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(17) (a) Substituents have a greater effect on the chemical shifts of the sulfhydryl proton in substituted benzenethiols ($\rho^- = -0.268$)[17b] than they have on the chemical shifts of the benzylic proton in substituted toluenes ($\rho = -0.200$),[17c] (b) S. H. Marcus and S. I. Miller, *J. Phys. Chem.*, **68**, 331 (1964). (c) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).
(18) We have found a positive ρ for hydrogen abstraction from substituted benzenethiols by *tert*-butyl radicals and a negative ρ for abstraction by undecyl radicals. These results will be discussed in a subsequent paper.
(19) W. C. Danen and D. G. Saunders, *J. Am. Chem. Soc.*, **91**, 5924 (1969).
(20) (a) In Danen's subsequent publications on eq 7,[20b,c] he used polar effects on both transition states and ground states and quotes very estensively and verbatim, with acknowledgment, from our letter to him dated Jan 30, 1974, in which we first presented the ideas developed in the present paper. (b) W. C. Danen, D. G. Saunders, and K. A. Rose, *J. Am. Chem. Soc.*, **96**, 4558 (1974). (c) W. C. Danen in "Methods in Free-Radical Chemistry", Vol. 5, E. S. Huyser, Ed., Marcel Dekker, New York, N.., 1975, pp 52–55.
(21) The right hand resonance structure in eq 9, drawn to emphasize the symmetrical charge distribution in this transition state, represents two other resonance structures, $Ph^+ I \cdot Ar$ and $Ph\cdot I^+ Ar$.
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(26) We have no direct evidence of the direction or magnitude of substituent effects on the bond dissociation energy (BDE) of the C–I bond. BDE's of substituted bromobenzenes, which should be proportional to BDE of the corresponding ArI's, have been reported from measuring the rate of formation of hydrogen bromide produced by pyrolysis of substituted bromobenzenes in toluene.[27] There is no apparent consistent effect of substituents on these bonds, except that ortho-substituted phenyl–Br bonds are generally stronger than meta and meta than para. However, the differences in BDE between substituted bromobenzenes and bromobenzene reported by Szwarc are small (generally less than 1 kcal/mol) and, therefore, probably unreliable.[28]
(27) M. Szwarc and D. Williams, *Proc. R. Soc. London, Ser. A*, **219**, 353 (1953).
(28) We also doubt Szwarc's results for another reason. Meta-substituted iodobenzenes are more reactive than the para compounds toward attack by phenyl and *p*-nitrophenyl radicals (see Figure 1). Like Danen,[19] we interpret these kinetic results to indicate that the C–I BDE's of the meta compounds are smaller than those of the para; this conclusion is contrary to Szwarc's ordering of BDE.
(29) As Zavitsas points out,[8] substituents also influence the bond strength of benzylic C–H bonds in toluenes. However, substituent effects on BDE in the iodobenzenes are probably more important than in toluenes because of the direct linkage of the iodine to the aromatic ring.
(30) S. G. Cohen, F. Cohen, and C. H. Wang, *J. Org. Chem.*, **28**, 1479 (1963).
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(32) We could have easily detected 5×10^{-4} M 4-nitrobiphenyl.
(33) (a) W. A. Pryor, J. T. Echols, and K. Smith, *J. Am. Chem. Soc.*, **88**, 1189 (1966); (b) W. A. Pryor, K. Smith, J. T. Echols, Jr., and D. L. Fuller, *J. Org. Chem.*, **37**, 1753 (1972).
(34) Using PhI as an iodine donor and 0.05 M NAT at 60 °C, $k_{Cl}/k_I = 1.3 \times 10^{-2}$ for C_2Cl_6 and 1.7×10^{-2} for CCl_4.
(35) (a) The results of the least-squares analysis are reported according to the following format:[35b] the slope of the least-squares line and its interval estimator (uncertainty) at the 95% confidence level are $b + (t)(s_b)$,[35c,36] the average standard deviation of the logarithms of the individual k_I/k_{Cl}'s is s_y,[36e] and the number of points is n. (b) W. H. Davis, Jr., and W. A. Pryor, *J. Chem. Educ.*, **53**, 285 (1976). (c) The slope of the least-squares line is b,[36a] and the standard deviation of the slope is s_b.[36b] It may be said with m% confidence that the true value of the slope lies within $(t_{n-2,1-m})(s_b)$ of the calculated slope, b.[36c] The Student's t value for n points and a confidence level of m%, $t_{n-2,1-m}$, can be obtained from a table of the distribution of t (two-tailed tests).[36d]
(36) G. W. Snedecor and W. G. Cochran, "Statistical Methods", 6th ed, Iowa State University, Ames, Iowa, 1967: (a) p 136; (b) p 138; (c) p 153; (d) p 549; (e) p 44.
(37) The difference in reactivity of meta and para substituted iodobenzenes is about the same for the *p*-nitrophenyl radical (see Figure 1) and the phenyl radical (see Figure 1 of ref 19). This suggests that this difference arises from BDE effects, which are independent of the abstracting radical, rather than transition state or intermediate effects, which would be different for the two radicals.
(38) R. Ito, T. Migita, N. Morikawa, and O. Simamura, *Tetrahedron*, **21**, 955 (1965).
(39) If electron-withdrawing substituents weaken the C–I bond as evidenced by the positive ρ's for eq 8 and 11, then each *p*-nitrophenyl radical reaction is less exothermic than the corresponding phenyl radical reaction. Since according to the BDE approach,[8] the absolute magnitude of ρ increases with decreasing exothermicity of the abstraction reaction, the ρ value for the *p*-nitrophenyl radical would be predicted to be larger than that for the phenyl radical. Thus, the prediction based on BDE effects alone is clearly erroneous.
(40) If our suggested order of bond dissociation energies is correct, the reactions of the *p*-nitrophenyl radical are more endothermic than are those of phenyl. Therefore, SETS should be more important in the reactions of the *p*-nitrophenyl radical because of this factor as well.

