Azabenzocycloheptenones. Part XVI.[1] Amino-ketones of the Tetrahydro-2-benzazepin-5-one Series

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Attempts to remove the tosyl group from 1,2,3,4-tetrahydro-8-methoxy-2-tosyl-2-benzazepin-5-one and 1,2-dihydro-8-methoxy-2-tosyl-2-benzazepin-5-one were unsuccessful. 2,3,4,5-Tetrahydro-8-methoxy-2-tosyl-1*H*-2-benzazepin-5-ol was detosylated by sodium in liquid ammonia and the product was converted into *N*-methyl, *N*-acetyl, and *N*-benzyloxycarbonyl derivatives, all of which were oxidised to the corresponding ketones. 2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-8-methoxy-2-benzazepin-5-one was catalytically hydrogenolysed to 1,2,3,4-tetrahydro-8-methoxy-2-benzazepin-5-one. *N*-Alkyl and *N*-benzyl 1,2,3,4-tetrahydro-2-benzazepin-5-ones could not be obtained by Friedel–Crafts cyclisation of the corresponding amino-acids.

To date, the only tetrahydro-2-benzazepin-5-one (I) derivatives that have been described were obtained[2] from 1,2,3,4-tetrahydro-8-methoxy-2-tosyl-2-benzazepin-5-one (I; R^1 = tosyl, R^2 = OMe), itself made by cyclisation of *N*-(*m*-methoxybenzyl)-*N*-tosyl-β-alanyl chloride (II; R^1 = tosyl, R^2 = Cl, R^3 = OMe). In the case of *N*-benzyl-*N*-tosyl-β-alanyl chloride (II; R^1 = tosyl, R^2 = Cl, R^3 = H) we could only obtain polymeric material, although other workers[3] claim to have isolated the ketone (I; R^1 = tosyl, R^2 = H) from this reaction.

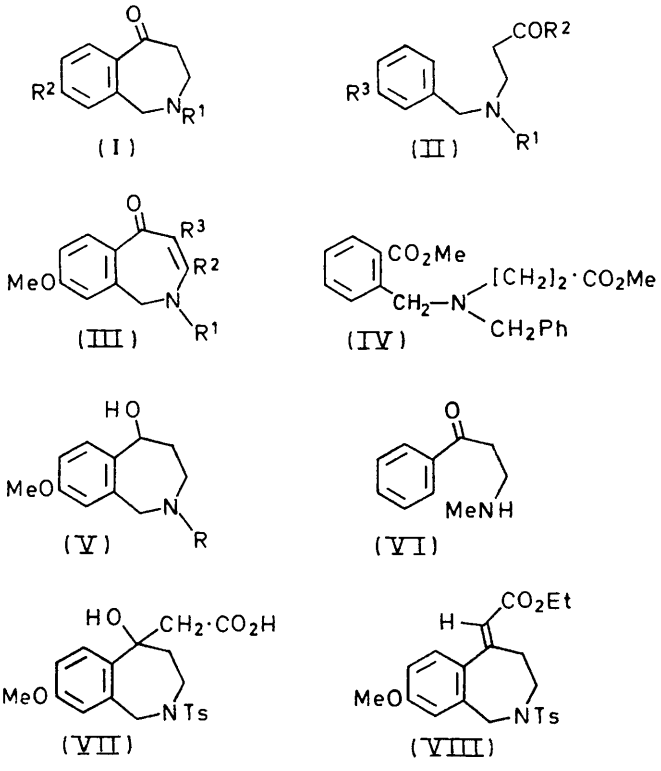
We now describe further work in this area, particularly the synthesis of amino-ketones (I; R^1 = H or Me, R^2 = OMe). Previous[2] efforts to remove the tosyl group directly from the tosyl ketone (I; R^1 = tosyl,

[1] Part XV, A. Cromarty, G. R. Proctor, and M. Shabbir, *J.C.S. Perkin I*, 1972, 2012.

[2] I. MacDonald and G. R. Proctor, *J. Chem. Soc.* (*C*), 1970, 1461.

[3] M. A. Rehman, D. Hussain, and S. Hussain, *J. Natural Sci. Math., Govt. Coll., Lahore*, 1969, **9**, 923.

R^2 = OMe) led to decomposition, and since the desired compound (I; R^1 = H, R^2 = OMe) is a Mannich base and likely to be labile we studied the dihydro-compound [2] (III; R^1 = tosyl, R^2 = R^3 = H) and its bromination product [either (III; R^1 = tosyl, R^2 = Br, R^3 = H) or



(III; R^1 = tosyl, R^2 = H, R^3 = Br)]. However, both reacted only sluggishly with polyphosphoric acid, giving intractable products. Reaction of the compound (III; R^1 = tosyl, R^2 = R^3 = H) with sodium methoxide or with potassium t-butoxide gave several inseparable products.

