2-Cyano-*N*-[1,1-bis(hydroxymethyl)ethyl]acetamide (IId).—A solution of 10.5 g. of 2-amino-2-methyl-1,3-propanediol and 11.3 g. of ethyl cyanoacetate in 50 ml. of absolute ethanol was heated under reflux for 1 hr. The solvent was removed *in vacuo* on a rotary evaporator. The solid residue amounted to 21 g., m.p. 127–130°. Recrystallization from ethyl acetate–ethanol afforded 12.7 g. of product, m.p. 130.5–131.5°.

3-Amino-*N*-[1,1-bis(hydroxymethyl)ethyl]benzo[*f*]quinoxaline-2-carboxamide (IIId).—To a solution of 0.9 g. of sodium metal in 200 ml. of absolute ethanol was added 6.9 g. of 1-nitroso-2-naphthylamine and 7.4 g. of 2-cyano-*N*-[1,1-bis(hydroxymethyl)-ethyl]acetamide. The reaction mixture was heated under reflux for 35 min. The solvent was removed *in vacuo* on a rotary evaporator. The solid residue was triturated with glacial acetic acid and then was washed with water. Continuous extraction of the solid with benzene afforded a total of 7 g. of product, m.p. 211–213°. Recrystallization from aqueous *N*,*N*-dimethylformamide afforded 4 g. of product, m.p. 218–219.5°.

3-Amino-*N*-[1,1-bis(chloromethyl)ethyl]benzo[*f*]quinoxaline-2-carboxamide (IVd).—A solution of 10 g. of 3-amino-*N*-[1,1-bis-(hydroxymethyl)ethyl]benzo[*f*]quinoxaline-2-carboxamide in 100 ml. of thionyl chloride was heated under reflux for 2 hr. The solvent was removed *in vacuo* on a rotary evaporator. The residue was made basic with 10% sodium carbonate solution, filtered, and washed thoroughly with water. The crude product amounted to 7.9 g., m.p. 176–181°. Several recrystallizations from benzene raised the melting point to 183–184°.

10-Chloromethyl-8,9,10,11-tetrahydro-10-methyl-12*H*-benzo-[5,6]quinoxalino[2,3-*e*][1,4]diazepin-12-one (Vd).—To a solution of 3 g. of IVd in 20 ml. of *N*,*N*-dimethylformamide was added 1.5 g. of powdered, anhydrous sodium carbonate. The reaction mixture was allowed to boil under reflux for 1 hr. and was then filtered. Water was added to the filtrate until precipitation of the product was complete. After filtration, the product had m.p. 212–214° and weighed 3.9 g. Recrystallization from benzene afforded 1.5 g. of product, m.p. 215–216°.

8,9,10,11-Tetrahydro-10-methyl-10-morpholinomethyl-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-one (Ve).—A solution of 3 g. of Vd in 30 ml. of morpholine was heated under reflux for 24 hr. The reaction mixture was cooled in ice and 10 ml. of water was added. A yellow precipitate was deposited which after removal by filtration amounted to 3 g., m.p. 192–193°. Several recrystallizations from benzene afforded 1 g. of product, m.p. 192–194°

8,9,10,11-Tetrahydro-12*H*-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-thione—To a solution of 2 g. of Va in 30 ml. of dry pyridine was added 2 g. of phosphorus pentasulfide. The reaction mixture was boiled under reflux for 80 min., cooled to room temperature, and poured into 70 ml. of hot water. The precipitate which deposited amounted to 2.5 g. After recrystallization from aqueous pyridine, the melting point was 254–256°.

Anal. Calcd. for $C_{15}H_{12}N_4S$: C, 64.26; H, 4.32; N, 19.99; S, 11.44. Found: C, 64.66; H, 4.17; N, 19.96; S, 11.55.

Acknowledgment.—The authors are indebted to Mr. Ronald D. Stewart for technical assistance and Dr. Gordon Ellis and staff for microanalytical results.

The Synthesis of a 1,3-Benzothiazine by a Novel Rearrangement of an N-Substituted Saccharin Derivative

HAROLD ZINNES, ROGER A. COMES, AND JOHN SHAVEL, JR.

