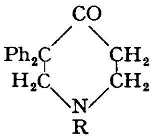
372. *Synthetic Analgesics and Related Compounds. Part II.* Some Derivatives of* 3 : 7-*Diaza*bicyclo[3 : 3 : 1]*nonane* (*Bispidine*).

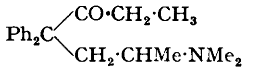
By Zu-Yoong Kyi and Walter Wilson.

Mannich condensations between phenyl-substituted acetones, formaldehyde, and ammonia or primary amines did not afford monocyclic γ-piperidones. 1 : 3-Diphenylacetone yielded highly crystalline bispidines (IV), whose reactions have been studied. The bispidines were mild local anæsthetics, but had negligible analgesic or other physiological activities.

Condensation of phenyl-substituted acetones with primary amines (or ammonia) and formaldehyde appeared to be a possible method for making the γ-piperidones (I and III), having some features of the potent analgesic drug amidone (II). Such reactions with phenylacetone or 1 : 1-diphenylacetone afforded oily mixtures of bases from which pure compounds were not isolated. However, 1 : 3-diphenylacetone readily gave highly crystalline products, at first believed to be γ-piperidones (III; R = Ph), but later proved to be bicyclic compounds (IV; R = Ph) of the 3 : 7-diaza*bicyclo*[3 : 3 : 1]nonane (bispidine) series.

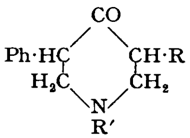


(I.)



$$Ph_2C\begin{array}{l}\diagup CO\cdot CH_2\cdot CH_3\\ \diagdown CH_2\cdot CHMe\cdot NMe_2\end{array}$$

(II.)



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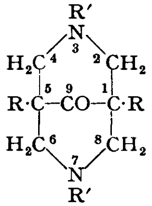
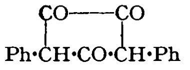
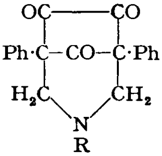


(IV.)



(V.)



(VI.)

Few bispidines have been described hitherto; the di-imide of propane-1 : 1 : 3 : 3-tetracarboxylic acid may be regarded as a tetraketobispidine (Guthzeit and Jahn, *J. pr. Chem.*, 1902, [ii], **66**, 5) and several 1 : 5-dicarbalkoxybispidines have been made by Mannich condensations from acetone-1 : 3-dicarboxylic esters (Mannich and Mohs, *Ber.*, 1930, **63**, 608; Mannich and Veit, *ibid.*, 1935, **68**, 506; Ugryumov, *Compt. rend. Acad. Sci.*, *U.S.S.R.*, 1940, **29**, 48; *Chem. Abs.*, 1941, **35**, 3644).

The bispidines obtained by us were 9-keto-compounds, which, like those described by Mannich and his co-workers (*loc. cit.*), did not react with common carbonyl reagents. Ugryumov (*loc. cit.*) converted dimethyl 9-keto-3 : 6 : 7 : 8-tetramethylbispidine-1 : 5-dicarboxylate into a monocyclic γ-piperidone by acid hydrolysis. The bispidines described herein were stable to hot dilute acids, and only very slightly decomposed by hot dilute alkalis. Monohydrochlorides were usually obtained; dihydrochlorides were occasionally formed but were less stable. One bispidine (IV; R = Ph, R′ = H) afforded both a mono- and a di-benzenesulphonyl derivative, confirming the structure of this compound.

