The combined aqueous washes were extracted for 3 days with CH_2Cl_2 in a Raab extractor. Evaporation of the solvent *in vacuo* left a semisolid residue (10.3 g) which was shown by vpc to consist of two major products. This mixture was dissolved in 25 ml of CH_2Cl_2 and chromatographed over silica gel using successively, pentane, pentane–CH_2Cl_2, CH_2Cl_2, and CH_2Cl_2–CH_3OH (9:1) as eluents. The eluates were collected in fractions of 50 ml each. The CH_2Cl_2 fraction afforded **cyclopentene-3-carboxylic acid** (**4**, 1.9 g, 9%) as a colorless oil: bp 68–70° (0.5 mm), lit.[10a] bp 65° (15 mm); ir (neat) 5.95 μ (C=O); nmr ($CDCl_3$) δ 12.25 (s, 1, CO_2H), 6.05–5.65 (m, 2, olefinic H), 3.80–3.40 (m, 1, $CHCO_2H$), and 2.30–1.90 (m, 4, CH_2). Both the amide **3** (mp 135–137°) and the anilide (mp 120–122°, lit.[10a] mp 120°) were prepared.

Anal. Calcd for $C_6H_8O_2$: C, 64.28; H, 7.14. Found: C, 64.42; H, 7.15.

The CH_2Cl_2–CH_3OH fractions led to **cyclopentene-3-carboxamide** (**3**, 7.85 g, 38%): mp 135–137° (from CH_2Cl_2); nmr ($CDCl_3$) δ 7.50–6.45 (two broad peaks which disappeared in DMSO-d_6, 2, $CONH_2$), 5.90–5.62 (m, 2, olefinic H), 3.57–3.20 (m, 1, CH), and 2.61–1.73 (m, 4, CH_2).

Catalytic reduction (5% Pd-C) of **4** in absolute EtOH at atmospheric pressure gave cyclopentanecarboxylic acid (**7**, 80%), bp 116–118° (60 mm), lit.[10b] bp 104° (11 mm). Similar reduction of **3** afforded **cyclopentanecarboxamide** (**6**, 82%), mp 178–180° (from CH_3Cl_2) (lit.[10b] mp 179°). Successive treatment of **7** with thionyl chloride and ammonia converted it to the amide **6** which was identical in all respects with **6** obtained from reduction of **3**.

Table I summarizes the results of studies of the reaction of **1** with CSI under various conditions.

Reduction of 2 with Benzenethiol–Pyridine.—A solution of pyridine (5.6 g, 0.70 mol) in 15 ml of acetone was added dropwise to a Dry Ice cooled and stirred solution of 10.5 g (0.05 mol) of **2** and 10.4 g (0.10 mol) of benzenethiol in 25 ml of acetone. After continued stirring for 1 hr, 60 ml of water was slowly added to precipitate the phenyl disulfide which was removed by filtration. The filtrate was extracted with five 25-ml portions of ether; the combined ether extracts were dried (Na_2SO_4) and filtered; and the solvent was removed *in vacuo* to give 4.5 g (75%) of **2-aza-3-ketobicyclo[2.2.1]heptane** (**5**) as an oil slightly contaminated with phenyl disulfide. Distillation at 80–82° (0.5 mm) gave **5** as a colorless viscous oil which solidified on cooling: mp 32–34°; ir (neat) 3.10 (NH) and 5.72 μ (C=O); nmr ($CDCl_3$) δ 7.28–6.72 (broad singlet which disappeared in D_2O, 1, NH), 4.20–3.98 (t, 1, NCH), 3.66–3.36 (m, 1, CH), and 2.20–1.10 (m, 6, CH_2).

Anal. Calcd for C_6H_9NO: C, 64.82; H, 8.15; N, 10.00. Found: C, 64.52; H, 8.03; N, 9.97.

Registry No.—Chlorosulfonyl isocyanate, 1189-71-5; **1**, 185-94-4; **2**, 24689-57-4; **3**, 24647-27-6; **4**, 2348-89-2; **5**, 24647-29-8.

(10) (a) Heilbron, I, "Dictionary of Organic Compounds," Vol. 1, Oxford University Press, London, 1965, p 647; (b) p 645.

