Synthesis of Some 1*H*-1,3-Benzodiazepines

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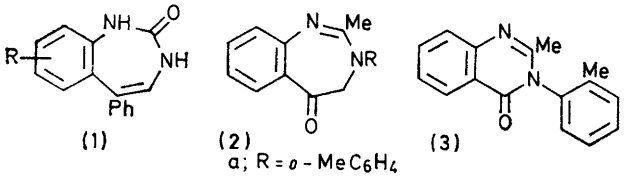
The synthesis of 3,4-dihydro-1*H*-1,3-benzodiazepine-2,5-dione has been carried out, and the reactivity at positions 2, 5, and 7 investigated. Attempts to introduce a 4,5-double bond resulted in rearrangement to quinolines and indoles.

THE novel rearrangement of quinazolones to 1,4-benzodiazepines discovered by Sternbach [1] and the subsequent discovery of potent physiological activity amongst the



(1) (2) (3)

a; R = *o*-MeC$_6$H$_4$

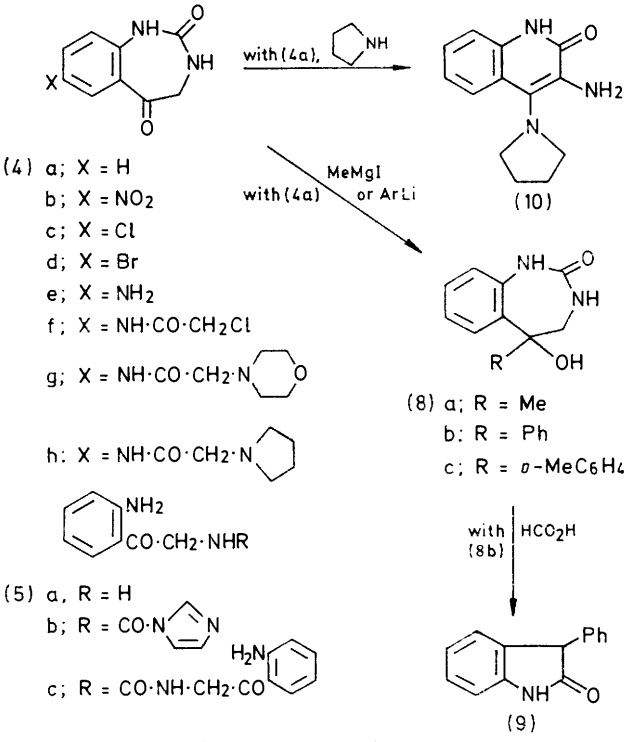
b; R = H

first reported members of the series [2] has led to intensive interest in the 1,4-benzodiazepines.[3] Many related series of heterocyclic systems have been investigated, and some thirty benzodiazepines have since achieved clinical acceptance. However, little work has been published on 1,3-benzodiazepines.[4] Our interest in quinazolones, together with the foregoing considerations, prompted us to synthesise and evaluate some hitherto unexplored 1,3-benzodiazepines. In particular the benzodiazepines (1), analogues of the 1,4-series, and (2), ' homo '-analogues of the hypnotic methaqualone (3), were of interest.

The ketone (4a) was envisaged as a key intermediate and was consequently synthesised from *o*-nitroacetophenone (see Experimental section). The critical step was the reaction of 2,2'-diaminoacetophenone [5] (5a) with 1,1'-carbonyldi-imidazole to give the imidazole-*N*-carboxamide (5b), the formation of the urea (5c) being avoided by use of a precipitation technique. The intermediate (5b) cyclised readily in hot water to give 3,4-dihydro-1*H*-1,3-benzodiazepine-2,5-dione (4a).

To investigate the effect of substitution at C-7 (important for biological activity in the 1,4-series) the nitro-, chloro-, and bromo-derivatives (4b—d) were obtained by appropriate electrophilic attack on the parent (4a). Reduction of the nitro-group with tin(II) chloride gave the amine (4e), which on chloroacetylation yielded the amide (4f). Subsequent treatment with secondary amines gave the aminoacetamides (4g and h).

The 5-oxo-group in the benzodiazepines (4) exhibits typical ketonic reactivity, forming oximes (6a and b) with hydroxylamine and reacting readily with sodium borohydride to give the secondary alcohols (7a—c). Attempted dehydration of the alcohol (7a) with acetic acid under reflux gave only the acetate (7d); more vigorous conditions resulted in degradation. The ketone (4a) reacted with Grignard reagents to give the carbinols (8a—c), but further attempts to introduce a 4,5-double bond by dehydration of these products were also unsuccessful. Thus in refluxing formic acid the carbinol (8b) rearranged to 3-phenylindolin-2-one (9), and reaction



(4) a; X = H
b; X = NO_2
c; X = Cl
d; X = Br
e; X = NH_2
f; X = NH·CO·CH_2Cl
g; X = NH·CO·CH_2·N
h; X = NH·CO·CH_2·N
NH_2
CO·CH_2·NHR

(5) a, R = H
b; R = CO·N
c; R = CO·NH·CH_2·CO
H_2N

(8) a; R = Me
b; R = Ph
c; R = *o*-MeC$_6$H$_4$

(10)

(9)

of the ketone (4a) with pyrrolidine, in an attempt to prepare the corresponding enamine, resulted in rearrangement to the quinoline (10).

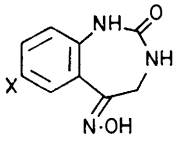
[1] L. H. Sternbach and E. Reeder, *J. Org. Chem.*, 1961, **26**, 1111.

[2] L. H. Sternbach, L. O. Randall, and S. R. Gustafson in ' Psychopharmacological Agents,' vol. 1, ed. M. Gordon, Academic Press, New York, 1964, p. 137.

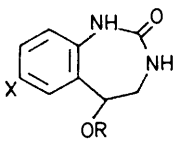
[3] ' The Benzodiazepines,' ed. S. Garattini, E. Mussini, and L. O. Randall, Raven Press, New York, 1973.

[4] T. P. Forrest, G. A. Dauphinee, and F. M. F. Chen, *Canad. J. Chem.*, 1974, **52**, 2725.

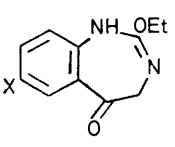
[5] S. Gabriel and W. Gerhard, *Ber.*, 1921, **54B**, 1067.



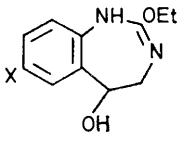
(6) a: X = H
b; X = NO_2



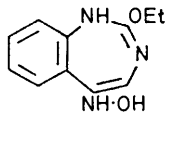
(7) a; X = H, R = H
b; X = NO_2, R = H
c; X = NH_2, R = H
d; X = H, R = Ac



(11) a; X = H
b; X = NO_2



(12) a; X = H
b; X = NO_2



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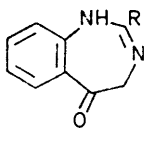
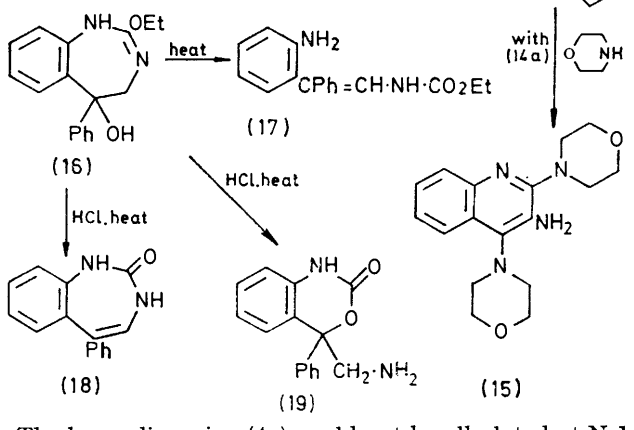


(14) a; R = N O
b; R = N



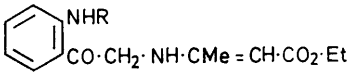
(16) (17) (18) (19) (15)

The benzodiazepine (4a) could not be alkylated at N-1 or N-3 under typical conditions, for example with sodium hydride–dimethyl sulphoxide or potassium carbonate–toluene. Treatment of the ureas (4a and b) with triethyloxonium tetrafluoroborate gave the pseudoureas (11a and b), however, in good yield. Subsequent reduction with sodium borohydride gave the alcohols (12a and b), and with hydroxylamine the ketone (11a) gave the hydroxylamine derivative (13) (as evidenced by the n.m.r. spectrum).

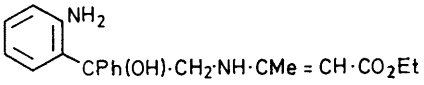
In an attempt to establish the reactivity of the pseudourea function, the product (11a) was treated with morpholine and with pyrrolidine to give the guanidines (14a and b). In the former case prolonged refluxing with morpholine or the use of an excess of acid catalyst caused rearrangement of the intermediate enamine to give the quinoline (15).

