A General Method for Preparing 2-Acetamidoacetanilides Having a Second Functional Group in the 2 Position and Affording an Access to 3-Acetamido-1,3-dihydro-2H-1,4-benzodiazepin-2-ones[1]

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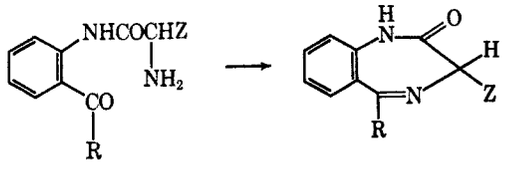
Received August 18, 1967

Base-catalyzed elimination of acetic acid from 2-(N-acetoxyacetamido)acetanilides to afford the reactive and unisolated 2-(acetylimino)acetanilides is described. Available nucleophiles add to the unsaturated imine bond to give 2-substituted 2-acetamidoacetanilides. Special cases are discussed, including a reaction of ammonia with an *o*-benzoyl-2-(N-acetoxyacetamido)acetanilide that leads ultimately to a 3-acetamido-1,4-benzodiazepine.

Pharmacologically important 1,4-benzodiazepines having functional substituents in the 3 position have been prepared in a variety of ways, each of which has depended ultimately upon an initial Polonovski rearrangement of the corresponding 4-oxide.[2] We sought to carry out cyclization reactions that would afford these 3-substituted benzodiazepines directly and have succeeded in preparing 3-acetamidobenzodiazepines in this manner.

The most favored synthesis of 1,4-benzodiazepin-2-ones has involved *o*-(2-aminoacetamido)phenyl ketones as intermediates but the products have had in the 3 position either no substituent or a nonfunctional one such as an alkyl group.[3] In order to accomplish a synthesis of a benzodiazepine having a 3-functional substituent it was necessary to have, at least as a transient intermediate, a compound of type I (eq 1), where

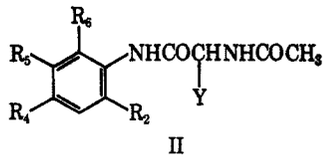


(1)

I

R is an alkyl or aryl group and Z is a functional group. In developing a preparation for such compounds a rather general synthesis has been achieved for *gem*-disubstituted compounds of type II in which Y is a functional group and R_2, R_4, R_5, and R_6 are optional.

Banfield, *et al.*,[4] have reported the ready addition of alcohols and amines to the double bond of N-acylketimines to form alkoxyacetamidodiarylmethanes and aminoacetamidodiarylmethanes and more recently similar additions have been recorded with N-acylaldimines.[5] These reactions suggested a method for making

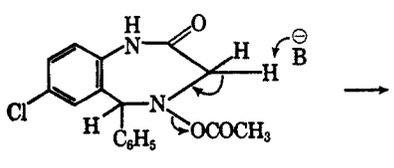


II

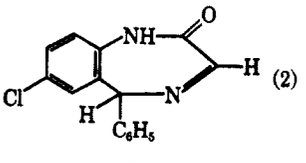
Compd	R_2	R_4	R_5	R_6	Y
IIa	COC_6H_5	Cl	H	H	NH_2
b	COC_6H_5	Cl	H	H	OC_2H_5
c	COC_6H_5	Cl	H	H	SC_2H_5
d	COC_6H_5	Cl	H	H	NC_5H_4O
e	COC_6H_5	Cl	H	H	$N(C_2H_5)_2$
f	COC_6H_5	Cl	H	H	$NHC_6H_4SO_2NH_2$
g	H	Cl	H	H	$NHSO_2C_6H_4NO_2$
h	H	Cl	H	H	$NHSO_2C_6H_4NH_2$
i	COC_6H_5	Cl	H	H	$NHCH_3$
j	CO_2CH_3	H	H	H	NH_2
k	CO_2CH_3	H	H	H	$NHCH_3$
l	CO_2H	Cl	H	H	NH_2
m	H	Cl	H	H	NH_2
n	CH_3	H	H	CH_3	$N(C_2H_5)_2$
o	$CONHCH_3$	Cl	H	H	$NHCH_3$
p	H	OCH_3	H	H	NC_4H_8O
q	SO_2NH_2	H	Cl	H	NC_4H_8O

II with Y = amino, alkoxy, or alkylthio groups. The earlier methods for the preparation of N-acylaldimines and N-acylketimines involve either direct reaction between a carbonyl compound and the necessary amide or acylation of the corresponding imine or intermediate Grignard complex. Neither method seemed to be suitable for the specific case (IIa) with which we were most concerned.

The base-catalyzed elimination (eq 2) of acetic acid from 4-acetoxy-7-chloro-1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-one (III) to afford the cyclic imine, 7-chloro-1,5-dihydro-5-phenyl-2H-1,4-



III



(2)

IV

(1) A preliminary communication has appeared: S. C. Bell, R. J. McCaully, and S. J. Childress, *Tetrahedron Letters*, 2889 (1965); presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p S14.

