Azabenzocycloheptenones. Part XIV.[1] Cyclisation of Amino-acid Derivatives to Tetrahydro-1-benzazepin-5-ones and Tetrahydroquinolin-4-ones

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Dieckmann cyclisation of methyl 3-(*o*-methoxycarbonylanilino)propionate (IV; R^1 = H, R^2 = R^3 = Me, n = 2) gives methyl 1,2,3,4-tetrahydro-4-oxoquinoline-3-carboxylate (V), some reactions of which are recorded. Similar cyclisation of the *N*-acetyl derivative of ethyl 4-(*o*-methoxycarbonylanilino)butyrate (IV; R^1 = H, R^2 = Me, R^3 = Et, n = 3) gives ethyl 1-acetyl-1,2,3,4-tetrahydro-5-oxo-1-benzazepine-4-carboxylate (III; R^1 = Ac, R^2 = CO_2Et, R^3 = H). Various *N*-methyl and *N*-phenyl derivatives of 4-anilinobutyric acid (XII; R^1 = R^2 = R^3 = H) can be cyclised by phosphoryl chloride in refluxing benzene to give derivatives of 1-methyl and 1-phenyl-1,2,3,4-tetrahydro-1-benzazepin-5-one.

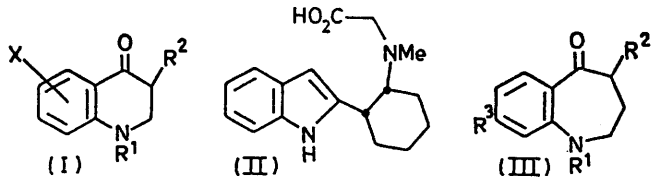
It is customary to protect the amino-group of amino-acids before submitting them to intramolecular cyclisation reactions. The tosyl group has been widely used in syntheses of tetrahydroquinolin-4-ones [1,2a] (but see ref. 2*b*) and of some tetrahydrobenzazepinones [3-5] by the Friedel–Crafts reaction. Cyclisation of unprotected tertiary amino-acids by Lewis acids has not been much studied, although recently the *N*-protonated form of the indole derivative (II) has been cyclised.[6] We report here the cyclisation of certain unprotected tertiary amino-acids which give tetrahydro-1-benzazepin-5-ones. Dieckmann reactions on appropriate diesters have yielded tetrahydro-1-benzazepin-5-one derivatives [7] (III) in which the tosyl group protected the secondary amino-function (R^1 = tosyl) and many tertiary amino-diesters have been cyclised to give rings of various sizes; [8] however, few examples are known in which secondary unprotected amino-diesters have been successfully cyclised under Dieckmann conditions.[8] We discuss such an example in this paper.

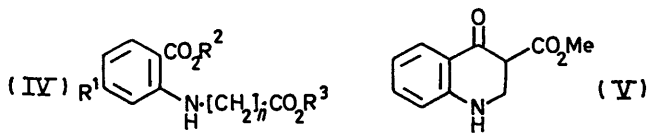
To deal first with the Dieckmann reaction: in 1957 it was reported [9] that the amino-diester (IV; R^1 = H, R^2 = R^3 = Me, n = 2) gave the tetrahydroquinolin-4-one ester (V) during an attempted acyloin reaction. We have re-examined this process and have improved it. Thus methyl anthranilate reacted with methyl acrylate (but not methyl methacrylate or methyl crotonate) in the presence of tin(IV) chloride or boron trifluoride to give the diester (IV; R^1 = H, R^2 = R^3 = Me, n = 2) (65%), which was cyclised by use of sodium hydride in toluene containing traces of methanol to give the product (V) (45%). The latter seemed an attractive intermediate for making bridged-ring compounds with bridgehead nitrogen atoms. However, we found that all reactions designed to alkylate the NH group alkylated the C-4 oxygen atom either before or after a dehydrogenation step: the products were of the type [VI; R = CH_2·CH(OH)·CH_2Cl] from chloromethyloxiran, (VI; R = CH_2·C_6H_4·CO_2Me-*o*) from methyl *o*-bromomethyltoluate, and [VI; R = $C(CO_2Me)$:$CH(CO_2Me)$] from dimethylacetylene dicarboxylate. The last-named product was also made from the reaction of methyl 4-hydroxyquinoline-3-carboxylate (VI; R = H) with dimethyl acetylenedicarboxylate. The ester (VI; R = H) was frequently obtained during purification of the keto-ester (V), for example by refluxing it in ethanol without exclusion of air.

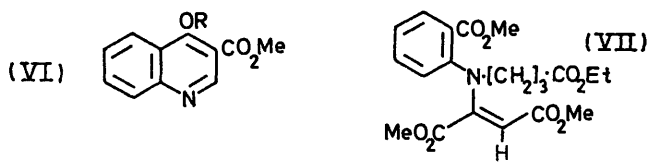
When the Dieckmann cyclisation conditions already described were applied to the higher homologue (IV; R^1 = H, R^2 = Me, R^3 = Et, n = 3),[7] intractable products were obtained; the *N*-methyl derivative of compound (IV; R^1 = H, R^2 = R^3 = Me, n = 3) had been cyclised by Astill and Boekelheide [10] and so we sought to apply their conditions to the diester (VII),[7] now obtained as a solid. In this case cyclisation followed

