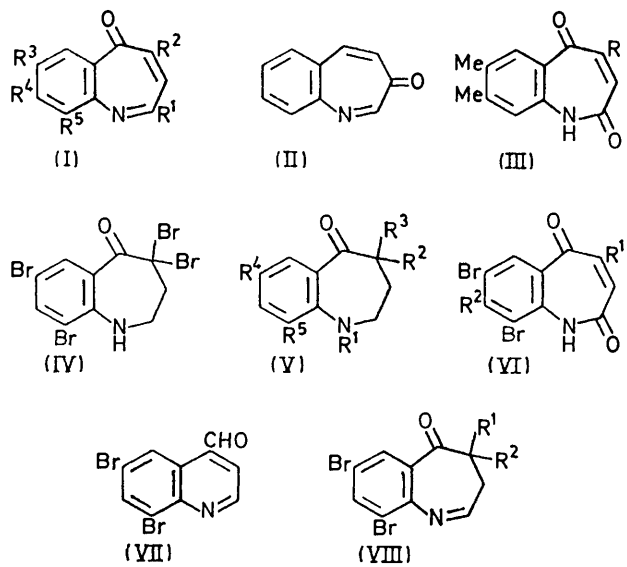
# Azabenzocycloheptenones. Part XV.[1] Synthesis of Benzazatropones and a Quinoline Aldehyde by the Dehydrogenation of Certain Tetrahydro-1-benzazepine Derivatives

By **A. Cromarty, G. R. Proctor,* and M. Shabbir,** Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL

4,4,7,9-Tetrabromo-1,2,3,4-tetrahydro-1-benzazepin-5-one (IV) reacts with lithium chloride in dimethylformamide to give 6,8-dibromoquinoline-4-carbaldehyde (VII) and with active manganese dioxide to give 4,7,9-tribromo-1-benzazepin-5-one (I; $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = Br$) and 4,7,9-tribromo-1-benzazepine-2,5-dione (VI; $R^1 = Br$, $R^2 = H$). The latter has been converted into 4,7,9-tribromo-2-chloro-1-benzazepin-5-one (I; $R^1 = Cl$, $R^4 = H$, $R^2 = R^3 = R^5 = Br$). 1,2,3,4-Tetrahydro-2-methyl-1-*p*-tolylsulphonyl-1-benzazepin-5-one (XIII; R = tosyl), the *N*-acetyl derivative (XIII; R = Ac) and several related compounds are reported. Treatment of ethyl γ-[*N*-(*o*-methoxycarbonylphenyl)acetamido]butyrate (XVI; $R^1 = Ac$, $R^2 = H$) with potassium t-butoxide gave ethyl γ-(1,2-dihydro-4-hydroxy-2-oxoquinolin-1-yl)butyrate (XVII).

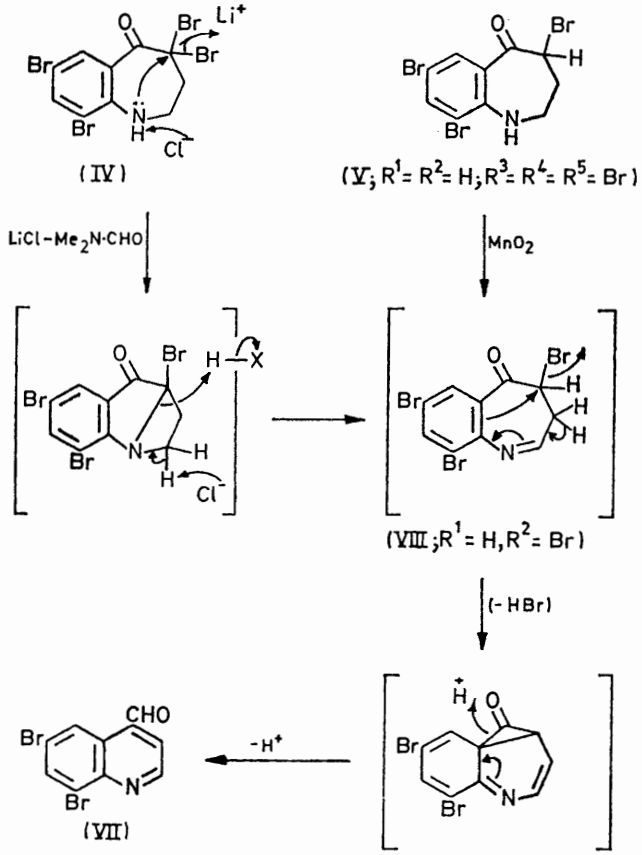
It has been our objective for some time [2-4] to synthesise 1-benzazepin-5-ones (benzazatropones) (I). Since 1-benzazepin-3-one (II) dimerised on formation [3] as also did dibenzo[*b*,*d*]azepin-7-ones,[5,6] we considered that a blocking group [2] at C-2 would be necessary to confer stability on the products, as we had found in the dibenz[*b*,*d*]azepin-7-one series.[5,6] However, we have discovered a route to 1-benzazepin-5-ones which allows access to both C-2 substituted and unsubstituted derivatives. The only previous report [7] of 1-benzazepin-5-ones concerns the synthesis of the 2-chloro-1-benzazepin-5-one (I; $R^1 = Cl$, $R^2 = p$-chloroanilino, $R^3 = R^4 = Me$, $R^5 = H$), made by the action of phosphoryl chloride on the keto-lactam (III; R = *p*-chloroanilino). A general route to such keto-lactams is the treatment of 1,2- and 1,4-naphthoquinones with azide ion.[8,9]