As an approach to the benzodiazepine analogues (1), the pseudourea (11a) was treated with Grignard reagents to produce a series of tertiary alcohols (Table), all of which were isolated as salts. Subsequent attempts to introduce the 4,5-double bond by dehydration were unsuccessful; the carbinol (16) for example rearranged on heating in benzene to the styrylcarbamate (17). In hot dimethylformamide however, the hydrochloride salt of (16) afforded a low yield of the benzodiazepine (18), along with the carbamate (17) and the benzoxazine (19). The structure of the oxazine (19) was confirmed by synthesis from the diamine (5) as follows. Reaction with ethyl acetoacetate was used to protect the alkylamine group by formation of the aminocrotonate (20a), and the ketone function was then converted into the tertiary alcohol (21). Cyclisation to the benzoxazine (22) with carbonyldi-imidazole proceeded smoothly and the protecting group was then removed with dilute acid.

Attempts to synthesise benzodiazepines of structure (23; R = alkyl) were also unsuccessful. For example, adducts (24a and b), obtained by the reaction of the diamine (5) with diethyl ethoxymethylenemalonate and ethoxymethylenemalononitrile, respectively, could not be cyclised under a variety of conditions in various solvents. The crotonate (20b), obtained by acetylation of the crotonate (20a), cyclised to the pyrrole (25) on heat-



(20) a; R = H
b; R = Ac



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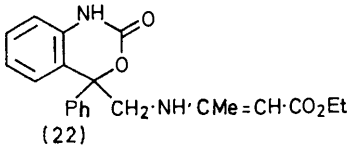

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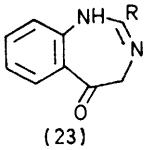

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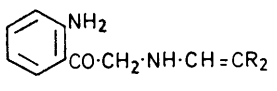
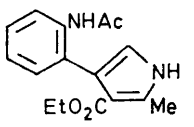


(24) a; R = CO_2Et
b; R = CN



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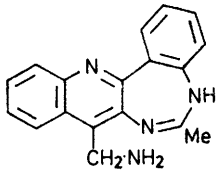


(26)

ing in acetic acid under reflux. On reaction with triethyl orthoacetate in refluxing ethanol, the diamine (5) afforded an unstable yellow crystalline compound thought to be the tetracyclic benzodiazepine (26), on the basis of its n.m.r. and mass spectral data. This product could have been formed *via* reaction of the desired benzodiazepine (2b) with the diamine (5a).

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were determined for potassium bromide discs with a Pye–Unicam SP 1000 spectrophotometer. N.m.r. spectra were determined with a Perkin-Elmer R12A spectrometer at 60 MHz, with tetramethylsilane as internal standard; all OH and NH peaks were removed by addition of D_2O. Petroleum refers to the fraction of b.p. 60—80°. All organic extracts were dried over magnesium sulphate.

2,2′-Diaminoacetophenone [5] (5a).—*N*-(*o*-Aminophenacyl)-phthalimide [5] (25 g) in concentrated hydrochloric acid (250 ml) was heated under reflux for 24 h, cooled, and filtered. The filtrate was basified with cooling (10N-sodium hydroxide), the precipitate was extracted with chloroform and the solvent was removed under reduced pressure. The residue was triturated with ether to give 2,2′-diaminoacetophenone (5a) [5] (93%) as a fine grey powder which could be stored below 0 °C; $\nu_{max.}$ 3 470, 3 445, 1 655, and 1 625 cm^{-1}.

N-(*o-Aminophenacylaminocarbonyl*)*imidazole* (5b).—A suspension of 2,2′-diaminoacetophenone (5a) (12 g) in dry ether (250 ml) was stirred vigorously and heated under reflux while a solution of *NN′*-carbonyldi-imidazole (12 g) in dry dichloromethane (120 ml) was added during 5 min. A granular brown solid was filtered off and washed with a little cold chloroform followed by ether to give *N*-(*o*-aminophenacylaminocarbonyl)imidazole (5b) (15 g, 77%), pale green prisms (from chloroform–petroleum), m.p. 150° (decomp.), *m/e* 176 (*M* − 68, loss of imidazole); $\nu_{max.}$ 3 415, 3 385, 3 285, 1 740, and 1 683 cm^{-1}; τ [$(CD_3)_2SO$] 1.17 (1 H, t, *J* 5 Hz, NH), 1.71 (1 H, s, imidazole 2-H), 2.00—3.54 (8 H, m, ArH, imidazole 4- and 5-H, and NH_2), and 5.20 (2 H, d, *J* 5 Hz, CH_2).

NN′-Bis-(*o-aminophenacyl*)*urea* (5c).—In the preparation of the imidazole (5b) slow crystallisation of the product during addition of the *NN′*-carbonyldi-imidazole allowed formation of a second product, which was isolated by virtue of its insolubility in chloroform to give *NN′-bis-*(*o-aminophenacyl*)*urea* (5c), as prisms (from dimethylformamide–ethanol), m.p. 230° (decomp.) (Found: C, 62.3; H, 6.0. $C_{17}H_{18}N_4O_2$ requires C, 62.6; H, 5.6%); $\nu_{max.}$ 3 440, 3 325, 1 650, and 1 610 cm^{-1}; τ[$(CD_3)_2SO$] 2.12—3.63 (14 H, m, ArH, NH_2, and NH), and 5.46 (4 H, d, *J* 5 Hz, CH_2).

*3,4-Dihydro-*1H-1,3-*benzodiazepine-*2,5-*dione* (4a).—A suspension of the imidazole (5b) (15 g) in water (500 ml) was stirred at 90 °C until the solid had dissolved. Cooling to room temperature caused crystallisation of the *benzodiazepine* (4a), (9.5 g, 88%), as prisms (from dimethylformamide–chloroform), m.p. 220° (decomp.) (Found: C, 61.4; H, 4.6; N, 16.0. $C_9H_8N_2O_2$ requires C, 61.4; H, 4.6; N, 15.9%); $\nu_{max.}$ 3 220, 3 085, 1 700, 1 677, 1 597, and 1 580 cm^{-1}; τ[$(CD_3)_2SO$] 0.69 (1 H, s, 1-H), 2.08 (1 H, dd, $J_{6.7}$ 8, $J_{6.8}$ 2 Hz, 6-H), 2.25—3.10 (4 H, m, ArH and 3-H), and 6.18 (2 H, d, *J* 5 Hz, CH_2).

*3,4-Dihydro-7-nitro-*1H-1,3-*benzodiazepine-*2,5-*dione* (4b).—A solution of concentrated nitric acid (1 ml) in concentrated sulphuric acid (2 ml) was added dropwise to a stirred solution of the diazepine (4a) (2 g) in concentrated sulphuric acid (20 ml) at 0—3 °C. After 2 h at room temperature the solution was poured into iced water to precipitate the *nitrobenzodiazepine* (4b) (1.5 g, 60%), as prisms (from dimethylformamide–methanol), m.p. 260° (decomp.) (Found: C, 49.1; H, 3.6. $C_9H_7N_3O_4$ requires C, 48.9; H, 3.2%); $\nu_{max.}$ 3 345, 1 715, 1 690, 1 615, and 1 585 cm^{-1}; τ[$(CD_3)_2SO$] 0.00 (1 H, s, 1-H), 1.37 (1 H, d, $J_{6.8}$ 3 Hz, 6-H), 1.68 (1 H, dd, $J_{6.8}$ 3, $J_{8.9}$ 9.5 Hz, 8-H), 2.05br (1 H, 3-H), 2.51 (1 H, d, $J_{8.9}$ 9.5 Hz, 9-H), and 6.08 (2 H, d, *J* 4.5 Hz, CH_2).

*7-Chloro-3,4-dihydro-*1H-1,3-*benzodiazepine-*2,5-*dione* (4c).—Acetic acid (50 ml) was saturated at room temperature with chlorine; the solution was then cooled to 16 °C and added to a stirred, cooled suspension of the diazepine (4a) (8.5 g) in acetic acid (50 ml) at such a rate that the temperature remained below 16 °C. The solution was allowed to warm to room temperature and was then poured into water to precipitate the *chlorobenzodiazepine* (4c) (5.5 g, 57.5%), as prisms (from dimethylformamide–methanol), m.p. 240° (Found: C, 51.5; H, 3.6; N, 13.3. $C_9H_7ClN_2O_2$ requires C, 51.3; H, 3.3; N, 13.3%); $\nu_{max.}$ 3 320, 1 727, 1 675br, 1 608, and 1 580 cm^{-1}; τ[$(CD_3)_2SO$] 0.47 (1 H, s, 1-H), 1.14 (1 H, d, $J_{6.8}$ 2.5 Hz, 6-H), 2.38 (1 H, dd, $J_{6.8}$ 2.5, $J_{8.9}$ 9 Hz, 8-H), 2.40br (1 H, 3-H), 2.60 (1 H, d, $J_{8.9}$ 9 Hz, 9-H), and 6.14 (2 H, d, *J* 5 Hz, CH_2).

