdot HOH\cdot S$ and with $S\cdot HOH\cdot S$), which is even slower than the rate constant calculated from the data obtained in expt 8 and 8′ (i.e., for reaction of **1** with $(S\cdot H)_3N$ plus $(S\cdot H)_3N\cdot HOH\cdot S$). Both Figure 2 and Figure 3 show that hydrolysis of **1** to give **7** does not occur competitively until most of the ammonia is consumed by conversion to products **4** and **5**.

The above results show clearly that hydrogen bonding of ammonia [with itself neat or in a nonpolar solvent to form $(NH_3)_n$, with added water to form $(NH_3)_n\cdot H_2O$, with proton acceptor solvents, S, to form $(S\cdot H)_3N$ and $(S\cdot H)_3N\cdot HOH\cdot S$, and with **1** to form $1\cdot(HNH_2)_n$, $1\cdot(HNH_2)\cdot H_2O$, and $1\cdot HN(H\cdot S)_2$] has a marked effect on the reactivity and selectivity for the overall interaction of **1** with ammonia. Apparently, the availability of the nucleophilic center and the bulk of the groups associated thereto by hydrogen bonding determine the ease with which these nucleophilic centers can approach the electrophilic centers of **1** to attain the necessary proximity required for the short-range forces of electronic mutual attraction first to become effective and finally to dominate over the steric factors.

Effect of Water on the Conversion of 4 to 5

Not only does water affect the selectivity during the reaction of **1** with NH_3 but it can also affect the product distribution even after conversion of **1** to products is complete. Weddige had reported[8] as early as 1887 that *o*-acetamidobenzamide (**4**, R = H) is converted slowly to 2-methylquinazolin-4-one (**5**, R = H) in aqueous solution at reflux. He noted, however, that this conversion is not fast enough to preclude the use of water as a good solvent

(8) A. Weddige, *J. Prakt. Chem.*, **36**, 141 (1887).

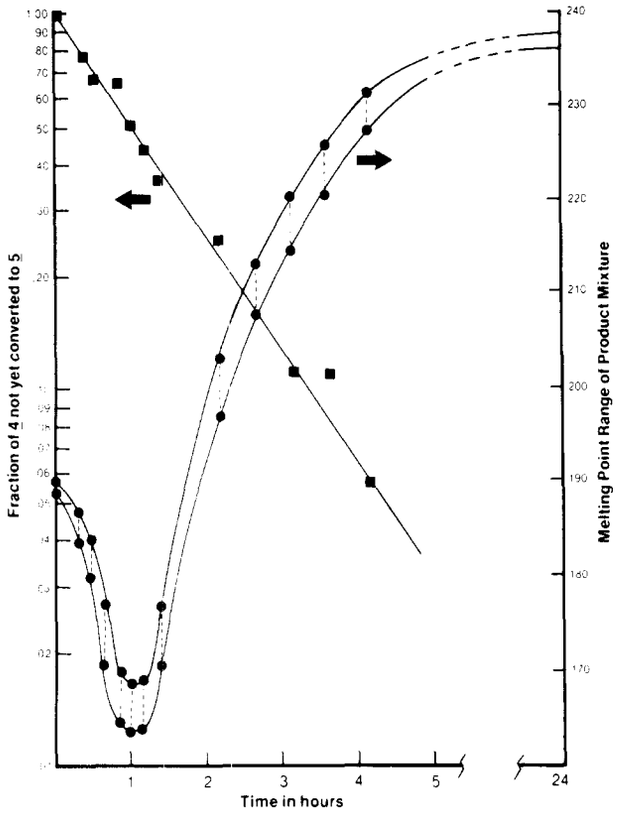


Figure 4. Conversion of *o*-acetamidobenzamide (4, R = H) to 2-methylquinazolin-4-one (5, R = H) in water at 90 °C.

for recrystalization of 4 unless the resulting solution is made strongly alkaline, which causes conversion to occur very rapidly. At first glance, this cyclodehydration in dilute aqueous solution appears to be contrary to the law of mass action. One would expect instead that the reverse would occur as reported by Scherrer[9] or that 4 would undergo hydrolysis to give 7 or even anthranilic acid.

We confirmed the observation of Weddige, however, that cyclodehydration does indeed occur in hot water. In fact, the yield of 5 is virtually quantitative, if sufficient time is allowed for the cyclodehydration to go to completion. The conversion of 4 to 5 is pseudo first order as shown in Figure 4 and the half-life of 4 in aqueous solution at 90 °C is about 1 h. In contrast, the half-life at this temperature in strongly basic solution is less than 1 min.

Although conversion is rapid in aqueous solution at 90 °C, it is insignificant at room temperature. Samples of 4 were recovered unchanged after continuous stirring with water or 10^{-3} M aqueous NH_4OH at room temperature for 7 days. Similarly, conversion in nonaqueous solvents is insignificant even at elevated temperatures, if the solvent is kept anhydrous. Thus, samples of 4 were recovered unchanged after several days at reflux in pyridine, dimethylsulfoxide, methanol and even liquid ammonia. Conversion of 4 to 5 occurs rapidly, if water is added to thse solutions at temperatures above 60 °C. Since these conditions are considerably more strenuous than those utilized in the present investigation of the reaction of 1 with ammonia, it is concluded that 4 and 5, isolated as products in the reaction mixtures of expt 1–15, with the possible exceptions of expt 8′ and 9, were formed competively via interaction of NH_3 with 1 rather than sequentially one from another, after conversion of 1 to products was complete. The formation of 5 in the reaction of 1 with NH_4OH in pyridine (expt 8′ and 9), however, may have occurred via cyclodehydration of 4.

