24. *Diazepines. Part II.* Some Bromination Experiments on Dihydrodiazepines.*

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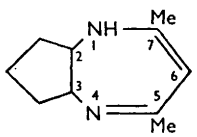
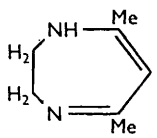
The bromination of two 2 : 3-dihydro-1 : 4-diazepines has been studied. One bromine atom only enters the molecule, by substitution, at the 6-position. This bromine atom is easily replaced by a methoxy- or ethoxy-group.

The preparation is recorded of a number of 2 : 3-benzo-1 : 4-diazepines [1] and 2 : 3-dihydro-1 : 4-diazepines,[2] but little systematic investigation of their chemical properties has been carried out, especially in the case of the dihydrodiazepines. As the first stage of an investigation of their properties, the bromination products derived from two 2 : 3-dihydro-5 : 7-dimethyl-1 : 4-diazepines have been studied.

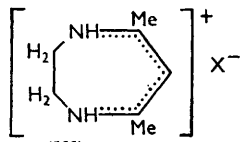
If 2 : 3-dihydro-5 : 7-dimethyl-2 : 3-*cyclo*pentano-1 : 4-diazepine (I) is treated with an equimolecular portion of bromine, an almost colourless product crystallises at once. More bromine will not react, even over a period of four days. The product contains two atoms of bromine, one of which is ionic, and is apparently a bromodihydrodiazepinium bromide.



(I)



(II)



(III)

Bromination of 2 : 3-dihydro-5 : 7-dimethyl-1 : 4-diazepine (II) or its hydrobromide or perchlorate (III; X = Br or ClO_4) similarly gives a bromodihydrodiazepinium bromide; again the diazepine reacts with only one molecule of bromine. Treatment of the resultant bromide with sodium hydroxide solution yields the corresponding bromodihydrodiazepine base. Bromination by *N*-bromosuccinimide gives the same product as is obtained by using bromine.

As only one bromine atom enters the molecule, it must presumably do so at a unique position, namely the 6-position. This is confirmed by the hydrolysis products obtained when the bromo-compound is kept in dilute sulphuric acid for some days. A lachrymatory oil separates, which contains bromine but no nitrogen. This oil shows acidic or enolic properties and with ferric chloride gives an intense purple colour. It has been pointed out [3] that α-substituted β-dicarbonyl compounds give violet, purple, or blue colours with ferric chloride: of all the simple β-dicarbonyl compounds listed in Beilstein's " Handbuch " those giving blue or purple colours with this reagent are indeed all α-substituted. It is likely therefore that the oil is 3-bromoacetylacetone. When the aqueous layer from the hydrolysis is basified, benzoyl and toluene-*p*-sulphonyl derivatives can be obtained from it which are identical (mixed m. p.) with those obtained from ethylenediamine. These hydrolysis products could only arise from 6-bromo-2 : 3-dihydro-5 : 7-dimethyl-1 : 4-diazepine.

Treatment of this 6-bromo-compound with potassium methoxide or ethoxide readily gives products which are apparently 6-methoxy- and 6-ethoxy-2 : 3-dihydro-5 : 7-dimethyl-1 : 4-diazepine respectively, as indicated by their molecular formulæ. That the

* Part I, *J.*, 1956, 2597.

[1] Thiele and Steimmig, *Ber.*, 1907, **40**, 955; Rupe and Huber, *Helv. Chim. Acta*, 1927, **10**, 846; Emmert and Gsottschneider, *Ber.*, 1933, **66**, 1871; Vaysman, *Trudy Inst. Khim. Khar'kov Gosudarst. Univ.*, 1938, **4**, 157; 1940, **5**, 57; Schmitt, *Annalen*, 1950, **569**, 17; Haley and Maitland, *J.*, 1951, 3155; King and Spensley, *J.*, 1952, 2144; Ried and Höhne, *Chem. Ber.*, 1954, **87**, 1801.

[2] Schwarzenbach and Lütz, *Helv. Chim. Acta*, 1940, **23**, 1139; Ried and Höhne, *Chem. Ber.*, 1954, **87**, 1811; Lloyd and Marshall, *J.*, 1956, 2597.

[3] Morgan and Drew, *J.*, 1924, **125**, 731; Henecka, *Chem. Ber.*, 1948, **81**, 179.

alcoholic alkali has brought about substitution, and not elimination producing compounds which with alcohol of crystallisation would have the same formulæ, is shown in that the picrates of these compounds are unchanged by acetic acid and acetic anhydride. The similarity of their ultraviolet spectra to that of the bromodihydrodiazepine also confirms this formulation.

Introduction of a bromine atom or alkoxy-group into the dihydrodiazepines causes little change in the general form of the spectra but there is a bathochromic displacement (about 24 mμ) of the main peak, this again being consistent with the structures assigned.

Experimental

2 : 3-Dihydro-5 : 7-dimethyl-2 : 3-*cyclo*pentano-1 : 4-diazepine (I) and 2 : 3-dihydro-5 : 7-dimethyl-1 : 4-diazepine (II) were prepared as described in Part I.

Bromination of the Diazepine (I).—Treatment of an ethereal solution of this base (0·33 g.) with an equimolar quantity of bromine gave an immediate precipitate of 6-*bromo*-2 : 3-*dihydro*-5 : 7-*dimethyl*-2 : 3-cyclo*pentano*-1 : 4-*diazepinium bromide* as pale yellow needles (0·54 g., 83%) which, recrystallised from water or ethanol, darken above 190°, fusing with decomposition at 360—370°. They are moderately soluble in water, less soluble in methanol or ethanol, insoluble in acetone, ether, chloroform, and carbon tetrachloride; the aqueous solution gives a halide reaction with silver nitrate (Found: C, 37·4; H, 5·1; N, 8·8; Br, 48·4. $C_{10}H_{16}N_2Br_2$ requires C, 37·0; H, 4·9; N, 8·6; Br, 49·4%).

