619. *The Chemotherapy of Filariasis. Analogues of Diethylcarbamazine (1-Diethylcarbamoyl-4-methylpiperazine) derived from 2 : 4′- and 4 : 4′-Dipiperidyl, Homopiperazine, and 4-Aminopiperidine.*

By P. Brookes, R. J. Terry, and James Walker.

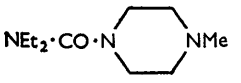
Analogues of diethylcarbamazine (1-diethylcarbamoyl-4-methylpiperazine) (I) derived from 2 : 4′- and 4 : 4′-dipiperidyl, homopiperazine, and 4-aminopiperidine have been prepared. Those analogues having the same pattern of substitution on the nitrogen atoms as that which favours activity in the piperazine series were active in reducing the numbers of circulating microfilariæ in cotton rats infected with *Litomosoides carinii*. The diethylsulphamoyl analogue of (I) and the corresponding homopiperazine derivative were also active. Though all the compounds examined were less active than (I), the results show that the piperazine nucleus is not essential for the characteristic biological action of diethylcarbamazine.

The introduction of filarial infections in cotton rats as a laboratory model led to the discovery of therapeutically effective derivatives of piperazine.[1] Piperazine itself, though now used in other forms of helminthiasis, is inactive, but the introduction of an ethoxycarbonyl group in the 1-position with a hydrogen atom or a small range of substituents in the 4-position of the piperazine ring gave compounds with marked activity in reducing the numbers of microfilariæ circulating in the peripheral blood. Lower alkyl groups in the 4-position up to the *n*-butyl group gave active compounds of increasing toxicity as the alkyl chain was lengthened, and other permissible substituents in the 4-position were the amidino- and the ethoxycarbonyl group. The ethoxycarbonyl group in the 1-position could be replaced by lower alkylcarbamoyl or dialkylcarbamoyl groups, and, of the resulting substances, 1-diethylcarbamoyl-4-methylpiperazine (diethylcarbamazine, " Hetrazan ") (I) has proved of value in the treatment of filarial infections in man and in other forms of helminthiasis. In spite of the dramatic effect produced by diethylcarbamazine (I) on the circulating microfilariæ *in vivo*, the drug appears to have no direct lethal action *in vitro* on the microfilariæ, and its precise mode of action has been a subject of interest in these laboratories for some years.[2] As, hitherto, the piperazine ring has been considered to be of fundamental importance,[3] the purpose of the present work was to study the effect on biological activity of the replacement of the piperazine ring in diethylcarbamazine by the ring systems of other strong cyclic diacidic bases, 2 : 4′- (II) and 4 : 4′-dipiperidyl (III), homopiperazine (IV), and 4-aminopiperidine (V) being selected for this purpose. Morley[4] examined derivatives of 1 : 2 : 3 : 4-tetrahydroquinoxaline and of 5 : 10-dihydro- and *trans*-1 : 2 : 3 : 4 : 5 : 10 : 11 : 12-octahydro-phenazine in the same connection but in none of his compounds was the *NN*′-substitution characteristic of diethylcarbamazine achieved and no biological results were recorded.

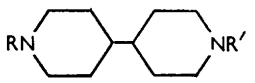
Two analogues of diethylcarbamazine (I) can theoretically be derived from 2 : 4′-dipiperidyl (II), namely, 1′-diethylcarbamoyl-1-methyl- (VI) and 1-diethylcarbamoyl-1′-methyl-2 : 4′-dipiperidyl (VII), and the first stage in the preparation of either was the appropriate protection of one of the imino-groups in 2 : 4′-dipiperidyl (II) itself. The unsymmetrical structure of 2 : 4′-dipiperidyl (II) with its relatively hindered 1-position favoured the formation of the 1′-benzyloxycarbonyl derivative (VIII) by the action of a toluene solution of benzyl chloroformate on 2 : 4′-dipiperidyl in aqueous-methanolic acid. Methylation of this derivative with formaldehyde and formic acid and removal of the benzyloxycarbonyl group with hydrogen bromide in acetic acid then gave 1-methyl-2 : 4′-dipiperidyl (IX). Benzoylation of the benzyloxycarbonyl compound (VIII) and removal

[1] Hewitt, White, Wallace, Stewart, Kushner, and SubbaRow, *J. Lab. Clin. Med.*, 1947, **32**, 1304.
[2] Hawking, Sewell, and Thurston, *Brit. J. Pharmacol.*, 1950, **5**, 217; Bangham, *ibid.*, 1955, **10**, 397, 406; Chase and Downes, *J.*, 1953, 3874.
[3] Cf. Hawking, *Pharmacol. Rev.*, 1955, **7**, 283.
[4] Morley, *J.*, 1952, 4002, 4008.

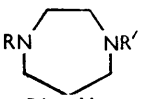
of the benzyloxycarbonyl group by catalytic hydrogenation, or by cautious treatment with hydrogen bromide in acetic acid, afforded 1-benzoyl-2 : 4′-dipiperidyl (X), which was likewise methylated with formaldehyde and formic acid to the 1′-methyl derivative, and gave access, on hydrolysis, to 1′-methyl-2 : 4′-dipiperidyl (XI). 1-Methyl-2 : 4′-dipiperidyl (IX) was converted into the 1′-ethoxycarbonyl- (XII), 1′-allylthiocarbamoyl- (XIII), 1′-amidino- (XIV), and 1′-phenylcarbamoyl- (XV) derivatives by the action of ethyl chloroformate, allyl *iso*thiocyanate, *S*-methylthiuronium sulphate, and phenyl *iso*cyanate respectively. The 1′-carbonyl chloride was obtained by the action of a large excess of carbonyl chloride on 1-methyl-2 : 4′-dipiperidyl, and with diethylamine gave 1′-diethylcarbamoyl-1-methyl-2 : 4′-dipiperidyl (VI); when only a slight excess of carbonyl chloride was used the product, after treatment with diethylamine, was shown by analysis to be carbonyl-1′ : 1′-bis-(1-methyl-2 : 4′-dipiperidyl). The diethylcarbamoyl derivative (VI) was also obtained by



