An Extension of the Smiles Rearrangement. The Displacement of an Aromatic Amide Group by an Amine Nitrogen[1]

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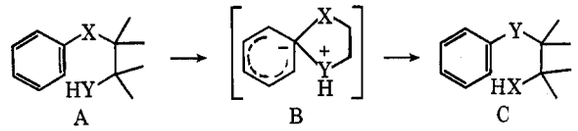
The reaction of a variety of 2-bromoacetanilides with amines has been shown to lead to an intramolecular nucleophilic aromatic rearrangement, analogous to the Smiles rearrangement. The reaction is facilitated by activation of the aromatic ring by electron-withdrawing groups in the ortho and para position. With sterically hindered amines no rearrangement is observed. The scope and mechanism of this rearrangement are discussed. The reaction is of synthetic utility for the formation of N^2-substituted phenylglycinamides.

Aromatic rearrangements which result in the migration of an aromatic system from one heteroatom to another belong to a class of reactions known as the Smiles rearrangement (A → B → C).[2]



A B C

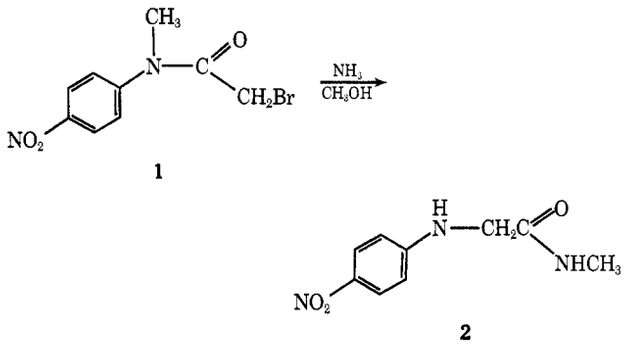
In most of the early work on the Smiles rearrangement, X was a sulfone group, Y was either an oxygen or nitrogen atom, and the two-carbon bridge was part of an aromatic ring. However, more recent investigations have shown that other heteroatom combinations are possible for X and Y. For example, (1) X can be oxygen, Y nitrogen, and the two-carbon bridge aromatic;[3] (2) X can be oxygen, Y nitrogen, and the bridge $-NC{=}O$;[4] (3) X can be oxygen, Y nitrogen, connected by a three-carbon bridge;[5] (4) X can be oxygen, and Y oxygen connected by either an aromatic[6] or an aliphatic bridge.[7]

However, no examples of a nitrogen–nitrogen Smiles rearrangement have been reported. The reaction of 2-bromoacetanilides with amines represents a novel extension of the Smiles rearrangement in which X and Y are nitrogen atoms connected by a two-carbon aliphatic bridge.

Results and Discussion

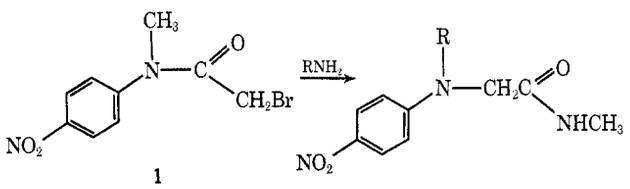
A typical example of this rearrangement is the reaction of 2-bromo-4′-nitro-*N*-methylacetanilide (**1**)[8] with methanolic ammonia, which leads to the rearranged glycinamide **2**.[9]

The rearrangement is not limited to the use of ammonia for the displacement of bromine, as almost any primary amine causes the formation of rearranged products. The results obtained from the reaction of **1** with amines are summarized in Table I. All reactions were carried out at room temperature in methanol or hexamethylphosphoric triamide (HMPA) with an excess of the appropriate amine. The rearrangements were followed by thin layer chromatography, and reaction times of 4–18 hr were needed in most cases to achieve complete rearrangement.

