Azocine Derivatives. Part I. Synthesis of 1-Benzazocin-6-one Derivatives by Direct Cyclisation

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Tetrahydro-1-benzazocin-6(5*H*)-one derivatives have been made by Dieckmann cyclisation of appropriate diesters, followed by hydrolysis. Attempts to make tetrahydro-1-benzazocin-5(6*H*)-ones and a tetrahydro-2-benzazocin-6(5*H*)-one by similar procedures failed.

REDUCED derivatives of monocyclic azocines have been known for some time. These have commonly been obtained, for example, by Beckmann rearrangement of cycloheptanone oximes,[1] Dieckmann cyclisation of appropriate amino-diesters,[2] or Favorskii-type rearrangement of a nine-membered lactam.[3] Azocines themselves have until recently been less well studied; however, Paquette and his co-workers [4] have made notable contributions in this area during the last five years. Both the biological activity of certain azocine derivatives (*e.g.* benzomorphans [5]) and the interesting structural possibilities in medium-sized rings prompted us to attempt the synthesis of some new azocine derivatives by methods developed by us in the azepine field. We deal here with some benzazocinones.

We set out to obtain intermediates in which the nitrogen atom of the heterocycle was separated by at least one carbon atom from a carbonyl group, which could then be used to bring about further transformations. Accordingly we have considered direct cyclisation of appropriate esters or acids by the Dieckmann and Friedel–Crafts reactions, respectively, leading to reduced 3-benzazocin-6-ones, 2-benzazocin-6-ones, and 1-benzazocin-5- and -6-ones.

During our work, Larsen and Scarborough [6] reported the synthesis of tetrahydro-3-benzazocin-6(5*H*)-ones by direct Friedel–Crafts cyclisation of *N*-mesyl and *N*-tosyl acids so we did not pursue our studies of this system. It seemed likely that tetrahydro-3-benzazocin-1(2*H*)-ones (I) could be obtained by adaptation of our Friedel–Crafts methods for the corresponding tetrahydro-3-benzazepin-5-ones,[7] but since this idea was being explored elsewhere [8] we attempted first a synthesis of the isomeric system tetrahydro-2-benzazocin-6(5*H*)-one [*e.g.* (II)]. Experience with 1-benzazepine derivatives [9] suggested that for ketones (II; R^2 = Ts) the Friedel–Crafts cyclisation is unsuitable, and because we suspected that the diester (III; R = Ts) required for Dieckmann cyclisation [to (II; R^2 = Ts)] might undergo base-catalysed elimination of the tosyl group,[10] we attempted to obtain the diester (III; R = Ph) instead. This compound, however, proved inaccessible; for example reaction of ethyl γ-bromobutyrate with methyl *o*-(anilinomethyl)benzoate (IV) gave only the *N*-phenylisoindolone (V).

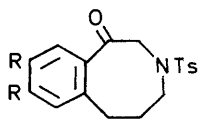
Turning our attention to tetrahydro-1-benzazocin-6(5*H*)-one derivatives [*e.g.* (VI)], we felt that the Dieckmann reaction, when applied to suitable diesters [*e.g.* (VII; R = Ts)] would lead to cyclisation [to (VI; $R^1 = CO_2Et$, R^2 = Ts)] *unless* a hitherto-unknown elimination reaction intervened [as depicted in (VIII)]. As a precaution, we investigated this possibility. 2-Pyrrolidones [11] have been obtained as shown in (IX) but the base-catalysed tosyl elimination has previously been seen to operate only between carbon and nitrogen atoms already joined by a σ-bond, *i.e.* in such a way as to produce initially an imine.[10] Suitable model compounds were constructed to explore the possibility that a carbanion could form a σ-bond to a nitrogen atom with concomitant loss of the *p*-tolylsulphinyl anion. Thus the ester (X) and the ketones (XI; R = Me or $PhCH_2$), made by conventional procedures,[12] were treated with various bases. In every case the starting material was recovered. Accordingly the process depicted in (VIII) would not be expected to take place in preference to Dieckmann cyclisation, and in fact this proved to be the case.

