Some pyrrolidines and azacycloheptanes related to reversed esters of pethidine

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The preparation of some *N*-substituted 3-phenylpyrrolidin-3-ols and their derivatives is described, and the hot-plate analgesia activities in mice of these compounds and related azacycloheptane derivatives reported. The effect of changes in ring size upon the analgesic activities of 4-phenylpiperidine derivatives is discussed.

THE aim of this work was to investigate the effect of ring contraction and expansion upon the analgesic activities of derivatives of 4-phenylpiperidine. Although several five- and seven-membered ring analogues of pethidine and related compounds are known (see Table 3), the comparative pharmacology of a trio of compounds, uniform in all respects except ring size, has not previously been reported.

Chemistry

The *N*-substituted 3-pyrrolidones (IV) required for the synthesis of the pyrrolidines (VI) were prepared by a Dieckmann reaction, sodium hydride serving as the cyclisation reagent. The acyclic precursors (III) were made by alkylating the secondary amino-nitriles (I) (from benzylamine or phenethylamine and acrylonitrile) with ethyl bromo-acetate followed by acid-catalysed ethanolysis of the resultant ester nitriles (II). These reactions were based on methods used in the

$$R = \text{(a) } Ph \cdot [CH_2]_2 \qquad \text{(b) } Ph \cdot CH_2 \qquad \text{(c) } Ph \cdot CO \cdot [CH_2]_2$$
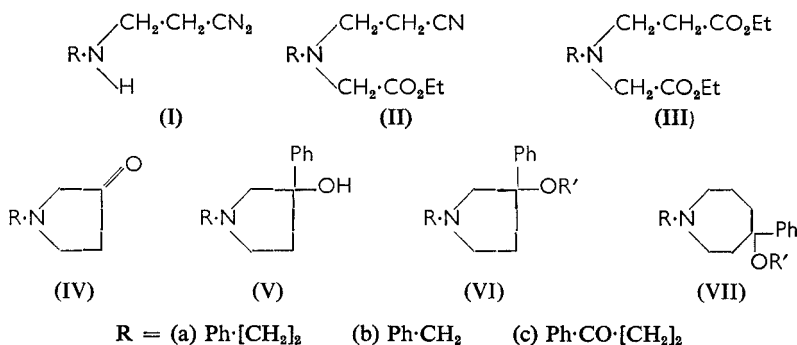
synthesis of 1-methyl-3-pyrrolidones (Cavalla, Davoll, Dean, Franklin, Temple, Wax & Winder, 1961). The pyrrolidone (IVa), with lithium phenyl, gave the tertiary alcohol (Va) which was esterified by acid anhydride-pyridine mixtures and converted to the methyl ether (VIa; R′ = Me) by hot methanol-sulphuric acid. Under the same reaction conditions corresponding 4-phenylpiperidin-4-ols formed analogous products, whereas the seven-membered-ring analogue (VIIa; R′ = H)

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underwent elimination (Casy & Birnbaum 1964). The Mannich bases (Vc and VIIc; R′ = H) were obtained by an exchange reaction between (2-benzoylethyl)trimethylammonium iodide and the appropriate secondary base (V and VII; R = R′ = H) (formed by catalytic debenzylation of corresponding N-benzyl derivatives). Addition of acetic anhydride to the complex formed between the pyrrolidone (IVa) and lithium 2-furyl gave the acetoxy ester of 3-(2-furyl)-1-phenethylpyrrolidin-3-ol. This ester darkened on storage and gave a tar-like product with one mole excess of hydrogen chloride in ethanol, a reagent which converts corresponding piperidine esters to ethyl ethers (Casy, Beckett & Armstrong, 1961). The synthesis and esterification of N-substituted 4-phenyl-azacycloheptan-4-ols (VII, R′ = H) have been described elsewhere (Casy & Birnbaum, 1964).

Pharmacology

The analgesic activities of the alcohols (V and VII; R′ = H) and their derivatives were determined in mice (after subcutaneous injection), using a hot-plate method based on that described by Eddy & Leimbach (1953) (Casy, Beckett, Hall & Vallance 1961); results are given in Table 1.