Solid-State Properties of *o*-Acetamidobenzamide

We noticed with some concern that the melting points for *o*-acetamidobenzamide (4, R = H) reported by earlier investigators are not in good agreement with one another. Weddige reported[8] in 1887 that reaction of *o*-acetamidobenzamide with acetic anhydride gives 4 in the form of dense colorless needles that melt at 170–171 °C with copious evolution of water [presumably to form 2-methylquinazolin-4-one (5, R = H)]. Anschutz reported[4] in 1901 that reaction of acetylanthranil with aqueous NH_4OH gives 4 in the form of fine white needles that melt at 177 °C without evolution of waters, and Takai reported[10] in 1968 that 4 prepared by the method of Weddige melts at 178–180 °C. The first sample we prepared, also via the method of Weddige, melted at 177–178 °C without evolution of water until the temperature of the melt was raised to 230 °C, where thermal cyclodehydration to give 5 occurred rapidly. The IR spectrum of this sample was virtually identical with that reported by Takai. Consequently, we tentatively assumed that the data reported by Takai for 4 were correct and that the differences noted by some of the earlier investigators were probably due to artifacts of equipment and/or technique.

The many samples of 4 isolated in our present investigation, however, exhibited an even broader range in melting point and other physical properties than those reported by the earlier investigators. Some of these data agreed with those reported by Weddige and others with those reported by Anschutz and by Takai. These observations, therefore, negate the tentative conclusion made earlier that the differences in the data reported from various laboratories were only due to artifacts.

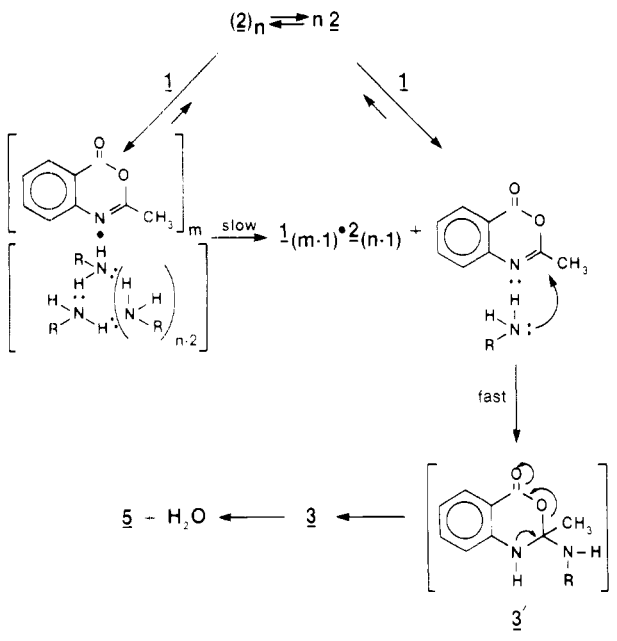
The samples of 4 we isolated from the product mixtures produced by reactions of NH_3 with 1 in pyridine usually melted at 169–171 or 180–181 °C without evolution of water. The IR spectra of these samples were identical with that reported by Takai. The samples of 4 we isolated from the reactions of 1 with concentrated aqueous NH_4OH melted either at 170–171 or 189–190 °C, usually without evolution of water. One sample, however, melted sharply at 170 °C with copious evolution of water. It resolidified at about 173–175 °C not to remelt again until the temperature was raised to 236–238 °C. This observation agrees with the original observation of Weddige. The IR spectra of the samples of 4 obtained via reaction with concentrated aqueous NH_4OH, however, were markedly different from those of the previous set (see paragraph at end of paper about supplementary material). Moreover, all our subsequent attempts to prepare 4 via reaction of *o*-aminobenzamide with acetic anhydride now gave samples that exhibited IR spectra identical with the latter rather than the former. The elemental analyses and the molecular weight by freezing point depression or by mass spectrometry for samples of both types were in agreement with one another and with the empirical formula for *o*-acetamidobenzamide (4, R = H). Similarly, the NMR spectra of these samples in Me_2SO-d_6 were identical and were in agreement with that expected for 4, thus verifying that both forms contained the same chemical units and that neither form is a hydrate of 4.

We suspected, therefore, that the different IR spectra were manifestations of different cyrstalline froms of the

(9) R. A. Scherrer and J. P. Beatty, *J. Org. Chem.*, 37, 1681 (1972).

(10) Y. Takai, "Infrared Data Committee of Japan", Sanyo Shuppen Boeki Co., Inc., Tokyo, Apr 1968, Curve No. 9549.