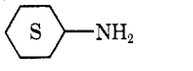
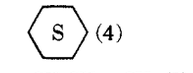
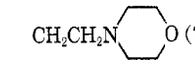


1 **2**

TABLE I



1

Amine	Product, R =	Yield, %
NH_3	H (**2**)	68
CH_3NH_2	CH_3 (**3**)	75
	 (**4**)	94
$CH_2{=}CHCH_2NH_2$	$CH_2CH{=}CH_2$ (**5**)	85
$(CH_3)_2NHCH_2CH_2NH_2$	$CH_2CH_2N(CH_3)_2$ (**6**)	59
	 (**7**)	69
CH_3ONH_2	OCH_3 (**8**)	38

The structures of the products were assigned on the basis of their chemical and physical properties (see Experimental Section). The mass spectra were especially significant since they showed, in most cases, the loss of *m/e* 58. This peak, which is the base peak, corresponds to the loss of $\cdot CONHCH_3$. The mass spectrum for compound **6** shows a base peak at *m/e* 58 which is assigned to the fragment $^+CH_2N(CH_3)_2$.

(1) A preliminary account of this work has been published: N. W. Gilman, P. Levitan, and L. H. Sternbach, *Tetrahedron Lett.*, 4121 (1970).

(2) For reviews of the Smiles rearrangement see (a) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 369 (1951); (b) R. M. Forbis, University of Illinois Organic Seminar Abstracts, 1st semester, 1968–1969, p 62.

(3) G. E. Bonvicino, L. G. Yogodzinski, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 4272 (1962).

(4) P. Baudet, M. Calin, and E. Cherbuliez, *Helv. Chim. Acta*, **47**, 1047 (1964).

(5) W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.*, **74**, 5187 (1952).

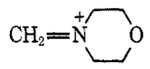
(6) J. D. Loudon, J. R. Robertson, J. N. Watson, and S. D. Alton, *J. Chem. Soc.*, 55 (1950).

(7) M. Harfenist and E. Thom, *J. Chem. Soc. D*, 730 (1969).

(8) T. Noguchi, Y. Hashimoto, T. Mori, and S. Kano, *J. Pharm. Soc. Jap.*, **88**, 1620 (1968).

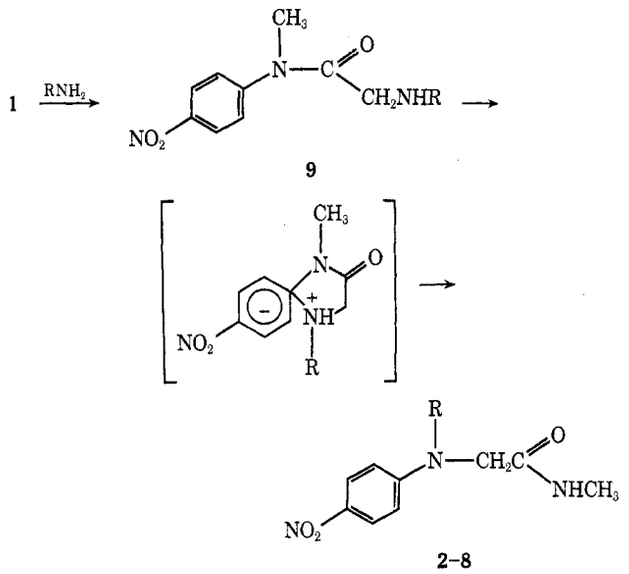
(9) The assignment of structure **2** was based on spectral data and on the acid hydrolysis of **2** which led to the known *N*-(4-nitrophenyl)glycine: L. Lantz and P. M. J. Obellianee, *Bull. Soc. Chim. Fr.*, 311 (1956).