TABLE 1. ANALGESIC ACTIVITIES OF AZACYCLOALKANOLS AND DERIVATIVES MEASURED BY THE HOT PLATE TEST IN MICE AFTER SUBCUTANEOUS INJECTION

Series No.	Structure	Activity		
		Pyrrolidine $(x = 1, y = 2)$	Piperidine $(x = y = 2)$	Azacycloheptane $(x = 2, y = 3)$
1	Ph·[CH₂]₂·N⟨[CH₂]x–Ph / [CH₂]y–OH	Inactive at 50 mg/kg	ED50 34 mg/kg[a] (0·8 × pethidine)	ED50 47 mg/kg (0·33 × pethidine)
2	Ph·[CH₂]₂·N⟨[CH₂]x–Ph / [CH₂]y–O·CO·Me	Inactive at 100 mg/kg	ED50 4·4 mg/kg (5·7 × pethidine)	ED50 7·2 mg/kg (2·5 × pethidine)
3	Ph·[CH₂]₂·N⟨[CH₂]x–Ph / [CH₂]y–O·CO·Et	Inactive at 100 mg/kg	ED50 1·5 mg/kg (17 × pethidine)	ED50 3·4 mg/kg (7 × pethidine)
4	Ph·[CH₂]₂·N⟨[CH₂]x–Ph / [CH₂]y–OMe	ED50 81 mg/kg (0·25 pethidine)	Inactive at 100 mg/kg[b]	—
5	Ph·CO·[CH₂]₂·N⟨[CH₂]x–Ph / [CH₂]y–OH	ED50 41 mg/kg (0·5 × pethidine)	—	ED50 38 mg/kg (0·5 × pethidine)
6	Ph·[CH₂]₂·N⟨[CH₂]x–O / [CH₂]y–O·CO·Me	Inactive at 100 mg/kg	Inactive at 200 mg/kg[c]	—

a   Beckett, Casy & Kirk (1959).
b   Casy & Armstrong (1964).
c   Casy, Beckett, Hall & Vallance (1961).

The ester (VIIa; R' = CO·Et), the most active non-piperidine derivative tested (seven times as active as pethidine in this test), was selected for a more detailed examination. After oral administration to mice, codeine and the ester (VIIa; R' = CO·Et) had ED50 values of 61·6 and 26·8 mg/kg respectively. After intravenous injection, the ester was 5·4 times as active as pethidine in producing a positive Straub tail response and three times more toxic (LD50 of ester 13·9 mg/kg; LD50 of pethidine 41·7 mg/kg). The ester had a Straub Index (i.v. LD50/i.v. ED50 for Straub tail effect) of 9·3, pethidine having the value 5·1. As Shemano & Wendel (1960) have claimed that this index shows some correlation with the addiction liability of analgesics, this result suggests that the ester may have addictive properties similar to, or somewhat greater than, those of pethidine. As an aid to characterising the ester as a morphine-like analgesic, the effect of nalorphine on its analgesic activity was examined. The ester was administered subcutaneously to five groups of 10 mice, four groups of which received graded doses of nalorphine at the same time. Pethidine was administered in a like manner to other groups of mice. Thirty min after injection, the presence of analgesia was determined by the hot-plate test. The results, summarised in Table 2, show that nalorphine at low dose levels antagonises the analgesic activity of the ester more effectively than it does that of pethidine.

TABLE 2. EFFECT OF NALORPHINE ON THE ANALGESIC ACTIVITY IN MICE OF 1-PHEN-ETHYL-4-PHENYL-4-PROPIONYLOXYAZACYCLOHEPTANE AND PETHIDINE AS MEASURED IN THE HOT PLATE TEST

Compound	Dose of nalorphine mg/kg	No. of animals with analgesia
1-Phenethyl-4-phenyl-4-propionyloxy- azacycloheptane hydrochloride .. 15 mg/kg	— 0·25 0·5 1·0 2·0	9/10 1/10 0/10 0/10 0/10
Pethidine hydrochloride .. 50 mg/kg	— 0·25 0·5 1·0 2·5	8/10 7/10 4/10 2/10 1/10

The development of tolerance in mice repeatedly treated with the ester was compared with that in animals receiving pethidine. The ester was given subcutaneously to a group of 20 mice, whilst a similar group was injected with pethidine, both drugs at approximately their ED90 doses. The injections were made on 5 days a week and the presence of analgesia was determined by the hot-plate test 30 min after injection. Complete tolerance developed to pethidine after eight-days administration, whereas after 16 days only 85% of the mice receiving the ester exhibited tolerance.

