Syntheses of Heterocyclic Compounds. Part XXIX.[1] Substituted 2,3-Dihydro-1*H*-1,5-benzodiazepines

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1,5-Benzodiazepine-2-spirocycloalkanes [as (6)] are made in a one-step condensation from *o*-phenylenediamine and cyclic ketones in cold ethanol in the presence of boron trifluoride–ether complex. The method is also applicable to acyclic ketones. The diazepines can also be prepared from the monohydrochloride of the base with a liquid ketone. Acylation, hydrolysis, reduction, and oxidation of some of these novel diazepines have been studied.

We reported recently that condensation of cyclohexanone with *o*-phenylenediamine in various solvents including water gives 2,3-dihydrobenzimidazole-2-spirocyclohexane [2] (1; $n = 5$). This compound is easily oxidised to the 2*H*-benzimidazole (2; $n = 5$) with which it forms a novel oxidation–reduction system.[3] Attempts to extend the reaction to cyclopentanone failed to give the corresponding dihydrobenzimidazole (1; $n = 4$), even with dehydrating agents. In sulpholan, at 100° for 15 min, a yellow solid, m.p. 138°, was isolated (50%) to which we assign the diazepine structure (3) for the following reasons. Its i.r. spectrum showed a band at 3340 cm^{-1} (NH) and the n.m.r. spectrum signals at τ 3·00 (m, 4 × ArH), 5·98 (s, N–H removable by D_2O), 7·35 (t, 3 aliphatic H's, *i.e.* H_a and H_b), and 8·30 (12H, m). Analytical and mass spectral data (*cf.* Experimental section) confirmed this assignment. Recently, Reddi *et al.*[4] have prepared this diazepine by interaction of cyclopentanone and *o*-phenylenediamine in methanol for 1 h at room temperature, but quote m.p. 128°. We were able to

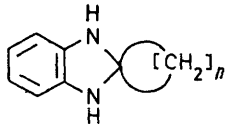
[1] Part XXVIII, J. Martin, O. Meth-Cohn, and H. Suschitzky, *J.C.S. Perkin I*, 1974, 2451.

[2] R. Garner, G. V. Garner, and H. Suschitzky, *J. Chem. Soc.* (*C*), 1970, 825.

[3] J. A. L. Herbert and H. Suschitzky, *Chem. and Ind.*, 1973 482.

[4] P. S. Reddi, C. V. Ratnam, and N. V. Subba Rao, *Indian J. Chem.*, 1972, **10**, 982.

confirm this method of preparation and the nature of the product, provided the reaction time was extended to 18 h. Cyclohexanone, when treated under similar conditions, gave only the dihydrobenzimidazole (1; $n = 5$). The reported azepine seems to be identical with ours, *e.g.* heating in dilute acid yielded phenylenediamine and 2-cyclopentylidenecyclopentanone (4). The yield of the azepine (3) was substantially improved (>90%) when *o*-phenylenediamine (1 equiv.) was made to react with cyclopentanone (2 equiv.) at 0—5° in ethanol containing BF_3–Et_2O (2 equiv.). A yellow BF_3-addition compound separated, from which the azepine (3) was obtained by passing gaseous ammonia through a suspension of the adduct in benzene. While 2-cyclopentylidenecyclopentanone (4), the suspected intermediate, will not condense with *o*-phenylenediamine, even in a hot solvent,



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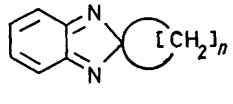

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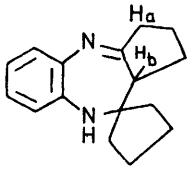

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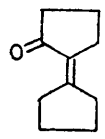