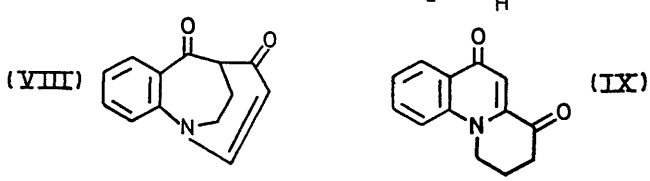
[1] Part XIII, A. Cromarty, K. E. Haque, and G. R. Proctor, *J. Chem. Soc.* (*C*), 1971, 3536.
[2] (*a*) W. S. Johnson, E. L. Woroch, and B. C. Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901; (*b*) J. Koo, *J. Org. Chem.*, 1963, **28**, 1134.
[3] D. N. Gupta, I. McCall, A. McLean, and G. R. Proctor, *J. Chem. Soc.* (*C*), 1970, 2191.
[4] I. MacDonald and G. R. Proctor, *J. Chem. Soc.* (*C*), 1970, 1461.
[5] M. A. Rehman and G. R. Proctor, *J. Chem. Soc.* (*C*), 1967, 58.
[6] P. Rosenmund, J. Bauer, and D. Sauer, *Chem. Ber.*, 1971, **104**, 1379.
[7] I. McCall, G. R. Proctor, and L. Purdie, *J. Chem. Soc.* (*C*), 1970, 1126.
[8] J. P. Schaefer and J. J. Bloomfield, *Org. Reactions*, 1967, **15**, 1.
[9] G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 1957, 2312.
[10] D. B. Astill and V. Boekelheide, *J. Amer. Chem. Soc.*, 1955, **77**, 4080.

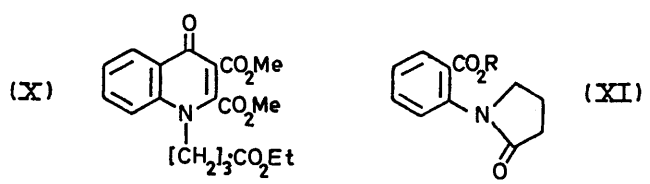
by acid hydrolysis yielded a compound of constitution $C_{13}H_{11}NO_2$ in low yield. The n.m.r. spectrum of this material rules out bridged-ring structures containing a seven-membered ring [*e.g.* (VIII)] and favours structure

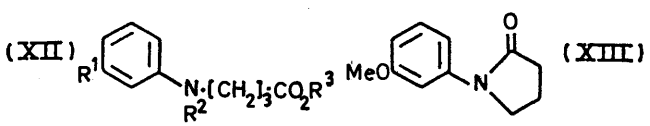


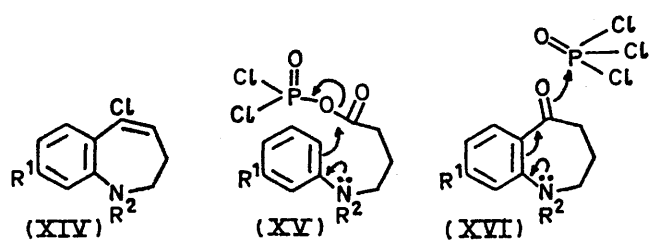












(IX), which we visualise to have arisen *via* compound (X). The first step [(VII) ⟶ (X)] could be formulated as proceeding either thermally or by acidic or basic catalysis. We next showed that no purely thermal reaction took place but that the starting material could be wholly consumed by reaction with sodium ethoxide in toluene at room temperature; as with potassium t-butoxide,[10] there were several products and acidic hydrolysis of the mixture yielded many more; among them was compound (IX), obtained in low yield. We were not able to identify compound (X) as an intermediate. It was not formed from (VII) by treatment with Lewis acids (boron trifluoride or polyphosphoric acid) either; in this case the diester (IV; $R^1 = H$, $R^2 = Me$, $R^3 = Et$, $n = 3$) was obtained in high yield.

The *N*-acetyl derivative of the diester (IV; $R^1 = H$, $R^2 = Me$, $R^3 = Et$, $n = 3$) proved to be more useful: it could be cyclised by sodium hydride in toluene, to give the keto-ester (III; $R^1 = Ac$, $R^2 = CO_2Et$, $R^3 = H$). The structure of the latter was established firmly by its hydrolysis to the previously reported amino-ketone (III; $R^1 = R^2 = R^3 = H$).

It had been reported [11] that heating the amino-diacid (IV; $R^1 = Cl$, $R^2 = R^3 = H$, $n = 2$) with acetic anhydride and potassium acetate gave the *N*-acetyltetrahydroquinolone (I; $R^1 = Ac$, $R^2 = H$, X = 7-Cl); we applied these conditions to the higher homologue (IV; $R^1 = R^2 = R^3 = H$, $n = 3$) [7] but found that none of the *N*-acetyl ketone (III; $R^1 = Ac$, $R^2 = R^3 = H$) was detectable. Instead the product was mainly acidic; we could not purify it but it was presumed to be (XI; R = H) since esterification gave compound (XI; R = Et). It is noteworthy that partial hydrolysis by acid or alkali of the diester (IV; $R^1 = H$, $R^2 = Me$, $R^3 = Et$, $n = 3$) gave a monoacid monomethyl ester, presumably (IV; $R^1 = R^3 = H$, $R^2 = Me$, $n = 3$), and not a 2-pyrrolidone (XI; R = Me). We associate this structural preference with hydrogen bonding in the anthranilates; acylation like alkylation [7] of *N*-alkylanthranilates appears to require forcing conditions. For example, acetylation of the amino-diester (IV; $R^1 = H$, $R^2 = Me$, $R^3 = Et$, $n = 3$) did not proceed with acetic anhydride in pyridine but was achieved in high yield by refluxing with acetic anhydride.

We now discuss the Friedel–Crafts cyclisation; *N*-alkyl-[12] and *N*-aryl-[13] tetrahydroquinolin-4-ones (I; $X = R^2 = H$, $R^1 = Me$ or Ph) have been made by this type of process but it has not been widely employed. First, a synthesis of the amino-acid (XII; $R^1 = OMe$, $R^2 = Me$, $R^3 = H$) was required. When ethyl γ-bromobutyrate was treated with *m*-anisidine, the product was principally the 2-pyrrolidone [14] (XIII), which could be converted into the amino-acid (XII; $R^1 = OMe$, $R^2 = R^3 = H$) by 25% sulphuric acid. However, all attempts to methylate the amino-acid led to regeneration of the pyrrolidone (XIII). Accordingly *N*-methyl *m*-anisidine [15] was treated with ethyl γ-bromobutyrate to give the amino-ester (XII; $R^1 = OMe$, $R^2 = Me$, $R^3 = Et$), which was hydrolysed to the desired amino-acid (XII; $R^1 = OMe$, $R^2 = Me$, $R^3 = H$). The latter gave unidentified products with polyphosphoric acid or with