*7-Bromo-3,4-dihydro-*1H-1,3-*benzodiazepine-*2,5-*dione* (4d).—Treatment of a solution of the diazepine (4a) in acetic acid at room temperature with bromine (1 mol. equiv.) and then pouring the solution into water gave a 1 : 1 mixture of the diazepine (4a) and the *bromobenzodiazepine* (4d), as prisms (from dimethylformamide), m.p. 254° (Found: C, 42.7; H, 3.0. $C_9H_7BrN_2O_2$ requires C, 42.4; H, 2.7%); $\nu_{max.}$ 3 320, 1 718, 1 660, 1 601, and 1 578 cm^{-1}; τ[$(CD_3)_2SO$] 0.52 (1 H, s, 1-H), 2.06 (1 H, d, $J_{6.8}$ 2.5 Hz, 6-H), 2.10—2.50br (1 H, 3-H), 2.33 (1 H, dd, $J_{6.8}$ 2.5, $J_{8.9}$ 9 Hz, 8-H), 2.71 (1 H, d, $J_{8.9}$ 9 Hz, 9-H), and 6.20 (2 H, d, *J* 5 Hz, CH_2). Increasing the quantity of bromine did not increase the yield of product.

*7-Amino-3,4-dihydro-*1H-1,3-*benzodiazepine-*2,5-*dione* (4e).—A solution of tin(II) chloride (10.4 g) in concentrated hydrochloric acid (50 ml) was added to a stirred suspension of the nitrodiazepine (4b) (2.6 g) in concentrated hydrochloric acid (25 ml) on an ice-bath. The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. The crystalline product was filtered off, washed with a little cold concentrated hydrochloric acid, and dissolved in water. The solution was filtered and then basified with 10N-sodium hydroxide to precipitate the *aminobenzodiazepine* (4e) (2.0 g, 90%), as yellow prisms (from ethanol), m.p. 255° (decomp.) (Found: C, 56.3; H, 4.6. $C_9H_9N_3O_2$ requires C, 56.4; H, 4.7%); $\nu_{max.}$ 3 365, 3 295, 3 200br, 3 060br, 1 700, and 1 660 cm^{-1}; τ[$(CD_3)_2SO$] 1.14 (1 H, d, $J_{1.3}$ 2.5 Hz, 1-H), 2.74br (1 H, 3-H), 2.82 (1 H, d, $J_{6.8}$ 2.5 Hz, 6-H), 3.14 (1 H, dd, $J_{6.8}$ 2.5, $J_{8.9}$ 9 Hz, 8-H), 2.94 (1 H, d, $J_{8.9}$ 9 Hz, 9-H), and 6.24 (2 H, d, *J* 5 Hz, CH_2).

*7-Chloroacetamido-3,4-dihydro-*1H-1,3-*benzodiazepine-*2,5-*dione* (4f).—A solution of the aminodiazepine (4e) (1.6 g) in dimethylformamide (50 ml) was treated with chloroacetyl chloride (1.0 ml) and 5 min later poured into water (250 ml) to give crystalline *chloroacetamidobenzodiazepine* (4f) (2.0 g, 89%) as prisms (from dimethylformamide–methanol), m.p. 250° (decomp.) (Found: C, 49.3; H, 4.0; N, 15.7. $C_{11}H_{10}ClN_3O_3$ requires C, 49.4; H, 3.7; N, 15.7%); $\nu_{max.}$ 3 292, 3 220, 3 110, 1 707, 1 670, 1 650, and 1 618 cm^{-1}; τ[$(CD_3)_2SO$] −0.33 (1 H, s, side-chain NH), 0.74 (1 H, d, $J_{1.3}$ 2 Hz, 1-H),

1.85 (1 H, d, $J_{6,8}$ 2 Hz, 6-H), 2.27 (1 H, dd, $J_{6,8}$ 2, $J_{8,9}$ 9 Hz, 8-H), 2.50br (1 H, 3-H), 2.71 (1 H, d, $J_{8,9}$ 9 Hz, 9-H), 5.80 (2 H, s, side-chain CH_2), and 6.22 (2 H, d, J 4.5 Hz, 4-H_2).

3,4-*Dihydro*-7-*morpholinoacetamido*-1H-1,3-*benzodiazepine*-2,5-*dione* (4g).—A suspension of the amide (4f) (1.7 g) in morpholine (10 ml) was warmed until the exothermic reaction had started. When all the solid had dissolved, the solution was poured into water to precipitate the *morpholinobenzodiazepine* (4g) (1.8 g, 89%), as prisms (from aqueous dimethylformamide), m.p. 255° (Found: C, 56.9; H, 6.0. $C_{15}H_{18}N_4O_4$ requires C, 56.6; H, 5.7%); $\nu_{max.}$ 3 270, 3 100, 1 690infl, 1 660, and 1 615 cm^{-1}; τ[$(CD_3)_2SO$] 0.27 (1 H, s, side-chain NH), 0.83 (1 H, d, $J_{1,3}$ 2 Hz, 1-H), 1.85 (1 H, d, $J_{6,8}$ 2 Hz, 6-H), 2.28 (1 H, dd, $J_{6,8}$ 2, $J_{8,9}$ 9 Hz, 8-H), 2.58br (1 H, 3-H), 2.77 (1 H, d, $J_{8,9}$ 9 Hz, 9-H), 6.20—6.50 (6 H, m, 4-H_2, morpholine 2- and 6-H_2), 6.93 (2 H, s, acetamide CH_2), and 7.45—7.65 (m, morpholine 3- and 5-H_2, and solvent).

3,4-*Dihydro*-7-*piperidinoacetamido*-1H-1,3-*benzodiazepine*-2,5-*dione* (4h).—A suspension of the amide (4f) (1.8 g) in dimethylformamide (10 ml) was treated with piperidine (1.0 g), warmed until a clear solution was obtained, and then diluted with water to give crystalline *piperidinoacetamidobenzodiazepinedione* (4h) (1.8 g, 84%), as prisms (from aqueous dimethylformamide), m.p. 255° (decomp.) (Found: C, 60.4; H, 6.4; N, 17.6. $C_{16}H_{20}N_4O_3$ requires C, 60.8; H, 6.4; N, 17.7%); $\nu_{max.}$ 3 355, 3 290, 3 235, 1 675br, and 1 617 cm^{-1}; τ[$(CD_3)_2SO$] 0.30 (1 H, s, side-chain NH), 0.79 (1 H, s, 1-H), 1.80 (1 H, d, $J_{6,8}$ 2.5 Hz, 6-H), 2.24 (1 H, dd, $J_{6,8}$ 2.5, $J_{8,9}$ 9 Hz, 8-H), 2.52br (1 H, 3-H), 2.72 (1 H, d, $J_{8,9}$ 9 Hz, 9-H), 6.22 (2 H, d, J 5 Hz, 4-H_2), 6.96 (2 H, s, acetamide CH_2), 7.40—7.70 (m, piperidine 2- and 6-H_2, and solvent), and 8.30—8.70br (6 H, piperidine 3-, 4-, and 5-H_2).

1,3,4,5-*Tetrahydro*-5-*hydroxyimino*-1,3-*benzodiazepin*-2-*one* (6a).—The diazepine (4a) (2.5 g) was suspended in a solution of hydroxylamine hydrochloride (5 g) and sodium hydroxide (2 g) in water (40 ml) and heated to the b.p. with addition of sufficient ethanol to give a clear solution. Cooling gave the crystalline *oxime* (6a) (2.1 g, 77.5%), as prisms (from 2-methoxyethanol–chloroform), m.p. 255° (decomp.) (Found: C, 56.5; H, 4.6. $C_9H_9N_3O_2$ requires C, 56.4; N, 4.7%); $\nu_{max.}$ 1 700 cm^{-1}.

1,3,4,5-*Tetrahydro*-5-*hydroxyimino*-7-*nitro*-1,3-*benzodiazepin*-2-*one* (6b).—Similar treatment of the diazepine (4b) afforded the *oxime* (6b) 70%) as yellow needles (from ethanol), m.p. 250° (decomp.) (Found: C, 45.8; H, 3.7; N, 23.3. $C_9H_9N_4O_4$ requires C, 45.8; H, 3.4; N, 23.7%); $\nu_{max.}$ 3 525, 1 665, and 1 600 cm^{-1}.