Scheme II



same chemical substance. This suspicion was verified by the corresponding X-ray powder diffraction patterns (see paragraph at end of paper about supplementary material) which were recorded by Dr. W. Thatcher of the 3M Co. For the sake of convenience we named the dimorphs α and β. The α form was assigned to the samples that exhibited an IR spectrum that agreed with that first reported by Takai, and the β form was assigned to those samples that exhibit the second IR spectrum observed later by us.

It was assumed that the existence of **4** in at least two crystalline forms is attributable to different modes of hydrogen bonding in the solid state. Subsequent crystallographic studies by Dr. M. C. Etter of the 3M Co. verified that this assumption is indeed correct and that the different modes appear to account for the differences in thermal behavior as discussed elsewhere.[11]

Summary

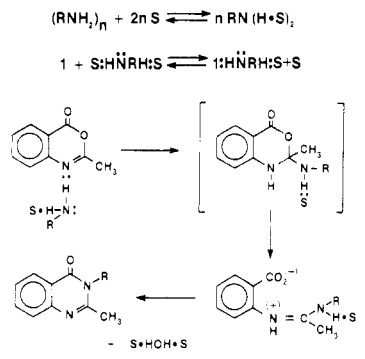
It was verified that reaction of acetylanthranil (**1**) with ammonia in anhydrous nonpolar solvents, such as benzene, is unusually slow and that the reaction selectivity favors formation of 2-methylquinazolin-4-one (**5**, R = H) plus water via pathway A. It was observed that the rate of this reaction is sixfold faster in a strong proton-acceptor solvent such as pyridine. Addition of small amounts of water to the former system increases the rate of reaction by 2 orders of magnitude and changes the selectivity sharply in favor of *o*-acetamidobenzamide formation. The same addition to the pyridine system, however, has the opposite effect; i.e., the rate is decreased by about half and the selectivity still favors formation of **5** via pathway A.

These observations are not consistent with a classical mechanism whereby a molecule of **1** combines with an isolated molecule of ammonia to give product **4** or **5**. They are consistent instead with a mechanism whereby **1** associates with a cluster of nucleophilic molecules to give a mixed complex that gives product **4** or **5**, depending on the molecular environment. In a neutral solvent (i.e., one which is neither a proton donor or an acceptor) this cluster is $(NH_3)_n$, in which all the nucleophilic centers are associated by hydrogen bonding. Although intermolecular monodentate association of this cluster with the heterocyclic nitrogen atom of **1** to give $1\cdot(HNH_2)_n$ is facile, subsequent formation of **4** or **5** via interaction of the nucleophilic centers of the ammonia cluster with the electrophilic centers of **1** at C-2 and C-4 is precluded, presumably because of the hydrogen bonding and steric hindrance, so that the rate of reaction is governed by the rate of formation of $1\cdot HNH_2$, which is converted spontaneously to **3** and then **5** plus H_2O as outlined in Scheme II.

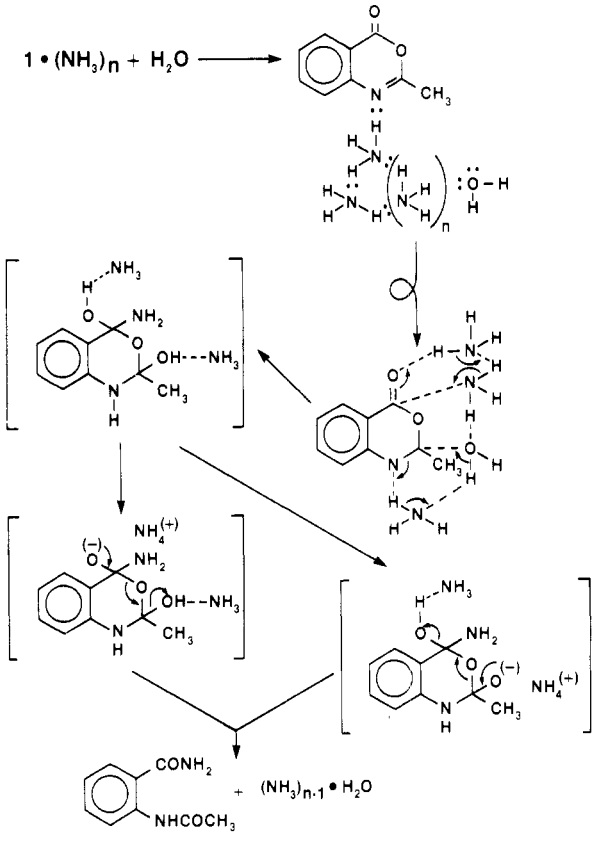
In a strong proton-acceptor solvent, S, these clusters are $(S\cdot H)_3N$ and $1\cdot HN(H\cdot S)_2$ in which the nucleophilic center of ammonia is fully exposed for interaction with the electrophilic centers of **1**, especially the adjacent center of C-2 as indicated in Scheme III. The overall rate of this conversion to product is affected by the bulk of the associated S.