[11] A. F. Bekhli, *Doklady Akad. Nauk S.S.S.R.*, 1955, **101**, 679 (*Chem. Abs.*, 1956, **50**, 3441).
[12] J. A. C. Allison, J. T. Braunholtz, and F. G. Mann, *J. Chem. Soc.*, 1954, 403.
[13] C. D. Hurd and S. Hayao, *J. Amer. Chem. Soc.*, 1954, **76**, 5065.
[14] J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1957, 4174.
[15] M. F. Millson and Sir Robert Robinson, *J. Chem. Soc.*, 1955, 3362.

phosphorus pentoxide in dimethylformamide or xylene, and also after being treated sequentially with thionyl chloride and with aluminium chloride in methylene dichloride. However, treatment of the amino-acid with phosphoryl chloride in refluxing benzene gave a pale yellow liquid (25%) which we identified as (XIV; R^1 = OMe, R^2 = Me) from its analytical and spectroscopic data (see Experimental section) and for the following reasons. The related amino acid (XII; R^1 = R^3 = H, R^2 = Me) reacted with phosphoryl chloride in toluene to give an analogous product (XIV; R^1 = H, R^2 = Me), and when this was refluxed with concentrated hydrochloric acid the *N*-methyl ketone [10,16] (III; R^1 = Me, R^2 = R^3 = H) was obtained; this was identical with the product obtained by methylation of the amino-ketone [17] (III; R^1 = R^2 = R^3 = H). Thus the presence of the seven-membered ring in structure (XIV; R^1 = H, R^2 = Me) was demonstrated; a similar interpretation for (XIV; R^1 = OMe, R^2 = Me) seems reasonable although in this case cyclisation *ortho*, rather than *para*, to the methoxy-group cannot be absolutely excluded.

The *N*-phenyl acid (XII; R^1 = R^3 = H, R^2 = Ph) was obtained by conventional procedures from diphenylamine and ethyl γ-bromobutyrate; it reacted with phosphoryl chloride in benzene to give the enol chloride (XIV; R^1 = H, R^2 = Ph) (8%) and the ketone (III; R^1 = Ph, R^2 = R^3 = H) (56%), the latter as a stable crystalline solid. In this case, the yield of cyclised products was much higher than in the *N*-methyl cases; this is probably because of the much lower base strength of the diphenylamine derivative (III; R^1 = Ph, R^2 = R^3 = H), which would be much less likely to react with the hydrogen chloride set free during the reaction. One can formulate all these reactions as proceeding initially *via* a chlorophosphate (XV) with cyclisation to the amino-ketone which then reacts further (XVI) with phosphoryl chloride, yielding ultimately the enol chloride (XIV); this allows an explanation of the fact that in the *N*-phenyl case (XII; R^1 = R^3 = H, R^2 = Ph), the ketone is the predominant product, because here (XVI; R^2 = Ph), the low basicity of the nitrogen atom impedes further reaction with electrophiles.

The foregoing developments make available some interesting tetrahydro-1-benzazepin-5-ones; however we were unable to extend the scope of the reaction to include groups capable of being removed at a later stage. Thus on the one hand the *N*-benzyl acid (XII; R^1 = OMe, R^2 = $PhCH_2$, R^3 = H) gave the 2-pyrrolidone (XIII) (apparently benzyl is too good a leaving group), and on the other we were unable to synthesise the 2,4-dinitrophenyl acids (XII; R^1 = OMe or H, R^2 = $C_6H_4(NO_2)_2$-2,4, R^3 = H). The *N*-methyl ketone (III; R^1 = Me, R^2 = R^3 = H) was not demethylated by treatment with oxygen in the presence of 30% palladised carbon.[18]

[16] J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1958, 3377.
[17] W. H. Bell, E. D. Hannah, and G. R. Proctor, *J. Chem. Soc.*, 1964, 4926.

EXPERIMENTAL

Methyl 3-(o-*Methoxycarbonylanilino*)*propionate* [9] (IV; R^1 = H, R^2 = R^3 = Me, n = 2).—(*a*) Methyl anthranilate (227 g), methyl acrylate (129 g), and tin(IV) chloride (15 g) were refluxed for 18 h. After addition of methyl acrylate (43 g) and refluxing for a further 24 h, the mixture was cooled, poured into aqueous sodium carbonate (in excess), and extracted with methylene dichloride. Vacuum distillation gave methyl anthranilate (70 g) and then the diester (142 g, 40%), b.p. 128—148° at 0·5 mmHg, which slowly solidified. A portion crystallised from light petroleum (b.p. 40—60°) in prisms, m.p. 33° (lit.,[9] 36°), mixed m.p. 33—35°.

(*b*) Methyl anthranilate (130 g) and boron trifluoride–ether complex (15 ml) were stirred at 70° while methyl acrylate (100 g) was added dropwise during 1 h. After a further 23 h stirring at 70°, the mixture was poured into ice and ammonium hydroxide solution (excess). The product (150 g, 65%), b.p. 136—140° at 0·4 mmHg, was identical with that obtained in (*a*).

Methyl 1,2,3,4-*Tetrahydro*-4-*oxoquinoline*-3-*carboxylate* (V).—The foregoing diester (40 g) in dry toluene (900 ml) and anhydrous methanol (1·6 g) was added dropwise under nitrogen with stirring to sodium hydride (50% dispersion in oil; 20 g) in dry toluene (1·2 l) during 15 min at 20°. The mixture was stirred for 4 h, refluxed for 45 min, cooled (ice), and then cautiously neutralised with dilute hydrochloric acid (to pH 6). The organic layer was washed with water, dried, and evaporated to give the product, which crystallised from methanol as a fine yellow powder, m.p. 117·5—118° (lit.,[9] 113°); $\nu_{max.}$ (Nujol) 3350 (NH), 1730 (ester), 1655 (C=O), and 1625 cm^{-1} (bonded β-keto-ester). The average yield of four preparations was 46·5%.