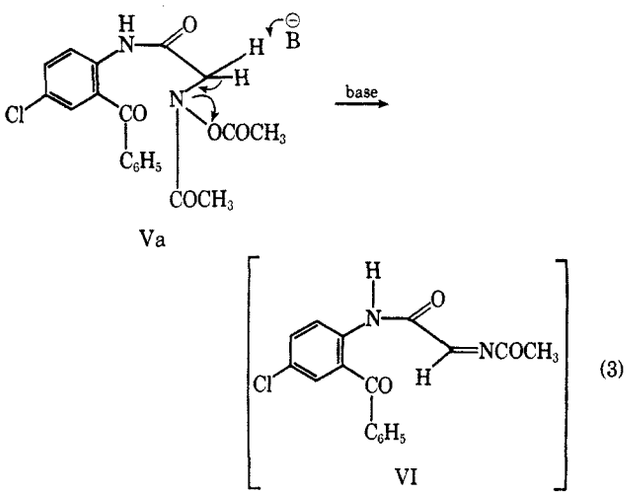
(2) After completion of this work, access to 3-chlorobenzodiazepines *via* 2-dichloromethylquinazoline 3-oxides [A. Stempel, E. Reeder, and L. H. Sternbach, *J. Org. Chem.*, **30**, 4267 (1965)] and *via* direct halogenation of benzodiazepines [R. I. Fryer, E. E. Garcia, and L. H. Sternbach, South African Patent, 66,7088 (1967)] was reported. 3-Carboxy derivatives have been obtained by cyclizations involving aminomalonic acid derivatives [J. Schmitt, Belgian Patent, 665,401 (1965)] and by direct attack of ethyl chloroformate upon benzodiazepinones unsubstituted in the 3 position [J. Hellerbach, A. Stempel, and L. H. Sternbach, South African Patent, 66,7243 (1967)].

(3) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).

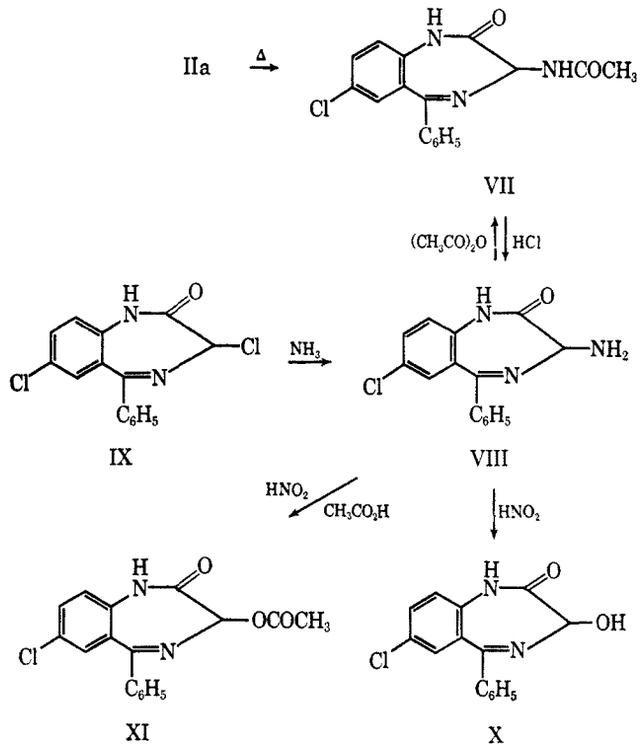
(4) J. E. Banfield, G. M. Brown, F. H. Davey, W. Davies, and T. H. Ramsay, *Australian J. Sci. Res.*, **A1**, 330 (1948).

(5) S. W. Breuer, T. Bernath, and D. Ben-Ishai, *Tetrahedron*, **23**, 2869 (1967).

benzodiazepin-2-one (IV), which we have reported,[6] suggested a method for the generation of the desired intermediate. The requirements for the occurrence of the elimination in III are an activated α-hydrogen atom and a suitable leaving group on the nitrogen atom. These requirements are met in the noncyclic compound Va, which by elimination of acetic acid would yield the desired acylaldimine (VI) (eq 3).



SCHEME I



Indeed, Va lost acetic acid in the presence of base but the resultant VI was so reactive toward addition of available nucleophiles that it has not been isolated. For example, Va upon treatment with sodium hydroxide in ethanol afforded IIb by addition of ethanol to the intermediate VI. The structure of IIb was confirmed through its nmr spectrum by the spin–spin coupling of its remaining α-hydrogen atom with that of the adjacent amide proton and by the presence of an ethoxy pattern. Ammonia in ethanol also caused elimination of acetic acid from Va, but in this case ammonia was the adding nucleophile instead of ethoxide and the desired IIa was obtained. Cyclization of IIa (Scheme I) to the 3-acetamidobenzodiazepine VII was brought about by mild heating. Direct comparison of VII obtained in this way was made with an authentic sample which, in turn, was prepared by acetylation of the corresponding 3-aminobenzodiazepine (VIII) derived from 3,7-dichloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IX).[7] The identity of the two samples gave further assurance that the elimination–addition reaction had proceeded as described above. It was possible to cleave the acetamido group in acid without ring destruction to give the 3-amino compound (VIII).

