TABLE I

EXPERIMENTAL DETAILS FOR PREPARATION OF BENZYL ESTER HYDROCHLORIDES FROM α-AMINO ACIDS

Product	Amount of starting material, g. (mmoles)	Benzyl alcohol, ml.	Thionyl chloride, ml.	M.p., °C. Obsd.	M.p., °C. Lit.	Yield, g. (%)
L-Phenylalanine benzyl ester (HCl)	3.3 (20)	125	20	202	203[a]	5.2 (90)
Glycine benzyl ester (HCl)	1.5 (20)	140	15	130	131–132[b]	3.0 (76)
S-Benzyl-L-cysteine benzyl ester (HCl)	2.11 (10)	125	20	92–93	91–97[a]	3.33 (100)
L-Glutamic dibenzyl ester (HCl)	2.94 (20)	105	20	93–95	94–95[c]	5.0 (69)

[a] Ref. 1. [b] Ref. 2. [c] B. Hargitay, A. J. Hubert, and R. Buyle, *Makromol. Chem.*, 56, 104 (1962).

solution until turbidity appeared. The mixture was then refrigerated for a few hours, during which time the benzyl ester hydrochloride crystallized. The product was collected by filtration and recrystallized from an absolute ethanol–ether mixture. Details for individual preparations are shown in Table I; the melting points obtained are in agreement with values reported in the literature. Important bands in the infrared spectra of all compounds included 2941 ($^+NH_3$ stretching), 1754 (ester carbonyl), 1205–1250 (C–O– stretching vibration), 738–727 cm.$^{-1}$ (monosubstituted benzene). The infrared data indicate the benzylation to have occurred at the carboxyl groups and not at the amino groups.

The Polonovski Rearrangement of Benzylideneaminoacetic Acid N-Oxides with Acid Anhydrides

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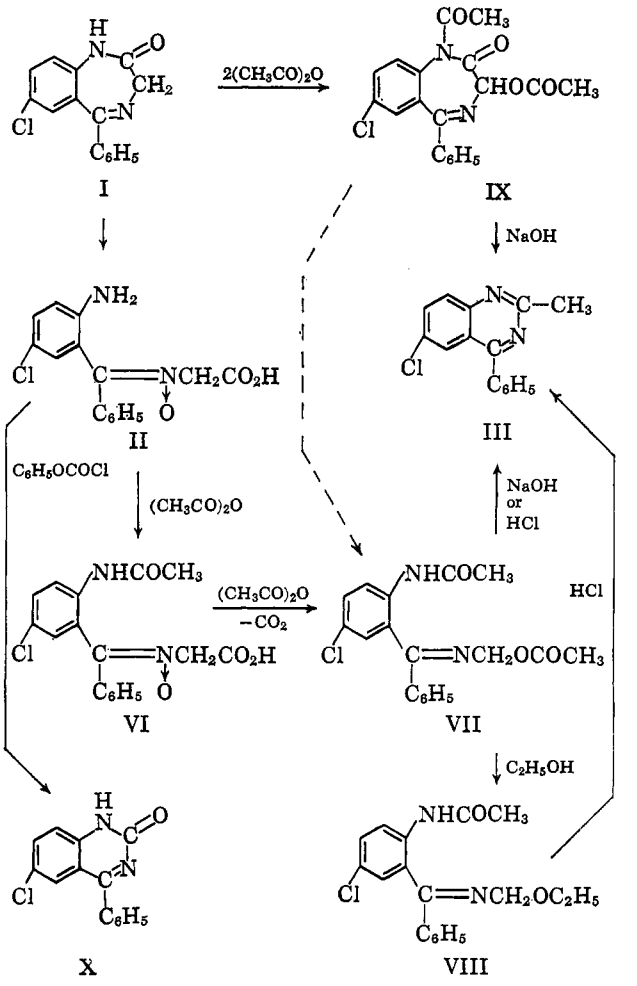
The formation of stable acetoxy compounds from a Polonovski-like rearrangement of N-oxides of cyclic compounds such as 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (I)[1,2] has recently been reported.[3–7] Hence it was of interest to examine the reaction of acetic anhydride with a similar noncyclic N-oxide, 2-amino-5-chloro-α-phenylbenzylideneaminoacetic acid N-oxide (II),[1,2] prepared by hydrolysis of I (see Scheme I).

