platinum oxide at room temperature and atmospheric pressure. After 1.98 l. of hydrogen had been absorbed, the reaction mixture was filtered through a bed of Celite, and the clear filtrate was concentrated *in vacuo*. The residual amber oil was crystallized from petroleum ether and the solid was collected to give 3.2 g. of off-white needles, m.p. 53–57°. This material gave a positive color test with nitrous acid and R salt.

C. From IV.—A solution of 10.0 g. of 2-[*o*-(*p*-toluenesulfonamido)phenyl]-2-oxazoline[2a] (IV) in 50 ml. of sulfuric acid was stored at room temperature for 14 hr. The reaction mixture was then poured into 320 ml. of 25% aqueous sodium hydroxide with cooling in an ice bath. The mixture was extracted four times with dichloromethane; the dichloromethane extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residual oil (5.0 g.) was crystallized from petroleum ether to give 4.1 g. of white needles, m.p. 52–56°. Two recrystallizations from petroleum ether gave the pure compound, m.p. 56–57°, undepressed on admixture with material prepared by either of the methods described above.

2-[*o*-(*p*-Toluenesulfonamido)phenyl]-2-oxazoline (IV).—To an ice-cold solution of 0.4 g. of 2-(*o*-aminophenyl)-2-oxazoline (Va) in 20 ml. of dry pyridine was added 0.5 g. of *p*-toluenesulfonyl chloride. After standing at room temperature for 18 hr. the reaction mixture was poured into several volumes of ice and diluted with cold water. The solid, which was separated by filtration, consisted of off-white needles (0.38 g.), m.p. 195–199°, undepressed on addition of IV prepared by cyclization of IIIa by the method of Santilli and Osdene.[2a]

Hydrolysis of 2-[*o*-(*p*-toluenesulfonamido)phenyl]-2-oxazoline (IV) to N-(2-Hydroxyethyl)-2-(*p*-toluenesulfonamido)benzamide (II).—A solution of 3.2 g. of IV in 40 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 17 hr. The reaction mixture was cooled to room temperature and neutralized with 3 *N* aqueous hydrochloric acid. An oil separated which was extracted with dichloromethane in four portions. The dichloromethane extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residual oil was crystallized from ethyl acetate–ether to give 0.9 g. of off-white prisms, m.p. 120–127°, which were recrystallized from benzene to give 0.6 g. of N-(2-hydroxyethyl)-2-(*p*-toluenesulfonamido)benzamide (II), m.p. 124–127°, undepressed on admixture of authentic material.

2-Aminoethyl 2-Aminobenzoate (VI).—A solution of 1.94 g. of 2-(*o*-aminophenyl)-2-oxazoline (Va) in 35 ml. of 1 *N* aqueous hydrochloric acid was refluxed overnight. The reaction mixture was cooled to room temperature, made basic with 3 *N* aqueous sodium hydroxide, and extracted three times with dichloromethane. The dichloromethane extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residual solid (1.5 g., needles, m.p. 70–75°) was purified by crystallization from ethyl acetate–petroleum ether (b.p. 60–70°). It formed colorless needles, m.p. 82–85°, λ_{max} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71. Found: C, 59.92; H, 6.43.

2-[*o*-(*p*-Toluenesulfonamido)phenyl]-2-thiazoline (IX). A. From IV.—A mixture of 5.0 g. of 2-[*o*-(*p*-toluenesulfonamido)-phenyl]-2-oxazoline (IV) and 5.0 g. of phosphorus pentasulfide with 75 ml. of pyridine was heated under reflux for 2 hr. The reaction mixture was cooled slightly and then poured into 250 ml. of hot water. After cooling to 20°, the mixture was neutralized with 30% hydrochloric acid and a gummy material precipitated. The supernatant liquid was decanted and the amorphous residue was crystallized from dilute pyridine. The solid was collected to give 2.4 g. of yellow rhomboids, m.p. 162–165°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85. Found: C, 58.06; H, 5.09.

B. From X.—A solution of 1.0 g. of X in 25 ml. of thionyl chloride was heated under reflux for 1 hr. Excess thionyl chloride was removed, the pale amber oil was dissolved in 25 ml. of toluene, and the pH was adjusted to 7 by the addition of triethylamine. The resulting solution was heated under reflux for 1 hr., then cooled to room temperature, and filtered through 10 g. of Florisil. The Florisil was eluted with 50 ml. of benzene. The benzene and toluene fractions were combined and concentrated to yield, on cooling, 350 mg. (38%) of 2-[*o*-(*p*-toluenesulfonamido)-phenyl]-2-thiazoline (IX), m.p. 161–162°, undepressed on admixture with the material prepared from the oxazoline as described above.