Acylanthranils. 3. The Influence of Ring Substituents on Reactivity and Selectivity in the Reaction of Acylanthranils with Amines

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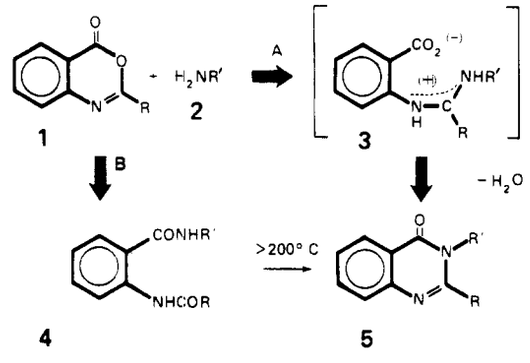
Sixteen acylanthranils were prepared and allowed to react with primary amines to give the corresponding benzamides, **4**, and/or quinazolones, **5**, which confirms the results of other investigators. The product distributions, however, are consistent with our recent suggestion that these products are formed competitively via alternative pathways A and B, as indicated in Scheme I, rather than sequentially **5** from **4** as believed originally. Although ring substituents on the acylanthranil affect markedly the overall *rate* of reaction, they do not necessarily affect *selectivity*. The latter is determined primarily by the electronic and steric factors associated with the substituent R at the 2 position only. As a general rule, the acetylanthranils, which are more reactive, favor pathway A, but the benzoylanthranils, which are less reactive, favor pathway B. Nevertheless the ratio k_A/k_B decreases with increase in bulk of the substituent R at the 2 position because of steric hindrance.

Our reinvestigation[1,2] of the reaction of acylanthranils, **1**, with primary amines, **2**, confirmed the reports of earlier investigators[3,4,5] that *o*-acylamidobenzamides, **4**, and/or the corresponding N-substituted quinazolones, **5**, are isolated as the major products if the reaction is made to occur at about 100 °C or above. We reported,[2] however, that on the one hand N-substituted *N'*-(2-carboxyphenyl)acetamidines, **3**, are almost always produced exclusively as the primary products of the reaction of acetylanthranil, **1b** (R = CH_3), with anilines at room temperature, and that these intermediates are convertible to the corresponding quinazolones by cyclodehydration in solution even at room temperature. On the other

hand, we noted that *o*-benzamidobenzanilide, **4a**, is produced exclusively[2] when benzoylanthranil, **1a** (R = Ph), is allowed to react with aniline below 150 °C. Since it was shown that the *o*-acylamidobenzamides, **4**, require fusion temperatures of about 250 °C for conversion to the corresponding quinazolones, **5**, it appears that below 150 °C **4** and **5** are produced by alternative pathways A and B as shown in Scheme I, and not

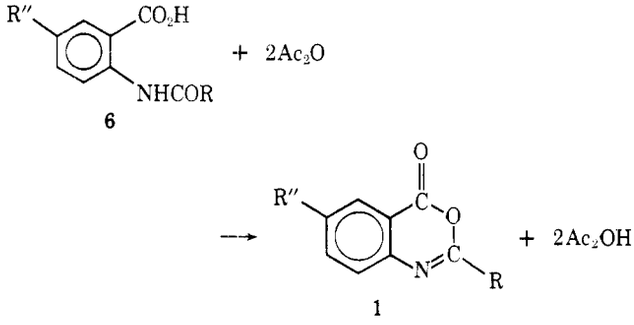
Scheme I



sequentially (**5** from **4**) as suggested by the earlier investigators. Therefore it is now of interest to determine why some acylanthranils follow pathway A exclusively, while others follow pathway B exclusively. Accordingly, the large body of apparently inconsistent results reported by the earlier investigators has been reinterpreted in light of the present realization that acylanthranils react via alternative pathways. Such a reconsideration leads to a more self-consistent pattern that shows how the reactivity and selectivity are dependent upon the electronic and steric factors associated with the molecular structure of the acylanthranil. Exposed areas of uncertainty are clarified herein by new experiments that complement the data already accumulated in the literature.

Results and Discussion

The acylanthranils, **1a–p**, were prepared by us in good yields (i.e., >50%) by cyclodehydration of the corresponding carboxylic acids **6** in acetic anhydride (or thionyl chloride) at reflux for several hours.



The melting point and ir data for this set of 16 acylanthranils are collected in Table I. The more reactive ones, such as acetylanthranil, were allowed to react at room temperature with a given amine, neat or in solution, whereas the less reactive ones, such as benzoylanthranil, required higher temperatures to effect complete reaction within a reasonable time interval as noted in Tables II and IV. The relative reactivities of these acylanthranils were evaluated qualitatively. The corresponding selectivities for reaction via pathways A relative to B, i.e., k_A/k_B = (**3** or **5**)/**4**, were calculated on the basis of the separation and materials balance procedure described previously.[2]

Zentmyer and Wagner[4] reported that the reactivity of acylanthranils varies considerably, as exemplified by acetylanthranil, which is quite sensitive to hydrolysis, and by benzoylanthranil, which is not. Since the former almost always follows pathway A whereas the latter appears to prefer pathway B, one might suspect that selectivity is related to reactivity. The relative rates of attack by a nucleophile at the 2 and 4 positions should be a function of the relative electrophilicities at these alternate sites, which in turn should be a function of the substituents on the acylanthranil, especially at the 2 position.

The results reported by Bogert,[3k] who caused several benzoylanthranils to react with aromatic amines neat at fusion temperature to give the corresponding quinazolones, and those reported by Wagner,[4] who caused another set of benzoylanthranils to react at 100 °C with aniline neat and with ammonia in ethanol at room temperature to give the corresponding *o*-benzamidobenzamide, are in light of the introduction mutually inconsistent. Although our result with the benzoylanthranil–aniline reaction confirmed the report of Wagner, it was important to show whether benzoylanthranil, **1a**, does indeed follow pathway B as a general rule, and to establish the conditions under which it might also follow pathway A. Accordingly, **1a** was made to react with the simple primary aliphatic amines, *n*-propylamine and *n*-butylamine, in diethyl ether at reflux overnight, with the diamines oxydianiline and hexamethylenediamine, neat and in solution at 140 °C for about 4 h, and with 4,4'-diaminodiphenyl sulfone neat at 250 °C for 4 h.

The results of these experiments are summarized in Tables II and III. They show that the corresponding mono- and bis-*o*-benzamidobenzamides, written symbolically in Table III as BNHR and BNHRNHB, respectively, were isolated in good yield for all reactions made to occur at or below 140 °C. Formation of the mono- and bisquinazolones, written symbolically in Table III as QR and QRQ, occurred only at 250 °C, as evidenced by the reaction with $(p\text{-}NH_2Ph)_2SO_2$ to give a mixture of $(QPh)_2SO_2$, $(BNHPh)_2SO_2$, and $BNHPhSO_2PhQ$ in the approximate ratio of 2/1/1, respectively. These results suggest that the quinazolones isolated by Bogert[3k] were formed sequentially via cyclodehydration of the corresponding *o*-benzamidebenzamides owing to his fusion temperatures that were above 200 °C, and support the conclusion that benzoylanthranils as a class do indeed react with amines via pathway B exclusively as noted by Wagner. These results also verify that benzoylanthranil, **1a**, is considerably less reactive than acetylanthranil, **1b**, which reacts exothermally with the above amines on contact via pathway A.