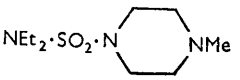
(I)



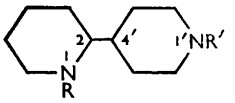
(III) R = R′ = H
(XVII) R = CO·O·CH$_2$Ph, R′ = H
(XVIII) R = CO·O·CH$_2$Ph, R′ = Me
(XIX) R = Me, R′ = H
(XX) R = Me, R′ = CO·NEt$_2$



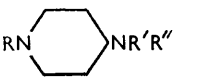
(IV) R = R′ = H
(XXI) R = H, R′ = Me
(XXII) R = CO·NEt$_2$, R′ = Me
(XXIII) R = SO$_2$·NEt$_2$, R′ = Me



(XXIV)



(II) R = R′ = H
(VI) R = Me, R′ = CO·NEt$_2$
(VII) R = CO·NEt$_2$, R′ = Me
(VIII) R = H, R′ = CO·O·CH$_2$Ph
(IX) R = Me, R′ = H
(X) R = CO·Ph, R′ = H
(XI) R = H, R′ = Me
(XII) R = Me, R′ = CO$_2$Et
(XIII) R = Me, R′ = CS·NH·C$_3$H$_5$
(XIV) R = Me, R′ = C(:NH)·NH$_2$
(XV) R = Me, R′ = CO·NHPh
(XVI) R = CO·NHPh, R′ = Me



(V) R = R′ = R″ = H
(XXV) R = Me, R′ = R″ = H
(XXVI) R = Me, R′ = CO$_2$Et, R″ = H
(XXVII) R = R′ = Me, R″ = CO·NEt$_2$
(XXVIII) R = R′ = Me, R″ = H
(XXIX) R = R′ = Me, R″ = CO$_2$Et
(XXX) R = CH$_2$Ph, R′ = R″ = H
(XXXI) R = H, R′ = R″ = Me
(XXXII) R = CO$_2$Et, R′ = R″ = Me
(XXXIII) R = CO·NEt$_2$, R′ = R″ = Me

the action of diethylcarbamoyl chloride on 1-methyl-2 : 4′-dipiperidyl, but great difficulty was experienced in characterising it (VI), as, without exception among those examined, salts containing biologically acceptable anions were deliquescent; the citrate gave analytical figures indicative of a sesquicitrate, and a further analytical check was obtained by using the tetraphenylboron salt. 1′-Methyl-2 : 4′-dipiperidyl (XI) failed to react with diethylcarbamoyl chloride under conditions similar to those used in the preparation of (VI) (above), presumably as the joint result of the steric hindrance of the 1-position and the spatial requirements of the ethyl groups [5] in diethylcarbamoyl chloride, but the phenylcarbamoyl derivative (XVI) was obtained by the action of phenyl *iso*cyanate. The steric hindrance of the 1-position in 2 : 4′-dipiperidyl (II) is also borne out by the formation from it of a monoamidino-derivative (XIV; R = H in place of Me) by the action of *S*-methylthiuronium sulphate.[6] The alternative route to the 1-diethylcarbamoyl derivative (VII) *via* the 1-carbonyl chlorde was not promising.

[5] Cf. Brown and Sujishi, *J. Amer. Chem. Soc.*, 1948, **70**, 2878; Brown and Eldred, *ibid.*, 1949, **71**, 445.

In similar fashion 4 : 4′-dipiperidyl (III) was converted into the 1-benzyloxycarbonyl (XVII) and the 1-benzyloxycarbonyl-1′-methyl derivative (XVIII). Removal of the protecting group gave 1-methyl-4 : 4′-dipiperidyl (XIX) which was converted by the two alternative methods used in the preparation of 1′-diethylcarbamoyl-1-methyl-2 : 4′-dipiperidyl (VI) into the required diethylcarbamazine analogue, 1-diethylcarbamoyl-1′-methyl-4 : 4′-dipiperidyl (XX). Trouble was again experienced with deliquescent salts, and the citrate, in this case also, gave analytical figures indicating that it was a sesquicitrate.

1-Methylhomopiperazine (XXI), prepared by a combination of known methods,[7] was converted by reaction with diethylcarbamoyl chloride and with diethylsulphamoyl chloride into 1-diethylcarbamoyl- (XXII) and 1-diethylsulphamoyl-4-methylhomopiperazine (XXIII) respectively, while 1-diethylsulphamoyl-4-methylpiperazine (XXIV) was similarly prepared from 1-methylpiperazine and diethylsulphamoyl chloride. The three compounds (XXII)—(XXIV) were characterised and tested in the form of citrates.

Diethylcarbamazine analogues derived from 4-aminopiperidine (V) may bear the diethylcarbamoyl group attached in the 1-position or attached to the extracyclic amino-group and both types have been obtained. Reduction of 1-methyl-4-piperidone oxime with sodium and ethanol gave 4-amino-1-methylpiperidine (XXV) from which an ethoxycarbonyl derivative (XXVI) was prepared but an attempt to prepare a diethylcarbamoyl derivative was unsuccessful. In contrast a diethylcarbamoyl derivative (XXVII) was readily obtained from 1-methyl-4-methylaminopiperidine (XXVIII), prepared by reductive amination of 1-methyl-4-piperidone in presence of methylamine, and the ethoxycarbonyl derivative (XXIX) was also prepared. Access to the alternative series was obtained *via* 1-benzyl-4-piperidone. Reduction of 1-benzyl-4-piperidone oxime gave 4-amino-1-benzylpiperidine (XXX) which was methylated with formaldehyde and formic acid to give 1-benzyl-4-dimethylaminopiperidine. Hydrogenolysis afforded 4-dimethylaminopiperidine (XXXI), from which the ethoxycarbonyl (XXXII) and the diethylcarbamoyl (XXXIII) derivative were prepared. The compounds (XXVII) and (XXIX) were characterised and tested as citrates, and the compounds (XXXII) and (XXXIII) as hydrochlorides; the compound (XXVI) was tested as a neutralised solution in hydrochloric acid.