We next examined the possibility of making amino-ketones (I; R^1 = Me, CH_2Ph, or Ac) by direct Friedel–Crafts cyclisation with phosphoryl chloride in benzene, a method which was successful for several amino-acids, giving amino-ketones of the 1-benzazepin-5-one series.[4] The amino-acids [(II; R^1 = Me, R^2 = OH, R^3 = OMe), (II; R^1 = CH_2Ph, R^2 = OH, R^3 = OMe or H), (II; R^1 = Ac, R^2 = OH, R^3 = OMe)] were synthesised by conventional procedures (see Experimental section) and were treated with several Friedel–Crafts reagents, including phosphoryl chloride, but no ketones were isolated. These failures to obtain amino-ketones by direct cyclisation are now understood to be due to the instability of the products (see later). Dieckmann cyclisation, a useful procedure in the tetrahydro-1-benzazepin-5-one series,[1,4] was unsuccessful in the present case: the diester (IV) was consumed on treatment with sodium hydride in refluxing toluene but no products could be isolated.

We next turned back to the prospect of removing the tosyl group from the tosyl ketone (I; R^1 = tosyl, R^2 = OMe) and, since the carbonyl group is frequently the cause of instability in such situations, we converted the tosyl ketone into the tosyl alcohol [2] (V; R = tosyl). The latter was unaffected by treatment with sodium in ethanol [5] but was converted in good yield into the amino-alcohol (V; R = H) by sodium in liquid ammonia. Selective acetylation [6] of the amino-alcohol (V; R^1 = H) gave the *N*-acetate (V; R = Ac), which was oxidised by dipyridinechromium(VI) oxide [7] to the *N*-acetyl ketone (I; R^1 = Ac, R^2 = OMe) in 72% overall yield. The oxidation step could also be carried out by use of the pyridine–sulphur trioxide complex and dimethyl sulphoxide in the presence of triethylamine.[8,9] In the n.m.r. spectrum of the acetyl ketone (I; R^1 = Ac, R^2 = OMe) the signal due to N·CO·CH_3 appears as two sharp singlets, as does that for the methoxy-group: this phenomenon is presumably due to the coexistence of two conformers, possibly associated with restricted rotation [10] of the *N*-acetyl bond since the corresponding amino-ketone did not show this effect. The *N*-acetyl acid (II; R^1 = Ac, R^2 = H, R^3 = OMe) also had two sharp N·CO·CH_3 signals in the n.m.r. spectrum. On the other hand, when the *N*-acetyl ketone (I; R^1 = Ac, R^2 = OMe) was brominated with phenyltrimethylammonium perbromide [11] and the product was treated with diazabicyclo[4.3.0]non-5-ene,[12] the derived αβ-unsaturated ketone (III; R^1 = Ac, R^2 = R^3 = H) had a normal n.m.r. spectrum in which neither the methoxy nor the *N*-acetyl signal was split.

When the *N*-acetyl ketone (I; R^1 = Ac, R^2 = OMe) was treated with a mixture of concentrated hydrochloric acid and acetic acid at 100°, t.l.c. detected the appearance of a new substance, presumably (I; R^1 = H, R^2 = OMe), but its formation was accompanied by the development of a deep violet colour. It therefore seemed necessary to seek a protecting group that could survive the oxidation reaction but could be removed under milder conditions, and the benzyloxycarbonyl group [13] was chosen. The amino-alcohol (V; R^1 = H) reacted with benzyl chloroformate to give the *N*-benzyloxycarbonyl alcohol (V; R^1 = $PhCH_2$·O·CO), which was oxidised with dipyridinechromium(VI) oxide to the *N*-benzyloxycarbonyl ketone (I; R^1 = $PhCH_2$·O·CO,

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[5] G. Hazebroucq, Ph.D. Thesis, Paris, 1966.
[6] R. B. Woodward and W. E. Doering, *J. Amer. Chem. Soc.*, 1945, **67**, 860.
[7] J. C. Collins, W. W. Hess, and E. J. Frank, *Tetrahedron Letters*, 1968, 3363.
[8] J. R. Parikh and W. E. Doering, *J. Amer. Chem. Soc.*, 1967, **89**, 5505; R. L. Augustine and D. J. Trecker, 'Oxidation,' Marcel Dekker, New York, 1971, vol. 2, p. 56.
[9] A. H. Fenselau and J. G. Moffat, *J. Amer. Chem. Soc.*, 1966, **88**, 1762 and earlier papers.
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[11] A. Marquet, M. Dvolaitzky, H. Kagan, L. Mamlock, C. Ouannes, and J. Jacques, *Bull. Soc. chim. France*, 1961, 1822.
[12] K. Eiter and H. Oediger, *Annalen*, 1965, **682**, 62.
[13] R. Boissonnas, *Adv. Org. Chem.*, 1963, **3**, 159.

