

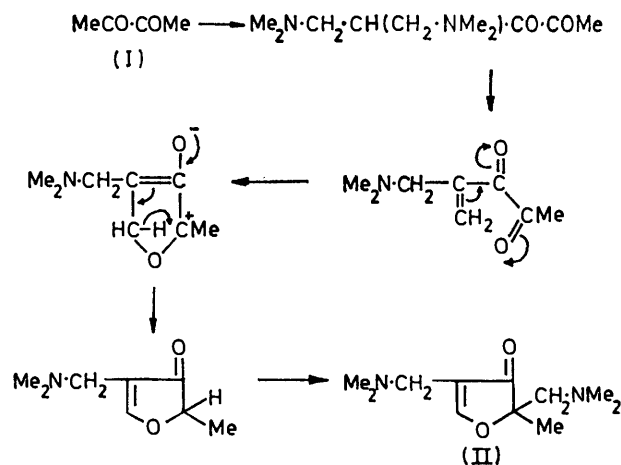
Mannich Reactions on 1,2-Diketones

By J. V. Greenhill,* P. H. B. Ingle, and Mohamed Ramli, School of Pharmacy, University of Bradford, Bradford 7

The product of a Mannich reaction on butane-2,3-dione depended upon the secondary base employed. With dimethylamine the product was 2,4-bisdimethylaminomethyl-2-methylfuran-3(2*H*)-one (II). With morpholine or *N*-methylpiperazine, a bis Mannich base derived from 2,5-dimethylbenzene-1,4-diol was obtained while pyrrolidine was the only base investigated which gave the expected open chain bis Mannich derivative.

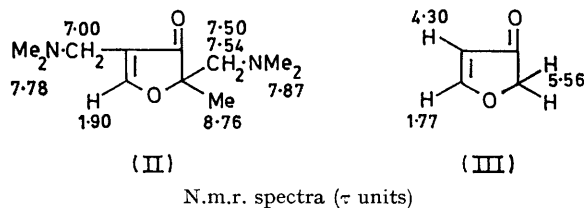
DURING an investigation into methods of synthesis of imidazoles of pharmacological interest,¹ an attempt was made to prepare the previously unknown 5-dimethylaminopentane-2,3-dione from butane-2,3-dione by the Mannich reaction.

From the reaction of dimethylamine hydrochloride, paraformaldehyde, and butane-2,3-dione (I) in ethanol either at room temperature or under reflux, the only product obtained was the furanone (II), probably *via* a mechanism of the type outlined in Scheme 1. The



SCHEME 1

structure of the furanone (II) was established from high resolution mass spectrometry and by comparison of the i.r. and n.m.r. spectra with those published² for the parent ring system (III).



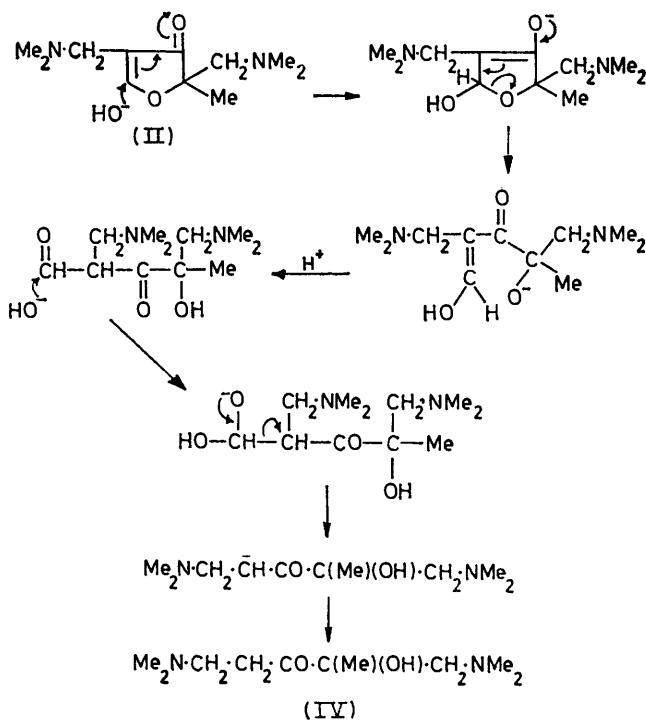
Every peak in the n.m.r. spectrum of compound (II) was a singlet except for the signal of the 2-methylene group, in which only lines 2 and 3 of the expected AB quartet were clearly visible. The i.r. spectrum of the bis Mannich base (II) was characterised by strong bands at 1700 (C=O) and 1618 cm^{-1} (C=C), *cf.* that

¹ P. H. B. Ingle, Ph.D. Thesis, University of Bradford, 1970.

