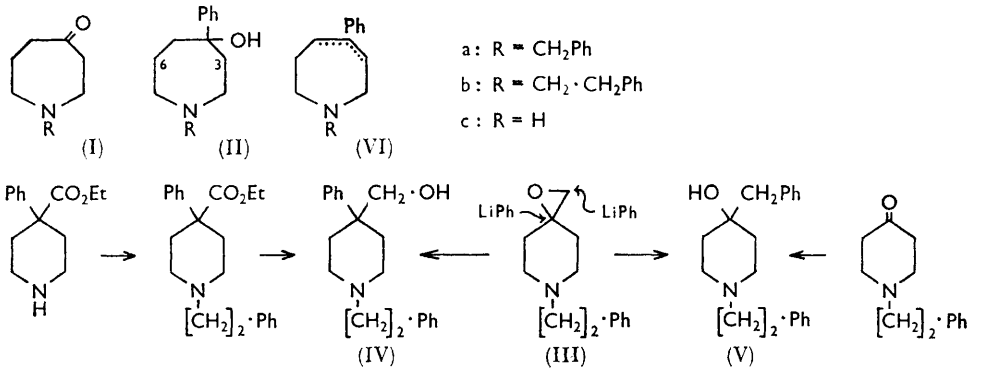
983. *Synthesis and Reactions of Some Azacycloheptan-4-ols.*

By A. F. Casy and H. Birnbaum.

4-Piperidones have been ring-expanded to azacycloheptanones by reaction with diazomethane, and evidence for oxide by-products has been obtained. 4-Phenylazacycloheptan-4-ols have been made from the azacycloheptanones, and their esterification and dehydration investigated. The ethanolysis and Thorpe–Ziegler cyclisation of *N*-(2-cyanoethyl)-*N*-(3-cyanopropyl)benzylamine has been studied. The cyclic product has been shown to have an enaminonitrile structure.

This work, undertaken as part of a study of the relation of ring size to pharmacological activity in compounds related to pethidine, required *N*-substituted azacycloheptan-4-ones (I) as intermediates. Of reported syntheses,[1-3] ring expansion of 4-piperidones by means of diazomethane proved to be the only practicable method. Treatment of the 4-piperidone in methanol with an ethereal solution of diazomethane of known strength, rather than generation of the reagent *in situ* as carried out by Morosawa,[2] reduced the possibility of ring expansion beyond the cycloheptanone and gave a purer product.



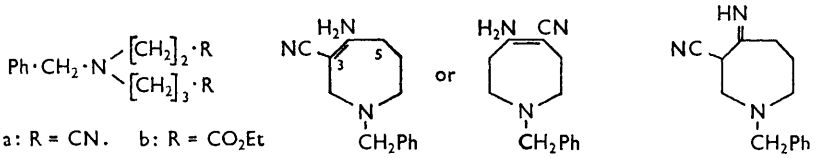
When treated with ethanolic hydrogen chloride, the azacycloheptanones (Ia and b) formed normal hydrochloride salts in marked contrast to the precursor piperidones which gave ethyl ketals with this reagent.[4] Initially, the azacycloheptanones were used after purification *via* their hydrochloride salts; later it was found that the crude ring-expanded product (distilled in some cases) could be satisfactorily employed. The tertiary alcohol (IIb) was obtained by the action of phenyl-lithium on the ketone (Ib) and also by alkylation of the noralcohol (IIc), obtained by catalytic debenzylation of the *N*-benzyl alcohol (IIa). Treatment of unpurified diazomethane-treated *N*-phenethyl-4-piperidone with phenyl-lithium led, in one instance, to an isomer of (IIb) having a higher melting point and different infrared spectrum. It was esterified by hot acetic anhydride–pyridine in contrast to the lower-melting isomer which underwent elimination under these conditions. If the epoxide (III) is formed in the ring-expansion (oxide by-products are known[5] to occur when ketones are treated with diazomethane) its subsequent reaction with phenyl-lithium could lead to the alcohols (IV) and (V). Both were synthesised by unambiguous routes; the 4-benzyl alcohol (V) was made from *N*-phenethyl-4-piperidone and benzylmagnesium