1,3,4,5-*Tetrahydro*-5-*hydroxy*-1,3-*benzodiazepin*-2-*one* (7a).—A suspension of the diazepine (4a) (2.5 g) in ethanol (50 ml) was stirred with sodium borohydride (0.25 g) for 2 h. Water (5 ml) was added and the solution was boiled for a few minutes and then evaporated to dryness under reduced pressure. The residue was triturated with a little water to give the *alcohol* (7a), 1.3 g, 51%, as prisms (from methanol–ether), m.p. 181° (Found: C, 60.3; H, 5.9; N, 15.4. $C_9H_{10}N_2O_2$ requires C, 60.7; H, 5.7; N, 15.7%); $\nu_{max.}$ 3 220, 3 100, 3 025, and 1 665 cm^{-1}; τ[$(CD_3)_2SO$] 1.33 (1 H, s, 1-H), 2.50—3.30 (5 H, m, ArH and 3-H), 4.60br (1 H, OH), 5.20—5.50 (1 H, m, 5-H), and 6.60—7.00 (2 H, m, 4H_2).

1,3,4,5-*Tetrahydro*-5-*hydroxy*-7-*nitro*-1,3-*benzodiazepin*-2-*one* (7b).—A suspension of the diazepine (4b) (1.3 g) in ethanol (50 ml) was stirred with sodium borohydride (0.13 g) for 1 h and the solution was then treated with aqueous 10N-acetic acid to give the crystalline *alcohol* (7b) (1.0 g, 76%), as prisms (from dimethylformamide–chloroform), m.p. 207° (decomp.) (Found: C, 48.4; H, 4.3; N, 18.6. $C_9H_9N_3O_4$ requires C, 48.4; H, 4.1; N, 18.8%); $\nu_{max.}$ 3 280—3 220, 3 105, 3 050, 1 665, 1 610, and 1 590 cm^{-1}; τ[$(CD_3)_2SO$] 0.62 (1 H, s, 1-H), 1.70 (1 H, d, $J_{6,8}$ 2.5 Hz, 6-H), 2.00 (1 H, dd, $J_{6,8}$ 2.5, $J_{8,9}$ 9 Hz, 8-H), 2.57br (1 H, 3-H), 2.77 (1 H, d, $J_{8,9}$, 9 Hz, 9-H), 4.05br (1 H, OH), 5.20—5.50 (1 H, m, 5-H), and 6.60—7.00 (2 H, m, 4-H_2).

7-*Amino*-1,3,4,5-*tetrahydro*-5-*hydroxy*-1,3-*benzodiazepin*-2-*one* (7c).—This was best prepared by reduction of the nitrodiazepine (7b) (2.5 g), by refluxing a solution in ethanol (100 ml) with hydrazine hydrate (2 ml) and 10% palladium–carbon for 1 h. The hot solution was filtered and allowed to cool to give the crystalline *amine* (7c) (1.5 g, 69%), as prisms (from ethanol), m.p. 195° (decomp.) (Found: C, 56.2; H, 5.8; N, 21.4. $C_9H_{11}N_3O_2$ requires C, 56.0; H, 5.7; N, 21.8%); $\nu_{max.}$ 3 360, 3 260, and 1 680 cm^{-1}; τ-[$(CD_3)_2SO$] 1.68 (1 H, s, 1-H), 3.10—3.40 (3 H, m, 3-, 6-, and 9-H), 3.60 (1 H, dd, $J_{6,8}$ 3, $J_{8,9}$ 8 Hz, 8-H), 4.61 (1 H, d, J 6 Hz, OH), 3.40br (3 H, 5-H and NH_2; after addition of D_2O: 1 H, t, J 4 Hz, 5-H), and 6.70—7.00 (2 H, m, 4-H_2).

5-*Acetoxy*-1,3,4,5-*tetrahydro*-1,3-*benzodiazepin*-2-*one* (7d).—A solution of the diazepine (7a) (3 g) in acetic acid (25 ml) was heated under reflux for 2 days, concentrated, and diluted with ether to give the crystalline *acetate* (7d) (1.2 g, 32%), as prisms (from methanol–ether), m.p. 206° (decomp.) (Found: C, 60.0; H, 5.6; N, 12.3. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%); $\nu_{max.}$ 3 335, 3 210, 3 170, 3 100, 1 715, and 1 660 cm^{-1}; τ[$(CD_3)_2SO$] 1.84 (1 H, t, J 5 Hz, 3-H), 2.50—3.20 (4 H, m, ArH), 4.56 (1 H, t, J 6 Hz, 5-H), 6.45 (2 H, apparent t, 4-H_2), and 8.13 (3 H, s, CH_3).

1,3,4,5-*Tetrahydro*-5-*hydroxy*-5-*methyl*-1,3-*benzodiazepin*-2-*one* (8a).—Dry tetrahydrofuran was added to a stirred suspension of the diazepine (4a) (3.5 g) in ethereal methylmagnesium iodide [from magnesium (2.4 g) and iodomethane (14.2 g)] until the ether began to boil. The mixture was heated under reflux overnight, cooled, and evaporated to dryness under reduced pressure. The residue was digested with water to give the *carbinol* (8a) (1.1 g, 29%), as prisms (from ethyl acetate), m.p. 210° (decomp.) (Found: C, 62.2; H, 6.4; N, 14.4. $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.3; N, 14.6%); $\nu_{max.}$ 3 383, 3 240br, 1 700, 1 675, and 1 597 cm^{-1}; τ[$(CD_3)_2SO$] 1.42 (1 H, s, 1-H), 2.28—3.32 (5 H, m, ArH and 3-H), 4.70 (1 H, s, OH), 6.70 (1 H, dd, $J_{3,4a}$ 4, $J_{4a,4b}$ 13 Hz, 4-H_a), 7.02 (1 H, dd, $J_{3,4b}$ 7, $J_{4a,4b}$ 13 Hz, 4-H_b), and 8.62 (3 H, s, Me).

1,3,4,5-*Tetrahydro*-5-*hydroxy*-5-*phenyl*-1,3-*benzodiazepin*-2-*one* (8b).—Dry tetrahydrofuran was added to a stirred suspension of the diazepine (4a) (2 g) in ethereal phenyllithium [from lithium (3 g) and bromobenzene (30 g)] until the ether began to boil. The mixture was heated under reflux overnight, cooled, and evaporated to dryness under reduced pressure. The residue was digested with the minimum of water to give the *carbinol* (8b) (1.1 g, 38%), as prisms (from ethyl acetate), m.p. 224° (Found: C, 70.6; H, 5.6; N, 10.6. $C_{15}H_{14}N_2O_2$ requires C, 70.9; H, 5.6; N, 11.0%); $\nu_{max.}$ 3 285; 3 220, 1 675, and 1 585 cm^{-1}; τ [$(CD_3)_2SO$] 1.43 (1 H, s, 1-H), 2.60—3.30 (10 H, m, ArH and 3-H), 3.98 (1 H, s, OH), and 6.57br (2 H, 4-H_2).

1,3,4,5-*Tetrahydro*-5-*hydroxy*-5-(*o-tolyl*)-1,3-*benzodiazepin*-2-*one* (8c).—The reaction of diazepine (4a) (2.5 g) with *o*-tolyl-lithium [from lithium (0.85 g) and *o*-bromotoluene (21 g)] as in the preparation of diazepine (8b) gave the *carbinol*

(8c) (2.0 g, 70%), prisms (from ethanol), m.p. 244° (decomp.) (Found: C, 71.3; H, 6.1. $C_{16}H_{16}N_2O_2$ requires C, 71.6; H, 6.0%); $\nu_{max.}$ 3 275, 3 230br, 3 110br, 1 685, and 1,595 cm^{-1}; τ[$(CD_3)_2SO$] 2.40—3.30 (9 H, m, ArH and 3-H), 4.12 (1 H, s, OH), 6.26 (1 H, dd, $J_{3.4a}$ 4.5, $J_{4a.4b}$ 13.5 Hz, 4-H_a), 6.96 (1 H, dd, $J_{3.4b}$ 7, $J_{4a.4b}$ 13.5 Hz, 4-H_b), and 8.04 (3 H, s, CH_3).

3-*Phenylindol*-2(3H)-*one* (9).—The diazepine (8b) (1.5 g) was heated under reflux in formic acid (5 ml) for 24 h. The solution was concentrated and diluted with ether to give crystalline 3-phenylindol-2(3*H*)-one (9) (0.8 g), m.p. 183—185° (lit.,[6] 185—187°) (Found: C, 80.6; H, 5.3; N, 6.7. Calc. for $C_{14}H_{11}NO$: C, 80.4: H, 5.3; N, 6.7%); i.r. and u.v. spectra identical with reported data.[7]

3-*Amino*-4-*pyrrolidino*-2(1H)-*quinolone* (10).—The diazepine (4a) (3 g), pyrrolidine (6 ml), and toluene-*p*-sulphonic acid (30 mg) were heated in refluxing, dry toluene (250 ml) under nitrogen for 24 h. The solvent was evaporated off under reduced pressure and the residue triturated in a little ethanol to give crystalline 3-*amino*-4-*pyrrolidino*-2(1H)-*quinolone* (10) (1.6 g), prisms (from chloroform–ether), m.p. 240° (decomp.) (Found: C, 58.3; H, 6.1; Cl, 13.3; N, 15.4. $C_{13}H_{15}N_3O$,HCl requires C, 58.7; H, 6.0; Cl, 13.4; N, 15.8%); $\nu_{max.}$ 3 490, 3 430, 3 380, 3 320, 1 665, 1 655, and 1 610 cm^{-1}; τ($CDCl_3$) 2.40—3.00 (4 H, m, ArH), 5.42 (2 H, s, NH_2), 6.45—8.82 (4 H, m, pyrrolidine 2- and 5-H_2), and 7.74—8.11 (4 H, m, pyrrolidine 3- and 4-H_2).