Vigorous treatment of II with acetic anhydride and isolation of the product by basification with sodium hydroxide unexpectedly gave 6-chloro-2-methyl-4-phenylquinazoline (III).[8] Compound II underwent analogous rearrangements with formic acetic anhydride and with chloroacetic anhydride, giving 6-chloro-4-phenylquinazoline (IV) and 6-chloro-2-chloromethyl-4-phenylquinazoline (V),[8] respectively.

In order to determine the course of the production of III, the isolation of the intermediates was attempted.

SCHEME I



Mild treatment of II with acetic anhydride gave the acetanilide (VI). More strenuous treatment of II (or similar treatment of VI) with acetic anhydride yielded 2′-(α-acetoxymethyliminobenzyl)-4′-chloroacetanilide (VII). Compound VII would result from the expected introduction of an acetoxy group onto the adjacent saturated methylene group of VI, accompanied by a facile decarboxylation of the intermediate. The infrared absorption spectrum of VII confirmed the presence of ester (5.73 μ) and amide (5.92 μ) functions and the absence of a carboxylic acid group. The n.m.r. spectrum ($CDCl_3$) of VII showed two methyl singlets (δ 2.00, 2.15) and one methylene singlet (δ 5.20). Treatment of VII with alkali or acid afforded III. Apparently the initial step with either acid or base is

(1) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).
(2) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).
(3) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962).
(4) S. C. Bell, C. Gochman, and S. J. Childress, *ibid.*, **28**, 3010 (1963).
(5) L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *ibid.*, **29**, 332 (1964).
(6) O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 4666 (1963).
(7) W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **29**, 1621 (1964).
(8) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

hydrolysis of the acetyl group of VII, with subsequent loss of formaldehyde and ring closure.

Heating VII in ethanol produced a compound (VIII) which retained an amide peak (5.94 μ) but no longer showed an ester peak in the infrared spectrum. The n.m.r. ($CDCl_3$) peaks at δ 2.19 (s) (N-acetyl), 4.63 (s) (methylene), 1.22 (t), and 3.60 (q) (ethoxy), together with the infrared data, indicated that the structure of VIII was 4′-chloro-2′-(α-ethoxymethyliminobenzyl)acetanilide, resulting from solvolysis of the acetoxy group in VII. Compound VIII, an N,O-acetal, was stable when treated with hot alkali, but when refluxed in alcoholic hydrochloric acid was converted to the hydrochloride salt of III. The ultraviolet absorption spectra of VII [$\lambda_{max}^{CHCl_3}$ 240 mμ (ϵ 36,700), 333 (7320)] and VIII [λ_{max}^{EtOH} 238 mμ (ϵ 29,100), 332 (2950)] were characteristic of *o*-acylaminobenzophenone imines.[9]

3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, prepared by rearrangement of I with acetic anhydride,[3] underwent further acetylation at the 1-position upon strong heating with acetic anhydride to form 3-acetoxy-1-acetyl-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IX). Interestingly, IX also gave III when treated with sodium hydroxide. It seems likely that the diazepine ring of IX, being unstable to alkali, undergoes hydrolytic cleavage to form the intermediate VII, which is thereupon converted into III.

In the reaction of II with phenylchloroformate, no pure intermediate was isolated. Treatment of the crude reaction product with bicarbonate gave 6-chloro-4-phenyl-2(1H)-quinazolinone (X).[10] A route leading to X could be proposed, similar to that discussed above for the formation of III.

Experimental Section[11]

2-Acetamido-5-chloro-α-phenylbenzylideneaminoacetic Acid N-Oxide (VI).—A mixture of 1.0 g. of II, 1 ml. of acetic anhydride, and 15 ml. of chloroform was refluxed for 15 min. The solution was concentrated to dryness *in vacuo*, and the residue was recrystallized from carbon tetrachloride, giving 0.6 g. of product, m.p. 155–156°.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.35; Cl, 10.23; N, 8.16. Found: C, 58.72; H, 4.41; Cl, 10.0; N, 8.18.

4′-Chloro-2′-(α-acetoxymethyliminobenzyl)acetanilide (VII).—A mixture of 5.0 g. of II and 50 ml. of acetic anhydride was heated on the steam bath, with stirring, for 30 min. During this time most of the solid dissolved and gas was evolved. The reaction mixture was cooled, filtered from impurities, and concentrated to dryness *in vacuo*. The residue was treated with a small amount of cold alcohol, and the resultant solid was filtered, giving 2.3 g. of VII, m.p. 123–125°. Recrystallization from cyclohexane did not change the melting point.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3$: C, 62.65; H, 4.96; Cl, 10.30; N, 8.12. Found: C, 62.71; H, 5.01; Cl, 10.25; N, 8.15.