Salicylamide–Acetylenedicarboxylate Reactions as a Route to Benzoxazinones[1]

NED D. HEINDEL AND LEE A. SCHAEFFER

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015

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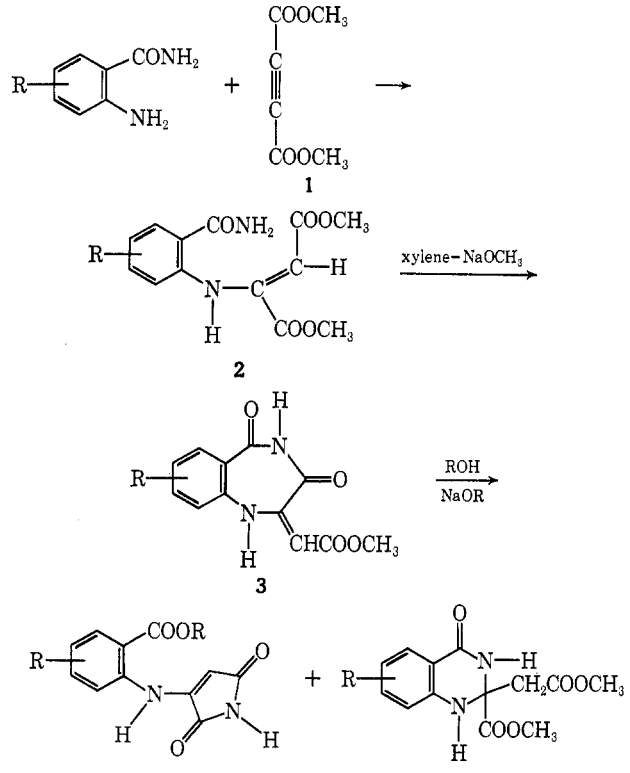
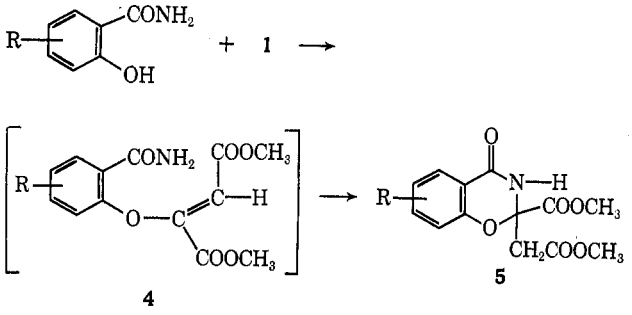
Previous reports from these laboratories have pointed to the considerable utility of acetylene esters in hetero ring-forming reactions.[2] We have noted that anthranilamides reacted with dimethyl acetylenedicarboxylate (**1**) to yield the corresponding anilinofumarates (**2**). These intermediate enamines underwent facile ring closure to 1,4-benzodiazepin-3,5-diones (**3**) which could be isolated in nonhydroxylic solvents but which



underwent ring-contraction rearrangement in alcoholic media to mixtures of maleimides and quinazolinones.[3]

Our studies on salicylamides and salicylanilides show that these systems more closely parallel the reactions of thiosalicylamide and **1**[4] rather than anthranilamides and **1**.[3] The amine and thiol additions were exothermic, required no base catalysis, and provided excellent yields of adducts which could be cyclized to seven-membered heterocyclics in the anthranilamide series and to six-membered benzothiazinones in the thiosalicylamide situation. The *o*-hydroxyamides yield exclusively six-membered benzoxazinones but they require base catalysis for both the OH-to-alkyne addition and for the cyclization step. With the exception of salicylamide and **1**, catalyzed by N-methylmorpholine, it is not possible to isolate the presumed intermediate phenol adducts (**4**).

Bases sufficiently strong to bring about hydroxyl addition to acetylenedicarboxylate are also capable of promoting cyclization to the benzoxazinones. This



(1) (a) Taken in part from the M.S. Thesis of L. A. S., Lehigh University, 1969. (b) Supported by Grant No. 1R01MH-13562 from the National Institute of Mental Health.

(2) See N. D. Heindel, P. D. Kennewell, and C. J. Ohnmacht, *J. Org. Chem.*, **34**, 1168 (1969), and references cited therein.

(3) N. D. Heindel, V. B. Fish, and T. F. Lemke, *ibid.*, **33**, 3997 (1968).

