# 3H-1,4-Benzodiazepine-2,5(1H,4H)-dione and Related Compounds

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Synthesis and reactions of 3H-1,4-benzodiazepine-2,5(1H,4H)-dione are described.

There are few reports in the literature about benzodiazepine derivatives: Condensation of *o*-phenylenediamine with malonic acid[1-4] acrylic acid[5-7] ethyl acetoacetate,[7-12] and acetylacetone[13] gave a number of 1,5-benzodiazepine derivatives. Recently Sternbach and co-workers[14] described a number of isomeric 1,4-benzodiazepines, which possess outstanding psychopharmacologic properties.[15] The best investigated compound of this series, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide has found wide therapeutic application. This led us to investigate simpler compounds with the same basic ring system. This paper describes the synthesis of 3H-1,4-benzodiazepine-2,5(1H,4H)-dione (III)[16] and its reduction with lithium aluminum hydride to 1H-2,3,4,5-tetrahydro-1,4-benzodiazepine (VII).

Attempts were first directed to the ring closure of N-(haloacetyl)anthranilic esters and amide with ammonia and other bases, but in every case the products were quinazoline-4(3H)-ones. An alternative scheme, starting with *o*-aminohippuric acid ethyl ester (I)[16] led to the desired compound through the intermediate piperidide (II), which was obtained in 50% yield from a hot solution of I in piperidine–methanol. On refluxing with acetic acid a quantitative ring closure to III was effected. Direct conversion of I to III was accomplished in boiling pyridine solution, but the yield was very poor. The infrared spectrum showed absorption bands for —NH— (3230 cm.$^{-1}$), for two carbonyl groups (1710 and 1685 cm.$^{-1}$), and for a methylene group in $\alpha$-position to a carbonyl (2930 and 1430 cm.$^{-1}$), in full agreement with the expected 3H-1,4-benzodiazepine-2,5(1H,4H)-dione (III).

The above synthesis did not exclude the possibility that ring closure had led to a cyclic polymeric substance with the same elementary composition and infrared spectrum similar to those expected of III. A molecular weight determination could not be used to resolve this problem because of the low solubility of the compound in question. Fortunately, this ambiguity was overcome by a different synthesis starting with the methyl ester of N-benzylanthranilic acid (IVb).[17] In this case the N-bromoacetyl derivative (V) could be readily cyclized with ammonia to 1-benzyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VI). The infrared and analytical data, including a molecular weight determination supported the assigned structure. On hydrogenation in the presence of palladium the benzyl group was removed to give III.

Additional support of structure III was furnished by reduction with lithium aluminum hydride to the completely desoxygenated 1H-2,3,4,5-tetrahydro-1,4-benzodiazepine (VIIa).[18] A minor by-product in the reduction was 1H-2,3-dihydro-1,4-benzodiazepine (VIII), which was identified by analytical data, infrared spectrum (3230 cm.$^{-1}$ for —NH— group and 1630 cm.$^{-1}$ for —C=N—), ultraviolet spectrum [233–234, 264–265, and 353–357 m$\mu$)], by comparison with its 7-nitro-5-phenyl analog[19] and also by its hydrogenation to VIIa.

3H-1,4-Benzodiazepine-2,5(1H,4H)-dione (III) is stable in aqueous alkali and glacial acetic acid. In hot 70% sulfuric acid it was degraded to anthranilic acid. It is stable in hot methanolic solution toward ammonia, but methylamine under the same conditions opens the seven-membered ring, giving *o*-aminohippuryl methylamide (IX).

## Experimental[20]

**o-Aminohippuric Acid Piperidide (II) from o-Aminohippuric Acid Ethyl Ester (I).**—The solution of 15 g. of I in 100 ml. of methanol and 100 ml. of piperidine was refluxed