² A. Hofmann, W. v. Philipsborn, and C. H. Eugster, *Helv. Chim. Acta*, 1965, **48**, 1322.

reported for the furanone (III) with strong bands at 1706 and 1572 cm^{-1} . Catalytic hydrogenation of compound (II) gave a saturated ketone, confirmed by spectroscopy (ν_{max} , 1750 cm^{-1} , typical of a 5-membered ring ketone; and no olefinic absorption). Sodium borohydride reduction of either the unsaturated (II) or saturated ketone gave a saturated alcohol. Resolution of the products has not yet been achieved.

Treatment of furanones with acid does not lead to hydrolysis, but with alkali results in ring opening.³ Heating compound (II) in dilute hydrochloric acid under reflux for 24 h produced no change in the u.v. spectrum. Treatment with dilute sodium hydroxide solution, however, produced a rapid change in the spectrum even at room temperature. I.r. and n.m.r. spectroscopy showed that the only product which could be isolated was the acyloin (IV), which could reasonably arise *via* the route outlined in Scheme 2.



SCHEME 2

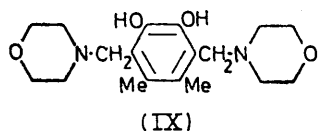
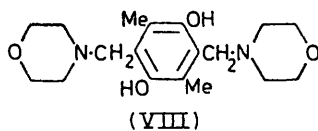
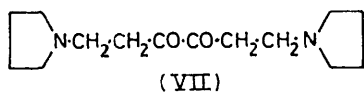
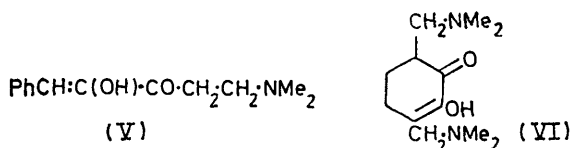
It was of interest to discover whether a similar Mannich reaction would occur with other 1,2-diketones and also from butane-2,3-dione with other secondary

³ C. H. Eugster, K. K. Allner, and R. Rosenkranz, *Chimia*, 1961, **15**, 516.

bases. Mannich reactions with pentane-2,3-dione and hexane-2,3-dione gave small yields of crude products both showing i.r. and n.m.r. spectra very similar to those obtained for the furanone (II), but these have so far resisted all attempts at purification.

The selenium dioxide oxidation of pentan-3-one (b.p. 103°) to pentane-2,3-dione⁴ (b.p. 110–112°) was incomplete and fractional distillation failed to remove unchanged starting material. When the Mannich reaction was carried out on the mixture, the only product which could be isolated was the previously unreported symmetrical bis Mannich derivative of pentan-3-one. When the diketone was prepared by nitrosation of pentan-2-one,⁵ the Mannich reaction gave the crude furanone derivative in low yield.

With hexane-3,4-dione or 1-phenylpropane-1,2-dione as substrates in ethanol, ethanediol, or dimethylformamide⁶ no Mannich base was detectable. 1-Phenylbutane-2,3-dione did react, but the product was the linear mono Mannich base (V), formulated as the mono



enol tautomer on the basis of i.r. bands at 1670 (C=O) and 1640 cm^{-1} (C=C). Finally, the reaction was carried out on cyclohexane-1,2-dione to give a bis Mannich base for which the u.v. and n.m.r. spectra indicated the enol form (VI). Results of bromine titrations indicate that cyclohexane-1,2-dione exists as the mono enol tautomer in the solid state but that in solution at 25° it changes over *ca.* 36 h into an equilibrium mixture containing only 45% of the mono enol form.⁷ The u.v. spectrum of the dione [λ_{max} (0.1 mm in EtOH) 266 nm (ϵ 6200)] was unchanged on standing at 25° for 24 h. The spectrum of the bis Mannich derivative (VI) exhibited a

hypsochromic, hypochromic shift over 24 h at 25° (see Experimental section).