Hegarty and Bruice[6] have shown that 2-amino-3,1,4-benzoxazone, **1c** (R = NH_2), reacts slowly with amines to give the corresponding *o*-uramidobenzamides. The qualitative results obtained in our laboratory confirm that **1c** is considerably less reactive than **1b** (R = CH_3) but somewhat more so that **1a** (R = Ph). It can be made to undergo intermolecular condensation, however, at its softening point, about 190 °C, where it does not really melt but is converted instead to a mixture of polymerization products that melts at 285–300 °C.

We prepared trifluoroacetylanthranil, **1d** (R = CF_3), to compare its reactivity and selectivity with those of **1a–c**. We noted that **1d** is considerably more reactive than **1b** as indicated by its sensitivity toward atmospheric moisture to give *o*-trifluoroacetamidobenzoic acid, and by its ease of reaction with alcohols to give the corresponding ester. In contrast **1b** is quite stable to atmospheric moisture and requires reflux temperature in alkaline alcohol to form the ester.

When **1d** was added to a solution of aniline or *p*-toluidine in benzene, the corresponding trifluoroacetamidines (**4d**) precipitated from solution almost immediately (Tables IV and V). In contrast, the corresponding acetamidine salts from **1b** require a few hours to complete reaction under the same conditions (Table IV). None of the corresponding diamide,

Table I. Cyclodehydration of 2-(RCONH)-5(R'')$PhCO_2H$ (6) to the Corresponding Acylanthranil, 1

R	R''	Mp of 6, °C	Dehydration agent	1	Mp of 1, °C	Important absorption bands in ir spectrum of 1, μ
Ph	H	180–181	*a*	**a**	122–123	5.6, 6.1, 7.6, 7.9, 9.4, 9.6, 9.8, 9.9, 13.0, 14.5
CH_3	H	185–186	*a*	**b**	86–87	5.7, 6.1, 7.4, 8.0, 8.4, 9.5, 10.0, 10.4, 12.9, 14.5
NH_2	H	141–142	*b*	**c**	*c*	3.0, 5.7, 5.9, 6.2, 7.6, 9.1, 9.8, 10.1, 13.1, 14.5
CF_3	H	185–186	*a*	**d***	51–52	5.6, 5.9, 7.4, 8.2, 8.5, 9.0, 10.2, 12.8, 13.2, 14.5
CH_3CH_2	H	118–119	*a*	**e**	84–85	5.7, 6.0, 6.2, 8.6, 8.8, 9.2, 9.8, 12.8, 14.5
$CH_3(CH_2)_{16}$	H	78–80	*a*	**f***	45–46	5.7, 6.1, 6.2, 8.6, 10.0, 10.5, 12.8, 13.9, 14.4
n-$C_8F_{17}SO_2NEtCH_2$	H	184–186	*a*	**g***	111–112	5.7, 6.0, 7.2, 8.3, 8.7, 9.4, 9.9, 10.4, 11.0, 13.0, 14.5
p-NO_2 Ph	H	234–235	*a*	**h**	208–210	5.6, 6.2, 6.5, 7.4, 9.4, 10.0, 11.5, 12.8, 13.1, 14.2, 14.5
p-NH_2Ph	H	226–227	*b*	**i**	221–223	2.9, 3.0, 5.7, 6.2, 6.4, 7.5, 8.0, 8.5, 9.5, 12.0, 13.1, 14.6
p-CH_3CONHPh	H		*d*	**j**	294–296	3.0, 5.7, 5.9, 6.3, 7.1, 7.6, 8.0, 8.5, 9.5, 11.8, 13.0, 13.6, 14.5
m-NO_2Ph	H	230–232	*a*	**k**	169–170	5.7, 6.1, 6.2, 6.5, 7.5, 9.5, 9.7, 10.0, 12.9, 13.4, 14.6
m-NH_2Ph	H	227–228	*b*	**l**	161–163	2.9, 3.0, 5.7, 6.3, 7.5, 7.8, 8.0, 8.2, 9.5, 9.9, 13.0, 13.9, 14.6
Ph	NO_2		*e*	**m**	168–169	5.7, 6.2, 6.3, 6.5, 7.4, 7.9, 9.2, 9.4, 9.6, 11.7, 12.8, 13.0, 14.2
Ph	NH_2		*f*	**n**	201–220	2.9, 3.0, 5.7, 6.1, 6.6, 7.3, 8.0, 9.5, 12.0, 12.9, 14.4, 14.7
CH_3	NO_2	215–216	*a*	**o**	162–163	5.7, 6.1, 6.2, 6.5, 7.3, 7.9, 8.4, 9.2, 9.4, 10.3, 11.5, 12.5, 13.3, 14.4
CH_3	Br	220–221	*a*	**p**	134–135	5.7, 6.0, 6.8, 8.0, 8.5, 9.5, 10.4, 11.9, 12.8, 14.4, 14.6

[a] Acetic anhydride at reflux. [b] Thionyl chloride in benzene at reflux. [c] 1c softens at 190 °C, but true melting occurs at 285–300 °C. [d] Prepared from 1i by reaction with Ac_2O. [e] 2-Amino-5-nitrobenzoic acid (mp 275–276 °C) converted directly to 1m by reaction with excess benzoyl chloride in pyridine at reflux. [f] Prepared from 1m by reduction with H_2 on Raney nickel in dioxane. * New compounds.

Table II. Reaction of Benzoylanthranil (1a, R = Ph) with Amines

Registry no.	Amine	Reaction conditions: Solvent	Time	Temp, °C	% 1a isolated as: 4	5	k_A/k_B = 5/4
62-53-3	H_2NPh	*a*	1 day	23	93		<1/25
101-80-4	$(p$-$H_2NPh)_2O$	*b*	4 h	Reflux	94		<1/25
		a	1 h	140	53		<1/25
80-08-0	$(p$-$H_2NPh)_2SO_2$	*a*	4 h	250	*e*	*e*	*e*
107-10-8	$H_2N(CH_2)_3H$	*c*	1 day	Reflux	97		<1/25
109-73-9	$H_2N(CH_2)_4H$	*c*	1 day	Reflux	98		<1/25
124-09-4	$H_2N(CH_2)_6NH_2$	*d*	4 h	Reflux	87		<1/25
		a	4 h	140	84		<1/25

[a] Neat. [b] Acetic acid. [c] Diethyl ether. [d] Pyridine. [e] Not determined since conditions known to cause conversion of 4 to 5; only half of product was isolated as the diquinazolone $(QPh)_2SO_2$ mp 364–365 °C. The other half was isolated as mixture of the bisbenzamido and benzamido monoquinazolone derivatives of 4,4'-diaminodiphenylsulfone [$(BNHPh)_2SO_2$ and $BNHPhSO_2PhQ$]. The corresponding characterization data are collected in Table III.