(1) R. Meyer, *Ann.*, **327**, 1 (1903).
(2) R. L. Shriner and P. G. Boermann, *J. Am. Chem. Soc.*, **66**, 1810 (1944).
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(5) G. B. Bachman and L. V. Hesley, *J. Am. Chem. Soc.*, **71**, 1985 (1949).
(6) W. Ried and G. Urlass, *Ber.*, **86**, 1101 (1953).
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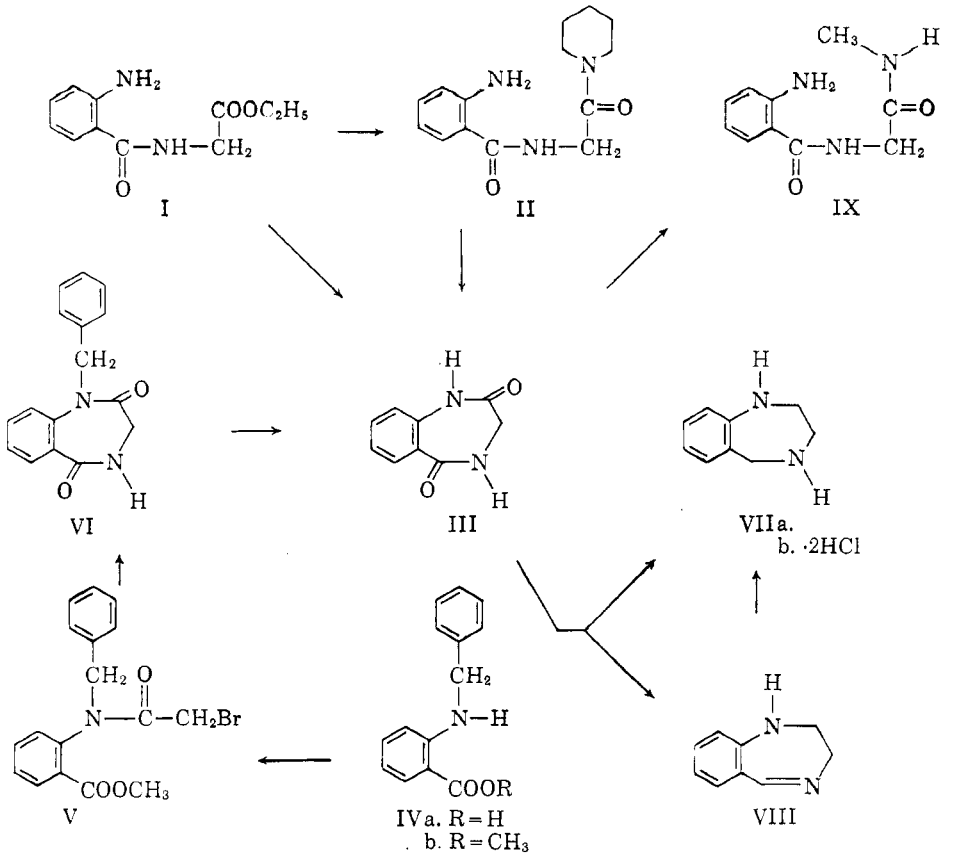
(17) J. Houben and W. Brassert, *Ber.*, **39**, 3233 (1906).
(18) S. Archer, J. R. Lewis, M. J. Unser, J. O. Hoppe, and H. Lape, *J. Am. Chem. Soc.*, **79**, 5783, 1957.
(19) J. A. Hill, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4430 (1961).
(20) All melting points are uncorrected. Elemental microanalyses were performed by Dr. A. Steyermark. Ultraviolet spectra were taken on a Cary Model 14M spectrophotometer. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer.




for 24 hr. After evaporation *in vacuo*, the sirupy residue was crystallized from acetone, giving 9 g. of II, m.p. 125–126°.

Infrared absorption: 3522 and 3430 cm.$^{-1}$ (—$NH_2$ group); 1630 cm.$^{-1}$ (amido carbonyl). Ultraviolet absorption $\lambda_{max}$ 211 mμ (ε 32,400); 250–251 mμ (ε 8500); 330 mμ (ε 4500).

*Anal.* Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.32; H, 7.33; N, 16.09. Found: C, 64.57; H, 7.83; N, 15.73.

**3H-1,4-Benzodiazepine-2,5(1H,4H)-dione (III) from II.**—The solution of 13 g. of II in 200 ml. of glacial acetic acid was refluxed for 4 hr. By addition of 200 ml. of water, III precipitated and was isolated by filtration; m.p. 327–327.5°, yield 8.5 g.

Infrared absorption: 3230 cm.$^{-1}$ (—N—H— group); 1710 and 1685 cm.$^{-1}$ (amido carbonyls); 2930 and 1430 cm.$^{-1}$ (methylene group). Ultraviolet absorption: $\lambda_{max}$ 215 mμ (ε 41,250); 272 (12,500); 292.5 (3500).