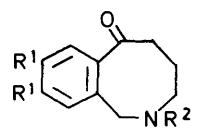
Treatment of methyl *N*-tosylanthranilate with ethyl 5-bromovalerate (*cf.* ref. 9) gave the diester (VII; R = Ts), which was treated with sodium hydride in dimethylformamide to give the keto-ester (VI; $R^1 = CO_2Et$, R^2 = Ts). Acid hydrolysis of the product gave the ketone (VI; R^1 = H, R^2 = Ts) in 30% overall yield from methyl *N*-tosylanthranilate. The *N*-mesyl ester (VII; $R = MeSO_2$) was made similarly and isolated, but on treatment with sodium hydride in dimethylformamide gave an intractable product.

We have explored the detosylation of the ketone (VI; R^1 = H, R^2 = Ts) and the possibility of finding transannular reactions involving C-5 and the nitrogen atom. Controlled bromination of compound (VI; R^1 = H,

[1] F. F. Blicke and N. J. Doorenbos, *J. Amer. Chem. Soc.*, 1954, **76**, 2317.
[2] N. J. Leonard and T. Sato, *J. Org. Chem.*, 1969, **34**, 1066, and earlier papers.
[3] H. T. Nagasawa and J. A. Elberling, *Tetrahedron Letters*, 1966, **44**, 5393.
[4] L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, 1971, **93**, 174, and earlier papers.
[5] K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Medicin. Chem.*, 1969, **12**, 405, and earlier papers.
[6] A. A. Larsen and H. Scarborough, U.S.P. 3,442,890 (*Chem. Abs.*, 1969, **71**, 61,249).
[7] M. A. Rehman and G. R. Proctor, *J. Chem. Soc.* (*C*), 1967, 58; I. MacDonald and G. R. Proctor, *ibid.*, 1969, 1312.
[8] R. E. Partch and J. Schlademan, personal communication.
[9] I. McCall, G. R. Proctor, and L. Purdie, *J. Chem. Soc.* (*C*), 1970, 1126, and earlier papers.
[10] E. D. Hannah, G. R. Proctor, and M. A. Rehman, *J. Chem. Soc.* (*C*), 1967, 256.
[11] D. B. Astill and V. Boekelheide, *J. Amer. Chem. Soc*, 1955, **77**, 4079; J. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1958, 3377; G. R. Proctor and R. H. Thomson, *ibid.*, 1957, 2302.
[12] M. A. Rehman, Ph.D. Thesis, University of Strathclyde, 1966.

R^2 = Ts) gave successively the monobromo- (VI; R^1 = Br, R^2 = Ts) and αα-dibromo-ketones; treatment


(I)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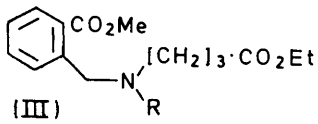
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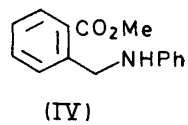
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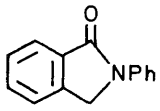
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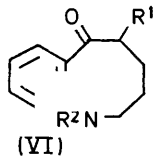
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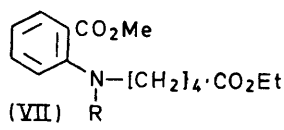
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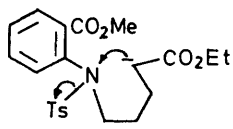
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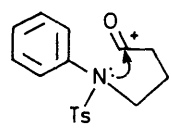
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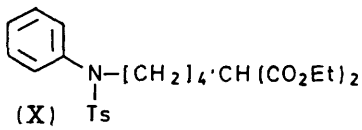
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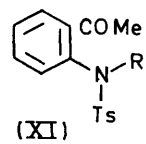
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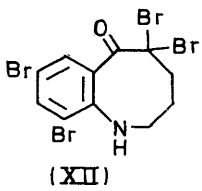
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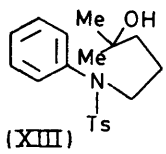
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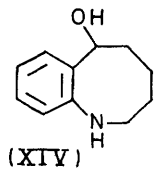
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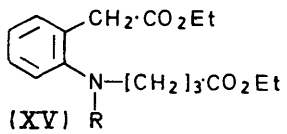
(XV)