[1] Yokoo and Morosawa, *Bull. Chem. Soc. Japan*, 1956, **29**, 631.
[2] Morosawa, *Bull. Chem. Soc. Japan*, 1958, **31**, 418.
[3] Martin, Pecher, Peeters, and Van Malder, *Bull. Soc. chim. belges*, 1958, **67**, 256.
[4] Beckett, Casy, and Kirk, *J. Medicin. Pharmaceut. Chem.*, 1959, **1**, 37.
[5] House, Grubbs, and Gannon, *J. Amer. Chem. Soc.*, 1960, **82**, 4099.

chloride and the 4-hydroxymethyl alcohol (IV) by alkylation of norpethidine with 2-phenethyl bromide and reduction of the product with lithium aluminium hydride. The higher-melting isomer and the 4-benzyl alcohol (V) were identical. 4-Benzyl alcohols were never encountered when ketones purified by salt formation were employed, acid treatment, of necessity, decomposing any epoxide present.

The alcohol (IIb) gave the alkene (VIb) when heated with acetic anhydride–pyridine, this product also resulting when the acetoxy-ester of the same alcohol was treated with hot methanol–sulphuric acid. Under the same conditions the corresponding piperidine derivatives give esters and methyl ethers, respectively.[4,6] The tendency for azacycloheptan-4-ols to undergo elimination reflects the high 3—6 interactions that obtain in seven-membered alicyclic rings; these interactions are relieved in corresponding cycloheptenes.[7] Alkenes also resulted when the alcohols (IIb and c) were heated with a mixture of acetic and hydrochloric acids. The double-bond position in the azacycloheptenes (VI) has not been established. Both alkenes were isolated as sharp-melting-point hydrochlorides which, from ultraviolet absorption data [$\lambda_{max.}$ (EtOH) 242 mμ (ε 12,800)], appeared to correspond to one of the isomeric azacycloheptenes (VI; R = Me) isolated by Diamond, Bruce, and Tyson [8] in separate reactions [$\lambda_{max.}$ (EtOH) 245 mμ (ε 10,500 and 12,400, respectively)]. The acetoxy- and propionoxy-esters of the alcohol (IIb) were subsequently obtained by decomposing the corresponding lithium salt with an acid anhydride, a method successfully applied to other elimination-prone tertiary alcohols.[6]

The synthesis of the ketone (Ia) by cyclisation was investigated. The acyclic precursor (VIIa) was made by treating *N*-(2-cyanoethyl)benzylamine (from benzylamine and acrylonitrile) with γ-bromobutyronitrile. Martin and his co-workers [3] described the cyclisation of compound (VIIa) (using sodium *N*-methylaniline–styrene) and Diamond [9] that of the *N*-methyl analogue (using lithium *N*-ethylaniline–naphthalene). The cyclic product was obtained in improved yield in this work by application of Diamond's procedure, but its hydrolysis to the ketone (Ia) could not be achieved. Sodium t-butoxide, used by Cavalla [10] as cyclisation agent in ring-closures giving analogous five-membered compounds, was ineffective in the present case. Spectroscopic data supports an enaminonitrile structure (VIII) rather than the originally proposed iminonitrile form (IX) for the cyclic

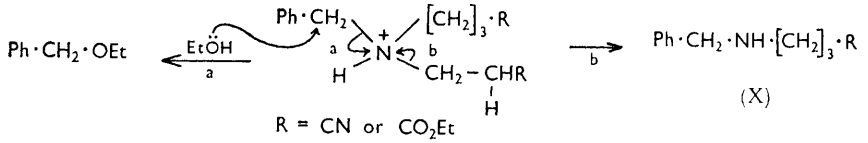


(VII) (VIII) (IX)

product.[3,9] It had $\nu_{max.}$ 3360 and 3150 (NH_2), 2180 (CN in conjugation with C=C·NH_2), and 1588 cm.$^{-1}$ (C=C), and $\lambda_{max.}$ 272 mμ (ε 11,400), consistent with the conjugated system of (VIII).[11] Further, its n.m.r. spectrum showed a signal at τ 6·55 (NH) that had an integral equal to that of the 2-proton signal at τ 6·3 due to the methylene moiety of the *N*-benzyl group. Ethanolysis of the dinitrile (VIIa) to give a product that could be cyclised by the Dieckmann process was also investigated. The diester (VIIb) was isolated in low yield (22%) after the dinitrile (VIIa) had been treated for 24 hours with ethanolic sulphuric acid; benzyl ethyl ether and ethyl 4-benzylaminobutanoate (X; R = CO_2Et) were also formed. The n.m.r. spectrum of the latter exhibited a complex band at τ 7·1—7·9 consistent with a trimethylene rather than a dimethylene chain (as present in the