R^2 = OMe) in 72·5% overall yield. This ketone showed a broad multiplet for the benzylic CH_2 n.m.r. signal, and a broad unresolved signal for the OMe group; again this is attributed to conformational effects. Catalytic hydrogenolysis then gave the amino-ketone (I; R^1 = H, R^2 = OMe) in quantitative yield. It proved to be unstable, developing a violet colour. Rapid distillation gave an analytical sample, for which the n.m.r. spectrum showed none of the conformational effects already discussed and for which the mass spectrum revealed not only the parent ion but a base peak at $M - C_2H_4$, a significant transformation already noted in the case of the tosyl ketone (I; R^1 = tosyl, R^2 = OMe).[14] Acetylation of the amino-ketone (I; R^1 = H, R^2 = OMe) yielded the same *N*-acetyl ketone (I; R^1 = Ac, R^1 = OMe) as that already described. Other Mannich bases have proved difficult to isolate; for example the closely related *N*-methyl-β-aminopropiophenone (VI) was only stable as the hydrochloride.[15]

Reductive methylation of the amino-alcohol (V; R = H) gave in good yield the *N*-methyl alcohol (V; R = Me), which was oxidised with active manganese dioxide[16] to the *N*-methyl ketone (I; R^1 = Me, R^2 = OMe); this was even more unstable than the amino-ketone (I; R^1 = H, R^2 = OMe). It decomposed on attempted purification and during efforts to form derivatives.

The instability of amino-ketones in this series is such that structural modifications to the carbonyl group are best carried out before removal of the *N*-tosyl group. Although the *N*-tosyl ketone (I; R^1 = tosyl, R^2 = OMe) does not form an acetal it does undergo the Reformatski and Wittig reactions normally, so that this molecule can undergo substitution at C-5, at C-1 (by use of the bromide previously reported[2]), and at N. Reactions at C-4 may be more difficult since the tosyl ketone (I; R^1 = tosyl, R^2 = OMe) is unstable to alkali and decomposes during attempts at enamine formation, but other methods remain to be tested.

EXPERIMENTAL

N-(m-*Methoxybenzyl*)-N-p-*tolylsulphonyl*-β-*alanine Methyl Ester*[2] (II; R^1 = tosyl, R^2 = R^3 = OMe).—*N*-Tosyl-β-alanine methyl ester (154·7 g), freshly roasted potassium carbonate (116 g), and *m*-methoxybenzyl bromide (133·5 g) were stirred and heated at 95—100° for 3 days. Addition of chloroform (800 ml), filtration, and evaporation yielded the product (227 g, 100%) as before.[2]

1,2,3,4-*Tetrahydro*-8-*methoxy*-2-p-*tolylsulphonyl*-2-*benzazepin*-5-*one*[2] (I; R^1 = tosyl, R^2 = OMe).—More consistent results were obtained when anhydrous aluminium chloride was added to the solution of acid chloride at −5° and the reaction was allowed to proceed during 1·5 h at 0—5° (yield 87% on 0·2 mol scale).

3(*or* 4)-*Bromo*-1,2-*dihydro*-8-*methoxy*-2-p-*tolylsulphonyl*-2-*benzazepin*-5-*one* (III; R^1 = tosyl, R^2 or R^3 = Br, R^3 or R^2 = H).— 1,2-Dihydro-8-methoxy-2-tosyl-2-benzazepin-5-one (1 g), *N*-bromosuccinimide (0·57 g), and carbon tetrachloride (170 ml) were refluxed for 4 h over a 150 W lamp. After filtration and evaporation, the product (1·4 g) was purified by chromatography on silica gel (benzene elution) and by crystallisation from ethanol to give *needles*, m.p. 183—184° (Found: C, 51·25; H, 3·95; N, 3·35. $C_{18}H_{17}BrNO_4S$ requires C, 51·2; H, 4·0; N, 3·3%), $\nu_{max.}$ (Nujol) 1630 cm^{-1} (C=O), τ 1·7 (1H, s, vinyl), 2·2—3·5 (7H, m, aryl), 5·4 (2H, s, 1-H_2), 6·2 (3H, s, OMe), and 7·6 (3H, s, CH_3).