In the case of compound **7**, the base peak appears at *m/e* 100 which corresponds to the fragment

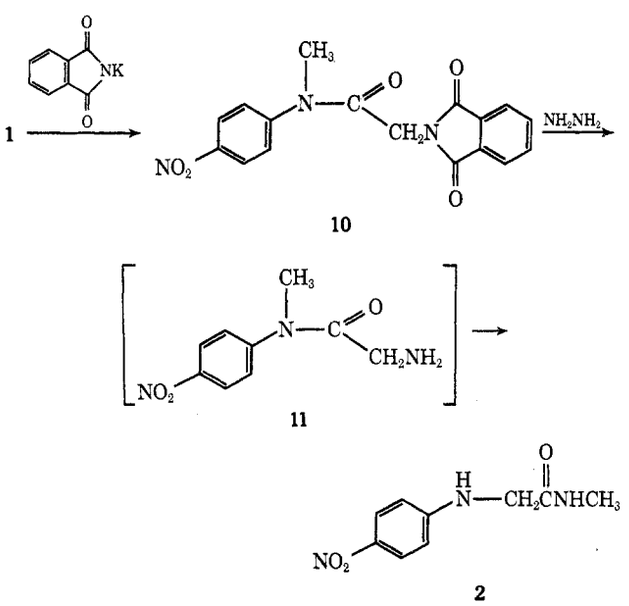


In all cases the products were yellow, whereas the starting material **1** was colorless. The color change is to be expected, since in the products the anilino nitrogen is in conjugation with the nitro group, whereas in **1** conjugation is interrupted since the anilino nitrogen is part of an amide function.

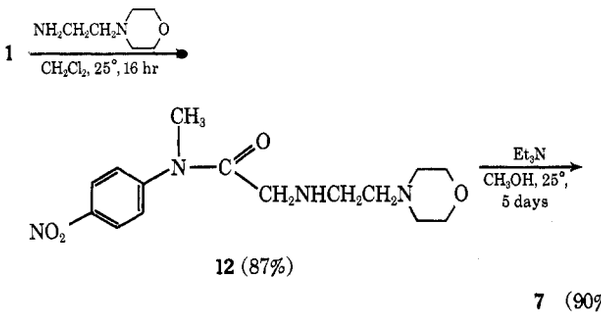
The most plausible mechanism for this reaction would appear to be, in analogy with other studies of the Smiles rearrangement,[10,11] the formation of the intermediate **9** followed by an aromatic displacement of an amide group.



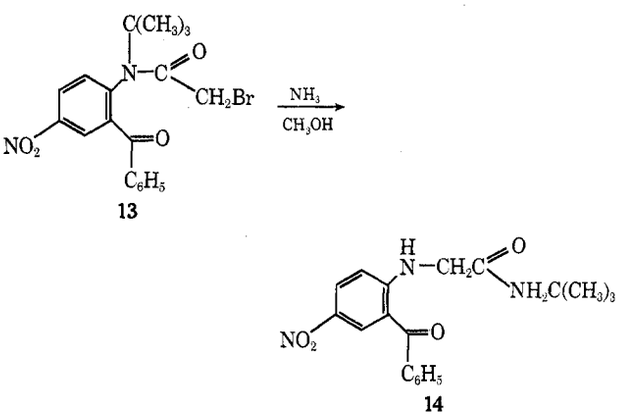
In support of this mechanism was the finding that the treatment of the phthalimido compound **10** with hydrazine led directly to the rearranged product **2**. The free amine **11**, which must be an intermediate in the reaction, could not be detected in the reaction mixture.



However, in one example, by substituting the nonpolar solvent methylene chloride for methanol, a normal SN2 substitution product was isolated, and in a separate experiment the product was found to undergo rearrangement. Thus, treatment of **1** with *N*-β-aminoethylmorpholine in CH_2Cl_2 gave **12**. The reaction of **12** with triethylamine in methanol (the rearrangement did not proceed to any extent in the absence of triethylamine) then led to the rearranged product **7**.



In an approach to the synthesis of 1-*tert*-butyl-1,3-dihydro-5-phenyl-1,4-(2*H*)-benzodiazepin-2-ones,[12] the reaction of compound **13** with ammonia was investigated.[13] However, the reaction of **13** with methanolic ammonia led only to the rearranged product **14**.