[6] Casy, Beckett, and Armstrong, *Tetrahedron*, 1961, **16**, 85.
[7] Pauncz and Ginsburg, *Tetrahedron*, 1960, **9**, 40.
[8] Diamond, Bruce, and Tyson, *J. Org. Chem.*, 1961, **26**, 2058.
[9] Diamond, Ph.D. Thesis, Temple University, 1955.
[10] Cavalla, *J.*, 1962, 4664.
[11] Baldwin, *J. Org. Chem.*, 1961, **26**, 3288.

alternative cleavage product, ethyl 3-benzylaminopropanoate). By-product formation may be formulated as shown, cleavage of the shorter *N*-substituents being favoured by resonance stabilisation of intermediates and/or products. Higher yields of the diester



(VIIb) could not be obtained by reducing the reaction time; a spectroscopic study of reaction progress showed significant amounts of nitrile to be present after 12·5 hours whilst by-products were detected after 1 hour. Attempts to cyclise the diester (VIIb) by means of sodium hydride failed.

The pharmacological activities of the described azacycloheptan-4-ols and derivatives will be reported elsewhere.

Experimental

Analyses were by Drs. Weiler and Strauss, Oxford. Equivalent weights of bases and salts were determined by titration with 0·02N-perchloric acid in glacial acetic acid with Oracet Blue B as indicator. Hydrochloride salts were made by treating the bases with a slight excess of ethanolic hydrochloric acid and adding ether to induce crystallisation.

1-*Benzylazacycloheptan-4-one* (Ia).—*Method A.* Diazomethane (14 g., 0·33 mole) in ether (800 ml.) was added over 4 hr. to a stirred solution of 1-benzyl-4-piperidone (45 g., 0·24 mole) in methanol (100 ml.) at −5 to −10°. The mixture was stirred overnight at room temperature and the solvent evaporated. The residue was dissolved in ether, the solution filtered, and the filtrate concentrated. The residual oil (46 g.) distilled at 104—110°/0·25 mm. and gave a hydrochloride, m. p. 189—191° (lit.,[1] 186—187°) (Found: C, 65·2; H, 7·3; N, 5·9%; Equiv., 239. Calc. for $C_{13}H_{18}ClNO$: C, 65·1; H, 7·5; N, 5·8%; Equiv., 240)

Method B. Potassium hydroxide (10 g.) in ethanol–water (40 ml.; 1 : 1) was added over 6 hr. to a stirred solution of 1-benzyl-4-piperidone (61 g.) and *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (81 g.) in methanol (100 ml.) at −5 to −10°. The mixture was stirred overnight at room temperature, filtered, and the filtrate concentrated. The residue, in chloroform, was extracted with aqueous sodium hydroxide, washed, dried (Na_2SO_4), and concentrated. The residual oil (43 g.) freed from ether-insoluble material, gave a hydrochloride identical with that obtained by method A.

1-Phenethylazacycloheptan-4-one (Ib) was obtained by treating 1-phenethyl-4-piperidone with diazomethane as described in method A. It gave a *hydrochloride*, m. p. 195° (Found: C, 65·8; H, 7·9; N, 5·6%; Equiv., 257. $C_{14}H_{20}ClNO$ requires C, 66·3; H, 7·9; N, 5·5%; Equiv., 254).

1-*Benzyl*-4-*phenylazacycloheptan*-4-*ol* (IIa).—The benzyl ketone (Ia) (44 g.) in ether was added to a stirred ethereal solution of phenyl-lithium, prepared from lithium (3·8 g.) and bromobenzene (42 g.), cooled in an ice-bath; the mixture was stirred for 1 hr. at room temperature and poured on to glacial acetic acid (30 ml.) and ice. The solid which separated was washed with ether, shaken with aqueous ammonia–ether and the organic phase dried (Na_2SO_4) and evaporated. The residual solid, m. p. 53° [from light petroleum (b. p. 60—80°)] with ethanolic hydrogen chloride gave the *azacycloheptanol* (IIa) *hydrochloride*, m. p. 204° (from ethanol) (Found: C, 71·45; H, 7·6; N, 4·5%; Equiv., 319. $C_{19}H_{24}ClNO$ requires C, 71·8; H, 7·6 N, 4·4%; Equiv., 318).