Ethyl N-(m-*Methoxybenzyl*)-N-*methyl*-β-*alanate* (II; R^1 = Me, R^2 = OEt, R^3 = OMe).—*N*-*m*-Methoxybenzylmethylamine[17] (30 g), ethyl acrylate (9·2 g), and boron trifluoride–ether complex (3 ml) were heated at 70° for 2 h. Ethyl acrylate (13·8 g) was added and heating was continued for 15 h. After cooling, addition of chloroform, and washing of the organic layer with aqueous sodium hydrogen carbonate, the *product* (33 g), obtained in the usual way, had b.p. 125—130° at 0·5 mmHg (Found: C, 66·4; H, 8·45; N, 5·5. $C_{14}H_{21}NO_3$ requires C, 66·9; H, 8·4; N, 5·55%), $\nu_{max.}$ (Nujol) 1735 cm^{-1} (ester C=O), τ 2·6—3·2 (4H, aryl), 5·85 (2H, q, CH_2 of Et), 6·2 (3H, s, OMe), 6·5 (2H, s, CH_2), 7·3 and 7·6 (each 2H, m, CH_2), 7·8 (3H, s, N·CH_3), and 8·75 (3H, t, CH_3).

N-(m-*Methoxybenzyl*)-N-*methyl*-β-*alanine* (II; R^1 = Me, R^2 = OH, R^3 = OMe).—The foregoing ester (52·2 g), dioxan (216 ml), sodium hydroxide (9·17 g), and water (216 ml) were stirred for 40 h. After extraction with benzene, the pH of the lower layer was adjusted to 7 with hydrochloric acid and the aqueous solution was evaporated to dryness *in vacuo*. The residue was extracted with methylene dichloride and crystallised from ethanol as *prisms* (90%), m.p. 115—116° (Found: C, 64·25; H, 7·8; N, 6·35. $C_{12}H_{17}NO_3$ requires C, 64·55; H, 7·65; N, 6·25%), $\nu_{max.}$ (Nujol) 1715 cm^{-1} (acid C=O), τ −2·9 (1H, s, exchangeable, OH), 2·53—3·1 (4H, m, aryl), 6·16 (3H, s, OMe), 6·25 (2H, s, CH_2), 7·1 and 7·4 (each 2H, m, CH_2), and 7·6 (3H, s, NCH_3).

N-*Benzyl*-N-(m-*methoxybenzyl*)-β-*alanine* (II; R^1 = $PhCH_2$, R^2 = OH, R^3 = OMe).—Ethyl *N*-benzyl-β-alanate[18] (35 g), *m*-methoxybenzyl bromide (42·6 g), anhydrous potassium carbonate (42 g), and dry acetone (900 ml) were refluxed for 24 h. The ester (165 g) obtained after filtration and removal of solvent was stirred with dioxan (200 ml), water (200 ml), and sodium hydroxide (8 g) for 48 h. After washing with benzene, the pH of the aqueous layer was adjusted to 7 and the solution was extracted with chloroform to give the *acid* (46 g) which did not solidify (Found: C, 71·5; H, 6·95; N, 4·75. $C_{18}H_{21}NO_3$ requires C, 72·3; H, 7·1; N, 4·7%), $\nu_{max.}$ (film) 3400 (OH) and 1700 (C=O) cm^{-1}, τ −2·2 (1H, s, exchangeable, OH), 2·5—3·2 (9H, m, aryl), 6·2 (3H, s, OMe), 6·25 and 6·3 (each 2H, m, CH_2), and 7·1 and 7·4 (each 2H, m, CH_2). The hydrobromide crystallised from acetone in *prisms*, m.p. 159—160° (Found: C, 57·0; H, 5·75; N, 3·8. $C_{18}H_{22}BrNO_3$ requires C, 56·9; H, 5·85; N, 3·7%). *NN*-Dibenzyl-β-alanine was similarly obtained as a gum.

Methyl N-*Benzyl*-N-(2-*methoxycarbonylethyl*)-β-*alanate* (IV).—Methyl *N*-benzyl-β-alanate[18] (25 g), 2-methoxy-

[14] G. R. Proctor and S. Aftalion, *Org. Mass Spectrometry*, 1969, **4**, 337.
[15] F. F. Blicke and J. H. Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 451.
[16] J. S. Belew and C. Tek-Ling, *Chem. and Ind.*, 1967, 1958.
[17] G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, 1968, **33**, 491.
[18] P. Southwick and R. Crouch, *J. Amer. Chem. Soc.*, 1953, **75**, 3413.

carbonylbenzyl bromide [19] (30 g), anhydrous potassium carbonate (25 g), and dry acetone (500 ml) were refluxed for 18 h. After filtration and evaporation, the product (44·8 g) was obtained as a gum. The *hydrobromide* crystallised from acetone as prisms, m.p. 143—144° (Found: C, 57·1; H, 5·55; N, 3·4. $C_{20}H_{24}BrNO_4$ requires C, 56·9; H, 5·75; N, 3·4%).