Bispidines were again the sole products when the reaction conditions were modified in the hope of isolating γ-piperidones (III; R = Ph), which are possibly formed intermediately (cf. Ugryumov, *loc. cit.*). 2 : 5-Diphenyl*cyclo*pentane-1 : 3 : 4-trione (V) (Claisen and Ewan, *Annalen*, 1895, **284**, 250) did not react with formaldehyde and primary amines, possibly because of its strongly acidic nature; the expected product (VI) would probably have been hydrolysed readily by alkalis to γ-piperidones (III; R = Ph). Attempts to prepare bispidines or γ-piperidones from ethyl 3-phenylacetone-1-carboxylate (ethyl γ-phenylaceto-

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acetate) (Libermann, Himbert, Hengl, and Kirchhoffer, *Compt. rend.*, 1949, **229**, 765), or by using acetaldehyde instead of formaldehyde in the original condensations afforded mixtures of oily bases. Benzaldehyde gave high yields of non-nitrogenous compounds (cf. Noller and Baliah, *J. Amer. Chem. Soc.*, 1948, **70**, 3853).

The bispidines described herein have been examined pharmacologically, and full details will be published elsewhere. The only significant activity was in producing local anæsthesia; the most potent compound (IV; R = Ph, R′ = Me) was about 1·3 times as active as procaine, on comparison by Bülbring and Wajda's method (*J. Pharmacol. Exper. Therap.*, 1945, **85**, 78).

EXPERIMENTAL.

Reaction of 1 : 1-*Diphenylacetone*.—A mixture of the ketone (10·5 g.) (m. p. 61—62°; Ruggli, Dahn, and Wegmann, *Helv. Chim. Acta*, 1946, **29**, 118), methylammonium acetate (4·6 g.), paraformaldehyde (4·5 g.), and absolute ethanol (30 c.c.) was refluxed for 6 hours. Unchanged 1 : 1-diphenylacetone (5·5 g.) and a brown oily base (4·5 g.) were isolated. The base did not crystallise and did not afford crystalline salts.

9-*Keto*-1 : 5-*diphenylbispidine* (IV; R = Ph, R′ = H).—1 : 3-Diphenylacetone (10·5 g.), ammonium acetate (7·7 g.), paraformaldehyde (6·6 g.), and absolute ethanol (30 c.c.) were refluxed for 3 hours. The solid which separated was recrystallised from trichloroethylene, affording 9-*keto*-1 : 5-*diphenylbispidine* (5·9 g., 40%) as transparent cubes, m. p. 256—257° (Found: C, 78·6; H, 6·7; N, 9·6. $C_{19}H_{20}ON_2$ requires C, 78·1; H, 6·85; N, 9·6%). It was soluble in chloroform or trichloroethylene, but almost insoluble in ethanol or acetone, and did not react with phenylhydrazine or hydroxylamine. The *monohydrochloride* crystallised from acetone–ethanol (1 : 2) in needles, m. p. 251—252° (Found: Cl, 10·4. $C_{19}H_{21}ON_2Cl$ requires Cl, 10·8%). Use of 21 g. of 1 : 3-diphenylacetone in the above condensation gave the same bispidine (4·7 g.) and no γ-piperidone or other products.

Attempted methylation. The bispidine (15 g.), paraformaldehyde (3 g.), and 85% formic acid (15 c.c.) were heated at 110—120° for 2 hours. Treatment with alcoholic hydrogen chloride gave the *hydrochloride* (15 g.), m. p. 272—274° (Found: C, 67·8; H, 6·5; N, 6·3%), of an unidentified water-soluble base, which was not the 3 : 7-dimethyl compound (see below). The appropriate acid chlorides in pyridine afforded crystalline benzenesulphonyl (m. p. 239—240°) and toluene-*p*-sulphonyl (m. p. 260—261°) derivatives.

Benzenesulphonyl derivatives. The base (2·9 g.) was dissolved in pyridine (5 c.c.) and chloroform (40 c.c.), and benzenesulphonyl chloride (1·7 g., 1 mol.) added. After 16 hours, the mixture was washed with water and the chloroform evaporated. Crystallisation from acetone gave the 3-*benzenesulphonyl* compound (1·0 g.), m. p. 218—219° (Found: C, 69·4; H, 5·0. $C_{25}H_{24}O_3N_2S$ requires C, 69·4; H, 5·55%). Treated again with excess of benzenesulphonyl chloride by the same method this gave the 3 : 7-*dibenzenesulphonyl* compound, crystallising from acetone as colourless cubes, m. p. 260—261° (Found: C, 64·9; H, 5·3. $C_{31}H_{28}O_5N_2S_2$ requires C, 65·0; H, 4·9%). The same compound was obtained in one stage from the original bispidine when excess of benzenesulphonyl chloride was used.