Warner-Lambert Research Institute, Morris Plains, New Jersey

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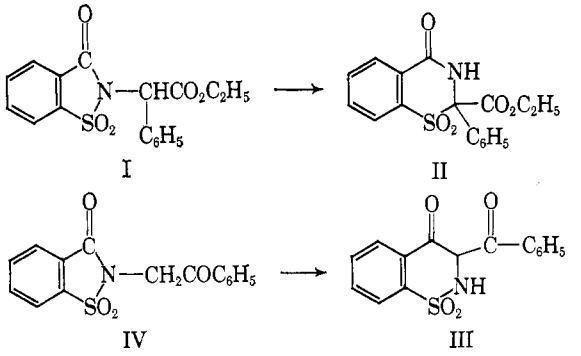
We wish to report the base-catalyzed ring expansion of an N-substituted saccharin derivative to give a 1,3-benzothiazine. Treatment of N-(α-phenylcarbethoxymethyl)saccharin (I) with sodium ethoxide in ethanol resulted in the formation of ethyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-dioxide (II) in 44% yield. This is in contrast to the work of Abe, *et al.*,[1] who obtained the 1,2-benzothiazine, III, when IV was made to undergo the same reaction



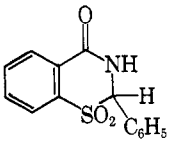
I II

IV III

conditions.[2] The latter reaction, which involves cleavage of a carboxamide linkage, has its counterpart in the phthalimide series.[3] These divergent reaction paths may be related to the relative stabilities of the carbanions formed by abstraction of an α-hydrogen from either I or IV. The formation of III from IV could arise by initial ethanolysis of the amide followed by a Dieckmann ring closure. On the other hand, the formation of the more stable carbanion from I may be favored over ethanolysis and this could react by direct attack on the electrophilic SO_2 group to give II.[4]

Reaction of II with sodium hydride in dimethylformamide followed by the addition of methyl iodide afforded the N-methyl derivative V. When this was subjected to aqueous ethanolic sodium hydroxide at room temperature, rapid saponification and decarboxylation took place to give 3-methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1,1-dioxide (VI).

Alkaline treatment of the parent compound (II) resulted in destruction of the 1,3-benzothiazine system as was shown by the rapid liberation of benzaldehyde as well as by the isolation of *o*-carboxybenzenesulfinic acid.[5] Evidently, initial saponification and decarboxylation took place to give VII. Since the N-methyl derivative (VI) was stable to base, the cleavage of the ring may have been initiated by alkaline removal of the amide proton. The instability of VII to alkali was



VII

confirmed by the immediate odor of benzaldehyde which was detected when a crystalline sample was stirred with aqueous alkali. Compound VII was isolated

(1) K. Abe, S. Yamamoto, and K. Matsui, *J. Pharm. Soc. Japan*, **86**, 1058 (1956); *Chem. Abstr.*, **51**, 3499 (1957).

(2) We have confirmed this work.

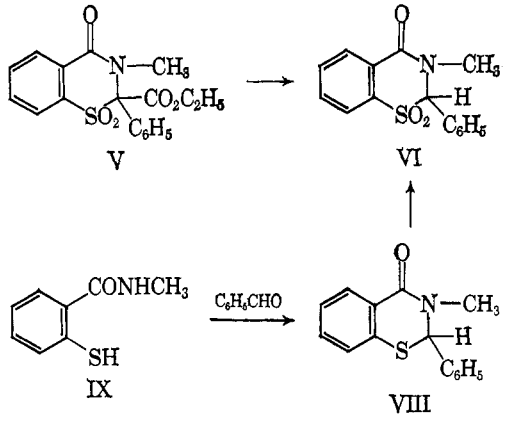
(3) S. Gabriel and J. Colman, *Ber.*, **33**, 980, 2630 (1900); **35**, 2421 (1902).