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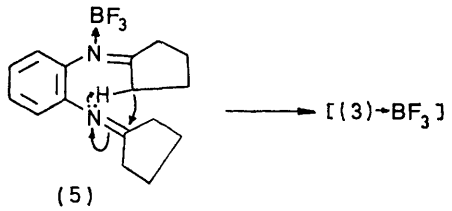
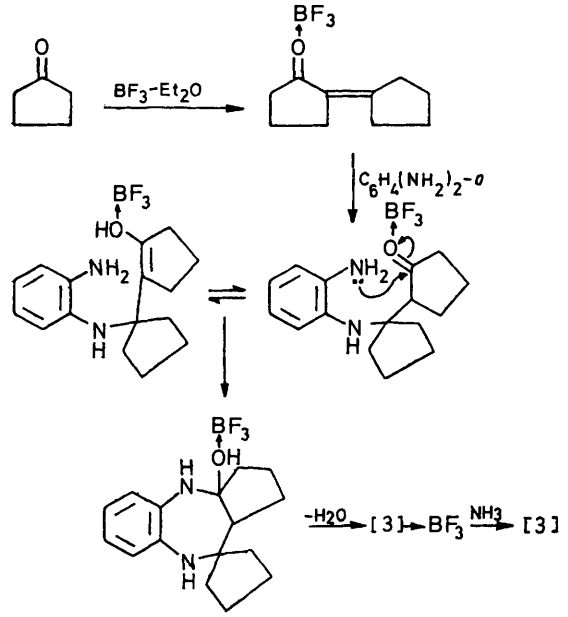


(5)

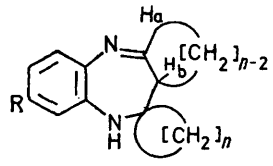
addition of BF_3–Et_2O results in the immediate formation of the diazepine (3). Also, since cyclopentanone readily undergoes self-condensation in the presence of the catalyst under the reaction conditions to give (4), a mechanism as in the Scheme appeared plausible for the azepine formation. As a confirmatory test of the proposed mechanism, we treated *p*-anisidine with cyclopentanone in the usual way and obtained the BF_3-adduct of the corresponding Schiff's base. No product involving the amine and the bicyclic ketone (4) was found, which was unexpected by analogy with the postulated scheme. The alternative pathway in which the bisanil (5) is a key intermediate cannot, therefore, be excluded [*cf.* (5) ⟶ (3)].

The BF_3 method proved to be generally applicable for the preparation of the novel 1,5-benzodiazepines (6; $n = 4$—7) from *o*-phenylenediamine or its 4-chloro-derivative and the appropriate cyclic ketone. Cycloheptanone needed a reaction time of *ca.* 7 days at room temperature and did not yield a stable BF_3-addition



Scheme

product. Cyclohexane-1,4-dione gave only a moderate yield of the expected diazepine (7) while cyclododecanone could not be made to react. Acyclic ketones (acetone, butan-2-one, and acetophenone) also produced good yields of the corresponding benzodiazepines (8; $R^1 = R^2 = Me$, or $R^1 = Me$, $R^2 = Et$, or $R^1 = Me$, $R^2 = Ph$). The obvious advantage of this route over the reported method which uses αβ-unsaturated,[5-7] or β-halogeno-ketones [5] lies in the efficiency and simplicity of the one-pot condensation of readily available materials. Moreover, Ried and Stahlhofen [7] were unable to obtain benzodiazepines from certain αβ-unsaturated ketones, owing to lack of carbonyl reactivity. For instance, benzylacetone



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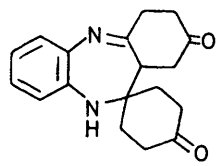

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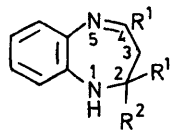


(8)

and phenylenediamine gave an adduct which, on strong heating, yielded 2-phenylbenzimidazole. By contrast, BF_3 catalysis produced the required 4-methyl-2-phenylbenzodiazepine [*cf.* (8)], albeit in small yield (*ca.* 10%).

[5] W. Ried and E. Torinus, *Chem. Ber.*, 1959, **92**, 2902; G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 1968, **68**, 747.

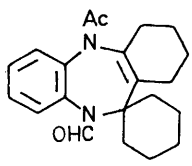
[6] J. Sprague, *U.S. Govt. Res. Reports*, 1959, **31**, 301 (*Chem. Abs.*, 1960, **54**, 12,156).

[7] W. Ried and P. Stahlhofen, *Chem. Ber.*, 1957, **90**, 815.

Mesityl oxide as well as 2-cyclohexylidenecyclohexanone[8] gave excellent yields of the corresponding benzodiazepines.