In summary the evidence shows the ester (VIIa; R' = CO·Et) to be more active than pethidine, but also more toxic and apparently possessing greater addiction liability. It is, however, active orally and tolerance develops at a slower rate than with pethidine (Fig. 1).
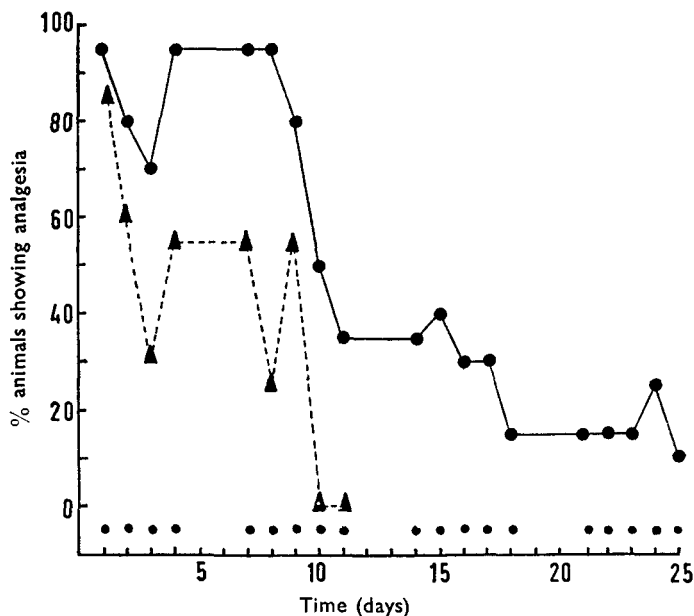
FIG. 1. The development of tolerance to the ester (VIIa, R' = COEt), 10 mg/kg/day (●——●) and pethidine hydrochloride, 45 mg/kg/day (▲– –▲) injected subcutaneously on days marked ●.

Discussion

The effect of changes in ring size upon the analgesic activities of 4-phenylpiperidines is most clearly seen in the esters of series 2 and 3 (Table 1), piperidine members being potent analgesics. Ring contraction by one methylene group abolishes activity, whereas an equal degree of ring expansion produces compounds in which approximately 40% of the activity of the six-membered-ring esters is retained. Further, results with the seven-membered-ring ester (VIIa, R' = CO·Et) indicate it to be a morphine-like analgesic; hence the nature of the retained activity is probably unaffected by ring expansion. These observations are consistent with published results from five- and seven-membered-ring compounds related to pethidine (see Table 3). All pyrrolidine derivatives reported are either inactive or nearly so. Prodilidine (No. 2, Table 3), one of the most active members of a series of esters of 1,2-dimethyl-3-phenylpyrrolidin-3-ol, is slightly less active than codeine in the antinociceptive test. Replacement of the N-methyl group by a phenethyl group (a change that enhances potency in 4-phenylpiperidine-type analgesics) reduces the activity of prodilidine by half (Cavalla, Selway, Wax, Scotti & Winder, 1962). The seven-membered-ring analogue of pethidine (Series 1, Table 3; ethoheptazine, Zactane) is one-third and one-fifth as active as the parent compound in rats and mice respectively in the hot-plate test. It has been used clinically with aspirin to alleviate moderate pain, has a low addiction liability and is probably not a morphine-type analgesic (see references cited by Beckett & Casy, 1962).