Of the other secondary bases used, none gave any furanone from butane-2,3-dione; diethylamine hydrochloride, piperidine hydrochloride, and *N*-methylaniline hydrochloride even in ethanediol under reflux⁶ failed. Pyrrolidine hydrochloride did react, but the product was the symmetrical bis Mannich base (VII), the presence of the 1,2-diketone system in which was confirmed by its conversion with *o*-phenylenediamine into a substituted quinoxaline. Morpholine hydrochloride again produced a bis Mannich base. Examination of the spectra indicated that this was a derivative of either hydroquinone (VIII) or catechol (IX).

The base-catalysed condensation of 1,2-diones to give substituted hydroquinones has been reported.⁸ Both compounds (VIII) and (IX) were prepared unequivocally by Mannich reactions on the corresponding dihydic phenols. As expected, the product from butane-2,3-dione was identical with the 2,5-dimethylhydroquinone (VIII). A similar product was obtained when *N*-methylpiperazine hydrochloride was used. During one preparation of 4,5-dimethylcatechol from 2-amino-4,5-dimethylphenol *via* the Sandmeyer reaction,⁹ aqueous hydrochloric acid was used instead of dilute sulphuric acid with the result that 2-chloro-4,5-dimethylphenol was obtained. This led to a mono Mannich base which is also reported.

It appears that at least three different types of Mannich base are available from butane-2,3-dione depending upon the nature of secondary amine hydrochloride, and all the reactions have given consistent results. So far we have been unable to suggest a reasonable hypothesis to account for this variation in reaction.

EXPERIMENTAL

U.v. spectra were recorded with a Unicam SP 800 spectrophotometer, i.r. spectra with a Unicam SP 200 machine (for films or KCl discs), and n.m.r. spectra with a Perkin-Elmer R 12 instrument for pure liquids, [²H]chloroform solutions of the base, and deuterium oxide solutions of the salt.

General Method for the Mannich Reactions.—A solution of the secondary base (2 mol) in ethanol (300 ml) was carefully acidified (conc. HCl). The 1,2-dione (1 mol) and paraformaldehyde (3 mol) were added and the mixture was heated under reflux for 2 h. Solvent and unchanged dione were evaporated (water pump) and the residue was dissolved in water (75 ml), washed with ether (3 × 25 ml), made basic (NH_4OH), and extracted with ether (8 × 25 ml). The combined extracts were dried (MgSO_4), the solvent was evaporated, and the residue was purified as indicated below. In this way were obtained: (i) 2,4-bisdimethylaminomethyl-2-methylfuran-3(2H)-one (II) (18%), b.p. 96–100° at 2.5 mmHg, λ_{max} (EtOH) 261 nm (ϵ 7000); *dihydrochloride*, m.p. 205–206° (from ethanol-ether) (Found: C, 46.7; H, 7.8; Cl, 24.7; N, 9.8.

⁴ H. L. Riley, B.P. 354,798/1931.

⁵ G. Ponzio, *Gazzetta*, 1921, **51**, 213.

⁶ J. V. Greenhill and M. D. Mehta, *J. Chem. Soc. (C)*, 1970, 1549.

⁷ G. Hesse and G. Krehbiel, *Annalen*, 1955, **593**, 35.

⁸ H. von Pechmann, *Ber.*, 1888, **21**, 1411.

⁹ L. E. Hinkel, W. T. Collins, and E. E. Ayling, *J. Chem. Soc.*, 1923, **123**, 2968.