In the foregoing preparations some material insoluble in methanol was usually obtained; the amounts of it increased when solutions of the product were refluxed in air. It crystallised from chloroform–methanol as cream microcrystals of methyl 4-hydroxyquinoline-3-carboxylate (VI; R = H), m.p. 230° (Found: C, 64·5; H, 4·3; N, 7·3. Calc. for $C_{11}H_9NO_3$: C, 65·05; H, 4·45; N, 6·9%); $\nu_{max.}$ (Nujol) 1710 cm^{-1} (ester C=O).

Reactions of Methyl 1,2,3,4-*Tetrahydro*-4-*oxoquinoline*-3-*carboxylate*.—(a) *With chloromethyloxiran*. The title compound (1 g), chloromethyloxiran (1 ml), boron trifluoride–ether complex (0·4 ml), and methylene dichloride were stirred together under nitrogen at 20° for 16 h, then poured into ammonium hydroxide solution. *Methyl* 4-(3-*chloro*-2-*hydroxypropoxy*)*quinoline*-3-*carboxylate* (0·5 g) was obtained by removal of solvent and recrystallisation from methanol in prisms, m.p. 198—200° [Found: C, 56·35; H, 4·65; Cl, 12·2; N, 5·1%; *M* (mass spectrum), 295·061549, 297·058875. $C_{14}H_{14}ClNO_4$ requires C, 56·85; H, 4·75; Cl, 12·0; N, 4·75%; *M*, 295·061129, 297·058179].

(b) *With methyl* o-*bromomethyltoluoate*. Methyl o-bromomethyltoluoate [19] (1·5 g) in dry carbon tetrachloride (30 ml) was added dropwise to the title compound (1·1 g) and freshly roasted potassium carbonate (0·7 g) in dry acetone (100 ml) with stirring during 30 min. The mixture was refluxed for 3 h, cooled, filtered, and evaporated to leave *methyl* 4-(o-*methoxycarbonylbenzyloxy*)*quinoline*-3-*carboxylate* (1·5 g), m.p. 205—207° (from methanol) (Found: C, 68·45; H, 5·15; N, 3·95. $C_{20}H_{17}NO_5$ requires C, 68·45; H, 4·9; N, 4·0%).

[18] B. A. Hess, jun., and V. Boekelheide, *J. Amer. Chem. Soc.*, 1969, **91**, 1672.
[19] E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, 1952, **17**, 1252.

(c) *With dimethyl acetylenedicarboxylate.* The title compound (5·3 g), dimethyl acetylenedicarboxylate (3 ml), and dry toluene (100 ml) were refluxed under nitrogen for 24 h and cooled. The product (4·5 g) was filtered off and recrystallised from methylene dichloride–methanol to give *methyl* 4-(1,2-*bismethoxycarbonylvinyloxy*)*quinoline*-3-*carboxylate* [Found: C, 59·15; H, 4·9; N, 4·35%; *M* (mass spectrum), 345·084600. $C_{17}H_{15}NO_7$ requires C, 59·2; H, 4·4; N, 4·05%; *M*, 345·084842]. T.l.c. showed traces of a second material with a slightly greater R_F value [benzene–methanol (10 : 1)] and the mass spectrum also contained a peak at *m/e* 347·100811 ($C_{17}H_{17}NO_7$ requires 347·100492). These products could not be separated. When methyl 4-hydroxyquinoline-3-carboxylate and dimethyl acetylenedicarboxylate reacted similarly in toluene, the same product, m.p. 174—176°, was obtained; in this case t.l.c. showed a single spot.

Reaction of Ethyl 4-(o-*Methoxycarbonylanilino*)*butyrate* [7] (IV; R^1 = H, R^2 = Me, R^3 = Et, *n* = 3) *with Dimethyl Acetylenedicarboxylate.*—The diester [7] (21 g), dimethyl-acetylenedicarboxylate (15 ml), and absolute methanol (200 ml) were refluxed for 20 h and the solvent was then removed *in vacuo*. The residue crystallised from ether in needles, m.p. 74—75° (8·5 g). The mother liquor was evaporated and the residue chromatographed on neutral alumina (benzene elution) to give a further 7·3 g of product, m.p. 73—74°. These materials gave i.r. and n.m.r. spectra identical with those previously recorded [7] for ethyl 4-[*N*-(1,2-bismethoxycarbonylvinyl)-*o*-methoxycarbonylanilino]-butyrate (VII).

Reactions of Ethyl 4-[N-(1,2-*Bismethoxycarbonylvinyl*)-o-*methoxycarbonylanilino*]*butyrate* (VII).—(a) *With potassium t-butoxide.* The title compound (2·1 g) in dry toluene (65 ml) was added with stirring at 120° under nitrogen to a suspension of potassium t-butoxide (0·65 g) in toluene (150 ml) during 1 h. After being slowly distilled until the b.p. reached 109°, the reaction mixture was cooled and treated with dilute hydrochloric acid (to pH 5). The organic layer was separated, the aqueous layer was extracted with methylene dichloride, and the combined organic extracts were evaporated to leave a gum (0·9 g), which was refluxed with concentrated hydrochloric acid (50 ml) for 20 h. On cooling and basification with ammonium hydroxide solution, the product (250 mg) was obtained by extraction with methylene dichloride, chromatography on neutral alumina, and recrystallisation from benzene as needles, m.p. 230°, of 2,3-*dihydro*-1H-*benzo*[c]-*quinolizine*-4,6-*dione* (IX) [Found: C, 73·4; H, 5·35; N, 6·4%; *M* (mass spectrum), 213·078499. $C_{13}H_{11}NO_2$ requires C, 73·3; H, 5·2; N, 6·6%; *M*, 213·078497]; $\nu_{max.}$ (Nujol) 1715 and 1630 cm^{-1} (C=O); τ 1·65 (1H, dd, *J* 8 and 1 Hz, *peri*-aromatic H), 2·2—2·72 (3H, m, aromatic), 3·1 (1H, s, olefinic), 5·78 (2H, t), 7·2 (2H, t), and 7·5—7·7 (2H, m).