We have commented previously [3] on the strange tendency of α-bromo-ketones of the tetrahydro-1-benzazepin-5-one series to undergo debromination rather than dehydrobromination; in the present work we have examined the tetrabromo-ketone [3] (IV) again and have found that although treatment of it with sodium iodide in pyridine or with 1,5-diazabicyclo[4,3,0]non-5-ene [10] caused debromination [to (V; $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Br$)], brief treatment with lithium chloride in dimethylformamide [11] led to dehydrobromination. The product ($C_{10}H_5Br_2NO$) could not have the azatropone structure (I; $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = Br$) because reduction with sodium borohydride converted it into a dihydro-derivative, the n.m.r. spectrum of which contained a two-proton singlet (τ 4·88) and an exchangeable OH singlet (τ 6·0) in place of a non-exchangeable one-proton singlet (τ −0·5). This strongly suggested that the dehydrobromination product was a quinoline aldehyde. The same product arose when the tribromo-ketone [3] (V; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Br$) was treated with active manganese dioxide prepared by ozonising manganese(II) nitrate.[12] The n.m.r. spectrum of the aldehyde contains two AB quartets at τ 0·6 and 2·06 ($J$ 2·5 Hz) and τ 0·67 and 1·66 ($J$ 5 Hz), which we assign to protons 5 and 7, and 2 and 3 of a quinoline nucleus by comparison with model compounds.[13,14] Thus the product ($C_{10}H_5Br_2NO$) is assigned structure (VII). It is possible that both processes proceed *via* a common intermediate, as shown in the Scheme. We were unable to obtain the known quinoline-4-carbaldehyde from α-bromobenzazepinone derivatives because, on the one hand, the αα-dibromo-ketone (V; $R^1 = R^4 =$




[1] Part XIV, G. R. Proctor, W. I. Ross, and A. Tapia, *J.C.S. Perkin I*, 1972, 1803.
[2] A. Cromarty, K. E. Haque, and G. R. Proctor, *J. Chem. Soc.* (*C*), 1971, 3536.
[3] E. D. Hannah, W. C. Peaston, and G. R. Proctor, *J. Chem. Soc.* (*C*), 1968, 1280.
[4] W. H. Bell, E. Hannah, and G. R. Proctor, *J. Chem. Soc.*, 1964, 4926.
[5] W. C. Peaston and G. R. Proctor, *J. Chem. Soc.* (*C*), 1968, 2481.
[6] G. R. Proctor and W. C. Peaston, *J. Chem. Soc.* (*C*), 1969, 2151.
[7] A. H. Rees and K. Simon, *Canad. J. Chem.*, 1969, **47**, 1227.
[8] G. Jones, *J. Chem. Soc.* (*C*), 1967, 1808.
[9] J. W. Moore, H. R. Shelden, and W. Weyler, *Tetrahedron Letters*, 1969, 1243.
[10] H. Oediger, H. J. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, 1966, **99**, 2012.
[11] E. W. Collington and G. Jones, *Chem. Comm.*, 1968, 958.
[12] J. S. Belew and C. Tekling, *Chem. and Ind.*, 1967, 1958.
[13] J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959, p. 268.
[14] G. Janzso and E. M. Philbin, *Tetrahedron Letters*, 1971, **4**, 3075.

$R^5$ = H, $R^2$ = $R^3$ = Br) was inaccessible and, on the other, the α-bromo-ketone (V; $R^1$ = $R^2$ = $R^4$ = $R^5$ = H, $R^3$ = Br) reacted with manganese dioxide to give an intractable mixture. Moreover, attempted catalytic

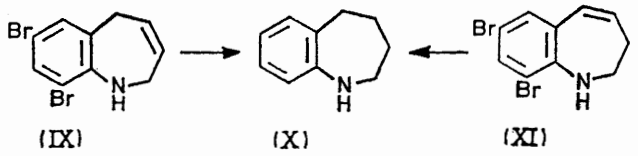



SCHEME

hydrogenolysis of the bromo-aldehyde (VII) yielded many products.

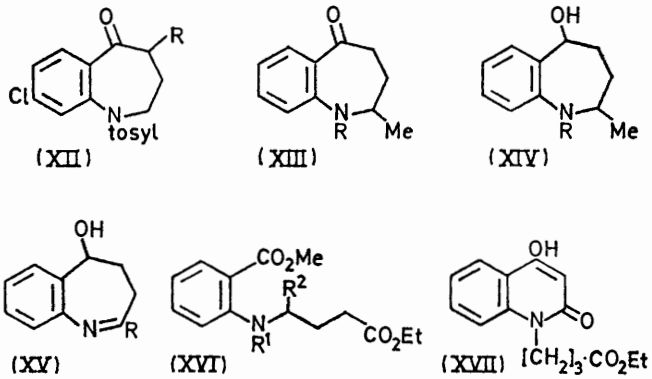
The common intermediate (VIII; $R^1$ = H, $R^2$ = Br) in our reaction Scheme has not the correct stereochemistry (models) to allow a *trans* elimination of hydrogen bromide between C-3 and C-4, but the imine (VIII; $R^1$ = $R^2$ = Br) would have the correct stereochemistry; accordingly we treated the tetrabromo-ketone (IV) with manganese dioxide [12] and isolated a compound ($C_{10}H_4Br_3NO$) which we regard as the ' benzazatropone ' (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = $R^5$ = Br) in the light of both spectroscopic evidence (see Experimental section) and the following transformations.