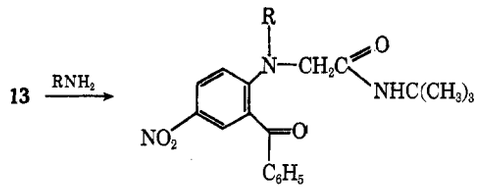


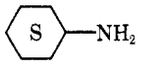
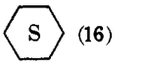
The substrate **13** was then found to undergo rearrangement with other primary amines in the same manner as compound **2**. The results are tabulated in Table II.

The experimental conditions were the same as those used for the reaction of **2** with amines (see preface to Table I). In all cases the products were yellow, whereas the starting bromoacetamido compound **13** is colorless. In all of the products except for compound **18**, the base peak in the mass spectrum was at *m/e* M − 100, where M is the molecular ion. The loss of 100 mass units corresponds to the fragment $(CH_3)_3CNHCO$. The side chain in **18** is also lost, so that in this case an ion appears at *m/e* 255 (M − 171). A

(10) J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).
(11) F. Pietra, *ibid.*, **23**, 504 (1969).
(12) For a review of the benzodiazepines see G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).
(13) For a successful synthesis of the 1-*tert*-butylbenzodiazepine see N. W. Gilman and L. H. Sternbach, *J. Heterocycl. Chem.*, **8**, 297 (1971).

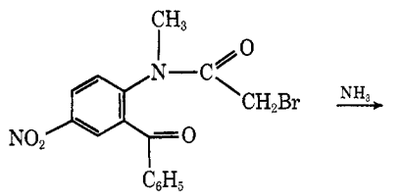
TABLE II



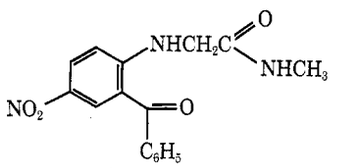
Amine	Product, R =	Yield, %
NH_3	H (**14**)	84
CH_3NH_2	CH_3 (**15**)	76
	 (**16**)	82
$CH_2{=}CHCH_2NH_2$	$CH_2CH{=}CH_2$ (**17**)	92
$(CH_3)_2NCH_2CH_2NH_2$	$CH_2CH_2N(CH_3)_2$ (**18**)	76
$(CH_3)_2NNH_2$	$N(CH_3)_2$ (**19**)	47

small peak at *m/e* 326 (M − 100) was also present (2% of base peak).[14]

The presence of the *tert*-butyl group in **13** was not a prerequisite for this rearrangement, since the *N*-methyl analog **23** also yielded **24** when treated with ammonia.



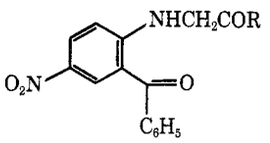
23



24

The structure of **24** was confirmed by the synthesis from **22**. The use of other substrates in the rearrangement was also investigated and the results are shown in Table III (experimental conditions as stated for Table I).

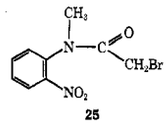
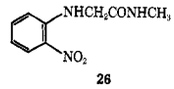
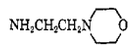
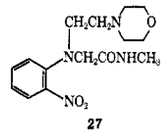
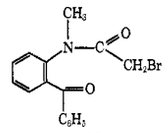
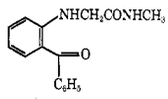
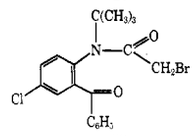
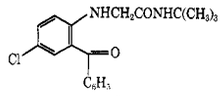
The use of **28** as a substrate shows that the ortho carbonyl group has a similar but less pronounced activating effect than the nitro group.[15,16]



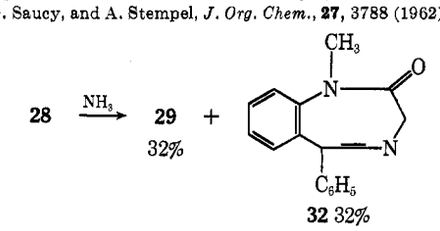
20, R = OEt
21, R = OH
22, R = Cl

(14) The structure of **14** was confirmed by an independent synthesis, starting from ethyl N^2-(2-benzoyl-4-nitrophenyl)glycinate (**20**) [G. A. Archer and L. H. Sternbach, U. S. Patent 3,317,518 (1966); *Chem. Abstr.*, **65**, 16988 (1966)]. The acid hydrolysis of **20** gave **21**, which with thionyl chloride yielded **22**, which upon treatment with *tert*-butylamine gave **14**.

