During the addition, which required 0.5 hr., the temperature was maintained at 65–75°. The ether was distilled through the Claisen head and collected in a receiver. After the addition was completed, the temperature was allowed to rise to 75°; the Claisen head was replaced with a reflux condenser. The mixture was vigorously agitated at 75–80° for 2.5 hr. and then cooled to 5°. A considerable quantity of magnesium salts had separated. These were dissolved by slowly adding 450 ml. of 8% hydrochloric acid. The layers were separated; the organic layer was washed with 200 ml. of 10% sodium chloride. The NaCl wash was extracted once with 100 ml. of heptane, which was combined with the original organic layer. The solution was filtered through calcium chloride and concentrated *in vacuo* on the stream bath. The cloudy yellow residual oil (293 g.) was fractionally distilled through a 20-in. heated Vigreux column. The product, tri-*n*-butyl-2-(1,3-butadienyltin, b.p. 80–90° (0.4 mm.), weighed 220 g. (76.4% yield).

Anal. Calcd. for $C_{16}H_{32}Sn$: C, 56.01; H, 9.44; Sn, 34.60; mol. wt., 343.1. Found: C, 55.7, 55.6; H, 9.4, 9.4; Sn, 34.8, 34.9; mol. wt., 340, 335 (cryoscopic in benzene).

The infrared spectrum had C=C absorption bands at 1620 and 1575 cm.$^{-1}$, a vinyl CH band at 985 cm.$^{-1}$, and methylene C–H bands at 894 and 910 cm.$^{-1}$. No peaks were present in the allene region 1900 to 2050 cm.$^{-1}$.

The n.m.r. spectrum was consistent showing the presence of saturated C–H and unsaturated CH protons in a ratio of 5.42 (theory requires 5.40). The ultraviolet spectrum (cyclohexane) had an ϵ_{max} of 11,600 at 220 mμ.

Diphenyl-2-(1,3-butadienyl)phosphine (IVb).—A 2-l. round-bottomed flask was equipped with a mechanical agitator, dropping funnel, and reflux condenser under a nitrogen blanket. It was charged with a solution of *ca.* 0.90 mole of 2-(1,3-butadienyl)magnesium chloride in 550 ml. of ether. To the well-agitated solution at room temperature was added a solution of 160 g. (0.724 mole) of diphenylchlorophosphine in 200 ml. of anhydrous ether. The addition required 3 hr. after which the mixture was stirred overnight at room temperature. The flask was cooled to 0°, and 700 ml. of 10% aqueous ammonium chloride was added carefully.

After stirring for 0.5 hr., the two layers were separated, and the aqueous layer was washed with 150 ml. of ether. The ether layers were combined, filtered, and concentrated *in vacuo* on the steam bath. The red-orange residue was taken up in 700 ml. of hot ethanol, filtered to remove about 5 ml. of orange oil, and cooled to 0°. The crude product which separated was collected, decolorized with Darco, and recrystallized from 500 ml. of ethanol. A pale yellow crystalline solid (74.5 g., 43.3%) which melted at 35–36.5° (uncor.) was obtained.

Anal. Calcd. for $C_{16}H_{15}P$: C, 80.65; H, 6.35; P, 13.00. Found: C, 80.3, 80.2; H, 6.0, 5.9; P, 12.77, 12.91.

The infrared spectrum had double bond absorptions at 1620 and 1575 cm.$^{-1}$, a vinyl C–H peak at 985 cm.$^{-1}$, and a methylene C–H band at 910 cm.$^{-1}$. There was no evidence for any allene absorption in the 1900- to 2050-cm.$^{-1}$ region. A very weak band at 1962 cm.$^{-1}$ was attributed to the aromatic rings.