2-*Ethoxy*-1,4-*dihydro*-1,3-*benzodiazepin*-5-*one* (11a).—The diazepine (4a) (6 g) was suspended in a solution of an excess of triethyloxonium tetrafluoroborate [8] in dry dichloromethane (200 ml) and stirred overnight at room temperature. The mixture was then heated under reflux for 3 h and cooled, and the solid material (8.5 g) was filtered off. The solid was suspended in ethyl acetate (200 ml) and shaken with an excess of aqueous potassium carbonate. Unchanged diazepine (4a) (2.5 g) was filtered off, and the organic layer was washed with water and evaporated to dryness under reduced pressure. The residue was triturated with petroleum to give the crystalline *ethoxybenzodiazepine* (11a) (3.2 g, 84% based on material consumed), prisms (from petroleum), m.p. 88° (Found: C, 54.6; H, 5.3; Cl, 14.8; N, 12.0. $C_{11}H_{12}N_2O_2$,HCl requires C, 54.8; H, 5.4; Cl, 14.7; N, 11.6%); $\nu_{max.}$ 3 310, 1 682, 1 660, and 1 621 cm^{-1}; τ($CDCl_3$) 1.99 (1 H, dd, $J_{6.7}$ 8, $J_{6.8}$ 1.5 Hz, 6-H), 2.40—3.10 (4 H, m, ArH and 1-H), 5.82 (2 H, q, J 7 Hz, O·CH_2), 5.93 (2 H, s, 4-H_2), and 8.76 (3 H, t, J 7 Hz, CH_3).

2-*Ethoxy*-1,4-*dihydro*-7-*nitro*-1,3-*benzodiazepin*-5-*one* (11b).—Reaction of the diazepine (4b) with triethyloxonium tetrafluoroborate as for the preparation of (11a) gave the *ethoxybenzodiazepine* (11b) (70%), a sprisms (from aqueous methanol), m.p. 110—111° (Found: C, 52.9; H, 4.7. $C_{11}H_{11}N_3O_4$ requires C, 53.0; H, 4.5%); $\nu_{max.}$ 3 320, 3 290infl, 1 700, 1 678, and 1 619 cm^{-1}; τ[$(CD_3)_2SO$] —0.64br (1 H, s, 1-H), 1.54 (1 H, d, $J_{6.8}$ 3 Hz, 6-H), 1.82 (1 H, dd, $J_{6.8}$ 3, $J_{8.9}$ 9 Hz, 8-H), 2.62 (1 H, d, $J_{8.9}$ 9 Hz, 9-H), 5.79 (2 H, q, J 7 Hz, O·CH_2), 6.04 (2 H, s, 4-H_2), and 8.70 (3 H, s, CH_3).

2-*Ethoxy*-4,5-*dihydro*-5-*hydroxy*-1H-1,3-*benzodiazepine* (12a).—A solution of the diazepine (11a) (2 g) in ethanol (40 ml) was stirred overnight at room temperature with sodium borohydride (0.5 g) and then evaporated to dryness under reduced pressure. The residue was dissolved in water, acidified with acetic acid, and then basified with potassium carbonate. The solution was extracted with ethyl acetate and the solvent removed under reduced pressure. The residual oil was dissolved in methanol, treated with an excess of ethereal hydrogen chloride, and then diluted with ethyl acetate and acetone to give the crystalline *benzodiazepine* (12a) *hydrochloride* (1.5 g, 63%), prisms (from methanol–ethyl acetate), m.p. 155° (decomp.) (Found: C, 54.4; H, 6.0; Cl, 14.7; N, 11.7. $C_{11}H_{14}N_2O_2$,HCl requires C, 54.5; H, 6.2; Cl, 14.6; N, 11.5%); $\nu_{max.}$ 3 300, 3 000—2 400, 1 674, 1 631, and 1 580 cm^{-1}; τ[$(CD_3)_2SO$] —1.00br (2 H, NH_2^+), 2.40—3.00 (4 H, m, ArH), 5.10 (1 H, t, J 4.5 Hz, 5-H), 5.20br (1 H, OH), 5.40 (2 H, q, J 7 Hz, O·CH_2), 6.30—6.50 (2 H, m, 4-H_2), and 8.61 (3 H, t, J 7 Hz, CH_3).

2-*Ethoxy*-4,5-*dihydro*-5-*hydroxy*-7-*nitro*-1H-1,3-*benzodiazepine* (12b).—A solution of the diazepine (11b) (0.75 g) in ethanol (35 ml) was stirred at room temperature for 24 h with sodium borohydride (0.75 g). The solution was acidified with 10N-acetic acid, basified with potassium carbonate, and then concentrated under reduced pressure to give the crystalline *benzodiazepine* (12b) (0.5 g, 66%), as yellow prisms (from aqueous ethanol), m.p. 153° (Found: C, 52.8; H, 5.4; N, 16.6. $C_{11}H_{13}N_3O_4$ requires C, 52.6; H, 5.2; N, 16.7%); $\nu_{max.}$ 3 280 and 1 630 cm^{-1}; τ[$(CD_3)_2SO$] 1.77 (1 H, d, $J_{6.8}$ 2.5 Hz, 6-H), 2.03 (1 H, dd, $J_{6.8}$ 2.5, $J_{8.9}$ 8.5 Hz, 8-H), 2.25br (1 H, 1-H), 2.96 (1 H, d, $J_{8.9}$ 8.5 Hz, 9-H), 4.01br (1 H, OH), 5.05—5.45 (1 H, m, 5-H), 5.81 (2 H, q, J 7 Hz, OCH_2), 6.45–6.90 (2 H, m, 4-CH_2), and 8.77 (3 H, t, J 7 Hz, CH_3).

2-*Ethoxy*-5-*hydroxyamino*-1H-1,3-*benzodiazepine* (13).—A solution of the diazepine (11a) (1.5 g) in ethanol (5 ml) was added to a hot solution of hydroxylamine hydrochloride (3 g) and sodium hydroxide (1.2 g) in water (25 ml). Ethanol was added to clear the solution, which was then boiled for a few minutes and allowed to cool to give the crystalline *benzodiazepine* (13) (1.5 g, 95%), as prisms (from aqueous ethanol), m.p. 170° (Found: C, 60.2; H, 5.9; N, 19.4. $C_{11}H_{13}N_3O_2$ requires C, 60.3; H, 5.9; N, 19.2%); $\nu_{max.}$ 3 180br and 1 618 cm^{-1}; τ[$(CD_3)_2SO$] 1.20 (1 H, dd, $J_{6.7}$ 9.5, $J_{6.8}$ 1.5 Hz, 6-H), 1.58 (1 H, s, 4-H), 2.00—2.60 (3 H, m, ArH), 5.53 (2 H, q, J 7 Hz, O·CH_2), and 8.58 (3 H, t, J 7 Hz, CH_3).

1,4-*Dihydro*-2-*morpholino*-1,3-*benzodiazepin*-5-*one* (14a).—A solution of the diazepine (11a) (0.5 g) in toluene (25 ml) was heated under reflux with morpholine (1 ml) and toluene-*p*-sulphonic acid (2 mg) for 24 h. The solution was cooled and extracted with 2N-hydrochloric acid (25 ml). The acidic solution was basified with potassium carbonate and extracted with ethyl acetate. The solvent was removed under reduced pressure, the residue dissolved in a little ethanol, and the solution treated with an excess of concentrated ethanolic toluene-*p*-sulphonic acid. The crystalline salt was filtered off, washed with acetone, and shaken with a mixture of ethyl acetate and aqueous potassium carbonate; the organic phase was evaporated to dryness to give the crystalline *morpholinobenzodiazepine* (14a) (0.25 g, 41.5%), as prisms (from ethyl acetate), m.p. 150° (remelts 170°) (Found: C, 55.3; H, 5.6; Cl, 12.5; N, 14.3. $C_{13}H_{15}N_3O_2$,-HCl requires C, 55.5; H, 5.7; Cl, 12.6; N, 14.9%); $\nu_{max.}$ 3 260, 1 664, 1 645, and 1 605 cm^{-1}; τ[$(CD_3)_2SO$] 2.16 (1 H, dd, $J_{6.7}$ 8.5, $J_{6.8}$ 2 Hz, 6-H), 2.30—3.20 (3 H, m, ArH), 6.16 (2 H, s, 4-H_2), 6.20—6.55 (4 H, m, morpholine 2- and 6-H_2), and 6.55—6.90 (4 H, m, morpholine 3- and 5-H_2).