When the ' benzazatropone ' was reduced with lithium aluminium hydride, several products were formed: one of these ($C_{10}H_9Br_2N$) was isolated and judged to have structure (IX) from the n.m.r. spectrum and from the mode of formation. When the latter was catalytically hydrogenated, the tetrahydro-compound (X) was formed, identical with the product from catalytic hydrogenation of the known dihydrobenzazepine (XI). Thus the presence of a seven-membered ring in the ' benzazatropone ' is demonstrated and structure (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = $R^5$ = Br) is beyond doubt. The compound (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = $R^5$ = Br) is very reactive, giving several products on treatment with dilute acid or alkali or on catalytic hydrogenation;




when it was treated with wet manganese dioxide it was transformed into a dione [presumably (VI; $R^1$ = Br, $R^2$ = H)], indeed the latter was the major product of reaction when the tetrabromo-ketone (IV) was treated with active manganese dioxide [12] that had not been ' azeotroped ' with benzene. Transformation of the ' benzazatropone ' (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = $R^5$ = Br) into the dione (VI; $R^1$ = Br, $R^2$ = H) is a characteristic reaction; it was also found to occur with the dibenzo[*b*,*e*]azepin-11-one system [15] and is presumed to proceed by hydration of the imine bond followed by oxidation of the carbinolamine system. Treatment of the dione (VI; $R^1$ = Br, $R^2$ = H) with phosphoryl chloride gave the chloro-substituted benzazatropone [7] (I; $R^1$ = Cl, $R^4$ = H, $R^2$ = $R^3$ = $R^5$ = Br).

To test the generality of the foregoing reactions we have made the 8-chloro-ketone (XII; R = H) by the standard procedure [16] from methyl 4-chloroanthranilate * and converted it *via* the tetrabromo-ketone (V; $R^1$ = H, $R^2$ = $R^3$ = $R^4$ = $R^5$ = Br, 8-Cl for H) into both the corresponding ' benzazatropone ' (I; $R^1$ = H, $R^2$ = $R^3$ = $R^5$ = Br, $R^4$ = Cl) and the dione (VI; $R^1$ = Br, $R^2$ = Cl). The ketone (V; $R^1$ = $R^2$ = $R^3$ = H, $R^4$ = $R^5$ = Br) reacted with active manganese dioxide to give the dione (VI; $R^1$ = $R^2$ = H).




The introduction of a blocking methyl group at C-2 of the 1-benzazepine skeleton has been surprisingly difficult. We have at last developed a synthesis of the ketone

* Supplied by Dr. M. D. Scott (G. D. Searle and Co.).

[15] I. McDonald and G. R. Proctor, *J. Chem. Soc.* (*C*), 1969, 1321.

[16] I. McCall, G. R. Proctor, and L. Purdie, *J. Chem. Soc.* (*C*), 1970, 1126.

(XIII; R = tosyl) by adaptations of the general method [16] (see Experimental section), but this ketone reacted with an excess of bromine in chloroform to give only the αα-dibromo-derivative [of (XIII; R = tosyl)] and not the expected tetrabromo-ketone analogous to (IV). Attempted detosylation with hydrogen bromide in acetic acid [17] or with hydrogen chloride in the presence of zinc chloride was also unsuccessful. The tosyl group was removed from the 5-hydroxy-compound (XIV; R = tosyl) with sodium in liquid ammonia, but the product (XIV; R = H) reacted with diethyl azodicarboxylate to give the imine (XV; R = Me). An analogous imine (XV; R = H) was similarly obtained from the amino-alcohol formed by reduction of the ketone (V; $R^1 = R^2 = R^3 = R^4 = R^5 = H$).[18]

We previously commented [16] on the problem of causing ethyl γ-bromovalerate to react with methyl anthranilate to give the amino-diester (XVI; $R^1 = H$, $R^2 = Me$); we find now that the latter compound can be obtained in low yield by a modified procedure and that it can be acetylated [to (XVI; $R^1 = Ac$, $R^2 = Me$)]. Cyclisation of the acetate with sodium hydride in toluene [1] followed by acidic hydrolysis gave the ketone (XIII; R = Ac) in 50% yield. Here again the *N*-protecting group is surprisingly resistant to acidic hydrolysis, a testimony to the blocking effect of the methyl group at C-2.

While re-examining the cyclisation of the acetyl diester [1] (XVI; $R^1 = Ac$, $R^2 = H$) we found potassium t-butoxide to be an unsuitable base for production of 1-benzazepine derivatives: a high yield was, however, obtained of a substance ($C_{15}H_{17}NO_4$) which we conclude is the quinolin-2-one (XVII). This is particularly strongly supported by the n.m.r. spectrum (see Experimental section) and by the mass spectrum, in which the molecular ion loses several successive expected fragments from the side chain leading to a base peak $C_9H_7NO_2$ (2,4-dihydroxyquinolinium). Compound (XVII) is sufficiently acidic to dissolve in sodium hydrogen carbonate solution, and is in fact a major product during the formation of the keto-ester [1] (V; $R^1 = Ac$, $R^2 = R^4 = R^5 = H$, $R^3 = CO_2Et$) by sodium hydride-induced cyclisation of the acetyl diester (XVI; $R^1 = Ac$, $R^2 = H$), from which the yield of acetyl ketone (V; $R^1 = Ac$, $R^2 = R^3 = R^4 = R^5 = H$) has never been above 20% (after hydrolysis). It is unusual to find the methyl group of an *N*-acetate apparently able to lose a proton and enter into a nucleophilic displacement reaction: *N*-substituted anthranilates are feebly basic and so their acetates are perhaps not typical amides; indeed examples are already known of *N*-acetylanthranilates which have been cyclised to hydroxyquinolines.[19]

As the routes to the C-2 methyl compounds (XIII; R = Ac and tosyl) are so inefficient, and the *N*-protecting groups so difficult to remove, further work in this area has been discontinued.

* Aldrich Chemical Company.

[17] D. I. Weisblat, B. J. Magerlein, and D. R. Myers, *J. Amer. Chem. Soc.*, 1953, **75**, 3630.

[18] A. McLean, Ph.D. Thesis, University of Strathclyde, 1972.