2-(1,3-Butadienyl)mercury(II) Chloride (IVc).—2-(1,3-Butadienyl)magnesium chloride was prepared as described above from 17.4 g. (0.192 mole) of 4-chloro-1,2-butadiene. The Grignard solution was added to a vigorously agitated slurry of 90 g. (0.33 mole) of powdered mercuric chloride in 100 ml. of anhydrous ether. After the exothermic reaction had abated, the mixture was stirred and refluxed for 10 min. The ether was removed in a nitrogen stream. The residual solid was refluxed with 400 ml. of ethanol for 10 min. and filtered hot. The filtrate was diluted with 300 ml. of boiling water, then allowed to cool slowly to 0°. The solid which separated was collected by suction filtration, recrystallized from 600 ml. of 50% aqueous ethanol, and dried in a vacuum desiccator. The product, 2-(1,3-butadienyl)-mercury(II) chloride, a white solid with a soft greenish cast, weighed 17.2 g. (31% yield). It had no melting point but began decomposing at 113°.

Anal. Calcd. for C_4H_5HgCl: C, 16.61; H, 1.74; Hg, 69.46; Cl, 12.26. Found: C, 16.5, 16.5; H, 2.2, 2.0; Hg, 64.7, 64.7; Cl, 11.9, 11.6.

The infrared spectrum was consistent with the assigned structure.

Acknowledgment.—The author wishes to express his gratitude to Dr. R. C. Ferguson for his assistance in interpreting the n.m.r. spectra and to Mr. J. A. Fisher for technical assistance. Helpful discussions with Drs. R. Pariser and A. L. Barney are acknowledged.

Nitrogen Heterocycles. I. Pyrrolidones

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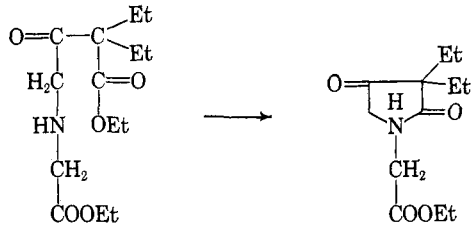
The condensation of ethyl γ-bromodialkylacetoacetate and ethyl glycinate results in pyrrolidine ring formation. The preparation of some derivatives of 3,3-dimethyl-2,4-pyrrolidinedione and of 3,3-diethyl-2,4-pyrrolidinedione is described.

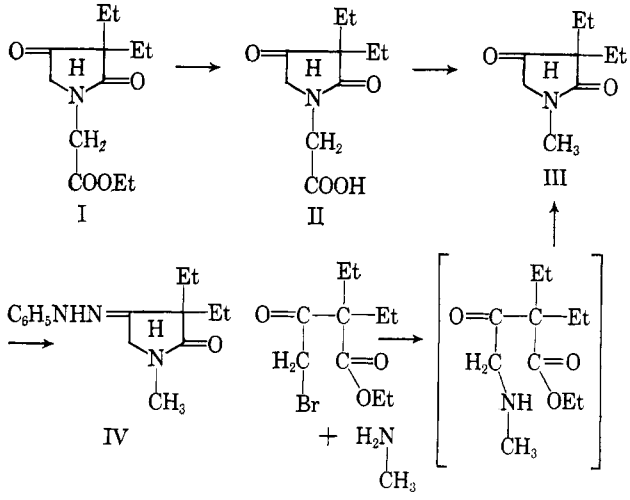
During the course of a study designed to uncover compounds with central depressant activity, ethyl γ-bromo-α,α-diethylacetoacetate[1] was condensed with ethyl glycinate to give 1-(carbethoxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (I).



On saponification followed by decarboxylation 1-(carboxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (II) and 1-methyl-3,3-diethyl-2,4-pyrrolidinedione (III) were obtained. The latter, on treatment with phenylhydrazine, gave the monohydrazine, 1-methyl-3,3-diethyl-4-phenylhydrazono-2-pyrrolidone (IV). The synthesis of 1-methyl-3,3-diethyl-2,4-pyrrolidinedione (III) was also effected by condensing ethyl γ-bromo-α,α-diethylacetoacetate and methylamine. The pyrrolidone structure of these compounds was confirmed by an infrared analysis of the acid (II) which showed a strained carbonyl band at 1765 cm.$^{-1}$ characteristic of carbonyl groups in five-membered rings. That the band was not associated with the carboxyl function was shown by its persistence on conversion of the acid to the triethylamine salt.

