Some Basic and Acidic Derivatives of 2,5-Dihydro-1*H*-1-Benzazepine as Potential Therapeutic Agents

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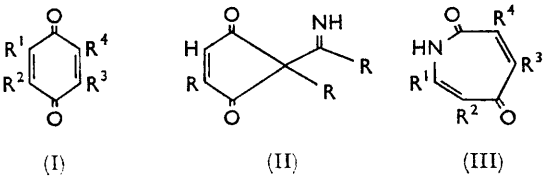
Degradative and spectroscopic evidence confirmed that the Schmidt reaction for naphthoquinones gave mainly 2,5-dioxo-2,5-dihydro-1*H*-1-benzazepines. Basic and acidic derivatives containing this ring system were prepared for evaluation as potential therapeutic agents.

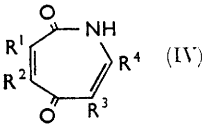
THE reaction of 2,5-dialkylbenzoquinones with sodium azide in concentrated sulphuric acid solution at 40—50° was first described by Caronna [1,2] who assigned to the products imidic structures (II). The reaction of quinones (Ia)—(Ie) with sodium azide as described by Folkers and his co-workers,[3,4] presented a direct method of obtaining the previously inaccessible 2,5-dioxo-2,5-dihydro-1*H*-azepines, which encouraged the investigation of the properties of some derivatives of this ring system as potential therapeutic agents. Folkers and his co-workers formulated their products as azepinediones (IIIa)—(IIIe), mainly on the basis of n.m.r. spectral data. They argued that, since the N*H* proton was demonstrably coupled to an olefinic proton, these two groups must be adjacent. Rickards and Smith [5] and Bedford *et al.*[6] revised the azepinedione structures (IIIa)—(IIIe) to (IVa)—(IVe), in which the amidic nitrogen is separated from the olefinic proton by a carbonyl group and the coupling observed by Folkers and his co-workers was thus of the cross-carbonyl type.[7] The Schmidt reaction for quinones thus proceeds predominantly at the less hindered carbonyl group, with the larger alkyl group migrating preferentially.

From the reaction of various naphthoquinones [(Ie) at 0°; (If)—(Ih) at 25°] with the same reagents, the 2,5-dioxo-2,5-dihydro-1*H*-1-benzazepines (IVe)—(IVh) have been isolated, by fractional crystallisation, as the major reaction products. The structures of these compounds are based on the following considerations.

All the benzazepinediones (IVe)—(IVh) showed similar ultraviolet absorption spectra and were therefore members of the same structural series. The mass spectra of the benzazepinediones (IVe)—(IVf) were of no assistance in ascertaining the point of insertion of the NH



(I) (II) (III)



(IV)

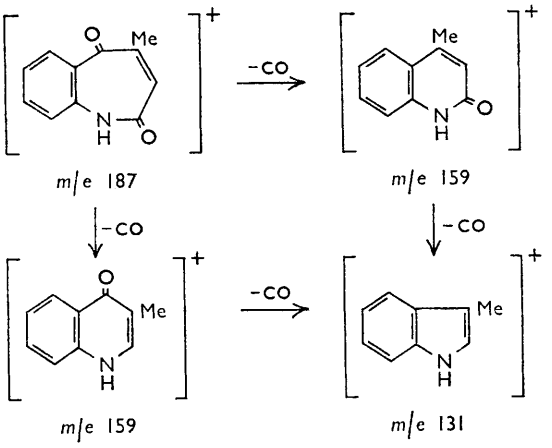
	R^1	R^2	R^3	R^4
a;	H	Me	H	Me
b;	H	Pr^i	H	Me
c;	H	Me	Me	Me
d;	Me	Me	Me	Me

	R_1	R_2	R_3 R_4
e;	H	Me	Benzo
f;	H	Cl	,,
g;	Cl	Cl	,,
h;	Cl	Br	,,

group. They were characterised by successive loss of carbon monoxide giving rise to substituted indoles, the spectra of which were then found to agree with published information (see Scheme).[8] Acid hydrolysis of (IVe) resulted in the isolation in good yield of 4-acetyl-2-hydroxyquinoline (V) the identity of which was confirmed by direct comparison with an authentic sample prepared by the method of Ochiai.[9] A similar rearrangement in alkaline solution has been observed by Rees.[10] The

[1] G. Caronna, *Gazzetta*, 1945, **75**, 91.
[2] G. Caronna and S. Palazzo, *Gazzetta*, 1953, **83**, 315.
[3] D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Letters*, 1965, **16**, 1071.
[4] D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron*, 1966, **22**, 1201.
[5] R. W. Rickards and R. M. Smith, *Tetrahedron Letters*, 1966, **22**, 2361.
[6] G. R. Bedford, G. Jones, and B. R. Webster, *Tetrahedron Letters*, 1966, **22**, 2367.
[7] A. Berger, A. Loewenstein, and S. Meiboom, *J. Amer. Chem. Soc.*, 1959, **81**, 62.
[8] H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, New York, 1964, and references cited therein.
[9] E. Ochiai, M. Takahashi, Y. Tamai, and K. Kataoka, *Chem. Pharm. Bull. (Tokyo)*, 1963, **11**, 137.
[10] A. H. Rees, *J. Chem. Soc.*, 1959, 3111.