(b) *With sodium methoxide.* The title compound (3·6 g), sodium methoxide (2·5 g), and dry toluene (70 ml) were left together under nitrogen at 20° for 3 days. Work-up as in (a) gave many products, including the diketone of m.p. 230° (120 mg).

(c) *With boron trifluoride.* The title compound (1·9 g), dry toluene (60 ml), and boron trifluoride–ether complex (0·5 ml) were left together at 20° for 48 h and then were refluxed for 45 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel; elution with ether–benzene (1 : 50) gave ethyl 4-(*o*-methoxycarbonylanilino)butyrate (IV; R^1 = H, R^2 = Me, R^3 = Et, *n* = 3) (650 mg).

(d) *With polyphosphoric acid.* The title compound (1·15 g) and polyphosphoric acid (15 g) were stirred together at 80—90° for 1 h. The mixture was then cooled, diluted with water, and extracted. As in (c), the product (600 mg) was the diester (IV; R^1 = H, R^2 = Me, R^3 = Et, *n* = 3).

Ethyl o-(2-*Oxopyrrolidin*-1-*yl*)*benzoate* (XI; R = Et). —4-(*o*-Carboxyanilino)butyric acid [7] (IV; R^1 = R^2 = R^3 = H, *n* = 3) (6 g), acetic anhydride (20 ml), and anhydrous potassium acetate [11] (6 g) were stirred together at 120° for 12 h and cooled. Addition of ice, extraction with methylene dichloride, and evaporation of the extract gave the crude product, which was refluxed with ethanol (250 ml) and concentrated sulphuric acid (1·5 ml) for 12 h. Work-up in the usual way gave a product which contained several substances (t.l.c.); chromatography on silica gel separated the desired *ester* (1·75 g), which crystallised from light petroleum (b.p. 60—80°) in clusters, m.p. 80—81° [Found: C, 67·5; H, 6·5; N, 6·05%; *M* (mass spectrum), 233·1058. $C_{13}H_{15}NO$ requires C, 67·0; H, 6·5; N, 6·0%; *M*, 233·1052]; $\nu_{max.}$ (Nujol) 1685—1710br cm^{-1} (ester and lactam); τ 2·12 (1H, d, aromatic), 2·4—2·95 (3H, m, aromatic), 5·71 (2H, q, CH_2), 6·2 (2H, m), 7·55 (2H, m), 7·8 (2H, m), and 8·66 (3H, t, Me).

4-(o-*Methoxycarbonylanilino*)*butyric Acid* (IV; R^1 = R^3 = H, R^2 = Me, *n* = 3).—Ethyl 4-(*o*-methoxycarbonyl-anilino)butyrate (IV; R^1 = H, R^2 = Me, R^3 = Et, *n* = 3) (5·5 g), ethanol (75 ml), and sodium hydroxide (2N; 10 ml) were refluxed together for 1 h and left at 20° overnight. Adjustment of the pH to 6 caused precipitation of the *product* (4·27 g), which crystallised from benzene–light petroleum (b.p. 60—80°) in micro-crystals, m.p. 92° [Found: C, 61·15; H, 6·35; N, 5·7. $C_{12}H_{15}NO_4$ requires C, 60·8; H, 6·4; N, 5·9%]; $\nu_{max.}$ (Nujol) 3350 (NH), 1710 (CO_2H), and 1680 cm^{-1} (aryl CO_2Me); τ −0·5 to 1·2 (br, 2 exch. H), 2·16 (1H, dd, aromatic), 2·6—2·8 (1H, m, aromatic), 3·3—3·6 (2H, m, aromatic), 6·2 (3H, s), 6·76 (2H, t), 7·54 (2H, t), and 8·04 (2H, m). The same material was obtained when the starting diester was stirred for 30 min with concentrated hydrochloric acid.

Ethyl 4-(N-*Acetyl*-o-*methoxycarbonylanilino*)*butyrate.*—The amino-diester (IV; R^1 = H, R^2 = Me, R^3 = Et, *n* = 3) (10 g) and acetic anhydride were refluxed together for 6 h, cooled, and poured into ice and aqueous sodium hydrogen carbonate (excess). The product (11·2 g) was obtained by extraction and distillation at 170° and 0·15 mmHg as a clear *oil* which did not crystallise (Found: C, 63·0; H, 6·8; N, 4·8. $C_{16}H_{21}NO_5$ requires C, 62·6; H, 6·9; N, 4·55%); $\nu_{max.}$ (film) 1720—1730 (ester) and 1665 cm^{-1} (NAc); τ 2·02 (1H, dd, *J* 8 and 1 Hz, aromatic), 2·3—2·9 (3H, m, aromatic), 5·94 (2H, q, CH_2), 6·13 (3H, s, Me of ester), 6·8 (2H, m), 7·7 (2H, m), 8·2 (2H, m), 8·25 (3H, s, Ac), and 8·8 (3H, t).

Ethyl 1-*Acetyl*-1,2,3,4-*tetrahydro*-5-*oxo*-1-*benzazepine*-4-*carboxylate* (III; R^1 = Ac, R^2 = CO_2Et, R^3 = H).—The foregoing diester (2·8 g) in dry toluene (50 ml) was added under nitrogen with stirring at 20° to sodium hydride (50% dispersion; 2·8 g). The mixture was refluxed with stirring for 24 h, then cooled, and acidified with dilute hydrochloric acid with cooling (ice). The organic layer was separated, washed with dilute aqueous sodium hydrogen carbonate, dried, and evaporated. The product, an oil (2·4 g), was chromatographed on silica gel; elution with ether–benzene (1 : 4) gave *material* which was purified by

distillation, b.p. 140° at 0·2 mmHg (Found: C, 65·4; H, 6·4; N, 4·7. $C_{15}H_{17}NO_4$ requires C, 65·5; H, 6·25; N, 5·1%); $\nu_{max.}$ ($CHCl_3$) 1720—1745m (ester) and 1620—1665s cm^{-1} (C=O and bonded ester); τ −2·65 (1H, s, exch.), 2—2·9 (4H, m, aromatic), 5·8 (2H, q, CH_2), 7·5—8·2 (4H, m), 8·28 (3H, s, Ac), and 8·68 (3H, t, Me). Signals at τ 2·55 and 6·2 are ascribed to the presence of some of the corresponding methyl ester; this is usual in β-keto-esters of this series.[7]