1,4-*Dihydro*-2-*pyrrolidino*-1,3-*benzodiazepin*-5-*one* (14b).—

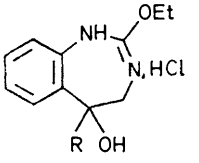
[6] J. Meisenheimer and H. Meis, *Ber.*, 1924, **57**, 289.
[7] H. E. Zaugg and R. W. DeNet, *J. Amer. Chem. Soc.*, 1962, **84**, 4576.
[8] H. Meerwein, *Org. Synth.*, 1966, **46**, 113.

A solution of the diazepine (11a), (0.4 g) in benzene (25 ml) was heated under reflux for 24 h with pyrrolidine (1 ml) and toluene-*p*-sulphonic acid (5 mg). The solution was evaporated to dryness under reduced pressure and the residue triturated with ether to give crystalline 2,5-dipyrrolidino-1*H*-1,3-benzodiazepine (0.3 g), m.p. *ca.* 140° (decomp.); $\nu_{max.}$ 3 460, 1 640, and 1 597 cm^{-1}; $\tau(CDCl_3)$ 2.50—3.40 (4 H, m, ArH), 4.11 (1 H, s, 4-H), 5.04br (1 H, s, 1-H), 6.40—6.70 (4 H, m, 2-pyrrolidino 2- and 5-H_2), 7.00—7.30 (4 H, m, 5-pyrrolidino 2- and 5-H_2), and 7.90—8.40 (8 H, m, 2 × pyrrolidine 3- and 5-H_2).

heated under reflux for more than 48 h, or if 1 mol. equiv. of toluene-*p*-sulphonic acid was used, the only product isolated was 3-*amino*-2,4-*dimorpholinoquinoline* (15) (30%), as prisms (from methanol), m.p. 110—111° (Found: C, 64.7; H, 6.9. $C_{17}H_{22}N_4O_2$ requires C, 65.0; H, 7.1%); $\nu_{max.}$ 3 450br and 1 620 cm^{-1}; $\tau(CCl_4)$ 1.71 (1 H, dd, $J_{5.6}$ 8.5, $J_{5,7}$ 1.5 Hz, 5-H), 2.20—2.90 (3 H, m, ArH), 5.80—6.40 (14 H, m, morpholine 2- and 6-H_2, and NH_2), and 7.20—7.50 (4 H, m, morpholine 3- and 5-H_2).

2-*Ethoxy*-4,5-*dihydro*-5-*hydroxy*-5-*phenyl*-1H-1,3-*benzodiazepine* (16).—The diazepine hydrochlorides in the Table were

2-Ethoxy-4,5-dihydro-1*H*-1,3-benzodiazepinium chlorides



(a) Yields, m.p.s, and analytical data

R	Yield (%)	M.p. (°C) *	Formula	% Found (required) C	H	Cl	N	F
Me	55	155 (decomp.)	$C_{12}H_{16}N_2O_2$, HCl	56.3(56.2)	6.6(6.6)	13.5(13.8)	11.2(10.9)	
Et	58	153 (decomp.)	$C_{13}H_{18}N_2O_2$, HCl	57.6(57.7)	7.1(7.0)	13.3(13.1)	10.7(10.3)	
$PhCH_2$	52	158 (decomp.)	$C_{18}H_{20}N_2O_2$, HCl	64.6(65.0)	6.3(6.3)	10.7(10.7)		
Ph	70	163 (remelts 215)	$C_{17}H_{18}N_2O_2$, HCl	63.9(64.0)	5.8(6.0)	11.3(11.1)	8.6(8.8)	
2-MeC_6H_4	49	173 [remelts >200 (decomp.)]	$C_{18}H_{20}N_2O_2$, HCl	64.6(65.0)	6.4(6.3)	10.7(10.7)	8.6(8.4)	
3-MeC_6H_4	54	156—158 (decomp.)	$C_{18}H_{20}N_2O_2$, HCl	65.2(65.0)	6.4(6.3)	10.4(10.7)	8.2(8.4)	
4-MeC_6H_4	46	147 (decomp.)	$C_{18}H_{20}N_2O_2$, HCl	65.0(65.0)	6.3(6.3)	10.8(10.7)		
4-EtC_6H_4	56	158—160	$C_{19}H_{22}N_2O_2$, HCl	66.2(65.8)	6.8(6.7)	10.1(10.2)	8.0(8.1)	
2-MeO·C_6H_4	52	156 [remelts >200 (decomp.)]	$C_{18}H_{20}N_2O_3$, HCl	61.7(62.0)	6.1(6.0)	9.9(10.2)	7.3(8.0)	
3-MeO·C_6H_4	52	145 (decomp.)	$C_{18}H_{20}N_2O_3$, HCl	61.6(62.0)	6.0(6.0)	10.1(10.2)		
4-MeO·C_6H_4	50	>210° (decomp.)	$C_{18}H_{20}N_2O_3$, HCl	61.9(62.0)	6.2(6.0)	10.2(10.2)	8.1(8.0)	
3-FC_6H_4	63	162—164	$C_{17}H_{17}FN_2O_2$, HCl	60.4(60.6)	5.5(5.4)	10.3(10.5)	8.2(8.3)	5.9(5.6)
4-FC_6H_4	63	159 (resolidifies)	$C_{17}H_{17}FN_2O_2$, HCl	60.3(60.6)	5.7(5.4)	10.4(10.5)	8.2(8.3)	5.9(5.6)
2-ClC_6H_4 [a]	72	145 (decomp.)	$C_{17}H_{17}ClN_2O_2$, H_2SO_4	49.8(49.4)	4.9(4.6)		6.7(6.8)	
3-ClC_6H_4	58	153—155	$C_{17}H_{17}ClN_2O_2$, HCl	57.9(57.8)	5.2(5.1)		7.9(7.9)	
4-ClC_6H_4	66	155	$C_{17}H_{17}ClN_2O_2$, HCl	57.8(57.8)	5.2(4.8)	19.8(20.1)	7.7(7.9)	
3-CF_3·C_6H_4	47.5	156—157 (decomp.)	$C_{18}H_{17}F_3N_2O_4$, HCl	55.8(55.9)	4.8(4.7)	9.0(9.2)	7.5(7.2)	15.0(14.7)
Thiophen-2-yl	45	153 (remelts >200)	$C_{15}H_{16}N_2O_2S$, HCl	55.4(55.5)	5.4(5.2)		8.2(8.6)	

(b) N.m.r. and i.r. data

R	N.m.r. data [τ values, J in Hz; solvent $(CD_3)_2SO$; at 60 MHz] Aromatic protons	OEt (q and t, *J* 7)	4-CH_2 (2 × d)	Miscellaneous	$\nu_{max.}$(KBr)/cm^{-1}
Me	2.10—3.00 (4 H, m)	5.30, 8.48	6.40, 6.60 (*J*15)	8.57 (3 H, s, 5-Me)	3 310, 1 668, 1 640, 1 578
Et	2.20—3.10 (4 H, m)	5.28, 8.53	6.31, 6.57 (*J*14)	8.30 [c] (2 H, CH_2), 9.05 (3 H, t, *J*7, CH_3)	3 260, 1 661, 1 632, 1 576
$PhCH_2$	2.30—3.20 (9 H, m)	5.38, [b] 8.59	6.33, 6.49 (*J*13)	7.02 (2 H, s, $PhCH_2$)	1 675, 1 631, 1 576
Ph	2.30—2.90 (9 H, m)	5.57, 8.81	6.01, 6.41 (*J*14)		3 330, 1 666, 1 630, 1 575
2-MeC_6H_4	2.20—3.10 (8 H, m)	5.45, 8.75	5.87, 6.57 (*J*14)	7.90 (3 H, s, Me)	3 330, 1 663, 1 626, 1 569
3-MeC_6H_4	2.30—3.20 (8 H, m)	5.53, 8.79	6.00, 6.40 (*J*14)	7.75 (3 H, s, Me)	3 305, 1 665, 1 630, 1 573
4-MeC_6H_4	2.30—3.00 (8 H, m)	5.56, 8.78	6.02, 6.42 (*J*13)	7.76 (3 H, s, Me)	3 310, 1 665, 1 628, 1 576
4-EtC_6H_4	2.30—3.00 (8 H, m)	5.50, 8.78 [d]	5.98, 6.38 (*J*12)	7.42 (2 H, q), 8.85 [d] (3 H, t) (*J*7 Et)	3 400, 1 665, 1 630, 1 575
2-MeO·C_6H_4	2.30—3.20 (8 H, m)	5.48, 8.70	5.84, 6.64 (*J*13)	6.60 (3 H, s, OMe)	3 260, 1 664, 1 640, 1 576
3-MeO·C_6H_4	2.30—3.50 (8 H, m)	5.52, 8.77	5.93, 6.41 (*J*13)	6.24 (3 H, s, OMe)	3 295, 1 668, 1 630, 1 604, 1 575
4-MeO·C_6H_4	2.30—3.30 (8 H, m)	5.55, 8.77	6.10 (*J*13) [e]	6.29 (3 H, s, OMe)	3 290, 1 665, 1 625, 1 574
3-FC_6H_4	2.30—3.10 (8 H, m)	5.50, 8.75	5.95, 6.35 (*J*15)		3 320, 1 660, 1 630, 1 590
4-FC_6H_4	2.30—2.90 (8 H, m)	5.54, 8.75	6.00, 6.40 (*J*14)		3 330, 1 663, 1 635, 1 575
2-ClC_6H_4 [a]	0.80—2.25 (8 H, m)	5.48, 8.58	5.61, 6.65 (*J*14)		3 100br, 1 680, 1 638, 1 578
3-ClC_6H_4	2.30—2.90 (8 H, m)	5.30, 8.75	5.98, 6.42 (*J*14)		3 300, 1 660, 1 630, 1 600, 1 570
4-ClC_6H_4	2.20—3.00 (8 H, m)	5.52, 8.75	6.01, 6.39 (*J*13)		3 340, 1 668, 1 632, 1 578
3-CF_3·C_6H_4	2.20—3.00 (8 H, m)	5.52, 8.76	5.95, 6.35 (*J*14)		3 280, 1 660, 1 625, 1 572
Thiophen-2-yl	1.20—2.30 (7 H, m)	5.50, 8.74	6.04, 6.30 (*J*13)		3 290, 3 200, 1 668, 1 635, 1 578