(4) Both of these mechanisms have been offered to explain the related rearrangement of α-phthalimidoacetic esters and α-phthalimido ketones to give 4-hydroxyisocarbostyrils; W. J. Gensler, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 378; C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

(5) H. Böhme and W. Schmidt [*Arch. Pharm.*, **286**, 330 (1953)] report the formation of *o*-carboxybenzenesulfinic acid by acid hydrolysis of 3,4-dihydro-2-methyl-4-oxo-2*H*-1,3-benzothiazine 1,1-dioxide.

in small yield from a reaction in which I was treated with sodium hydride in dimethylformamide at room temperature.[6]

The structure of VI was confirmed by an independent synthesis. 3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3H)-one (VIII) was prepared by the acid-catalyzed condensation of N-methylthiosalicylamide (IX) with benzaldehyde as described by Moreau and Delacoux.[7]



Treatment of this sulfide with hydrogen peroxide in acetic acid at room temperature for 24 hr. resulted in the formation of the corresponding sulfoxide. Continued oxidation for 10 days gave the sulfone VI which was identical in every respect with the product obtained from alkaline treatment of V.

Experimental[8]

N-(α-Phenylcarbethoxymethyl)saccharin (I).—A mixture of 200 g. (0.8 mole) of ethyl α-bromophenylacetate, 250 g. (1.2 moles) of sodium saccharin, and 500 ml. of dimethylformamide was heated with stirring at 105–115° for 45 min. and was poured into 5 l. of water. The resulting gum was solidified by trituration with several portions of water. The solid was dissolved in methylene chloride; the solution was washed with water, dried over sodium sulfate, and concentrated to a small volume. To this was added 300 ml. of ethanol and the resulting solution was distilled at atmospheric pressure until crystals began to separate. On cooling, there was obtained 150.5 g. of product, m.p. 127–128°. The analytical sample was prepared by dissolving a portion in a mixture of methylene chloride and ethanol and distilling at atmospheric pressure until crystals began to separate; it had m.p. 129–130°.

Anal. Calcd. for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06; S, 9.28. Found: C, 58.88; H, 4.48; N, 4.08; S, 9.42.

Ethyl 3,4-Dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide (II).—A solution of sodium ethoxide, prepared from 6.9 g. (0.3 mole) of sodium and 135 g. of ethanol, was heated to 40° and 51.8 g. (0.15 mole) of N-(α-phenylcarbethoxymethyl)saccharin was added all at once as the powder. The mixture was quickly heated to 50–55° and maintained at this temperature for 5 min. It was then rapidly cooled to 25° and 150 ml. of 9% hydrochloric acid was added as rapidly as was consistent with maintaining the temperature at 30–35°. The ethanol was removed by distillation *in vacuo* and the remaining aqueous solution was extracted with methylene chloride. Evaporation of the dried (sodium sulfate) methylene chloride solution gave an oil which was crystallized by dissolving in 50 ml. of ethanol, concentrating to about one-half the volume, and refrigerating. There was obtained 19.5 g. (37%) of product, m.p. 137–138°. Recrystallization from ethanol gave material, m.p. 139–140°; ν_{max} 3200, 1680, and 1154 cm.$^{-1}$; λ_{max} mμ (ε), 265 sh (2860), 271 sh (2655), 278 (2540), 286 sh (2020); λ_{min} 275 (2480).

Anal. Calcd. for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06; S, 9.28. Found: C, 59.33; H, 4.34; N, 4.27; S, 9.25.

Evaporation of the solvent from the mother liquor of the initial crystallization and trituration of the residue with isopropyl ether gave a solid which was recrystallized from isopropyl alcohol to give 3.5 g. (7%) of material, m.p. 120–124°; this was shown by infrared and thin-layer chromatography to be a slightly impure sample of the first crop product. The remainder of the reaction product could not be purified further. A thin-layer chromatogram gave six spots, one of which (estimated to represent 15–20% of the total) corresponded to II.