Surprisingly, in view of the well-known susceptibility of benzodiazepines to rearrangements, treatment of VIII with nitrous acid led to the 3-hydroxy compound (X, oxazepam) in excellent yield. (See Scheme I.) The corresponding 3-acetoxy compound (XI) was obtained in similar yield when the nitrous acid treatment was carried out in acetic acid.

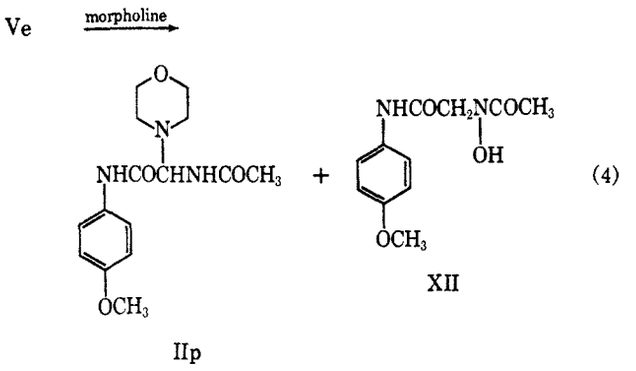
The extreme reactivity of the intermediate N-acylaldimine VI suggested the general usefulness of the elimination–addition reaction for preparing compounds of type II and some study was given to its application for this purpose. The study has so far been limited to acetanilides. Although there is some effect of the aromatic substituents on the ease of the elimination—the presence of electron-withdrawing groups such as carbethoxy, sulfamoyl, and benzoyl as well as the halogens results in better yields than is the case with electron-donating groups—the reaction itself would not appear to be limited to the anilides.

The ease of addition of nucleophiles to the N-acyliminoacetanilides is similar to the reactivity reported for the N-acylketimines.[4] Following base treatment of Va, the addition of mercaptans and α-pyridone as well as the already mentioned addition of alcohols and amines has been observed. Thus, compound Va with triethylamine and ethylmercaptan gave 2-acetamido-2′-benzoyl-4′-chloro-2-ethylthioacetanilide (IIc), with sodium 2(1H)-pyridone produced 2-acetamido-2′-benzoyl-4′-chloro-2-(1,2-dihydro-2-oxo-1-pyridyl)-acetanilide (IId), and with diethylamine in ethanol gave 2-acetamido-2′-benzoyl-4′-chloro-2-diethylaminoacetanilide (IIe). Sulfanilamide reacted with Va in the presence of triethylamine at its aromatic amino group to afford IIf, as shown by a negative diazo coupling test. *p*-Nitrobenzenesulfonamide reacted at the sulfonamide group with 2-(N-acetoxyacetamido)-4′-chloroacetanilide (Vd) to give IIg which was reduced catalytically to afford IIh.

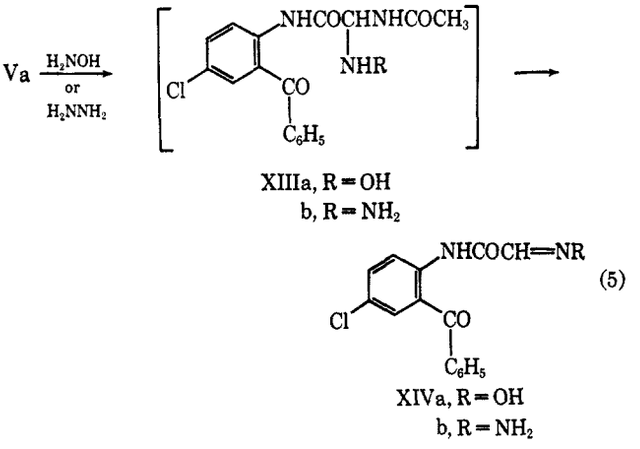
An occasional side reaction of the elimination–addition reaction involved attack of the base or nucleophile on the carbonyl group of the N-acetoxy group to give 2-(N-hydroxyacetamido)acetanilides, illustrated by the preparation of 2-(N-hydroxyacetamido)-4′-methoxyacetanilide (XII) (eq 4). The amount of the side

(6) S. C. Bell, R. J. McCaully, and S. J. Childress, *J. Med. Chem.*, **11**, 172 (1968).

(7) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).



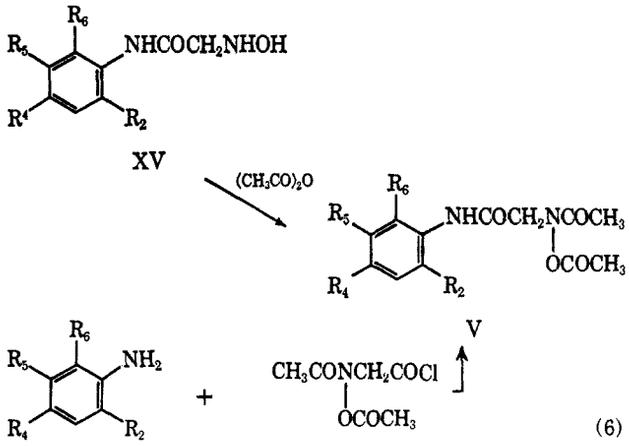
reaction was determined in some measure by the reaction conditions. When the 2-(N-acetoxyacetamido)-acetanilides were added to an excess of base and nucleophile at about 70° the extent of the side reaction was minimal. Another type of side reaction occurred when hydroxylamine or hydrazine was used as the base-nucleophile. The expected products from Va were XIIIa and XIIIb but each lost acetamide to give the corresponding oxime (XIVa) and hydrazone (XIVb) as shown in eq 5.