The 1-methylpyrrolidinedione (III) on treatment with hydroxylamine gave the monoxime (V) which was catalytically reduced to the amine. The latter was not identified as such but was condensed with benzenesul-

(1) M. Conrad and R. Gast, *Ber.*, **31**, 2954 (1898).



fonyl chloride to give 1-methyl-3,3-diethyl-4-phenylsulfonamido-2-pyrrolidione (VI).

When butylamine and benzylamine were used instead of methylamine in the interaction with the γ-bromacetoacetate, 1-butyl-3,3-diethyl-2,4-pyrrolidinedione (VII) and 1-benzyl-3,3-diethyl-2,4-pyrrolidinedione (VIII) were obtained, respectively.

Replacement of the bromodiethylacetoacetate with ethyl γ-bromo-α,α-dimethylacetoacetate[2] in the reaction with ethyl glycinate gave the dimethyl analog of I, namely, 1-(carbethoxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (IX). Hydrolysis of the ester gave the acid (X) whose pyrrolidone structure was confirmed by infrared analysis in exactly the same way as for the diethyl analog. Decarboxylation of the acid proved difficult. In one successful experiment, the decarboxylation product was treated with phenylhydrazine to give 1,3,3-trimethyl-1,4-phenylhydrazino-2-pyrrolidone (XI), but subsequent attempts to prepare 1,3,3-trimethyl-2,4-pyrrolidinedione (XII) by this method failed. The latter was finally prepared by condensing the bromdimethylacetoacetate with methylamine. As with the diethyl analog, it gave the 4-isonitroso derivative (XIII) on treatment with hydroxylamine. Catalytic reduction of the isonitroso compound and treatment of the product with benzenesulfonyl chloride gave 1,3,3-trimethyl-4-phenylsulfonamido-2-pyrrolidone (XIV).

Substitution of ammonia in place of methylamine in the interaction with the bromacetoacetate derivative gave 3,3-dimethyl-2,4-pyrrolidinedione (XV), a compound previously reported by Conrad and Hock.[3]

The details of synthesis of the compounds not previously reported in the literature are given in the Experimental section.

Experimental[4]

Derivatives of 3,3-Diethylpyrrolidinedione. A. 1-(Carbethoxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (I).—To a solution of 21 g. (0.2 mole) of ethyl glycinate in 25 ml. of benzene was added dropwise, with stirring, 26.5 g. of ethyl γ-bromo-α,α-diethylacetoacetate in 25 ml. of benzene. Heat was evolved and a precipitate of ethyl glycinate hydrochloride appeared. When precipitation was complete, the mixture was filtered and the benzene was removed from the filtrate. The residue was distilled to give the product in the form of a viscous, colorless liquid, b.p. 130–132° (0.55 mm.), $n^{24}D$ 1.4675.

Anal. Calcd. for $C_{12}H_{19}NO_4$ (mol. wt., 241): C, 59.7; H, 7.9; sapon. equiv., 241. Found: C, 59.6; H, 7.9; sapon. equiv., 248.

B. 1-(Carboxymethyl)-3,3-diethyl-2,4-pyrrolidinedione (II).—A mixture of 8.5 g. of the ester (I) and 18 ml. of 2 *N* NaOH was refluxed for 1 hr. The mixture was concentrated to one-half volume under vacuum and was then neutralized with 12 ml. of 3 *N* hydrochloric acid. The oil which separated was extracted with ether. The ether solution was dried with sodium sulfate and filtered; the ether was removed to give a solid residue. The residue on recrystallization from a benzene–carbon tetrachloride mixture gave the product in the form of fine white needles, m.p. 127–129°.

Anal. Calcd. for $C_{10}H_{15}NO_4$ (mol. wt., 213): C, 56.4; H, 7.0. Found: C, 56.3; H, 7.1.