## EXPERIMENTAL

*Reactions of* 4,4,7,9-*Tetrabromo*-1,2,3,4-*tetrahydro*-1-*benzazepin*-5-*one* [4] (IV).—(a) *With sodium iodide.* The tetrabromo-ketone (1 g) in pyridine (50 ml) was refluxed with sodium iodide (6 g) for 2 h in the dark under nitrogen. The mixture was cooled, poured into water, and extracted with ether; the extract was washed with water and dried. Evaporation left a gum (400 mg) which was chromatographed on neutral alumina to give 7,9-dibromo-1,2,3,4-tetrahydro-1-benzazepin-5-one [4] (V; $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = Br$) (100 mg), mixed m.p. 90° [Found: *M* (mass spectrum), 318·902771. Calc. for $C_{10}H_9NO^{79}Br^{81}Br$, *M*, 318·903220].

(b) *With* 1,5-*diazabicyclo*[4,3,0]*non*-5-*ene.** The title compound (1 g) in dry benzene (50 ml) was refluxed with 1,5-diazabicyclo[4,3,0]non-5-ene (800 mg) until t.l.c. showed it was all consumed. Work-up and thick-plate chromatography gave the same product (170 mg) as in (a).

(c) *With lithium chloride.*[11] The title compound (3 g), freshly distilled dimethylformamide (50 ml), and lithium chloride (7·8 g) were kept for 15 min at 160°. The mixture was poured into water and extracted with benzene; the extract was washed with water, dried, and evaporated to give a gum (1·3 g). Chromatography on silica gel and elution with benzene gave 6,8-*dibromoquinoline*-4-*carbaldehyde* (VII) (660 mg) as yellow needles, m.p. 159° [from benzene–light petroleum (b.p. 60—80°)] [Found: C, 38·45; H, 1·5; N, 4·5%; *M*(mass spectrum), 316·87164, 314·87246, 312·87487. $C_{10}H_5Br_2NO$ requires C, 38·15; H, 1·6; N, 4·5%; *M*, 316·86995, 314·87192, 312·87389], $\nu_{max.}$ (Nujol) 1700 $cm^{-1}$ (C=O), τ −0·45 (1H, s), 0·59—0·64, 2·14—2·19 (2H, AB system, *J* 5 Hz), 0·67—0·695, and 1·65—1·675 (2H, AB system, *J* 2·5 Hz). Reduction of this material by sodium borohydride gave a quantitative yield of 6,8-*dibromo*-4-*hydroxymethylquinoline*, m.p. 189° [from benzene–light petroleum (b.p. 60—80°)] [Found: C, 38·25; H, 2·3; N, 4·6. $C_{10}H_7Br_2NO$ requires C, 37·9; H, 2·25; N, 4·45%], $\nu_{max.}$ (Nujol) 3436 $cm^{-1}$ (OH), τ 0·79—0·87, 2·12—2·2 (2H, AB system, *J* 5 Hz), 1·55 (2H, s), 4·88 (2H, s), 5·4—6·4 (1H, exchangeable).

(d) *With manganese dioxide.* The title compound (2 g), manganese dioxide [12] (10 g; freshly prepared), and dry benzene (100 ml) were refluxed for 4 h; the mixture was filtered and the solvent removed to leave an orange solid (1·3 g). Chromatography on neutral deactivated alumina and elution with benzene gave first 4,7,9-*tribromo*-1-*benzazepin*-5-*one* (I; $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = Br$) (600 mg), m.p. 158° [from benzene–light petroleum (b.p. 80—100°)] [Found: C, 30·95; H, 1·2; N, 3·85%); *M*(mass spectrum), 396·7773. $C_{10}H_4{}^{81}Br_3NO$ requires C, 30·5; H, 1·0; N, 3·55%; *M*, 396·7785], $\nu_{max.}$ (Nujol) 1672 $cm^{-1}$ (C=O), τ 1·73 and 2·38 (2H, AB system, *J* 5 Hz), and 1·79 and 1·87 (2H, AB system, *J* 2 Hz), $\lambda_{max.}$ (EtOH) 213, 249, and 326 nm (ε 15,710, 13,330, and 4484). Further elution with benzene gave 4,7,9-*tribromo*-1-*benzazepine*-2,5-*dione* (VI; $R^1 = Br$, $R^2 = H$) (330 mg) which crystallised from methylene dichloride–light petroleum (b.p. 60—80°) as yellow needles, m.p. 174° [Found: C, 29·35, H, 1·05; N, 3·6%; *M*(mass spectrum), 412·76989. $C_{10}H_4{}^{81}Br_3NO_2$ requires C, 29·3; H, 1·0; N, 3·4%; *M*, 412·77347], $\nu_{max.}$

[19] J. N. Ashley, W. H. Perkin, jun., and R. Robinson, *J. Chem. Soc.*, 1930, 382; R. E. Lutz, J. F. Codington, R. J. Rowlett, jun., A. J. Deinet, and P. S. Bailey, *J. Amer. Chem. Soc.*, 1946, **68**, 1810.

(Nujol) 1650 $cm^{-1}$ (C=O), τ 1·5br (1H, exchangeable), 2·3 (2H, s), and 2·49 (1H, s).

(e) *With anhydrous manganese dioxide.* Freshly prepared manganese dioxide [12] (10 g) and dry benzene (150 ml) were refluxed for 2 h under a Dean–Stark trap in an atmosphere of dry nitrogen. After cooling and addition of the title compound (2 g), the mixture was refluxed and stirred for 4 h with the Dean–Stark trap attached. Work-up as before gave only the first product (m.p. 158°) described in (d).