Ts = *p*-$MeC_6H_4·SO_2$

with an excess of bromine yielded the tetrabromo-compound (XII). These results parallel those obtained for the corresponding 1-benzazepine derivatives.[13] None of these bromides underwent any reaction with silver perchlorate in dimethylformamide or with anhydrous aluminium bromide in benzene, reactions designed to create carbonium ions at C-5 which might have initiated a Ts^+ elimination [*cf.* (IX)]. These failures are probably not entirely due to the presence of a carbonyl group at C-6, since we have previously [12] found that treatment of the favourably constructed tertiary alcohol (XIII) with acid did not lead to any tosyl elimination. Treatment of the ketone (VI; R^1 = H, R^2 = Ts) with sodium ethoxide in benzene caused a reaction but we were unable to purify the products. The ketone (VI; R^1 = H, R^2 = Ts) was reduced by sodium borohydride to the corresponding alcohol, which was detosylated by sodium in liquid ammonia to the expected amino-alcohol (XIV), the yields in both steps being nearly quantitative.

In order to obtain also tetrahydro-1-benzazocin-5(6*H*)-ones we have synthesised the diesters (XV; R = $MeSO_2$ or Ts) by conventional procedures, but in the Dieckmann reaction they gave intractable products: we can offer no explanation for this.

Thus, of the cases we have examined, only tetrahydro-1-benzoazocin-6(5*H*)-one derivatives have been obtained, but the procedure used is simple and yields are satisfactory.

EXPERIMENTAL

Ethyl γ-[N-(o-Ethoxycarbonylmethylphenyl)-p-tolylsulphonylamino]butyrate (XV; R = Ts).—A mixture of ethyl *o*-(*p*-tolylsulphonylamino)phenylacetate [10] (9 g), ethyl γ-bromobutyrate (10 g), and anhydrous potassium carbonate (14 g) was refluxed in dry acetone (150 ml) with stirring for 18 h, and filtered. The filtrate was evaporated *in vacuo* to leave a red oil which was chromatographed on neutral alumina. Elution with benzene gave unchanged ethyl γ-bromobutyrate and then the product (XV; R = Ts) (10·1 g, 83%) as a viscous yellow liquid which could not be crystallised or distilled, $\nu_{max.}$ (film) 1725 cm^{-1} (C=O). The corresponding *diacid* crystallised from ethanol–water as white needles, m.p. 175—176° (Found: C, 58·4; H, 5·2; N, 3·6. $C_{19}H_{21}NO_6S$ requires C, 58·6; H, 5·4; N, 3·6%), $\nu_{max.}$ (Nujol) 1710 cm^{-1} (C=O).

Attempted Cyclisation of the Diester (XV; R = Ts).—(*a*) To a stirred solution of the diester (4·47 g, 0·01 mol) in dry dimethylformamide (200 ml) under dry, prepurified nitrogen, was added sodium hydride (50% dispersion; 0·48 g, 0·01 mol) during 1 h. The mixture was then stirred for 2 h, and the temperature raised to 80° and maintained there for 18 h. After cooling, the mixture was poured into an excess of ice–dilute hydrochloric acid and extracted with benzene. The extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated *in vacuo* to leave a dark oil (1·32 g) which was shown (t.l.c.) to be a complex mixture. This material was refluxed in a mixture of glacial acetic acid (10 ml), concentrated hydrochloric acid (5 ml), ethanol (5 ml), and water (5 ml), for 96 h, and cooled. The mixture was then diluted with water and extracted with benzene. The extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated *in vacuo* to leave a red oil (0·15 g), from which no identifiable products were isolated.

(*b*) To a stirred suspension of potassium (0·98 g, 0·052 g-atom) in dry toluene (100 ml) at 75—80° under dry, prepurified nitrogen, was added t-butyl alcohol (1·85 g, 0·025 mol) in toluene (50 ml), and the mixture was stirred for 2 h. The diester (4·47 g, 0·01 mol) in toluene (75 ml) was added

[13] E. D. Hannah, W. C. Peaston, and G. R. Proctor, *J. Chem. Soc.* (*C*), 1968, 1280.

during 0·5 h and the mixture was then stirred for 1 h at 80°, refluxed for 1 h, and cooled. Ethanol was carefully added, then water (excess), and the layers were separated. The organic layer was washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, dried, and evaporated *in vacuo* to leave a dark yellow gum (0·04 g) which was not further investigated.