We also assessed hydrogen chloride as a catalyst for this condensation. No interaction of the diamine and ketone occurred in cold ethanolic hydrochloric acid and tars were produced on boiling. However, addition of *o*-phenylenediamine monohydrochloride to neat cyclopentanone was exothermic and on cooling the reaction mixture, the diazepine hydrochloride (6; $n = 4$) was obtained in 80% yield. Corresponding hydrochlorides were produced from acetone, cyclohexanone, and β-decalones but this method is limited to liquid ketones. Mechanistically, these reactions undoubtedly involve proton catalysis in a way analogous to the BF_3 reactions.

Because of the novelty of the spirodiazepines we investigated some of their general chemistry. The diazepine (3) derived from cyclopentanone was readily hydrolysed in hot hydrochloric acid (4M) to give *o*-phenylenediamine and 2-cyclopentylidenecyclopentanone (4), while under the same conditions the cyclohexane diazepine (6; $n = 5$) gave the amine and starting ketone. The less complete hydrolysis of the diazepine (3) may be due to the reluctance of $sp^2 \longrightarrow sp^3$ transitions in cyclopentane systems,[9] owing to the importance of *I*-strain. Treatment of (3) with activated manganese dioxide gave the hydroxy-compound (3; OH for H_a), apparently a novel oxidation of an organic nitrogen compound[10] by this reagent. The oxidation failed with the cyclohexyl homologue (6; $n = 5$). Attempts to acetylate or formylate the latter diazepine (6; $n = 5$) in the usual way also failed, resulting in tars. However, a mixture of formic acid and acetic anhydride produced a crystalline diacyl compound which, on the basis of analytical and spectral data, agrees with the *NN'*-diacyl derivative (9), or its isomer in which the positions of the acyl groups are reversed. Reduction of the benzodiazepines (3) and (6; $n = 5$) with lithium aluminium hydride or catalytically with palladium–charcoal under hydrogen yielded the tetrahydro-compounds (10; $R^1 = R^2 = H$, $n = 4$ or 5) in high yield. Acetylation of the cyclohexyl compound (10; $R^1 = R^2 = H$, $n = 5$) gave the acetyl derivative (10; $R^1 = Ac$, $R^2 = H$, $n = 5$) but attempts at preparing the diacetyl derivative proved abortive. A mixture of formic acid and acetic anhydride produced the diformyl derivative (10; $R^1 = R^2 = CHO$, $n = 5$).



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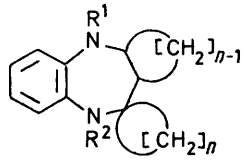

(10)

TABLE 1

Preparative data for the diazepines (6)

R	n	Yield (%)	M.p. (°C)	Reaction time	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
H	4	91	138	10 min	79·85	8·5	11·45	$C_{16}H_{20}N_2$	79·95	8·4	11·65
Cl	4	81	136	15 min	69·65	7·2	10·0	$C_{16}H_{19}ClN_2$	70·0	6·95	10·2
H	5	84	130	2 h	80·1	8·7	9·9	$C_{18}H_{24}N_2$	80·5	9·0	10·45
H	6	40	148	5 days	81·25	9·7	9·1	$C_{20}H_{28}N_2$	81·1	9·45	9·45
H	7	56	134	7 days	81·95	10·2	8·25	$C_{22}H_{32}N_2$	81·4	9·95	8·65

TABLE 2

Spectral data of the diazepines (6)

R	n	$\nu_{max.}$(Nujol)/cm^{-1} NH	C=N	C=C	N.m.r. data (τ values, J in Hz; $CDCl_3$ solutions at 60 MHz) Aromatic protons	NH	$H_a + H_b$	Aliphatic protons
H	4	3334	1658	1600	3·0 (4H, m)	5·98 *	7·35 (3H, t)	8·30 (12H, m)
Cl	4	3278	1650	1595	2·7 (1H, d, J 8) 3·25 (1H, dd, J 2 and 8), 3·35 (1H, d, J 2)	5·90 *	7·38 (3H, t)	8·28 (12H, m)
H	5	3290	1640	1600	3·0 (4H, m)	6·20 *	7·45 (3H, t)	8·40 (16H, m)
H	6	3275	1630	1600	3·0 (4H, m)	6·30 *	7·30 (3H, t)	8·45 (20H, m)
H	7	3255	1635	1600	3·0 (4H, m)	5·95 *	7·32 (3H, t)	8·45 (24H, m)

* Removed by D_2O.

