The mixture was hydrolyzed and worked up in the usual manner. The concentrated organic layer was chromatographed on alumina. The petroleum ether eluates gave 7.1 g. of crude 1,3-bis(triphenylsilyl)propane, m.p. 116–122°. Recrystallization from the same solvent raised the melting point to 131–132° and afforded 4.9 g. (58.4%) of pure product. Concentration of the petroleum ether filtrates gave 1.86 g. (23.8%) of triphenylsilane, identified by comparison of the infrared spectra. From the ethyl acetate eluates, there was obtained 0.4 g. (4.8%) of triphenylsilanol, m.p. and m.m.p. 151–153°.

Reaction of Triphenylsilyllithium with *n*-Butyl *p*-Toluenesulfonate.—To a solution of *n*-butyl *p*-toluenesulfonate (10.96 g., 0.048 mole) in 50 ml. of tetrahydrofuran (THF) was added 0.096 mole of triphenylsilyllithium in 200 ml. of THF. When the addition was complete, Color Test I was indefinite; the green color of the color test developed very slowly and then only with a large excess of iodine. The mixture was stirred overnight and hydrolyzed. After the usual separation, extraction and drying techniques, the concentrated oil was chromatographed on a column of alumina. Elution with petroleum ether gave 12.04 g. of impure *n*-butyltriphenylsilane, m.p. 82–86°. After recrystallization from ethanol, 10.8 g. (71.1%) of pure product was obtained, m.p. and m.m.p. 85–86.5°.

The ethanol-insoluble material (1.04 g.) was recrystallized from a benzene–petroleum ether mixture to give 0.48 g. (1.5%) of tetraphenylsilane, m.p. and m.m.p. 232–234°. Also, the infrared spectra were superimposable.

The reaction was repeated using the silyllithium reagent and sulfonate. After stirring 30 min. at room temperature, chlorotriphenylsilane (3 g., 0.01 mole) was added and then the mixture was carbonated. Addition of petroleum ether to the concentrated organic layer gave 0.14 g. (0.28%) of hexaphenyldisilane. Chromatography of the filtrate gave 8.35 g. (55%) of *n*-butyltriphenylsilane, m.p. 84–86°. Concentration of the mother liquor afforded 1.12 g. of a mixture of triphenylsilane and *n*-butyltriphenylsilane as determined by infrared analysis. Elution with benzene and ethanol gave 3.53 g. (22%) of triphenylsilanol, m.p. and m.m.p. 149–151°.

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Structure of Cyclization Products of Substituted 2-Amino-N-(2-hydroxyethyl)benzamides

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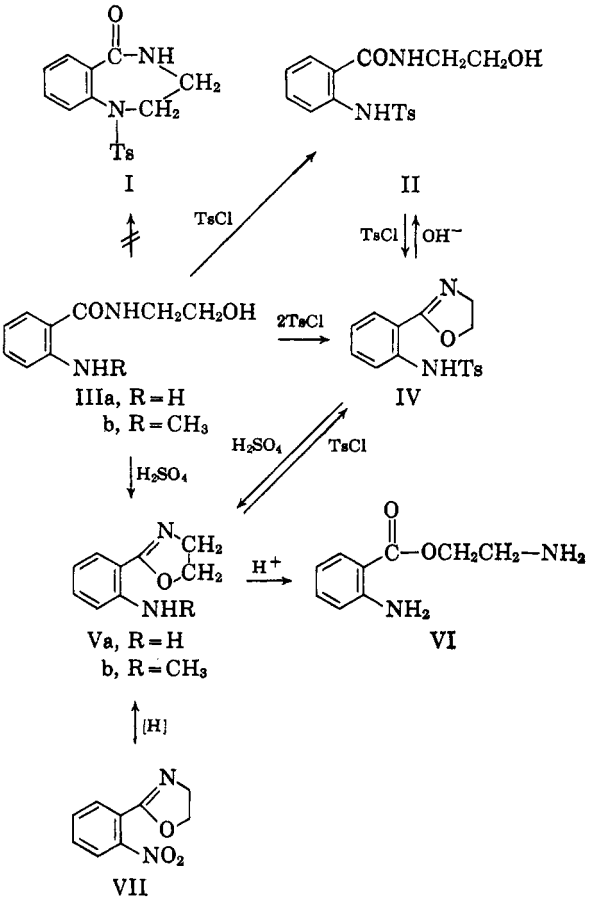
In view of our experience in the 1,4-benzodiazepine field[1] we were highly interested in a recently published new method for the synthesis of compounds of this type and related heterocyclic products.[2] This method consists in the cyclization of substituted 2-amino-N-(2-hydroxyethyl)benzamides with dehydrating agents. For example, treatment of the hydroxyethylamide IIIa with *p*-toluenesulfonyl chloride was reported to yield the benzodiazepine I (Scheme I).