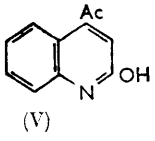
isolation of 4-acetyl-2-hydroxyquinoline (V) thus located the nitrogen atom as being adjacent to the benzene ring.



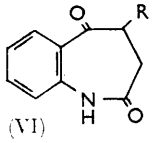
SCHEME

Catalytic reduction of (IVe) over palladium–carbon gave a dihydro-derivative (VIa), whilst both the chloro-substituted benzazepinediones (IVf) and (IVg) gave (VIb). The ultraviolet spectra of these reduced benzazepinediones closely resembled that of *o*-*N*-acetylaminoacetophenone,[11] thus confirming the position of insertion of the NH group. The base peak in the mass spectra of the reduced benzazepinediones (VIa) and (VIb) occurred at *m/e* 120 and was formed in both cases, at least partially, by the direct decomposition of the molecular ion [*m** 76·2 for (VIa) and *m** 82·3 for (VIb)]. This main fragment ion *m/e* 120 $(C_7H_6NO)^+$ decomposed further by an initial loss of 28 mass units (*m** 70·5) followed by a further sequential loss of 27 mass units (HCN, *m** 45·9) giving an ion *m/e* 65, which was probably the cyclopentadienyl cation. All the major fragments above 92 mass units contained a nitrogen atom, consistent with the formulation of (VIa) and (VIb) as 2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepines.

Alkylation of the sodium salt of (IVe) with methyl iodide at room temperature gave an *N*-methyl derivative.



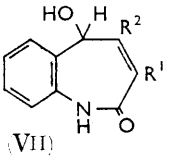
(V)



(VI)

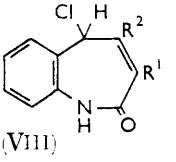
a; R = Me
b; R = H

In order to exploit any biological activity inherent in this novel ring system, methods were sought to introduce basic and acidic substituents. For example, nucleophilic substitution of a benzylic halogen atom at position 5 appeared to be an attractive method. Sodium borohydride reduction of the 2,5-dioxo-2,5-dihydro-1*H*-1-benzazepines (IVe)—(IVg) at 0° gave 5-hydroxy-2-oxo-2,5-dihydro-1*H*-1-benzazepines (VIIa)—(VIIc), which were then treated in chloroform suspension with thionyl chloride to yield 5-chloro-2-oxo-2,5-dihydro-1*H*-1-benzazepines (VIIIa)—(VIIIc). No satisfactory method for purifying these products could be found. The crude material was therefore used directly in reactions with nucleophiles.



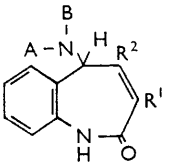
(VII)

	R^1	R^2
a;	H	Me
b;	H	Cl
c;	Cl	Cl

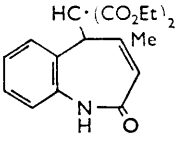


(VIII)

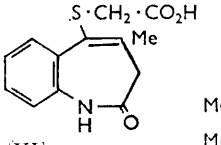
	R^1	R^2	A–N–B
a;	H	Me	$-NMe_2$
b;	H	Me	$-NEt_2$
c;	H	Me	–N⟨ ⟩
d;	H	Me	–N⟨ ⟩
e;	H	Me	–N⟨ ⟩O
f;	H	Me	–N⟨ ⟩NMe
g;	H	Cl	–N⟨ ⟩
h;	Cl	Cl	–N⟨ ⟩
i;	Cl	Cl	–N⟨ ⟩O
j;	Cl	Cl	–N⟨ ⟩NMe



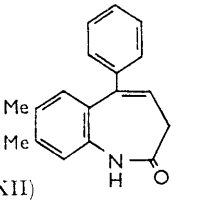
(IX)



(X)



(XI)



(XII)

The substitution reactions were carried out in dimethylformamide and a variety of basic (IXa)—(IXj), neutral (X), and acidic (XI) products was isolated. Some of the basic derivatives [*e.g.*, (IXa)—(IXj)] were moderately effective in controlling electrically induced convulsions in mice ($ED_{50} \sim 100$ mg./kg.) and showed considerable anti-inflammatory activity.

All the basically substituted benzazepinones (IXa)—(IXj) showed similar infrared absorption, the amide band falling consistently between 1680—1660 cm.$^{-1}$, with the dichloro-derivatives absorbing near lower value. Their n.m.r. spectra were complicated by long-range interactions of the allylic (–C*H*=C–C*H*–) and cross-carbonyl (=C*H*–CON*H*–) type. The coupling constant linking the olefinic and benzylic protons fell in the range 1·5—2·0 c./sec. A coupling of this magnitude was more likely for allylic protons (J = 0·5—2 c./sec.)

[11] P. Gammaticakis, *Bull. Soc. chim. France*, 1953, 93.

than for vicinal protons (J = 4—10 c./sec.), thus confirming that in the Schmidt reaction the quinone ring has been enlarged at the more basic, less hindered carbonyl group. The addition of deuterium oxide to solutions of the compounds, or alternatively decoupling at the N*H* resonant frequency, simplified the olefinic multiplets to patterns expected for allylically coupled protons.