EXPERIMENTAL

1,5-Benzodiazepines.—(*a*) The required ketone (0·1 mol) dissolved in ethanol (20 ml) containing BF_3–Et_2O (0·1 mol) was cooled in an ice-bath. After 0·5—2 h (depending on the ketone) a solution of *o*-phenylenediamine (0·05 mol) in ethanol (30 ml) was added with stirring over 5 min. Within 5—10 min the BF_3-adduct of the azepine separated as a bright yellow solid. Scratching and cooling induced this precipitation in some cases. The product was filtered off, washed with ether, and air dried. Gaseous ammonia was passed for *ca.* 5 min through a well-stirred suspension of the adduct to precipitate BF_3,NH_3 as a white solid which was filtered off, and the diazepine was obtained by driving off the solvent. Spectral and analytical results are in Tables 1 and 2.

The reaction with *o*-phenylenediamine and 1,4-cyclohexadione as above gave 1,3,4,10,11,11a-*hexahydrodibenzo*-[b,e][1,4]*diazepine*-11-*spirocyclohexone*-2,4'-*dione* (7) in 3 h,

[8] H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, 1956, **78**, 4394.

[9] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 265.

[10] O. Meth-Cohn and H. Suschitzky, *Chem. and Ind.*, 1969, 443.

m.p. 212° (Found: C, 72·85; H, 6·8; N, 9·5. $C_{18}H_{20}N_2O_2$ requires C, 72·9; H, 6·85; N, 9·5%).

(*b*) Cyclopentanone (0·02 mol) and *o*-phenylenediamine (0·01 mol) were heated in sulpholan (10 ml) on a water-bath for 15 min. The solution was poured into cold water (200 ml) and the emulsion extracted with ether. The solvent was driven off to yield a yellow tar which, on trituration with petroleum (b.p. 40—60°)–ethyl acetate gave 1,2,3,9,10,10a-*hexahydrocyclopenta*[b][1,5]*benzodiazepine*-10-*spirocyclopentane* (6; $n = 4$), m.p. 138°.

(*c*) BF_3–Et_2O (0·01 mol) was added to a stirred solution of 2-cyclopentylidenecyclopentanone (0·01 mol) [11] and *o*-phenylenediamine (0·01 mol) in ethanol (50 ml) and the solution was cooled in ice. Within 5—10 min the yellow BF_3–benzodiazepine adduct precipitated. The free benzodiazepine (6; $n = 4$) was liberated as before, m.p. 138°.

(*d*) Cyclododecanone (0·02 mol), *o*-phenylenediamine (0·01 mol), and BF_3–Et_2O (0·02 mol) were kept in ethanol (100 ml) at room temperature for 8 days. On working up in the usual way, the starting materials were recovered almost quantitatively.

(*e*) *o*-Phenylenediamine monohydrochloride (0·01 mol) was added to cyclohexanone (10—15 ml) and the mixture stirred on a water-bath for 5 min. The dark red solution was cooled in ice and the bright yellow benzodiazepine hydrochloride filtered off and washed with a little acetone. The *hydrochloride*, m.p. 202°, showed $\nu_{max.}$ (Nujol) 3280 (NH) and 2550 ($\overset{+}{N}H$) cm^{-1} (Found: C, 70·6; H, 8·0; N, 9·5. $C_{18}H_{25}ClN_2$ requires C, 70·9; H, 8·2; N, 9·2%). The hydrochloride was stirred in benzene and gaseous ammonia passed through the suspension to give the benzodiazepine, m.p. 130°, in 82% yield.

Reactions of Alicyclic Ketones.—(i) 2,3-*Dihydro*-2,2,4-*trimethyl*-1H-1,5-*benzodiazepine* (8; $R^1 = R^2 =$ Me). Acetone was treated as described in method (*a*) above to give this benzodiazepine (85%) as pale yellow prisms [from petroleum (80—100°)], m.p. 126° (lit.,[7] 125°); $\nu_{max.}$ (Nujol) 3300 (NH) and 1640 cm^{-1} (C=N); τ (60 MHz; $CDCl_3$) 3·08 (m, 4 ArH), 6·98 (s, removed by D_2O, NH), 7·70 (s, Me), 7·82 (s, $-CH_2-$), and 8·76 (s, 2 Me).