6-Chloro-2-methyl-4-phenylquinazoline (III). A.—To a suspension of 0.5 g. of VII in 10 ml. of ethanol was added 4 ml. of 4 *N* sodium hydroxide. The resultant solution was diluted with water to give 0.2 g. of III, m.p. 105–107°, identical with an authentic sample.[8]

B.—To 2.0 g. of VII was added 15 ml. of 6 *N* hydrochloric acid and 30 ml. of ethanol. The compound dissolved, and after several minutes a solid precipitated out. There was filtered off 0.8 g. of the hydrochloride salt of III.

C.—To a suspension of 0.3 g. of VIII in 3 ml. of alcohol, 1 ml. of 6 *N* hydrochloric acid was added and the resultant clear solution was heated to reflux. After several minutes a solid separated. The reaction mixture was cooled, and 0.15 g. of solid, m.p. 183–185°, was collected and found to be identical with the product formed by B.

D.—To a suspension of 1.0 g. of IX in 25 ml. of ethanol was added 3 ml. of 4 *N* sodium hydroxide. The reaction mixture darkened at first but after several minutes became lighter. After standing for 1 hr. the solution was diluted with 50 ml. of water, and the precipitate was collected, yielding 0.6 g. of III, m.p. 105–106°.

6-Chloro-4-phenylquinazoline (IV).—To a solution of 10 ml. of 98–100% formic acid and 5 ml. of acetic anhydride was added 1.0 g. of II. The solution was stirred at room temperature for 1 hr., heated at 60° for 30 min., cooled, and diluted with a large volume of water. A sticky precipitate was separated from the aqueous layer and recrystallized from an alcohol–water mixture, giving 0.3 g. of IV, m.p. 136–138°.

Anal. Calcd. for $C_{13}H_9ClN_2$: C, 69.84; H, 4.74; Cl, 14.73; N, 11.65. Found: C, 69.42; H, 4.51; Cl, 14.30; N, 11.81.

4′-Chloro-2′-(α-ethoxymethyliminobenzyl)acetanilide (VIII).—A solution of 2.3 g. of VII was refluxed in 50 ml. of ethanol for 30 min. and chilled. The precipitate (1.3 g., m.p. 114–116°) was recrystallized from cyclohexane. After drying to constant weight the product had a melting point of 118–120°.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_2$: C, 65.38; H, 5.80; Cl, 10.72; N, 8.48. Found: C, 65.45; H, 5.69; Cl, 10.60; N, 8.42.

6-Chloro-4-phenyl-2(1H)-quinazolinone (X).—To a solution of 1.0 g. of II in 15 ml. of dioxane was added, with stirring, 2.0 ml. of phenylchloroformate. The solution was diluted with water, neutralized with sodium bicarbonate solution, and extracted with ether. The ether was evaporated, alcohol was added to the residue, and the product was filtered off, yielding 0.7 g. of X, m.p. >300°, identical with an authentic sample.[10]

3-Acetoxy-1-acetyl-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IX).—A mixture of 5.0 g. of I and 50 ml. of acetic anhydride was refluxed for 1 hr. The solvent was removed *in vacuo*, and the residue was recrystallized twice from cyclohexane, giving 3.8 g. of IX, m.p. 170–172°.

Anal. Calcd. for $C_{19}H_{15}ClN_2O_4$: C, 61.54; H, 4.08; N, 7.56. Found: C, 61.69; H, 4.34; N, 7.15.

Acknowledgment.—We are indebted to Dr. Gordon Ellis and his associates for the microanalyses and to Dr. Charles Hetzel and Mr. Bruce Hofmann for the spectra.

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(11) The melting points are uncorrected. The infrared spectra were determined in KBr pellets. The n.m.r. spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as the internal reference.

Isomerization of *o*-Phenylphenol to *m*-Phenylphenol

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We recently had occasion to attempt a Friedel–Crafts acylation of *o*-phenylphenol using aluminum chloride as catalyst and isolated, as a major product of the reaction, *m*-phenylphenol. This represents a further example of phenyl group migration, a reaction that has been studied recently by Olah[1] and Wynberg[2] and is of further significance because *m*-phenylphenol has been, to date, a relatively inaccessible chemical.

The isomerization of *o*-phenylphenol to *m*-phenylphenol proceeds rapidly at 100° in the presence of

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