Infrared showed a band for a strained carbonyl at 1765 $cm.^{-1}$. Ammonia passed into an ether solution of the acid gave the ammonium salt which on recrystallization from ethanol was obtained in the form of colorless prisms, m.p. 149–152°.

Anal. Calcd. for $C_{10}H_{18}N_2O_4$ (mol. wt., 230): C, 52.2; H, 7.8. Found: C, 52.4; H, 7.9.

C. 1-Methyl-3,3-diethyl-4-phenylhydrazono-2-pyrrolidone (IV).—Ten grams of the carboxymethyl pyrrolidone (II) was decarboxylated by heating under reflux (270–275°) for 2 hr. It was then distilled to give a viscous yellow liquid, b.p. 90–95° (4 mm.), $n^{27}D$ 1.4675. The distillate was dissolved in dilute ethanol; phenylhydrazine was added in excess and the mixture was heated on a steam bath for 1 hr. to give a precipitate of the phenylhydrazone. Recrystallization from dilute ethanol gave white prisms, m.p. 185–189° with prior softening.

Anal. Calcd. for $C_{15}H_{21}N_3O$ (mol. wt., 259): C, 69.5; H, 8.1; N, 16.2. Found: C, 69.6; H, 8.2; N, 16.2.

The distillate was substantially 1-methyl-3,3-diethyl-2,4-pyrrolidinedione (III), a compound which was subsequently prepared by the method described in D.

D. 1-Methyl-3,3-diethyl-2,4-pyrrolidinedione (III).—To a mixture containing 150 ml. of 30% methylamine in ethanol and 400 ml. of ether was added dropwise, with stirring and cooling, 100 g. of ethyl γ-bromo-α,α-diethylacetoacetate. The mixture was stirred for 4 hr. The precipitated methylamine hydrobromide was filtered off and the solvents were removed under vacuum. The liquid residue was distilled to give a colorless liquid, b.p. 84° (0.65 mm.), $n^{26}D$ 1.4665.

Anal. Calcd. for $C_9H_{15}NO_2$ (mol. wt., 169): C, 63.9; H, 8.9; N, 8.3. Found: C, 64.5; H, 8.8; N, 8.4.

A portion of the product treated with phenylhydrazine in dilute ethanol gave a phenylhydrazone melting at 183–190° with prior softening. A mixture melting point with IV was undepressed.

Anal. Calcd. for $C_{15}H_{21}N_3O$ (mol. wt., 259): C, 69.5; H, 8.1; N, 16.2. Found: C, 69.5; H, 8.4; N, 15.8.

E. 1-Methyl-3,3-diethyl-4-isonitroso-2-pyrrolidone (V).—A mixture of 5 g. of the pyrrolidinedione (III), 6 g. of hydroxylamine hydrochloride, 30 ml. of pyridine, and 25 ml. of ethanol was refluxed for 2 hr. The solvents were removed under vacuum, and the residue was washed with cold water and recrystallized from dilute ethanol to give white prisms, m.p. 125–127°.

Anal. Calcd. for $C_9H_{16}N_2O_2$ (mol. wt., 184): C, 58.7; H, 8.7; N, 15.2. Found: C, 58.5; H, 8.2; N, 15.3.

F. 1-Methyl-3,3-diethyl-4-phenylsulfonamido-2-pyrrolidone (VI).—A solution of 10 g. of the isonitroso compound in methanol was reduced with hydrogen in the presence of Raney nickel at 50 p.s.i. and room temperature. When the reduction was complete, the mixture was filtered and the solvent was removed under vacuum. The liquid residue was treated with 50 ml. of 2 *N* NaOH and 8 ml. of benzenesulfonyl chloride was added with shaking. The mixture was acidified with hydrochloric acid and cooled to give a white precipitate. Recrystallization from dilute ethanol gave white prisms, m.p. 151.5–153.5°.

Anal. Calcd. for $C_{15}H_{22}N_2O_3S$ (mol. wt., 310): C, 58.1; H, 7.1. Found; C, 57.9; H, 7.1.