4,7,9-*Tribromo*-2-*chloro*-1-*benzazepin*-5-*one* (I; $R^1$ = Cl, $R^4$ = H, $R^2$ = $R^3$ = $R^5$ = Br).—4,7,9-Tribromo-1-benzazepine-2,5-dione (400 mg) and phosphoryl chloride (1 ml) were heated for 1 h at 100°. The cooled mixture was poured into ice and dilute aqueous sodium carbonate solution and extracted with methylene dichloride. The *product* (300 mg; m.p. 140°) was purified by chromatography on a short silica column, by crystallisation from light petroleum (b.p. 60—80°), and by sublimation *in vacuo*; final m.p. 142° [Found: C, 28·6; H, 0·72; N, 3·7%; *M*(mass spectrum), 432·73506. $C_{10}H_3{}^{81}Br_3{}^{37}ClNO$ requires C, 28·05; H, 0·7; N, 3·3%; *M*, 432·73663], $\nu_{max.}$ (Nujol) 1665 $cm^{-1}$ (C=O), τ 1·75—1·95 (2H, m), and 2·55 (1H, s).

*Reaction of* 4,7,9-*Tribromo*-1,2,3,4-*tetrahydro*-1-*benzazepin*-5-*one with Manganese Dioxide.*—The title compound (1 g) and manganese dioxide [12] (3 g) in dry benzene were refluxed for 24 h. The product (750 mg), obtained in the usual way, crystallised in needles, m.p. and mixed m.p. 158—159° with 6,8-dibromoquinoline-4-carbaldehyde prepared previously. The title compound was recovered unchanged after treatment with lithium chloride in dimethylformamide for 12 min at 160°, after refluxing for 6 h with lithium carbonate in dimethylformamide, or after storage at 20° for 34 h with sodium iodide in dimethylformamide.

7,9-*Dibromo*-1-*benzazepine*-2,5-*dione* (VI; $R^1$ = $R^2$ = H).—7,9-Dibromo-1,2,3,4-tetrahydro-1-benzazepin-5-one (V; $R^1$ = $R^2$ = $R^3$ = H, $R^4$ = $R^5$ = Br) (1 g), manganese dioxide [12] (5 g), and dry benzene (100 ml) were refluxed for 24 h. Work-up as usual gave a gum (180 mg) which was purified by thick-plate chromatography (Merck alumina grade E) and by crystallisation from ethanol to give *needles*, m.p. 149° [Found: *M*(mass spectrum), 330·86620. $C_{10}H_5{}^{81}Br^{79}BrNO_2$ requires *M*, 330·86684], $\nu_{max.}$ (Nujol) 3335 (N–H) and 1645 (C=O) $cm^{-1}$, τ 1·4br (1H, exchangeable), 1·89 and 2·03 (2H, AB system, *J* 2 Hz), 3·13 (1H, s), and 3·16 (1H, d, *J* 1 Hz).

*Reduction of* 4,7,9-*Tribromo*-1-*benzazepin*-5-*one* (I; $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = $R^5$ = Br).—The title compound (500 mg), lithium aluminium hydride (450 mg), and tetrahydrofuran were refluxed for 1 h. T.l.c. showed the presence of five compounds. The usual work-up was followed by chromatography on neutral alumina (twice); elution with benzene gave 7,9-*dibromo*-2,5-*dihydro*-1-*benzazepine* (IX) (50 mg), which crystallised from benzene–light petroleum (b.p. 60—80°) in plates, m.p. 100—102° [Found: C, 39·9; H, 2·85; N, 4·7%; *M*(mass spectrum), 302·9056. $C_{10}H_9Br_2N$ requires C, 39·6; H, 2·95; N, 4·6%; *M*, 302·9083], $\nu_{max.}$ (Nujol) 3495 $cm^{-1}$ (NH), τ 2·9 (1H, s), 2·94 (1H, d, *J* 10 Hz), 3·28 (1H, s), 3·56 (1H, d, *J* 10 Hz), 6·1br (1H, s, exchangeable), 6·7—6·83 (2H, m), and 7·0—7·12 (2H, m).

2,3,4,5-*Tetrahydro*-1-*benzazepine* (X) *Hydrobromide.*—7,9-Dibromo-2,5-dihydro-1-benzazepine (IX) (40 mg) was hydrogenated in absolute ethanol (10 ml) with palladised charcoal (10%; 11 mg). The *product* was obtained as usual and purified by crystallisation from methylene dichloride–light petroleum (b.p. 60—80°) (to give prisms, m.p. 212—213°) and by sublimation *in vacuo* (Found: C, 52·25; H, 6·1; N, 6·2. $C_{10}H_{14}BrN$ requires C, 52·7; H, 6·2; N, 6·15%). Basification gave the free amine (X), whose i.r. spectrum was identical with that of material made previously,[4] the benzoate had m.p. and mixed m.p. 86°.[4] Hydrogenation of 7,9-dibromo-2,3-dihydro-1-benzazepine (XI) gave the same results.

4-*Bromo*-1,2,3,4-*tetrahydro*-1-*benzazepin*-5-*one* (V; $R^1$ = $R^2$ = $R^4$ = $R^5$ = H, $R^3$ = Br).— 4,4-Dibromo-1,2,3,4-tetrahydro-1-*p*-tolylsulphonyl-1-benzazepin-5-one (V; $R^1$ = tosyl, $R^2$ = $R^3$ = Br, $R^4$ = $R^5$ = H) (4·6 g) and phenol (2 g) were stirred for 3 h with hydrogen bromide in acetic acid (30%; 23 g) [17] at 20° and poured into ether. The precipitate was shaken with ammonium hydroxide and chloroform and the organic layer was separated. Evaporation of the chloroform left the *product*, which was purified by chromatography on neutral alumina and by crystallisation from benzene–light petroleum (b.p. 60—80°) to give a yellow powder (1·0 g), m.p. 114—115° (Found: C, 50·4; H, 4·4; N, 6·1; Br, 32·8. $C_{10}H_{10}BrNO$ requires C, 50·05; H, 4·15; N, 5·85; Br, 33·3%), $\nu_{max.}$ (Nujol) 3350 (NH) and 1672 $cm^{-1}$ (C=O), τ 2·28 (1H, dd, $J_A$ 8, $J_B$ 1 Hz), 2·75 (1H, dt, $J_A$ 8, $J_B$ 1 Hz), 3·2 (2H, t, *J* 8 Hz), 4·9—5·1 (1H, m), 5·25br (1H, s, exchangeable), 6·3—6·7 (1H, m), 6·8—7·3 (2H, m), and 7·4—7·75 (1H, m). Treatment of this compound with active manganese dioxide caused decomposition, and careful addition of bromine in chloroform gave 4,7,9-tribromo-1,2,3,4-tetrahydro-1-benzazepin-5-one (V; $R^1$ = $R^2$ = H, $R^3$ = $R^4$ = $R^5$ = Br) and 4,4,7,9-tetrabromo-1,2,3,4-tetrahydro-1-benzazepin-5-one (V; $R^1$ = H, $R^2$ = $R^3$ = $R^4$ = $R^5$ = Br).

