Azocine Derivatives. Part II.[1] Synthesis of Benzazocine Derivatives by Ring-expansion of Dihydrobenzazepines with Dibromocarbene

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Methods of ring-expansion for preparation of benzazocine derivatives have been explored. 2,3,4,5-Tetrahydro-1-*p*-tolylsulphonyl-1-benzazepin-5(1*H*)-one has been converted sequentially into the enol ether, which in turn gave a dibromocarbene adduct. This was ring-expanded to 2,3,4,5-tetrahydro-1-*p*-tolylsulphonyl-1-benzazocin-6(5*H*)-one and to the corresponding enol ether.

We have previously shown [2] that ring-expansion of 1,2-dihydroquinoline derivatives is a useful method for preparation of some dihydro-1-benzazepin-5-ones and 1-benzazepines. It was, therefore, of interest to find if the method was applicable to the higher homologues since the required starting materials, tetrahydrobenzazepinones, are readily available.[3] We report here on the scope of the procedure.

The tosylate (I; R = tosyl) was converted by reaction with triethyl orthoformate into the enol ether (II; R^1 = OEt, R^2 = tosyl), which reacted with dibromocarbene [prepared either from phenyl(tribromomethyl)mercury [4] (50%) or from bromoform and sodium t-butoxide in benzene–pentane [5,6] (60%)] to give the cyclopropane (III; R^1 = OEt, R^2 = tosyl). Ring-expansion was achieved in two ways. First, treatment with silver nitrate in aqueous ethanol,[7] gave a product (50%), which spectroscopic evidence (see Experimental section) suggested was the benzazocinone (IV). This conclusion was supported by catalytic hydrogenation of the ketone (IV), which gave the hexahydro-alcohol (V), identical with the substance obtained by reduction of the previously described ketone [1] (VI; R = H), itself the product of direct Dieckmann cyclisation. Similar ring-expansion of the lower homologue [2] gave a poor yield of the benzazepinone. We ascribe this to the reactivity of the enone, which contains a doubly activated CH_2 group; the benzazocinone (IV) would not, be expected to be unduly reactive. When the adduct (III; R^1 = OEt, R^2 = tosyl) was heated under reflux in aqueous pyridine a product was obtained in 87% yield to which we allocate the structure (VII) particularly since it could be converted into the enone (IV) on treatment with silica gel. The ring-expansion to the dihydrobenzazocine (VII) only proceeded in 14% yield in anhydrous pyridine; [7]

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[3] (*a*) I. McCall, G. R. Proctor, and L. Purdie, *J. Chem. Soc.* (*C*), 1970, 1126; (*b*) M. A. Rehman and G. R. Proctor, *ibid.*, 1967, 58; (*c*) I. MacDonald and G. R. Proctor, *ibid.*, 1970, 1461.

[4] (*a*) D. Seyferth, J. M. Burlitch, and J. K. Heeren, *J. Org. Chem.*, 1962, **27**, 1491; (*b*) J. M. Burlitch and D. Seyferth, *J. Organometallic Chem.*, 1965, **4**, 127.

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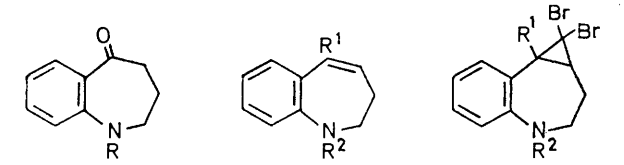
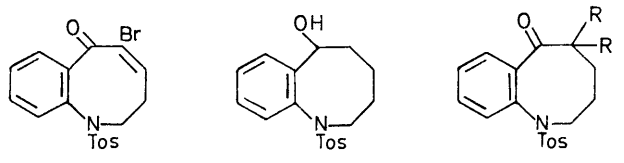
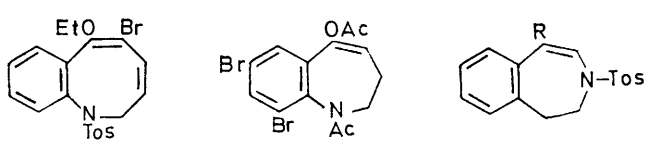
this implies the assistance of water in the transfer of a proton from the intermediate allyl cation to the base, pyridine. The ketone (IV) could not be transformed into its enol ether (VII) by treatment with triethyl orthoformate, and the enol ether (VII) failed to undergo addition with tetracyanoethylene.