2-Amino-N-(2-mercaptoethyl)benzamide (XII).—A mixture of 20 g. (0.177 mole) of 2-aminoethanethiol hydrochloride, 11.5 g. (0.071 mole) of isatoic anhydride, 9.85 g. of sodium carbonate, and 200 ml. of methanol was heated under reflux for 1.5 hr. Solvent was removed and the residue was partitioned between 300 ml. of dichloromethane and 300 ml. of water. The organic layer was washed, dried, and evaporated to give, after recrystallization from a methanol–benzene mixture, 12.5 g. (98.4%) of the benzamide XII as white prisms, m.p. 132–134°.

Anal. Calcd. for $C_9H_{12}N_2OS$: C, 55.07; H, 6.16. Found: C, 55.12; H, 5.66.

N-(2-Mercaptoethyl)-2-(*p*-toluenesulfonamido)benzamide (X).—A solution of 2.0 g. of XII in 20 ml. of pyridine was cooled to 0° and was treated with 2.2 g. of *p*-toluenesulfonyl chloride, added in small portions. The reaction mixture was kept at 0–5° for 3 hr. and then it was poured into 450 ml. of water. The water was decanted from the oil which separated. The oil was dissolved in 100 ml. of chloroform which was then dried and concentrated to a small volume. Methanol was added and the product (2.7 g., 75.7%) crystallized as white prisms, m.p. 194–196°.

Anal. Calcd. for $C_{16}H_{18}N_2O_3S_2$: C, 54.83; H, 5.18. Found: C, 54.85; H, 5.05.

2-Amino-N-(2-methylthioethyl)benzamide (XIII). A. From Isatoic Anhydride.—A solution of 3.0 g. of isatoic anhydride and 5.0 g. of 2-aminoethylmethyl sulfide[9] in 50 ml. of methanol was heated under reflux for 1.5 hr. Solvent was removed under reduced pressure and the residue was dissolved in 100 ml. of dichloromethane. The solution was washed with water (three 100-ml. portions), dried over sodium sulfate, filtered, and evaporated to give 3.5 g. of colorless oil. This oil was dissolved in ether and filtered over 35 g. of Florisil to give, after removal of the solvent, 2.8 g. (72.5%) of the product as white prisms, m.p. 66–68°. Recrystallization from an ether–petroleum ether mixture increased the melting point to 68–69°.

Anal. Calcd. for $C_{10}H_{14}N_2OS$: C, 57.11; H, 6.71. Found: C, 57.15; H, 6.79.

B. From XII.—A solution of 1 g. (5.56 mm) of 2-amino-N-(2-mercaptoethyl)benzamide (XII) in 10 ml. of N,N-dimethylformamide was treated at room temperature with 0.33 g. (6.1 mmoles) of sodium methoxide. The mixture was stirred for 10 min., cooled to 0°, and treated at this temperature with 1.6 g. (11 mmoles) of methyl iodide. After 1 hr. of stirring at 0°, the reaction mixture was poured into water and the products were extracted into dichloromethane (three 50-ml. portions). The organic layers were combined, washed with water (three 50-ml. portions), dried over sodium sulfate, and evaporated. The oil (0.9 g.) thus obtained was dissolved in ether and filtered over 10 g. of Florisil to give, after removal of solvent, 0.3 g. (61.9%)[10] of 2-amino-N-(2-methylthioethyl)benzamide, m.p. 67–68°, which was undepressed on admixture with the authentic sample prepared as described above. Further elution of the Florisil with ethyl acetate gave 0.55 g. of unreacted starting material.

Acknowledgment.—We thank Dr. A. Steyermark, Mr. S. Traiman, Dr. F. Vane, and Dr. V. Toome for the microanalyses, infrared, n.m.r., and ultraviolet spectra respectively.

(9) C. W. Crane and H. N. Rydon, *J. Chem. Soc.*, 766 (1947).
(10) Based on starting material consumed.