Biological tests were carried out according to the general method of Sewell and Hawking [8] on cotton rats infected in the laboratory with *Litomosoides carinii* by exposure to tropical rat mites which had been in contact with a heavily infected donor rat. Microfilarial counts were made at the outset of treatment and at intervals of 2—3 days for a total of 14 days. The condition of the adult worms was determined at autopsy. 1′-Diethylcarbamoyl-1-methyl-2 : 4′- (VI) and 1-diethylcarbamoyl-1′-methyl-4 : 4′-dipiperidyl (XX) sesquicitrates were markedly active in reducing the numbers of circulating microfilariæ. One other derivative, 1′-ethoxycarbonyl-1-methyl-2 : 4′-dipiperidyl (XII), tested as a neutralised solution in hydrochloric acid, was of doubtful activity, and the remaining dipiperidyl derivatives, (XIII)—(XVI), were inactive. The five derivatives, (XXVI), (XXVII), (XXIX), (XXXII), and (XXXIII) of 4-aminopiperidine, the homopiperazine derivatives, (XXII) and (XXIII), and 4-diethylsulphamoyl-1-methylpiperazine (XXIV) all caused the numbers of circulating microfilariæ to fall although none was as potent as diethylcarbamazine (I). No compound tested in this investigation appeared to have any action on the adult worms, nor, in fact, does diethylcarbamazine (I). After the completion of this work, Reinertson and Thompson [9] reported that 1-diethylcarbamoyl-4-methylhomopiperazine (XXII) hydrochloride had about one-quarter to one-half of the activity of diethylcarbamazine in reducing the numbers of circulating microfilariæ of

[6] King and Wright, *J.*, 1939, 253.

[7] (*a*) *Org. Synth.*, 1940, **20**, 35; (*b*) McElvain, *J. Amer. Chem. Soc.*, 1924, **46**, 1721; (*c*) Dickerman and Lindwall, *J. Org. Chem.*, 1949, **14**, 530; (*d*) Sommers, Michaels, and Weston, *J. Amer. Chem. Soc.*, 1954, **76**, 5805.

[8] Sewell and Hawking, *Brit. J. Pharmacol.*, 1950, **5**, 239.

[9] Reinertson and Thompson, *Antibiotics and Chemotherapy*, 1955, **5**, 566.

L. carinii in naturally infected cotton rats. Although none of the compounds described above approaches diethylcarbamazine (I) in activity, the results nevertheless dispose of the belief that the presence of the piperazine ring is essential for the characteristic biological action of diethylcarbamazine, but the pattern of substitution on the nitrogen atoms that is most favourable in the piperazine series appears to be necessary for activity when applied to 2 : 4′-dipiperidyl (II) and gave active compounds when applied to 4 : 4′-dipiperidyl (III), homopiperazine (IV), and 4-aminopiperidine (V).

Experimental

1′-Benzyloxycarbonyl-2 : 4′-dipiperidyl (VIII).—A solution of 2 : 4′-dipiperidyl (8·4 g.) in methanol (50 c.c.) was neutralised to bromocresol-purple with concentrated hydrochloric acid, and treated with a toluene solution (10 c.c. of 85% w/v) of benzyloxycarbonyl chloride [10] (8·5 g.), added in small portions (0·5 c.c.) with constant stirring. After each addition time was allowed for reaction to occur before adjustment of the pH to the neutral point of the indicator with 6N-sodium hydroxide. When all the benzyloxycarbonyl chloride had been added (45—60 min.), water (100 c.c.) was added and the solution was concentrated to remove organic solvents. The residual aqueous solution was rendered strongly acidic in the cold with concentrated hydrochloric acid, and three extractions with benzene removed crude 1 : 1′-dibenzyloxycarbonyl-2 : 4′-dipiperidyl. The aqueous phase was brought to pH *ca.* 12 with cold 50% sodium hydroxide solution and again extracted with benzene. On evaporation of the washed, dried extract, crude 1′-benzyloxycarbonyl-2 : 4′-dipiperidyl was obtained as a pale straw-coloured syrup (12·2 g.), which did not crystallise and could not be distilled; it was characterised as the *picrate*, which crystallised from dimethylformamide–ether in yellow prisms, m. p. 231—232° (Found : C, 53·8; H, 5·3; N, 13·1. $C_{18}H_{26}O_2N_2,C_6H_3O_7N_3$ requires C, 54·2; H, 5·5; N, 13·2%).

Similar results were obtained when bromophenol-blue was used as indicator.

1′-Benzyloxycarbonyl-1-methyl-2 : 4′-dipiperidyl.—A mixture of 1′-benzyloxycarbonyl-2 : 4′-dipiperidyl (6·0 g.) and 100% formic acid (2·3 g.), prepared with cooling, was heated with 35% aqueous formaldehyde solution (3 c.c.) under reflux on the water-bath for 4 hr. Addition of an equivalent of hydrobromic acid and evaporation to dryness under reduced pressure afforded a gum (8·0 g.), which failed to crystallise, as also did the free base prepared from it. The base was characterised as the *picrate*, which separated from ethanol in rosettes of pale yellow needles, m. p. 217° (Found : C, 54·3; H, 5·6; N, 12·9. $C_{19}H_{28}O_2N_2,C_6H_3O_7N_3$ requires C, 55·0; H, 5·7; N, 12·8%).