G. 1-Butyl-3,3-diethyl-2,4-pyrrolidinedione (VII).—To a solution of 58.4 g. of *n*-butylamine in 400 ml. of ether was added dropwise, with stirring and cooling, 106 g. of ethyl γ-bromo-α,α-diethylacetoacetate. The addition took 1 hr. and stirring was continued for 2 hr. after addition was complete. The precipitated salt was filtered off and the ether was removed. Distilla-

(2) M. Conrad, *Ber.*, **30**, 856 (1897).
(3) M. Conrad and K. Hock, *ibid.*, **32**, 1200 (1899).
(4) All melting points are corrected.

tion of the residue gave a pale yellow oil, b.p. 97–102° (0.4 mm.), $n^{25}D$ 1.4645.

Anal. Calcd. for $C_{12}H_{21}NO_2$ (mol. wt., 211): C, 68.3; H, 10.0; N, 6.6. Found: C, 68.4; H, 9.8; N, 6.6.

H. 1-Benzyl-3,3-diethyl-2,4-pyrrolidinedione (VIII).—A solution of 43 g. of benzylamine in 200 ml. of ether was interacted with 53 g. of the bromoacetoacetate in accordance with the procedure described under G to give a colorless liquid, b.p. 145° (0.55 mm.), $n^{26}D$ 1.5235.

Anal. Calcd. for $C_{15}H_{19}NO_2$ (mol. wt., 245): C, 73.5; H, 7.8; N, 5.7. Found: C, 73.8; H, 8.0; N, 5.9.

Derivatives of 3,3-Dimethylpyrrolidinedione. A. 1-(Carbethoxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (IX).—A solution of 30 g. of ethyl glycinate in 25 ml. of benzene was treated with 34.5 g. of ethyl γ-bromo-α,α-dimethylacetoacetate[2] in 25 ml. of benzene in accordance with the procedure described under A above for the diethylacetoacetate. The product was a colorless liquid, b.p. 112° (0.2 mm.), $n^{26}D$ 1.4634, which tended to solidify to a low melting solid.

Anal. Calcd. for $C_{10}H_{15}NO_4$ (mol. wt., 213): C, 56.4; H, 7.0. Found: C, 56.3; H, 7.0; sapon. equiv., 188.

B. 1-(Carboxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (X).—The ester (IX, 5 g.) was hydrolyzed as described for the diethyl analog with 12 ml. of 2 *N* NaOH to give the acid in the form of small white needle clusters (from ethyl acetate), m.p. 128–130°; infrared analysis showed a band for a strained carbonyl at 1765 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{11}NO_4$ (mol. wt., 185): C, 51.8; H, 5.9. Found: C, 52.0; H, 6.1.

C. 1,3,3-Trimethyl-2,4-pyrrolidinedione (XII).—A mixture of 200 g. of methylamine in ethanol (30% solution) was dissolved in 1000 ml. of ether and treated with 200 g. of the bromoacetoacetate according to the procedure previously described for the diethyl analog to give a colorless liquid, b.p. 141–144° (46 mm.), $n^{26}D$ 1.4720. The liquid partially solidified on standing. It was therefore chilled and filtered; the crystalline material was recrystallized from an ether–petroleum ether (b.p. 40–60°) mixture to give soft white crystals, m.p. 47–50°.

Anal. Calcd. for $C_7H_{11}NO_2$ (mol. wt., 141): C, 59.7; H, 7.8; N, 9.9. Found: C, 59.6; H, 7.7; N, 9.9.

The same compound could be made by decarboxylation of 1-(carboxymethyl)-3,3-dimethyl-2,4-pyrrolidinedione (X). The product so obtained was treated with phenylhydrazine in the conventional manner to give yellow flakes (from ethanol) of 1,3,3-trimethyl-4-phenylhydrazono-2-pyrrolidone (XI), m.p. 167–173° (with prior softening).