TABLE III

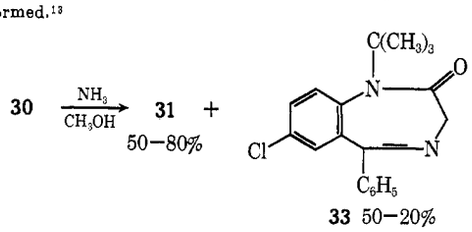
Substrate	Amine	Product	Yield %
 **25**	NH_3	 **26**	93
25		 **27**	66
 **28**	NH_3	 **29**	32
 **30**	NH_3	 **31**	77

(15) The low yield in this case (reaction in methanol) is due to competitive normal substitution and cyclization of the substitution product to the known benzodiazepine, **32**: L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).



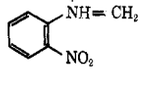
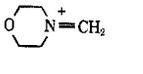
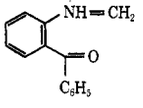
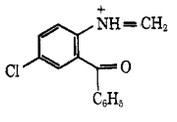
32 32%

In a similar manner the rearrangement of **30** proceeds in high yield in HMPA, but, if done in methanol, mixtures of **31** and the benzodiazepine **33** are formed.[13]



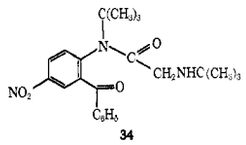
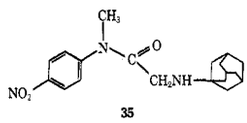
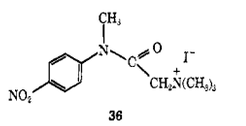
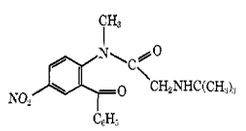
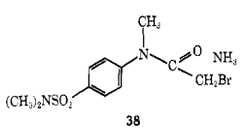
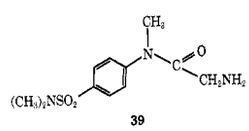
33 50–20%

(16) As in the previous examples, the fragmentation patterns in the mass spectra indicated that a rearrangement had occurred. In all cases, the base peak was due to the fragment $^+RNH{=}CH_2$, as shown below.

Product	Molecular ion, *m/e*	Base peak	Fragment
26	209	151	
27	322	100	
29	268	210	
31	344	244	

Although most of the previously discussed reactions lead to clean rearranged products, in some examples, no rearrangement took place. These cases are listed in Table IV.

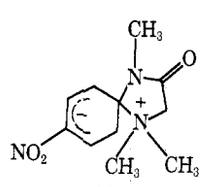
TABLE IV

Substrate	Amine	Product	Yield, %
13	$(CH_3)_3CNH_2$	 34	54
1		 35	51
1	$(CH_3)_2NH$	 36	87[a]
23	$(CH_3)_3CNH_2$	 37	56
		 38	
		 39	64

[a] The crude oily product was treated with methyl iodide to give the solid methiodide derivative.

The formation of the unrearranged products **34**, **35**, and **37** is undoubtedly due to the steric bulk of the nucleophilic amine, which prevents the formation of the five membered ring transition state required for a rearrangement.

If secondary amines, as in the preparation of **36**, are used in the reaction, no rearrangement would be expected, since this would necessitate the formation of the intermediate **40** which would simply revert back to the unrearranged compound.