1-Methyl-2 : 4′-dipiperidyl (IX) *Dihydrobromide and Dihydrochloride.*—1′-Benzyloxycarbonyl-1-methyl-2 : 4′-dipiperidyl hydrobromide (8·0 g.) was dissolved in a 33% solution of hydrogen bromide in glacial acetic acid (20 c.c.), and the mixture was kept, protected from atmospheric moisture, for 1 hr., at the end of which evolution of carbon dioxide had ceased. Addition of two volumes of ether then precipitated *1-methyl-2 : 4′-dipiperidyl dihydrobromide*, sometimes as a solid but more often as a stiff gum (5·6 g.); it crystallised from methanol–ethyl acetate in colourless prisms, m. p. 300° (decomp.) (Found : C, 38·2; H, 6·5; N, 8·0. $C_{11}H_{22}N_2,2HBr$ requires C, 38·4; H, 7·0; N, 8·1%).

The *dihydrochloride*, prepared from the free base in dry ether, separated from methanol–ethyl acetate in colourless prisms, m. p. 318—320° (decomp.) (Found : C, 51·9; H, 8·8; N, 10·8. $C_{11}H_{22}N_2,2HCl$ requires C, 51·8; H, 9·4; N, 11·0%).

1′-Ethoxycarbonyl-1-methyl-2 : 4′-dipiperidyl (XII).—1-Methyl-2 : 4′-dipiperidyl dihydrochloride (2·55 g.) was treated with excess of 50% aqueous sodium hydroxide solution, and the free base was taken up in benzene. The dried benzene solution was then boiled under reflux for 6 hr. with anhydrous sodium carbonate (1·1 g.) and ethyl chloroformate (1·1 g.), cooled, and filtered. Fractionation of the filtrate afforded an oil (2·1 g.), b. p. 128—131°/0·07 mm., characterised as the *picrate*, which separated from dimethylformamide–ether in yellow needles, m. p. 188—190° (decomp.) (Found : C, 49·8; H, 5·7. $C_{14}H_{26}O_2N_2,C_6H_3O_7N_3$ requires C, 49·7; H, 6·0%). The hydrochloride was deliquescent.

1′-Allylthiocarbamoyl-1-methyl-2 : 4′-dipiperidyl (XIII).—The free base from 1-methyl-2 : 4′-dipiperidyl dihydrochloride (2·55 g.) was treated under reflux in boiling alcoholic solution (20 c.c.) with allyl *iso*thiocyanate (1·0 g.) for 90 min., and evaporation of the solution gave a

[10] *Org. Synth.*, 1943, **23**, 13.

crystalline solid (2·47 g.). Recrystallisation from benzene–light petroleum afforded 1′-*allylthiocarbamoyl*-1-*methyl*-2 : 4′-*dipiperidyl* as colourless needles, m. p. 128° (Found : C, 64·1; H, 8·8; N, 14·5. $C_{15}H_{27}N_3S$ requires C, 64·1; H, 9·6; N, 14·9%).

1′-*Amidino*-1-*methyl*-2 : 4′-*dipiperidyl* (XIV) *Sulphate*.—A solution of 1-methyl-2 : 4′-dipiperidyl (1·82 g.) and *S*-methylthiuronium sulphate [11] (1·3 g.) in 65% aqueous ethanol (15 c.c.) was boiled under reflux for 3 hr., at the end of which evolution of methanethiol had ceased. The solution, rendered slightly acid by the addition of a few drops of 2N-sulphuric acid, was taken to dryness, affording a solid residue. Recrystallisation from methanol–ethyl acetate gave colourless prisms of 1′-*amidino*-1-*methyl*-2 : 4′-*dipiperidyl sulphate tetrahydrate*, which lost most of its water of crystallisation at 100° but did not melt below 350° (Found : C, 36·8; H, 8·3; N, 14·7; loss at 100°, 16·1. $C_{12}H_{24}N_4,H_2SO_4,4H_2O$ requires C, 36·6; H, 8·6; N, 14·2; $4H_2O$, 18·2%).

1-*Methyl*-1′-*phenylcarbamoyl*-2 : 4′-*dipiperidyl* (XV).—A solution of 1-methyl-2 : 4′-dipiperidyl (1·82 g.) in dry benzene (10 c.c.) was boiled under reflux with phenyl *iso*cyanate (1·2 g.) for 1 hr. The gum (2·9 g.), left on removal of the solvent, crystallised on trituration with dry ether, and recrystallisation from chloroform–light petroleum afforded 1-*methyl*-1′-*phenylcarbamoyl*-2 : 4′-*dipiperidyl* as colourless needles, m. p. 166—167° (Found : C, 72·1; H, 8·4; N, 14·2. $C_{18}H_{27}ON_3$ requires C, 71·8; H, 9·0; N, 14·0%).

Diethylcarbamoyl Chloride.—A toluene solution (48 c.c.) of carbonyl chloride (9·9 g.) was cooled in carbon dioxide–acetone, and diethylamine (14·6 g.) was added slowly with stirring. The mixture was allowed to come to room temperature and remain overnight before removal of the precipitated diethylamine hydrochloride. Fractionation of the filtrate gave diethylcarbamoyl chloride (7·5 g., 55%), b. p. 45—47°/0·5 mm., b. p. 186—189°/760 mm., n_D^{25} 1·456. Hantzsch and Sauer [12] record b. p. 186°, while Sekera, Jakubec, Král, and Vrba [13] record b. p. 81—85°/20 mm.