(ii) 2,3-*Dihydro*-2-*methyl*-2,4-*diphenyl*-1H-1,5-*benzodiazepine* (8; R^1 = Me, R^2 = Ph). Acetophenone was treated as described in method (*a*). The red BF_3-adduct crystallised out overnight. Basification with gaseous ammonia gave the *benzodiazepine monohydrate* (80%) as yellow prisms [from petroleum (40—60°)], m.p. 102°; $\nu_{max.}$ (Nujol) 3340 (NH) and 1610 cm^{-1} (C=N); τ (60 MHz; CCl_4) 2·20 (m, 14 ArH), 5·25 (NH, removed by D_2O), 6·82 (1H, d, *J* 13 Hz), 7·13 (1H, d, *J* 13 Hz), and 8·30 (s, Me) (Found: C, 79·8; H, 6·8; N, 8·4. $C_{22}H_{20}N_2,H_2O$ requires C, 79·9; H, 6·7; N, 8·5%).

Reactions of the 1,5-*Benzodiazepines.*—(a) *Hydrolysis.* A solution of the benzodiazepine (6; $n = 4$) (1 g) in hydrochloric acid (25 ml; 4M) was heated under reflux for 1·5 h and then steam-distilled. The steam distillate was extracted with ether and dried ($MgSO_4$). Evaporation of the solvent gave 2-cyclopentylidenecyclopentanone [identified by i.r. and by its 2,4-dinitrophenylhydrazone, m.p. 230° (lit.,[12] 232°)]. The acidic solution gave *o*-phenylenediamine on addition of ammonia.

The benzodiazepine (6; $n = 5$) was treated as above to give cyclohexanone and *o*-phenylenediamine almost quantitatively.

(b) *Oxidation with activated* MnO_2. The benzodiazepine (6; $n = 4$) (1 g) and activated manganese dioxide (5 g) were stirred in benzene (100 ml) for 72 h at room temperature. The manganese dioxide was filtered off, washed with benzene (4 × 25 ml), and the combined filtrates and washings were evaporated to dryness. 1,2,3,9,10,10a-*Hexahydrocyclopenta*[b][1,5]*benzodiazepine*-10-*spirocyclopentan*-3-*ol* (3; OH for H_a) was obtained as white clusters (1 g) [from petroleum (40—60°)], m.p. 170°; $\nu_{max.}$ (Nujol) 3600—3100 (OH), 3360 (NH), 1658 cm^{-1} (C=N); τ (60 MHz; $CDCl_3$) 2·05 (m, 3 ArH), 5·35 and 5·65 (OH and NH removed by D_2O), 7·40 (m, 2 aliphatic H), and 8·30 (m, 12 aliphatic H) (Found: C, 74·6; H, 7·5; N, 11·1. $C_{16}H_{20}N_2O$ requires C, 74·9; H, 7·8; N, 10·9%).

When the benzodiazepine (6; $n = 5$) was treated as above, it was recovered quantitatively.

(c) *Reduction.* The benzodiazepine (6; $n = 4$) (5 g), ethanol (250 ml), and palladium–charcoal (*ca.* 0·1 g of 10%) were shaken under hydrogen (5 atm) for 2 h. The catalyst was filtered off and the solvent removed to give 1,2,3,3a,4,9,10,10a-*octahydrocyclopenta*[b][1,5]*diazepine*-10-*spirocyclopentane* (10; $R^1 = R^2 =$ H, $n = 4$) (5 g) as white needles (from methanol), m.p. 124°; $\nu_{max.}$ (Nujol) 3380 and 3350 cm^{-1} (NH); τ (60 MHz; $CDCl_3$) 3·22br (s, 4 ArH), 6·45 (2NH, removed by D_2O), 7·15br (s, 1 aliphatic H), and 83·5 (m, 15 aliphatic H) (Found: C, 79·0; H, 8·8; N, 11·2. $C_{16}H_{22}N_2$ requires C, 79·3; H, 9·0; N, 11·5%).