2,3,4,5-*Tetrahydro*-8-*methoxy*-2-p-*tolylsulphonyl*-1H-2-*benzazepin*-5-*ol* (V; R = tosyl).—To 1,2,3,4-tetrahydro-8-methoxy-2-*p*-tolylsulphonyl-2-benzazepin-5-one (10 g) in ethanol (100 ml), sodium borohydride (5 g) was slowly added with stirring. After being stirred for 16 h, the mixture was diluted with water and extracted with chloroform, from which the product (9·5 g) was obtained in the usual way. It crystallised from ethanol as *prisms*, m.p. 109° (Found: C, 62·4; H, 6·2; N, 3·95. $C_{18}H_{21}NSO_4$ requires C, 62·3; H, 6·1; N, 4·05%).

2,3,4,5-*Tetrahydro*-8-*methoxy*-1H-2-*benzazepin*-5-*ol* (V; R = H).—The foregoing tosyl derivative (12 g) in tetrahydrofuran (100 ml) was added to stirred liquid ammonia (700 ml). Gradual addition of sodium (1·8 g) over 1 h was followed by immediate addition of ammonium chloride (in excess), after which the suspension became green. When the ammonia had evaporated, water (100 ml) and methylene dichloride was added and the product (5·5 g) was obtained by extraction in the usual way. Crystallisation from benzene–ethanol gave *prisms*, m.p. 138—139° (Found: C, 68·1; H, 7·7; N, 7·55. $C_{11}H_{15}NO_2$ requires C, 68·4; H, 7·85; N, 7·25%), $\nu_{max.}$ (Nujol) 3280 cm^{-1} (OH and NH), τ 2·6—3·4 (3H, m, aryl), 5·1 (1H, dd, $J_{4a,5}$ 7, $J_{4b,5}$ 3 Hz, 5-H), 5·8—7·0 (4H, m, 1-H_2 and 3-H_2), 6·2 (3H, s, OMe), 7·7 (2H, s, exchangeable, OH and NH), and 8·0 (2H, m, 4-H_2).

2-*Acetyl*-2,3,4,5-*tetrahydro*-8-*methoxy*-1H-2-*benzazepin*-5-*ol* (V; R = Ac).—Acetic anhydride (1 ml), the foregoing amino-alcohol (2 g), and methanol (30 ml) were stirred for 2 h. After removal of the solvent, addition of chloroform, washing with aqueous sodium hydrogen carbonate solution, and evaporation of the chloroform, the *product* (2·23 g) was obtained as prisms, m.p. 127—128° (from ethanol) (Found: C, 65·9; H, 7·1; N, 5·95. $C_{13}H_{17}NO_3$ requires C, 66·4; H, 7·3; N, 5·95%), $\nu_{max.}$ (Nujol) 3380 (OH) and 1630 (NAc) cm^{-1}, τ 2·8—3·4 (3H, m, aryl), 5·1 (1H, dd, $J_{4a,5}$ 7, $J_{4b,5}$ 3 Hz, 5-H), 5·3—6·4 (4H, m, 1-H_2 and 3-H_2), 5·9 (3H, s, OMe), 7·2 (1H, s, exchangeable, OH), 7·8—8·3 (2H, m, 4-H_2), and 7·95 (3H, s, NAc).

2-*Acetyl*-1,2,3,4-*tetrahydro*-8-*methoxy*-2-*benzazepin*-5-*one* (I; R^1 = Ac, R^2 = OMe).—(*a*) Dipyridinechromium(VI) oxide [7] (14·7 g), the acetyl derivative (V; R = Ac) (2·23 g), and dry methylene dichloride (300 ml) were shaken for 5 min. The mixture was then left for 30 min, filtered, and evaporated. The crude product was redissolved in toluene; the solution was filtered and evaporated to give the product (1·75 g, 79%) which crystallised from ethanol at −20° giving *needles*, m.p. 87—88° (Found: C, 67·4; H, 6·5; N, 6·2. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·45; N, 6·0%), $\nu_{max.}$ (Nujol) 1680 (aryl C=O) and 1640 cm^{-1} (NAc), τ 2·0—3·2 (3H, m, aryl), 5·15 and 5·35 (2H, 2s from 1-H_2 of each conformation), 6·16 and 6·18 (3H, 2s from OMe of each conformation), 6·3 (2H, m, 3-H_2), 6·85—7·0 (2H, m, 4-H_2), and 7·94 and 7·96 (3H, 2s from NAc of each conformation).