3 : 7-*Diacetyl*-9-*keto*-1 : 5-*diphenylbispidine* (IV; R = Ph, R′ = CO·CH₃).—9-Keto-1 : 5-diphenylbispidine (2 g.) was dissolved in chloroform (25 c.c.) and pyridine (8 c.c.), and acetic anhydride (6 c.c.) added. After 16 hours, the mixture was washed with water and the chloroform evaporated. The residue was crystallised from acetone–ethanol (1 : 1), affording glistening flakes, m. p. 235—236°, of the 3 : 7-*diacetyl* compound (Found: C, 73·2; H, 6·3. $C_{23}H_{24}O_3N_2$ requires C, 73·4; H, 6·4%). Over 70% of the compound was recovered unchanged after being boiled for 3 hours with concentrated hydrochloric acid (1 part) and ethanol (4 parts).

9-*Keto*-3 : 7-*dimethyl*-1 : 5-*diphenylbispidine* (IV; R = Ph, R′ = Me).—1 : 3-Diphenylacetone (21 g.), methylammonium acetate (18·4 g.), and paraformaldehyde (15 g.) were dissolved in ethanol (60 c.c.) and boiled for 4 hours. Ethanol was distilled off, and unchanged ketone removed, leaving the 3 : 7-*dimethyl* compound (19·4 g., 61%), which crystallised from ethanol as colourless needles, m. p. 150—151° (Found: C, 78·9; H, 7·7. $C_{21}H_{24}ON_2$ requires C, 78·75; H, 7·5%). The same product was obtained in similar yield from the reactants in glacial acetic acid. The bispidine was recovered quantitatively after treatment with phenylhydrazine, hydroxylamine, benzenesulphonyl chloride–pyridine, or hot concentrated alcoholic hydrogen chloride. Boiling for 2 hours with 10% aqueous-alcoholic potassium hydroxide gave traces of volatile amine, but 88% of unchanged bispidine was recovered. The *dihydrochloride* was obtained from the components in ethanol, and, recrystallised from ethanol–ethyl acetate, had m. p. 201—202° (Found: Cl, 17·8. $C_{21}H_{26}ON_2Cl_2$ requires Cl, 18·1%). On dissolution of the dihydrochloride in water and cooling to 0°, the *monohydrochloride* (m. p. 130—132°, from ethanol–acetone) separated (Found: C, 64·4; H, 7·5; Cl, 8·9. $C_{21}H_{25}ON_2Cl,2H_2O$ requires C, 64·2; H, 7·4; Cl, 9·0%).

9-*Keto*-1 : 5-*diphenyl*-3 : 7-*di*-n-*propylbispidine* (IV; R = Ph, R′ = Pr^n).—*n*-Propylammonium acetate (23·8 g.) was used instead of methylammonium acetate in an experiment similar to the preceding one. The product was isolated as the sparingly soluble *monohydrochloride* (28 g., 62%), m. p. 120° (decomp.) after crystallisation from acetone–ethanol (Found: C, 66·9; H, 8·2; Cl, 7·9. $C_{25}H_{33}ON_2Cl,2H_2O$ requires C, 66·9; H, 8·25; Cl, 7·9%). The free *bispidine* had m. p. 114·5—115° (from acetone–ethanol) (Found: C, 79·5; H, 8·3. $C_{25}H_{32}ON_2$ requires C, 79·8; H, 8·5%).