*Anal.* Calcd. for $C_9H_8N_2O_2$: C, 61.34; H, 4.58. Found: C, 61.36; H, 4.63.

**N-Benzylanthranilic Acid Methyl Ester (IVb). From IVa.**—The solution of 20 g. of IVa in 500 ml. of methanol saturated with hydrogen chloride was refluxed for 3 hr. The reaction mixture was then poured on ice, made alkaline with 3 *N* sodium hydroxide, extracted with methylene chloride, washed, dried, and evaporated. The residue was crystallized from methanol, yielding 13 g. of IVb, m.p. 51.5–52.5°.

*Anal.* Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.97; H, 6.04; N, 5.96.

**1-Benzyl-3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VI) from IVb.**—To the solution of 12.6 g. of IVb and 4.2 g. pyridine in 500 ml. of ether was added dropwise 10.6 g. of bromoacetyl bromide with stirring. The resulting suspension was stirred for additional 2 hr., filtered from pyridinium bromide, and evaporated. The green sirupy N-bromoacetyl derivative V was dissolved in 1 l. of methanol, and the solution was saturated at room temperature with ammonia. After 8 hr., the reaction mixture was evaporated and the residue recrystallized twice from methylene chloride–ether, giving 11 g. of VI, m.p. 189–190°. Infrared absorption: 3410 cm.$^{-1}$ (—N—H—); 1680 and 1666 cm.$^{-1}$ (carbonyl groups); 2940 and 1404 cm.$^{-1}$ (methylene group). Ultraviolet absorption: $\lambda_{max}$ 214 mμ (ε 34,100); 245 (10,500); 284–286 (2800).

*Anal.* Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52; mol. wt., 266.13. Found: C, 71.90; H, 5.53; N, 10.25; mol. wt., 267.

**3H-1,4-Benzodiazepine-2,5(1H,4H)-dione (III) from VI.**—To the solution of 3 g. of VI in 300 ml. glacial acetic acid were added 300 mg. of 10% palladium–charcoal catalyst and the mixture hydrogenated for 48 hr. at 60° and 60 p.s.i. The catalyst was filtered off and the solution evaporated. The residue was crystallized from acetone, giving 1.8 g. of III, in all respects identical with the sample previously obtained.

**1H-2,3,4,5-Tetrahydro-1,4-benzodiazepine Dihydrochloride (VIIb) and 1H-2,5-Dihydro-1,4-benzodiazepine (VIII) from III.**—To the suspension of 2 g. of lithium aluminum hydride in 400 ml. of absolute tetrahydrofuran was added 2 g. of III at 0°. The reaction mixture turned green, and was refluxed for 1 hr. Slow addition of saturated aqueous sodium sulfate at 0° decomposed the excess of reagent and the complex of products, and after a clear solution was obtained, anhydrous sodium sulfate was added and the solution filtered off. After evaporation, methanol was added to the sirupy residue, a minor precipitate was filtered off, and the crystals were recrystallized from methanol, giving VIII, m.p. 244–246°. Infrared absorption: 3200 cm.$^{-1}$ (—NH— group); 1630 cm.$^{-1}$ (—C=N— group); 2980 cm.$^{-1}$ (methylene group). Ultraviolet absorption: $\lambda_{max}$ 233–234 mμ (ε 39,500); 264–265 (6800); 353–357 (4900).

*Anal.* Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.57; H, 7.02; N, 18.61.

When shaken in methanol solution with hydrogen in the presence of palladium, VIII gave VIIa.

The evaporation of the methanolic mother liquors gave sirupy 1H-2,3,4,5-tetrahydro-1,4-benzodiazepine, VIIIa, which showed the following infrared absorption: strong 2980 cm.$^{-1}$ (methylene group); 3400 cm.$^{-1}$ (—NH— group). It was dissolved in 10 ml. of methanol. Ether saturated with hydrochloric acid was added causing precipitation of VIIb; m.p. 243-244°, after recrystallization from methanol–acetone, yield 2 g. Infrared absorption: 3000–2400 cm.$^{-1}$ (ammonium salt bands). Ultraviolet absorption: $\lambda_{max}$ 220 mμ (ε 2700); 242–243 (7450); 287–291 (1800).