If water is added to the neutral solvent system, the monodentate intermolecular complex $1\cdot(HNH_2)_n$ is converted immediately to $1\cdot(HNH_2)_n\cdot H_2O$, which can rearrange quickly in turn to a multidentate complex that yields product **4** via a von Grotthus-like mechanism[12] perhaps

Scheme III



Scheme IV



(11) L. A. Errede, M. C. Etter, R. C. Williams, and S. M. Darnauer, *J. Chem. Soc., Perkin Trans. 2*, in press.

as outlined in Scheme IV. Addition of water to the strong proton acceptor solvent system, however, has a much smaller effect because of association with solvent to form S·HOH·S and some $(S{\cdot}H)_3N{\cdot}HOH{\cdot}S$, which only serves to decrease accordingly the rate of interaction with 1 to give 3.

The reactions of 1 with water, with alcohols, and with primary amines were also studied kinetically and found to be affected by hydrogen bonding with the solvent and added solutes as described above. The results obtained in these investigations were consistent with the concept that the rate of reaction of the nucleophile with 1 depends markedly on the manner in which this nucleophile is associated with its molecular environment by hydrogen bonding. The data accumulated in these studies will be reported in subsequent papers.

Experimental Section

(1) Reaction of Acetylanthranil (1) with NH_3 in Homogeneous Solution. (a) In Benzene. (i) In Dry Benzene To Give 2-Methylquinazolin-4-one (5, R = H; Expt 1). The reaction of 1 in dry benzene (and in dry diethyl ether) with anhydrous NH_3 gas to give 5 is described in a previous publication.[2] The conversion is pseudo first order, and the half-life of 1 at room temperature under these conditions is about 32 h.

(ii) In Wet Benzene To Give the Ammonium Salt of Acetamidobenzoic Acid (7) and 5 (Expt 3). Anhydrous ammonia gas was metered at the rate of 60 bubbles/min through a solution of 1 (3.2 g) in benzene (50 cm^3) that had been exposed overnight at room temperature to atmospheric moisture. A white precipitate (0.5 g, mp 173–174 °C) formed immediately. This was removed by filtration and identified by its melting point and its IR spectrum in Nujol (absorption bands at 3.0–4.0, 6.0, 6.3, 6.6, and 6.7 μm) as the ammonium salt of 7. Anhydrous ammonia was again bubbled through the mother liquor. A white precipitate (mp 235–237 °C, 1.8 g, 49% of 1) accumulated very slowly over the next 2 days and was separated as described previously. This product was identified as 5 by its melting point and by comparison of its IR spectrum with that of an authentic sample. The mother liquor was evaporated to dryness, leaving a residue (1.6 g) which was identified by its IR spectrum to be unreacted 1.

(iii) In Dry Benzene with Wet Ammonia Gas To Give *o*-Acetamidobenzamide (4, R = H; Expt 2). A stream of air that was passed through concentrated aqueous NH_4OH at 23 °C was metered at the rate of 60 bubbles/min into a solution of 1 (3.2 g) in dry benzene (50 cm^3). A white precipitate began to form within a few minutes, and the precipitation appeared to be complete within 1 h. The product mixture (3.4 g, mp 172–174 °C) was identified by its IR spectrum as the α form of 4, with a minor amount of the ammonium salt of 7. This was verified by extraction of the product mixture with cold water and acidification of the extract with dilute mineral acid to give a white precipitate (0.2 g, 182–184 °C) which was identified as *o*-acetamidobenzoic acid (7).

(b) In Concentrated Aqueous Ammonium Hydroxide to Give 4 (Expt 4). Crystalline acetylanthranil (1, 5 g) was added slowly to a well-stirred aqueous solution (100 cm^3) of concentrated ammonium hydroxide (i.e., about 30% NH_3). The needlelike crystals dissolved rapidly with concomitant formation of a finely divided precipitate, which was removed by filtration and dried. The product (4.5 g) exhibited two melting points. If the compound was heated slowly (i.e., 1 °C/min from 150 °C to the melting point), the melting point was 189–190 °C with subsequent evolution of H_2O occurring in the melt at 195–230 °C to form 2-methylquinazolin-4-one (5, R = H). Solidification occurred on cooling and remelting occurred at 236–238 °C indicating complete conversion by thermal cyclodehydration. If the crystals were heated rapidly from room temperature to 160 °C and then at the rate of 5 °C min, melting occurred at 170 °C with simultaneous copious evolution of water, followed by rapid resolidification to a white crystalline mass, which remelted at 236–238 °C. The IR spectrum of this sample of 5 was identical with that of an authentic sample, but the IR spectrum of its precursor 4 was markedly different from that reported earlier by Takai[10] and that observed earlier by us for *o*-acetamidobenzamide, which was prepared by acetylation of *o*-aminobenzamide.[13] The X-ray diffraction patterns of the two forms (α and β) are also different (see paragraph at the end of this paper about availability of the IR and X-ray spectra as supplementary material). The elementary analysis for the product obtained from aqueous NH_4OH (the β form) is consistant with the empirical formula of 4. Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.62; N, 15.73; mol wt 178.2. Found: C, 60.9; H, 5.7; N, 15.8; mol wt 179 (by mass spectroscopy). The NMR data (Me_2So-d_6) for the β form [τ −1.6 (br, NH), 1.74 and 2.30 (NH_2), 1.4–3.0 (complex, Ar), 7.89 (s, CH_3)] were also consistent with the structure of *o*-acetamidobenzamide and identical with those obtained earlier for the α form prepared from *o*-amidobenzamide by acetylation of anthranilamide. Separate recrystallization of the α and β forms from methanol did not cause conversion from one crystalline form to the other. Suprisingly, recrystallization from methanol of a 50:50 mixture of the α and β forms gave approximately the same mixture. Recrystallization of the α form from aqueous $NaHCO_3$, however, gave the β form, and recrystallization of the β form from pyridine gave a mixture of the α and β forms. The mother liquor from which 4 was removed by filtration was evaporated to dryness under vacuum in a rotary film evaporator. The residue was dissolved in water (50 cm^3) and acidified with dilute HCl to give *o*-acetamidobenzoic acid in the form of white crystals (0.7 g, mp 182–184 °C).