4d, was produced via the alternative route, as indicated by the ir spectrum of the product and its complete solution in dilute $NaHCO_3$.

The ir spectra of the trifluoroacetamidines, **3d**, obtained by reaction of **1d** with aniline and with toluidine, differ somewhat from those of the corresponding hydrocarbon acetamidines, **3b**. The OH absorptions of the former[2] are typical of a carboxylic acid rather than an internal amidine salt as manifested by the latter, which are broad and different in form. In addition the position of the carbonyl absorption for the trifluoroacetamidines are lower in wavelength, changing from about 6.3 μ for the hydrocarbon acetamidines to 5.9 μ for the trifluoroacetamidines which are relatively insoluble in water or in dilute aqueous acid. These observations are in keeping with the expected markedly decreased basicity of the fluoroacetamidines owing to the strong electronegative influence of the CF_3 group.

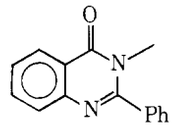
The preparation of formylanthranil, **1q** (R = H), and 6-bromoformylanthranil, **1r** (R = H; R' = Br), was reported by Wagner[4] and by Bogert.[3f] These acylanthranils were described by them as unstable and extremely sensitive to atmospheric moisture. Reaction with ammonia gave the corresponding quinazolones, **5q** and **5r**, which we now presume were formed via pathway A as indicated in Scheme I. The reported qualitative description of their work suggests that the reactivities of **1q** and **1r** are comparable to that of **1d** and considerably greater than **1b**.

From the foregoing discussion, it is possible to establish

Table III. Characterization Data for Products Obtained by Reaction of 1a with Amines Listed in Table II

Product[a]	Mp, °C	Key ir bands, μ
B-NHPh	286–287	3.0, 6.0, 6.5
$(B\text{-}NHPh)_2O$[b]	300–301	3.0, 6.0, 6.5, 8.1
$(Q\text{-}Ph)_2SO_2$[b]	364–365	5.9, 7.5, 8.6
$B\text{-}NH(CH_2)_3H$	134–135	3.0, 6.0, 6.1, 6.5
$B\text{-}NH(CH_2)_4H$	122–123	3.0, 6.0, 6.1, 6.5
$B\text{-}NH(CH_2)_6NH\text{-}B$[b]	182–183	3.0, 6.0, 6.1, 6.5

[a] B indicates *o*-(PhCONH)PhCO group, Q indicates group



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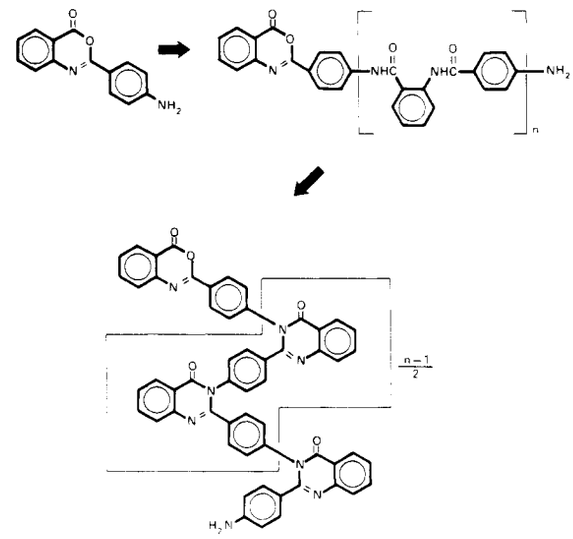
i. [b] Satisfactory combustion analytical data for C, H, N (±0.7%) were reported for these compounds. Ed.

qualitatively that the relative reactivities for these five acylanthranils are in the order **d** (R = CF_3) > **q** (R = H) > **b** (R = CH_3) > **c** (R = NH_2) ≃ **a** (R = Ph). This order appears to follow the expected influence on electrophilicity at the 2 position owing to electronic induction and/or resonance contribution of the corresponding R substituent. The position of lowest reactivity for the phenyl group might be ascribed in part to steric hindrance, but not necessarily. A phenyl group is weakly electron withdrawing by induction, but strongly electron contributing when acting in resonance with a >C=N– (or >C=O) group, so that the net effect, like that of NH_2, is to decrease the electrophilicity at the 2 position, thereby favoring pathway B while decreasing the overall rate of reaction. That the more reactive acylanthranils, **1d, 1q** and **1b,** follow pathway A preferentially and the less reactive acylanthranils, **1c** and **1a,** follow pathway B preferentially suggest that the electronic effect might have an important influence on reactive selectivity, at least when R is small.

If the electronic effect were indeed the dominant factor that influences selectivity, then it should be possible to mitigate the extreme converse selectivities manifested by acetylanthranil and benzoylanthranil, by means of appropriate ring substituents that influence the electrophilicity at the 2 and/or 4 positions owing to electronic resonance. The results of Bogert[3] and Wagner,[4] however, show that the corresponding *o*-benzamidobenzamides are obtained universally, when ammonia[3] or aniline[3,4] are caused to react at about 100 °C with *o*- and *p*-toluylanthranils, with *o*- and *p*-chlorobenzoylanthranils, and with *o*-, *m*-, and *p*-nitrobenzoylanthranils. Our results with **1h** (R = *p*-NO_2Ph) and **1k** (R = *m*-NO_2Ph) verified their observations, and showed qualitatively that the reactivities of **1h** and **1m** (R = Ph; R″ = NO_2) were greater than that of **1a** (R = Ph) but less that that of **2b** (R = CH_3) whereas **1k** was about the same as **1a.** The reactivity of *p*-aminobenzoylanthranil, **2i** (R = *p*NH_2Ph), was so low that it was recovered unchanged after 8 days in aniline or in aqueous NaOH at room temperature. Despite their low reactivity the bifunctional acylanthranils, **1i** and **1n,** can be made to undergo intermolecular condensation by fusion just above their melting points for about 10 min to give the corresponding polyamides, as indicated by the sharp bands at 3.0, 6.1, and 6.6 μ in their spectra of the products. Longer times and higher temperatures cause progressive conversion to the corresponding polyquinazolone as indicated by the disappearance of the sharp bands at 3.0, 6.1, and 6.6 μ and the appearance of a sharp band at 5.9 μ in the ir spectra. This conversion is illustrated in Scheme II