(4) N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *ibid.*, **32**, 2678 (1967).

method, therefore, does constitute a convenient one-step synthesis of a hitherto unknown type of substituted 1,3-benzoxazin-4-ones (**5**). Nmr and mass spectral studies (see Experimental Section) eliminate the alternative isomeric 1,4-benzoxazepin-4-ones as the possible reaction products. These six-membered heterocyclic compounds are prepared in 45–93% yields, with one exception, by the sodium methoxide catalyzed reaction of the corresponding salicylamide or salicylanilide with **1**. The condensation of 1-hydroxy-2-naphthamide with dimethyl acetylenedicarboxylate was exceedingly sluggish and presumably reflects a *peri* steric effect at the hydroxyl.

The intermediate adduct, **4**, isolated from the N-methylmorpholine-catalyzed addition of salicylamide and **1** was of fumarate geometry reflecting a transoid addition. Amines[5,6] and thiols[4,7] have been observed to add with similar *trans* stereospecificity. Previous workers in amine–acetylene ester adducts have noted that both geometric isomers are necessary to make an accurate structure assignment by nmr.[8,9] Reliable stereoelectronic criteria permit fumarate assignment to the more deshielded vinyl resonance.[9]

Although we obtained only one isomer of **4** (single vinyl resonance in nmr) we were able to prepare suitable maleate–fumarate models for spectral comparison by thermal equilibration of the adducts of **1** with methyl salicylate and methyl 5-chlorosalicylate. The fumarate vinyl proton in these substances was detected at δ 6.68 and the maleate vinyl at 5.00–5.03 ppm. In **4** the vinyl singlet was observed at δ 6.75 ppm thus permitting its assignment as a fumarate isomer.

Molecular models show that this intermediate adduct, **4**, is sterically capable of undergoing cyclization to a seven- or eight-membered system by amide displacement upon the corresponding side-chain ester, or of undergoing Michael-type internal NH addition to the six-membered system (benzoxazinones) or the seven-membered system (benzoxazepinones).

Even under experimental conditions (xylene/sodium methoxide) which effected excellent conversions of **2** to the benzodiazepine, **3**, none of the benzoxazepine counterpart was detected from **4**. Invariably, elemental analysis and nmr and infrared spectroscopy supported the benzoxazinone structure, **5**. The ring closure of **4** was indeed base catalyzed since prolonged reflux in methanol returned starting material. Amine bases can bring about cyclization but best results were obtained with sodium methoxide in methanol.

Experimental Section[10]

2-Carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (**6**).—A solution of 2.74 g (20 mmol) of salicylamide, 2.84 g (20 mmol) of **1**, and 0.11 g (2 mmol) of sodium methoxide in 64 ml of methanol was refluxed for 24 hr and concentrated *in vacuo*. Cooling precipitated white crystals of **6**: 2.55 g (46%); from methanol, mp 128.0–129.5°; nmr spectrum ($CDCl_3$) δ 3.31 (AB q, 2, J = 18 Hz, $-CH_2-$), 3.76 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), and 6.9–8.1 ppm (m, 5, Ar **H** and **NH**); ir spectrum (KBr) 3183 (NH) and 1754, 1742, 1675 cm^{-1} (C=O); mass spectrum (72 eV) m/e (rel intensity) 279 (<1), 220 (100), 206 (29), and 121 (35).[11]

Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.66; N, 5.02. Found: 55.77; H, 4.53; N, 5.10.

2-Carbomethoxy-2-carbomethoxymethyl-6-bromo-2,3-dihydro-4H-1,3-benzoxazin-4-one (**7**).—The reaction of 5-bromosalicylamide and **1** as described above gave a 56% yield of the bromobenzoxazinone, **7**: from benzene, mp 156.5–158.0°; nmr spectrum ($CDCl_3$) δ 3.31 (AB q, 2, J = 18 Hz, $-CH_2-$), 3.79 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 6.78–7.18 (m, 3, Ar **H**) and 7.80 ppm (broad s, 1, **NH**); ir spectrum (KBr) 3180 (NH) and 1757, 1730, 1687 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{12}BrNO_6$: C, 43.58; H, 3.35; N, 3.91. Found: C, 43.79; H, 3.42; N, 3.93.