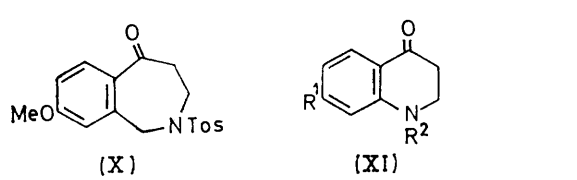
(I) (II) (III)



(IV) (V) (VI)



(VII) (VIII) (IX)



(X) (XI)

The successful ring-expansion of the adduct (III; R^1 = OEt, R^2 = tosyl) makes several 1-benzazocine derivatives available since we find that the tetrahydrobenzazocinone (IV) is not available by dehydrobromination of the 5,5-dibromo-derivative [1] (VI; R = Br) (*cf.* the corresponding 1-benzazepines in ref. 2). We feel that the bulk of the tosyl group interferes with approach of the base since brominated, detosylated derivatives of the tetrahydroketone (I; R = H) have been dehydrobrominated [8] recently, and we have demonstrated [2] that replacement of tosyl by the mesyl group in 1,2-dihydropyridines causes a dramatic steric effect during reaction at an apparently distant centre.

The adduct (III; R^1 = H, R^2 = tosyl) was obtained (80%) from the dihydrobenzazepine (II; R^1 = H, R^2 = tosyl) only by generating dibromocarbene from phenyl(tribromomethyl)mercury; [4] the alternative method (see before) [5,6] failed. However, the adduct was very stable, being recovered after heating under reflux in such diverse reagents as quinoline, silver nitrate in aqueous ethanol, and silver acetate in acetic acid. The enol acetate [9] (VIII) gave the corresponding dibromocarbene adduct, but treatment with potassium hydroxide in aqueous ethanol [10] resulted in an intractable gum. We were unable to obtain enol ethers from the *N*-phenyl (I; R = Ph), *N*-methyl (I; R = Me), or *N*-acetyl ketone (I; R = Ac) so it would appear that at present this transformation is limited to *N*-sulphonyl enol ethers.

Tetrahydro-3-benzazepin-1-one [3b] failed to form the enol ether or acetate (IX; R = OEt or OAc). The corresponding olefin [3b] (IX; R = H), however, was obtained and treated with phenyl(tribromomethyl)mercury to give the expected adduct in 40% yield. This adduct, like the corresponding 1-benzazepine derivatives (III; R^1 = H, R^2 = tosyl) did not undergo ring-expansion and since we have previously found the enol ether inaccessible in the tetrahydro-2-benzazepinone series [3c] (X), the possibilities for ring-expansion seem to be limited to the 1-benzazocines.

Ring-expansion by two carbon atoms is attractive. Cyclohexanone enamines have been shown to react with dimethyl acetylenedicarboxylate leading eventually to substituted cyclo-octadienes; [11] enol ethers [12] and enamines [13] of 5-membered ring *N*-heterocycles have been similarly expanded. Unfortunately we have been frustrated in attempts to use these methods for azocine derivatives since the enamine [14] of *N*-methylpiperid-4-one gave many products with dimethyl acetylenedicarboxylate and also we could not prepare morpholine or pyrrolidine enamines from the tetrahydroquinol-4-ones (XI; R^1 = Cl [15] or H, R^2 = tosyl or Ac [16]). The enol ether of the 6-methoxy-derivative of the quinolone (XI; R^1 = H, R^2 = tosyl) reacted slowly with dimethyl acetylenedicarboxylate but gave many products.