1-*Methyl*-2 : 4′-*dipiperidyl*-1′-*carbonyl Chloride Hydrochloride*.—A solution of 1-methyl-2 : 4′-dipiperidyl (3·65 g.) in dry toluene (40 c.c.) was added slowly and with vigorous stirring to an ice-cold solution of carbonyl chloride (10 g.) in dry toluene (70 c.c.). The mixture was stirred for 1 hr. after all the base had been added, and then kept at room temperature overnight. The precipitated solid (4·0 g., 71%) was collected and washed with dry toluene and with dry ether. It was deliquescent, but recrystallisation from dry dioxan afforded colourless prisms of 1-*methyl*-2 : 4′-*dipiperidyl*-1′-*carbonyl chloride hydrochloride*, m. p. 211—213° (decomp.) (Found : C, 51·6; H, 7·3; N, 10·0. $C_{12}H_{21}ON_2Cl,HCl$ requires C, 51·3; H, 7·8; N, 10·0%).

When this reaction was carried out with only a slight excess of carbonyl chloride, and the product was treated with diethylamine, a crystalline solid was obtained. Recrystallisation from benzene–light petroleum gave colourless plates, m. p. 208—209°, and analysis showed the substance to be *carbonyl*-1′ : 1′-*bis*-(1-*methyl*-2 : 4′-*dipiperidyl*) (Found : C, 71·0; H, 10·6; N, 14·3. $C_{23}H_{42}ON_4$ requires C, 70·8; H, 10·8; N, 14·4%).

1′-*Diethylcarbamoyl*-1-*methyl*-2 : 4′-*dipiperidyl* (VI) *Sesquicitrate*.—(*a*) Pure crystalline 1-methyl-2 : 4′-dipiperidyl dihydrochloride (84·7 mg.) was added to triethylamine (100 mg.) in dry chloroform (4 c.c.), followed by diethylcarbamoyl chloride (42 mg.) in dry chloroform (1 c.c.). After remaining at room temperature overnight the chloroform was removed by distillation and ether was added. The precipitated triethylamine hydrochloride was removed and the filtrate was reduced to small bulk (*ca.* 5 c.c.). A dried ethereal solution (5 c.c.) of citric acid (72 mg.) was added and the precipitated citrate was collected at the centrifuge, washed with dry ether, and dried in a vacuum. The substance was deliquescent, and, in attempts to observe the m. p., it frothed at *ca.* 55°; analysis showed the substance to be a *sesquicitrate* (Found : C, 52·2; H, 7·6; N, 7·7. $C_{16}H_{31}ON_3,1\frac{1}{2}C_6H_8O_7$ requires C, 52·7; H, 7·6; N, 7·4%).

The base was further characterised as the tetraphenylboron salt. The sesquicitrate was dissolved in water and treated with an aqueous solution of sodium tetraphenylboron (" Kalignost ").[14] The resulting white precipitate was set aside for 45 min. before it was collected, washed, and dried in a vacuum (Found : C, 79·5; H, 8·3; N, 7·3. $C_{16}H_{31}ON_3,C_{24}H_{21}B$ requires C, 79·9; H, 8·5; N, 7·0%).

(*b*) A solution of diethylamine (2·2 g.) in dry toluene (20 c.c.) was added slowly and with stirring to 1-methyl-2 : 4′-dipiperidyl-1′-carbonyl chloride hydrochloride (2·8 g.) suspended in

[11] *Org. Synth.*, Coll. Vol. II, p. 411.
[12] Hantzsch and Sauer, *Annalen*, 1898, **299**, 90.
[13] Sekera, Jakubec, Král, and Vrba, *Chem. Listy*, 1952, **46**, 762.
[14] Cf. Zeidler, *Z. physiol. Chem.*, 1952, **291**, 177.

dry toluene (20 c.c.). The mixture was then heated on the steam-bath for 2 hr., cooled, and diluted with an equal volume of dry ether. The precipitated diethylamine hydrochloride was removed and the filtrate was evaporated, to give crude 1'-diethylcarbamoyl-1-methyl-2 : 4'-dipiperidyl as a pale brown oil (2·5 g.). The citrate was prepared in dry ether and found to be identical with the salt isolated as in (*a*) (Found : C, 52·6; H, 7·4; N, 7·5%).

1'-*Methyl*-2 : 4'-*dipiperidyl* (XI).—(i) Anhydrous sodium carbonate (1·0 g.) was added to a solution of 1'-benzyloxycarbonyl-2 : 4'-dipiperidyl (3·0 g.) in dry benzene, and the mixture was treated dropwise with benzoyl chloride (1·4 g.). The mixture was heated under reflux for 1 hr., and then filtered. Removal of the solvent left a gum (4·0 g.) which failed to solidify.

(ii) The preceding crude 1-benzoyl-1'-benzyloxycarbonyl-2 : 4'-dipiperidyl (15 g.) in absolute alcohol was stirred in hydrogen at 120°/35 atm. for 12 hr. in presence of 5% palladised charcoal (1 g.). Removal of catalyst and evaporation gave a gum; attempts to characterise this product were fruitless as all the salts examined were either gummy or highly deliquescent solids.

(iii) The preceding 1-benzoyl-2 : 4'-dipiperidyl (9·0 g.) was methylated in the usual way with 35% aqueous formaldehyde (3·4 c.c.) and 90% formic acid (3·4 c.c.). Isolation of the resulting 1-benzoyl-1'-methyl-2 : 4'-dipiperidyl as the free base gave a gum (7·5 g.); the *picrate* crystallised from dimethylformamide–ether in yellow needles, m. p. 172—173° (Found : C, 55·9; H, 5·6; N, 13·3. $C_{18}H_{26}ON_2,C_6H_3O_7N_3$ requires C, 55·9; H, 5·6; N, 13·6%).