We sought to extend this method to the synthesis of an analog of I in which the tosyl group was replaced by a methyl group. Thus, we treated the N-methyl

SCHEME I



derivative IIIb with thionyl chloride and obtained a product of the expected elemental composition. This compound showed an infrared absorption band at 1639 cm.$^{-1}$ (6.1 μ) as did the products described by Santilli and Osdene[2a]; however, closer investigation indicated that it could not be the postulated benzodiazepine. The n.m.r. spectrum shows a doublet at δ = 2.9 p.p.m. due to the N-methyl group, which collapses to a singlet on exchange with deuterium oxide. This shows that the proton attached to the nitrogen of the methylamino group is still intact and that the reaction has taken an alternative course to form the oxazoline derivative Vb. Indeed, Cornforth[3] cites several examples of the synthesis of oxazolines by similar methods.

In order to establish whether or not the presence of an N-methyl group had affected the course of the cyclization reaction we repeated the reactions which were reported by Santilli and Osdene[2a] to give the benzodiazepine I. We obtained a product possessing the physical properties reported by them, but found that this compound was not a 1,4-benzodiazepine derivative, but rather the 2-aminophenyloxazoline derivative IV.

The structure was established by comparison of the detosylated product Va, obtained by treatment of IV with concentrated sulfuric acid,[2a] with an authentic sample of 2-(*o*-aminophenyl)-2-oxazoline prepared by catalytic reduction of the nitrophenyloxazoline VII described by Leffler and Adams.[4] Leffler and Adams

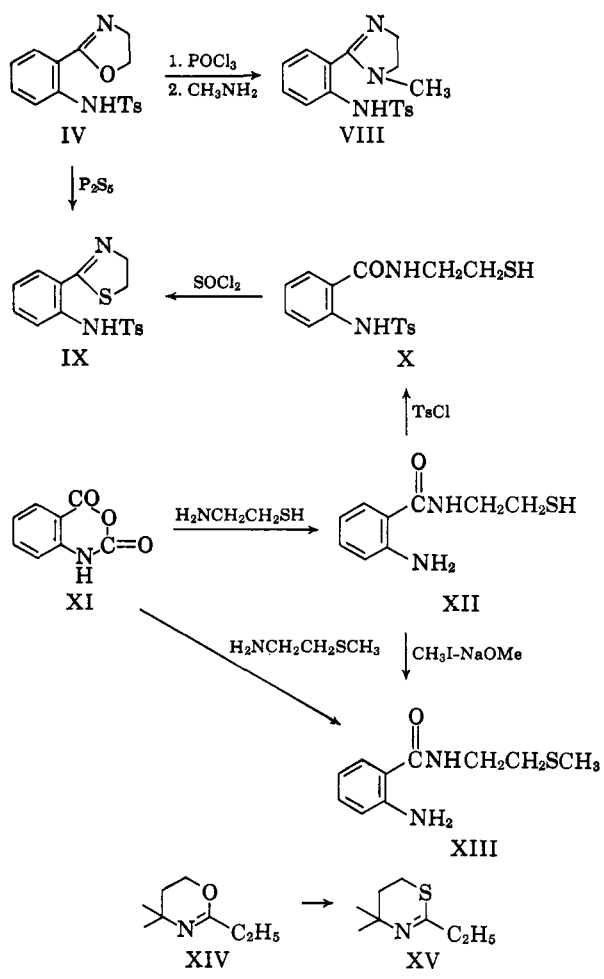
(1) Paper XXIV: W. Metlesics, R. F. Tavares, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1311 (1965), and previous papers in this series; see also M. Uskoković, J. Iacobelli, and W. Wenner, *ibid.*, **27**, 3606 (1962).

(2) (a) A. Santilli and T. S. Osdene, *ibid.*, **29**, 1998 (1964); (b) *ibid.*, **29**, 2066 (1964).

(3) J. W. Cornforth, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 378.

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

SCHEME II



prepared this compound by reduction with iron and acid. The samples produced by both methods were identical in every respect. Compound Va could be retosylated under mild conditions to give IV which indicates that no rearrangement had occurred during the detosylation step. Furthermore the infrared band at 1645 cm.$^{-1}$ (6.08 μ, C=N) is present in both compounds. Hydrolysis of Va with dilute acid[5] produced VI which has a strong band at 1700 cm.$^{-1}$ consistent with its formulation as an ester. Hydrolysis of IV with dilute alkali gave II which was also obtained by treatment of IIIa with 1 mole of tosyl chloride.[2a] Both of these hydrolytic reactions would have been impossible if the cyclization product of IIIa had structure I. This is additional proof that the product to which structure I has been ascribed is actually IV, and it is therefore quite likely that other products obtained by the same method[2] are also oxazoline derivatives.

