Acylanthranils. 1. The Pathway of Quinazolone Formation in the Reaction of Acylanthranils with Anilines[1]

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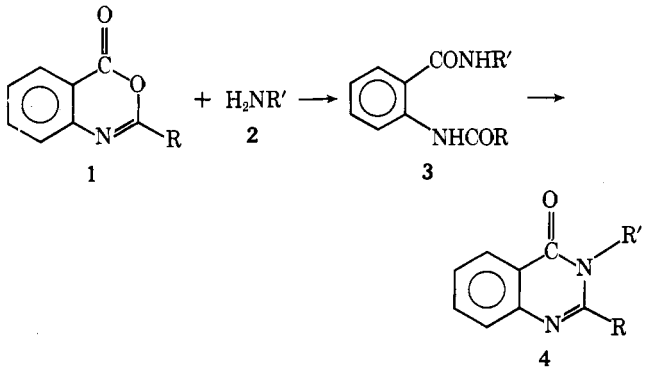
Received October 23, 1975

Reinvestigation of the reaction of benzoxazinones, 1 (i.e., acylanthranils), with anilines, 2, to give *o*-acylamidobenzanilides, 3, and/or quinazolones, 4, has shown that the accepted pathway for the sequential formation of 4 from 3 is not correct. These products are formed concurrently via alternative pathways. The precursor of 4 is not 3, but rather a *N*-(2-carboxyphenyl)-*N'*-arylacylamidine, 5, a heretofore unobserved intermediate which is converted to 4 even at room temperature.

Interest in the reaction of benzoxazinones, 1, with primary amines, 2, has been renewed owing to the potential use of the products produced thereby as physiologically active compounds[2] or as thermostable polymers.[3,4] The early work with this reaction was done ca. 1900 by Heller, Bogert, and others,[5] who reported that *o*-acylamidobenzamides, 3, and/or the corresponding quinazolones, 4, were the major products. They proposed that 4 was formed from 3 during the course of this reaction, which usually was carried out at reflux temperature in a solvent such as toluene. This sequential pathway appeared to be consistent with all the observed results, and is still recorded in modern reference books[6] as the accepted pathway as shown below:



A considerable amount of the early work was done using 2-methyl-4*H*-benzoxazin-4-one (**1a**). This compound was given the trivial name acetylanthranil,[5] presumably to emphasize that it is the anhydride obtained conveniently from acetylanthranilic acid by cyclodehydration in acetic anhydride at reflux temperature. Acetylanthranil is an interesting semiacid anhydride that undergoes many of the reactions of true acid anhydrides, but at a slower rate.

Initially,[4] our own research was directed toward high-performance polymers from bifunctional acylanthranils and diamines. In the course of this research, it was of interest to establish how easily the neutral diamide form, 3, could be converted thermally to the basic quinazolone form, 4, as per the proposed pathway. A set of acylamidobenzamides were used as model compounds for these conversions, which were monitored by differential thermal analysis (DTA). The data are shown in Table I. In view of the accepted pathway, it was surprising to note that the minimum temperature required for thermal cyclodehydration to the corresponding quinazolone was about 250 °C. Since this minimum temperature is more than 100 °C above the highest temperature used to react acylanthranils with amines, the accepted pathway, which requires that 4 be produced sequentially from 3 under relatively mild conditions, became suspect, and this uncertainty required clarification.