The 2-(N-acetoxyacetamido)acetanilides (V) used in the present work were synthesized by either of two routes (see eq 6): (1) direct acetylation of the corresponding hydroxylamines (XV), themselves obtainable from hydroxylamine and the halo derivatives, and (2) treatment of the requisite anilines (XVI) with N-acetoxyacetamidoacetyl chloride.[8] The reaction ensuing upon acetylation of XVb was complex and gave XVII. (See Scheme II.) It seems reasonable that diacetylation of the hydroxyamino function was accompanied by cyclization to a 3,1-benzoxazin-4-one which facilitated proton abstraction and initiated the elimination–addition reaction. Addition of acetate to the postulated acylaldimine afforded XVII. One of the intermediates (Vb) proposed in this pathway was prepared independently by treating 5-chloroanthranilic acid (XVIb) with N-acetoxyacetamidoacetyl chloride. Compound Vb gave XVII upon treatment with acetic anhydride. The infrared and nmr spectra of XVII are consistent with the structure given and are detailed in the Experimental Section. Treatment of XVII with methylamine resulted in ring opening and displacement of acetate to afford IIo.

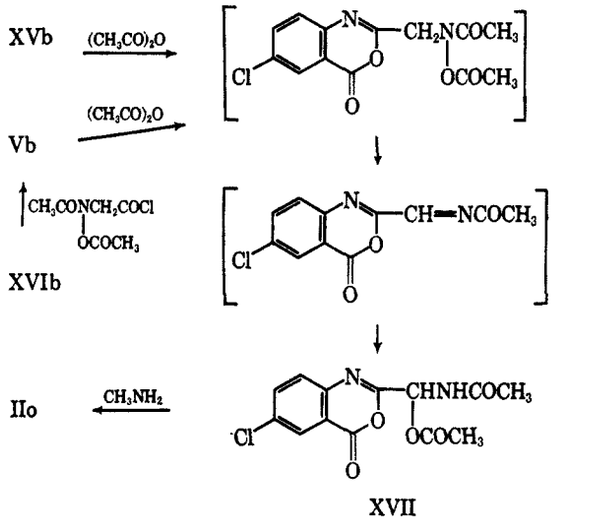
In a companion case, 2-amino-4-chlorobenzenesulfonamide (XVIc) was treated with N-acetoxyacetamido-

(8) S. C. Bell, R. J. McCaully, and S. J. Childress, *J. Heterocyclic Chem.*, in press.

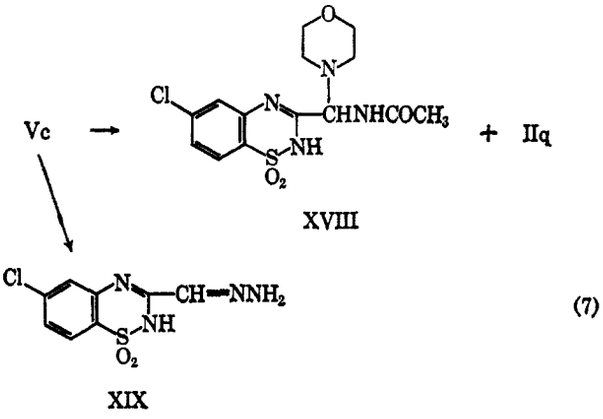


Compounds			R_2	R_4	R_5	R_6
		Va	COC_6H_5	Cl	H	H
XVIb	XVb	Vb	CO_2H	Cl	H	H
XVIc		Vc	SO_2NH_2	H	Cl	H
	XVd	Vd	H	Cl	H	H
	XVe	Ve	H	OCH_3	H	H
XVIf		Vf	CO_2CH_3	H	H	H
XVIg		Vg	CH_3	H	H	CH_3

SCHEME II



acetyl chloride to yield Vc. Here, treatment with the base morpholine not only brought about the elimination–addition reaction affording IIq, but also caused cyclization to the benzothiadiazine XVIII (eq 7).



With hydrazine and Vc, elimination–addition, cyclization, and elimination of acetamide occurred to yield XIX.

A small sampling of additional examples of II, V, and XV has been included in the Experimental Section in order to illustrate further the generality of the reactions.

Experimental Section[9]

2-Acetamido-2′-benzoyl-4′-chloro-2-ethoxyacetanilide (IIb).—To a suspension of 1.3 g of Va[8] in 30 ml of ethanol was added dropwise a solution of 4 *N* sodium hydroxide until the reaction solution remained strongly basic. Upon dilution with water 0.8 g of product formed, mp 199–201° (from acetonitrile).