[a] As hydrosulphate [b] Further split. [c] Unresolved. [d] These assignments could be reversed. [e] Partly obscured.

* All recrystallised from methanol–ethyl acetate.

The solid was dissolved in 2N-hydrochloric acid (5 ml), set aside for 10 min, basified with sodium carbonate, and extracted with ethyl acetate. Evaporation under reduced pressure and trituration of the residue with ether gave crystalline 1,4-*dihydro*-2-*pyrrolidino*-1,3-*benzodiazepin*-5-*one* (14b) (0.18 g, 40%), as yellow prisms (from ethyl acetate), m.p. 152—154° (decomp.) (Found: C, 68.3; H, 6.2; N, 18.2. $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6; N, 18.3%); $\nu_{max.}$ 3 285, 1 662, and 1 605 cm^{-1}; $\tau[(CD_3)_2SO]$ 2.10—3.30 (5 H, m, ArH and 1-H), 6.30 (2 H, s, 4-H_2), 6.40—6.80 (4 H, m, pyrrolidine 2- and 5-H_2), and 8.00—8.30 (4 H, m, pyrrolidine 3- and 4-H_2).

3-*Amino*-2,4-*dimorpholinoquinoline* (15).—If, in the preparation of the diazepine (14a), the reaction mixture was prepared by the reaction of the diazepine (11a) with an appropriate Grignard reagent, the following being typical of the conditions used. A solution of phenylmagnesium iodide [from magnesium (1.2 g) and iodobenzene (5.6 ml)] in ether (50 ml) and benzene (50 ml) was stirred and heated under reflux while a solution of the diazepine (11a) (2 g) in ether (25 ml) was added at such a rate that the initial yellow precipitate redissolved. After heating for a further 2 h the mixture was stirred into aqueous N-ammonium chloride (100 ml). The organic layer was washed with water and treated with methanolic hydrogen chloride to precipitate the *hydrochloride* of (16) (2.2 g, 70%), as prisms (from methanol–ethyl acetate), m.p. 163° (remelts 215°) (Found: C, 63.9; H, 5.8; Cl, 11.3; N, 8.6. $C_{17}H_{18}N_2O_2$,HCl requires

C, 64.0; H, 6.0; Cl, 11.1; N, 8.8%); for i.r. and n.m.r. data see Table.

Ethyl 2-(2-*Aminophenyl*)*styrylcarbamate* (17).—An aqueous solution of the hydrochloride (5.4 g) of the diazepine (16) was basified with potassium carbonate and extracted with benzene. The benzene solution was heated under reflux for 2 days, the solvent was removed under reduced pressure, and the residue was triturated in ether to give the crystalline *carbamate* (17) (2.8 g, 52%), as prisms (from methanol), m.p. 127—128° (Found: C, 72.3; H, 6.3; N, 10.1. $C_{17}H_{18}N_2O_2$ requires C, 72.3; H, 6.4; N, 9.9%); $\nu_{max.}$ 3 320, 3 240, 3 230br, 1 718, and 1 654 cm^{-1}; τ[$(CD_3)_2SO$] 1.44 (1 H, d, *J* 10 Hz, NH), 2.40—3.60 (10 H, m, ArH and CH), 5.58br (2 H, NH_2), 5.92 (2 H, q, *J* 7 Hz, CH_2), and 8.82 (3 H, t, *J* 7 Hz, CH_3).

Decomposition of 2-*Ethoxy*-4,5-*dihydro*-5-*hydroxy*-5-*phenyl*-1H-1,3-*benzodiazepine* (16) *Hydrochloride*.—A solution of the hydrochloride of (16) (0.5 g) in dimethylformamide (10 ml) was heated at 100 °C for 20 min and then poured into water (50 ml). (*a*) The precipitate was filtered off and washed with ethyl acetate to give 1,3-*dihydro*-5-*phenyl*-1,3-*benzodiazepin*-2-*one* (18) (0.15 g, 38%), as prisms (from methanol), m.p. 250° (Found: C, 76.1; H, 5.2; N, 11.8. $C_{15}H_{12}N_2O$ requires C, 76.2; H, 5.1; N, 11.9%); $\nu_{max.}$ 3 250, 3 140, 3 050, 1 698, 1 660, and 1 585 cm^{-1}; τ[$(CD_3)_2SO$] 1.93 (1 H, s, 1-H), 2.60—3.40 (10 H, m, ArH and 3-H), and 3.84 (1 H, d, *J* 6 Hz, 4-H). (*b*) The ethyl acetate washings from (*a*) were evaporated to dryness under reduced pressure to give the styrylcarbamate (17) (0.1 g, 23%), identical with the analysed sample (m.p., mixed m.p., and i.r. and n.m.r. spectra). (*c*) The aqueous mother liquor was basified with potassium carbonate and extracted with ethyl acetate. The solvent was removed under reduced pressure to give a solid. The solid was dissolved in methanol and treated with ethereal hydrogen chloride to afford crystalline 4-*aminomethyl*-1,4-*dihydro*-4-*phenyl*-3,1-*benzoxazin*-2-*one* (19) *hydrochloride* (0.1 g, 22%), as prisms (from methanol–ethyl acetate), m.p. 260° (Found: C, 62.1; H, 5.5; Cl, 12.0; N, 9.4. $C_{15}H_{14}N_2O_2$,HCl requires C, 62.0; H, 5.2; Cl, 12.2; N, 9.2%); $\nu_{max.}$ 3 460br, 1 705, and 1 602 cm^{-1}; τ[$(CD_3)_2SO$] −0.65 (1 H, s, 1-H), 1.50br (3 H, s, NH_3^+), 2.20—3.15 (9H, m, ArH), and 6.03 and 6.55 (2 × 1 H, 2 × d, *J* 14 Hz, CH_2). The benzoxazine (19) was also prepared by dissolving the crotonate (22) (4 g) in methanolic 0.5N-hydrochloric acid (40 ml), warming, filtering, and diluting with ethyl acetate (200 ml) to give the crystalline hydrochloride (2.5 g, 79%), identical with the analysed sample (m.p., mixed m.p., and i.r. and n.m.r. spectra).

Ethyl 3-(2-*Aminophenacylamino*)*crotonate* (20a).—A solution of 2,2′-diaminoacetophenone (5a) (5 g) in ethyl acetoacetate (10 ml) and ethyl acetate (25 ml) was boiled until a solid crystalline mass was formed. The mixture was cooled, diluted with ether, and filtered to give the *crotonate* (20a) (7.3 g, 84%), prisms (from chloroform–petroleum), m.p. 172° (decomp.) (Found: C, 63.6; H, 6.8; N, 10.9. $C_{14}H_{18}N_2O_3$ requires C, 64.1; H, 6.9; N, 10.7%); $\nu_{max.}$ 3 445, 3 335, 3 290, 1 645, 1 615, 1 590, and 1 570 cm^{-1}; τ[$(CD_3)_2SO$] 0.96 (1 H, t, *J* 5 Hz, NH), 2.10—3.60 (6 H, m, ArH and NH_2), 5.16 (2 H, d, *J* 5 Hz, phenacyl CH_2), 5.56 (1 H, s, crotonate CH), 6.01 (2 H, q, *J* 7 Hz, ethyl CH_2), 8.08 (3 H, s, crotonate CH_3), and 8.85 (3 H, t, *J* 7 Hz, ethyl CH_3).