Ethyl o-(N-*Methylsulphonylamino*)*phenylacetate*.— To ethyl *o*-aminophenylacetate [10] (25 g) in pyridine (150 ml) at 0° was added methanesulphonyl chloride (35 g); the mixture was set aside for 18 h, and then poured into an excess of ice–dilute hydrochloric acid. The solid product formed *needles*, m(52 98—99° (from ethanol) (Found: C, 51·65; H, 5·75; 14;0·55. $C_{11}H_{15}NO_4S$ requires C, 51·45; H, 5·85; N, 5·45%), τ 2·08br (1H, s, exch., NH), 2·42—2·83 (4H, m), 5·84 (2H, q), 6·29 (2H, s), 6·95 (3H, s), and 8·73 (3H, t), $\nu_{max.}$ (Nujol) 3310 (N–H) and 1720 cm^{-1} (C=O).

Ethyl γ-[N-(o-*Ethoxycarbonylmethylphenyl*)*methylsulphonylamino*]*butyrate* (XV; R = $MeSO_2$).—A vigorously stirred mixture of the foregoing ester (40 g), ethyl γ-bromobutyrate (39 g), and anhydrous potassium carbonate (21 g) was refluxed in dry acetone (450 ml) for 3 h, and cooled. The mixture was diluted with water and benzene. The organic layer was washed, dried, and evaporated *in vacuo* to give the *product* as a yellow liquid which slowly solidified. Recrystallisation from methylene dichloride–light petroleum (b.p. 60—80°) yielded white prisms (52 g, 92%), m.p. 68—70° (Found: C, 55·45; H, 6·8; N, 4·0. $C_{17}H_{25}NO_6S$ requires C, 54·95; H, 6·8; N, 3·8%), τ 2·5—2·8 (4H, m), 5·75—6·03 (4H, m), 6·24 (2H, s), 6·38 (2H, t), 7·08 (3H, s), 7·68 (2H, t), 8·17 (2H, t), and 8·76 (6H, m), $\nu_{max.}$ (Nujol) 1730 cm^{-1} (C=O).

Reaction of Aniline with Methyl o-*Bromomethylbenzoate*.—Aniline (7 g, 0·075 mol), methyl *o*-bromomethylbenzoate [14] (13·1 g, 0·075 mol), and anhydrous potassium carbonate (10·5 g, 0·075 mol) were refluxed in dry acetone (200 ml) with stirring for 16 h. The cooled mixture was then diluted with water and benzene. The organic layer was washed thoroughly with dilute hydrochloric acid and then concentrated hydrochloric acid.

The dilute hydrochloric acid washings were neutralised with dilute sodium hydroxide solution and extracted with methylene dichloride. The organic extract was washed, dried, and evaporated *in vacuo* to leave *methyl* o-(*anilinomethyl*)*benzoate* (IV) as a red oil (8·01 g) which was not further purified, $\nu_{max.}$ (film) 3400 (N–H) and 1700 cm^{-1} (C=O). Similar work-up of the concentrated hydrochloric acid washings gave dimethyl αα′-phenyliminodi-p-toluoate as a brown solid which crystallised from chloroform–ethanol, as white prisms (3·9 g), m.p. 164—166° (Found: C, 73·85; H, 6·4; N, 3·6. $C_{24}H_{23}NO_4$ requires C, 74·05; H, 5·9; N, 3·6%), τ 1·91—3·48 (13H, m), 4·94 (4H, s), and 6·15 (6H, s), $\nu_{max.}$ (Nujol) 1700 cm^{-1} (C=O).

Reaction of Methyl o-(*Anilinomethyl*)*benzoate with Ethyl* γ-*Bromobutyrate*.—The amine (6·25 g), ethyl γ-bromobutyrate (5·85 g), and anhydrous potassium carbonate (4·1 g) were refluxed with stirring in dry acetone (50 ml) for 16 h. The cooled mixture was diluted with water and methylene dichloride and the organic layer was washed, dried, and evaporated *in vacuo* to leave a dark oil which solidified. Recrystallisation from ethanol gave 2,3-*dihydro*-N-*phenylisoindol*-1-*one* (V) (4·5 g) as plates, m.p. 160—161° (Found: C, 80·95; H, 5·55; N, 7·1. $C_{14}H_{11}NO$ requires C, 80·45; H, 5·3; N, 6·75%), τ 2·18—2·91 (9H, m) and 5·18 (2H, s), $\nu_{max.}$ (Nujol) 1680 cm^{-1} (C=O).