We observed that acetylanthranil (**1a**) reacts with amines at an appreciable rate even at room temperature, so that the reflux temperatures employed by the earlier researchers were unnecessary, and may even have obfuscated proper interpretation of their results. In the reaction of **1a** with aniline, it was noticed that some of the product separated from solution as a white precipitate easily isolated by filtration. The dry powder melted sharply at 115–116 °C with evolution of a gas, and its elementary analysis was consistent with the empirical formula $C_{15}H_{14}O_2N_2$, which corresponds to a one-to-one adduct, **5a**, of acetylanthranil and aniline. This adduct dissolved in warm acetone–water solution, but it decomposed slowly in this solvent to give equivalent amounts of *N*-acetylanthranilic acid, **6**, and aniline. It dissolved in warm dilute aqueous $NaHCO_3$ with evolution of some CO_2. It dissolved even more rapidly in cold dilute NaOH and in cold dilute HCl, indicating that the compound was some form of internal salt or zwitterion. The salt is unstable in aqueous solution, especially at pH >7, and a precipitate begins to form within 0.5 h and appears to be complete within 4 h. This precipitate, which represented 80% of the dissolved salt, was identified as *N*-phenyl-2-methylquinazol-4-one (**4a**). The rest was isolated as *N*-acetylanthranilic acid and aniline in about equivalent amounts. A sample of the salt product was converted by fusion at ca. 130 °C to give almost quantitatively **4a** with evolution of an equivalent amount of water.

The ir spectrum of the adduct, **5a**, in KBr confirms a saltlike structure (broad band at 3–4 and at ca. 6.3 μ). It rules out the presence of amide carbonyl groups (no absorption band at 5.7–6.0 μ), but supports the presence of NH (band at 2.9 μ), –C=N– (band at 6.1 μ), monosubstituted phenyl (band at 14.4 μ), and an ortho-disubstituted phenyl group (12.9 μ). The NMR spectrum of the adduct dissolved in alkaline D_2O indicates only one form of CH_3 group (τ 8.12), and a complex aromatic pattern in the region τ 1.6–3.2. It was concluded, therefore, that the adduct, **5a**, of acetylanthranil and aniline is an internal amidine salt.

Only about half the acetylanthranil was recovered as insoluble **5a**. The rest remained in the excess aniline used as solvent. In order to recover the other half, the mother liquor was concentrated almost to dryness by distillation at 80 °C in an evacuated system. The residue was a mixture whose major component (about 60%) was **4a**. The other major component (about 30%) was identified as *N,N'*-diphenylacetamidine (**7**), which was produced apparently by aniline exchange with the 2-carboxyaniline group as indicated in Chart I.

When **5a** was subjected to reaction conditions approximating those used by the early investigators, namely in solvents such as pyridine or toluene and some amine as catalyst at reflux temperatures, it was converted within mimutes to **4a**. This result is in sharp contrast to the observation made earlier that ortho diamides of type 3 are stable under these conditions and indeed are not converted to 4 unless consid-

Table I. Thermal Conversion of *o*-(Acylamido)benzamides (3) to Quinazolones (4)

R′	R	3 mp, °C	4 mp, °C	Temp of convn, °C, by DTA[a]	Registry no. 3	Registry no. 4
Ph	CH_3	160–162	147–148	300–310	54364-31-7	2835-23-1
Ph(CO_2H)-*o*	CH_3	215–216	255–257	340–360	58426-37-2	4005-06-5
Ph	Ph	280–281	120–121	290–310	18543-23-2	22686-82-4
H	CH_3	187–188	240–241	250–270	16353-13-2	1769-24-0
$(CH_2)_6NHCOPh$-($NHCOCH_3$)-*o*	CH_3	203–204	174–177	340–370	58426-47-4	58426-48-5

[a] Differential thermal analysis.