A Re-examination of Ring Closure Reactions of Substituted 2-Aminobenzamides and Related Compounds[1a]

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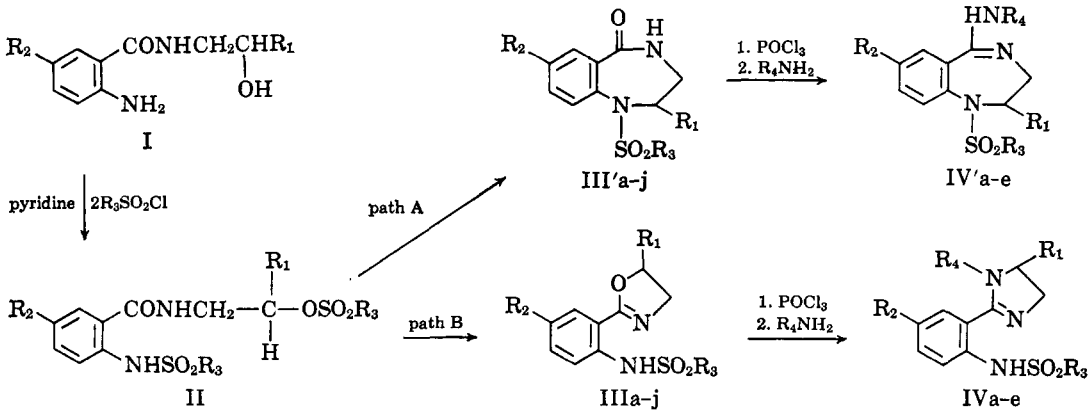
Recently, we reported on methods of preparing 5H-1,4-benzodiazepin-5-ones from 2-amino-N-(2-hydroxy-

(1) (a) Subsequent to the completion of our manuscript we received, through the courtesy of Dr. L. H. Sternbach, a copy of a Note in which conclusions similar to those discussed in the present report were reached: G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 2098 (1965). (b) A. A. Santilli and T. S. Osdene, *ibid.*, **29**, 1998 (1964).

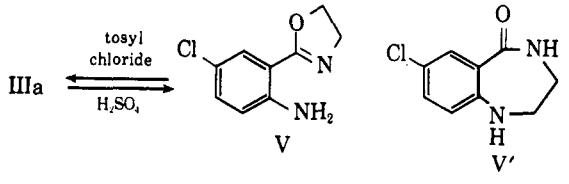
CHART I[a]



[a] See Tables I–III of ref. 1b for the identity of R_1, R_2, R_3, and R_4.

alkyl)benzamides (I) *via* ring-closure reactions involving intramolecular eliminations of alkyl or arylsulfonic acid (see Chart I). It later became apparent through additional chemical evidence as well as n.m.r. spectroscopy that these compounds are, in fact, the isomeric oxazolines (IIIa–j) rather than the benzodiazepinones (III'a–j).

The first member of the series which cast doubt on our originally proposed structures and alerted us to the alternative oxazoline structure was IIIa (R_1 = H, R_2 = Cl, R_3 = *p*-tolyl). The sulfuric acid hydrolysis product of this material was a compound reported as 7-chloro-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one (V') but which is now known to be 2-(2-amino-5-chlorophenyl)-2-oxazoline (V). The presence of a broad singlet at δ 6.09 integrating for two protons which vanished on deuteration established the equivalency of the two exchangeable protons.[2] The exchangeable protons in V' are not equivalent, one being a lactam proton, the other an amino proton. Further confirmation of the presence of the aromatic NH_2 group was provided by a positive color test on diazotization and coupling with alkaline β-naphthol. The band at 6.12 μ in the infrared spectrum of V is due to the presence of the C=N group in the oxazoline moiety. Cyclodehydrochlorination of 2-amino-5-chloro-N-(2-chloroethyl)benzamide as previously reported gave a product identical with the hydrolysis product of IIIa which is presently known to be V. Since the reaction of V with tosyl chloride gave a sulfonamide equivalent in every respect to IIIa obtained *via* path B, the direct tosylation of V constitutes an alternative synthetic path to IIIa.



It follows that the acid hydrolysis product of IIIj (R_1 = R_2 = H, R_3 = *p*-tolyl) is 2-(2-aminophenyl)-2-oxazoline instead of 1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one. Confirmation of the oxazoline structure was provided by a direct comparison with an authentic sample prepared by the reduction of 2-(2-nitrophenyl)-2-oxazoline as described by Leffler and Adams.[3]

Since the conversion of 2-oxazolines to 2-thiazolines with phosphorus pentasulfide has been previously reported,[4a] it is now apparent that the thiation product of IIIj is 2-[2-(*p*-tolylsulfonamido)phenyl]-2-thiazoline[4b] instead of 1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5H-1,4-benzodiazepine-5-thione.

The ring closure of 2-anilino-N-(2-hydroxyethyl)-benzamide with 1 molar equiv. of methanesulfonyl chloride affords 2-(*o*-anilinophenyl)-2-oxazoline instead of 1,2,3,4-tetrahydro-1-phenyl-5H-1,4-benzodiazepin-5-one. Again the A_2B_2 pattern is observed in the n.m.r. spectrum of the product.[2] The presence of an exchangeable proton upfield at δ 10.54 is attributed to the Ar_2NH proton.