(*b*) Pyridine–sulphur trioxide complex [8] (0·37 g) was added to the *N*-acetyl alcohol (V; R = Ac) (0·18 g) and triethylamine (0·77 g) in dimethyl sulphoxide (2·03 ml) with vigorous stirring. After 16 h the solution was poured into dilute hydrochloric acid and extracted with chloroform; the extract was washed thoroughly with water and worked up in the usual way to give the product (0·12 g, 67%) as in (*a*). On a smaller scale a slightly improved yield was obtained by use of 50% less dimethyl sulphoxide.

2-*Acetyl*-1,2-*dihydro*-8-*methoxy*-2-*benzazepin*-5-*one* (III; R^1 = Ac, R^2 = R^3 = H).—The foregoing *N*-acetyl ketone (0·4 g) in tetrahydrofuran (16 ml) was treated with phenyltrimethylammonium perbromide [11] in tetrahydrofuran (8 ml) over 30 min. The mixture was filtered; evaporation of the filtrate then left a gum (0·52 g) which was stirred for 18 h with 1,5-diazabicyclo[4.3.0]non-5-ene [12] (0·25 ml) and benzene (3 ml). After being washed with dilute hydrochloric acid, the organic layer was evaporated *in vacuo*, yielding the crude product (0·21 g, 54%) which was chromatographed on silica gel (elution with 1% methanol in chloroform) and crystallised from ethanol to give *needles*, m.p. 121—122° [Found: *M* (mass spec.), 231·0892. $C_{13}H_{13}NO_3$ requires *M*, 231·0895], $\nu_{max.}$ (Nujol) 1700 (aryl C=O) and 1627 cm^{-1} ($NCOCH_3$), τ 2·25 (1H, d, $J_{3,4}$ 10 Hz, 3-H), 2·7—3·2 (3H, m, aryl), 4·35 (1H, d, $J_{3,4}$ 10 Hz, 4-H), 5·15 (2H, s, 1-H_2), 6·2 (3H, s, OMe), and 7·7 (3H, s, NAc).

Ethyl N-m-*Methoxybenzyl*-β-*alanate* (II; R^1 = H, R^2 = OEt, R^3 = OMe).—(*a*) *m*-Methoxybenzylamine [20] (24 g), ethyl acrylate (17·5 g), and ethanol (65 ml) were left together for 18 h and then distilled to give the product (b.p. 125—140° at 0·1 mmHg) as a clear liquid (30·1 g, 70·7%), $\nu_{max.}$ 3400 (NH) and 1725 cm^{-1} (ester).

(*b*) *m*-Methoxybenzaldehyde (7·25 g), ethyl β-alanate [21] (6·29 g), and dry toluene (125 ml) were refluxed overnight (Dean–Stark trap). Evaporation of the solvent then left the imino-ester (12 g), $\nu_{max.}$ 1645 (C=N) and 1725 cm^{-1} (ester). This was hydrogenated in ethanol over palladium–charcoal (0·75 g, 10%) and the product (6·93 g, 59%) was obtained as usual.

N-*Acetyl*-N-m-*methoxybenzyl*-β-*alanine* (II; R^1 = Ac, R^2 = H, R^3 = OMe).—Acetic anhydride (28 g) was added to the foregoing amino-ester (30·3 g) in pyridine (100 ml); the mixture was left for 16 h, then poured into ice–water. After extraction with chloroform in the usual way, the *N*-acetyl ester (30 g) was stirred for 8·5 h with sodium hydroxide (4·2 g) in water (156 ml) and tetrahydrofuran (156 ml), and the mixture was then extracted with benzene. Acidification of the aqueous layer gave the product (20·2 g, 62%), which crystallised from ethanol in *prisms*, m.p. 106—107° (Found: C, 62·0; H, 6·65; N, 5·5. $C_{13}H_{17}NO_4$ requires C, 62·15; H, 6·8; N, 5·6%), $\nu_{max.}$ (Nujol) 3500—3200 (OH), 1645 (NAc), and 1715 cm^{-1} (CO_2H), τ −1·3 (1H, s, exchangeable, OH), 2·6—3·4 (4H, m, aryl), 5·45 (2H, s, benzylic CH_2), 6·23 and 6·25 (3H, 2s, OMe), 6·4 (2H, m, 4-H_2), 7·4 (2H, m, 3-H_2), and 7·8 and 7·9 (3H, 2s, NAc).