Ethyl 1,2,3,4,5,6-*Hexahydro*-6-*oxo*-N-p-*tolylsulphonyl*-1-*benzazocine*-5-*carboxylate* (VI; R^1 = CO_2Et, R^2 = Ts).—To a stirred solution of methyl *N*-*p*-tolylsulphonylanthranilate (45·75 g, 0·15 mol) in dry dimethylformamide (800 ml) under dry, prepurified nitrogen, sodium hydride (50% dispersion; 7·2 g, 0·15 mol) was slowly added during 1 h. After a further 2 h, ethyl 5-bromovalerate (31·5 g, 0·15 mol) in dry dimethylformamide (20 ml) was added, and the temperature was raised to 80° and maintained there for 18 h. To the cooled mixture was added sodium hydride (50% dispersion; 7·2 g, 0·15 mol) and stirring was continued at room temperature for 2 h, and then at 80° for 18 h. The mixture was then cooled, diluted with an excess of ice–dilute hydrochloric acid, and extracted with benzene. The extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated *in vacuo* to leave a red oil (46 g), a sample of which crystallised from ethanol to give *prisms*, m.p. 152—153° (Found: C, 62·6; H, 5·55; N, 3·4. $C_{21}H_{23}NO_5S$ requires C, 62·8; H, 5·3; N, 3·5%), τ −2·5 (1H, s, exch.), 2·43—2·98 (8H, m), 5·78 (2H, q), 6·24 (2H, m), 7·3 (2H, m), 7·61 (3H, s), 8·52 (2H, m), and 8·69 (3H, t), $\nu_{max.}$ (Nujol) 1645 cm^{-1} (C=O).

2,3,4,5-*Tetrahydro*-N-p-*tolylsulphonyl*-1-*benzazocin*-6(1H)-*one* (VI; R^2 = H, R^2 = Ts).—The foregoing crude keto-ester (45 g) was refluxed in a mixture of glacial acetic acid (220 ml), concentrated hydrochloric acid (40 ml), ethanol (100 ml), and water (40 ml) for 96 h, and cooled. The mixture was then added to an excess of water and extracted with benzene. The extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated *in vacuo* to leave a yellow solid (16·85 g, 30% overall) which crystallised from ethanol as prisms, m.p. 144—145° (Found: C, 65·6; H, 5·95; N, 4·45. $C_{18}H_{19}NO_3S$ requires C, 65·6; H, 5·8; N, 4·25%), τ 1·96—2·78 (8H, m), 6·32 (2H, t), 6·8 (2H, t), 7·61 (3H, s), and 8·3 (4H, m), $\nu_{max.}$ (Nujol) 1665 cm^{-1} (C=O).

Reaction of 2,3,4,5-*Tetrahydro*-N-p-*tolylsulphonyl*-1-*benzazocin*-6(1H)-*one with Hydroxylamine*.—A mixture of the ketone (0·5 g), hydroxylamine hydrochloride (0·5 g), and anhydrous sodium carbonate (1 g) was refluxed in absolute ethanol (25 ml) for 2 h, and filtered. On cooling, the *oxime* crystallised as white plates (0·45 g), m.p. 208—210° (Found: C, 62·85; H, 5·7; N, 8·25. $C_{18}H_{20}N_2O_3S$ requires C, 62·8; H, 5·8; N, 8·1%), τ (C_5D_5N) 1·84—2·99 (8H, m), 5·2br (1H, s), 6·33 (2H, t), 6·57 (2H, t), 7·78 (3H, s), and 8·37 (4H, m), $\nu_{max.}$ (Nujol) 3400 cm^{-1} (O–H).

Reaction of Methyl N-*Methylsulphonylanthranilate with Ethyl* 5-*Bromovalerate*.—To a stirred solution of the sulphonamide (11·5 g, 0·005 mol) in dry dimethylformamide (75 ml) under dry, prepurified nitrogen, sodium hydride (50% dispersion; 2·4 g, 0·05 mol) was slowly added during 1 h. After a further 1·5 h, ethyl 5-bromovalerate (10·5 g, 0·05 mol) in dry dimethylformamide (25 ml) was added, and the temperature was raised to 90° and maintained there for 16 h. The cooled mixture was diluted with water, acidified, and extracted with ether. The extract was washed, dried, and evaporated *in vacuo* to leave a dark liquid (17·74 g) which was chromatographed on silica gel. Elution with benzene–ether (19 : 1) gave a mixture of starting materials and then *ethyl* 5-[N-(o-*methoxycarbonylphenyl*)*methylsulphonylamino*]*valerate* (14·5 g, 81%) (VII; R = $MeSO_2$) as a yellow liquid which could not be crystallised or distilled (Found: C, 54·35; H, 6·9; N, 4·1. $C_{16}H_{23}NO_6S$ requires C, 53·85; H, 6·5; N, 3·9%), τ 2·05—2·62

[14] E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, 1952, **17**, 1252.