(iv) A solution of the preceding 1-benzoyl-1'-methyl-2 : 4'-dipiperidyl (7·5 g.) in 20% hydrochloric acid (50 c.c.) was boiled under reflux for 6 hr. The solution was cooled and basified with 50% aqueous sodium hydroxide. Extraction with benzene gave 1'-methyl-2 : 4'-dipiperidyl as a pale brown oil (4·7 g.). All the salts of this base examined were deliquescent, but, by taking stringent precautions, a *citrate* was obtained by precipitation from ethereal solution, and, in attempts to observed the m. p., softened progressively from *ca.* 45° and frothed at 85° (Found : C, 54·6; H, 8·9; N, 7·6. $C_{11}H_{22}N_2,C_6H_8O_7$ requires C, 54·5; H, 8·0; N, 7·5%).

1'-*Methyl*-1-*phenylcarbamoyl*-2 : 4'-*dipiperidyl* (XVI).—A solution of 1'-methyl-2 : 4'-dipiperidyl (1·2 g.) in dry benzene (10 c.c.) was boiled under reflux for 1 hr. with phenyl *iso*cyanate (0·78 g.). Removal of the solvent gave a gum. The highly deliquescent *citrate* crystallised from ethanol–ether; it softened and melted over the range 65—85° (Found : C, 58·1; H, 7·1; N, 7·9. $C_{18}H_{27}ON_3,C_6H_8O_7$ requires C, 58·4; H, 7·1; N, 8·5%).

1-*Benzyloxycarbonyl*-4 : 4'-*dipiperidyl* (XVII).—4 : 4'-Dipiperidyl (8·4 g.), purified by sublimation, was dissolved in methanol (100 c.c.), and the solution was neutralised to bromophenol-blue with concentrated hydrochloric acid. A hydrochloride was precipitated at this stage but redissolved during the reaction with benzyloxycarbonyl chloride, carried out as described for the 2 : 4'-compound. 1-Benzyloxycarbonyl-4 : 4'-dipiperidyl was obtained as an orange-brown viscous oil (8·3 g.). Similar results were obtained when bromocresol-purple was used as the indicator. The product was characterised as the *picrate*, which crystallised from ethanol in yellow needles, m. p. 156—158° (Found : C, 54·5; H, 5·8; N, 13·7. $C_{18}H_{26}O_2N_2,C_6H_3O_7N_3$ requires C, 54·2; H, 5·5; N, 13·2%).

1-*Benzyloxycarbonyl*-1'-*methyl*-4 : 4'-*dipiperidyl* (XVIII) *Hydrochloride*.—The preceding substance was methylated with formaldehyde and formic acid in the manner described above in analogous cases, yielding a pale brown gum. The *hydrochloride* separated from methanol–ethyl acetate in prisms, m. p. 198—200° (Found : C, 64·6; H, 8·3; N, 7·8. $C_{19}H_{28}O_2N_2$,HCl requires C, 64·7; H, 8·2; N, 7·9%).

1-*Methyl*-4 : 4'-*dipiperidyl* (XIX) *Dihydrochloride*.—The preceding substance was treated with a 33% solution of hydrogen bromide in glacial acetic acid as described for the 2 : 4'-isomer, affording the base in 78% yield. The *dihydrochloride* separated from methanol–ethyl acetate in prisms, m. p. 306—308° (Found : C, 51·8; H, 9·5; N, 10·6. $C_{11}H_{22}N_2$,2HCl requires C, 51·8; H, 9·4; N, 11·0%).

1-*Methyl*-4 : 4'-*dipiperidyl*-1'-*carbonyl Chloride Hydrochloride*.—1-Methyl-4 : 4'-dipiperidyl (3·6 g.) was treated with carbonyl chloride as described for 1-methyl-2 : 4'-dipiperidyl, affording a highly deliquescent solid (2·8 g., 50%) which, recrystallised from anhydrous dioxan, had m. p. 288—290° (Found : C, 51·2; H, 9·1; N, 10·2. $C_{12}H_{21}ON_2Cl$,HCl requires C, 51·3; H, 7·8; N, 10·0%).

1-*Diethylcarbamoyl*-1'-*methyl*-4 : 4'-*dipiperidyl* (XX) *Sesquicitrate*.—1-Methyl-4 : 4'-dipiperidyl-1'-carbonyl chloride hydrochloride (2·8 g.) was treated with diethylamine (2·2 g.) as described for the 2 : 4'-isomer, yielding a gummy solid (2·2 g.). The hydrochloride was deliquescent, as were other salts prepared from it. A deliquescent citrate was, however, prepared

in dry ether and recrystallised from methanol–ethyl acetate; in attempts to observe the m. p. the substance frothed at *ca.* 100°, and analysis showed it to be a *sesquicitrate* (Found: C, 53·0; H, 7·7; N, 7·2. $C_{16}H_{31}ON,1\frac{1}{2}C_6H_8O_7$ requires C, 52·7; H, 7·6; N, 7·4%).

The same product was obtained on treating 1-methyl-4 : 4′-dipiperidyl with diethylcarbamoyl chloride.

The *tetraphenylboron salt* was prepared as described for the 2 : 4′-dipiperidyl analogue (Found: C, 80·2; H, 8·2. $C_{16}H_{31}ON_3,C_{24}H_{21}B$ requires C, 79·9; H, 8·5%).