In view of these results, it may be concluded that elimination of alkylsulfonic and arylsulfonic acid in II proceeds *via* path B to afford the oxazolines IIIa–j.[5] Cyclodehydrochlorination proceeds in the same fashion to afford the oxazoline rather than the diazepinone.

The amino derivatives which were obtained from the reaction of oxazolines (III) with phosphorus oxychloride followed by reaction with amines are therefore 2-imidazolines (IVa–e). Precedence for this reaction is given by the fact that 2-oxazolines are known to undergo cleavage with thionyl chloride to the β-chloroalkylbenzamides[6] which in turn have been shown by Partridge and Turner[7] to be converted to imidazolines under reaction conditions similar to those we employed.

Evidence that structures VII and VIII are correct as originally reported has been obtained. The isomeric oxazole structure (IX) was rejected as an alternative to VII since the compound failed to diazotize and couple with alkaline β-naphthol and the n.m.r. spectrum was not consonant with IX. The spectrum of VII has a CH_2 doublet centered at δ 4.09 which on deuteration of the sample reverts to a singlet. A

(2) N.m.r. spectra were determined in deuteriochloroform (tetramethylsilane as internal standard) with a Varian A-60 spectrophotometer. The spectra of V, IIIa, and other oxazolines in this report characteristically show two sets of CH_2 protons centered at approximately δ 4.2 and 4.3 in an A_2B_2 pattern.

(3) M. T. Leffler and R. Adams, *J. Am. Chem. Soc.*, **59**, 2252 (1937).

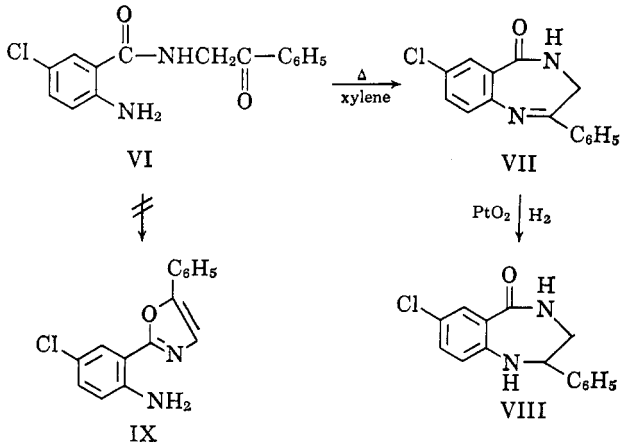
(4) (a) H. A. Bruson and J. W. Eastes [*ibid.*, **59**, 2011 (1937)] reported the preparation of 5,5-dimethyl-2-mercaptothiazoline from the corresponding oxazoline by the action of P_2S_5. (b) Field, *et al.*[1a] have substantiated this conclusion by an alternative synthesis of this compound.

(5) R. N. Boyd and R. C. Rittner [*J. Am. Chem. Soc.*, **82**, 2032 (1960)] have reported the syntheses of 2-oxazolines through the action of *o*-toluenesulfonyl chloride on acylaminoalkanols.

(6) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).

(7) M. W. Partridge and H. A. Turner, *J. Chem. Soc.*, 1308 (1949).

single exchangeable lactam proton is found as a broad singlet at δ 8.70. Since the formation of VIII *via* the lithium aluminum hydride reduction of VII might be considered equivocal, VIII was prepared by the catalytic reduction of VII. The products prepared by both methods of reduction were found to be identical in all respects. Upon deuteration of VIII, the CH_2 multiplet centered at δ 3.59 reverts to a doublet. A CH triplet is centered at δ 4.85 and is unchanged upon deuteration. A broad NH singlet is found at δ 4.33 and a CONH singlet at δ 7.4 both of which vanish on deuteration of the sample.



In a related study it has been found that cyclodehydrochlorination of 3-amino-N-(2-chloroethyl)benzo[*f*]quinoxaline-2-carboxamide afforded 3-amino-2-(2-oxazolin-2-yl)benzo[*f*]quinoxaline instead of 8,9,10,11-tetrahydro-12H-benzo[5,6]quinoxalino[2,3-*e*][1,4]-diazepin-12-one.[8] That the product of reaction is the oxazoline rather than the diazepinone is supported by the fact that the product obtained on diazotization is 3-hydroxy-N-(2-hydroxyethyl)benzo[*f*]quinoxaline-2-carboxamide. Diazotization of 3-amino-N-(2-hydroxyethyl)benzo[*f*]quinoxaline-2-carboxamide also afforded the latter product. Formation of this compound from the diazepinone would be impossible. Since the other members of the series were prepared in the same way, they, too, are undoubtedly oxazolines.