TABLE 3. ANALGESIC ACTIVITIES OF SOME PHENYLAZACYCLOALKANES

Series No.	Structure	Activity		
		Pyrrolidine $(x = 1, y = 2)$	Piperidine $(x = y = 2)$	Azacycloheptane $(x = 2, y = 3)$
1	Me·N$\langle$[CH$_2$]x/Ph, [CH$_2$y]/CO·OEt	Inactive in mice at 200 mg/kg[a]	(Pethidine) ED50 9·9 mg/kg in mice[b] ED50 11·2 mg/kg in rats[c]	(Ethoheptazine) ED50 42·6 mg/kg in mice[b] ED50 33·5 mg/kg in rats[c]
2	Me, Me·N —O·CO·Et Ph	(Prodilidine) 0·8 × codeine in rats[d]	—	—
3	Me·N$\langle$[CH$_2$]x/OH, [CH$_2$]y/CO.Et	—	(Ketobemidone) ED50 1·6 mg/kg in mice[b]	ED50 16·5 mg/kg in rats (0·7 × pethidine)[c]
4	Me·N$\langle$[CH$_2$]x/Ph, [CH$_2$]y/SO$_2$Et	—	1 × pethidine in mice[e]	ED50 32 mg/kg in rats (0·3 × pethidine)[c]
5	Me, Me·N$\langle$CH$_2$—CH/Ph, [CH$_2$]y/O·CO·Et	—	(Alphaprodine) ED50 1·9 mg/kg (Betaprodine) ED50 0·7 mg/kg in mice[b]	(Proheptazine) ED50 1·0 mg/kg in mice[b]

a Macdonald & others (1946); b Eddy, Halbach & Braenden (1956); c Braenden, Eddy & Halbach (1955); d Cavalla & others (1961); e Buchi & others (1952).

The azacycloheptane derivatives of series 3, 4 and 5 (Table 3) similarly retain some of the activity of their piperidine analogues. Proheptazine (series 5, Table 3) is a potent analgesic probably of the morphine-type [it produces physical dependence when administered in relatively high doses (Eddy, Halbach & Braenden 1956)]. Its activity cannot be compared directly with that of a piperidine congener since its stereochemistry has not been established.

The results show, in general, that the analgesic property measured is retained (although in reduced degree) in seven-membered-ring analogues of active piperidine derivatives but is absent or weak in five-membered congeners. This generalisation may be interpreted in terms of differences in the relative orientation of, and distance between, the basic centre and the aromatic group in such compounds. These structural parameters, considered of importance in the association between drug molecules and the analgesic receptor (Beckett & Casy 1965), appear to be optimal in a six-membered ring. Although the relationship of the two features must be modified when an additional methylene group is included in the nitrogen-containing ring, the molecule is free to adopt a wide range of conformations (Eliel 1962), some of which may satisfy (in part) requirements for drug-receptor association. In contrast, the distance between

the nitrogen atom and the aromatic group in pyrrolidine derivatives must of necessity be less than that obtaining in piperidine analogues; further, the orientation of the two features is restricted to narrower limits through the more rigid, planar nature of the 5-membered ring (Eliel 1962).

In most instances, the pK_a values of pyrrolidine derivatives are approximately one unit lower than those of piperidine and azacyclo-heptane analogues (Birnbaum 1964). It is difficult, however, to assess the influence of reduced basic character upon the activities of pyrrolidine derivatives, because, while causing the proportion of ionised to non-ionised molecules in the vicinity of the receptor to be lower than that obtaining in piperidine and azacycloheptane congeners (drug-receptor association is considered to involve protonated molecules), it would also be expected to facilitate transport of drug molecules to the active site [lipid barriers are more easily penetrated by unionised molecules (Brodie & Hogben 1957)].

Experimental

Melting-points are uncorrected. Analyses 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 using Oracet Blue B as indicator. Salts were crystallised from ethanol-ether unless otherwise stated. Free bases were recovered from acidic reaction products by treatment with aqueous ammonia and ether extraction.

N-(2-*Cyanoethyl*)*phenethylamine* (Ia). Acrylonitrile (53 g, 1 mole) was added to phenethylamine (121 g, 1 mol) at a rate such that the tempera-ture of the mixture did not rise above 30°. The product was left at room temperature for 14 days and then distilled to give the secondary amine (Ia) (164 g), b.p. 122°/0·4 mm. (Found: equiv. wt 175. Calc. for $C_{11}H_{14}N_2$: 174). It gave a *hydrobromide*, m.p. 166° from ethanol. Found: C, 52·7; H, 5·95; N, 10·65; equiv. wt 258. $C_{11}H_{15}BrN_2$ requires C, 51·8; H, 5·9; N, 11·0%; equiv. wt 255. *N*-(2-Cyanoethyl)benzylamine (Ib), b.p. 131–134°/0·65 mm (Martin, Pecher, Peeters & Van Malder, 1958, report b.p. 148–150°/1 mm), was prepared similarly from acrylo-nitrile and benzylamine. It gave a hydrobromide, m.p. 184°. (Martin & others, 1958, report m.p. 176°). Found: C, 49·6; H, 5·6; N, 11·9; equiv. wt 243. $C_{10}H_{13}BrN_2$ requires C, 49·8; H, 5·4; N, 11·6%; equiv. wt 241.