(4H, m), 5·84 (2H, q), 6·11 (3H, s), 6·38 (2H, m), 7·06 (3H, s), 7·73 (2H, m), 8·4 (2H, m), 8·62 (2H, t), and 8·79 (3H, t), $\nu_{max.}$ (film) 1720 cm^{-1} (C=O).

Reaction of the Diester (VII; R = $MeSO_2$) *with Sodium Hydride.*—To a stirred solution of the diester (3·5 g, 0·01 mol) in dry dimethylformamide (200 ml) under dry, prepurified nitrogen, sodium hydride (50% dispersion; 0·48 g, 0·01 mol) was added during 1 h. The mixture was then stirred for 2 h, and the temperature raised to 80° and maintained there for 11 h. The cooled mixture was then poured into an excess of ice–dilute hydrochloric acid and extracted with benzene. The extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated *in vacuo* to leave a black oil (2·01 g). This material was refluxed in a mixture of glacial acetic acid (10 ml), concentrated hydrochloric acid (5 ml), ethanol (5 ml), and water (5 ml) for 96 h, and cooled. The mixture was then diluted with water and extracted with benzene. The extract was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated *in vacuo*, but no product was obtained. The acidic and alkaline washings were neutralised and extracted with methylene dichloride. The acidic washings gave no product and the alkaline washings gave a yellow oil (0·2 g) from which no identifiable products were isolated.

*5-Bromo-2,3,4,5-tetrahydro-*N-p-*tolylsulphonyl-1-benzazocin-6(1H)-one* (VI; R^1 = Br, R_2 = Ts).—2,3,4,5-Tetrahydro-*N-p*-tolylsulphonyl-1-benzazocin-6(1*H*)-one (2 g) in chloroform (20 ml) was treated with bromine (0·3 ml); the mixture was stirred at room temperature for 2 h, then evaporated *in vacuo* to leave a yellow solid (2·2 g) which yielded *plates*, m.p. 142—143° (from ethanol) (Found: C, 53·25; H, 4·55; N, 3·85. $C_{18}H_{18}BrNO_3S$ requires C, 52·95; H, 4·4; N, 3·45%), $\nu_{max.}$ (Nujol) 1695 cm^{-1} (C=O). The monobromide was recovered unchanged from heating with either silver perchlorate in dimethylformamide at 100° or aluminium bromide in refluxing benzene.

*5,5-Dibromo-2,3,4,5-tetrahydro-*N-p-*tolylsulphonyl-1-benzazocin-6(1H)-one.*— 2,3,4,5-Tetrahydro-*N-p*-tolylsulphonyl-1-benzazocin-6(1*H*)-one (1 g) in chloroform (20 ml) was treated with bromine (0·3 ml); the mixture was stirred at room temperature for 3 h, then evaporated *in vacuo*, and the residue crystallised from ethanol to give *plates* (0·92 g), m.p. 125—126° (decomp.) (Found: C, 44·7; H, 3·55; N, 2·75. $C_{18}H_{17}Br_2NO_3S$ requires C, 44·35; H, 3·5; N, 2·85%), $\nu_{max.}$ (Nujol) 1720 cm^{-1} (C=O).

*Reaction of 5,5-Dibromo-2,3,4,5-tetrahydro-*N-p-*tolylsulphonyl-1-benzazocin-6(1H)-one with Zinc.*—The dibromide (1·3 g) and zinc dust (2 g) were refluxed in methanol for 2 h; the mixture was filtered and the filtrate was evaporated *in vacuo* to leave 2,3,4,5-tetrahydro-*N-p*-tolylsulphonyl-1-benzazocin-6(1*H*)-one as a yellow oil (0·84 g) which crystallised from ethanol as needles, m.p. and mixed m.p. 143—145°.