The benzodiazepine (6; $n = 5$) (5 g) was reduced by the above method to give 2,3,4,4a,5,10,11,11a-*octahydro*-1H-*dibenzo*[b,e][1,5]*diazepine*-11-*spirocyclohexane* (10; $R^1 = R^2 = H$, $n = 5$) (5 g) as white needles (from methanol), m.p. 111°; $\nu_{max.}$ (Nujol) 3390 and 3362 cm^{-1} (NH); τ (60 MHz; $CDCl_3$) 3·28 (s, 4 ArH), 6·25br (s, >CH–), 6·88 (2 NH removed by D_2O), and 8·50 (m, 19 aliphatic H) (Found: C, 79·9; H, 9·4; N, 10·6. $C_{18}H_{26}N_2$ requires C, 80·0; H, 9·7; N, 10·4%).

(d) *Acylation.* The benzodiazepine (6; $n = 5$) (1 g) was heated under reflux with formic acid (10 ml; 98%) for 15 min. The acid was driven off under vacuum to yield a black intractable tar. However, when a mixture of formic acid (4·6 g) and acetic acid (10 g) was used, 5-*acetyl*-1,2,3,4,10,11-*hexahydro*-5H-*dibenzo*[b,e][1,5]*diazepine*-11-*spirocyclohexane*-10-*carbaldehyde* (9) was obtained as white needles (from methanol), m.p. 209°; $\nu_{max.}$ (Nujol) 1680 and 1664 cm^{-1} (CO); τ (60 MHz; $CDCl_3$) 1·85 (s, CHO) and 3·05 (m, 16 aliphatic H) (Found: C, 74·2; H, 7·9; N, 8·5. $C_{21}H_{26}N_2O_2$ requires C, 74·5; H, 7·7; N, 8·3%). Acetyl chloride and triethylamine did not effect acetylation.

Acylation of the Benzodiazepine (10; $R^1 = R^2 = H$, $n = 5$).—The title compound (1 g) was heated under reflux in a mixture of formic acid (4·6 g; 98%) and acetic anhydride (10·2 g) for 15 min. The solution was evaporated to dryness *in vacuo* and the residue triturated with cold methanol. 2,3,4,4a,5,10,11,11a-*Octahydro*-1H-*dibenzo*[b,e]-[1,5]*diazepine*-11-*spirocyclohexane*-5,10-*dicarbaldehyde* (10; $R^1 = R^2$ = CHO, $n = 5$) gave prisms (from methanol), m.p. 194°; $\nu_{max.}$ (Nujol) 1680 cm^{-1} (CO); τ (60 MHz; $CDCl_3$) 1·69 (s, CHO), 1·75 (s, CHO), 2·60 (m, 4 ArH), 5·18br (s, 1 aliphatic H), 7·70 (m, 4 aliphatic H), and 8·40 (15 aliphatic H) (Found: C, 73·9; H, 8·0; N, 8·9. $C_{20}H_{26}N_2O_2$ requires C, 73·6; H, 8·0; N, 8·6%).

The benzodiazepine (10; $R^1 = R^2 = H$, $n = 5$) was acetylated with acetyl chloride in dry benzene in the presence of triethylamine. Trituration of the residue with cold ethyl acetate–petroleum (40—60°) gave 5-*acetyl*-

[11] D. Varech, C. Quannes, and J. Jacques, *Bull. Soc. chim. France*, 1965, **6**, 1662.

[12] G. Hesse and M. Maurer, *Annalen*, 1962, **658**, 21.

2,3,4,4a,5,10,11,11a-*octahydro*-1H-*dibenzo*[b,e][1,5]*diazepine*-11-*spirocyclohexane* (10; R^1 = Ac, R^2 = H, n = 5) (0·6 g), m.p. 155° (from ethyl acetate–benzene); $\nu_{max.}$ (Nujol) 3375 (NH) and 1645 cm^{-1} (CO); τ (60 MHz; $CDCl_3$) 3·08 (m, 4 ArH), 5·1br (s, 1 aliphatic H), 6·52 (NH removed by D_2O), 8·20 (s, CH_3CO), and 7·95 and 8·45 (m, 19 aliphatic H) (Found: C, 76·8; H, 9·0; N, 9·2. $C_{20}H_{28}N_2O$ requires C, 76·9; H, 9·0; N, 9·0%).

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