2-*Benzyloxycarbonyl*-2,3,4,5-*tetrahydro*-8-*methoxy*-1H-2-*benzazepin*-5-*ol* (V; R = $PhCH_2{\cdot}O{\cdot}CO$).—Benzyloxycarbonyl chloride (1·02 g), the amino-alcohol (V; R = H) (1·15 g), water (10 ml), tetrahydrofuran (10 ml), and sodium carbonate (0·6 g) were stirred together for 30 min. The mixture was evaporated, water and chloroform were added to the residue, and the layers were separated; evaporation of the organic layer gave the product (1·75 g,

[19] E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, 1952, **17**, 1252.
[20] M. G. Ettlinger and A. J. Lundeen, *J. Amer. Chem. Soc.*, 1956, **78**, 1952.
[21] M. Viscontini and H. Buhler, *Helv. Chim. Acta*, 1967, **50**, 1289.

90%) as a buff solid, $\nu_{max.}$ (Nujol) 3450 (OH) and 1680 cm^{-1} ($N{\cdot}CO_2{\cdot}CH_2Ph$).

2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-8-methoxy-2-benzazepin-5-one (I; $R^1 = PhCH_2{\cdot}O{\cdot}CO$, $R^2 = OMe$).—Dipyridinechromium(VI) oxide (8·2 g) was shaken for 5 min with the foregoing benzyloxycarbonyl alcohol (1·75 g) in dry methylene dichloride (200 ml), and left for 30 min. The previously described work-up gave the product (1·41 g, 81%), which crystallised from ethanol as *prisms*, m.p. 73—74° (Found: C, 69·7; H, 6·0; N, 4·5. $C_{19}H_{19}NO_4$ requires C, 70·2; H, 5·9; N, 4·3%), $\nu_{max.}$ (Nujol) 1670 (aryl C=O) and 1680 cm^{-1} ($N{\cdot}CO_2{\cdot}CH_2Ph$), τ 2·0—3·3 (8H, m, aryl), 4·95 (2H, s, $CO_2{\cdot}CH_2Ph$), 5·3 (2H, m, 1-H_2), 6·3 (5H, m, OMe and 4-H_2), and 6·95—7·1 (2H, m, 3-H_2).

1,2,3,4-Tetrahydro-8-methoxy-2-benzazepin-5-one (I; R^1 = H, R^2 = OMe).—The foregoing ketone (1·52 g) was hydrogenated for 45 min over palladium–carbon (10%; 0·16 g) in methanol. After filtration, the solution (t.l.c. of which showed a single new spot) was divided into three. A portion was evaporated below 40° and the residue rapidly distilled at 180° and 0·05 mmHg, giving a colourless *oil* which slowly turned violet [Found: C, 69·1; H, 7·0; N, 7·1%; *M* (mass spec.), 191·0945. $C_{11}H_{13}NO_2$ requires C, 69·05; H, 6·9; N, 7·3%; *M*, 191·0946], $\nu_{max.}$ (film) 3320 (NH) and 1670 cm^{-1} (C=O), τ 2·25 (1H, d, $J_{6,7}$ 9 Hz, 6-H), 3·25 (1H, dd, $J_{6,7}$ 9, $J_{7,9}$ 3 Hz, 7-H), 3·35 (1H, d, $J_{7,9}$ 3 Hz, 9-H), 5·95 (2H, s, 1-H_2), 6·2 (3H, s, OMe), 6·9 (2H, m, 4-H_2), 7·2 (2H, m, 3-H_2), and 8·1 (1H, s, exchangeable, NH). A second portion was treated with gaseous hydrogen chloride in ether and gave a white *hydrochloride*, $\nu_{max.}$ (Nujol) 2350—2750 ($R_2\overset{+}{N}H_2$) and 1680 cm^{-1} (C=O), which turned violet in a sealed vessel. A third portion was acetylated with acetic anhydride and anhydrous potassium carbonate to give 2-acetyl-1,2,3,4-tetrahydro-8-methoxy-2-benzazepin-5-one (I; R^1 = Ac, R^2 = OMe), identical with that prepared previously.

