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THE THERMAL MICHAEL REACTION—II[1]
MANNICH BASE STRUCTURE[2]

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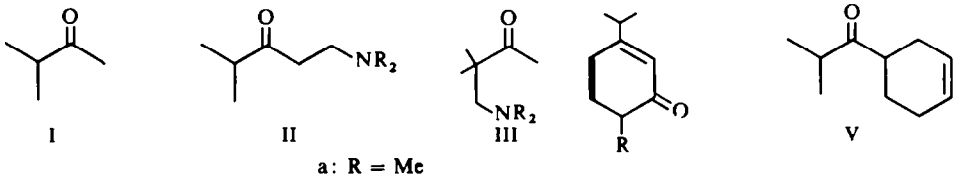
Abstract—The structures of a number of Mannich bases have been checked by NMR, the deshielding effect of N-protonation being used to identify adjacent protons. Whilst Mannich bases lacking a β-proton can react Michael-wise via a rearrangement, their quaternary methiodides do not. On this evidence, anomalous literature reports can be rationalised.

OUR use of Mannich bases in the synthesis of 1,5-diketones,[3] and in particular our observation[1] that under thermal conditions, even Mannich bases which lack a β-proton are able to take part in a Michael reaction via a rearrangement (Eq. a) has led us to question structural evidence which is based on chemical reactions.

(a)

The evidence is confusing. Thus within the past thirteen years, Mannich bases derived from 1 have been described, with conviction as II[4], as III[5] and as a mixture of them both.[6] On the one hand, the syntheses of IV from IIa and ethyl acetoacetate,[4] of V from IIb and butadiene[4] and of carvenone (VI) from IIc[7] clearly confirm structure II; on the other, NMR evidence,[5] points unequivocally to IIIa. Finally, the separation[6] of IIb and IIIb by fractional distillation of the crude reaction product shows that



I II III V

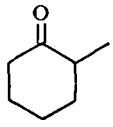
a: R = Me
b: R = Et
c: R_2NH = morpholine

IV: R = H
VI: R = Me

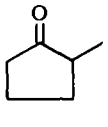
in at least one case (R = Et), a mixture is formed, and suggests that the dimethylamine and morpholine Mannich bases are also mixtures.

Similar confusion surrounding the bases derived from the ketones VII and VIII has been admirably summarised elsewhere.[8] Chemical evidence[9,10] points clearly to IX, but House has shown[8] by NMR that the Mannich base is a mixture; principally X, accompanied by a smaller amount of IX.

In each of these instances, the available chemical evidence has proved to be misleading, and it is important to know why; i.e. whether this is due to a thermal transformation (e.g. III → II) induced by distillation and occurring during the reaction, or to the genuine presence of the isomer (II) in the crude product— or indeed to both.



VII



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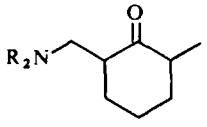
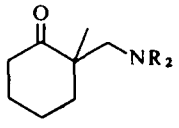


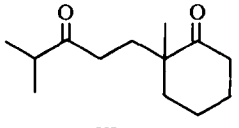
IX



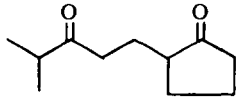
X

In other words, what significance, if any, can we attach to chemical evidence? Depending on the answer to this question, it might be necessary to reassess the accepted structures of many Mannich bases. This paper sets out to answer that question.

A TLC analysis of the crude Mannich bases prepared from the ketones, I, VII and VIII showed that all were mixtures; and since any technique which involved heat was suspect, attempts were made to separate these mixtures chromatographically. Only the first was amenable, and yielded the isomer IIa (22%) and IIIa (76%) which were identified by NMR (see Table and Experimental). With pure specimens of IIa and IIIa available, the chemical evidence was reinvestigated. At the outset, we examined the effect of heat on a pure specimen of IIIa. Distillation afforded a crude condensate which showed a weak (extra) doublet at 8·85 τ, but no pure product was ever isolated, and much polymer was produced. Several attempts were then made to condense VII with the methiodide of IIIa under Robinson–Michael conditions,[11] but in no case was any condensation product (e.g. XI) detected (GLC). Under identical conditions, the crude methiodide of the mixed bases (IIa and IIIa) gave an 8% yield of XI, which must therefore be derived from the minor component (IIa). As previously reported[1] the pure base IIIa condensed with cyclopentanone under Thermal-Michael conditions to give a 31% yield of XII. Thus, a ββ-disubstituted Mannich base can rearrange when heated, but its methiodide can not. This is consistent with the mechanism of transaminomethylation[12,1] and with Hellmann's report[13] that although XIII reacts thermally with indole, (in the presence or absence of NaOH) affording XIV, its methiodide or methosulphate fails to react under the same conditions.