3 : 7-*Dibenzyl*-9-*keto*-1 : 5-*diphenylbispidine* (IV; R = Ph, R′ = CH₂Ph).—1 : 3-Diphenylacetone (21 g.), benzylamine (21·6 g.), paraformaldehyde (15 g.), and ethanol (80 c.c.), after boiling for 4 hours, gave the *bispidine* (31 g., 65%), which crystallised from acetone in cubes, m. p. 161—162° (Found:

C, 84·1; H, 6·5; N, 6·3. $C_{33}H_{32}ON_2$ requires C, 83·9; H, 6·8; N, 5·95%). Similar yields were obtained with benzylammonium acetate (33·6 g.) in place of benzylamine, or in boiling glacial acetic acid. The *monohydrochloride*, recrystallised from acetone–ethanol, had m. p. 233—234° (Found: N, 5·5; Cl, 7·2. $C_{33}H_{33}ON_2Cl$ requires N, 5·5; Cl, 7·0%).

3 : 7-*Di-2'-hydroxyethyl-9-keto-*1 : 5-*diphenylbispidine* (IV; R = Ph, R' = $CH_2{\cdot}CH_2{\cdot}OH$).—A mixture of 1 : 3-diphenylacetone (21 g.), 2-hydroxyethylammonium acetate (24·2 g.), paraformaldehyde (15 g.), and ethanol (80 c.c.) was refluxed for 5 hours and excess of water then added. Unchanged ketone was removed by extraction with ether. The aqueous solution was made strongly alkaline and extracted with chloroform, yielding the *bispidine* (19 g., 50%), m. p. 176—177° (from acetone) (Found: C, 72·7; H, 7·1. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4%). The *monohydrochloride* was recrystallised from 80% ethanol and had m. p. 204—205° (Found: C, 64·0; H, 7·3; Cl, 8·3. $C_{23}H_{29}O_3N_2Cl,H_2O$ requires C, 63·5; H, 7·2; Cl, 8·2%).

3 : 7-*Di-2'-chloroethyl-9-keto-*1 : 5-*diphenylbispidine* (IV; R = Ph, R' = $CH_2{\cdot}CH_2Cl$).—The above diol (7·8 g.) was boiled for 1 hour with thionyl chloride (10 c.c.) in chloroform (50 c.c.). After removal of volatile compounds, the residue was crystallised from ethanol–water (1 : 2), giving the *monohydrochloride* (7·1 g., 80%), m. p. 195—196° (decomp.) (Found: Cl^-, 7·7. $C_{23}H_{27}ON_2Cl_3$ requires Cl^-, 7·8%). The hydrochloride was suspended in cold water, aqueous sodium hydroxide added, and the free *bispidine* isolated by extraction with chloroform; the base had m. p. 154—155° (from ethanol–acetone) (Found: C, 65·5; H, 6·1. $C_{23}H_{26}ON_2Cl_2$ requires C, 66·2; H, 6·2%); it was soluble in acetone or chloroform, but only slightly soluble in ethanol.

Reaction of Benzaldehyde with 1 : 3-*Diphenylacetone.*—The ketone (10·5 g.), methylamine (3·2 g.), benzaldehyde (21·2 g.), and glacial acetic acid (30 c.c.), boiled for 30 minutes, afforded only 1 : 3 : 4-triphenylbut-3-en-1-one (14 g., 93%), m. p. 161—162° (Goldschmiedt and Spitzauer, *Monatsh.*, 1903, **24**, 725, give m. p. 163°). A similar experiment with phenylacetone (13·4 g.) replacing 1 : 3-diphenylacetone afforded an unidentified nitrogen-free ketone, crystallising from ethanol in yellow needles (7·8 g.), m. p. 114—115° (Found: C, 82·6; H, 5·2%), which was not identical with any of the several compounds previously reported from the reaction of benzaldehyde with phenylacetone (Goldschmiedt *et al.*, *Monatsh.*, 1897, **18**, 437; 1898, **19**, 406; 1901, **22**, 659). The same compound was obtained in boiling ethanol, or by using benzylamine instead of methylamine.

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THE CHEMISTRY DEPARTMENT,
THE UNIVERSITY, BIRMINGHAM, 15.

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