The nmr spectrum ($CDCl_3$) showed peaks for the ethoxy group at δ 1.33 (CH_3, t) and 3.76 (CH_2, q, J = 7 cps) and the amide methyl group at 2.08 (s). The NH peak at 6.80 (d) vanished upon deuteration and the methine doublet at 5.62 (J = 9 cps) became a singlet. There were infrared peaks at 3.11 (NH), 5.84 (aromatic amide), 6.01 (aliphatic amide), and 6.10 μ (benzoyl).

Anal. Calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.90; H, 5.11; Cl, 9.46; N, 7.48. Found: C, 60.63; H, 5.12; Cl, 9.43; N, 7.55.

2-Acetamido-2-amino-2′-benzoyl-4′-chloroacetanilide (IIa).—Compound Va (1.0 g) was added at 0° to 100 ml of ethyl alcohol saturated with ammonia and the mixture was stirred for 15 hr. After evaporation of the solvent *in vacuo*, the residue was dissolved in benzene and cooled. The resultant precipitate, 0.27 g, mp 125–130°, was collected and recrystallized from acetonitrile to a constant melting point of 140–142°.

Anal. Calcd for $C_{17}H_{16}ClN_3O_3$: C, 59.05; H, 4.67; Cl, 10.25; N, 12.15. Found: C, 58.76; H, 4.40; Cl, 10.4; N, 11.87.

3-Acetamido-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (VII).—To 200 ml of ethanol saturated with ammonia was added 7.0 g of Va with stirring. After standing overnight at room temperature, the solution was concentrated *in vacuo* and the residue was dissolved in benzene. The white solid obtained upon cooling [3.8 g, mp 274–275° (from ethanol)] was identical with a sample of VII prepared by treating 3-amino-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (VIII) with acetic anhydride in pyridine.

Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.29; H, 4.30; N, 12.82. Found: C, 62.15; H, 4.15; N, 2.94.

3-Amino-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (VIII). Method A.—Compound VII (1 g) was dissolved in methanol containing excess hydrogen chloride and allowed to stand for 18 hr. The solution was diluted with water and made alkaline with ammonium hydroxide. The resultant solid, 0.65 g, was collected and recrystallized from ethanol to give VIII, mp 205–206°.

Method B.—A solution of 5.0 g of 3,7-dichloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IX)[7] in 50 ml of dimethoxyethane was added to 50 ml of a saturated solution of ammonia in dimethoxyethane, and after stirring for 20 min, the salt was filtered off and the solvent was removed *in vacuo*. The residue was dissolved in cold acetonitrile and the hydrochloride salt (3.1 g) was precipitated by the addition of alcoholic hydrogen chloride. Recrystallization from ethanol gave VIII hydrochloride hemialcoholate, mp 225–226°.

Anal. Calcd for $C_{15}H_{12}ClN_3O \cdot HCl \cdot 0.5C_2H_5OH$: C, 55.66; H, 4.07; Cl, 20.54; N, 12.12. Found: C, 55.62; H, 4.57; Cl, 20.51; N, 12.36.

The hydrochloride salt of VIII was treated with a sodium carbonate solution to give the base, mp 205–206° (from alcohol).

Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; Cl, 12.41; N, 14.71. Found: C, 63.20; H, 4.36; Cl, 12.20; N, 14.86.

7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (X).—To a warm solution of 10.0 g of VIII in 200 ml of 0.5 *N* hydrochloric acid was added dropwise an aqueous 5% solution of 3 g of sodium nitrite. The solid (9 g) that formed was collected and recrystallized from alcohol giving X, mp 205–206°, identical with an authentic sample.[7]

3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XI), mp 239–241°,[7] was prepared in a similar manner from VIII using acetic acid as solvent.

4′-Chloro-2-iodoacetanilide.—A mixture of 10.0 g of 2,4′-dichloroacetanilide, 15 g of sodium iodide, and 300 ml of acetone was heated under reflux for 4 hr. The reaction mixture was filtered from sodium chloride and evaporated to dryness and the residue was recrystallized from ethanol to give 10.8 g of product, mp 174–176°.

Anal. Calcd for C_8H_7ClINO: C, 32.51; H, 2.39; Cl, 11.99. Found: C, 32.70; H, 2.24; Cl, 11.54.

5-Chloro-2-chloroacetamidobenzoic acid, mp 214–217°, was prepared in the usual way from 5-chloroanthranilic acid and chloroacetyl chloride.

Anal. Calcd for $C_9H_7Cl_2NO_3$: C, 43.56; H, 2.84; Cl, 28.58; N, 5.64. Found: C, 44.02; H, 3.08; Cl, 28.40; N, 5.59.

2-Iodoacetamido-5-chlorobenzoic acid, mp 186–188°, was made in the same way as was 4′-chloro-2-iodoacetanilide.

Anal. Calcd for $C_9H_7ClINO_3$: Cl, 10.44; I, 37.38; N, 4.12. Found: Cl, 10.40; I, 37.4; N, 4.38.