*Anal.* Calcd. for $C_9H_{12}N_2 \cdot 2HCl$: C, 48.88; H, 6.38; N, 12.67; Cl, 32.06. Found: C, 49.19; H, 6.58; N, 12.67; Cl, 31.55.

**o-Aminohippurylmethylamide (IX) from III.**—The suspension of 1 g. of III in 1000 ml. of methanol was saturated for 5 hr. at 60° with methylamine, when a clear solution was obtained. After evaporation, the residue was crystallized from acetone, giving 600 mg. of IX, m.p. 170–174°. Infrared absorption: 3450 and 3320 cm.$^{-1}$ (—$NH_2$ and —NH—); 1656 and 1642 cm.$^{-1}$ (—C=O groups). Ultraviolet absorption: $\lambda_{max}$ 213 mμ (ε 25,800); 250–251 mμ (ε 7800); 330–332 mμ (ε 3800).

*Anal.* Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.95; H, 6.32; N, 20.28. Found: C, 58.51; H, 6.50; N, 20.17.

**Anthranilic (X) Acid from III.**—The solution of 1 g. of III in 10 ml. 70% sulfuric acid was heated 15 min. at 140° and poured on ice. The mixture was made alkaline with concentrated aqueous sodium hydroxide. Addition of acetic acid precipitated X, m.p. 143–145°, which showed the same infrared spectrum as commercial anthranilic acid.

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# Synthesis of the *s*-Triazine System. VI.[1] Preparation of Unsymmetrically Substituted *s*-Triazines by Reaction of Amidine Salts with Imidates

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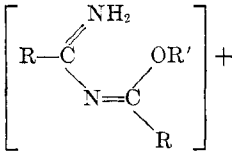
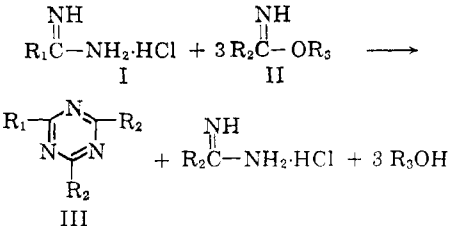
A wide variety of unsymmetrically substituted *s*-triazines are obtained by the reaction of amidine salts with the lower aliphatic imidates. The predominant product generally has one substituent radical derived from the amidine and two from the imidate reactant. The reaction occurs at a useful rate at ordinary temperatures and under conditions which are only weakly basic.

The cotrimerization of two alkyl imidates in the presence of an acidic catalyst is a convenient and sometimes practical route to a variety of interesting unsymmetrically substituted *s*-triazines.[1] However, this is inherently a random process and we have continued to search for more selective synthetic methods. The proposed mechanism for the imidate trimerization reaction[2] suggested that an intermediate "dimer" was involved which had the structure



It seemed possible that reaction of an amidine salt with an imidate might also lead to such a structure.[3] If so and if further reaction with a second imidate molecule took place as would be expected, this process would permit control of introduction of unlike R—groups into the final *s*-triazine product. Thus, the group introduced with the amidine reactant could be different from the two groups introduced as the imidate. This paper reports the development of this proposition into a widely applicable method for the synthesis of unsymmetrically substituted *s*-triazines.

Somewhat fortuitously, the reaction studied first was that of 2-methylpseudourea hydrochloride (I, R = $CH_3O$) with ethyl acetimidate. This work at once proved the feasibility of the method and demonstrated that the stoichiometry approached that expected for the reaction,[5]



On this basis the yield of 2-methoxy-4,6-dimethyl-*s*-triazine (III. $R_1$ = $CH_3O$, $R_2$ = $CH_3$) averaged 73%. About 10% of trimethyl-*s*-triazine was obtained and acetamidine hydrochloride was re-

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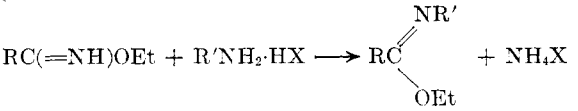
(3) Such a reaction would be analogous to the following, of which several examples are known[4]:



(4) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(5) The ammonium chloride eliminated at some point in the desired reaction inevitably converts an equivalent amount of imidate to amidine salt.[6]