(c) In Liquid NH_3 To Give 4 and Some 2-Methylquinazolin-4-one (Expt 5). About 10 g of anhydrous NH_3 gas was condensed into a 150-cm^3 round-bottomed flask containing powdered acetylanthranil (1, 3.2 g) and fitted with a reflux condenser chilled with dry ice–acetone. The mixture was swirled gently for 1 min to obtain uniformity. After the solution was allowed to react at reflux for an additional 2 min, the liquid ammonia was allowed to escape by evaporation. The IR spectrum of the dry residue (mp 178–181 °C) indicated that it was mostly starting material (about 95%), the rest being 2-methylquinazolin-4-one (i.e., the ratio of 1 to 5 was about 20:1). The sample was leached with 5% aqueous $NaHCO_3$ to remove starting material by conversion to *o*-acetamidobenzoic acid. The IR spectrum of the residue (0.2 g) showed that this was a mixture of 4 and 5 in the ratio of about 1:3.

About 50 g of anhydrous NH_3 gas was condensed into a second 150-cm^3, round-bottomed flask containing 3.2 g of 1. Reaction was allowed to occur at reflux temperature (i.e., about −33 °C) for 10 min before the ammonia was again removed by evaporation. The IR and NMR spectra of this residue (mp 155–160 °C) indicated it was a mixture of 1, the α form of 4, and 5 in a ratio of about 5:14:1, respectively. The sample was leached with 5% aqueous $NaHCO_3$ to remove 1, and the IR spectrum of the residue (2.5 g) indicated that it was a mixture of 4 and 5 in the ratio of about 10:1.

The second experiment was repeated with the modification that reaction was allowed to occur at reflux temperature for 20 min before termination by evaporation to dryness as before. The IR and NMR spectra of this residue indicated that conversion of 1 was complete and that the product was a mixture of 4 in its α form and 5 in a ratio of about 19:1, respectively.

(d) In Pyridine To Give 5 and 4. (i) At Reflux Temperature with Excess Anhydrous Ammonia Gas (Expt 7). Anhydrous NH_3 was bubbled through a stirred solution of acetylanthranil (150 g) in pyridine (500 cm^3) which was kept at reflux temperature for 3 h and then overnight at room temperature. During this time a white crystalline product (84 g, mp 283–240 °C) separated from solution. It was collected by filtration and then recrystallized from ethanol to give 2-methylquinazolin-4-one (5, R = H) in the form of long delicate needles (75 g, mp 240–240.5 °C), which was identified by its melting point, IR spectrum in Nujol (absorption bands at 3.1-3.6, 5.9, and 6.2 μm which are essentially the same as those reported by Pouchart)[14] and by its

(12) C. J. von Grotthus, *Justus Liebigs Ann. Chem.*, 58, 54 (1806); A. G. Debus, "Worlds Who's Who in Science", The A. N. Marquis Co., Chicago, 1968, p 712; C. C. Gillespie "Dictionary of Scientific Biography", Vol. 5, Charles Scribner's Sons, New York 1972, p 558.

(13) Part 1: L. A. Errede, *J. Org. Chem.*, 41, 1763 (1976).

elemental analyses. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49; mol wt 160.18. Found: C, 67.2; H, 4.9; N, 17.5; mol wt 163.

The pyridine mother liquor, from which **5** was removed by filtration, was evaporated to dryness. The residue (70 g) was recrystallized from ethanol (200 cm^3) to *o*-acetamidobenzamide a white crystalline compound (37 g, mp 194–195 °C), which was characterized as a salt by its IR spectrum. A portion of this salt (30 g) was dissolved in warm aqueous $NaHCO_3$ with evolution of CO_2 and the mixture then cooled to room tepmperature to induce crystalization. The precipitate (15.1 g, mp 239–240 °C) was identified as **5** by its melting point and IR spectrum, which were identical with those of the above sample of **5**. The aqueous $NaHCO_3$ mother liquor was acidified with dilute aqueous HCl to give a white precipitate (13.6 g, mp 184–186 °C) which was identified as *o*-acetamidobenzoic acid (**7**) by comparison of its IR spectrum and melting point with those of an authentic sample. These results indicated that the compound with a melting point of 194–195 °C was the 1:1 salt of **5** and **7**. This was verified by dissolving molar equivalents of the base **5** and the acid **7** in hot water and then cooling the solution to room temperature to yield the salt in the form of white granules (mp 194–195 °C), the IR spectrum of which was identical with that of the salt isolated earlier.