Hydrolysis of Ethyl 1-*Acetyl*-1,2,3,4-*tetrahydro*-5-*oxo*-1-*benzazepine*-4-*carboxylate* (III; R^1 = Ac, R^2 = CO_2Et, R^3 = H).—The keto-ester (500 mg) was refluxed for 8 h with acetic acid (10 ml), ethanol (10 ml), concentrated hydrochloric acid (3 ml), and water (3 ml). The mixture was then evaporated to dryness *in vacuo* and treated with dilute sodium hydroxide solution and methylene dichloride. The organic layer was washed with water, dried, and evaporated. The crude product was chromatographed over silica gel; elution with benzene–ether (95 : 5) gave first 1,2,3,4-tetrahydro-1-benzazepin-5-one (III; R^1 = R^2 = R^3 = H) (105 mg), identical with material previously prepared,[17] and then 1-acetyl-1,2,3,4-tetrahydro-1-benzazepin-5-one (III; R^1 = Ac, R^2 = R^3 = H) (64 mg), identical with the acetate previously described.[17]

Ethyl 4-(N-*Methyl*-m-*anisidino*)*butyrate* (XII; R^1 = OMe, R^2 = Me, R^3 = Et).—*N*-Methyl-*m*-anisidine [15] (45 g, 0·33 mol) and ethyl 4-bromobutyrate [7] (100 g, 0·51 mol) were heated at 110° for 24 h with stirring. The cooled mixture was poured into an excess of saturated sodium hydrogen carbonate solution and extracted with benzene. The extract was washed, dried, and evaporated *in vacuo* to leave an oil (75 g), which was distilled to give unchanged ethyl 4-bromobutyrate (6 g), b.p. 28—32° at 0·1 mmHg, and then the *product* (64 g, 98%), obtained as a colourless liquid, b.p. 148—154° at 0·2 mmHg (Found: C, 67·2; H, 8·15; N, 6·0. $C_{14}H_{21}NO_3$ requires C, 66·9; H, 8·4; N, 5·6%); τ 2·7—2·9 (1H, m), 2·58—2·73 (3H, m), 5·83 (2H, q), 6·2 (3H, s), 6·64 (2H, t), 7·06 (3H, s), 7·66 (2H, t), 8·09 (2H, m), and 8·75 (3H, t); $\nu_{max.}$ (film) 1720 cm^{-1} (C=O).

4-(N-*Methyl*-m-*anisidino*)*butyric Acid* (XII; R^1 = OMe, R^2 = Me, R^3 = H).—Ethyl 4-(*N*-methyl-*m*-anisidino)-butyrate (64 g) was refluxed with sodium hydroxide (11 g) in aqueous ethanol (500 ml) for 4 h. The mixture was cooled, poured into water, and extracted with benzene. The aqueous layer was carefully acidified (pH 6) and extracted with methylene dichloride. The organic extract was washed, dried, and evaporated *in vacuo* to leave an oil, which was distilled to give the *product* as a pale yellow liquid (50 g, 88%), b.p. 160—162° at 0·2 mmHg (Found: C, 64·4; H, 7·65; N, 6·15. $C_{12}H_{17}NO_3$ requires C, 64·6; H, 7·7; N, 6·25%); τ 1·4br (1H, s, exch.), 2·8 (1H, m), 3·62 (3H, m), 6·2 (3H, s), 6·62 (2H, t), 7·05 (3H, s), 7·58 (2H, t), and 8·07 (2H, m); $\nu_{max.}$ (film) 1700 cm^{-1} (C=O).

Reaction of 4-(N-*Methyl*-m-*anisidino*)*butyric Acid with Phosphoryl Chloride*.—The acid (12 g, 0·045 mol) and phosphoryl chloride (4 ml, 0·046 mol) were refluxed in dry benzene (750 ml) for 15 h with stirring. The mixture was cooled and poured into an excess of saturated sodium hydrogen carbonate solution. The organic layer was washed, dried, and evaporated to leave a dark oil (6·1 g), which was chromatographed on neutral alumina. Elution with benzene gave 5-*chloro*-2,3-*dihydro*-8-*methoxy*-1-*methyl*-1-*benzazepine* (XIV; R^1 = OMe, R^2 = Me) as a pale yellow liquid (2·9 g, 25%), b.p. 132—134° at 0·4 mmHg [Found: C, 64·05; H, 6·25; N, 6·85%; *M* (mass spectroscopy), 223·076490, 225·073858. $C_{12}H_{14}ClNO$ requires C, 64·65; H, 6·35; N, 6·3%; *M*, 223·07686, 225·073436]; τ 2·27 (1H, d), 3·37—3·5 (2H, m), 3·59 (1H, t), 6·18 (3H, s), 6·76 (2H, t), 7·1 (3H, s), and 7·63 (2H, q); $\nu_{max.}$ (film) 1600 cm^{-1} (C=C). The *hydrobromide* crystallised from acetone as plates, m.p. 157—160°, $\nu_{max.}$ (Nujol) 1615 cm^{-1} (C=C).

Further elution, with solvents of increasing polarity, yielded mixtures from which no identifiable products were isolated.