*Ethyl* γ-[N-(o-*Methoxycarbonylphenyl*)-p-*tolylsulphonylamino*]*valerate* (XVI; $R^1$ = *tosyl*, $R^2$ = Me).—Methyl *N*-*p*-tolylsulphonylanthranilate (15·25 g), ethyl γ-bromovalerate [16] (15·5 g), and sodium carbonate (13 g; freshly roasted) were stirred for 24 h at 115°; ethyl γ-bromovalerate (25 g) and sodium carbonate (20 g) were then added and stirring was continued for 24 h at 110°. The cooled mixture was shaken with chloroform and filtered; evaporation left the product (24 g), which was purified by chromatography on silica gel (benzene elution) and by recrystallisation from light petroleum (b.p. 60—80°) to give *blades*, m.p. 68—69° (Found: C, 61·4; H, 6·2; N, 3·05. $C_{22}H_{27}NO_6S$ requires C, 60·95; H, 6·25; N, 3·2%), $\nu_{max.}$ (KCl) 1690—1740br $cm^{-1}$ (ester), τ 2·0—3·0 (8H, m), 5·7—6·0 (2H, q), 5·6—5·8 (1H, m), 6·1 (3H, s), 7·6 (3H, s), 7·7—7·9 (2H, m), 7·95—8·75 (2H, m), 8·7 (3H, d), and 8·9 (3H, t).

1,2,3,4-*Tetrahydro*-2-*methyl*-1-p-*tolylsulphonyl*-1-*benzazepin*-5-*one* (XIII; R = *tosyl*).—To potassium t-butoxide [from potassium (100 g)] in dry toluene (1·5 l) was added the previous diester (180 g) in dry toluene (1 l) with stirring under nitrogen at 80° during 3 h. The mixture was stirred at 110° for 24 h and then at 140° for 1 h, until the distillate had b.p. 110°. After cooling in ice and addition of ethanol and dilute hydrochloric acid (in excess), the crude keto-ester was obtained from the toluene layer as usual and hydrolysed by the previously described [16] method. The *product* (60 g) was purified by chromatography on alumina and recrystallisation from ethanol to give prisms, m.p. 122° (Found: C, 65·4; H, 5·6; N, 4·3. $C_{18}H_{19}NO_3S$ requires C, 65·7; H, 5·8; N, 4·15%), $\nu_{max.}$ 1680 $cm^{-1}$ (C=O), τ 2·3—2·9 (8H, m), 5·6 (1H, m), 7·6 (3H, s), 7·4—7·7 (2H, m), 7·9—8·3 (2H, m), and 7·73 (3H, d).

4,4-*Dibromo*-1,2,3,4-*tetrahydro*-2-*methyl*-1-p-*tolylsulphonyl*-1-*benzazepin*-5-*one* [4] [4,4-*Dibromo-derivative of* (XIII; R =

*tosyl*)].—To the ketone from the previous experiment (4 g) in chloroform (40 ml), bromine (2 ml) was added and the mixture was left for 5 days. It was then washed with dilute aqueous sodium hydrogen carbonate and evaporated to give the *product* (3·5 g), needles, m.p. 135° (from ethanol) (Found: N, 2·8. $C_{18}H_{17}Br_2NO_3S$ requires N, 2·9%), τ 2·3—2·9 (8H, m), 5·25 (1H, m), 7·0—7·7 (2H, m), 7·65 (3H, s), and 8·6 (3H, d, *J* 8 Hz).

1,2,3,4-*Tetrahydro*-2-*methyl*-1-p-*tolylsulphonyl*-1-*benzazepin*-5-*ol* (XIV; R = *tosyl*).—To 1,2,3,4-tetrahydro-2-methyl-1-*p*-tolylsulphonyl-1-benzazepin-5-one (XIII; R = tosyl) (3 g) in ethanol (30 ml), sodium borohydride (0·1 g) was added in small portions. The mixture was stirred overnight at 20°, then poured into ice; the usual work-up gave the *product* (2·8 g) (from methylene dichloride–light petroleum (b.p. 60—80°)] as needles, m.p. 97° (Found: C, 65·45; H, 6·8; N, 4·35. $C_{18}H_{21}NO_3S$ requires C, 65·25; H, 6·4; N, 4·25%).

1,2,3,4-*Tetrahydro*-2-*methyl*-1-*benzazepin*-5-*ol* (XIV; R = H).—The compound from the previous experiment (1·9 g) in liquid ammonia (125 ml) was stirred while sodium (650 mg) was added slowly in small pieces until a blue colour persisted. The mixture was stirred for a further 4 min and ammonium chloride (in excess) was added. After evaporation of ammonia, the product (990 mg) was extracted as usual with chloroform to give a gum which crystallised from methylene dichloride–light petroleum (b.p. 60—80°) as a *powder*, m.p. 115° (Found: C, 75·05; H, 8·4; N, 8·0. $C_{11}H_{15}NO$ requires C, 74·6; H, 8·55; N, 7·9%), $\nu_{max.}$ (Nujol) 3300 (NH) and 3320 (OH) cm$^{-1}$, τ 2·58—3·25 (4H, m), 5·2—5·38 (1H, m), 6·6—7·4 (3H, m, 2 exchangeable), 7·9—8·6 (4H, m), and 8·84 (3H, d).