The ethanol mother liquor, from which the above salt was removed by filtration, was evaporated to dryness. The residue (31 g) was recrystallized from hot water to give *o*-acetamidobenzamide (**4**, R = H) in the form of white crystals (27 g, mp 180–181 °C) which was identified as the α form by its melting point and IR spectrum and by elemental analyses. Anal. Calcd for $C_9H_{10}O_2N_2$: C, 60.67; H, 5.62; N, 15.73; mol wt 178.2. Found: C, 60.8; H, 5.9; N, 15.9; mol wt 174 (by vapor-phase osmometry).

Thus, 0.93 mol of **1** was made to react with anhydrous NH_3 in pyridine at reflux, and 67% of **1** was recovered as **5**, 18% as **4**, and 12% as *o*-acetamidobenzoic acid (**7**) which corresponds to a selectivity ratio of 3.7:1 **5**/**4**.

(ii) At Room Temperature with Limited Ammonia (Expt 8 and 8′). In another experiment, a mixture of acetylanthranil (**1**) and *o*-acetamidobenzoic acid (**7**) in a molar ratio of 4:1, respectively, was dissolved in 0.50 cm^3 of pyridine that was saturated with NH_3 at room temperature, i.e., $[NH_3]$ = 0.21 M. This concentration was calculated from the data supplied to us by Dr. J. S. Marhevka of the 3M Co., who found that the solubility of NH_3 in pyridine at room temperature is 3.6 g/L. The conversion of **1** and NH_3 to products **5**, **4**, and **7** was monitored by proton NMR spectroscopy. The ratio of the proton intensity for the three methyl hydrogens (τ 7.69) of **1** to those (τ 7.88) in **2** in the initial spectrum was used to establish the ratio of **1** to **7** as 4:1 in the original powdered sample (0.04 g) that was dissolved in 0.5 cm^3 of pyridine–NH_3 solution to form the homogeneous system contained in the NMR tube. Spectra were recorded periodically over the next 26 h, during which time the peak at τ 7.69 decreased to 48% of its original intensity. It was not possible to follow the disappearance of NH_3 because its absorption became extremely broad. Consequently, it was assumed to parallel the disappearance of **1** on the basis of stoichiometry. The accumulation of 2-methylquinazolin-4-one (**5**, R = H) was indicated by the monotonic increase in absorption at τ 7.48 which was identified by comparison with the NMR spectrum of an authentic sample in pyridine as the absorption peak for the three hydrogen atoms of the methyl substituent in **5**. The monotonic increase in the intensity of this peak was equal to the decrease in τ 7.69 (i.e., the CH_3 of **1**) during the first 3 h. Thereafter, a peak appeared at τ 7.85, which we identified by comparison with an authentic sample in pyridine as the absorption for the hydrogen atoms of the methyl substituent in *o*-acetamidobenzamide. The intensity of this peak increased from being just barely detectable at 3 h to 8% of that at τ 7.48, which remained essentially constant after the first 5 h. The peak at τ 7.88, which we associated with that for the hydrogen atoms of the methyl substituent in *o*-acetamidobenzoic acid (**7**), remained essentially constant during the first 6 h and increased only about 10% during the next 16 h, owing to interaction of **1** with accumulated water of reaction.

(14) C. J. Pauchart, Ed., "Aldrich Library of Infrared Spectra", 2nd ed., Aldrich Chemical Co., Milwaukee, WI, 1975 Curve No. 1226B.

The sums of the intensities for the methyl hydrogens of **1**, **4**, **5**, and **7** in each spectra recorded at time t were normalized to 50 units, which was then converted to concentration units on the basis that 50 intensity units corresponds to 0.5 M for the sum total of solutes. These data are plotted in Figure 2, which shows clearly the sequence in which formation of **5**, **4**, and **7** become competitive.

The plot of log $[1]/[NH_3]$ as a function of time was a straight line during the first 3 h. The second-order rate constant calculated from the slope of this initial line was 0.053 L/(mol min). Thereafter, the rate decreased steadily as the reaction was complicated by interaction with the products, H_2O, **4**, and **5**.

Additional ammonia in the form of concentrated ammonium hydroxide (0.0014 cm^3, 28.8% NH_3, density 0.896 g/cm^3) was added at t = 30 h to the 0.5-cm^3 solution contained in the NMR tube (expt 8′), and the conversion to products was again monitored by proton NMR spectroscopy over the next 70 h. The concentrations of acetylanthranil, NH_3, and H_2O deduced from the NMR spectrum recorded immediately after this addition were 0.18, 0.14, and 0.52 M, respectively. No evidence for *o*-acetamidebenzamide was recorded in this spectrum. Apparently the addition of more ammonia and excess water caused rapid conversion to 2-methylquinazolin-4-one as discussed in the text. The time study for this conversion during the next 30 h was similar to that shown in Figure 3, which is the plot of the data recorded in expt 9 for the reaction of acetylanthranil with excess ammonia and water in pyridine. When conversion of NH_3 to **5** was almost complete (i.e., about 30 h later), evidence was again recorded in the NMR spectra that *o*-acetamidobenzamide was being produced and that a small amount of *o*-acetamidobenzoic acid was being accumulated, owing to interaction with water, as noted in Figures 2 and 3.