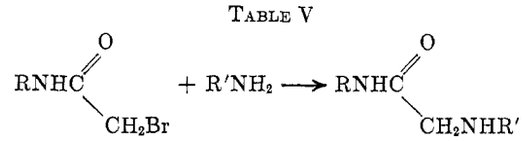


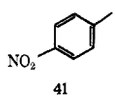
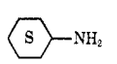
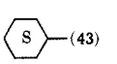
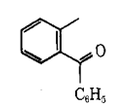
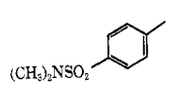
40

The reaction of **38** with ammonia to give only the unrearranged product **39** was unexpected. Absence of rearrangement may be due to the fact that the *N*,*N*-dimethylsulfamoyl group is not electron withdrawing enough to induce rearrangement. This, however, was not investigated in detail.[17]

In all of the previous examples, tertiary bromoacetanilides were used. The use of secondary bromoacetanilides was also investigated, but in no case were rearrangements noted. The results are summarized in Table V.

TABLE V



Substrate, R =	Amine	Product, R′ =	Yield, %
 41	CH_3NH_2	CH_3 (42)	74
41		 (43)	97
41	$CH_2{=}CHCH_2NH_2$	$CH_2{=}CHCH_2$ (44)	67
 45	CH_3NH_2	CH_3 (46)	72
 47	CH_3NH_2	CH_3 (48)	78

In the case of the secondary bromoacetanilides, there is increased electronegative charge on the anilino nitrogen, which would make the displacement reaction less likely to occur than in the case of the tertiary anilides.[18]

From a comparison of all the results obtained for the nitrogen–nitrogen Smiles rearrangement, a few generalities about the reaction can be formulated.

(1) The starting bromoacetanilide must be tertiary in order for rearrangement to occur.

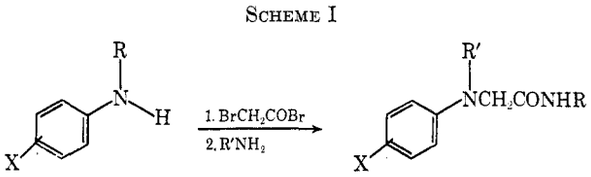
(2) Sterically hindered amines lead only to the simple substitution products without any rearrangement.

(3) The polarity of the solvent is important with the more polar solvents giving better yields of rearranged products.

(4) The activation of the aromatic ring by electron-withdrawing groups greatly facilitates the rearrangement.

Although many of the rearranged products can be synthesized by alternate routes, the simplicity of the rearrangement should find synthetic utility for the preparation of glycinamides according to the generalized Scheme I.

SCHEME I



X = ortho or para electron-withdrawing group

Table VI lists the analytical data for all new compounds described in this report.[18a]

(17) The structures of the unrearranged products were established by comparison of the nmr and mass spectra with spectra obtained on rearranged compounds with similar structures. In the products **34**, **35**, **37**, and **39**, the base peak in each case is due to the fragment $CH_2{=}NHR^+$, where R is *tert*-butyl, adamantyl, *tert*-butyl, and hydrogen, respectively. This pattern is in sharp contrast to products resulting from rearrangements, in which case none of the products show this type of ion.

(18) As in the examples given in Table IV, all of the above products have base peaks in the mass spectra resulting from the loss of the fragment $CH_2{=}NHR^+$.

(18a) NOTE ADDED IN PROOF.—After submission of this manuscript for publication, a further example of the nitrogen–nitrogen Smiles rearrangement appeared in print: K. Ishizumi, S. Inaba, and H. Yamamoto, *Chem. Pharm. Bull.*, **20**, 592 (1972).