4′-Chloro-2-hydroxyaminoacetanilide (XVd).—To a solution of 120 g of 4′-chloro-2-iodoacetanilide in 800 ml of ethanol at 75° was added a solution of 88 g of hydroxylamine hydrochloride in 400 ml of 4 *N* sodium hydroxide. The solution was heated at 80° for 10 min, chilled, and diluted with 1 l. of water. The crude product (69 g), after recrystallization from benzene, had mp 144–146°.

Anal. Calcd for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; Cl, 17.67; N, 13.97. Found: C, 48.35; H, 4.53; Cl, 17.9; N, 13.73.

Similarly prepared was **5-chloro-2-hydroxyaminoacetamidobenzoic acid (XVb)** from 2-iodoacetamido-5-chlorobenzoic acid.

Anal. Calcd for $C_9H_9ClN_2O_4$: C, 44.18; H, 3.71; Cl, 14.49. Found: C, 44.58; H, 3.78; Cl, 14.35.

Preparations of V. Method A. 2-(N-Acetoxyacetamido)-5′-chloro-2′-sulfamoylacetanilide (Vc).—N-Hydroxyaminoacetic acid (2.0 g) was stirred in 30 ml of acetic anhydride under a nitrogen atmosphere at 50° for 15 min. Undissolved acid (0.32 g) was filtered from the solution and the filtrate was concentrated to a yellow oil. The residual reagent was removed by flushing several times with toluene. The crystalline residue remaining after the final evaporation of toluene was dissolved in a solution of 6 ml of thionyl chloride in 20 ml of methylene chloride. After heating the solution for 5 min at reflux in a nitrogen atmosphere the solvent and the excess reagent were removed *in vacuo*. The residue, dissolved in 40 ml of methylene chloride, was added to a solution of 8.4 g of 2-amino-4-chlorobenzenesulfonamide (XVIc) in 50 ml of dimethoxyethane with stirring. After 1 hr at room temperature 4.4 g of the hydrochloride of the starting amine was filtered off. The filtrate was concentrated *in vacuo* and the residue was triturated in ethanol and filtered to give 2.9 g of Vc, mp 155–157°. Recrystallization from ethanol raised the melting point to 157–159°.

Anal. Calcd for $C_{12}H_{14}ClN_3O_6S$: C, 39.61; H, 3.88; Cl, 9.75; N, 11.55. Found: C, 39.96; H, 3.87; Cl, 9.70; N, 11.63.

Method B. 2-(N-Acetoxyacetamido)-4′-chloroacetanilide (Vd).—A mixture of 4.0 g of 4′-chloro-2-hydroxyaminoacetanilide (XVd) and 100 ml of acetic anhydride was heated on the steam bath for 20 min and concentrated to dryness *in vacuo*. The residue was triturated in 2-propanol. The resultant solid was filtered and washed with 2-propanol and hexane giving 4.8 g of Vd, mp 135.0–135.5°.

Anal. Calcd for $C_{12}H_{13}ClN_2O_4$: C, 50.62; H, 4.60; N, 9.84. Found: C, 50.80; H, 4.61; N, 9.70.

The following compounds were prepared by the foregoing methods as indicated.

2-(N-Acetoxyacetamido)-4′-methoxyacetanilide (Ve), mp 146–147°, was prepared from 4′-methoxy-2-hydroxyaminoacetanilide (XVe) *via* method B.

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00. Found: C, 56.11; H, 5.95; N, 10.14.

2-[2-(N-Acetoxyacetamido)acetamido]-5-chlorobenzoic acid (Vb), mp 182–183°, was prepared from 5-chloroanthranilic acid (XVIb) *via* method A.

Anal. Calcd for $C_{13}H_{13}ClN_2O_6$: C, 47.50; H, 3.98; Cl, 10.78; N, 8.52. Found: C, 47.72; H, 4.13; Cl, 10.7; N, 8.37.

(9) The melting points have not been corrected. The infrared spectra were taken in KBr pellets and the nmr spectra were taken in solvents containing TMS as the internal standard.

Methyl 2-[2-(N-acetoxyacetamido)acetamido]benzoate (Vf), mp 94–96°, was prepared from methyl anthranilate (XVIf) *via* method A.

Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.69; H, 5.18; N, 8.96.

2-(N-Acetoxyacetamido)-2′,6′-dimethylacetanilide (Vg), mp 200–201.5°, was prepared from 2,6-xylidine (XVIg) *via* method A.

Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.31; H, 6.20; N, 10.39.

N-[(6-Chloro-4-oxo-4H-3,1-benzoxazin-2-yl)acetoxymethyl]-acetamide (XVII).—A solution of 3.6 g of 5-chloro-2-hydroxyaminoacetamidobenzoic acid (XVb) (or 4.8 g of Vb) and 50 ml of acetic anhydride was heated for 1 hr on the steam bath and partially concentrated. White crystals, 2.1 g, mp 208–210° dec, were obtained on cooling.