Ethyl 4-(N-*Methylanilino*)*butyrate*.—*N*-Methylaniline (50 ml, 0·5 mol) and ethyl 4-bromobutyrate (100 g, 0·5 mol) were heated at 100° with stirring for 20 h. The mixture was cooled, shaken with an excess of saturated sodium hydrogen carbonate solution, and extracted with benzene. The extract was washed, dried, and evaporated *in vacuo* to leave an oil (104 g), which was distilled to give unchanged ethyl 4-bromobutyrate (4·7 g), b.p. 40—60° at 0·2 mmHg, and then the *product* as a light yellow liquid (50·15 g, 80%), b.p. 110—121° at 0·2 mmHg (Found: C, 70·8; H, 8·8; N, 6·65. $C_{13}H_{19}NO_2$ requires C, 70·65; H, 8·05; N, 6·35%); τ 2·68—2·95 (2H, m), 3·27—3·48 (3H, m), 5·88 (2H, q), 6·63 (2H, t), 7·0 (3H, s), 7·71 (2H, t), 8·14 (2H, m), and 8·75 (3H, t), $\nu_{max.}$ (film) 1720 cm^{-1} (C=O).

4-(N-*Methylanilino*)*butyric Acid*.—Ethyl 4-(*N*-methylanilino)butyrate (25 g) was refluxed with sodium hydroxide (5 g) in aqueous ethanol (200 ml) for 2 h. The mixture was cooled, poured into an excess of water, and extracted with benzene. The aqueous layer was carefully neutralised (to pH 7) with dilute hydrochloric acid and extracted with methylene dichloride. The extract was washed, dried, and evaporated *in vacuo* to leave a clear oil (which turned blue in air), b.p. 145—150° at 0·05 mmHg. Crystallisation from methanol–water gave white *needles* (21 g, 95%), m.p. 38—40° (Found: C, 68·0; H, 8·2; N, 7·15. $C_{11}H_{15}NO_2$ requires C, 68·45; H, 7·85; N, 7·25%); τ −1·15br (1H, s, exch.), 2·56—2·85 (2H, m), 3·12—3·36 (3H, m), 6·59 (2H, t), 7·05 (3H, s), 7·58 (2H, t), and 8·08 (2H, m); $\nu_{max.}$ (film) 1690 cm^{-1} (C=O).

Reaction of 4-(N-*Methylanilino*)*butyric Acid with Phosphoryl Chloride*.—The acid (13 g, 0·068 mol) and phosphoryl chloride (6 ml, 0·069 mol) were refluxed in dry toluene (400 ml) for 17 h. The mixture was cooled, poured into an excess of ice–dilute ammonia solution, and separated. The organic layer was washed, dried, and evaporated *in vacuo* to leave a red oil (4·3 g), which was chromatographed on neutral alumina. Elution with benzene gave 5-*chloro*-2,3-*dihydro*-1-*methyl*-1-*benzazepine* as a colourless oil (1·95 g, 15%), b.p. 100—110° at 0·1 mmHg [Found: C, 68·05; H, 6·1; N, 7·55%; *M* (mass spectroscopy), 193·065299, 195·062510. $C_{11}H_{12}ClN$ requires C, 68·4; H, 6·25; N, 7·25%; *M*, 193·065823, 195·062873]; τ 2·07—3·05 (4H, m), 3·43 (1H, t), 6·71 (2H, t), 7·06 (3H, s), and 7·63 (2H, q); $\nu_{max.}$ (film) 1600 cm^{-1} (C=C). The *hydrobromide* crystallised from acetone as colourless plates, m.p. 160—161°, $\nu_{max.}$ (Nujol) 1625 cm^{-1} (C=C) (Found: C, 48·35; H, 4·85; N, 4·95. $C_{11}H_{13}BrClN$ requires C, 48·1; H, 4·75; N, 5·1%).

Further elution, with benzene–ether (19 : 1), gave a pale green oil (3·7 g) which slowly crystallised. Recrystallisation from ether gave white needles, m.p. 68—71° 4-(N-*methylanilino*)*butyramide* (Found: C, 69·25; H, 8·25; N, 14·45. $C_{11}H_{15}N_2O$ requires C, 69·05; H, 8·15; N, 14·6%); τ 2·75—3·35 (4H, m), 4·0—4·7br (2H, s), 6·62 (2H, t), 7·06 (3H, s), 7·74 (2H, t), and 8·08 (2H, m), $\nu_{max.}$ (Nujol) 3380 and 3180 (N–H) and 1650 cm^{-1} (C=O).

2,3,4,5-*Tetrahydro*-1-*methyl*-1-*benzazepin*-5-*one* (III;

R^1 = Me, R^2 = R^3 = H).—2,3,4,5-Tetrahydro-1-benzazepin-5-one [17] (2 g) and methyl iodide (30 ml) were heated in a pressure bottle at 60° for 44 h. The mixture was cooled, poured into an excess of sodium thiosulphate solution, and extracted with methylene dichloride. The organic extract was washed, dried, and evaporated *in vacuo* to yield the product as a light yellow oil (2·08 g, 98%), which was distilled; b.p. 90—92° at 0·15 mmHg (lit.,[16] 112° at 0·2 mmHg), $\nu_{max.}$ (film) 1665 cm^{-1} (C=O) (lit.,[16] 1665 cm^{-1}). The 2,4-dinitrophenylhydrazone crystallised from methanol as orange needles, m.p. 195—200° (lit.,[16] 203°).

Hydrolysis of 5-*Chloro*-2,3-*dihydro*-1-*methyl*-1-*benzazepine*.—The enol chloride (0·1 g) in concentrated hydrochloric acid was refluxed for 17 h, cooled, basified with sodium hydroxide solution, and extracted with methylene dichloride. The organic extract was washed, dried, and evaporated *in vacuo* to leave 2,3,4,5-tetrahydro-1-methyl-1-benzazepin-5-one as a light yellow liquid (0·065 g, 80%), identical with the sample described in the previous section.