2,3,4,5-Tetrahydro-5,5,8,10-tetrabromo-1-benzazocin-6(1H)-one (XII).—To a solution of 2,3,4,5-tetrahydro-*N-p*-tolylsulphonyl-1-benzazocin-6(1*H*)-one (0·85 g) in chloroform (3 ml) was added a solution of bromine (1 ml) in chloroform (5 ml) and the resultant fuming solution was left for 48 h. The yellow precipitate (1·02 g, 82%) afforded the *tetrabromide* as yellow prisms, m.p. 195—196° (from ethanol) (Found: C, 26·95; H, 1·55; N, 3·05. $C_{11}H_9Br_4NO$ requires C, 26·85; H, 1·8; N, 2·85%), $\nu_{max.}$ (Nujol) 3280 (N–H) and 1715 cm^{-1} (C=O).

The tetrabromide was recovered unchanged from heating with either silver perchlorate in dimethylformamide at 100° or aluminium bromide in refluxing benzene.

*1,2,3,4,5,6-Hexahydro-*N-p-*tolylsulphonyl-1-benzazocin-6-ol.*—Sodium borohydride (0·15 g) was added in portions to a solution of 2,3,4,5-tetrahydro-*N-p*-tolylsulphonyl-1-benzazocin-6(1*H*)-one (1·1 g) in absolute ethanol; the mixture was stirred at room temperature for 16 h then treated with an excess of ice–dilute hydrochloric acid and extracted with chloroform. The extract was washed with sodium carbonate solution and water, dried, and evaporated *in vacuo* to leave the *product* (1·05 g, 95%), which crystallised from methanol as white prisms, m.p. 166—168° (Found: C, 65·8; H, 6·4; N, 4·05. $C_{18}H_{21}NO_3S$ requires C, 65·35; H, 6·35; N, 4·25%), $\nu_{max.}$ (Nujol) 3470 cm^{-1} (O–H).

*Reaction of 1,2,3,4,5,6-Hexahydro-*N-p-*tolylsulphonyl-1-benzazocin-6-ol with Sodium in Liquid Ammonia.*—To a stirred suspension of the alcohol (0·52 g, 0·0016 mol) in liquid ammonia (*ca.* 25 ml) was added sodium (0·16 g, 0·007 mol). After 10 min, while the blue colour persisted, ammonium chloride was added. When the solution was colourless, the ammonia was allowed to evaporate, and methanol, then water and chloroform were added. The organic layer was washed, dried, and evaporated *in vacuo* to leave *1,2,3,4,5,6-hexahydro-1-benzazocin-6-ol* (XIV) (0·26 g, 93%) which crystallised from methylene dichloride–light petroleum (b.p. 60—80°) as white plates, m.p. 86—88° (Found: C, 74·05; H, 8·35; N, 8·05. $C_{11}H_{15}NO$ requires C, 74·55; H, 8·5; N, 7·9%), τ 2·8—3·15 (4H, m), 5·14 (1H, m), 5·62br (2H, s, exch., OH and NH), 6·96 (2H, m), and 7·9—8·8 (6H, m), $\nu_{max.}$ (Nujol) 3320, 3240, and 3220 cm^{-1} (N–H and O–H).

*Reaction of 2,3,4,5-Tetrahydro-*N-p-*tolylsulphonyl-1-benzazocin-6(1H)-one with Sodium Ethoxide.*—A solution of the ketone (1 g) in dry benzene (10 ml) was added to a stirred suspension of sodium ethoxide [from sodium (0·5 g)] in dry benzene (10 ml); the mixture was stirred for 12 h, after which time all the starting material had reacted (t.l.c.). The mixture was diluted with water and the layers were separated. The organic layer was washed, dried, and evaporated *in vacuo* to leave a yellow oil (0·52 g) from which no identifiable products were isolated. Attempted acetylation also failed to provide any recognisable products.

No toluene-*p*-sulphinic acid was detected after neutralisation and extraction of the aqueous layer.