The nmr spectrum DMSO-d_6 had methyl peaks at δ 2.40 (s) and 2.18 (s). Upon deuteration the amide proton doublet at 9.35 disappeared and the methine doublet at 7.0 (J = 9 cps) became a singlet. The infrared spectrum had carbonyl peaks at 5.60, 5.71, and 6.00, NH at 3.06, and amide II at 6.52 μ.

Anal. Calcd for $C_{13}H_{11}ClN_2O_5$: C, 50.25; H, 3.56; Cl, 11.41; N, 9.02. Found: C, 50.32; H, 3.52; Cl, 11.40; N, 8.85.

The following compounds were prepared in the same way as IIa.

2-Acetamido-2′-benzoyl-4′-chloro-2-ethylthioacetanilide (IIc), mp 118–119°, was prepared from Va, ethylmercaptan, and triethylamine.

Anal. Calcd for $C_{19}H_{19}ClN_2O_3S$: C, 58.37; H, 4.90; N, 7.17. Found: C, 58.43; H, 4.83; N, 7.11.

2-Acetamido-2′-benzoyl-4′-chloro-2-(1,2-dihydro-2-oxo-1-pyridyl)acetanilide (IId), mp 204–206°, was prepared from Va and sodium pyridone.

Anal. Calcd for $C_{22}H_{18}ClN_3O_4$: C, 62.36; H, 4.28; Cl, 8.37; N, 9.92. Found: C, 62.30; H, 4.31; Cl, 8.4; N, 9.99.

2-Acetamido-2′-benzoyl-4′-chloro-2-diethylaminoacetanilide (IIe), mp 150–152°, was prepared from Va and diethylamine.

Anal. Calcd for $C_{21}H_{24}ClN_3O_3$: C, 62.76; H, 6.02; Cl, 8.83; N, 10.46. Found: C, 62.59; H, 5.75; Cl, 8.9; N, 10.16.

2-Acetamido-2′-benzoyl-4′-chloro-2-(*p*-sulfamoylanilino)acetanilide (IIf), mp 204–206°, was prepared from Va, sulfanilamide, and triethylamine.

Anal. Calcd for $C_{23}H_{21}ClN_4O_5S$: C, 55.14; H, 4.23; Cl, 7.08; N, 11.18. Found: C, 55.14; H, 4.15; Cl, 7.42; N, 10.86.

2-Acetamido-2′-benzoyl-4′-chloro-2-methylaminoacetanilide (IIi), mp 142–143.5°, was prepared from Va and methylamine.

Anal. Calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.08; H, 5.04; Cl, 9.85; N, 11.68. Found: C, 60.19; H, 5.18; Cl, 9.85; N, 11.46.

Methyl 2-(2-acetamido-2-aminoacetamido)benzoate (IIj), mp 144–146°, was prepared from Vf and ammonia.

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.48. Found: C, 54.34; H, 5.61; N, 15.83.

Methyl 2-(2-acetamido-2-methylaminoacetamido)benzoate (IIk), mp 143–145°, was prepared from Vf and methylamine.

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.05. Found: C, 55.76; H, 6.14; N, 14.85.

2-(2-Acetamido-2-aminoacetamido)-5-chlorobenzoic acid hydrate (III), mp 143–145°, was prepared from Vb and ammonium hydroxide.

Anal. Calcd for $C_{11}H_{12}ClN_3O_4 \cdot H_2O$: C, 43.50; H, 4.65; Cl, 11.73; N, 13.84; H_2O, 5.93. Found: C, 43.39; H, 4.97; Cl, 12.00; N, 13.38; H_2O, 6.39.

2-Acetamido-2-amino-4′-chloroacetanilide (IIm), mp 171–173°, was prepared from Vd and concentrated ammonium hydroxide.

Anal. Calcd for $C_{10}H_{12}ClN_3O_2$: C, 49.69; H, 5.01; Cl, 14.67. Found: C, 49.58; H, 5.24; Cl, 14.8.

2-Acetamido-2-diethylamino-2′,6′-dimethylacetanilide (IIn), mp 177–179°, was prepared from Vg and diethylamine.

Anal. Calcd for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found: C, 65.97; H, 8.59; N, 14.15.

2-Acetamido-4′-methoxy-2-morpholinoacetanilide (IIp), mp 184–186°, was prepared from 2-(N-acetoxyacetamido)-4′-methoxyacetanilide (Ve) and morpholine.

Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.13; H, 6.82; N, 13.52.

The filtrate from the above reaction was concentrated to dryness and water was added to afford a solid that was collected and recrystallized from ethanol giving 2-(N-hydroxyacetamido)-4′-methoxyacetanilide (XII), mp 153–155°.

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.99; N, 11.76. Found: C, 55.14; H, 6.06; N, 11.76.

2-Acetamido-4′-chloro-2-methylamino-2′-methylcarbamoylacetanilide (IIo).—To a solution of 10 ml of 30% methylamine in water and 50 ml of ethanol was added 1.0 g of XVII. After stirring for 15 min the solution was concentrated *in vacuo* and the residue was suspended in water and filtered. There was obtained 0.8 g of crude product which after recrystallization from acetonitrile had mp 186–189°.