Chart I

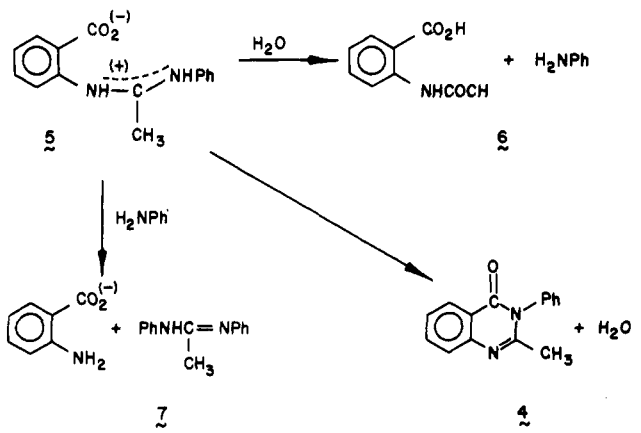
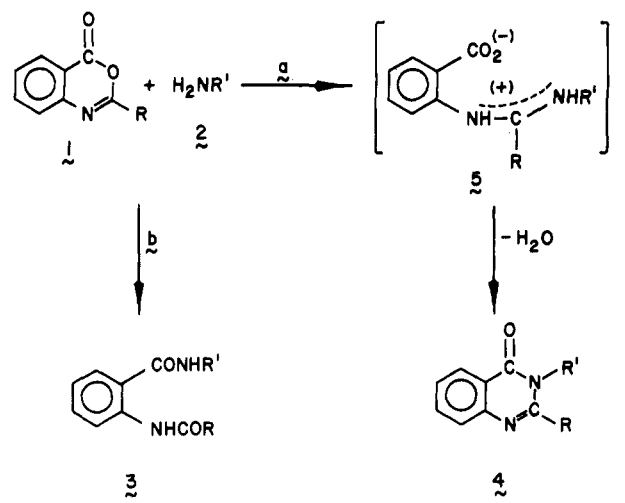


Chart II



erably more strenuous conditions are employed, such as fusion above 250 °C.

When **1a** was allowed to react at room temperature with *p*-toluidine (**2b**) and with *p*-(*N*,*N*-dimethylamino)aniline (**2c**) in a neutral solvent, the corresponding amidine salts (**5b** and **5c**) were isolated in very good yields (>90%). In these cases, the salt product was separated by filtration and the mother liquor was then diluted with ether to cause precipitation of the soluble portion, thereby precluding conversion to the corresponding quinazolone, **4**, or diarylacetamidine, **7**, which occurs at higher temperatures and in excess amine.

When benzoylanthranil (i.e., 2-phenyl-4*H*-3,1-benzoxazin-4-one, **1b**) was made to react with aniline in benzene at reflux temperature, *o*-acetamidobenzanilide (**2b**) was obtained almost exclusively, which is in sharp contrast to the results obtained with acetylanthranil (**1a**). The reactivity of **1b** is considerably less than that of **1a**, and consequently, the higher temperature was required to effect conversion to products within a reasonable time interval. This temperature difference, however, as well as the change from a methyl substituent to a phenyl at the 2 position of the anthranil, may account for the sharp change in selectivity, and further investigation is required to establish the cause of the inversion in selectivity. Nevertheless, the results do show that the products **3** and **4** are formed via alternate pathways a and b, as shown in Chart II, and not sequentially as believed earlier.

Although results reported here for **1a** and **1b** represent extreme cases in selectivity, they are not necessarily typical. The results obtained by others,[2,5,6] who caused numerous acylanthranils to react with numerous amines, indicate that a mixture is usually produced, with **3** as the major component instead of **4**. These results infer that b is the preferred pathway which is consistent with the known relative reactivity of >C=O vs >C=N- groups. More work is planned, however, to understand better the parameters that affect selectivity and overall rate of reaction.

Although the amidine salts of type **5** have never previously been isolated, one was postulated by Scherrer and Beatty[7] as a very short-lived intermediate in the reaction of 2,3-diphenyl-4(3*H*)-quinazolinone (i.e., *N*,2-diphenylquinazol-4-one) in alcoholic NaOH to give aniline and anthranilic acid. In a sense, the Scherrer reaction is the reverse of that discussed in this paper.

Experimental Section

A. Preparation of Acetylanthranil (1a). A solution of anthranilic acid (1 mol) in acetic anhydride (0.5 l.) was made to react at reflux temperature for 2 h. The excess solvent was removed by distillation at atmospheric pressure. The residue was separated by distillation under vacuum and the fraction boiling in the range 125–132 °C at 8 mmHg pressure was collected as an oil that solidified to a white solid. The solid was recrystallized from heptane to give acetylanthranil in the form of long, white, dense needles (mp 81–82 °C, lit. mp 81–82 °C[8]) in 85% yield.