2-Carbomethoxy-2-carbomethoxymethyl-6-chloro-2,3-dihydro-4H-1,3-benzoxazin-4-one (**8**).—When equimolar quantities (30 mmol) of 5-chlorosalicylamide and **1** were treated as above a 45% yield, mp 158.5–160.0°, from benzene, of **8** was obtained: nmr spectrum ($CDCl_3$) δ 3.30 (AB q, 2, J = 18 Hz, $-CH_2-$), 3.77 and 3.78 each (s, 3, OCH_3), 6.90–7.95 (m, 3, Ar **H**), and 7.68 ppm (broad s, 1, **NH**); ir spectrum (KBr) 3185 (NH) and 1759, 1735, 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{12}ClNO_6$: C, 49.76; H, 3.83; N, 4.47. Found: C, 49.88; H, 3.84; N, 4.44.

2-Carbomethoxy-2-carbomethoxymethyl-6,8-diiodo-3-(4-iodophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (**9**).—A suspension of 5.91 g (10 mmol) of 3,4′,5-triiodosalicylanilide,[12] 1.70 g (12 mmol) of **1**, and 1 mmol of sodium methoxide in 50 ml of methanol was refluxed with stirring for 24 hr. Concentration and cooling precipitated a greenish-white solid which was recrystallized from 1:1 benzene: petroleum ether (60–110°) to yield 5.34 g (73%) of the white benzoxazinone, **9**: from benzene, mp 187–188°; nmr spectrum (trifluoroacetic acid) δ 3.42 (d, 2, $-CH_2-$), 3.72 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 7.1–8.5 ppm (m, 6, Ar **H**); ir spectrum (KBr) 1755, 1735 and 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{14}I_3NO_6$: C, 31.11; H, 1.91; I, 51.98. Found: C, 30.90; H, 1.85; I, 51.89.

2-Carbomethoxy-2-carbomethoxymethyl-3-phenyl-2,3-dihydro-4H-1,3-benzoxazin-4-one (**10**) was prepared by dropwise addition of 30 mmol of **1** to a solution of 30 mmol of salicylanilide and 3 mmol of sodium methoxide in 50 ml of methanol. The addition required 30 min and the mixture was then stirred at room temperature for 24 hr during which time the benzoxazinone, **10**, precipitated. Concentration of the mother liquors produced additional material for a total of 9.89 g (93%) of white microneedles: from methanol, mp 170–172°; nmr spectrum (trifluoroacetic acid) δ 3.42 (s, 2, $-CH_2-$), 3.55 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), and 7.0–8.1 ppm (m, 9, Ar **H**); ir spectrum (KBr) 1762, 1748 and 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.23; H, 4.79; N, 3.94. Found: C, 64.44; H, 5.01; N, 3.92.

2-Carbomethoxy-2-carbomethoxymethyl-3,4-dihydro-2H-naphth[2,1-*e*]1,3-oxazin-4-one (**11**) was prepared by reaction of 5.61 g (30 mmol) of 1-hydroxy-2-naphthamide, 4.26 g (30 mmol) of **1**, and 0.16 g (3 mmol) of sodium methoxide in 32 ml of methanol. After 4-hr reflux the reaction mixture was cooled and filtered to remove 2.15 g of 1-hydroxy-2-naphthamide. The oily residue was diluted with cold ether and filtered to isolate 1.0 g (10%) of the naphthoxazinone, **11**: from methanol, mp 150.5–152.0°; nmr spectrum ($CDCl_3$) δ 3.45 (s, 2, $-CH_2-$), 3.70 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), and 7.3–8.4 ppm (m, 7, Ar **H** and **NH**); ir spectrum (KBr) 3190 (NH) and 1755, 1742 and 1675 cm^{-1}(C=O).

Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.01; H, 4.56; N, 4.26. Found: C, 62.16; H, 4.73; N, 4.29.

Comparison of the infrared spectrum of the oily mother liquors with that of an authentic sample[13] revealed that the material was mainly dimethyl methoxyfumarate, the product of the addition of methanol to **1**.

(5) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(6) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 3339 (1967).

(7) W. E. Truce in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, pp 112–120.

(8) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

(9) J. E. Dolfini, *ibid.*, **30**, 1298 (1965).