Experimental[9]

7-Chloro-1,2,3,4-tetrahydro-2-phenyl-5H-1,4-benzodiazepin-5-one (VIII) *via* Catalytic Reduction of VII.—A suspension of 2.7 g. of VII in 50 ml. of absolute ethanol containing 0.15 g. of platinum oxide was allowed to absorb hydrogen in a Parr apparatus for 12.5 hr. The reaction mixture was then heated on a steam bath and filtered. The crystals which were deposited out of solution after cooling the filtrate amounted to 1.5 g., m.p. 166–171°. Recrystallization from ethyl acetate raised the melting point to 172–174°. A mixture melting point with the sample prepared *via* lithium aluminum hydride reduction of VII gave no depression. The infrared spectra were identical.

3-Hydroxy-N-(2-hydroxyethyl)benzo[f]quinoxaline-2-carboxamide. Method A.—Sodium nitrite (1.0 g.) was added in portions to a stirred suspension of 0.5 g. of 3-amino-2-(2-oxazolin-2-yl)benzo[*f*]quinoxaline in 10 ml. of 3 *N* sulfuric acid. After a considerable amount of frothing, an essentially clear solution was obtained. The reaction mixture was then filtered and the filtrate was neutralized with 10% sodium bicarbonate solution. A yellow precipitate was deposited which, after removal by filtration, amounted to 0.4 g., m.p. 284–286°. Recrystallization from aqueous N,N-dimethylformamide raised the melting point to 287–289°; λ_{max} 5.97 (C=O) and 6.51 μ (amide II).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.64; H, 4.47; N, 14.62.

Method B.—Nitrosation of 0.3 g. of 3-amino-N-(2-hydroxyethyl)benzo[*f*]quinoxaline-2-carboxamide with 0.5 g. of sodium nitrite in 10 ml. of 3 *N* sulfuric acid in the manner described above afforded a product which, after recrystallization from aqueous N,N-dimethylformamide, amounted to 0.2 g., m.p. 286–289°. A mixture melting point with the product obtained by method A gave no depression. The infrared spectra were identical.

Acknowledgment.—The authors are grateful to Dr. S. J. Childress for many helpful discussions and suggestions and to Dr. Charles A. Hetzel for his assistance with the n.m.r. spectra.

(8) A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29**, 2066 (1964).

(9) Melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were determined in potassium bromide pellets using a Perkin-Elmer Model 21 spectrophotometer. The details of other preparative procedures are given in our previous papers (see ref. 1b and 8).

Coulombic Interaction between *ortho* Substituent and Nucleophile in the Bimolecular Displacement Reaction

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Dispersion forces have long been recognized as a factor affecting equilibria and reaction rates. Bunnett[1] observed that in several bimolecular nucleophilic reaction series nucleophiles of high polarizability were found to be especially reactive, relative to nucleophiles of low polarizability, with substrates having highly polarizable substituents at or near the reaction site. He attributed the enhancement in reaction rate to London forces when the transition state structure is such as to bring highly polarizable groups close to one another. Bunnett and Reinheimer[2] estimated the London force interaction from the reaction rate ratios of *ortho*-substituted benzyl chlorides with methoxide, thiophenoxide, and iodide ions. More recently Reinheimer[3] examined the *o*-CH_3:*p*-CH_3 and *o*-Br:*p*-Br reaction rate ratios of benzyl chlorides with the same nucleophiles. He demonstrated that calculations of the magnitude of London forces operating in the transition state indicated that the differences in rate ratios with MeO^-, $C_6H_5S^-$, and I^-, for a given *ortho* substituent, may be assigned to these forces. However, it was previously pointed out by the author[4] that comparison of the *o*-CH_3:*p*-CH_3 and *o*-Br:*p*-Br rate ratios, with the same reagents, showed trends contrary to those expected from London interactions alone; *i.e.*, charged nucleophiles invariably gave higher *ortho*:*para* rate ratios with the less polarizable methyl group than with the more polarizable bromo group.[5] Our interest in

(1) J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5969 (1957).

(2) J. F. Bunnett and J. D. Reinheimer, *J. Am. Chem. Soc.*, **84**, 3284 (1962).

(3) D. Dalrymple, J. Reinheimer, D. Barnes, and R. Baker, *J. Org. Chem.*, **29**, 2647 (1964).

(4) A. J. Sisti and S. Lowell, *ibid.*, **29**, 1635 (1964).

(5) For a detailed treatment of the data, see ref. 3 and 4.