B. Reaction of Acetylanthranil (1a) with Anilines. 1. With Aniline (2a) to Give 5a, 4a, and 7. Acetylanthranil (26 g) (**1a**) was dissolved at room temperature in aniline (100 g) (**2a**) to give a clear solution, which soon became turbid as a white precipitate began to form throughout the solution. Precipitation appeared to be complete within 4 h, and the mixture was separated by filtration. The precipitate was slurried in ether and recollected by filtration to yield 22 g of product as a white powder (mp 115–116 °C).

Anal. Calcd for $C_{15}H_{14}O_2N_2$: C, 70.85; H, 5.55; N, 11.01; O, 12.60. Found: C, 70.7; H, 5.9; N, 10.9; O, 12.5.

The ir and the NMR spectra are consistent with the amidine salt structure **5a** as discussed in the body of this report.

A sample of **5a** (2 g) was dissolved at room temperature in a minimum amount of 2% aqueous NaOH and then diluted twofold. The clear solution became cloudy within 0.5 h and precipitation appeared to be complete within 8 h. The product was collected by filtration and recrystallized from heptane to give *N*-phenyl-2-methylquinazol-4-one (**4a**) in the form of pearl-white platelets (1.7 g, mp 147–148 °C). The compound was identified by its ir spectrum and elemental analysis.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; mol wt. 236.38. Found: C, 76.6; H, 5.6; N, 11.8; mol wt, 242.

The compound was converted to its hydrochloride salt by reaction with HCl in ether. The salt was recrystallized from hot water to give the hydrochloride of **4a** in the form of pearl-white platelets (mp 275–277 °C).

Anal. Calcd for $C_{15}H_{13}N_2OCl$: Cl, 13.5. Found: Cl, 13.5.

Another sample of **5a** (1 g) was fused at 120 °C for about 0.5 h during which time an equivalent amount of water was liberated, and the melt resolidified as a white solid. The solid was recrystallized to give **4a** in the form of white flakes (0.9 g, mp 147–148 °C).

The aniline solution, from which **5a** was removed by filtration, was evaporated to dryness at <1 mmHg pressure and 80 °C. The residue was digested with 10% aqueous HCl, leaving a white, saltlike residue (15 g) which was recrystallized from hot water to give the hydrochloride of **4a** in the form of pearl-white platelets (mp 275–277 °C; no depression with an authentic sample). The aqueous acid extract was neutralized with NaOH. A yellowish-white powder precipitated and was removed by filtration. This powder (2.5 g) was recrystallized from heptane to give *N,N'*-diphenylacetamidine (**7**) in the form of white crystals (mp 126–127 °C; no depression with an authentic sample).[9] The compound was also identified by its ir spectrum, identical with that of an authentic sample.

When 0.16 mol of **1a** was made to react with **2a** as solvent, 54% of **1a** was isolated as **5a**, 30% as **4a**, and 15% as **7**.

2. In *p*-Toluidine (2b) to Give 5b. Acetylanthranil (0.1 mol) was dissolved in **2b** (0.6 mol) to give a clear solution which became turbid soon thereafter as the product began to precipitate from solution. Precipitation appeared to be complete after 4 h. The precipitate (mp 119–120 °C) was collected by filtration and washed with Et_2O. The mother liquor containing the excess aniline was diluted 20-fold with ether and additional precipitate (mp 119–120 °C) formed which was also collected by filtration. The combined precipitates represented a 95% yield of *N*-(2-carboxyphenyl)-*N'*-(*p*-tolyl)acetamidine (**5b**), identified by its ir spectrum and its elemental analysis.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 72.0; H, 6.1; N, 10.3.

A sample of **5b** (1.0 g) was dissolved in 0.5% aqueous base to give a clear solution. A few minutes thereafter, the solution became cloudy with the formation of the quinazolone, which precipitated as a white powder. Precipitation appeared to be complete within 1 h, and the product (0.9 g) was collected by filtration, dried, and recrystallized from heptane to give *N*-(*p*-tolyl)-2-methylquinazol-4-one (**4b**) in the form of long, flat needles (mp 151–152 °C). The assigned structure of **4b** was verified by its ir spectrum.