Anal. Calcd. for $C_{13}H_{17}N_3O$ (mol. wt., 231): C, 67.5; H, 7.4. Found: C, 67.8; H, 7.6.

D. 1,3,3-Trimethyl-4-isonitroso-2-pyrrolidone (XIII).—A mixture of 10 g. of the dione (XII), 12 g. of hydroxylamine hydrochloride, 60 ml. of pyridine, and 60 ml. of ethanol was interacted as described for the diethyl analog to give small white needles of the product (from dilute ethanol), m.p. 211–212°.

Anal. Calcd. for $C_7H_{12}N_2O_2$ (mol. wt., 156): C, 53.8; H, 7.7; N, 18.0. Found: C, 53.8; H, 7.2; N, 18.1.

E. 1,3,3-Trimethyl-4-phenylsulfonamido-2-pyrrolidone (XIV).—A solution of 8 g. of the isonitroso compound (XIII) in methanol was reduced, and the reduction product was treated with benzenesulfonyl chloride in the manner previously described for the diethyl analog to give white spires (from dilute ethanol) of the product, m.p. 163–165°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3S$ (mol. wt., 282): C, 55.3; H, 6.4. Found: C, 55.4; H, 6.3.

Acknowledgment.—The authors are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Mr. S. Traiman for the infrared studies.

5*H*-1,4-Benzodiazepin-5-ones. Ring-Closure Reactions of Substituted 2-Aminobenzamides

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Several new 5*H*-1,4-benzodiazepin-5-ones were prepared from 2-aminobenzamides by ring closures involving intramolecular eliminations of alkylsulfonic or arylsulfonic acids, cyclodehydrochlorination, and cyclodehydration reactions. Some chemical transformations of the new compounds are presented.

During recent years, considerable effort has been expended toward the synthesis of 1*H*-1,4-benzodiazepines,[1] a group of compounds having interesting psychopharmacologic properties. In the course of our investigations into the preparation of centrally active drugs, we arrived at several routes for preparing novel 5*H*-1,4-benzodiazepin-5-ones through ring closures involving elimination reactions in suitably substituted 2-aminobenzamides.[2]

The first method involved the reaction of a 2-amino-*N*-(2-hydroxyalkyl)benzamide (I) with an alkylsulfonyl or arylsulfonyl chloride. The method is illustrated best by the preparation of 1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (IIIj). 2-Amino-*N*-(2-hydroxyethyl)benzamide (Ie), obtained from the reaction of 2-aminoethanol with isatoic anhydride, was treated with 2 molar equiv. of *p*-toluenesulfonyl chloride at 0–5° in pyridine. After several hours, the addition of water to the reaction mixture resulted in the precipitation of a solid which, on heating in ethanol, gave IIIj. It subsequently was shown that the cyclization occurred during the attempted purification of intermediate II, since the solid initially obtained had an infrared absorption spectrum significantly different from IIIj. The spectrum of the rather labile intermediate has an amide II band at 6.4 μ and is compatible with the open-chain structure of the *p*-toluenesulfonate ester of 2-*p*-toluenesulfonamido-*N*-(2-hydroxyethyl)benzamide. The amide II band is absent in the spectrum of IIIj, as expected, since it is a cyclic amide. The same reaction was carried out in stepwise fashion using 1 equiv. of *p*-toluenesulfonyl chloride. The product isolated was *N*-(2-hydroxyethyl)-2-*p*-toluenesulfonamidobenzamide. When the latter product in pyridine was treated with a 2nd molar equiv. of *p*-toluenesulfonyl chloride and the reaction worked up in the customary manner, IIIj again was obtained.

(1) (a) A. Stempel and F. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962); (b) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962); (c) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962); (d) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Chem.*, **5**, 63 (1962); (e) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962); (f) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(2) M. Uskoković, J. Iacobelli, and W. Wenner [*ibid.*, **27**, 3606 (1963)] have described the preparation of 3*H*-1,4-benzodiazepin-2,5(1*H*,4*H*)-diones from substituted 2-aminobenzamides.