$C_{11}H_{22}Cl_2N_2O_2$ requires C, 46.3; H, 7.8; Cl, 24.9; N, 9.8%; *dihydrobromide*, m.p. 199—200° (from methanol-ethyl acetate) (Found: C, 35.6; H, 6.1; Br, 42.5; N, 7.2. $C_{11}H_{22}Br_2N_2O_2$ requires C, 35.3; H, 5.9; Br, 42.7; N, 7.5%); (ii) 1,5-bisdimethylamino-2,4-dimethylpentan-3-one *dihydrochloride*, obtained when pentane-2,3-dione contaminated with pentan-3-one was used in the above reaction, m.p. 193—194° (from ethanol-ether); ν_{max} 1715 cm^{-1} (C=O), τ 8.62 (6H, d, J 7 Hz, $2 \times$ Me) (Found: C, 48.4; H, 9.2; Cl, 25.9; N, 10.6. $C_{11}H_{26}Cl_2N_2O$ requires C, 48.4; H, 9.5; Cl, 26.0; N, 10.3%); (iii) 5-dimethylamino-2-hydroxy-1-phenylpent-1-en-3-one *hydrochloride* (V) (26%), m.p. 168—169° (from ethanol-ether) (Found: C, 60.9; H, 7.2; Cl, 13.7; N, 5.4. $C_{13}H_{18}ClNO_2$ requires C, 61.0; H, 7.1; Cl, 13.9; N, 5.5%); (iv) 3,6-bisdimethylaminomethyl-2-hydroxycyclohex-2-enone (VI) (24%), m.p. 75° [from light petroleum (b.p. 40—60°)] (Found: C, 64.1; H, 9.5; N, 12.5. $C_{12}H_{22}N_2O_2$ requires C, 63.7; H, 9.7; N, 12.4%), λ_{max} (EtOH) 274 nm (ϵ 6200), λ_{max} (EtOH, after 24 h at 25°) 284 nm (ϵ 3900); *hydrochloride*, m.p. 158—159°, ν_{max} 1635 (C=C) and 1680 cm^{-1} (C=O), τ 5.98 (2H, s, $\cdot N \cdot CH_2 \cdot C \cdot$) (Found: C, 48.5; H, 7.7; Cl, 23.3; N, 9.1. $C_{12}H_{24}Cl_2N_2O_2$ requires C, 48.1; H, 7.7; Cl, 23.7; N, 9.4%); (v) 1,6-dipyrrolidin-1-ylhexane-3,4-dione (VII) *dihydrochloride* (44%), m.p. 259—260° (from methanol), ν_{max} 1715 cm^{-1} (C=O) (Found: C, 51.3; H, 7.9; Cl, 21.6; N, 8.7. $C_{14}H_{24}Cl_2N_2O_2$ requires C, 51.7; H, 8.0; Cl, 21.9; N, 8.6%). Reaction with 1,2-diaminobenzene gave 2,3-bis-[2-(pyrrolidin-1-yl)ethyl]quinoxaline, m.p. 84—85° [from benzene-light petroleum (b.p. 40—60°)] (Found: C, 73.7; H, 8.5; N, 17.3. $C_{20}H_{28}N_4$ requires C, 74.0; H, 8.7; N, 17.3%); *dihydrobromide*, m.p. 204—205° (from ethanol) (Found: C, 49.1; H, 6.1; N, 11.4. $C_{20}H_{30}Br_2N_4$ requires C, 49.4; H, 6.2; N, 11.5%). Reaction with 3,4-diaminotoluene gave 6-methyl-2,3-bis-[2-(pyrrolidin-1-yl)ethyl]quinoxaline *dihydrobromide*, m.p. 205—206° (from ethanol) (Found: C, 50.6; H, 6.5; N, 10.8. $C_{21}H_{32}Br_2N_4$ requires C, 50.4; H, 6.5; N, 11.2%); (vi) 2,5-dimethyl-3,6-bismorpholinomethylbenzene-1,4-diol (VIII) (10%), m.p. 208—209° (from benzene), τ 6.30 (12H, m, $ArCH_2 \cdot N$ and $\cdot CH_2 \cdot O \cdot CH_2 \cdot$), 7.43 [8H, t, $\cdot CH_2 \cdot N(CH_2Ar) \cdot CH_2 \cdot$], and 7.85 (6H, s, Me) (Found: C, 64.2; H, 8.2; N, 8.2. $C_{18}H_{28}N_2O_4$ requires C, 64.3; H, 8.4; N, 8.3%); (vii) 2,5-dimethyl-3,6-bis-[(4-methylpiperazin-1-yl)methyl]benzene-1,4-diol (15%), m.p. 217—218° [from benzene-light petroleum (b.p. 40—60°)] (Found: C, 66.0; H, 9.2; N, 15.3. $C_{20}H_{34}N_4O_2$ requires C, 66.3; H, 9.5; N, 15.5%); (viii) 4,5-dimethyl-3,6-bismorpholinomethylbenzene-1,2-diol (IX) (90%), by substitution of 4,5-dimethylbenzene-1,2-diol for the diketone in the Mannich reaction, m.p. 157—158° [from light petroleum (b.p. 100—120°)], τ 6.29 (12H, m), 7.45 (8H, t), and 7.90 (6H, s) (Found: C, 64.5; H, 8.1; N, 8.3. $C_{18}H_{28}N_2O_4$ requires C, 64.3; H, 8.4; N, 8.3%); and (ix) 6-chloro-3,4-dimethyl-2-morpholinomethylphenol (88%), by substitution of 6-chloro-3,4-dimethylphenol for the diketone, m.p. 83—84° [from

light petroleum (b.p. 80—100°)] (Found: C, 61.4; H, 7.0; Cl, 13.9; N, 5.7. $C_{13}H_{18}ClNO_2$ requires C, 61.0; H, 7.1; Cl, 13.9; N, 5.5%).