3. In *p*-(Dimethylamino)aniline (2c) to Give 5c. Acetylanthranil (0.1 mol) was dissolved at room temperature in **2c** (0.2 mol) to give a clear solution, which became a semisolid mixture within 4 h. The mixture was diluted with Et_2O and separated by filtration. The amount isolated represented 96% of the expected amidine salt, **5c**, whose assigned structure was verified by its ir spectrum and its elemental analysis.

Anal. Calcd for $C_{17}H_{19}O_2N_3$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.5; H, 6.6; N, 14.2.

The salt began to melt at 160 °C, but it was converted at this temperature to the corresponding quinazolone, **4c**, which solidified from the melt. A sample of the amidine salt (1 g), contained in a test tube, was fused in an oil bath kept at 180 °C. The salt melted rapidly with evolution of water vapor which was condensed on the cool upper portion of the test tube. The melt resolidified within a few minutes. The product was recrystallized from ethanol–water solution to give *N*-(*p*-dimethylaminophenyl)-2-methylquinazol-4-one (**4c**), in the form of white crystals (0.8 g, mp 227–228 °C). The compound was identified by its ir spectrum and elemental analysis.

Anal. Calcd for $C_{17}H_{17}ON_3$: C, 73.09; H, 6.14; N, 15.04; mol wt, 279.4. Found: C, 73.1; H, 6.3; N, 14.9; mol wt, 278.

Another sample of **5c** (2.0 g) was dissolved in dilute aqueous NaOH. Precipitation of the quinazolone, **4c**, began within 5 min and was complete within 1 h. The product (1.8 g) was identified as **4c** by its ir spectrum and its melting point, 227–228 °C, which showed no depression when mixed with the product obtained by fusion.

Reaction of Benzoylanthranil (1b) with Aniline to Give *o*-Benzamidobenzanilide (3b). Benzoylanthranyl (3 g, mp 122 °C), which was prepared according to the procedure of Anschutz,[10] was allowed to react overnight at reflux temperature with aniline (3 g) in benzene (50 ml). The product separated in the form of a white powder (3.8 g, mp 286–287 °C). It was identified as *o*-benzamidobenzanilide (**3b**) by its melting point and ir spectrum, which were identical with those of an authentic sample.

Acknowledgment. The author is indebted to Dr. J. J. McBrady for interpretation of the ir and NMR spectra.

Registry No.—**1a**, 525-76-8; **1b**, 1022-46-4; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 99-98-9; **4a** HCl, 52692-90-7; **4b**, 22316-59-2; **4c**, 58426-38-3; **5a**, 34264-61-4; **5b**, 58426-41-8; **5c**, 58426-42-9; **7**, 621-09-0; anthranilic acid, 118-92-3.

References and Notes

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Acylanthranils. 2. The Problem of Selectivity in the Reaction of Acetylanthranil with Anilines

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Received October 23, 1975

Anilines attack acetylanthranils preferentially at the carboimino center rather than at the carbonyl center despite the greater reactivity of the latter group toward nucleophilic agents. Anthranilic acid is a notable exception that gives predominantly *o*-(*o*-acetamidobenzamido)benzoic acid, the product produced via reaction at the carbonyl site.

Reinvestigation[1] of the reaction of benzoxazinones (i.e., acylanthranils), **1**, with anilines, **2**, showed that the diamide, **3**, and quinazolone, **4**, products are formed via alternate pathways a and b as shown in Chart II of ref 1, and not sequentially **4** from **3** as was suggested by earlier investigators.[2]

Acylanthranils undergo many of the reactions of acid anhydrides, but at a much slower rate. They can be considered in effect as cyclic mixed anhydrides that react with amines via two alternative electrophilic sites, namely at the carbonyl group to give via pathway b a neutral diamide **3**, or at the carboimino group to give via pathway a an amidine salt **5**. Presumably the reaction via both pathways is kinetically first