Ethyl 3,4-Dihydro-3-methyl-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide (V).—To a slurry of 4.0 g. of a 53.4% mineral oil dispersion of sodium hydride (0.075 mole) in 250 ml. of dimethylformamide was added a solution of 26.0 g. (0.075 mole) of ethyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-dioxide (II) in 250 ml. of dimethylformamide, the temperature being maintained at 0 to 10° during the addition. The reaction mixture was stirred at room temperature for 2.5 hr. and 30 ml. of methyl iodide was added while maintaining the temperature at 0 to 10° during the addition. After stirring for 1 hr. at room temperature, the mixture was poured into 2 l. of ice-water. On stirring and scratching, a crystalline solid separated from solution. This was washed with water and dried *in vacuo* at 60° to give 24.6 g. of material, m.p. 90–93°, whose infrared spectrum was practically identical with that of the analytical sample. Recrystallization from 65 ml. of ethanol gave 17 g. of product, m.p. 103–104°. Another recrystallization from ethanol gave analytically pure material, m.p. 104–105°; ν_{max} 1744, 1674, 1235, and 1165 cm.$^{-1}$; λ_{max} mμ (ε), 266 (2900), 272 (3100), 279 (3100), 287 (2640); λ_{min} 262 (2700), 268 (2850), 275 (2920), 285 (2600).

Anal. Calcd. for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90; S, 8.92. Found: C, 60.02; H, 4.83; N, 3.76; S, 9.21.

Reaction of Ethyl 3,4-Dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide (II) with Alkali.—When a solution of 3.5 g. (0.01 mole) of ethyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-dioxide in 40 ml. of 0.05 *N* sodium hydroxide was prepared at room temperature, there was immediately noted the odor of benzaldehyde and the solution became cloudy. After standing overnight at room temperature, the mixture was extracted with ether and the ether was distilled off *in vacuo* to yield 1.0 g. of an almost colorless oil which had the characteristic odor of benzaldehyde. The oil was dissolved in 25 ml. of ethanol and was treated with excess 2,4-dinitrophenylhydrazine reagent to give 1.0 g. of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 230–235°; recrystallization gave m.p. and m.m.p. 239–240°.

The aqueous layer from the ether extraction was acidified with hydrochloric acid, filtered, and taken to dryness at 30° using a flash evaporator. The residue was extracted with ether using a Soxhlet apparatus and evaporation of the solvent followed by drying *in vacuo* at 40° gave 1.1 g. of *o*-carboxybenzenesulfinic acid, which melted at 120–125°, resolidified, and remelted at 200°[9]; ν_{max} 2520, 1690, 1115, 1070, 1050, and 1020 cm.$^{-1}$.

Anal. Calcd. for $C_7H_6O_4S$: C, 45.16; H, 3.25; S, 17.22. Found: C, 45.25; H, 3.28; N, 0.0; S, 16.78.

3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3H)-one 1,1-Dioxide (VI). A. Preparation by Alkaline Treatment of Ethyl 3,4-Dihydro-3-methyl-4-oxo-2-phenyl-2*H*-1,3-benzothiazine-2-carboxylate 1,1-Dioxide.—To a suspension of 15 g. (0.042 mole) of the ester in 1000 ml. of ethanol was added 84 ml. of 1.0 *N* aqueous sodium hydroxide. After stirring at room temperature for a few minutes, a precipitate began to separate from the solution. The stirring was continued overnight and the precipitate, which was identified as sodium carbonate, was filtered off. The filtrate was concentrated *in vacuo* to a small volume and 3000 ml. of water was added. The resulting white precipitate was col-

(6) Here the same rearrangement took place as with sodium ethoxide in ethanol. The only isolable product (VII) probably arose through saponification and decarboxylation in the alkaline solution resulting from the hydrolysis of the reaction mixture.

(7) R. C. Moreau and E. Delacoux, *Bull. soc. chim. France*, 502 (1962).

(8) Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The infrared spectra were all carried out as Nujol mulls and the ultraviolet spectra were determined as solutions in 95% ethanol. Homogeneity of the analytical samples was checked by thin-layer chromatography on silica gel G (Stahl) using a 50:50 mixture of *n*-heptane and acetone as the eluent. Chromatograms were developed by placing them in a closed vessel containing iodine crystals. We are indebted to Mrs. U. Zeek for the microanalyses and to Mr. R. Puchalski for the spectral data.