Scheme II



using **1i** as the model. Self-condensation of *m*-aminobenzoylanthranil, **1l** (R = *m*-NH_2Ph), is more facile than that of **1i** (or **1m**) and it goes smoothly at 170 °C neat or in solution to give high molecular weight linear polyamide. Again longer reaction times at higher temperature cause progressive cyclodehydration to thermally stable polyquinazolone polymers that melt above 300 °C and are soluble in formic acid or in *m*-cresol. Inherent viscosities in *m*-cresol were in the range of 0.2–0.5.

From these results and the observed relative sensitivity to moisture, it was deduced qualitatively that the relative reactivities of the ring substituted benzoylanthranils listed in

Table IV. Reaction of Acylanthranils 1 with Aniline in Benzene at 23 °C

Acylanthranil, R (R″)	1	Rxn time, days	% isolated as product 4	3	5	Selectivity (3 or 5)/4 k_A/k_B =
Ph	a	1[a]	93			<1/25
CH_3	b	0.2		95		>50/1
CF_3	d	5 min		71		>50/1
CH_3CH_2	e	1	11	Oil	86	9/1
$CH_3(CH_2)_{16}$	f	1	Grease (20)[b]	Oil	78[c]	4/1[b]
$n\text{-}C_8F_{17}SO_2NEtCH_2$	g	7	76	Oil (15)[d]		1/6
CH_3 (6-NO_2)	l	5 min		99		>50/1
CH_3 (6-Br)	m	0.1		95[e]		>50/1
CF_3	d	5 min[f]		92[f]		>50/1

[a] Neat in aniline. [b] Ir indicated that grease was ca. 80% 4f, from which was calculated that 20% 1f units isolated as 4f. [c] 5f was an oil. It was converted quantitatively to its HCl salt (mp 189–191 °C). [d] Ir indicated that this oil was ca. 60% 3g, from which was calculated that 15% 1g was isolated as 3g. Some hydrolysis to *o*-acylamidobenzoic acid occurred during workup. [e] Ir indicated that residue left as product was mostly 3c. Mixture dissolved in dilute aqueous base to give a clear solution from which 5m precipitated overnight. [f] 3d, the reaction product obtained with *p*-toluidine instead of aniline.

Table V. Characterization Data for Products Obtained by Reaction of Aniline with Acylanthranils as Listed in Table IV

1	Product	Mp, °C	Key ir bands, μ
a	4a[a]	286–287	3.0, 6.0, 6.5
b	3b	115–116	See ref 1
d	3d	105–106	3.0–4.0, 5.9, 6.0
e	4e	156–157	3.0, 6.1, 6.5
	5e	125–126	5.9, 6.2
f	5f HCl[a]	189–191	5.9, 6.2
g	4g	108–110	3.0, 5.9, 6.0, 6.5, 8.0, 8.8
l	3l	67–68	3.2, 4.2, 6.2, 6.6
	5l	220–221	5.9, 6.3, 6.5, 7.4
m	5m	186–187	5.9, 6.2
d	3d'[b]	103–104	3.1, 4.1, 5.9, 6.0

[a] See Table III, footnote *a*. [b] 3d' is *N*-(*o*-carboxyphenyl)-*N'*-(*p*-tolyl)acetamidine formed by reaction of **1d** with *p*-toluidine in benzene.

Table I are in the order **1b** (R = CH_3) > **m** (R = Ph; R″ = NO_2) ≃ **h** (R = *p*-NO_2Ph) > **k** (R = *m*-NO_2Ph) > **a** (R = Ph) > **l** (R = *m*-NH_2Ph) > **i** (R = *p*-NH_2Ph) ≃ **n** (R = Ph; R″ = NH_2) ≃ **j** (R = *p*-CH_3CONHPh). This order of reactivity parallels the expected influence in electrophilicity at the 2 position owing to the electronic contribution of the ring substituent through resonance and/or induction; electron-withdrawing groups enhance reactivity and electron-donating groups decrease reactivity about as predicted by theory. It is reasonable to assume, therefore, that the same will be true for all the many ring-substituted benzoylanthranils reported by the early investigators. In all those experiments that were carried out below 150 °C the product isolated was the corresponding *o*-benzamidobenzamide. These consistent results indicate than such reaction of the benzoylanthranil occurs universally via pathway B, despite a reactivity markedly affected by ring substituents. That is to say a significant change in reactivity has virtually no effect on the selectivity of benzoylanthranils.

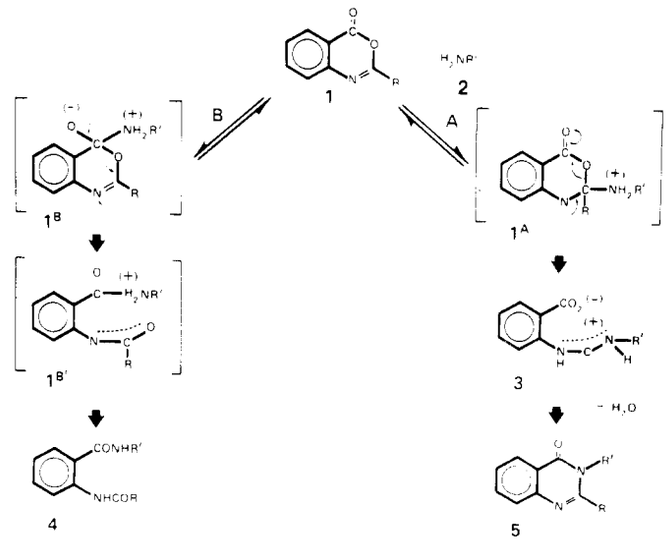
Similarly, the reinterpretation of the data reported for acetylanthranils also indicates a steadfast preference for one pathway exclusive of the other. But in sharp contrast, the acetylanthranils prefer route A. Bogert[3] had prepared the 5-, 6-, and 7-nitroacetylanthranils, 6-bromoacetylanthranil, 6-carboxyacetylanthranil, and the 6- and 7-acetamidoacetylanthranils. These compounds were made to react at about 100 °C with simple aliphatic and aromatic amines. The reported major product, with but one exception, was the corresponding quinazolone, which we now presume was formed via pathway A as shown in Scheme I. The one exception was the reaction of 7-acetamidoacetylanthranil with 2-aminobutane, which gave the corresponding 2,5-di(acetamido)benzamide. To be certain, however, that the ring-substituted quinazolones were indeed formed by cyclodehydration of the acetamidines, **3**, and not the *o*-acetamidobenzamides, **4**, owing to the activating influence of the ring substituents, the acetylanthranils **1o** (R = CH_3; R″ = NO_2) and **1p** (R = CH_3; R″ = Br) were prepared by us (Table I) and allowed to react with aniline in benzene at room temperature. As expected, the corresponding insoluble amidine salts, **3o** and **3p** (Tables IV and V), were isolated in very good yields. These intermediates were then converted almost quantitatively to the corresponding quinazolones **5o** and **5p** by cyclodehydration neat at 120 °C and at room temperature in dilute aqueous base. These results confirm that reaction via pathway A is indeed general for all acetylanthranils.