Two transformations of the carbonyl group of the compound of the postulated structure I were also described by Santilli and Osdene.[2a] These resulted in its conversion to a thioamide group with phosphorus pentasulfide and to an amidine group by successive treatment with phosphorus oxychloride and a primary amine. On the basis of structure IV these products may be reformulated as the thiazoline IX and the imidazoline VIII (see Scheme II). A close analogy for the conversion of IV to IX is the conversion of XIV to XV on treatment with phosphorus pentasulfide.[6] Presumably the imidazoline is formed by analogous processes.

In order to prove the structure of compound IX, we synthesized it by an unequivocal route. Isatoic anhydride (XI), on treatment with 2-aminoethanethiol, gave compound XII. That this compound was the amide and not the isomeric thio ester was shown by its methylation to the S-methyl derivative XIII which was identical with the compound obtained from the reaction of isatoic anhydride with 2-aminoethylmethyl sulfide. Compound XII was then tosylated to X which in turn, on treatment with thionyl chloride,[7] yielded the expected thiazoline derivative, IX.

(5) See, for example, R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, **83**, 4835 (1961), for a discussion of the hydrolysis of 2-methyloxazoline.

Experimental[8]

2-Methylamino-N-(2-hydroxyethyl)benzamide (IIIb).—A mixture of 88.5 g. of N-methylisatoic anhydride, 91.5 g. of 2-aminoethanol, and 850 ml. of water was stirred under reflux for 15 min., then diluted with water, and extracted five times with dichloromethane. The extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residual mass was heated with hot alcohol, filtered, and diluted with water until the first turbidity appeared. After cooling, an oil separated which was discarded.

The dilute alcoholic solution which had been decanted from the oil was concentrated to dryness *in vacuo*. The residual mass was crystallized from *n*-pentane and yielded 68 g. of tan plates (m.p. 75–79°). An analytical sample was obtained as off-white plates after two recrystallizations from ethyl acetate–hexane, m.p. 77.5–79°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27. Found: C, 61.78; H, 7.40.

2-(*o*-Methylaminophenyl)-2-oxazoline (Vb). Method A.—A solution of 2.9 g. of 2-(methylamino)-N-(2-hydroxyethyl)benzamide (IIIb) in 10 ml. of concentrated sulfuric acid was stirred at 55–65° for 10 min. The reaction mixture was poured into 50 ml. of ice–water and made basic with concentrated aqueous ammonia while the temperature was maintained at 10–20° by cooling. The solid was collected to give 2.3 g. of off-white plates, m.p. 60–64°.

Method B.—A solution of 3.88 g. of 2-(methylamino)-N-(2-hydroxyethyl)benzamide in 20 ml. of chloroform was added to a solution of 3.2 g. of thionyl chloride in 20 ml. of chloroform while the mixture was cooled to 25–30°. After it had been stirred at 30° for 30 min., the reaction mixture was concentrated *in vacuo*. The residue was diluted with a saturated sodium bicarbonate solution and extracted five times with dichloromethane. The dichloromethane extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residual yellow fluorescent oil was dissolved in 50 ml. of 2-ethoxyethanol and stirred under reflux in the presence of 3.08 g. of sodium carbonate. The reaction mixture was cooled and filtered by gravity. The clear filtrate was concentrated *in vacuo* to give an amber oil which was crystallized from isopropyl alcohol–water. The solid was collected to give 2.1 g. of plates, m.p. 55–60°. An analytical sample was obtained as colorless plates after two recrystallizations from isopropyl alcohol, m.p. 62–62.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86. Found: C, 68.57; H, 7.02.

2-(*o*-Aminophenyl)-2-oxazoline (Va). A. From IIIa.—A solution of 1.8 g. of 2-amino-N-(2-hydroxyethyl)benzamide[2a] in 10 ml. of concentrated sulfuric acid was heated at 55–65° for 10 min. with stirring. The reaction mixture was poured onto 30 ml. of ice and water and the solution was made basic with aqueous ammonia while the temperature was maintained at 5–10° by means of an ice bath. The solid was collected to give 0.4 g. of white needles, m.p. 54–57°.

B. From VII.—A solution of 4.7 g. of 2-(*o*-nitrophenyl)-2-oxazoline[4] in 225 ml. of ethanol was hydrogenated over 0.5 g. of

(6) A. I. Meyer, *J. Org. Chem.*, **25**, 1147 (1960).

(7) See J. M. Sprague and A. H. Land, ref. 3, p. 681.

(8) All melting points are corrected. Identities were proved by mixture melting point and comparison of infrared spectra. Petroleum ether refers to a fraction of b.p. 30–60°.

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).