2,4-Bisdimethylaminomethyl-2-methyltetrahydrofuran-3-one *Dihydrochloride*.—2,4-Bisdimethylaminomethyl-2-methylfuran-3(2H)-one *dihydrochloride* (10 g) in methanol (150 ml) was hydrogenated over 10% palladised charcoal (5 g) until 1 mol. equiv. of hydrogen had been absorbed (10 h). The solution was filtered and the solvent was evaporated to give the *dihydrochloride* (8.7 g, 86%), m.p. 167—168° (from ethanol-ether) (Found: C, 45.8; H, 8.4; Cl, 24.7; N, 9.5. $C_{11}H_{24}Cl_2N_2O_2$ requires C, 46.0; H, 8.4; Cl, 24.7; N, 9.8%); the *dinitrophenylhydrazone dihydrochloride* had m.p. 205—206° (from methanol-ether) (Found: C, 44.1; H, 6.0; Cl, 14.8; N, 18.0. $C_{17}H_{28}Cl_2N_6O_5$ requires C, 43.7; H, 6.0; Cl, 15.2; N, 18.0%).

2,4-Bisdimethylaminomethyl-2-methyltetrahydrofuran-3-ol *Dihydrochloride*.—(a) When the above hydrogenation was carried out with 5% rhodium on charcoal (5 g), 2 mol. equiv. of hydrogen were absorbed in 9 h and the reaction stopped. Filtration and evaporation gave the *alcohol dihydrochloride* (8.8 g, 85%), m.p. 249—250° (from ethanol-ether) (Found: C, 45.7; H, 9.1; Cl, 24.5; N, 9.3. $C_{11}H_{26}Cl_2N_2O_2$ requires C, 45.7; H, 9.0; Cl, 24.7; N, 9.7%).

(b) A solution of sodium borohydride (0.9 g) in water (12 ml) was added dropwise to a solution of the dihydrofuranone *dihydrochloride* (2 g) in methanol (50 ml) and stirred for 1 h. Concentrated hydrochloric acid (3 ml) was added and the solvent was evaporated. The residue was dissolved in water (20 ml), washed with ether (2×15 ml), made basic (NH_4OH), and extracted with dichloromethane (3×20 ml). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue was treated with hydrogen chloride to give the *alcohol dihydrochloride* (1.7 g, 84%), m.p. and mixed m.p. with sample prepared by method (a) 249—250°.

1,5-Bisdimethylamino-2-hydroxy-2-methylpentan-3-one (IV).—A solution of the *dihydrochloride* of the furanone (II) (6 g) in 0.4N-sodium hydroxide (300 ml) was stood at room temperature for 8 h. After acidifying with concentrated hydrochloric acid, the solution was reduced in volume to 25 ml, the residue was washed with ether (3×25 ml), made basic (NH_4OH), and extracted with ether (4×25 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give the *pentanone* (2.6 g, 61%), b.p. 76—80° at 1.5 mmHg, ν_{max} 1705 cm^{-1} (C=O), τ 7.0—7.7 (6H, m, $3 \times CH_2$), 7.81 (12H, s, $2 \times NMe_2$), and 8.87 (3H, s, C-Me); the *dihydrochloride* had m.p. 202—203° (from methanol-ether) (Found: C, 43.5; H, 8.8; Cl, 25.9; N, 10.4. $C_{10}H_{24}Cl_2N_2O_2$ requires C, 43.6; H, 8.8; Cl, 25.8; N, 10.2%); the *dihydrobromide* had m.p. 208—209° (from methanol-ethyl acetate) (Found: C, 33.3; H, 6.5; N, 7.7. $C_{10}H_{24}Br_2N_2O_2$ requires C, 33.0; H, 6.6; N, 7.7%).

[2/179 Received, 28th January, 1972]