The reaction of 5-chloro-4-methyl-2-oxo-2,5-dihydro-1*H*-1-benzazepine (VIIIa) with thioglycollic acid gave an anomalous product which on the basis of spectroscopic results is best formulated as (XI) in which the double-bond has migrated to the 4,5 position. The mass spectrum was characterised by the loss of 42 mass units (*m** 185·7) followed by a loss of 59 mass units (*m** 118·8). Accurate mass measurements showed these to be losses of CH_2=CO and $-CH_2CO_2H$. The n.m.r. spectrum showed no absorption in the olefinic region and was characterised by a singlet (2H) at τ 6·95 ($-S-CH_2COO^-$) and an AB pattern (2H) centred at τ 7·3 ($-CO-CH_2C=$).

The mass spectrum of 7,8-dimethyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1-benzazepine (XII) † prepared by intramolecular acylation of the aromatic amine showed an analogous loss of 42 mass units (CH_2=CO) on electron bombardment. The loss of 42 mass units thus appears to be a characteristic of 2-oxo-2,3-dihydro-1*H*-1-benzazepines.

EXPERIMENTAL

Melting points were determined in capillary tubes. Ultraviolet spectra were measured for methanol solutions on a Bausch and Lomb, 505 spectrophotometer. Nuclear magnetic resonance spectra were determined for deuteriochloroform solutions using tetramethylsilane as an internal standard on a Varian model A-60 instrument. Decoupling experiments were carried out using a Varian model H.A. 100 spectrometer. Infrared spectra were recorded for Nujol mulls on a Perkin-Elmer model 21 spectrophotometer. Mass spectra were measured using an A.E.I., model MS 9 spectrometer.

*Synthesis of 2,5-Dioxo-2,5-dihydro-*1H*-1-benzazepines.*—To a solution of the naphthaquinone (100 g.) in concentrated sulphuric acid (500 ml.) at 0° sodium azide (1 mole) was added in small portions. The solution was stirred at this temperature until no more nitrogen was evolved (2—3 days). The mixture was poured on crushed ice (2 kg.) and the precipitated product filtered off and washed with water. If after addition of the sodium azide no nitrogen was evolved at 0°, the mixture was allowed to warm to room temperature (25°) and stirred until nitrogen evolution was complete at this temperature.

*4-Methyl-2,5-dioxo-2,5-dihydro-*1H*-1-benzazepine* (IVe). This was prepared from the naphthoquinone (Ie) at 0°. Crystallisation (×2) from aqueous ethanol gave the 1*H*-1-benzazepine (IVe) (50%) as a crystalline solid, m. p. 200—202° (Found: N, 7·5. Calc. for $C_{11}H_9NO_2$: N, 7·5%), $\nu_{max.}$ 3175, 3125, 1675 (NHCO), 1653 (αβ-unsaturated carbonyl), 1621, 1600, and 1577 cm.$^{-1}$; $\lambda_{max.}$ 235, 275, and 348 mμ (log ε 4·26, 3·91, and 3·33); τ −0·6 (1H, broad N*H*), 1·94—2·94 (4H, complex, Ar*H*), 3·19 (1H, multiplet, =C*H*), and 7·75 (3H, doublet, =C−CH_3). The peaks of greatest diagnostic value in the mass spectrum were found at *m/e* 187 (61%) (M^+ calc. for $C_{11}H_9NO_2$: 187), 159 (91%) (*m** 135·1), 158 (40%), 131 (54%) (*m** 107·8), 130 (100%) (*m** 129·2), 103 (13%) (*m** 81·6), 92 (35%), 77 (15%), 68 (16%), 65 (31%), 63 (39%), and 51 (16%).

*4-Chloro-2,5-dioxo-2,5-dihydro-*1H*-1-benzazepine* (IVf). This was prepared from the naphthoquinone (If) at room temperature. Crystallisation (×3) from aqueous ethanol gave the 1H-1-*benzazepine* (IVf) as yellow plates (22%), m. p. 205—206° (Found: C, 58·0; H, 2·8; Cl, 17·1; N, 6·4. $C_{10}H_6ClNO_2$ requires C, 57·8; H, 2·9; Cl, 17·1; N, 6·7%), $\nu_{max.}$ 3155, 3077, 1658 (NHCO), 1634 (αβ-unsaturated carbonyl), 1600, and 1562 cm.$^{-1}$; $\lambda_{max.}$ 242, 281, and 357 mμ (log ε 4·26, 3·91, and 3·32). The peaks of greatest diagnostic value in the mass spectrum were found at *m/e* 207 (17%) ($C_{10}H_6ClNO_2$ requires M^+, 207), 179 (16%), 172 (100%) (*m** 142·8), 153 (23%), 151 (75%), 144 (26%) (*m** 120·5), 124 (14%) (*m** 101·8), 116 (48%) (*m** 93·4), 92 (30%), 89 (90%) (*m** 68·3), 76 (17%), 64 (46%), 63 (66%), 53 (26%), and 50 (29%).

*3,4-Dichloro-2-5-dioxo-2,5-dihydro-*1H*-1-benzazepine* (IVg). This was prepared from the naphthoquinone (Ig) at room temperature. Crystallisation (×2) from acetone gave the 1H-1-*benzazepine* (IVg) as yellow needles (49%), m. p. 260—262° (Found: C, 49·6; H, 2·2; Cl, 29·0; N, 5·6. $C_{10}H_5Cl_2NO_2$ requires C, 49·5; H, 2·1; Cl, 29·3; N, 5·8%); $\nu_{max.}$ 3185, 1666 (NHCO), 1605, 1592, and 1562 cm.$^{-1}$; $\lambda_{max.}$ 249, 274, and 350 mμ (log ε 4·21, 4·08, and 3·23).