(9) Ref. 5 reports m.p. 124–126° followed by resolidification and remelting at 287–291°.

lected by filtration, washed with water, and dissolved in methylene chloride, and the dried (sodium sulfate) methylene chloride solution was distilled to dryness. Trituration of the residue with petroleum ether (b.p. 40–60°) gave 9.7 g. of white crystals, m.p. 170–171°. Recrystallization from ethanol gave material with m.p. 170–171°; ν_{max} 1671 and 1156 cm.$^{-1}$; λ_{max} mμ (ϵ), 270 (3270), 277 (3180), 286 (2680); λ_{min} 268 (3250), 274 (3180), 283 (2500).

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.61; H, 4.66; N, 4.93; S, 11.21.

B. Preparation by Oxidation of 3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one.—To a solution of 3.5 g. (0.014 mole) of the thioether[7] in 25 ml. of glacial acetic acid was added 20 ml. of 30% hydrogen peroxide. The solution was allowed to stand at room temperature for 10 days and was then poured into 300 ml. of water. The resulting white precipitate was collected, washed well with water, and dissolved in methylene chloride, and the dried (sodium sulfate) methylene chloride solution was distilled to dryness. The residue was triturated with low boiling petroleum ether to give 3.3 g. of product, m.p. 170–171°, which was shown by mixture melting point and by comparison of infrared and ultraviolet spectra to be identical with material prepared by A.

2-Phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1,1-Dioxide (VII).—To a suspension of 0.8 g. of 53.4% mineral oil dispersion of sodium hydride (0.015 mole) in 50 ml. of dimethylformamide was added a solution of 5 g. (0.015 mole) of N-(α-phenylcarbethoxymethyl)saccharin in 25 ml. of dimethylformamide, the temperature being maintained between 0 and 10°. The orange solution was stirred at room temperature for 3 hr. and then was poured into 1000 ml. of absolute ether. A gum separated, and this became a semisolid after several triturations with fresh portions of ether. The semisolid was dissolved in 150 ml. of water and on acidification of this solution with dilute hydrochloric acid there was obtained a white precipitate. This was filtered off, washed with water, and was dried *in vacuo* at 60° to give 0.7 g. of material, m.p. 177–178°. Recrystallization from ethanol yielded a product, m.p. 185–186°; ν_{max} 3200, 1680, and 1154 cm.$^{-1}$; the ultraviolet spectrum was identical with that of the corresponding N-methyl compound (VI).

Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.53; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.37; H, 4.23; N, 5.15; S, 11.64.

On stirring a portion of this compound with 1 *N* sodium hydroxide, there was immediately noted the odor of benzaldehyde.

3-Methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one 1-Oxide.—To a solution of 5.2 g. (0.02 mole) of 3-methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)-one in 60 ml. of glacial acetic acid was added 20 ml. of 30% hydrogen peroxide. The solution was allowed to stand at room temperature for 24 hr. and was then poured into 400 ml. of ice–water. Extraction with methylene chloride followed by drying over sodium sulfate and evaporation of the solvent gave an oil. This was crystallized from 40 ml. of ethanol to yield 3.0 g. of product, m.p. 170–172°. Recrystallization did not change the melting point. Mixture melting point with a sample of the corresponding sulfone gave a 20° depression; ν_{max} 1656, 1640, 1052, no significant absorption at 1100–1200 cm.$^{-1}$; λ_{max} mμ (ϵ), 272 (2800), 280 (2750), 289 sh (2420); λ_{min} 276 (2700), 285 (2490).

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; S, 11.82. Found: C, 66.23; H, 4.80; S, 11.85.