It was noted in these experiments that reaction of **1o** (R = CH_3; R″ = NO_2) with aniline to give insoluble acetamidine **3o** is complete within 5 min, indicating that the reactivity of **1o** is greater than that of **1b** (R = CH_3) and about comparable to that of **1d** (R = CF_3). The reactivity of **1p** (R = CH_3; R″ = Br) appeared to be somewhat faster than that of **1b**, but less than that of **1o**.

From these qualitative comparisons it was deduced that the relative reactivities for this set of acetylanthranils are in the order **d** (R = CF_3) ≥ **o** (R = CH_3; R″ = NO_2) > **p** (R = CH_3; R″ = Br) > **b** (R = CH_3). Here again it is noticed that the order of reactivity parallels the expected influence on the electrophilicity at the 2 and 4 positions owing to the electronic contribution of the ring substituents through resonance and/or induction. Accordingly, it was logical to assume in the absence of confirmatory experiments that the reactivities of the 6- and 7-acetamidoacetylanthranils prepared by Bogert would be less than that of **1b**. The qualitative description of Bogert's results appears to indicate that the reactivities of these two acetamido substituted acetylanthranils are comparable with that of benzoylanthranil. His results also indicate clearly that the products of reaction at about 100 °C with simple alkylamines and anilines are the corresponding quinazolone despite the reduced reactivity. Again marked changes in reactivity owing to the added electronic influence of ring substituents had no significant effect on the charactersitic selectivity manifested by the parent acylanthanil.

It is concluded, therefore, that the reactivity of the acylanthranil is not the important parameter that determines its selectivity. It is suspected that the relative stability of the corresponding transition states **1A** and **1B** produced by nucleophilic addition of an amine at the 2 and 4 positions, respectively, is an important consideration which at least in part is determined by the electronic character of the R substituent at the 2 position. In our preceding publication,[2] it was suggested that the apparent anomalous preference of acetylanthranil for reaction with anilines via pathway A instead of B, despite an expected electrophilicity of the >C=O group at the 4 position greater than that of the >C=N– group at the 2 position, might be rationalized on the basis that transition states, **1A** and **1B**, are in equilibrium with one another through **1** as shown in Scheme III. Since it is easier to transfer negative

Scheme III



charge to a more electronegative center (i.e., from N to O), **1A** is converted more readily to a stable product **3** (via pathway A) than **1B** which requires transfer of negative charge from O to N in order to cascade to a stable product **4** (via pathway B).

This rationale serves equally well to explain the selectivity noted with **1d** (R = CF_3) and **1q** (R = H), but not that noted

Table VI. Comparison of Reactivity and Selectivity of Acylanthranils at 23 °C and ca. 100 °C as a Function of the Substituent R at the 2 Position

Rel reactivity of 1	b	>	e	>	s	>	f	>	g	≃	a
R	CH_3		Et		*n*-Pr		$H(CH_2)_{17}$		n-$C_8F_{17}SO_2NEtCH_2$		Ph
k_A/k_B = 5/4 at 23 °C	>50		9				~4		~1/6		<1/25
Approximate k_A/k_B at ca. 100 °C calcd from data taken from ref 4			2		1						

with **1a** (R = NH_2) and **1a** (R = Ph) which prefer pathway B. Rationalization of the latter selectivity requires additional considerations that could possibly offset the advantage of facile negative charge transfer from N to O. In the case of **1c** (R = NH_2) the reverse transfer from O to N is perhaps aided by the presence of two amido centers to share the negative charge. This is not true for **1a,** however, which leaves steric hindrance as a possible mitigating factor that raises the energy barrier to formation of **1a.**

If steric hindrance is indeed an important parameter that affects selectivity, then the ratio of reaction via pathway A to that via pathway B [i.e., k_A/k_B = (**3** or **5**)/**4**] should decrease with increase in bulk of the R substituent at the 2 position within a set of acylanthranils of about the same electronic character. The data already reported, however, appear to be conflicting and not amenable to clear-cut differentiation between the alternative pathways. Bogert et al.[3p] caused ammonia to react at about 100 °C with 2-R-6-bromo-3,1,4-benzoxazones, where R is H, CH_3, Et, *n*-Pr, *i*-Pr, and *i*-Bu, and they reported only the isolation of the corresponding quinazolones. On the other hand, Zentmyer and Wagner, who caused *n*-propionylanthranil and *n*-butyrylanthranil to react with aniline at about 100 °C, reported[4] the corresponding benzanilides, **4,** as the only products isolated in significant amounts. The yields of isolated products, however, accounted at best for only about 50% of the acylanthranil units made to react with aniline.

To test this "steric" hypothesis the acylanthranils **1b, 1c,** and **1f** (Table I) were allowed to react with 1 equiv of aniline in benzene at room temperature. The products were separated and the selectivity, k_A/k_B, calculated on the basis of almost total recovery of the acylanthranil units as described previously.[2] The results are summarized in Tables IV and V.

It is noticed that both **4** and **5** were isolated in significant amounts from **1e** and **1f,** and that the selectivity ratio k_A/k_B decreases from >50/1 for **1b** (R = CH_3) to about 4/1 for **1f** [R = $(CH_2)_{17}H$] with the greater change associated with the change from R = CH_3 (**1b**) to R = CH_2CH_3, (**1e**). The distribution of products obtained with **1f** is somewhat uncertain owing to the long aliphatic chain, which made it difficult to separate the products quantitatively; oils and greases were obtained instead of crystalline compounds. The major product, **5f,** was isolated pure as the hydrochloride salt, but the minor product, **4f,** could be isolated only as a smaller neutral fraction that contained unidentified impurities. The amount of **4f** in this fraction was estimated from the ir and NMR spectra. The k_A/k_B ratio of ca. 4/1 for **1f** indicates only that **5f** was still the major product even when *n* is 17, but that the proportion of **4f** to **5f** was only half that realized with **1e** (R = CH_2CH_3; k_A/k_B = 9/1).