*4-Bromo-3-chloro-2,5-dioxo-2,5-dihydro-*1H*-1-benzazepine* (IVh). This was prepared from the naphthoquinone (Ih) at room temperature. Crystallisation (×3) from acetone gave the 1H-1-*benzazepine* (IVh) as a yellow crystalline solid (12%), m. p. 282—284° (decomp.) (Found: C, 41·7; H, 1·8; N, 4·6. $C_{10}H_5BrClNO_2$ requires C, 41·9; H, 1·75; N, 4·9%), $\nu_{max.}$ 3175, 1675, 1658 (broad), 1600, 1585, and 1553 cm.$^{-1}$; $\lambda_{max.}$ 248, 278, and 348 (log ε 4·10, 4·04, and 3·23).

*4-Methyl-2,5-dioxo-2,3,4,5-tetrahydro-*1H*-1-benzazepine* (VIa).—A solution of the 1*H*-1-benzazepine (IVe) (0·6 g.) in chloroform (25 ml.) was hydrogenated at s.t.p. using 5% palladium–carbon (0·3 g.) as catalyst. Crystallisation of the crude product from isopropyl alcohol–light petroleum (b. p. 60—80°) gave the 1H-1-*benzazepine* (VIa) (0·35 g.) as colourless needles, m. p. 149—150° (Found: C, 69·8; H, 5·8; N, 7·6. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%), $\nu_{max.}$ 3205, 3115, 1667, 1603, and 1580 cm.$^{-1}$; $\lambda_{max.}$ (ethanol) 229, 265, and 317 mμ (log ε 4·47, 3·88, and 3·43); τ 0·7 (1H, broad, N*H*), 2·0 (1H, doublet of doublets, J = 7·5 and 2·2 c./sec., Ar*H*), 2·3—3·1 (3H, complex, Ar*H*), 6·8—7·3 (3H, complex, CO−C*H*−), and 8·62 (3H, doublet, J = 6·5 c./sec., =C−CH_3). The peaks of greatest diagnostic value in the mass spectrum occurred at *m/e* 189 (75%) ($C_{11}H_{11}NO_2$ requires M^+ 189), 174 (50%), 161 (10%) (*m** 137·1), 160 (15%), 146 (23%) (*m** 122·5), 121 (16%), 120 (100%) (*m** 76·2), 119 (53%), 92 (63%) (*m** 70·5), 91 (19%), 90 (18%), 69 (23%), and 65 (20%) (*m** 45·9).

*2,5-Dioxo-2,3,4,5-tetrahydro-*1H*-1-benzazepine* (VIb).—(*a*) A solution of the 1*H*-1-benzazepine (IVg) (1 g.) in acetic acid (100 ml.) was hydrogenated at s.t.p. using 5% palladium–carbon (0·5 g.) as catalyst. Crystallisation (×2) of the crude product from ethanol gave the 1H-1-*benzazepine* (VIb) (0·2 g.) as needles, m. p. 191—192° (Found: C, 68·6;

† This compound was kindly supplied by Dr. R. F. Maisey of these laboratories.

H, 5·35; N, 8·0. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%), $\nu_{max.}$ 3240, 3150, 1660, and 1570 cm.$^{-1}$; $\lambda_{max.}$ 228, 254, and 315 mμ (log ε 4·11, 3·90, and 3·47); τ 1·0 (1H, broad, N*H*), 2·02 (1H, doublet of doublets, J = 8 and 2 c./sec., Ar*H*), 2·3—3·15 (3H, complex, Ar*H*), and 6·8—7·4 (4H, complex, $COCH_2$–CH_2CO). The peaks of the greatest diagnostic value in the mass spectrum occurred at *m/e* 175 (66%) ($C_{10}H_9NO_2$ requires M^+ 175), 147 (15%) (*m** 123·5), 146 (32%) (*m** 145·0), 121 (11%), 120 (100%) (*m** 82·3), 119 (15%), 92 (38%) (*m** 70·5), 77 (4%), 65 (17%) (*m** 45·9), and 55 (9%).

(*b*) A solution of the 1*H*-1-benzazepine (IVf) (1 g.) in acetic acid (100 ml.) was hydrogenated at s.t.p. using 5% palladium–carbon (0·5 g.) as catalyst. Crystallisation (×2) of the crude product from ethanol gave the 1*H*-1-benzazepine (VIb) (0·2 g.) as needles, m. p. 191—192°. This product was identical in all respects with the product obtained in (*a*).