N-Nitrosoamides. VI. Nitrosocarbamates and Nitrosoamides of Amino Acids. The Preparation of Diazoacetic and Diazopropionic Esters[1]

EMIL H. WHITE AND RONALD J. BAUMGARTEN[2]

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

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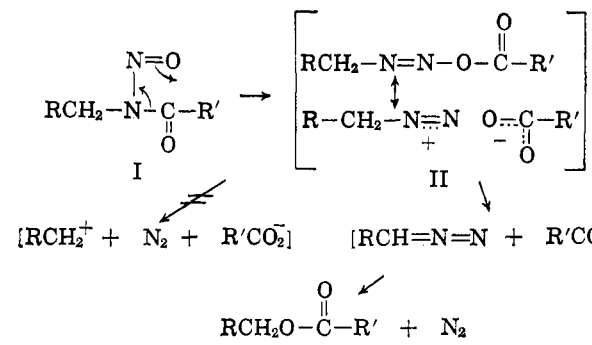
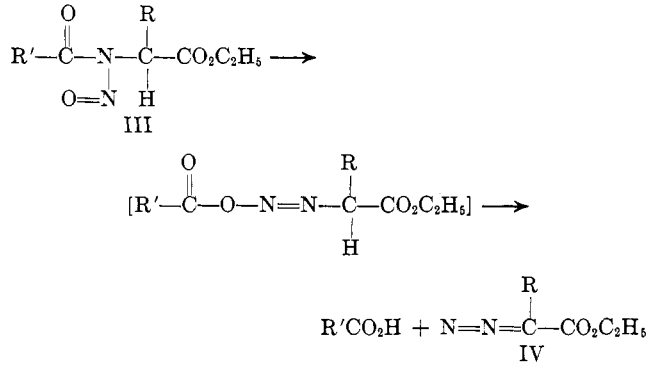
N-Nitrosoamides of primary carbinamines (I) decompose to give the corresponding esters *via* a reaction

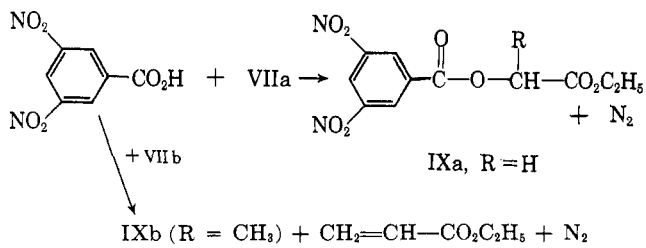


series involving diazo alkanes as intermediates.[3] The carbonium ion pathway, found for the decomposition of nitrosoamides of secondary carbinamines,[1] is not followed, presumably because of the relatively high energy of a primary carbonium ion (formed by the loss of nitrogen from II). The decomposition of nitrosoamides or nitrosocarbamates of amino acid esters (III) also yields the corresponding diazo compound (IV), which, in this case, can be isolated because of the low general reactivity of α-diazocarbonyl compounds. We report here the decomposition of several of these nitroso compounds.[4]



N-Nitrosocarbamates.—These derivatives of glycine and alanine were readily prepared by the acylation of the corresponding esters, and subsequent nitrosation of the carbamates with either nitrogen tetroxide or nitrous acid. The pyrolysis of compounds VIa and VIb at 125–135° and 50–100 mm. (under conditions whereby the product was distilled from the reaction vessel) led to *ca.* 70% yields of the corresponding diazo esters (Scheme I).

The diazo esters were identified through their infrared spectra, and assayed by the reaction with 3,5-dinitrobenzoic acid. These dinitrobenzoate derivatives, which apparently have not been reported previously, were prepared from ethyl chloroacetate and ethyl lactate for comparison purposes. The diazo



(1) Paper V in this series: E. H. White and C. A. Aufdermarsh, Jr., *J. Am. Chem. Soc.*, **83**, 1179 (1961).

(2) Taken in part from a thesis submitted by R. J. Baumgarten to the Faculty of the Graduate School at The Johns Hopkins University in partial fulfillment of the requirements for the Ph.D. degree.

(3) E. H. White and C. A. Aufdermarsh, Jr., *J. Am. Chem. Soc.*, **83**, 1174 (1961).

(4) Preliminary results were given by E. H. White, *ibid.*, **77**, 6013 (1955).