N-(2-*Cyanoethyl*)-N-*ethoxycarbonylmethylphenethylamine* (IIa). Ethyl bromoacetate (83·5 g, 0·5 mole) was added over a period of 2 hr to a stirred mixture of the secondary base (Ia) (87 g, 0·5 mol), anhydrous potassium carbonate (69 g, 0·5 mole) and ethyl methyl ketone (200 ml) maintained at the reflux temperature. When addition was complete the mixture was heated for a further 6 hr under reflux, filtered and the filtrate evapora-ted. The residue was distilled to give the *tertiary base* (IIa) (122 g), b.p. 172–174°/1·1 mm. Found: C, 69·05; H, 7·8; N, 10·5; equiv. wt 261. $C_{15}H_{20}N_2O_2$ requires C, 69·2; H, 7·7; N, 10·8%; equiv. wt 260.

N-(2-*Cyanoethyl*)-N-*ethoxycarbonylmethylbenzylamine* (IIb), b.p. 160°/0·9 mm, was similarly prepared from the secondary amine (Ib). (Found: equiv. wt 244. Calc. for $C_{14}H_{18}N_2O_2$: 246). It gave a *hydrobromide*, m.p. 148°. Found: C, 51·4; H, 5·6; N, 8·45; equiv. wt 328. $C_{14}H_{19}BrN_2O_2$ requires C, 51·4; H, 5·8; N, 8·6%; equiv. wt 327.

N-(2-*Ethoxycarbonylethyl*)-N-*ethoxycarbonylmethylphenethylamine* (IIIa). *Method* 1. Dry hydrogen chloride was passed into a solution of the cyano-ester (IIa) (26 g) in ethanol (100 ml) for 5·5 hr, ammonium chloride separating after the gas had been passed for 2 hr. The mixture was then heated under reflux for 3 hr, left at room temperature overnight, and then filtered. The filtrate (and ethanol washings) was evaporated, and the free base, liberated from the residual oil, was distilled to give the diester (IIIa) (25·8 g, 82%) b.p. 148–152°/0·3 mm. (Found: equiv. wt 302. Calc. for $C_{17}H_{25}NO_4$: 307). It had an intense absorption peak at 1735 cm^{-1} (ester carbonyl); nitrile absorption bands near 2250 cm^{-1} were absent.

Method 2. A mixture of the cyano-ester (IIa) (78 g), concentrated sulphuric acid (120 g) and ethanol (180 ml) was heated under reflux for 18 hr, cooled, and diluted with water (350 ml). The free base, liberated by means of aqueous potassium carbonate solution (20%) was distilled to give the diester (IIIa) (68 g, 74%), b.p. 154–158°/0·7 mm. Its infrared spectrum was identical with that of the compound obtained by method 1. Attempts to prepare a crystalline derivative of the diester (IIIa) failed. N-(2-*Ethoxycarbonylethyl*)-N-*ethoxycarbonylmethylbenzylamine* (IIIb), b.p. 144°/0·75 mm, was prepared from the cyano-ester (IIb) by Method 1. Found: C, 65·8; H, 8·1; equiv. wt 294. $C_{16}H_{23}NO_4$ requires C, 65·5; H, 7·85%; equiv. wt 293.