Hydrolysis of 4-*Methyl*-2,5-*dioxo*-2,5-*dihydro*-1H-1-*benzazepine* (IVe).—The 1*H*-1-benzazepine (IVe) (1 g.), ethanol (15 ml.), water (30 ml.), and conc. hydrochloric acid (15 ml.) were heated on a water-bath until a clear solution was obtained (2 hr.). The solution was neutralised (pH 7) with sodium hydroxide solution and extracted with chloroform (2 × 75 ml.). The chloroform solution was dried ($MgSO_4$) and the solvent removed (0·65 g.). Crystallisation from benzene–light petroleum (b. p. 60—80°) gave *compound* (V) as needles (0·35 g.), m. p. 191—193° (Found: C, 70·7; H, 4·8; N, 7·5. $C_{11}H_9NO_2$ requires C, 70·6; H, 4·8; N, 7·5%), $\nu_{max.}$ 1675 (sh) and 1660 cm.$^{-1}$; $\lambda_{max.}$ 231, 280, and 341 (log ε 4·37, 3·67, and 3·68); τ −2·65 (1H, broad, N*H*), 1·98 (1H, doublet, J = 8 c./sec. Ar*H*), 2·3—2·84 (3H, complex, Ar*H*), 3·04 (1H, singlet, =C*H*), and 7·32 (3H, singlet, CH_3CO–). The peaks of greatest diagnostic value in the mass spectrum were found at *m/e* 187 (100%) ($C_{11}H_9NO_2$ requires M^+, 187), 172 (42%) (*m** 158·2), 145 (33%), 144 (29%) (*m** 120·6), 117 (12%), 116 (44%) (*m** 93·5), 107 (30%), 90 (90%), 89 (21%) (*m** 68·3), 75 (8%), 63 (12%), 51 (8%), and 43 (52%). Mixed m. p. determinations and comparison of n.m.r. i.r., u.v., and mass spectra established that this compound was identical with 4-acetyl-2-hydroxyquinoline prepared from 4-acetylquinoline *N*-oxide by Ochiai's method.[9]

5-*Hydroxy*-4-*methyl*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (VIIa).—The 1*H*-1-benzazepine (IVe) (2 g.) was suspended in methanol (20 ml.) at 0° and treated with sodium borohydride (0·5 g.). The mixture was stirred at 0° for 1 hr.; acidification with dilute hydrochloric acid gave the 1H-1-*benzazepine* (VIIa) as rods, m. p. 221—223° (Found: C, 70·0; H, 5·9; N, 7·4. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%), $\nu_{max.}$ 3240 (OH), 3100 (NH), 1648, 1600, and 1570 cm.$^{-1}$.

4-*Chloro*-5-*hydroxy*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (VIIb).—The 1*H*-1-benzazepine (IVf) (7·9 g.) was suspended in methanol (100 ml.) at 0° and treated with sodium borohydride (2·2 g.). The mixture was stirred at 0° for 1 hr., acidified with dilute hydrochloric acid, and the resulting solid (5·1 g.) crystallised from ethanol–light petroleum (b. p. 60—80°) to give the 1H-1-*benzazepine* (VIIb) as rhombs, m. p. 185—188° (decomp.) (Found: C, 57·15; H, 4·1; Cl, 17·1; N, 6·7. $C_{10}H_8ClNO_2$ requires C, 57·3; H, 3·85; Cl, 16·9; N, 6·7%), $\nu_{max.}$ 3350, 1660, 1640, and 1575 cm.$^{-1}$.

3,4-*Dichloro*-5-*hydroxy*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (VIIc).—The 1*H*-1-benzazepine (IVg) (2 g.) was suspended in methanol (50 ml.) at 0° and treated with sodium borohydride (0·64 g.). The mixture was stirred at 0° for 1 hr., acidified with dilute hydrochloric acid, and the resulting solid (1·8 g.) crystallised from isopropyl alcohol–light petroleum (b. p. 60—80°) to give the 1H-1-*benzazepine* (VIIc), m. p. 183—186° (decomp.) (Found: C, 49·3; H, 2·9; N, 5·4. $C_{10}H_7Cl_2NO_2$ requires C, 49·2; H, 2·9; N, 5·7%), $\nu_{max.}$ 3370, 3150, 1660, 1640, and 1580 cm.$^{-1}$.

5-*Chloro*-4-*methyl*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (VIIIa).—The 1*H*-1-benzazepine (VIIa) (1 g.) was suspended in chloroform (25 ml.) and treated with thionyl chloride (0·7 ml.). The resulting solution was heated under reflux for 5 min. and the solvent removed leaving the crude 1*H*-1-benzazepine (VIIIa) as a solid, m. p. 130—132°. The infrared spectrum showed no band at 3240 (OH) cm.$^{-1}$, and as decomposition was encountered during crystallisation the compound was not characterised further, $\nu_{max.}$ 3140, 1670, 1660, and 1570 cm.$^{-1}$.

4,5-*Dichloro*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (VIIIb).—A suspension of the 1*H*-1-benzazepine (VIIb) (0·5 g.) in chloroform (25 ml.) was cooled to −5° and treated with thionyl chloride (0·4 ml.). Removal of the solvent, keeping the bath temperature below 20°, gave the crude 1*H*-1-benzazepine (VIIIb) as a white solid (0·5 g.). The infrared spectrum confirmed the disappearance of a band at 3350 cm.$^{-1}$ present in the starting material. The material was not characterised further owing to its labile nature.