1-*Diethylcarbamoyl*-4-*methylhomopiperazine* (XXII) *Citrate*.—To a solution of 1-methylhomopiperazine [7] (0·23 g.) in dry chloroform (3 c.c.) was added triethylamine (0·2 g.), followed by diethylcarbamoyl chloride (0·27 g.) in dry chloroform (2 c.c.). After 18 hr. at room temperature the chloroform was removed and dry ether (20 c.c.) was added. The precipitated triethylamine hydrochloride was removed and evaporation then gave crude 1-diethylcarbamoyl-4-methylhomopiperazine as a pale brown oil (0·35 g.). The *citrate* separated from propanol–ether in needles, m. p. 110—112° (Found: C, 50·0; H, 7·8; N, 10·4. $C_{11}H_{23}ON_3,C_6H_8O_7$ requires C, 50·4; H, 7·7; N, 10·4%). The *picrate* crystallised from dimethylformamide–ether in yellow prisms, m. p. 137—138° (Found: C, 46·0; H, 5·8; N, 18·8. $C_{11}H_{23}ON_3,C_6H_3O_7N_3$ requires C, 46·2; H, 5·9; N, 19·0%).

1-*Diethylsulphamoyl*-4-*methylpiperazine* (XXIV) *Citrate*.—(i) Diethylsulphamoyl chloride was prepared by the method of Binkley and Degering [15] except that the reaction mixture was not boiled; the product was a colourless oil, b. p. 51—52°/0·7 mm., n_D^{25} 1·4625.

(ii) 1-Methylpiperazine dihydrochloride monohydrate (0·96 g.) was made into a slurry in chloroform (10 c.c.), and triethylamine (1·5 g.) was added. The solution was dried (Na_2SO_4) and diethylsulphamoyl chloride (0·86 g.) in dry chloroform (5 c.c.) was added slowly. The product was isolated in the same manner as the preceding one, and crude 1-diethylsulphamoyl-4-methylpiperazine was obtained as a pale yellow oil. The *citrate* separated from propanol–ether in needles (1·25 g.), m. p. 151° (Found: C, 42·2; H, 6·8. $C_9H_{21}O_2N_3S,C_6H_8O_7$ requires C, 42·2; H, 6·8%). A maleate has been described by Morren *et al.*[16]

1-*Diethylsulphamoyl*-4-*methylhomopiperazine* (XXIII) *Citrate*.—Prepared similarly from 1-methylhomopiperazine (0·57 g.), crude 1-diethylsulphamoyl-4-methylhomopiperazine was a yellow oil (90% yield). The *citrate* crystallised from propanol in needles (1·65 g.), m. p. 161—163° (Found: C, 43·7; H, 7·0; N, 9·3; S, 7·0. $C_{10}H_{23}O_2N_3S,C_6H_8O_7$ requires C, 43·6; H, 7·0; N, 9·5; S, 7·3%).

4-*Amino*-1-*methylpiperidine* (XXV) *Dihydrochloride*.—(i) 1-Methyl-4-piperidone [17] was converted into the oxime hydrochloride as described by Dickerman and Lindwall.[7c]

(ii) 1-Methyl-4-piperidone oxime hydrochloride (8·2 g.) was dissolved in absolute alcohol (100 c.c.) and treated with a solution of sodium ethoxide (from 1·15 g. of sodium) in ethanol (50 c.c.). Precipitated sodium chloride was removed and the filtrate was brought to the b. p. on the steam-bath. When boiling vigorously the solution was removed from the bath, and sodium (11·5 g.) was added as quickly as possible without loss of ethanol. The solution was then concentrated until separation of sodium ethoxide was troublesome, water (50 c.c.) was added, and the remainder of the alcohol distilled off, the addition of water being repeated during this process. The remaining aqueous solution was saturated with potassium carbonate and extracted with ether (3 × 50 c.c.). The dried extract gave 4-amino-1-methylpiperidine as a pale yellow oil (2·9 g.). The *dihydrochloride* separated from methanol–ethyl acetate in colourless needles, m. p. 242—244° (Found: C, 38·5; H, 8·4; N, 14·4; Cl, 37·7. $C_6H_{14}N_2,2HCl$ requires C, 38·5; H, 8·6; N, 15·0; Cl, 38·0%).

4-*Ethoxycarbonylamino*-1-*methylpiperidine* (XXVI).—Triethylamine (1·5 g.) in dry chloroform (5 c.c.) was added to 4-amino-1-methylpiperidine dihydrochloride (0·94 g.) in dry chloroform (20 c.c.), and the resulting clear solution was treated with ethyl chloroformate (0·54 g.) in the same solvent (5 c.c.), with ice-cooling. 4-Ethoxycarbonylamino-1-methylpiperidine (0·7 g.), isolated in the usual way, separated from light petroleum in colourless needles, m. p. 65—67° (Found: C, 58·0; H, 9·6; N, 15·1. $C_9H_{18}N_2O_2$ requires C, 58·1; H, 9·7; N, 15·0%).

1-*Methyl*-4-*methylaminopiperidine* (XXVIII) *Dihydrochloride*.—A mixture of 1-methyl-4-piperidone (1·13 g.) and methylamine (0·31 g.; 0·96 c.c. of a 33% w/v solution) in ethanol

[15] Binkley and Degering, *J. Amer. Chem. Soc.*, 1939, **61**, 3250.
[16] Morren, Trolin, Denayer, and Grivsky, *Bull. Soc. chim. belges*, 1950, **59**, 228.
[17] Bolyard and McElvain, *J. Amer. Chem. Soc.*, 1929, **51**, 922.

(10 c.c.) was hydrogenated at atmospheric pressure and room temperature in the presence of Adams's platinum oxide catalyst (0·2 g.) for 3 hr. Removal of the catalyst and evaporation of the solvent gave crude 1-methyl-4-methylaminopiperidine as a colourless oil (1·0 g.); the *dihydrochloride* separated from methanol–ethyl acetate in needles, m. p. 252—254° (Found: C, 41·6; H, 9·0; N, 13·3. $C_7H_{16}N_2,2HCl$ requires C, 41·8; H, 9·0; N, 14·0%).