(10) Proton nmr spectra were obtained on a Varian A-60 spectrometer and are reported in δ (parts per million) units from TMS. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E spectrometer and infrared spectra on a Perkin-Elmer 257 spectrometer, calibrated against polystyrene. Combustion analyses were provided by Dr. George I. Robertson, Jr., Florham Park, N. J.

(11) Fragment ions corresponding to the loss of CH_3COOCH_3 (m/e 206) and to the loss of $COOCH_3$ (m/e 220) have been observed in a related quinazolinone diester (ref 3), and support the benzoxazinone assignment in this case.

(12) U. S. Patent 2,906,711 (1960); *Chem. Abstr.*, **54**, 3873 (1960).

(13) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).

Dimethyl *o*-carboxamidophenoxyfumarate (4) was prepared by stirring together at room temperature for 24 hr a solution of 20 mmol each of salicylamide, 1, and N-methylmorpholine in 27 ml of diethyl ether. Addition of water and agitation precipitated 0.76 g (14%) of the phenol adduct, 4, which was recrystallized from methanol: mp 124.5–126.5°; nmr spectrum ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 6.75 (s, 1, vinyl **H**), 7.6 (broad s, 2, NH_2), and 6.6–8.2 ppm (m, 4, Ar **H**); ir (KBr) 3440, 3344, 3300, and 3240 (NH) and 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.66; N, 5.02. Found: 55.63; H, 4.69; N, 5.07.

Cyclization of 4 in Xylene–Sodium Methoxide.—A solution of 0.40 g (1.4 mmol) of dimethyl *o*-carboxamidophenoxyfumarate, 4, and a catalytic quantity of sodium methoxide (0.4 mmol) in 50 ml of xylene was refluxed for 17 hr, filtered, and concentrated. The crude crystals were washed with cold ether and filtered to yield 0.18 g (45%) of the benzoxazinone, 6, identified by melting point and ir comparison with authentic sample.

Dimethyl *o*-carbomethoxyphenoxy-2-butene-1,4-dioate (12) was synthesized by allowing an ethereal solution of 0.20 mol each of methyl salicylate, triethylamine, and 1 to stand at room temperature for 2 days. The ether was removed, the residue dissolved in benzene, washed well with water, dried ($MgSO_4$), and distilled to yield 37.6 g (64%) of a pale yellow oil: bp 175–180° (1 Torr); nmr spectrum ($CDCl_3$) δ 3.70, 3.78, 3.92, 3.94, 3.98 and 4.03 for the respective methoxy singlets, 5.00 (s, 1, maleate vinyl **H**, 50%), 6.68 (s, 1, fumarate vinyl **H**, 50%) and 6.8–8.2 ppm (m, 4, Ar **H**).

Anal. Calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.73. Found: C, 57.20; H, 4.71.

Dimethyl *o*-carbomethoxy-*p*-chlorophenoxy-2-butene-1,4-dioate (13) was prepared from methyl 5-chlorosalicylate as described above: bp 181–184° (1 Torr); 63%; nmr spectrum ($CDCl_3$) δ 3.62, 3.68, 3.71, 3.78, 3.93 and 3.95 for the methoxy singlets, 5.03 (s, 1, maleate vinyl **H**, 42%), 6.68 (s, 1, fumarate vinyl **H**, 58%) and 6.8–8.1 ppm (m, 3, Ar **H**).

Anal. Calcd for $C_{14}H_{13}ClO_7$: C, 51.14; H, 3.96. Found: C, 51.19; H, 4.08.

Registry No.—**1**, 762-42-5; **4** (R = H), 24704-24-3; **6**, 24716-40-3; **7**, 24716-41-4; **8**, 24716-42-5; **9**, 24716-43-6; **10**, 24716-44-7; **11**, 24716-45-8; **12** maleate, 24704-25-4; **13** maleate, 24710-88-1; **12** fumarate, 24710-82-5; **13** fumarate, 24710-83-6.

Fragmentation of a Sydnone *via* Elimination[1a,b]

LEONARD J. FLIEDNER, JR., AND I. MOYER HUNSBERGER[1c]

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01002

Received November 3, 1969

Although a number of characteristic reactions of sydnones have been thoroughly documented,[2] a novel type of fragmentation reaction has now been encountered during the course of an attempted preparation of 3-sydnonealanine (**2a**). It was hoped that **2a** would possess carcinolytic activity because certain sydnones have tumor-inhibiting properties (*cf.* ref 2), the alanine moiety is biologically compatible, and there is a striking structural and electronic (zwitterionic) similarity between **2a** and the isomeric azaserine (**4**), the latter being a well-known antileukemic agent.