3,4,5-*Trichloro*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (VIIIc).—The 1*H*-1-benzazepine (VIIc) (10·5 g.) was suspended in chloroform (250 ml.) and treated with thionyl chloride (22 ml.). The solution was heated under reflux (7 hr.), treated with a further quantity of thionyl chloride (11 ml.), and heating under reflux continued until a clear solution was obtained (4 hr.). Removal of the solvent gave the crude 1*H*-1-benzazepine (VIIIc) (11·4 g.) as a yellow solid. The infrared spectrum showed no band at 3370 (OH) cm.$^{-1}$ and as decomposition was encountered during crystallisation the compound was not further characterised.

Nucleophilic Substitution Reactions of 5-*Chloro*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (VIII).—A solution of the 1*H*-1-benzazepines (VIII) (2 g.) in dimethylformamide (50 ml.) was treated with the appropriate amine (5 mol.) and the solution heated. The dimethylformamide was removed, the residue dissolved in dilute hydrochloric acid (5N; 100 ml.) and extracted with chloroform (100 ml.). Basification (pH > 10) of the residual aqueous solution and extraction with chloroform (2 × 100 ml.) gave the crude product usually as a white solid.

5-*Dimethylamino*-4-*methyl*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (IXa). This was prepared from the 1*H*-1-benzazepine (VIIIa) (153° for 30 min.). Crystallisation from acetone gave the 1H-1-*benzazepine* (IXa) as colourless needles (67%), m. p. 226—227° (Found: C, 72·1; H, 7·3; N, 12·8. $C_{13}H_{16}N_2O$ requires C, 72·2; H, 7·5; N, 12·95%), $\nu_{max.}$ 3145, 2750, 1675 (NHCO), 1629, and 1585 cm.$^{-1}$; τ 2·5—3·0 (4H, complex, Ar*H*), 4·12 (1H, multiplet, =C*H*), 6·79 (1H, doublet, J = 1·6 c./sec., ArC*H*<), 7·91 (singlet, N–CH_3), and 7·98 (doublet, –C–CH_3) (9H).

5-*Diethylamino*-4-*methyl*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (IXb). This was prepared from the 1*H*-1-benzazepine (VIIIa) (153° for 30 min.). Crystallisation from light petroleum (b. p. 80—100°) gave the crystalline 1H-1-*benzazepine* (68%), m. p. 124—127° (Found: C, 73·5; H, 8·4; N, 11·8. $C_{15}H_{20}N_2O$ requires C, 73·7; H, 8·25; N,

11·5%), $\nu_{max.}$ 3175, 2762, 1686 (NHCO), 1634, and 1587 cm.$^{-1}$; τ 0·64 (1H, broad, N*H*), 2·65—3·0 (4H, complex, Ar*H*), 4·22 (1H, multiplet, =C*H*), 6·16 (1H, doublet, J = 1·5 c./sec., ArC*H*<), 7·58 (4H, quartet, N–CH_2–CH$_3$), 7·98 (3H, doublet, J = 1·6 c./sec., =C–CH_3), and 9·17 (6H, triplet, N–CH$_2$–CH_3).

4-*Methyl*-2-*oxo*-5-*piperidino*-2,5-*dihydro*-1H-1-*benzazepine* (IXd). This was prepared from the 1*H*-1-benzazepine (VIIIa) (153° for 30 min.). Crystallisation from toluene gave the 1H-1-*benzazepine* (IXd) (49%) as a crystalline solid m. p. 214—216° (Found: C, 74·8; H, 9·0; N, 10·6. $C_{16}H_{20}N_2O$ requires C, 74·9; H, 7·9; N, 10·9%), $\nu_{max.}$ 3135, 2778, 2740, 1675 (NHCO), 1626, and 1582 cm.$^{-1}$; τ 0·28 (1H, broad, N*H*), 2·65—3·0 (4H, complex, Ar*H*), 4·21 (1H, multiplet =C*H*), 6·67 (1H, doublet, J = 1·5 c./sec., ArCH<), 7·8 (4H, complex, N–CH_2–), 7·98 (3H, doublet, J = 1·6 c./sec., =C–CH_3), and 8·64 (6H, complex, –CH_2–CH_2–CH_2–).

4-*Methyl*-5-*morpholino*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (IXc). This was prepared from the 1*H*-1-benzazepine (VIIIa) (153° for 30 min.). Crystallisation from aqueous acetone gave the 1H-1-*benzazepine* (IXe) (80%) as a crystalline solid, m. p. 194—196° (Found: C, 69·6; H, 7·0; N, 10·9. $C_{15}H_{18}N_2O_2$ requires C, 69·7; H, 7·0; N, 10·85%), $\nu_{max.}$ 3236, 1672 (NHCO), 1626, and 1582 cm.$^{-1}$; τ 0·28 (1H, broad, N*H*), 2·65—3·0 (4H, complex, Ar*H*), 4·11 (1H, multiplet, =C*H*), 6·43 (4H, triplet, O–CH_2–), 6·56 (1H, doublet, J = 1·8 c./sec., ArC*H*<), 7·70 (4H, complex, –N–CH_2–), and 7·95 (3H, doublet, J = 1·6 c./sec., =C–CH_3).