EXPERIMENTAL

2,3-Dihydro-5-ethoxy-1-p-tolylsulphonyl-1H-1-benzazepine (II; R^1 = OEt, R^2 = tosyl).—2,3,4,5-Tetrahydro-1-*p*-tolylsulphonyl-1-benzazepin-5(1*H*)-one [3a] (15 g), triethyl orthoformate (20 ml), and toluene-*p*-sulphonic acid (0·2 g) were heated in absolute ethanol (180 ml) for 3 h under reflux, cooled, neutralised with potassium ethoxide–ethanol, poured into an excess of water and extracted with benzene. The organic layer was washed and dried, and the solvent was evaporated *in vacuo* to give an oil, which yielded the desired *product* from light petroleum (b.p. 80—100°) as white needles (14·05 g, 86%) m.p. 97—98° (Found: C, 66·25; H, 6·35; N, 4·25. $C_{19}H_{21}NO_3S$ requires C, 66·45;

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H, 6·15; N, 4·1%), τ 2·2—2·8 (8H, m), 5·3 (1H, t), 5·89 (2H, t), 6·64 (2H, q), 7·56 (3H, s), 7·86 (2H, m), and 8·75 (3H, t), $\nu_{max.}$ (Nujol) 1650 cm^{-1} (C=C).

1,1-*Dibromo*-8b-*ethoxy*-1,1a,2,3,4,8b-*hexahydro*-4-p-*tolylsulphonylcyclopropa*[d][1]*benzazepine* (III; R^1 = OEt, R^2 = tosyl).—(a) A solution of the foregoing benzazepine tosylate (10 g) in dry benzene (100 ml) was added to a stirred suspension of sodium t-butoxide (9·6 g) in dry n-pentane (100 ml) and the mixture cooled to −20°. Bromoform (25·3 g) in dry benzene (10 ml) and dry n-pentane (10 ml) was added dropwise during 45 min, the temperature never exceeding −15°. When addition was complete, the mixture was stirred at −15° for 1 h and then at room temperature for 1 h, poured into an excess of water, and the organic layer was separated, washed, dried, and evaporated *in vacuo* to leave the *product*, as white needles (9·1 g, 60%), m.p. 148—149° (from ethanol).

(b) A mixture of the tosylate (II; R^1 = OEt, R^2 = tosyl) (4 g) and phenyl(tribromomethyl)mercury [4b] (8 g) was heated under reflux in dry benzene (100 ml) with stirring for 4 h. After cooling and filtration, the solvent was evaporated *in vacuo* to leave a dark brown oil which was chromatographed on neutral alumina. Benzene elution gave [after discarding a fore-run containing phenylmercury(II) bromide] the desired product (3·07 g, 51%), m.p. 147—149° undepressed on admixture with a sample prepared as in (a) (Found: C, 46·8; H, 4·15; N, 2·7. $C_{20}H_{21}Br_2NO_3S$ requires C, 46·75; H, 4·1; N, 2·7%), τ 1·96—2·66 (8H, m), 6·02—6·8 (6H, m), 7·55 (3H, s), 8·07 (1H, t), and 8·82 (3H, t).

5-*Bromo*-6-*ethoxy*-1,2-*dihydro*-1-p-*tolylsulphonyl*-1-*benzazocine* (VII).—The previous dibromocyclopropa-derivative (0·5 g) was heated under reflux in pyridine–water (30 ml; 1 : 1 v/v) for 18 h, cooled, poured into an excess of crushed ice–dilute hydrochloric acid and extracted with benzene. The extract was washed with dilute hydrochloric acid and water, dried, and the solvent was evaporated *in vacuo* leaving the product as a light yellow solid (0·34 g, 81%) which was crystallised from light petroleum (b.p. 60—80°) as needles, m.p. 152—153° [Found: C, 55·1; H, 4·7; N, 3·15%; *M* (mass spectroscopy), 433·033827. $C_{20}H_{20}{}^{79}BrNO_3S$ requires C, 55·25; H, 4·65; N, 3·25%; *M*, 433·034771], τ 2·2—2·98 (8H, m), 4·06 (1H, dt), 4·85 (1H, dt), 5·28—6·05 (2H, m), 6·24 (2H, q), 7·56 (3H, s), and 8·7 (3H, t), $\nu_{max.}$ (Nujol) 1650 cm^{-1} (C=C).