XI



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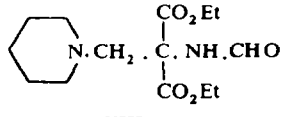
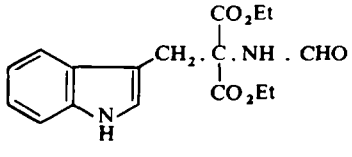
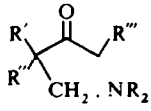


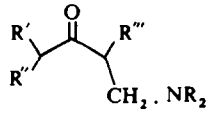
XIII



XIV



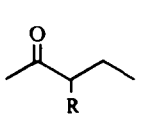
XV



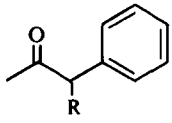
XVI

It is not unlikely that the thermal rearrangement of ββ-disubstituted Mannich bases quoted here, is a general one. Most of the known examples of transaminomethylation are intermolecular,[1] but there is no *a priori* reason why the process cannot be intramolecular. Consequently, any structural evidence which purports to distinguish between the types XV and XVI, and which involves moderate heat, must be viewed with suspicion. Evidence accruing from the corresponding methiodides will be genuine, but such reactions can only identify type XVI, which may well be the *minor* component of a mixture. The compelling evidence produced by Robinson[9] in favour of IX illustrates this point.

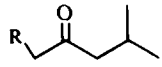
Since chemically derived structural evidence is so untrustworthy it seemed appropriate to re-examine the structures of a number of Mannich bases by NMR spectroscopy. In each case, the product was converted into a crystalline salt, and thus the structure assigned refers only to the major reaction product; no attempt was made to analyse mixtures. As detailed in the Experimental section, the dimethylamine-Mannich bases formed from the ketones XVII and XVIII are correctly formulated[4,14] as XIX and XX, but surprisingly XXI yields XXIII. This structure, which has been



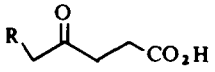
XVII: R = H
XIX: R = $CH_2 . NMe_2$



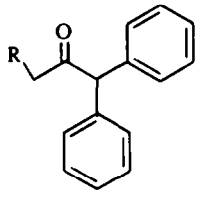
XVIII: R = H
XX: R = $CH_2 . NMe_2$



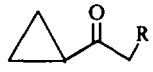
XXI: R = H
XXIII: R = $CH_2 . NMe_2$



XXII: R = H
XXIV: R = $CH_2 . NMe_2$



XXV: R = H
XXVI: R = $CH_2 . NMe_2$



XXVII: R = H
XXVIII: R = $CH_2 . NMe_2$

independently established by Spencer[15] for the diethylamine analogue confirms an earlier assignment.[4] Laevulinic acid (XXII) yields XXIV and XXV yields XXVI as claimed[16,17] although the reasons are obscure. The cyclopropyl ketone XXVII gives XXVIII, thus confirming the earlier assignments based on a negative CHI_3 reaction.[18]

It might be expected that the structure of the Mannich base formed from an unsymmetrical ketone could be predicted from theoretical principles[19] or would at least reflect the distribution of enols formed under acid catalysis.[20] Indeed the bases formed from the ketones VII, VIII, XVII and XXII correspond, in orientation, to the major product of bromination or enol-acetylation.[21,22] However as Spencer has pointed out,[15] independent studies of the enol-acetylation of XXI have yielded wildly disparate results,[21,22] and it must therefore be assumed that the factors governing enolisation are still imperfectly understood.