4-*Methyl*-2-*oxo*-5-*pyrrolidino*-2,5-*dihydro*-1H-1-*benzazepine* (IXc). This was prepared from the 1*H*-1-benzazepine (VIIIa) (153° for 30 min.). Crystallisation from acetone gave the 1H-1-*benzazepine* (IXc) (51%) as a crystalline solid m. p. 242—243° (Found: C, 74·6; H, 7·2; N, 11·8. $C_{15}H_{18}N_2O$ requires C, 74·35; H, 7·5; N, 11·6%), $\nu_{max.}$ 3125, 1666 (NHCO), 1618, and 1575 cm.$^{-1}$; τ 0·6 (1H, broad, N*H*), 2·54—3·1 (4H, complex, Ar*H*), 4·20 (1H, multiplet, =C*H*), 6·60 (1H, doublet, J = 1·5 c./sec., ArC*H*<), 7·3—8·0 (4H, multiplet, –CH_2–N), 7·97 (3H, doublet, J = 1·6 c./sec., =C–CH_3), and 8·2—8·5 (4H, multiplet, –CH_2–CH_2–).

4-*Methyl*-5-(4-*methylpiperazino*)-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (IXf). This compound was prepared from the 1*H*-1-benzazepine (VIIIa) (153° for 30 min.). Crystallisation from light petroleum (b. p. 100—120°) gave the 1H-1-*benzazepine* (IXf) (62%) as a crystalline solid, m. p. 189—191° (Found: C, 70·7; H, 8·1; N, 15·6. $C_{16}H_{21}N_3O$ requires C, 70·8; H, 7·8; N, 15·5%), $\nu_{max.}$ 3125, 2778, 2740, 1675 (NHCO), 1626, and 1582 cm.$^{-1}$; τ 0·52 (1H, broad, N*H*), 2·6—3·0 (4H, complex, Ar*H*), 4·18 (1H, multiplet, =C*H*), 6·10 (1H, doublet, J = 1·5 c./sec., ArC*H*<), 7·35—7·8 (8H, complex, N–CH_2–CH_2–N), 7·82 (3H, singlet, N–CH_3), and 7·96 (3H, doublet, J = 1·6 c./sec., =C–CH_3).

4-*Chloro*-2-*oxo*-5-*piperidino*-2,5-*dihydro*-1H-1-*benzazepine* (IXg). This was prepared from the 1*H*-1-benzazepine (VIIIb) (153° for 30 min.). Chromatography on neutral alumina (Woelm) and crystallisation from light petroleum (b. p. 100—120°) gave the 1H-1-*benzazepine* (IXg), m. p. 182—183° (Found: C, 65·2; H, 6·3; Cl, 12·4; N, 10·3. $C_{15}H_{17}ClN_2O$ requires C, 65·1; H, 6·1; Cl, 12·8; N, 10·1%), $\nu_{max.}$ 3175, 2770, 2720, 1667, 1625, and 1580 cm.$^{-1}$; τ 0·08 (1H, broad, N*H*), 2·6—3·0 (4H, complex, Ar*H*), 3·8 (1H, quartet, C*H*), 6·20 (1H, doublet, J = 2·0 c./sec., ArC*H*<), 7·4—8·1 (4H, complex, N–CH_2–), and 8·58 (6H, complex, –CH_2–CH_2–CH_2–).

3,4-*Dichloro*-5-*morpholino*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (IXi). This compound was prepared from the 1*H*-1-benzazepine (VIIIc) (100° for 1 hr.). Crystallisation (×2) from light petroleum (b. p. 100—120°) gave the 1H-1-*benzazepine* (IXi) as a solid, m. p. 202—204° (Found: C, 54·0; H, 4·3; N, 9·1. $C_{14}H_{14}Cl_2N_2O_2$ requires C, 53·7; H, 4·5; N, 8·9%), $\nu_{max.}$ 3170, 1660, 1600, and 1590 cm.$^{-1}$; τ 0·02 (1H, broad, –N*H*), 2·5—2·92 (4H, complex, Ar*H*), 6·00 (1H, singlet, ArC*H*<), 6·41 (4H, triplet, –CH_2–O–CH_2), and 7·32—8·10 (4H, multiplet, –CH_2–N–CH_2–).

3,4-*Dichloro*-2-*oxo*-5-*piperidino*-2,5-*dihydro*-1H-1-*benzazepine* (IXh). This was prepared from the 1*H*-1-benzazepine (VIIIc) (100° for 1 hr.). Crystallisation (×2)from light petroleum (b. p. 100—120°) gave 1H-1-*benzazepine* (IXh) (36%) as a crystalline solid, m. p. 202—204° (decomp.) (Found: C, 58·2; H, 5·2; N, 8·7. $C_{15}H_{16}Cl_2N_2O$ requires C, 57·9; H, 5·1; N, 9·0%), $\nu_{max.}$ 3175, 3125(sh), 2778, 2740, 1658, 1603 and 1587, cm.$^{-1}$; τ –0·04 (1H, broad, N*H*), 2·40—2·90 (4H, complex, Ar*H*), 6·06 (1H, singlet, ArC*H*<), 7·35—8·1 (4H, complex, N–CH_2–), and 8·60 (6H, complex, –CH_2–CH_2–CH_2–).