4-*Phenylazacycloheptan*-4-*ol* (IIc).—A mixture of the 1-benzylazacycloheptanol (IIa) (31 g.) in ethanol (1 l.) and palladium–charcoal (4 g.; 10%) was shaken with hydrogen at room temperature and pressure. After 3·5 hr. (2·6 l. of hydrogen absorbed), the mixture was filtered and concentrated. The residue gave the *azacycloheptanol* (IIc) *hydrochloride* (20 g.), m. p. 98° (from ethanol–ether) (Found: C, 60·9; H, 8·2; N, 6·3%; Equiv., 237. $C_{12}H_{18}ClNO,\frac{1}{2}H_2O$ requires C, 60·9; H, 8·0; N, 5·9%; Equiv., 237). A mixture of the azacycloheptanol (IIc)

(16 g.), 2-phenethyl bromide (18 g.), sodium hydrogen carbonate (42 g.), and benzene (200 ml.) was heated under reflux for 48 hr. The product was filtered and extracted with dilute aqueous hydrochloric acid. The free base (17 g.), recovered from the aqueous extract by means of ammonia–ether, gave 1-phenethylazacycloheptan-4-ol (IIb) hydrochloride, m. p. 161°, identical with the product derived from the ketone (Ib) (see below).

Reaction of the Ketone (Ib) *with Phenyl-lithium.*—The ketone (43 g.), treated with phenyl-lithium [from lithium (3·1 g.) and bromobenzene (34·5 g.)] in the manner described for the synthesis of compound (IIa), gave the *azacycloheptanol* (IIb) *hydrochloride* (28 g.), m. p. 163° (Found: C, 72·2; H, 7·8; N, 4·1%; Equiv., 334. $C_{20}H_{26}ClNO$ requires C, 72·4; H, 7·8; N, 4·2%; Equiv., 332). In one experiment 4-*benzyl*-1-*phenethylpiperidin*-4-*ol* (V) *hydrochloride*, m. p. 233—235°, was obtained (Found: C, 72·4; H, 7·3; N, 3·95%; Equiv., 327. $C_{20}H_{26}ClNO$ requires C, 72·4; H, 7·8; N, 4·2%; Equiv., 332), identical (mixed m. p. and infrared spectrum) with an authentic sample (see below). It gave a 4-*acetoxy-derivative*, m. p. and mixed m. p. 232°, on treatment with hot acetic anhydride–pyridine (Found: C, 70·6; H, 7·6; N, 3·5%; Equiv., 373. $C_{22}H_{28}ClNO_2$ requires C, 70·7; H, 7·5; N, 3·75%; Equiv., 374).

Unambiguous Synthesis of the Alcohols (IV) *and* (V).—Treatment of ethyl 4-phenylpiperidine-4-carboxylate with 2-phenethyl bromide by the method of Elpern and his co-workers [12] gave ethyl 1-phenethyl-4-phenylpiperidine-4-carboxylate hydrochloride, m. p. 192—194° (lit.,[12] 193—195°). The corresponding free base (6·7 g.) in ether (30 ml.) was added to a stirred suspension of lithium aluminium hydride (0·75 g.) in ether (100 ml.) The mixture was heated under reflux for 2·5 hr., decomposed with water, and filtered. The filtrate was dried (Na_2SO_4) and evaporated, and the residue treated with ethanolic hydrogen chloride, when 4-*hydroxymethyl*-1-*phenethyl*-4-*phenylpiperidine* (IV) *hydrochloride*, m. p. 167°, separated (Found: C, 71·8; H, 8·0; N, 4·1%; Equiv., 328. $C_{20}H_{26}ClNO$ requires C, 72·4; H, 7·8; N, 4·2%; Equiv., 332). 1-Phenethyl-4-piperidone (20·3 g.) in ether was added to an ethereal solution of benzylmagnesium chloride prepared from benzyl chloride (25 g.) and magnesium (4·8 g.). The product, processed in the usual manner, gave the 4-benzylpiperidinol (V) hydrochloride, m. p. 233·5° (from ethanol), identical with the previously described material. The free base gave a hydrobromide, m. p. 220° (from ethanol) (lit.,[13] 218°). A mixture of the 4-benzylpiperidinol (V) (3·5 g.), pyridine (5 ml.), and acetic anhydride (5 ml.) was heated under reflux for 3 hr. and evaporated under reduced pressure. The residue gave the acetoxy-ester hydrochloride of (V), m. p. 233° (from ethanol), identical with previously described material. The free base gave a hydrobromide, m. p. 241° (from ethanol) (lit.,[13] 241°).