1-*Phenethyl*-3-*pyrrolidone* (IVa). The diester (IIIa) (15·4 g, 0·05 mol) was added to a stirred suspension of sodium hydride (50% suspension in mineral oil, 2·4 g, 0·05 mole) in xylene (60 ml) maintained at 60°. A vigorous initial reaction, subsequently controlled by the rate of addition, ensued; when the addition was complete the mixture was heated under reflux for 3 hr, cooled and treated with water to decompose any excess of sodium hydride. The product was extracted with hydrochloric acid (6N, 80 ml) (one drop of this extract gave a blood-red colour with aqueous $FeCl_3$), and the extract heated under reflux for 3 hr (the product gave no coloration with aqueous $FeCl_3$). The solution was evaporated to small bulk and made alkaline with a concentrated aqueous solution of sodium hydroxide. The oil (7·5 g) which separated was isolated and distilled to give the pyrrolidone (IVa) (4·7 g, 50%) b.p. 108–110°/0·5 mm. (Found: equiv. wt 192. Calc. for $C_{12}H_{15}NO$: 189), as a colourless oil which rapidly darkened on exposure to the atmosphere. It gave a *hydrochloride*, m.p. 153°. Found: C, 64·3; H, 6·9; N, 6·1; equiv. wt 227. $C_{12}H_{16}ClNO$ requires C, 63·9; H, 7·1; N, 6·2%; equiv. wt 226. 1-*Benzyl*-3-*pyrrolidone* (IVb), b.p. 109°/1·1 mm, was similarly prepared from the diester (IIIb). It gave a *hydrochloride*, m.p. 192°. Found: C, 62·6;

H, 6·5; N, 6·6; equiv. wt 216. $C_{11}H_{14}ClNO$ requires C, 62·4; H, 6·6; N, 6·6%; equiv. wt 212.

1-*Phenethyl-3-phenylpyrrolidin-3-ol* (Va) *and derivatives.* Freshly prepared 1-phenethyl-3-pyrrolidone (14·3 g, 0·075 mol) in ether (75 ml) was added to a stirred, ice-cooled solution of lithium phenyl in ether (75 ml), prepared from lithium (1·3 g, 0·19 mole) and bromobenzene (14·3 g, 0·09 mol). The product, after being stirred for 1 hr at room temperature, was decomposed with ice and glacial acetic acid (12 ml); the solid which separated after storage at 5° was collected and washed with ether. The free base (17·5 g) derived from this solid was treated with ethanolic HBr to give 1-*phenethyl-3-phenylpyrrolidin-3-ol* (Va) *hydrobromide*, m.p. 121°. Found: C, 62·2; H, 6·2; N, 4·3; equiv. wt 351. $C_{18}H_{22}BrNO$ requires C, 62·1; H, 6·3; N, 4·0%; equiv. wt 348. A mixture of the pyrrolidinol (Va) (8 g), acetic anhydride (12 ml) and pyridine (12 ml) was heated under reflux for 3 hr, xylene added and the solvents evaporated under reduced pressure. The residue, with a slight excess of ethanolic HCl, gave 3-*acetoxy-1-phenethyl-3-phenylpyrrolidine* (VIa, R' = CO·Me) *hydrochloride* (6 g), m.p. 163°. Found: C, 69·4; H, 7·2; equiv. wt 349. $C_{20}H_{24}ClNO_2$ requires C, 69·5; H, 6·95%; equiv. wt 346. The corresponding 3-*propionyloxypyrrolidine* (VIa, R' = CO·Et) *hydrochloride*, m.p. 171°, was similarly prepared using propionic anhydride (no pyridine). Found: C, 70·15; H, 7·2; N, 4·0; equiv. wt 362. $C_{21}H_{26}ClNO_2$ requires C, 70·1; H, 7·2; N, 3·9%; equiv. wt 360. A mixture of the 3-acetoxypyrrolidine (VIa, R' = CO·Me) hydrochloride (2 g), concentrated sulphuric acid (10 ml) and dry methanol (50 ml) was heated under reflux for 6 hr. Excess of aqueous ammonia was added, and the precipitated NH_4Cl removed by filtration. The filtrate (and methanol washings) was concentrated and then diluted with water. The oil (1·4 g) which separated was isolated and treated with methanolic HCl to give 3-*methoxy-1-phenethyl-3-phenylpyrrolidine* (VIa, R' = Me) *hydrochloride*, m.p. 194° from methanol-ether. Found: C, 71·95; H, 7·8; N, 4·3; equiv. wt 319. $C_{19}H_{24}ClNO$ requires C, 71·8; H, 7·6; N, 4·4%; equiv. wt 318. It had an absorption peak at 1095 cm^{-1} (characteristic of the C–O stretching frequency in related 4-alkoxypiperidines, Casy, Beckett & Armstrong, 1961.