TABLE VI[a]

Compd	Crystd[b] from	Color, shape	Mp, °C	Formula
2	A + H	Yellow needles	176–177	$C_9H_{11}N_3O_3$
3	A + H	Yellow needles	184–186	$C_{10}H_{13}N_3O_3$
4	A + H	Yellow prisms	193–195	$C_{15}H_{21}N_3O_3$
5	B + H	Yellow prisms	150–151.5	$C_{12}H_{15}N_3O_3$
6	A + H	Yellow prisms	125–127.5	$C_{13}H_{20}N_4O_3$[c]
7	MC + H	Yellow prisms	153–155	$C_{15}H_{22}N_4O_4$
8	MC + H	Yellow prisms	131–132	$C_{10}H_{13}N_3O_4$
10	E	Colorless needles	203–205	$C_{17}H_{13}N_3O_5$
12	A + H	Yellow prisms	89–91	$C_{15}H_{22}N_4O_4$
13	E	Off-white needles	203–204	$C_{19}H_{15}BrN_2O_4$
14	B + P	Yellow crystals	175–176	$C_{17}H_{21}N_3O_4$
15	A + H	Yellow crystals	153–155	$C_{20}H_{23}N_3O_4$
16	d	Yellow foam		$C_{23}H_{31}N_3O_4$
17	d	Yellow foam		$C_{22}H_{25}N_3O_4$
18	e	Yellow foam		$C_{23}H_{30}N_4O_4$
19	MC + H	Yellow needles	176–177	$C_{21}H_{26}N_4O_4$
23	e	Pale yellow gum		$C_{16}H_{13}BrN_2O_4$
24	MC + H	Yellow needles	250.5–251.5	$C_{16}H_{15}N_3O_4$
25	Et + P	Colorless prisms	57–59	$C_9H_9BrN_2O_3$
26	M	Orange needles	163–165	$C_9H_{11}N_3O_3$
27	e	Brown oil		$C_{15}H_{22}N_4O_4$
28	E	Colorless prisms	89–90	$C_{16}H_{14}BrNO_2$
29	B + H	Yellow plates	150–152	$C_{16}H_{16}N_2O_2$
30	MC + P	Colorless prisms	161–162	$C_{19}H_{19}BrClNO_2$
31	Heptane	Yellow needles	147–149	$C_{19}H_{21}ClN_2O_2$
34	Et + P	Off-white prisms	108–109	$C_{23}H_{29}N_3O_4$
35	E + H_2O	Yellow prisms	171–172.5	$C_{19}H_{25}N_3O_3$
36	E	Yellow prisms	197–199	$C_{12}H_{13}IN_3O_3$
37	MC + P	Yellow crystals	119.5–120.5	$C_{20}H_{23}N_3O_4$
38	A + H	Colorless needles	111–113	$C_{11}H_{15}BrN_2O_3S$
39	B + H	Colorless needles	127–129	$C_{11}H_{17}N_3O_3S$
41	E + H_2O	Yellow needles	175–176.5	$C_8H_7BrN_2O_3$
42	MC + P	Pale yellow prisms	98–99	$C_9H_{11}N_3O_3$
43	E	Pale yellow plates	125–127	$C_{14}H_{19}N_3O_3$
44[f]	M + E	Colorless prisms	237–239	$C_{11}H_{18}N_3O_3 \cdot HCl$
46	d	Yellow oil		$C_{16}H_{16}N_2O_2$
48	MC + P	Colorless needles	115–117	$C_{11}H_{17}N_3O_3S$

[a] Elemental analyses for all new compounds were submitted to the reviewers and found to be within acceptable limits (except for 6). [b] A = acetone, B = benzene, E = ethyl alcohol, Et = ether, H = hexane, MC = methylene chloride, M = methyl alcohol, P = petroleum ether (bp 30–60°). [c] A satisfactory carbon analysis could not be obtained. All spectra were in agreement with proposed structure. [d] Purified by chromatography. [e] Purified by preparative tlc. [f] Converted to the hydrochloride salt for analysis.

Experimental Section

All melting points are corrected. The nmr spectra were determined on a Varian A-60 instrument, using tetramethylsilane as an internal standard, the ir spectra were determined on a Beckmann IR-9 instrument, and the mass spectra on a CEC-110B instrument.