Anal. Calcd $C_{13}H_{17}ClN_4O_3$: C, 49.91; H, 5.49; Cl, 11.34; N, 17.91. Found: C. 49.75; H, 5.08; Cl, 11.5; N, 18.34.

2-Acetamido-4′-chloro-2-(*p*-nitrophenylsulfonamido)acetanilide (IIg), mp 206–208°, was made from Vd, *p*-nitrobenzenesulfonamide, and triethylamine in the same way as IIa.

Anal. Calcd for $C_{16}H_{15}ClN_4O_6S$: C, 45.03; H, 3.54; N, 13.10. Found: C, 44.76; H, 3.67; N, 12.86.

2-Acetamido-4′-chloro-2-sulfanilamidoacetanilide (IIh), mp 188–189°, was prepared by catalytic reduction of the above nitro compound (IIg).

Anal. Calcd for $C_{16}H_{17}ClN_4O_4S$: C, 48.39; H, 4.32; N, 14.12. Found: C, 48.48; H, 4.29; N, 14.16.

2-Acetamido-5′-chloro-2-morpholino-2′-sulfamoylacetanilide (IIq).—To a chilled solution of 10 ml of morpholine and 50 ml of water was added with strring 2.0 g of Vc. After standing at room temperature for 0.5 hr the solution was concentrated *in vacuo*. The residue was dissolved in water and several drops of acetic acid were added to produce a precipitate (0.5 g) which was collected and recrystallized from acetonitrile affording IIq, mp 194–196°.

Anal. Calcd for $C_{14}H_{19}ClN_4O_5S$: C, 43.02; H, 4.64; Cl, 9.07. Found: C, 43.23; H, 4.88; Cl, 9.0.

Further acidification of the filtrate from the above reaction mixture with acetic acid produced 1.3 g of **3-[acetamido(morpholino)methyl]-6-chloro-2H-1,2,4-benzothiadiazine 1,1-dioxide (XVIII)**, mp 188–190°, which after recrystallizaton from ethanol had mp 199–201°.

Anal. Calcd for $C_{14}H_{18}ClN_4O_4$: C, 45.10; H, 4.60; Cl, 9.51. Found: C, 45.50; H, 4.60; Cl, 9.35.

6-Chloro-2H-1,2,4-benzothiadiazine-3-carboxaldehyde 1,1-Dioxide Hydrazone (XIX).—To a mixture of 15 ml of hydrazine hydrate and 60 ml of ethanol was added 6.0 g of Vc. The solution was stirred for 1 hr, concentrated to dryness and diluted with water. There was obtained 5.0 g of XIX which after recrystallization from Methyl Cellosolve had mp 264–266°.

Anal. Calcd for $C_8H_7ClN_4O_2S$: C, 37.14; H, 2.73; N, 21.71. Found: C, 37.14; H, 2.68; N, 21.39.

Compounds similarly prepared are given as follows.

2′-Benzoyl-4′-chloroglyoxylanilide 2-oxime (XIVa), mp 163–165°, was prepared from Va and hydroxylamine.

Anal. Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.51; H, 3.65; Cl, 11.71; N, 9.26. Found: C, 59.49; H, 3.62; Cl, 11.75; N, 8.93.

2′-Benzoyl-4′-chloroglyoxylanilide 2-hydrazone (XIVb), mp 197–199°, was prepared from Va and hydrazine.

Anal. Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.55; H, 3.83; N, 13.84.

Registry No.—IIa, 4266-77-7; IIb, 15037-85-1; IIc, 15037-86-2; IId, 15037-87-3; IIe, 15037-88-4; IIf, 15037-89-5; IIg, 15076-99-0; IIh, 15037-90-8; IIi, 15037-91-9; IIj, 15037-92-0; IIk, 15037-93-1; III, 15037-94-2; IIm, 15037-95-3; IIn, 15037-96-4; IIo, 15037-97-5; IIp, 15077-00-6; IIq, 15037-98-6; Vb, 15037-99-7; Vc, 15038-00-3; Vd, 15038-01-4; Ve, 15038-02-5; Vf, 15038-03-6; Vg, 15038-04-7; VII, 4173-63-1; VIII, 894-77-9; VIII hydrochloride, 894-78-0; X, 604-75-1; XI, 1824-74-4; XII, 15038-09-2; XIVa, 14559-84-3; XIVb, 15038-11-6; XVb, 15038-12-7; XVd, 15038-13-8; XVII, 15038-14-9; XVIII, 15156-50-0; XIX, 15038-15-0; 4′-chloro-2-iodoacetanilide, 15038-16-1; 5-chloro-2-chloroacetamidobenzoic acid, 14422-50-5; 2-iodoacetamido-5-chlorobenzoic acid, 15038-18-3.

Acknowledgment. We are grateful to Mr. Bruce Hofmann for analytical service, to Dr. Charles Hetzel for nmr spectra, and to Mr. George L. Conklin and Mr. Carl Gochman for technical assistance.