N-p-Tolylsulphonyl-4-anilinobutan-1-ol.[12]—Ethyl γ-(*N*-phenyl-p-tolylsulphonylamino)butyrate [11] (36·1 g) in dry tetrahydrofuran (100 ml) was added with stirring during 1·5 h under nitrogen to lithium aluminium hydride (1·9 g) in dry tetrahydrofuran (50 ml). After being refluxed for 2 h and cooled, the mixture was poured into ice–dilute hydrochloric acid and extracted with chloroform. The extract was washed with dilute sodium hydroxide solution and water, dried, and evaporated leaving the product (22 g) which crystallised from benzene–light petroleum (b.p. 60—80°) as *needles*, m.p. 71° (Found: C, 63·45; H, 6·5; N, 4·25. $C_{15}H_{21}NO_3S$ requires C, 63·9; H, 6·6; N, 4·25%), $\nu_{max.}$ (Nujol) 3268 cm^{-1} (OH).

*N-4-Bromobutyl-*N-p-*tolylsulphonylaniline.*[12]—To the foregoing alcohol (21 g) in dry benzene (60 ml) at 0—5° was added phosphorus tribromide (7 g) in dry benzene (50 ml) with stirring. After 12 h at 0°, the mixture was filtered, and the filtrate washed with aqueous sodium carbonate solution (5%) and water, and dried. Chromatography on neutral alumina [elution with light petroleum (b.p. 60—80°)–benzene (4 : 1)] and crystallisation from light petro-

leum (b.p. 80—100°) gave *cubes*, m.p. 78—78·5° (13·6 g) (Found: C, 53·75; H, 5·4; Br, 20·6; N, 3·9. $C_{15}H_{20}BrNO_2S$ requires C, 53·35; H, 5·2; Br, 21·0; N, 3·9%).

Diethyl N-p-*Tolylsulphonylamino*-4-*anilinobutylmalonate* (X).[12]—Diethyl malonate (4·5 g) was added to sodium ethoxide [from sodium (0·7 g) in ethanol (10 ml)] and then, with vigorous stirring, the foregoing bromide (10·7 g) in ethanol (15 ml) was added during 1 h. The mixture was refluxed for 2 h and then the solvent was removed *in vacuo*. The crude product was chromatographed on silica gel; elution with benzene–light petroleum (b.p. 60—80°) (1 : 1) gave a yellow oil (9·2 g), b.p. 185—190° at 0·1 mmHg (Found: C, 66·8; H, 7·2; N, 3·25. $C_{24}H_{31}NO_6S$ requires C, 67·1; H, 7·3; N, 3·25%), $\nu_{max.}$ (film) 1730 cm^{-1} (ester). This material was unchanged after treatment with (*a*) sodium ethoxide in toluene at 20°, (*b*) sodium hydride in tetrahydrofuran at reflux, or (*c*) potassium t-butoxide in dimethyl sulphoxide at 20°.

N-p-*Tolylsulphonyl*-o-*methylaminoacetophenone* (XI; R = Me).[15]—*N*-*p*-Tolylsulphonyl-*o*-aminoacetophenone (1 g) and benzene (100 ml) were shaken for 1 h with an ion-exchange resin (IRA 410; 20 g) which had been previously washed with sodium hydroxide solution and water. Methyl iodide (12 ml) was then added and the mixture was left at 20° for 96 h. After filtration and removal of solvent, the product (960 mg) crystallised from methanol in *cubes*, m.p. 116° (Found: C, 63·4; H, 5·5; N, 4·65. $C_{16}H_{17}NO_3S$ requires C, 63·35; H, 5·5; N, 4·6%), $\nu_{max.}$ (Nujol) 1686 cm^{-1} (C=O). The same product was obtained by the reaction of methyl iodide and *o*-aminoacetophenone in aqueous sodium hydrogen carbonate at 100°, followed by treatment with toluene-*p*-sulphonyl chloride in pyridine.

N-*p*-*Tolylsulphonyl*-o-*benzylaminoacetophenone* [15] (XI; R = $PhCH_2$).—This was obtained like the methyl analogue and crystallised from ethanol in *cubes*, m.p. 130° (Found: C, 69·6; H, 6·0. $C_{22}H_{21}NO_3S$ requires C, 69·65; H, 5·55%). Both sulphonamides were unchanged after treatment with (*a*) sodium methoxide in toluene at 120°, (*b*) potassium t-butoxide in dimethyl sulphoxide at 20°, or (*c*) sodium hydroxide in ethylene glycol at reflux.

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[15] W. Paterson, Ph.D. Thesis, University of Glasgow, 1964.