Ethyl 4-*Diphenylaminobutyrate* (XII; R^1 = H, R^2 = Ph, R^3 = Et).—A mixture of diphenylamine (16·9 g, 0·1 mol), ethyl 4-bromobutyrate (39 g, 0·2 mol), and freshly roasted potassium carbonate (20 g, 0·15 mol) was stirred at 130° for 5 h, cooled, diluted with water, and extracted with benzene. The organic extract was washed, dried, and evaporated *in vacuo* to leave a light yellow liquid (40·2 g), which was distilled to give ethyl 4-bromobutyrate (14 g), b.p. 40—60° at 0·2 mmHg, and diphenylamine (7·1 g), b.p. 98—112° at 0·2 mmHg; this left the product as a pale yellow liquid (14·7 g, 50%), which could not be distilled and was not further purified; τ 2·6—3·09 (10H, m), 5·83 (2H, q), 6·23 (2H, t), 7·62 (2H, t), 8·0 (2H, m), and 8·75 (3H, t), $\nu_{max.}$ (film) 1725 cm^{-1} (C=O).

4-*Diphenylaminobutyric Acid* (XII; R^1 = R^3 = H, R^2 = Ph).—The foregoing crude ester (14·7 g) in a solution of sodium hydroxide (3 g) in aqueous ethanol was refluxed for 2 h, cooled, diluted with water, and extracted with benzene. The aqueous layer was carefully acidified (to pH 6) and extracted with methylene dichloride. The organic extract was washed, dried, and evaporated *in vacuo* to leave the *product* as a brown oil (9·94 g, 77%) which slowly crystallised. Recrystallisation from ethanol–water gave white needles, m.p. 80—81° (Found: C, 75·1; H, 6·6; N, 5·6. $C_{16}H_{17}NO_2$ requires C, 75·5; H, 6·7; N, 5·5%); τ −0·9br (1H, s, exch.), 2·6—3·09 (10H, m), 6·22 (2H, t), 7·56 (2H, t), and 8·0 (2H, m); $\nu_{max.}$ (Nujol) 1695 cm^{-1} (C=O).

Reaction of 4-*Diphenylaminobutyric Acid with Phosphoryl Chloride*.—The amino-acid (8 g, 0·031 mol) and phosphoryl chloride (3 ml, 0·035 mol) were refluxed in dry benzene (400 ml) with stirring for 15 h. The mixture was cooled and poured into an excess of saturated sodium hydrogen carbonate solution. The organic layer was washed, dried, and evaporated *in vacuo* to leave a brown oil (6·95 g), which was chromatographed on neutral alumina. Elution with benzene gave 5-*chloro*-2,3-*dihydro*-1-*phenyl*-1-*benzazepine* (0·57 g, 8%) (XIV; R^1 = H, R^2 = Ph) as an unstable oil, b.p. 140—150° at 0·4 mmHg [Found: *M* (mass spectroscopy), 255·08198, 257·08034. $C_{16}H_{14}ClN$ requires *M*, 255·08147, 257·07852]; τ 2·0—2·14 (1H, m), 2·7—2·88 (5H, m), 3·13—3·25 (3H, m), 3·61 (1H, t), 6·21 (2H, t), and 7·48 (2H, q); $\nu_{max.}$ (film) 1600 cm^{-1} (C=C).

Further elution, with benzene–ether (99 : 1) gave 2,3,4,5-*tetrahydro*-1-*phenyl*-1-*benzazepin*-5-*one* (III; R^1 = Ph, R^2 = R^3 = H) (3·8 g, 56%), which crystallised from light petroleum (b.p. 40—60°) as yellow needles, m.p. 65—66° [Found: C, 80·2; H, 6·05; N, 6·4%; *M* (mass spectroscopy) 237·116096. $C_{16}H_{15}NO$ requires C, 80·5; H, 6·35; N, 6·1%; *M*, 237·115347]; τ 2·07 (1H, d), 2·55—3·04 (8H, m), 6·12 (2H, t), 7·19 (2H, t), and 7·76 (2H, m); $\nu_{max.}$ (Nujol) 1650 cm^{-1} (C=O).

4-(N-*Benzyl*-m-*anisidino*)*butyric Acid* (XII; R^1 = OMe, R^2 = CH_2Ph, R^3 = H).—*N*-Benzyl-*m*-anisidine (11 g, 0·05 mol), ethyl 4-bromobutyrate (20 g, 0·1 mol), and anhydrous sodium carbonate (10·6 g, 0·075 mol) were heated at 110° with stirring for 20 h. The mixture was cooled, poured into an excess of water, and extracted with benzene. The extract was washed, dried, and evaporated *in vacuo* to leave a red viscous liquid (25·89 g), which was distilled to remove the excess of ethyl 4-bromobutyrate. The residue in a solution of sodium hydroxide (3 g) in aqueous ethanol (100 ml) was refluxed for 2·5 h, cooled, poured into an excess of water, and extracted with benzene. The aqueous layer was carefully acidified (to pH 6) and extracted with methylene dichloride. The organic extract was washed, dried, and evaporated *in vacuo* to leave the *product* as a pale red liquid (11·43 g, 96%) which was not further purified; τ 2·05br (1H, s, exch.), 2·7—3·63 (9H, m), 5·46 (2H, s), 6·25 (3H, s), 6·56 (2H, t), 7·61 (2H, t), and 8·13 (2H, m); $\nu_{max.}$ (film) 1705 cm^{-1} (C=O).

Reaction of 4-(N-*Benzyl*-m-*anisidino*)*butyric Acid with Phosphoryl Chloride*.—The amino-acid (3 g, 0·01 mol) and phosphoryl chloride (1 ml, 0·01 mol) were refluxed in dry benzene (150 ml) with stirring for 4 h. The mixture was cooled and poured into an excess of ice and saturated sodium hydrogen carbonate solution. The organic layer was washed, dried, and evaporated *in vacuo* to leave a yellow oil (2·3 g). Crystallisation from ether–light petroleum (b.p. 40—60°) yielded 1-*m*-methoxyphenyl-2-pyrrolidone as white needles, m.p. 52—54°, identical (mixed m.p.) with an authentic sample.

We thank G. D. Searle and Co. for a fellowship (to A. T.), Roche Products Ltd., for a studentship (to I. R.), and Mrs. I. M. Bell, Miss M. Lennon, and Mr. A. McLean for technical assistance.

[2/166 *Received*, 27*th January*, 1972]