The plot of log $[1]/[NH_3]$ during the first 3 h after the addition of NH_4OH was again a straight line. The second-order rate constant calculated from the slope of this line was k = 0.018 L/(mol min), which is slower than that observed in the absence of added water.

(iii) At Room Temperature with Excess Ammonia and Water (Expt 9). One milliliter of concentrated hydroxide (28.8% NH_3, density 0.896 g/cm^3, from Baker Co.) was added to 49 cm^3 of pyridine. A 0.5-cm^3 sample of this solution was added to 0.040 g of a mixture of powdered acetylanthranil (46%) and *o*-acetamidobenzoic acid (54%) which was contained in an NMR tube. The conversion of **1** to products was monitored by proton NMR spectroscopy as described above, and the results of this time study are plotted in Figure 3. The plot of log $[NH_3]/[1]$ as a function of time was a straight line during the first 3 h. The initial second-order rate constant calculated from the slope of this line was k = 0.028 L/(mol min).

(e) In MeOH To Give Methyl *o*-Acetamidobenzoate (Expt 10). Anhydrous NH_3 was bubbled through a solution of **1** (1.6 g) in methanol (150 cm^3) for about 1 h. The product separated in the form of a white precipitate (1.8 g, mp 97–99 °C) which was identified as the methyl ester of *o*-acetamidobenzoic acid by its IR spectrum (absorption bands at 3.0, 5.9, 6.3, 7.9, and 8.2 μm) and NMR (Me_2SO-d_6) spectrum [τ −0.56 (br, NH), 1.6–2.9 (Ar), 6.13 (s, CH_3O), 7.87 (s, CH_3C).

In another experiment (expt 11), **1** (1.6 g) was made to react at room temperature for about 10 min with a solution of NH_4OH (30% NH_3, 10 cm^3) and methanol (90 cm^3) to give *o*-acetamidobenzamide (1.3 g) as the major product, which was isolated by evaporation of the mixture to dryness and then washing the residue with cold aqueous $NaHCO_3$ solution. Similar results were obtained by using ethanol (expt 12 and 13).

(2) Heterogeneous Reaction of Powdered Acetylanthranil (1) with NH_3 Vapor. (a) With Anhydrous NH_3 To Give 5 and the α Form of 4 (Expt 14). Finely powdered acetylanthranil (16 g) was dusted evenly over the bottom of a narrow rectangular glass tray (3 in wide, 24 in. long, and 2 in in height) that was fitted with a rubber-sealed glass cover, an inlet at one end, and an outlet at the other. The system was purged with a rapid stream of anhydrous ammonia gas for 5 min. Thereafter the gas was metered into the system at the rate of 60 bubbles/min. Samples of the powder were removed periodically for IR and NMR analyses. The IR spectra showed progressive conversion of **1** to products **5** and **4** in its α form. They indicated also that the ratio of these two products was changing with percent conversion. The

fraction (f_t) of unconverted 1 at time t was determined from the IR spectra by using the ratio of the intensity of the absorption band at 5.7 μm, which is due to the carbonyl band for 1, to the intensity of the absorption band at 6.2 μm, which is an aromatic band found in all samples and, consequently, remains relatively constant. The decrease in f_t as a function of t is first order as shown in Figure 1, from which was deduced that the half-life of 1 under these conditions is about 90 h.

The NMR spectra of the samples, removed after 8, 76, and 296 h, showed that the components of the mixture were 1, 5, and 4 and that the corresponding ratio changed from 90:9:1 after 8 h to 6:3:1 after 76 h to 2:9:9 after 296 h.

(b) With NH_3 Vapor Saturated with H_2O To Give 4 (Expt 15). Experiment 14 was repeated with the modification that air was metered into the system after it was bubbled through concentrated aqueous NH_4OH (i.e., 30% NH_3). Samples were removed after 1.5, 3, 5, 6.5, and 22 h. The data (Figure 1) show that the conversion of 1 to products is first order and that the half-life for 1 under these conditions is about 2 h, which is considerably shorter than that with pure anhydrous NH_3 gas. The IR spectra of all but the last sample indicated that the product of interaction was the α form of 4. The IR spectrum of the last sample taken after 22 h showed that product mixture was mostly the β form of 4 (about 95%) with a small amount of the ammonium salt of *o*-acetamidobenzoic acid (about 5%).