4-(N-*Ethoxycarbonyl*-N-*methylamino*)-1-*methylpiperidine* (XXIX) *Citrate*.—1-Methyl-4-methylaminopiperidine dihydrochloride and ethyl chloroformate were allowed to react as described for 4-amino-1-methylpiperidine, and the crude product was obtained as an oil (82% yield); the *citrate* crystallised from propanol in colourless prisms, m. p. 153—155° (Found: C, 49·0; H, 7·1; N, 7·4. $C_{10}H_{20}O_2N_2,C_6H_8O_7$ requires C, 49·0; H, 7·2; N, 7·2%).

4-(N-*Diethylcarbamoyl*-N-*methylamino*)-1-*methylpiperidine* (XXVII) *Citrate*.—Prepared in the usual manner from 1-methyl-4-methylaminopiperidine dihydrochloride and diethylcarbamoyl chloride, the crude product was an oil (80% yield); the *citrate* separated from propanol in colourless prisms, m. p. 164—165° (Found: C, 51·4; H, 7·8; N, 9·8. $C_{12}H_{25}ON_3,C_6H_8O_7$ requires C, 51·5; H, 7·9; N, 10·0%).

1-*Benzyl*-4-*piperidone Oxime*.—1-Benzyl-4-piperidone hydrochloride[18] (22·6 g.) was treated with a solution of hydroxylamine hydrochloride (7·0 g.) in dry pyridine (70 c.c.), and the mixture was heated for 3 hr. on the steam-bath, a crystalline solid separating. The mixture was cooled in ice and 1-*benzoyl*-4-*piperidone oxime hydrochloride* (11·5 g.) was collected; recrystallisation from ethanol gave colourless needles, m. p. 223—225° (Found: C, 59·7; H, 7·2; N, 11·1. $C_{12}H_{16}ON_2,HCl$ requires C, 59·9; H, 7·1; N, 11·6%).

Treatment with an alcoholic solution of sodium ethoxide gave the free *oxime*, which separated from chloroform–light petroleum in needles, m. p. 126—128° (Found: C, 70·5; H, 7·9; N, 13·0. $C_{12}H_{16}ON_2$ requires C, 70·6; H, 7·8; N, 13·7%).

4-*Amino*-1-*benzylpiperidine* (XXX) *Dihydrochloride*.—1-Benzyl-4-piperidone oxime hydrochloride (9·6 g.) was converted into 4-amino-1-benzylpiperidine (6·8 g.) as described for 4-amino-1-methylpiperidine; the *dihydrochloride* separated from methanol–ethyl acetate in colourless plates, m. p. 275°, which appeared from the analysis to be hydrated (Found: C, 51·2; H, 7·7; N, 9·9. $C_{12}H_{18}N_2,2HCl,H_2O$ requires C, 51·2; H, 7·7; N, 10·0%).

1-*Benzyl*-4-*dimethylaminopiperidine Dihydrochloride*.—4-Amino-1-benzylpiperidine (6·8 g.) was treated with formaldehyde and formic acid in the usual way. Excess of concentrated hydrochloric acid was finally added and the mixture was taken to dryness. 1-*Benzyl*-4-*dimethylaminopiperidine dihydrochloride* crystallised from methanol–ethyl acetate in prisms (7·3 g.), m. p. 305—308° (Found: C, 57·6; H, 8·1; N, 9·6; Cl, 23·7. $C_{14}H_{22}N_2,2HCl$ requires C, 57·8; H, 8·3; N, 9·6; Cl, 24·4%).

4-*Dimethylaminopiperidine* (XXXI) *Dihydrochloride*.—1-Benzyl-4-dimethylaminopiperidine dihydrochloride (5·8 g.) was hydrogenated in methanol (200 c.c.) at 100°/25 atm. for 20 hr. in presence of 5% palladised charcoal (1·5 g.). Removal of the catalyst and evaporation gave 4-*dimethylaminopiperidine dihydrochloride* (3·5 g.), which separated from methanol–ethyl acetate in prisms, m. p. 297—298° (Found: C, 41·5; H, 8·9; N, 13·6; Cl, 35·0. $C_7H_{16}N_2,2HCl$ requires C, 41·8; H, 9·0; N, 13·9; Cl, 35·3%).

4-*Dimethylamino*-1-*ethoxycarbonylpiperidine* (XXXII).—4-Dimethylaminopiperidine dihydrochloride (1·0 g.), as a slurry in dry chloroform (10 c.c.), was treated with triethylamine (1·5 g.), followed by ethyl chloroformate (0·55 g.), added dropwise with cooling in ice. Isolated in the usual way 4-dimethylamino-1-ethoxycarbonylpiperidine was an oil (1·0 g.). The hydrochloride was deliquescent, but the *picrate* separated from dimethylformamide–ether in yellow needles, m. p. 128—130° (Found: C, 44·7; H, 5·3; N, 16·4. $C_{10}H_{20}O_2N_2,C_6H_3O_7N_3$ requires C, 44·8; H, 5·4; N, 16·3%).

1-*Diethylcarbamoyl*-4-*dimethylaminopiperidine* (XXXIII).—4-Dimethylaminopiperidine dihydrochloride (1·0 g.), as a slurry in dry chloroform (10 c.c.), was treated with triethylamine (1·5 g.), followed by diethylcarbamoyl chloride (0·68 g.). The product, isolated in the usual way, was an oil (1·1 g.). No suitable salt for characterisation was found as all those examined were deliquescent. Free 1-diethylcarbamoyl-4-dimethylaminopiperidine was therefore purified by distillation (b. p. 110—112°/0·5 mm.) (Found: C, 63·8; H, 10·9. $C_{12}H_{25}ON_3$ requires C, 63·5; H, 11·0%).

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[18] Bolyard, *J. Amer. Chem. Soc.*, 1930, **52**, 1030; Brookes and Walker, following paper.