The significant shift in selectivity toward pathway B as a function of *n* of the group $(CH_2)_nH$ at the 2 position might also be attributed to the small but monotonic increase in electropositive induction, which is also a function of *n*. To examine this possibility requires simply to compare the corresponding product distribution obtained with an acylanthranil that has a long chain electronegative group attached to the R substituent, which should mitigate the electropositive contribution at the 2 position. Accordingly, *N*-ethyl-*n*-perfluorooctylsulfonamidoacetylanthranil, **1g,** was prepared and allowed to react with aniline as described in the Experimental Section. The results, given in Table IV, show that the selectivity ratio for **1g,** i.e., k_A/k_B = 1/6, is markedly smaller than that realized with **1f,** and that reaction with **1g** decidedly favors pathway B. Despite the mitigating effect of the fluorocarbon sulfonamide group on electropositive induction, the branch at the amide nitrogen atom apparently provides sufficient steric hindrance to an approaching nucleophile so as to enhance the shift toward reaction via pathway B.

It was noted qualitatively that the reactivities of the acetylanthranils **1e, 1f,** and **1g** toward moisture and amines decrease in that order and are intermediate between **1b** and **1a.** This order of reactivity appears to parallel a decreasing trend in k_A/k_B. A similar decreasing order of reactivity was noted by Zentmyer and Wagner[4] for the acylanthranils **1b, 1e,** *n*-butyrylanthranil (**1s**), and **1a.** Unfortunately their reported yield data do not permit accurate calculation of selectivity owing to poor materials balance. If one assumes, however, that the unrecovered acylanthranil units were lost as soluble alternative product **3** (or **5**) then the ratio (100% − **4**)/**4** gives approximate selectivity values at about 100 °C, which appear to parallel qualitatively, though not quantitatively, the order for selectivity values at 23 °C observed by us as indicated in Table VI.

The quantitative discrepancy between our results at 23 °C and those of Zentmyer and Wagner at about 100 °C may be due to the temperature difference, since it was noted by us that the ratio k_A/k_B decreases at higher reaction temperatures as will be discussed in a subsequent publication.

Although the order of reactivity noted in Table VI might be attributed to the combined influence of the electronic character and bulk size of the substituent R at the 2 position, the parallel order for decreasing k_A/k_B can only be attributed to steric hindrance, since a corresponding change in selectivity was not manifested either by amino (or acetamido) substituted acetylanthranils, which were markedly slower than **1b,** nor by nitro substituted benzoylanthranils, which were markedly faster than **1a** as discussed previously.

In summary, it was shown that the wealth of reported information[3] regarding the reaction of acylanthranils with amines to give quinazolones, **5,** and/or benzamides, **4,** which were inconsistent and even conflicting when interpreted on the original assumption that **5** is formed sequentially from **4** by cyclodehydration, now fall into a self-consistent pattern, when reinterpreted in light of the recent suggestion that **5** and **4** are formed competitively via alternative pathways A and B respectively as illustrated in Scheme I. The electronic character and bulk size of the substituent R at the 2 position of the acylanthranil are dominant factors that influence the rate and selectivity of reaction with a given amine, as noted in the relative reactivities toward aniline for the set **1d** (R = CF_3) > **1b** (R = CH_3) > **1a** (R = Ph) and the overwhelming preference of **1d** and **1b** for pathway A, whereas **1a** has the converse preference for pathway B. Selectivity, however, is not a function of reactivity alone, since it is possible to mitigate markedly the reactivity of acetylanthranils and benzoylanthranils by the presence of ring substituents that influence accordingly the electrophilicity at the 2 and/or 4 positions by

resonance and/or induction without affecting the selectivity of the parent acylanthranil. Selectivity appears to be determined by the relative efficiency for conversion of the transition states **1A** and **1B** to stable products **3** and **4**, respectively, as discussed in terms of Scheme III, and the bulk size of the substituent R at the 2 position. The relative reactivity and the selectivity ratio k_A/k_B decrease with increase in bulk of R as indicated by the order in the set of acylanthranils **b** (R = CH_3) > **e** (R = Et) > **f** [R = $(CH_2)_{17}H$] > **g** [R = $CH_2NESO_2(CF_2)_8F$]. This order of reactivity and selectivity is consistent with progressively greater impediment to approach of a nucleophile to the electrophilic center at the 2 position.

As mentioned earlier, one example, namely, the reported isolation of 2,5-di(acetamido)-*N*-(2-butyl)benzamide as the major product of reaction of 7-(acetamido)acetylanthranil with 2-aminobutane at about 100 °C instead of the expected quinazolone, does not yet fit into the overall pattern as discussed thus far. It is probable, however, that this apparent exception may in fact be the result of steric hindrance on the part of the amine. It is intended, therefore, to investigate the reaction of aliphatic amines with acetylanthranil at room temperature to see how the product distribution is affected in turn by bulky substituent on the amine coreactant.

Experimental Section

A. General Procedure for Preparation of Acylanthranils, 1. This procedure is a variation of those already published.[3,7] In our hands it appeared to be quite general and gave positive results in good yields (i.e., >50%) even with some difficult examples that were reported earlier as negative.

The organic acid precursor, **6**, was converted to the corresponding acyl chloride by treatment with thionyl chloride at reflux temperature for 2 h. The excess reagent was removed under vacuum and the desired product separated from the residue by distillation. The acyl chloride was dissolved in pyridine and then added dropwise to a well-stirred solution of anthranilic acid in pyridine kept at 0 °C. The solvent was removed under vacuum in a rotary film evaporator, and the residue was recrystallized from a suitable solvent to yield the corresponding *o*-acylamidobenzoic acid in the form of white crystals. The acid was converted to the corresponding acylanthranil by treatment with refluxing acetic anhydride (or thionyl chloride) for 2 h. The product, which usually crystallized on cooling, was separated by filtration. The mother liquor was concentrated to about one-fifth its volume to yield a second crop of crystals on cooling. The overall yields from the organic acid to the corresponding acylanthranil were usually above 50%. The results obtained for the preparation of acylanthranils **1a–p** are summarized in Table I. Only the procedures for the fluorocarbon acylanthranils, which are novel compounds, are described in more detail below.