2,3,4,5-Tetrahydro-8-methoxy-2-methyl-1H-2-benzazepin-5-ol (V; R = Me).—2,3,4,5-Tetrahydro-8-methoxy-1*H*-2-benzazepin-5-ol (0·39 g), formaldehyde (40% aqueous; 2 g), and methanol (10 ml) were hydrogenated over platinic oxide (0·065 g) for 24 h. Filtration, and evaporation of the filtrate yielded the product (0·4 g, 95·5%), pure enough for use. Distillation at 180° and 0·3 mmHg gave a yellow *oil* (Found: C, 69·15; H, 7·95. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·25%), $\nu_{max.}$ (film) 3350 cm^{-1} (OH), τ 2·7—3·4 (3H, m, aryl), 5·25 (1H, q, $J_{4a,5}$ 7, $J_{4b,5}$ 3 Hz, 5-H), 6·3 (5H, s, OMe and 1-H_2), 6·5 (1H, s, exchangeable, OH), 7·2 (2H, m, 3-H_2), 7·7 (3H, s, NMe), and 7·9—8·2 (2H, m, 4-H_2). The *methiodide* crystallised from ethanol in prisms, m.p. 183—184° (Found: C, 44·4; H, 5·75; N, 4·0. $C_{13}H_{20}INO_2$ requires C, 44·7; H, 5·7; N, 4·0%).

Attempted Isolation of 1,2,3,4-Tetrahydro-8-methoxy-2-methyl-2-benzazepin-5-one (I; R^1 = Me, R^2 = OMe).—The benzazepinol (V; R = Me) (0·28 g) and manganese dioxide [16] (1·4 g) were stirred in dry methylene dichloride (25 ml) for 4 h. T.l.c. then showed disappearance of starting material and formation of one new product. Evaporation below 30° left a yellow gum [$\nu_{max.}$ 1675 cm^{-1} (C=O)] but this turned violet on warming and decomposed on attempted distillation. A freshly prepared sample which gave a single spot on t.l.c. was treated with sodium borohydride in ethanol to yield the benzazepinol (V; R = Me) as before.

2,3,4,5-Tetrahydro-5-hydroxy-8-methoxy-2-p-tolylsulphonyl-1H-2-benzazepine-5-acetic Acid (VII).—Granulated zinc (3·04 g) and ethyl bromoacetate (1·07 g) were added to the *N*-tosyl ketone (I; R^1 = tosyl, R^2 = OMe) (2 g) in tetrahydrofuran (40 ml) and dry benzene (40 ml). Iodine (0·1 g) was then added and the mixture was refluxed vigorously with stirring for 1 h. After a further addition of zinc (3·04 g), iodine (0·1 g), and ethyl bromoacetate (1·07 g), and a reflux period of 30 min, three further portions of zinc (3·04 g) and iodine (0·1 g) were added at 30 min intervals. After 5 h at reflux, the mixture was cooled and filtered, and the filtrate evaporated yielding an oil (2·5 g) which was partly purified by chromatography on silica gel (elution with 10% ether–benzene) [$\nu_{max.}$ (film) 3500 (OH) and 1720 cm^{-1} (ester)]. Hydrolysis with sodium hydroxide in aqueous dioxan at 20° yielded the *acid* (0·67 g, 28·5%), crystallising from ethanol in prisms, m.p. 160—161° (Found: C, 59·0; H, 5·65; N, 3·45. $C_{20}H_{23}NO_4S$ requires C, 59·3; H, 5·7; N, 3·45%), $\nu_{max.}$ (Nujol) 3500 (OH) and 1720 cm^{-1} (CO_2H), τ 0·7 (2H, s, exchangeable OH and CO_2H), 2·0—3·2 (7H, m, aryl), 5·2 (2H, s, 1-H_2), 5·8—6·5 (5H, overlapping, 3-H_2 and OMe), 6·8 (2H, m, $CH_2{\cdot}CO_2H$), and 7·2—7·8 (5H, overlapping, 4-H_2 and Me).

Wittig Reaction on 1,2,3,4-Tetrahydro-8-methoxy-2-p-tolylsulphonyl-2-benzazepin-5-one.—Sodium hydride (50% dispersion; 0·56 g) was added to triethyl phosphonoacetate [22] (2·62 g) in bis-(2-methoxyethyl) ether (10 ml). When hydrogen evolution had ceased the *N*-tosyl ketone (I; R^1 = tosyl, R^2 = OMe) (2 g) in the same solvent (80 ml) was added and the solution was stirred for 2 h and poured into water. A chloroform extract was washed with water, dried, and evaporated to yield a gum (3 g), which was chromatographed on silica gel. Elution with methanol–chloroform (1 : 99) yielded the ester [presumably (VIII)] as an oil (2·2 g), which showed a single spot on t.l.c.; $\nu_{max.}$ (film) 1725 (ester C=O) and 1670 cm^{-1} (CH=CH).

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[22] W. Wadsworth and W. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.