1-*Phenethyl*-4-*phenylazacyclohept*-3(*or* 4)-*ene* (VIb).—A mixture of the cycloheptanol (IIb) (6 g.), concentrated hydrochloric acid (30 ml.), and glacial acetic acid (60 ml.) was heated under reflux for 1 hr. The product was concentrated under reduced pressure, made basic with aqueous ammonia, and extracted with ether. The dried extract was evaporated and the residue (5 g.) treated with an excess of ethanolic hydrogen chloride to give the *cycloheptene* (VIb) *hydrochloride* m. p. 193° (Found: C, 77·2; H, 7·75; N, 4·5%; Equiv., 319. $C_{20}H_{24}ClN$ requires C, 76·55; H, 7·7; N, 4·5%; Equiv., 314). It had $\lambda_{max.}$ (EtOH) 242 mμ (ε 12,900). 4-*Phenylazacyclohept*-3(*or* 4)-*ene* (VIc) *hydrochloride* was similarly prepared from the cycloheptanol (IIc). It had m. p. 189—191° and $\lambda_{max.}$ (EtOH) 242 mμ (ε 12,800) (Found: C, 69·4; H, 7·6; N, 6·8%; Equiv., 210. $C_{12}H_{16}ClN$ requires C, 68·7; H, 7·6; N, 6·7%; Equiv., 210). Treatment of the cycloheptanol (IIb) with acetic anhydride–pyridine, in the manner described for the acetylation of the piperidinol (V), gave the cycloheptene (VIb) hydrochloride, m. p. and mixed m. p. 193°.

4-*Acetoxy*-1-*phenethyl*-4-*phenylazacycloheptane*.—The cycloheptanol (IIb) (6 g.) in ether was added to a solution of phenyl-lithium in ether prepared from lithium (0·7 g.) and bromobenzene (8 g.). The mixture was stirred at room temperature for 1 hr., treated with acetic anhydride (10 ml.) in ether (20 ml.), heated under reflux for 6 hr., and poured on to ice and glacial acetic acid (10 ml.). The solid which separated was washed with ether and the basic ester (6·4 g.) isolated as usual. It gave 4-*acetoxy*-1-*phenethyl*-4-*phenylazacycloheptane hydrochloride*, m. p. 174°, when neutralised with ethanolic hydrogen chloride (Found: C, 69·1; H, 7·5; N, 3·8%; equiv., 379. $C_{22}H_{28}ClNO_2,\frac{1}{2}H_2O$ requires C, 69·0; H, 7·6; N, 3·7%; Equiv., 383).

1-*Phenethyl*-4-*phenyl*-4-*propionyloxyazacycloheptane hydrochloride*, m. p. 138—143°, was similarly prepared (Found: C, 69·6; H, 7·7%; Equiv., 395. $C_{23}H_{30}ClNO,\frac{1}{2}H_2O$ requires C, 69·6; H, 7·8%; Equiv., 397). When a mixture of the acetoxy-ester of (IIb) (2·5 g.),

[12] Elpern, Gardner, and Grumbach, *J. Amer. Chem. Soc.*, 1957, **79**, 1951.
[13] Beckett, Casy, and Phillips, *J. Medicin. Pharmaceut. Chem.*, 1960, **2**, 245.

methanol (100 ml.), and concentrated sulphuric acid (12 ml.) was heated under reflux for 6 hr. the cycloheptene (VIb) hydrochloride, identical with an authentic sample, was isolated.

N-(2-*Cyanoethyl*)-N-(3-*cyanopropyl*)*benzylamine* (VIIa).—γ-Bromobutyronitrile (89 g.) in n-butanol (50 ml.) was added over 4 hr. to a mixture of *N*-benzyl-2-cyanoethylamine [14] (106 g.), sodium carbonate (95 g.), potassium iodide (5 g.), and n-butanol at reflux temperature. This temperature was maintained for 24 hr., the mixture filtered, and the solid washed with ether. The combined filtrate and washings were concentrated under reduced pressure, diluted with ether, and extracted with aqueous hydrochloric acid. The basic oil (136 g.), recovered as usual from this extract, was fractionally distilled to give unchanged secondary base (25 g.), b. p. 120—160°/0·35 mm. and the tertiary base (VIIa) (105 g.), b. p. 190—192°/0·25 mm. (lit.,[3] 205—208°/0·6 mm.) (Found: C, 74·0; H, 7·6; N, 18·35. Calc. for $C_{14}H_{17}N_3$: C, 74·0; H, 7·5; N, 18·5%).