5-*Bromo*-2,3-*dihydro*-1-p-*tolylsulphonyl*-1-*benzazocin*-6(1H)-*one* (IV).—The cyclopropa[*d*][1]benzazepine (III; R^1 = OEt, R^2 = tosyl) (3 g) was dissolved in ethanol (100 ml), and silver nitrate (4·2 g) in water (5 ml) added to the mixture, which was heated under reflux for 3 h. After cooling and filtration to remove the precipitated silver bromide, the mixture was poured into an excess of water and extracted with benzene. The organic layer was separated, washed, and dried, and the solvent was evaporated *in vacuo* to leave a brown solid which was chromatographed on neutral alumina. Elution with benzene–ether (19 : 1) gave the desired *product* (1·2 g, 48%) as pale yellow prisms, m.p. 183—184° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 53·35; H, 3·95; N, 3·35. $C_{18}H_{16}BrNO_3S$ requires C, 53·2; H, 3·95; N, 3·45%), τ 2·14—2·92 (9H, m), 6·22 (2H, t), 7·58 (3H, s), and 7·81 (2H, m), $\nu_{max.}$ (Nujol) 1655 cm^{-1} (C=O).

Hydrolysis of 5-*Bromo*-6-*ethoxy*-1,2-*dihydro*-1-p-*tolylsulphonyl*-1-*benzazocine* (VII).—The enol ether (0·32 g) in benzene was poured onto a column of silica gel and left for 16 h. Elution with benzene–ether (19 : 1) gave the 1-benzazocin-6(1*H*)-one (IV) (0·23 g, 78%) which was purified as before and had m.p. 182—184° undepressed on admixture with a sample prepared as before.

Reduction of the 1-*Benzazocin*-6(1H)-*one* (IV).—The title compound (31 mg) was hydrogenated (1 atm) in ethanol (60 ml) over palladised charcoal (20 mg, 10%) for 24 h. After filtration and removal of solvent, the residue (13 mg) was recrystallised from light petroleum (b.p. 60—80°) in needles, m.p. 164—165°. This was identical (i.r., t.l.c., and mixed m.p.) with 1,2,3,4,5,6-*hexahydro*-1-p-*tolylsulphonyl*-1-*benzazocin*-6-*ol* (V) prepared by catalytic hydrogenation (conditions as above) of 2,3,4,5-tetrahydro-1-*p*-tolylsulphonyl-1-benzazocin-6(1*H*)-one (VI; R = H).

Attempted Dehydrobromination of 5,5-*Dibromo*-2,3,4,5-*tetrahydro*-1-p-*tolylsulphonyl*-1-*benzazocin*-6(1H)-*one* (VI; R = Br).—The dibromide was recovered after treatment with triethylamine in chloroform for 24 h at 20°. Heating the mixture for 8 h under reflux caused extensive decomposition.

1,1-*Dibromo*-1,1a,2,3,4,8b-*hexahydro*-4-p-*tolylsulphonylcyclopropa*[d][1]*benzazepine* (III; R^1 = H, R^2 = tosyl).—2,3-Dihydro-1-*p*-tolylsulphonyl-1*H*-1-benzazepine [9] (4 g) and phenyl(tribromomethyl)mercury [4b] (8 g) were heated under reflux with stirring in dry benzene (100 ml) for 7 h. After cooling, the mixture was filtered and the solvent was evaporated *in vacuo* to leave a dark oil, which was chromatographed on neutral alumina. Benzene elution gave [after discarding a fore-run containing phenylmercury(II) bromide] the desired *product* as a light yellow oil (5·2 g, 81%) which crystallised from ethanol as white needles, m.p. 134—136° (Found: C, 45·5; H, 3·85; N, 2·95. $C_{18}H_{17}Br_2NO_2S$ requires C, 45·95; H, 3·6; N, 2·95%), τ 2·2—2·7 (8H, m), 5·67 (2H, td), 6·52 (2H, m), 7·55 (3H, s), 8·0 (1H, d), and 8·33 (1H, td).