3,4-*Dichloro*-5-(4-*methylpiperazino*)-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (IXj). This compound was prepared from the 1*H*-1-benzazepine (VIIIc) (100° for 1 hr.). Crystallisation (×2) from light petroleum (b. p. 100—120°) gave the 1H-1-*benzazepine* (IXj) (42%) as a crystalline solid, m. p. 191—192 (Found: C, 55·0; H, 5·4; N, 13·1. $C_{15}H_{17}Cl_2N_3O$ requires C, 55·3; H, 5·25; N, 12·9%), $\nu_{max.}$ 1666, 1645, 1610, and 1585 cm.$^{-1}$; τ 0·61 (1H, broad, N*H*), 2·6—2·85 (4H, complex, Ar*H*), 6·04 (1H, singlet, ArC*H*<), 7·5—7·8 (8H, complex, N–CH_2–CH_2–N), and 7·81 (3H, singlet, N–CH_3).

5-*Bis*(*ethoxycarbonyl*)*methyl*-4-*methyl*-2-*oxo*-2,5-*dihydro*-1H-1-*benzazepine* (X). A solution of diethyl malonate (1·6 g.) in dimethylformamide (25 ml.) was treated with sodium hydride (50%; 0·5 g.). After the reaction had subsided (1 hr.) the 1*H*-1-benzazepine (VIIIa) (2·07 g.) was added and the mixture heated under reflux for 2 hr. The dimethylformamide was removed, water (100 ml.) was added and the solid which seperated, was collected. Crystallisation from acetone gave the 1H-1-*benzazepine* (X) (1·1 g.) as rhombs, m. p. 191—192° (Found: C, 65·5; H, 6·3; N, 4·2. $C_{18}H_{21}NO_5$ requires C, 65·2; H, 6·4; N, 4·2%), $\nu_{max.}$ 3175, 1751, 1724, 1667, 1626, and 1587 cm.$^{-1}$; τ 0·85 (1H, broad, N*H*), 2·6—2·9 (4H, complex, Ar*H*), 4·11 (1H, multiplet, =C*H*), 5·5—6·3 (6H, complex), 7·78 (3H, doublet, J = 1·5 c./sec., =C–CH_3), 8·73 (3H, triplet, $CO_2CH_2CH_3$), and 9·05 (3H, triplet, $CO_2CH_2CH_3$).

5-(*Carboxymethylthio*)-4-*ethyl*-2-*oxo*-2,3-*dihydro*-1H-1-*benzazepine* (XI). A solution of the 1*H*-1-benzazepine (IXa) (4 g.) in dimethylformamide (50 ml.) was treated with thioglycollic acid (4·45 g.) and the mixture heated under reflux for 30 min. The dimethylformamide was removed, water (100 ml.) was added and the product extracted with ethyl acetate (2 × 250 ml.). Crystallisation (×2) from acetone gave the 1H-1-*benzazepine* (XII) (1·45 g.) as a crystalline solid, m. p. 184—185° (Found: C, 59·2; H, 4·8; N, 5·2; S, 12·0. $C_{13}H_{13}NO_3S$ requires C, 59·3; H, 5·0; N, 5·3; S, 12·15%), $\nu_{max.}$ 3247, 2941—2273 broad, 1695, 1631, 1621, 1595, and 1560 cm.$^{-1}$, τ (sodium deuteroxide) 2·07—2·69 (4H, complex, Ar*H*), 6·96 (2H, singlet, –S–CH_2CO$\bar{O}$), 7·32 (2H, singlet, –COCH_2C=), and 7·67 (3H, singlet, =C–CH_3). The peaks of greatest diagnostic value in its mass spectrum occurred at *m/e* 263 (34%) ($C_{13}H_{13}NOS$ requires M^+, 263), 221 (69%) (*m** 185·7), 204 (9%), 176

(16%), 172 (17%), 162 (100%) (*m** 118·8), 144 (24%), 130 (16%), 115 (19%), 77 (21%), 51 (19%), and 45 (19%).

1,4-*Dimethyl*-2,5-*dioxo*-2,5-*dihydro*-1*H*-1-*benzazepine*. The 1*H*-1-benzazepine (IVe) (2 g.) was dissolved in dry dimethylformamide (150 ml.) and sodium hydride (0·64 g.) added. The yellow solution was treated with methyl iodide (1·51 g.) and stirred at room temperature for 12 hr. Removal of the dimethylformamide and addition of water (100 ml.) gave a solid (1·2 g.) which was filtered and washed with water. Crystallisation (×2) from cyclohexane gave 1,4-*dimethyl*-2,5-*dioxo*-2,5-*dihydro*-1H-1-*benzazepine* (0·53 g.), m. p. 84—86° (Found: C, 71·3; H, 5·8; N, 7·2. $C_{12}H_{11}NO_2$ requires C, 71·6; H, 5·5; N, 7·0%), $\nu_{max.}$ 1667, 1642, 1608, and 1587 cm.$^{-1}$; τ 2·3—2·85 (4H, complex, Ar*H*), 3·35 (1H, quartet, =C*H*), 6·50 (3H, singlet, N–CH_3), and 7·86 (3H, doublet, J = 1·5 c./sec., =C–CH_3). The peaks of greatest diagnostic value in the mass spectrum occurred at *m/e* 207 (100%) ($C_{12}H_{11}NO_2$ requires M^+, 201), 186 (25%), 173 (100%) (*m** 148·9), 172 (74%), 159 (19%), 145 (75%) (*m** 143·1), 144 (85%) (*m** 143·1), 131 (12%), 130 (35%), 104 (17%), 90 (10%), 82 (51%), 77 (38%), 63 (17%), 56 (18%), and 51 (17%).

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