3-*Acetoxy-3-(2-furyl)-1-phenethylpyrrolidine.* The pyrrolidone (IVa) (33 g) in ether was added to a stirred, ice-cooled solution of lithium 2-furyl in ether [prepared from lithium (2·8 g), bromobenzene (31·4 g) and freshly distilled furan (13·6 g)]. Acetic anhydride (34 ml) in ether was then added, the mixture stirred at room temperature for 1 hr and poured onto crushed ice and glacial acetic acid (34 ml). Basic material (37·3 g), isolated from the solid which separated, was purified by chromatographing on alumina and eluting with light petroleum (b.p. 40–60°): benzene (9:1) to give the impure 3-acetoxypyrrolidine (19·5 g) as a yellow oil. This oil, with slightly less than an equimolar quantity of ethanolic HCl gave 3-*acetoxy-3-(2-furyl)-1-phenethylpyrrolidine hydrochloride*, m.p. 127° decomp. from ethanol. Found: C, 64·2; H, 6·5;

N, 4·4; equiv. wt 339. $C_{18}H_{22}ClNO_3$ requires C, 64·4; H, 6·6; N, 4·2%; equiv. wt 336. The salt decomposed on exposure to the atmosphere and when treated with acid reagents.

1-*Benzyl*-3-*phenylpyrrolidin*-3-*ol* (Vb) *and related compounds*. 1-Benzyl-3-pyrrolidone (IVb) (44 g) was treated with lithium phenyl [prepared from lithium (3·9 g) and bromobenzene (43 g)] in the usual manner to give the *pyrrolidinol* (Vb) *hydrochloride* (18 g), m.p. 156°. Found: C, 71·4; H, 6·8; N, 4·6; equiv. wt 285. $C_{17}H_{20}ClNO$ requires C, 70·5; H, 6·9; N, 4·6%; equiv. wt 290. This salt (15·2 g) in ethanol (300 ml) was shaken with hydrogen at room temperature and pressure in the presence of palladised charcoal (10%, 1·5 g); the uptake of hydrogen (1600 ml) required 24 hr. The mixture was filtered, the filtrate evaporated and the residue (9·9 g) crystallised from ethanol-ether to give 3-*phenyl-pyrrolidin*-3-*ol* (V, R = H) *hydrochloride*, m.p. 148°. Found: C, 59·55; H, 6·9; N, 7·1; equiv. wt 197. $C_{10}H_{14}ClNO$ requires C, 60·15; H, 7·0; N, 7·0%; equiv. wt 200. Nitrogen was passed for 8 hr through a mixture of the pyrrolidinol (V, R = H) (1·8 g), (2-benzoylethyl)tri-methylammonium iodide (3·8 g), anhydrous Na_2CO_3 (2·4 g) and dimethylformamide (35 ml). Water (200 ml) was added and the cloudy product stored at 5° whereupon the impure 1-(2-benzoylethyl)-3-phenyl-pyrrolidin-3-ol (Vc) (2·5 g), m.p. 76° separated. It gave a hydrochloride, m.p. 156°. Found: C, 68·05; H, 6·8; N, 4·5; equiv. wt 329. $C_{19}H_{22}ClNO_2$ requires C, 68·8; H, 6·6; N, 4·2; equiv. wt 332.

1-(2-*Benzoylethyl*)-4-*phenyl*-1-*azacycloheptan*-4-*ol*) was similarly pre-pared from 4-phenyl-1-azacycloheptan-4-ol (Casy & Birnbaum, 1964). It gave a *hydrochloride*, m.p. 148–150°. Found: C, 69·8; H, 7·1; N, 4·4; equiv. wt 353. $C_{21}H_{26}ClNO_2$ requires C, 70·1; H, 7·2; N, 3·9%; equiv. wt 360.

The infrared absorption spectra of all compounds described were consistent with assigned structures and were recorded on a Unicam S.P. 200 spectrophotometer.

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