Preparation of the 2-Bromoacetanilides.—The 2-bromoacetanilides were prepared by bromoacetylation of the corresponding anilines utilizing method D of Sternbach, *et al.*[15] The following compounds are known: **1**,[8] **13**,[13] **30**,[13] **41**,[19] **45**,[15] and **47**.[20] The other 2-bromoacetanilides were prepared as follows: (a) **23** from 2-*N*-methylamino-5-nitrobenzophenone;[21] (b) **25** from commercially available 2-nitro-*N*-methylaniline (Eastman Organic Chemicals); (c) **28** from 2-*N*-methylaminobenzophenone;[22] (d) **38** from 4-dimethylsulfamoyl-*N*-methylaniline (**49**).[23]

General Procedure for the Reaction of 2-Bromoacetanilides with Amines.—A solution of the 2-bromoacetanilide (0.05–0.1 *M*) and an excess of the appropriate amine in either methanol or HMPA was stirred at room temperature until the reaction was complete. The course of the reaction was followed by thin layer chromatography. The solution was concentrated, and the residue was dissolved in CH_2Cl_2. After the solution was washed with saturated $NaHCO_3$ and saturated NaCl, the organic phase was dried ($MgSO_4$) and concentrated, and the residue was recrystallized from the appropriate solvent.

***N*-Methyl-4′-nitro-2-phthalimidoacetanilide (10).**—A solution of 1.0 g (3.66 mmol) of **1** and 676 mg (3.66 mmol) of potassium phthalimide in 10 ml of hexamethylphosphoric triamide was heated at 90–95° for 2 hr, cooled, and poured into 125 ml of H_2O. The resulting solid was filtered, washed with H_2O, and recrystallized from EtOH to yield 960 mg (77%) of **10** as white needles, mp 203–205°.

Preparation of 2 from 10.—A mixture of 1.3 g (3.8 mmol) of **10** 5.7 ml (11.4 mmol) of hydrazine hydrate, 20 ml of EtOH, and 20 ml of $CHCl_3$ was stirred at room temperature for 4 hr. The solvents were removed *in vacuo* and the residue was treated with H_2O. Filtration gave 520 mg (65%) of **2** as a yellow solid, mp 175–176.5°. All spectral data were identical with those obtained on a sample of **2** prepared by treating **1** with ammonia.

Registry No.—**1**, 23543-31-9; **2**, 31108-40-4; **3**, 37102-88-8; **4**, 37102-89-9; **5**, 37102-90-2; **6**, 37102-91-3; **7**, 37102-92-4; **8**, 37103-93-5; **10**, 37103-94-6; **12**, 37103-95-7; **13**, 33186-46-8; **14**, 33186-47-9; **15**, 37102-98-0; **16**, 37102-99-1; **17**, 37156-96-0; **18**, 37156-97-1; **19**, 37103-00-7; **23**, 37103-01-8; **24**, 34466-64-3; **25**, 37103-03-0; **26**, 37103-04-1; **27**, 37156-98-2; **28**, 37103-05-2; **29**, 37103-06-3; **30**, 33191-28-5; **31**, 33186-45-7; **34**, 37103-09-6; **35**, 37103-10-9; **36**, 37103-11-0; **37**, 37103-12-1; **38**, 37103-13-2; **39**, 37103-14-3; **41**, 3598-91-2; **42**, 37103-16-5; **43**, 37103-17-6; **44** (HCl), 37103-18-7; **45**, 14439-71-5; **46**, 37103-20-1; **47**, 37103-21-2; **48**, 37103-22-3.

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(19) R. A. Nyquist, *Spectrochim. Acta*, **19**, 1595 (1963).

(20) Seishi Takagi, Japanese Patent 10,775 (1960); *Chem. Abstr.*, **55**, 587a (1961).

(21) L. H. Sternbach, R. Ian Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(22) L. H. Sternbach, R. Ian Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

(23) Compound **49** was prepared by methylation of 4-dimethylsulfamoylaniline: J. Walker, *J. Chem. Soc.*, 686 (1940).