(c) Reaction of 1 with Air Saturated with Water Vapor. The bottoms of two shallow weighing flasks were dusted evenly with a layer of finely powdered acetylanthranil. The flasks were then placed in a much larger closed chamber that was saturated with water vapor at 22 °C. One powdered sample was weighed periodically in order to monitor the increase in weight owing to reaction of 1 with H_2O to give *o*-acetamidobenzoic acid which occurs stoichiometrically. Small aliquots of powdered sample were removed periodically from the other flask to monitor by proton NMR in pyridine the conversion of acetylanthranil to *o*-acetamidobenzoic acid. The ratio of proton integrations for the methyl group of 1 to the sum total of proton integrations for the methyl groups in 1 and its product was used as a measure of mole fraction, x, of residual reactant at time t. This ratio was in good agreement with the corresponding ratio of the weight increase at time t to the total weight after 6 days in air saturated with water vapor at 22 °C. Both gave the same linear plot of log x as a function of t with a half-life $t_{1/2}$ = 35 h, as shown in Figure 1.

(3) Preparation of *o*-Acetamidobenzamide from *o*-Aminobenzamide. Powdered isatoic anhydride (30 g) was added to 100 cm^3 of a 10% aqueous ammonium hydroxide solution saturated with ammonium acetate. The mixture was warmed to initiate the reaction, which was accompanied by considerable frothing. When the frothing subsided, the mixture was heated on a steam bath with virgorous stirring for an additional hour. The clear solution was cooled to room temperature and *o*-amidobenzamide separated in the form of white platelets (21 g, mp 103–105 °C). The product was identified by its IR spectrum, which was identical with that of an authentic sample. The platelets were added to acetic anhydride (30 cm^3). Reaction occurred exothermically to give a clear solution, which crystallized on cooling to a dense mass of granular cubic crystals (21 g, mp 178–180 °C, with subsequent evolution of water at 235–270 °C to give 5 which solidified on cooling and remelted at 230-233 °C). This product was identified as the α form of *o*-acetamidobenzamide by its IR spectrum. After the α form was first isolated in our laboratory, however, subsequent attempts to prepare the α form via this procedure gave only the β form which melted at 186–188 °C.

The α and β forms and mixtures thereof could be recrystallized from MeOH and Me_2SO without change. Recrystallization from aqueous $NaHCO_3$, however, gives the β form exclusively. On the other hand, recrystallization of the β form from pyridine gives a mixture of the α and β forms, but the α form can be recovered unchanged from pyridine even after 3 days at reflux temperature.

(4) Conversion of 4 to 5 in Aqueous Solution at °C. A mixture of *o*-acetamidobenzamide (3.5 g, β form) and water (200 cm^3) was warmed to 90 °C in a three-necked, round-bottomed flask fitted with a stirrer, reflux condenser, and thermometer to give a clear solution, from which aliquot samples (10 cm^3) were removed periodically. Each sample was cooled to room temperature to induce crystallization. The precipitate was collected by filtration. The corresponding melting point and IR spectrum were noted to follow the conversion from 4 to 5 as a function of time. The fraction of 4 remaining unchanged at time t was calculated from the IR spectrum by using the absorption band at 13.3 μm, which is an aromatic band characteristic of the β form, as the indicator band and that at 6.3 μm, which is an aromatic band characteristic of both 4 and 5 and consequently remained essentially constant, as a reference band.

The fraction (f_t) of 4 not yet converted to 5 at time t is plotted in Figure 4 as a function of time. It shows that this conversion is first order and that the half-life of 4 under these reaction conditions is about 1 h. The corresponding melting point of the recovered solute at time t is also shown in Figure 4. It changed from 188–189 °C for pure 4 in its β form to a minimum of 163–168 °C at about 50% conversion to 5 and then up to 236–238 °C at 100% conversion to 5 showing that little or no side products are formed in the conversion.

Registry No. 1, 525-76-8; 2 (R = H), 7664-41-7; 4 (R = H), 33809-77-7; 5 (R = H), 1769-24-0; 7, 89-52-1; methyl *o*-acetamidobenzoate, 2719-08-6; *o*-aminobenzamide, 88-68-6.

Supplementary Material Available: The IR spectra and the X-ray diffraction patterns for the α and β forms of *o*-acetamidobenzamide (2 pages). Ordering information is given on any current masthead page.

Silanes in Organic Synthesis. 8. Preparation of Vinylsilanes from Ketones and Their Regiospecific Cyclopentenone Annulation[1]

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A general method is described for the formation of vinylsilanes from ketones. Thus, conversion to the benzene- or *p*-toluenesulfonylhydrazone and sequential treatment with *n*-butyllithium and chlorotrimethylsilane in anhydrous tetramethylethylenediamine proceeds regiospecifically to afford the less substituted vinylsilane (in unsymmetrical cases). Friedel–Crafts acylation with acryloyl chlorides and aluminum chloride and subsequent Nazarov cyclization with Lewis acid catalysis results in cyclopentenone annulation. Numerous examples that reveal the scope of this process are described. Due to accompanying polymerization, annulation with acryloyl chloride itself is least efficient. This complication can, however, be averted through use of β-chloropropionyl chloride and dehydrochlorination with 1,5-diazabicyclo[5.4.0]undec-5-ene prior to ring closure.

The decade of the 70's has witnessed the improvisation of a dazzling array of new methods for the construction of carbon–carbon bonds. Of these, the area commonly referred to as *vinylic substitution* has perhaps witnessed

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