Bromination of the Diazepine (II).—A solution of this base (4·3 g.) in dry ether was treated with bromine until no more solid was precipitated. This solid, recrystallised from ethyl acetate–methanol as yellow needles, m. p. 207—208° (5·9 g., 60%), was 6-bromo-2 : 3-dihydro-5 : 7-dimethyl-1 : 4-diazepinium bromide. Treatment of this in water with excess of sodium hydroxide gave 6-*bromo*-2 : 3-*dihydro*-5 : 7-*dimethyl*-1 : 4-*diazepine*, m. p. 122—123° (Found: C, 41·6; H, 5·4; N, 13·7; Br, 39·1. $C_7H_{11}N_2Br$ requires C, 41·4; H, 5·4; N, 13·8; Br, 39·4%). This base forms a *perchlorate*, pale yellow needles (from water), m. p. 161—162°, sparingly soluble in methanol and ethanol, soluble in water and acetone (Found: C, 28·8; H, 4·1; N, 9·8; Hal, 38·2. $C_7H_{12}O_4N_2BrCl$ requires C, 27·7; H, 4·0; N, 9·2; Hal, 38·1%), and a *picrate*, m. p. 207—209° (Found: C, 36·3; H, 3·2; N, 16·0; Br, 17·9. $C_{13}H_{14}O_7N_5Br$ requires C, 36·1; H, 3·2; N, 16·2; Br, 18·5%). The hydrochloride or perchlorate of the starting material was also readily brominated in chloroform or methanol, to give the 6-bromo-derivative (90%).

Bromination with N-*Bromosuccinimide*.—The perchlorate of the base (II) (2·24 g., 0·010 mole) and *N*-bromosuccinimide (2·0 g., 0·011 mole) in chloroform were heated under reflux for 2 hr. The bromodihydrodiazepinium perchlorate separated from the solution mixed with succinimide. Recrystallised from water it had m. p. 161—162° (1·86 g., 61%).

Acid Degradation of the Bromodihydrodiazepine from (II).—The base (9·0 g.) was added to 2N-sulphuric acid and kept for 5 days. An oil (6 g.) separated which was lachrymatory, dissolved in aqueous sodium hydroxide, contained bromine but no nitrogen, and gave an intense purple colour with ferric chloride solution. With Brady's reagent it gave an orange gum. The residual acid solution was extracted with ether and made alkaline with sodium hydroxide, and portions were shaken with benzoyl chloride and toluene-*p*-sulphonyl chloride severally. The dibenzoyl (m. p. 252—253°) and ditoluene-*p*-sulphonyl (m. p. 161—162°) derivatives of ethylenediamine were formed. These m. p.s were not depressed on admixture with genuine samples. In another hydrolysis 2·0 g. of the bromo-base gave 2·4 g. of dibenzoylethylenediamine (91%).

6-*Ethoxy*-2 : 3-*dihydro*-5 : 7-*dimethyl*-1 : 4-*diazepine*.—Potassium hydroxide (4 g.) in ethanol (30 ml.) was added to a solution of the bromodihydrodiazepinium bromide (5 g.) in ethanol (30 ml.), and the mixture heated under reflux for 30 min. and then kept overnight. Potassium bromide (4·08 g., 97%) was filtered off, and the solution acidified with concentrated hydrobromic acid, filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in 10% aqueous sodium hydroxide (50 ml.) and this solution extracted with ether (6 × 20 ml.). Removal of ether from the extract gave a brown gum which crystallised. It is soluble in many organic solvents, but not light petroleum or benzene, and gives a *picrate*, m. p. 167·5—168·5° (from ethanol) (Found: .C, 44·8; H, 4·8; N, 17·2. $C_{15}H_{19}O_8N_5$ requires C, 45·3; H, 4·8; N, 17·6%). This picrate was also obtained by refluxing the bromo-hydrobromide from (III; X = Br) with ethanolic alkali and adding picric acid directly

2 : 3-*Dihydro*-6-*methoxy*-5 : 7-*dimethyl*-1 : 4-*diazepine*.—The bromodihydrodiazepine (6·44 g.) and potassium hydroxide (2·15 g.) in methanol (30 ml.) were heated under reflux for 2 min. After cooling and removal of the precipitated potassium bromide, picric acid (10·6 g.) in boiling methanol (60 ml.) was added. The hot solution was filtered from potassium picrate, and the *methoxydihydrodiazepinium picrate* which separated recrystallised from methanol; it had m. p. 157—159° (Found: N, 17·6. $C_{14}H_{17}O_8N_5$ requires N, 18·3%). This picrate and that of its ethoxy-analogue were unchanged when heated with acetic acid–acetic anhydride.

Ultraviolet spectra (*in* MeOH).

2 : 3-Dihydro-5 : 7-dimethyl-1 : 4-diazepinium derivative	$\lambda_{max.}$. (mμ)	log ε	2 : 3-Dihydro-5 : 7-dimethyl-1 : 4-diazepinium derivative	$\lambda_{max.}$. (mμ)	log ε
Cation (III)	325	4·3	6-Methoxy-	349, 256	4·3, 3·1
2 : 3-*cyclo*Pentano- (in H_2O)...	325	4·2	6-Ethoxy-	352, 256	4·2, 2·9
6-Bromo-	349, 260	4·1, 3·0			

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