Trifluoroacetylanthranil, 1d. Trifluoroacetyl chloride was prepared by reaction of trifluoroacetic acid with PCl_5. The gas was dried over Drierite and collected at −78 °C. About 0.45 mol of this acyl chloride was recollected in a well-stirred solution of anthranilic acid (0.4 mol) and pyridine (300 ml) kept at 0 °C at atmospheric pressure. The transfer occurred over a period of 1 h. The excess pyridine was removed by evaporation under vacuum. The residue was dissolved in cold, dilute, aqueous NaOH and reprecipitated by addition of cold, dilute HCl to give in about 95% yield *o*-trifluoroacetylanthranilic acid as a white powder (mp 185–186 °C), which was identified by its ir spectrum and partial elementary analysis.

Anal. Calcd for $C_9H_6NO_3F_3$: N, 6.01; neut equiv, 233.2. Found: N, 6.1; neut equiv, 236.

The acid was then converted to the acylanthranil, **1d**, in about 90% yield as described in the general procedure. The product was recrystallized from heptane to give **1d** as off-white crystals (mp 51–52 °C). Trifluoroacetylanthranil was identified by its ir spectrum (Table I) and its partial elementary analysis.

Anal. Calcd for $C_9H_4NO_2F_3$: N, 6.51; neut equiv, 215.1. Found: N, 6.3; neut equiv, 218.

A sample of **1d** was converted to ethyl *o*-(trifluoroacetamido)benzoate (mp 80–81 °C) by reaction with ethanol at room temperature using a trace amount of NaOEt as catalyst. The derivative was characterized by its ir spectrum and its neutralization equivalent in a nonaqueous solvent.

Anal. Calcd for $C_9H_{10}NO_3F_3$: 262.4. Found: 264.

***N*-Ethyl-*n*-perfluorooctylsulfonamidoacetylanthranil, 1g.** *N*-Ethyl-*n*-perfluorooctylsulfonamidoacetic acid (mp 156–157 °C), which was prepared by R. Guenthner of the 3M Co., was converted to the corresponding acyl chloride by reaction with thionyl chloride. After removal of excess thionyl chloride the residue was recrystallized from hexane to give *N*-ethyl-*n*-perfluorooctylsulfonamidoacetyl chloride in the form of tiny, white crystals (mp 66–67 °C). The acyl chloride was made to react with anthranilic acid in toluene kept at reflux temperature for 2 h. The product, which was collected by filtration, was recrystallized from hot benzene to give the expected *o*-acetamidobenzoic acid in the form of white crystals (mp 184–186 °C). The acid was converted to the corresponding acylanthranil by cyclodehydration in hot acetic anhydride. The product was recrystallized from heptane to give *N*-ethyl-*n*-perfluorooctylsulfonamidoacetylanthranil, **1g**, in the form of white crystals (mp 111–112 °C).

The assigned configuration was confirmed by its ir spectrum (Table I).

B. General Procedure for Reaction of Aniline with Acylanthranils. A solution of aniline in benzene was added slowly to a solution of an equivalent amount of the acylanthranil in benzene kept at room temperature. If precipitation began within the working day, reaction was allowed to continue until precipitation appeared to be complete, otherwise it was allowed to occur overnight. The solvent was removed by evaporation under vacuum in a rotary film evaporator and the residue was separated as described previously.[2] The assignment of structures was based on the chemistry of the separation procedure and support as needed by ir, NMR, and elemental analysis. The results are summarized in Table IV and the supporting analytical data are collected in Table V.

C. Reaction of Benzoylanthranil, 1a, with Amines. The general procedure for reaction of acylanthranil with anilines described under B was modified as indicated in Table II to accommodate the much lower reactivity of benzoylanthranil relative to that of acetylanthranil. Reaction of **1e** with 1 equiv of aniline in benzene and with *n*-propylamine or *n*-butylamine in diethyl ether were carried out at reflux temperature for 24 h. Reactions with oxydianiline in acetic acid and with hexamethylenediamine in pyridine were carried out at reflux for 4 h. The fusion reactions with equivalent amounts of oxydianiline, 4,4′-diaminodiphenyl sulfone, and hexamethylenediamine were carried out under nitrogen for 4 h at 140, 250, and 140 °C, respectively. The products were separated and identified essentially as described above under B. The results are summarized in Table II, and the supporting analytical data for the corresponding *o*-benzamidobenzamide products, written symbolically as BNHR, and that for the quinazolone of 4,4′-diaminodiphenyl sulfone, written symbolically as $(QPh)_2SO_2$, are collected in Table III.

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

Registry No.—**1a,** 1022-46-4; **1b,** 525-76-8; **1c,** 15607-11-1; **1d,** 16062-71-8; **1e,** 2916-09-8; **1f,** 16062-70-7; **1g,** 16062-73-0; **1h,** 16063-05-1; **1i,** 16063-04-0; **1j,** 60498-31-9; **1k,** 16063-03-9; **1l,** 60498-32-0; **1m,** 16062-68-3; **1n,** 60498-33-1; **1o,** 10073-89-9; **1p,** 19165-25-4; **3b,** 34264-61-4; **3d,** 60498-34-2; **3d′,** 58426-41-8; **3l,** 60498-35-3; **4a,** 18543-23-2; **4e,** 25628-85-7; **4g,** 60498-36-4; **5e,** 5260-41-3; **5f** HCl, 60498-37-5; **5l,** 60498-38-6; **5m,** 22686-82-4; **6a,** 579-93-1; **6b,** 89-52-1; **6c,** 610-68-4; **6d,** 19165-29-8; **6e,** 19165-26-5; **6f,** 19165-27-6; **6g,** 19157-34-7; **6h,** 6307-10-4; **6i,** 60498-39-7; **6j,** 60498-40-0; **6k,** 60498-41-1; **6l,** 60498-42-2; **6m,** 4809-61-4; **6n,** 60498-43-3; **6o,** 3558-18-7; **6p,** 38985-79-4; $(B\text{-}NHPh)_2O$, 60498-44-4; $(Q\text{-}Ph)_2SO_2$, 60498-45-5; $B\text{-}NH(CH_2)_3H$, 26060-09-3; $B\text{-}NH(CH_2)_4H$, 22812-98-2; $B\text{-}NH(CH_2)_6NH\text{-}B$, 60498-46-6.

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