4-*Amino*-1-*benzyl*-3(*or* 5)*cyanoazacyclohept*-3(*or* 4)*ene* (VIII).—A mixture of lithium (2·1 g.), freshly distilled *N*-ethylaniline (48 g.), naphthalene (25 g.), and ether (500 ml.) was heated under reflux until all the lithium had dissolved. The basic dinitrile (VIIa) (22·7 g.) in ether (300 ml.) was added over 4 hr. to the vigorously stirred product. The lithium derivative (11·5 g.) which separated was collected, washed with ether, and dissolved in an excess of dilute aqueous acetic acid. After 1 hr. the solution was made basic with aqueous ammonia and extracted with chloroform. The extract was dried and evaporated, and the residue crystallised from methanol to give the cyanoazacycloheptene (VIII), m. p. 180° (lit.,[3] 180—181°) (Found: C, 74·0; H, 7·4; N, 18·6%; Equiv., 230. Calc. for $C_{14}H_{17}N_3$: C, 74·0; H, 7·5; N, 18·5%; Equiv., 227), $\nu_{max.}$ 3360 and 3150 (NH_2), 2184 (CN in conjugation with C=C·NH_2), and 1588 cm.$^{-1}$ (conjugated C=C), and $\lambda_{max.}$ (EtOH) 272 mμ (ε 11,400). Its n.m.r. spectrum had a band in the region τ 2·6—2·7 (5 aromatic protons) and singlets at τ 6·3 (2 methylene protons of *N*-benzyl) and τ 6·55 (2 amino-protons).

Ethanolysis of N-(2-*Cyanoethyl*)-N-(3-*cyanopropyl*)*benzylamine*.—A mixture of the dinitrile (VIIa) (45 g.), ethanol (120 ml.), and concentrated sulphuric acid (78 g.) was heated under reflux for 24 hr. The cooled product was diluted with water (250 ml.) and the oil which separated extracted with ether. The dried extract was evaporated and the residue distilled to give benzyl ethyl ether (13 g.), b. p. 187°, identical with an authentic sample. The basic oil (22 g.), isolated from the aqueous phase was distilled to give, as first fraction, ethyl 4-benzylaminobutanoate (4 g.), b. p. 114—124°/0·18 mm. Its n.m.r. spectrum showed bands at τ 2·6—2·9 (5 aromatic protons), τ 6·3 (singlet, 2 methylene protons of *N*-benzyl), τ 7·1—7·9 (complex band, 6 protons of trimethylene chain), τ 8·05 (singlet, one NH proton) and τ 8·7—8·95 (triplet, 3 methyl protons). It had $\nu_{max.}$ 3330 (NH) and 1725 cm.$^{-1}$ (ester C=O) and gave a *hydrochloride*, m. p. 156° (from ethanol) (Found: C, 60·1; H, 7·6; N, 5·6%; Equiv., 258. $C_{13}H_{20}ClNO_2$ requires C, 60·6; H, 7·8; N, 5·4%; Equiv., 258). The diester (VIIb) (14 g., 22%), b. p. 140°/0·05 mm., 164—166°/0·2 mm. (lit.,[1] 171—173°/0·1 mm.) was obtained as the third fraction (Found: C, 67·5; H, 8·5%; Equiv., 323. Calc. for $C_{18}H_{27}NO_4$: C, 67·3; H, 8·4%; Equiv., 321). A middle fraction (3 g.), b. p. 126—164°/0·18 mm., a mixture of the secondary and tertiary amines, was also obtained. The diester (VIIb) was isolated in 27% yield when the reflux period was reduced to 14 hr.

The n.m.r. spectra were obtained on a 60 M.c. Varian A-60 instrument (in $CDCl_3$ with tetramethylsilane as internal standard). The infrared spectra were measured on a Unicam S.P. 100 spectrophotometer; solids were examined in Nujol.

We thank Miss J. Lovenack, School of Pharmacy, University of London and Mr. G. McDonough for carrying out the n.m.r. and infrared measurements, respectively.

School of Pharmacy,
Chelsea College of Science and Technology,
London S.W.3.

[*Received, April 27th*, 1964.]

[14] Surrey, *J. Amer. Chem. Soc.*, 1949, **71**, 3354.