Ethyl 3-(2-*Acetamidophenacylamino*)*crotonate* (20b).—A dry solution of the crotonate (20a) (3.5 g) in pyridine (25 ml) and benzene (25 ml) was stirred and cooled on an ice-bath while a solution of acetyl chloride (1.5 ml) in benzene (10 ml) was added. The solution was set aside overnight at room temperature, then stirred into water. The organic layer was washed well with water and evaporated to dryness under reduced pressure. Trituration of the residual oil with ether gave the crystalline *crotonate* (20b) (2.5 g, 61%), as yellow prisms (from ethyl acetate), m.p. 120° (decomp.) (Found: C, 62.8; H, 6.7; N, 9.7. $C_{16}H_{20}N_2O_4$ requires C, 63.1; H, 6.6; N, 9.2%); $\nu_{max.}$ 3 300, 1 700, 1 668, and 1 664 cm^{-1}; τ($CDCl_3$) −1.42br (1 H, s, amide NH), 0.77br (1 H, t, *J* 5.5 Hz, amine NH), 1.20 (1 H, dd, *J* 2 and 8 Hz, phenyl 6-H), 2.00—3.05 (3 H, m ArH), 5.23 (2 H, d, *J* 5.5 Hz, phenacyl CH_2), 5.39 (1 H, s, crotonate CH), 5.87 (2 H, q, *J* 7 Hz, ethyl CH_2), 7.81 and 8.06 (2 × 3 H, 2 × s, amide CH_3 and crotonate CH_3), and 8.74 (3 H, t, *J* 7 Hz, ethyl CH_3).

Ethyl 3-[β-(2-*Aminophenyl*)-β-*hydroxyphenethylamino*]*crotonate* (21).—A solution of the crotonate (20a) (6 g) in benzene (300 ml) was run into a stirred, refluxing solution of phenylmagnesium iodide [from magnesium (2.4 g) and iodobenzene (11.1 ml)] in ether (75 ml) and benzene (75 ml) at such a rate that the initial yellow precipitate redissolved. After heating for a further 3 h the mixture was stirred into aqueous N-ammonium chloride (200 ml); the organic phase was washed and evaporated under reduced pressure to give the *crotonate* (21) (4.8 g, 62%), as prisms (from ethyl acetate), m.p. 172—174° (Found: C, 71.0; H, 6.9; N, 7.9. $C_{20}H_{24}N_2O_3$ requires C, 70.6; H, 7.1; N, 8.2%); $\nu_{max.}$ 3 485, 3 385, 3 320infl, 1 624, 1 600, and 1 577 cm^{-1}; τ[$(CD_3)_2SO$] 1.20br (1 H, t, *J* 4 Hz, NH), 2.30—3.40 (9 H, m, ArH), 3.67 (1 H, s, OH), 4.81 (2 H, s, NH_2), 5.88 (1 H, s, crotonate CH), 5.65—6.05 (4 H, m, phenethyl CH_2), 8.09 (3 H, s, crotonate CH_3), and 8.63 (3 H, t, *J* 7 Hz, ethyl CH_3).

Ethyl 3-[(1,4-*Dihydro*-2-*oxo*-4-*phenyl*-2H-3,1-*benzoxazin*-4-*yl*)*methylamino*]*crotonate* (22).—A solution of the crotonate (21) (6 g) and 1,1′-carbonyldi-imidazole (3.6 g) in dry benzene (200 ml) was heated under reflux for 2 h, concentrated under reduced pressure, and allowed to cool to give the crystalline *benzoxazine* (22) (4.5 g, 70%), as prisms (from methanol–ether), m.p. 231° (Found: C, 68.6; H, 6.0; N, 7.5. $C_{21}H_{22}N_2O_4$ requires C, 68.8; H, 6.1; N, 7.7%); $\nu_{max.}$ 1 720, 1 642, 1 612, and 1 599 cm^{-1}; τ[$(CD_3)_2SO$] −0.31br (1 H, oxazine NH), 1.31 (1 H, t, *J* 5 Hz, methylamino NH), 2.10—3.20 (9 H, m, ArH), 5.65 (1 H, s, CH), 5.90 (2 H, m, methylamino CH_2), 6.12 (2 H, q, *J* 7 Hz, ethyl CH_2), 8.10 (3 H, s, crotonate CH_3), and 8.91 (3 H, t, *J* 7 Hz, ethyl CH_3).

Diethyl 2-*Aminophenacylaminomethylenemalonate* (24a).—2,2′-Diaminoacetophenone (5a) (1.5 g) and diethyl ethoxymethylenemalonate (2.2 g) were mixed in ethyl acetate (10 ml). Heat was evolved and the solution solidified. Dilution with ether enabled the *malonate* (24a) (2.8 g, 87%) to be filtered off as needles (from ethanol), m.p. 156° (Found: C, 60.4; H, 6.7; N, 9.1. $C_{16}H_{20}H_2O_5$ requires C, 60.0; H, 6.3; N, 8.7%); $\nu_{max.}$ 3 440, 3 340, 3 260, 1 680, 1 660, and 1 620br cm^{-1}; τ($CDCl_3$) 0.0—0.5br (1 H, NH), 1.87—3.38 (5 H, m, ArH and CH), 3.60br (2 H, NH_2), 5.26 (2 H, d, *J* 4.5 Hz, CH_2), 5.72 and 5.83 (2 × 2 H, 2 × q, *J* 7 Hz, 2 × ethyl CH_2), and 8.65 and 8.73 (2 × 3 H, 2 × t, *J* 7 Hz, 2 × ethyl CH_3).

2-*Aminophenacylaminomethylenemalononitrile* (24b).—2,2′-Diaminoacetophenone (5a) (1.5 g) and ethoxymethylenemalononitrile (1.3 g) were heated with ethyl acetate (2 ml) on a water-bath until the solution solidified. Dilution with ethanol enabled the *malononitrile* (24b) (2 g, 88.5%) to be filtered off as prisms (from ethanol), m.p. 200° (decomp.)

(Found: C, 63.5; H, 4.5; N, 24.5. $C_{12}H_{10}N_4O$ requires C, 63.7; H, 4.5; N, 24.8%); $\nu_{max.}$ 3 485, 3 335, 3 295, 2 200, 2 185, 1 640br, and 1 605 cm^{-1}; τ[$(CD_3)_2CO$] 2.10—3.55 (8 H, m, ArH, CH, NH and NH_2) and 5.02 (2 H, s, CH_2).

Ethyl 4-(2-*Acetamidophenyl*)-2-*methylpyrrole*-3-*carboxylate* (25).—A solution of the crotonate (20b) (0.5 g) in glacial acetic acid (2 ml) was heated under reflux for 1 h, cooled, and diluted with ether to give the crystalline *ester* (25) (0.24 g, 51%), as prisms (from chloroform–petroleum), m.p. 86° (remelts 165°) (Found: C, 66.7; H, 6.2. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3%); $\nu_{max.}$ 3 370, 3 250, 3 190, 3 095, 1 680infl, and 1 650 cm^{-1}; τ($CDCl_3$) 0.30br (1 H, pyrrole NH), 1.80—2.10 (1 H, m, phenyl 6-H), 2.19 (1 H, s, acetamide NH), 2.50—3.00 (3 H, m, ArH), 3.64 (1 H, d, *J* 3 Hz, pyrrole 5-H), 5.92 (2 H, q, *J* 7 Hz, ethyl CH_2), 7.53 (3 H, s, pyrrole 2-CH_3), 8.02 (3 H, s, acetamide CH_3), and 8.93 (3 H, t, *J* 7 Hz, ethyl CH_3).

Reaction of 2,2′-*Diaminoacetophenone with Triethyl Orthoacetate*.—A solution of the diamine (5a) (1.6 g) and triethyl orthoacetate (1.8 g) in ethanol (60 ml) was heated under reflux for 2 days and then evaporated to dryness under reduced pressure. The residue was dissolved in 5.5N-hydrochloric acid (20 ml) and washed with chloroform. The aqueous phase was basified with potassium carbonate and extracted with chloroform, and the solvent was removed under reduced pressure. Trituration of the residue with ether gave 8-aminomethyl-6-methyl-5*H*-quinolino[3,2-*d*][1,3]-benzodiazepine (26) (0.9 g, 62%), yellow crystals (from ethyl acetate), m.p. 230—240° (decomp.), *m/e* 288 (M^+, 100%) and 287 ($M - 1$, 80); $\nu_{max.}$ 3 405, 3 380, 3 315, 1 625, and 1 610 cm^{-1}; τ($CDCl_3$) 1.90—3.30 (8 H, m, ArH), 2.00—5.00br (3 H, 3 × NH), 4.88 (2 H, s, CH_2), and 8.00 (3 H, s, CH_3).

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