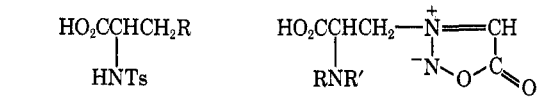
(1) (a) Sydnones. V. Part IV: C. J. Thoman, S. J., D. J. Voaden, and I. M. Hunsberger, *J. Org. Chem.*, **29**, 2044 (1964). (b) This investigation was supported, in part, by a research grant (CA-05478) from the National Cancer Institute of the U. S. Public Health Service. (c) To whom all inquiries should be sent. This paper is taken, in part, from the Ph.D. dissertation of L. J. F., University of Massachusetts, 1965.

(2) F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964).

The projected synthesis of **2a** involved a standard sequence of reactions proceeding from the selectively protected 3-amino-2-(tosylamino)propionic acid (**1b**),[3] which was readily available by Hofmann degradation of N^2-tosylasparagine (**1a**).[3–5] Condensation of **1b** with glycolonitrile[6] followed by acid hydrolysis of the resulting glycinonitrile **1c** and nitrosation of the corresponding glycine **1d** were all carried out in good yield.

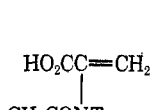
The cyclodehydration of **1e** with acetic anhydride under a variety of conditions gave two products (A and B) or mixtures thereof. Optimum yields (*ca.* 65%) of one of these compounds (A), mp 176–178° dec, were realized after 24 hr at room temperature, whereas heating for 30 min or allowing the reactants to stand at room temperature for 2 weeks produced a second compound (B), mp 143–145° dec, in 30–50% yield along with dark-colored, noncrystalline products.

The presence of both the sydnone ring and the *p*-toluenesulfonamido groups in A was indicated by ultraviolet maxima at 300 and 232 mμ, respectively. Identification of A as the N-acetyl derivative **2c** of the expected sydnone **2b** was supported also by its infrared spectrum, which showed the sydnone ring CH absorption[2] as well as three closely spaced bands in the 1700–1730-cm^{-1} region (C=O). No sulfonamide NH stretching absorption was observed.

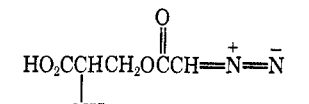


1a, R = $CONH_2$
b, R = NH_2
c, R = $NHCH_2CN$
d, R = $NHCH_2CO_2H$
e, R = $N(NO)CH_2CO_2H$

2a, R = R′ = H
b, R = H; R′ = Ts
c, R = CH_3CO; R′ = Ts



3



4

Ts = *p*-$CH_3C_6H_4SO_2$

N-Acetyl-N-tosylalanine (**5b**) was prepared from N-tosylalanine (**5a**)[4] and acetic anhydride as a model to assist in the assignment of the carbonyl bands of **2c**. Infrared comparison (Nujol) of the two compounds suggests that the high-frequency band (1728 cm^{-1}) of **2c** is the sydnone carbonyl. Differentiation of the carbonyl bands of **2c** was effected further by examining the spectra of **2c** and **5b** in dioxane. Assignments (see Experimental Section) were determined by comparison with N-acetyl-N-tosylglycine in which the positions (in dioxane) of the acetamido (1712 cm^{-1}) and carboxyl (1754 cm^{-1}) functions have been established.[7]

The formation of B from the N-nitrosoglycine **1e** *via* the intermediate sydnone **2c** appeared likely since B

(3) The terms tosylamino and tosyl refer to the *p*-toluenesulfonamido and *p*-tolylsulfonyl functions, respectively.

(4) Since the starting materials for the syntheses described herein were DL-asparagine and DL-alanine, all compounds with an asymmetric center have the DL configuration.

(5) J. Rudinger, K. Poduska, and M. Zaoral, *Collect. Czech. Chem. Commun.*, **25**, 2022 (1960).

(6) J. M. Tien and I. M. Hunsberger, *J. Amer. Chem. Soc.*, **83**, 178 (1961).

(7) M. Zaoral and J. Rudinger, *Collect. Czech. Chem. Commun.*, **26**, 2316 (1961).