Attempted Ring-expansion of 1,1-*Dibromo*-1,1a,2,3,4,8b-*hexahydro*-4-p-*tolylsulphonylcyclopropa*[d][1]*benzazepine*.—(a) The dibromocyclopropa-derivative was unaffected on heating with pyridine, quinoline, silver nitrate in aqueous ethanol, silver acetate in acetic acid, or triethylamine under reflux.

(b) To a stirred solution of the dibromocyclopropa-derivative (0·47 g) in pyridine (20 ml) was added a solution of sodium hydroxide (0·05 g) in ethanol (20 ml) and the mixture stirred at room temperature for 4·5 h, poured into an excess of ice–dilute hydrochloric acid and extracted with benzene. The organic extract was washed and dried, and the solvent was evaporated *in vacuo* to leave a dark oil (0·41 g), which could not be crystallised. Attempted chromatography on neutral alumina gave intractable mixtures, from which no identifiable products could be isolated.

1,1-*Dibromo*-1,1a,2,3,4,8b-*hexahydro*-2-p-*tolylsulphonylcyclopropa*[a][3]*benzazepine* [*Dibromocarbene Adduct of* (IX; R = H)].—1,2-Dihydro-3-*p*-tolylsulphonyl-3-benzazepine [3b] (IX; R = H) (3 g) and phenyl(tribromomethyl)-mercury [4b] (8 g) were heated under reflux with stirring in dry benzene (100 ml) for 15 h. After being cooled, the mixture was filtered and the solvent was evaporated *in vacuo* to leave an oil which was chromatographed on silica gel. Elution with benzene gave the desired *product* as an oil, which crystallised from benzene–light petroleum (b.p. 60—80°) as white needles (1·7 g, 38%), m.p. 150—151° [Found: C, 45·65; H, 3·45; N, 3·15%; *M* (mass spectroscopy), 472·929942. $C_{18}H_{17}{}^{81}Br_2NO_2S$ requires C, 45·95; H, 3·6; N, 2·95%; *M*, 472·930833], τ 1·97—2·85 (8H, m),

6·43 (2H, t), 6·68 (2H, t), 6·95 (1H, d), 7·15 (1H, d), and 7·49 (3H, s).

This compound was unaffected on heating with either silver nitrate or silver perchlorate in aqueous ethanol under reflux.

4-*Acetyl*-1,1,5,7-*tetrabromo*-1,1a,2,3,4,8b-*hexahydrocyclopropa*[d][1]*benzazepin*-8b-*yl Acetate* [*Dibromocarbene adduct of* (VIII)].—1-Acetyl-7,9-dibromo-2,3-dihydro-1*H*-1-benzazepin-5-yl acetate [9] (1·4 g) and phenyl(tribromomethyl)-mercury [4b] (5·08 g) were heated in dry benzene (120 ml) under reflux with stirring for 17 h. On cooling, the mixture was filtered and the solvent was evaporated *in vacuo* to leave a brown oil which yielded the desired *product* from methanol as light brown prisms (0·48 g, 24%), m.p. 202—204° [Found: C, 31·75; H, 2·1; N, 2·25%; *M* (mass spectroscopy), 574·757434. $C_{15}H_{13}{}^{79}Br_2{}^{81}Br_2NO_3$ requires C, 31·45; H, 2·3; N, 2·45%; *M*, 574·759157], $\nu_{max.}$ (Nujol) 1750 (C=O; ester) and 1650 cm^{-1} (C=O; amide).

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