Treatment of 1,2,3,4-tetrahydro-2-methyl-1-*p*-tolylsulphonyl-1-benzazepin-5-one with sodium in liquid ammonia yielded several products of which the title compound was one.

4,5-*Dihydro*-2-*methyl*-3H-1-*benzazepin*-5-*ol* (XV; R = Me).—1,2,3,4-Tetrahydro-2-methyl-1-benzazepin-5-ol (600 mg), diethyl azodicarboxylate (900 mg), and chloroform (50 ml) were refluxed for 36 h. After removal of the solvent, the product was chromatographed on neutral deactivated alumina to give needles (from light petroleum), m.p. 87° (Found: C, 75·55; H, 7·5; N, 7·95. $C_{11}H_{13}NO$ requires C, 75·4; H, 7·5; N, 8·0%), $\nu_{max.}$ 3300 cm$^{-1}$ (OH) (no carbonyl absorption), τ 2·85—3·5 (4H, m), 4·95 (1H, m), 5·7—6·4 (1H, exchangeable), 7·2—8·2 (4H, m), and 8·36 (3H, s).

*Ethyl* γ-[N-(5-*chloro*-2-*methoxycarbonylphenyl*)-p-*tolylsulphonylamino*]*butyrate* (XVI; $R^1$ = *tosyl*, $R^2$ = H, 5′-Cl *for* H).—Methyl 4-chloro-*N*-*p*-tolylsulphonylanthranilate [20] (55 g) and ethyl γ-bromobutyrate (40 g) reacted in dimethylformamide (350 ml) with sodium hydride (9·6 g; 50% dispersion) as described previously.[16] The product (45 g) was purified by chromatography on silica gel and by crystallisation from light petroleum (b.p. 60—80°) to give *prisms*, m.p. 83° (Found: C, 55·55; H, 5·2; N, 3·0. $C_{21}H_{24}ClNO_6S$ requires C, 55·55; H, 5·35; N, 3·1%), $\nu_{max.}$ (Nujol) 1735 and 1695 cm$^{-1}$ (esters), τ 2·0—3·15 (7H, m), 5·85 (2H, q), 6·18 (3H, s), 6·34 (2H, t), 7·56 (3H, s), 7·4—7·85 (2H, m), 7·85—8·4 (2H, m), and 8·78 (3H, t).

*Methyl* 8-*Chloro*-2,3,4,5-*tetrahydro*-5-*oxo*-1-p-*tolylsulphonyl*-1-*benzazepine*-4-*carboxylate* (XII; R = $CO_2Me$).—The diester (67 g) from the previous experiment, sodium hydride (50% dispersion; 7·5 g), ' spectroscopic ' ethanol (0·5 ml), and dry toluene (500 ml) were stirred under nitrogen for 1 h at 20° and then for 3 h at 110°. After cooling and work-up in the usual way, the product (60 g) crystallised from methanol in *needles*, m.p. 130° (Found: C, 55·55; H, 4·4; Cl, 8·6. $C_{19}H_{18}ClNO_5S$ requires C, 55·9; H, 4·4; Cl, 8·7%], $\nu_{max.}$ (Nujol) 1655 and 1620 cm$^{-1}$ (ketone and H-bonded ester), τ −2·05 (1H, s, exchangeable), 2·3—2·8 (7H, m), 5·84 (2H, t), 6·2 (3H, s), 7·5 (3H, s), and 7·6 (2H, t). This sample contained *ca.* 20% of the corresponding ethyl ester, τ −2·15(s), 5·75(q), 8·6(t); ester interchange is commonly found in these reactions.[1,16]

8-*Chloro*-1,2,3,4-*tetrahydro*-1-p-*tolylsulphonyl*-1-*benzazepin*-5-*one* (XII; R = H).—The foregoing keto-ester (10 g), acetic acid (60 ml), ethanol (20 ml), water (10 ml), and concentrated hydrochloric acid (10 ml) were refluxed for 48 h. After cooling, dilution with water, and extraction with chloroform, the product (6·0 g) crystallised from ethanol and from light petroleum (b.p. 60—80°) in *prisms*, m.p. 96—97° (Found: C, 58·4; H, 4·6; Cl, 10·15. $C_{17}H_{16}ClNO_3S$ requires C, 58·4; H, 4·5; Cl, 10·05%), $\nu_{max.}$ (KCl) 1680 cm$^{-1}$ (C=O), τ 2·2—2·7 (7H, m), 6·15 (2H, t), 7·47—7·6 (2H, m), 7·55 (3H, s), and 7·9—8·2 (2H, m).

4,4,7,9-*Tetrabromo*-8-*chloro*-1,2,3,4-*tetrahydro*-1-*benzazepin*-5-*one* (V; $R^1$ = H, $R^2$ = $R^3$ = $R^4$ = $R^5$ = Br, 8-Cl *for* H).—The foregoing ketone (2 g), bromine (3 ml) and chloroform (30 ml) were left overnight. The precipitated product (2·4 g) crystallised from ethanol in yellow *prisms*, m.p. 142° (Found: C, 23·9; H, 1·2; N, 3·05. $C_{10}H_6Br_4ClNO$ requires C, 23·45; H, 1·15; N, 2·75%), $\nu_{max.}$ (Nujol) 3380 (NH) and 1680 cm$^{-1}$ (C=O).

4,7,9-*Tribromo*-8-*chloro*-1-*benzazepin*-5-*one* (I; $R^1$ = H, $R^2$ = $R^3$ = $R^5$ = Br, $R^4$ = Cl).—4,4,7,9-Tetrabromo-8-chloro-1,2,3,4-tetrahydro-1-benzazepin-5-one (4 g) and dry benzene (300 ml) were refluxed for 1 h with active manganese dioxide [12] (20 g) which had been previously refluxed for 4 h in dry benzene under a Dean–Stark trap. After cooling and filtration, evaporation left the *product* (1·15 g), which was purified by chromatography on neutralised deactivated alumina, and by crystallisation; m.p. 158—160° [from dry benzene–light petroleum (b.p. 80—100°)] (Found: C, 28·2; H, 0·85; N, 3·2. $C_{10}H_3Br_3ClNO$ requires C, 28·05; H, 0·7; N, 3·3%), $\nu_{max.}$ (Nujol) 1655 (C=O), 1640sh (C=N?), and 1615w cm$^{-1}$ (C=C?), τ 1·72 (1H, s), 1·75 (1H, d, *J* 6 Hz), and 2·42 (1H, d, *J* 6 Hz).

4,7,9-*Tribromo*-8-*chloro*-1-*benzazepine*-2,5-*dione* (VI; $R^1$ = Br, $R^2$ = Cl).—If the previous experiment was carried out with manganese dioxide that had not been ' azeotroped ' immediately before use, the product was the title *compound*, m.p. 198° (Found: C, 27·6; H, 0·75; N, 3·5. $C_{10}H_3Br_3ClNO_2$ requires C, 27·55; H, 0·7; N, 3·2%), $\nu_{max.}$ (Nujol) 1665 and 1650 (C=O), and 1605 cm$^{-1}$ (C=C), τ 1·5br (1H, s, exchangeable), 1·88 (1H, s), and 2·48 (1H, s).

*Ethyl* γ-[N-(o-*Methoxycarbonylphenyl*)*acetamido*]*valerate* (XVI; $R^1$ = Ac, $R^2$ = Me).—Methyl anthranilate (200 g) and ethyl γ-bromovalerate [16] (100 g) were stirred at 115° for 36 h. Work-up as previously described gave ethyl 4-(*o*-methoxycarbonylanilino)valerate (30 g), b.p. 130—140° at 0·05 mmHg. This was refluxed with acetic anhydride (in excess) 6 h. The *acetate* (23 g), isolated as before,[1] had b.p. 170° at 0·1 mmHg (Found: C, 64·15; H, 7·45; N, 4·6. $C_{17}H_{23}NO_5$ requires C, 63·65; H, 7·2; N, 4·35%), $\nu_{max.}$ (Nujol) 1725 (ester) and 1660 cm$^{-1}$ (*N*-acetate).

1-*Acetyl*-1,2,3,4-*tetrahydro*-2-*methyl*-1-*benzazepin*-5-*one* (XIII; R = Ac).—The foregoing acetate (22 g) was refluxed and stirred for 48 h with sodium hydride (11 g; 50%

[20] D. N. Gupta, I. McCall, A. McLean, and G. R. Proctor, *J. Chem. Soc.* (*C*), 1970, 2191.

in oil) and dry toluene (1 l) under nitrogen. Work-up as before [1] and acidic hydrolysis gave the *product* (6 g), purified by chromatography on silica gel, crystallisation from benzene–light petroleum (b.p. 60—80°), and vacuum sublimation; m.p. 123° (Found: C, 71·6; H, 6·85; N, 6·15. $C_{13}H_{15}NO_2$ requires C, 71·95; H, 7·0; N, 6·45%), $\nu_{max.}$ (Nujol) 1685 (aryl C=O) and 1655 $cm^{-1}$ (*N*-acetate), $\tau$ 2·1—2·9 (4H, m), 4·8—5·1 (1H, m), 7·3—8·0 (2H, m), 8·25 (3H, s), 8·3—8·7 (2H, m), and 8·83 (3H, d).

*Reaction of Ethyl γ-[N-(o-Methoxycarbonylphenyl)acetamido]butyrate* (XVI; $R^1$ = Ac, $R^2$ = H) *with Potassium t-Butoxide*.—The title compound (21·5 g) in dry toluene (200 ml) was added slowly at 80° during 2 h with stirring under nitrogen to potassium t-butoxide [from potassium (15 g)] in dry toluene (400 ml). The temperature was raised to 125° during 3 h and then the mixture was cooled (ice) and ethanol was added, followed by dilute hydrochloric acid. The product (10 g) was obtained by extracting the toluene solution thrice with sodium hydrogen carbonate solution, and isolated in the usual way; it crystallised from aqueous ethanol in *prisms*, m.p. 190—192° [Found: C, 66·05; H, 5·9; N, 4·95%; *M*(mass spectrum), 275·1160. $C_{15}H_{17}NO_4$ requires C, 66·5; H, 6·25; N, 5·1%; *M*, 275·1158], $\nu_{max.}$ (Nujol) 1729s (ester), 1638w (carbonyl), and 1610w $cm^{-1}$ (C=C), $\tau$ 1·67 (1H, d), 2·3—2·5 (2H, m), 2·6—2·85 (1H, m), 3·62 (1H, s, exchangeable), 5·5 (2H, t), 5·86 (2H, q), 7·46 (2H, t), 7·7—8·0 (2H, m), and 8·86 (3H, t).

We thank Mrs. I. M. Bell and Miss M. Lennon for technical assistance, the Bristol Company (Syracuse) for a studentship (to M. S.), and the trustees of the Charles S. Crawford endowment for a studentship (to A. C.).

[2/616 *Received*, 16*th March*, 1972]