In examining the NMR spectra of Mannich bases, difficulty arises in distinguishing between signals due to HC—N and HC—C=O because of their similar chemical shifts. In order to avoid error we have found it convenient to study the spectrum of the picrate or hydrochloride. Salt formation not only removes minor isomers and decomposition products, it specifically deshields protons on C adjacent to N, and although the displacement is not constant (Table) variations are small, and remote protons are virtually unaffected. By comparing the spectra of the base and its picrate, HC—N signals can be identified unambiguously.

TABLE. DESHIELDING (Δ) OF α Me.N.CH_2.β CH— INDUCED BY PROTONATION

	Chemical shift (τ)								Δ(ppm)		
	Base[a]				Picrate[a]						
	αMe	αCH_2	βCH	Other	αMe	αCH_2	βCH	Other	αMe	αCH_2	βCH
Et_3N	—	7·45	8·96	—	—	6·70	8·62	—	—	0·75	0·34
Et_3N	[b]—	7·46	9·01	—	[b]—	6·81	8·73	—	—	0·65	0·28
Bu_3N	—	7·60	—	9·1[c]	—	6·84	—	9·03[c]	—	0·78	—
Et_2NH	—	7·33	8·91	—	—	6·80	8·67	—	—	0·53	0·24
$(CH_2)_5NH$	—	7·21	—	—	—	6·73	—	—	—	0·48	—
Bu_2NH	—	7·39	—	—	—	6·88	—	—	—	0·51	—
IIIa	7·8	7·6	—	7·81[d]	7·05	6·6	—	7·78	0·75	1·0	—
X	7·8	7·5	—	—	7·0	6·7	—	—	0·8	0·8	—
XIX	7·75	7·35	—	7·8[d]	7·05	6·8	—	7·72[d]	0·7	0·55	—
XX	7·84	—	—	8·0[d]	7·04	—	—	7·91[d]	0·8	—	—
		Base[a]				Hydrochloride[a]					
Et_3N	—	7·45	8·96	—	—	6·81	8·58	—	—	0·64	0·38
Et_3N	[b]—	7·46	9·01	—	[b]—	6·81	8·73	—	—	0·65	0·28

[a] Solvent $CDCl_3$ unless otherwise indicated
[b] Solvent D_2O
[c] δ CH_3 signal
[d] CH_3.C=O signal

EXPERIMENTAL

IR spectra were measured on a Unicam SP 200 G instrument and NMR spectra, on a Perkin Elmer RS 10 (60 mc) machine using $CDCl_3$ as solvent (unless otherwise indicated) and TMS as internal standard; G.C. data were obtained on a Perkin Elmer F.11 instrument; m.ps were taken on a Kofler hot-stage microscope and are uncorrected.

Separation of 5-dimethylamino-2-methylpentanone-3 (IIa) *and 3-dimethylaminomethyl-3-methylbutanone-2* (IIIa). The isomeric mixture of bases was prepared as described[4,5] and a 180 mg sample was separated on a preparative chromatographic plate by means of 14% diethylamine-benzene, into a non-polar component (IIIa; 130 mg) and a polar component (IIa; 30 mg). Both isomers showed N—CH_2 bands in the IR at 2800 cm^{-1} and 2850 cm^{-1}. The picrate[5] of the non-polar component (m.p. 145–147°; EtOH) showed NMR signals at τ 8·6 (6H; s), 7·78 (3H; s), 7·05 (6H; s) and 6·6 (2H; s). The free base showed signals at τ 8·9 (6H; s), 7·81 (3H; s), 7·80 (6H; s) and 7·60 (2H; s). The picrate[5] of the polar component (m.p. 143–145°; EtOH) showed signals at τ 8·85 (6H; d: J = 7 Hz), 7·3 (1H; m), 7·09 (6H; s) and 6·7 (4H; m). The mixture of bases afforded a crude methiodide[4] which could be purified by crystallization from EtOH, yielding a product of m.p. 184–185°, identical with that prepared directly from IIIa. Its NMR spectrum (in D_2O) showed signals at τ 8·6 (6H; s), 7·54 (3H; s), 6·78 (8H; s) and 6·10 (2H; s).

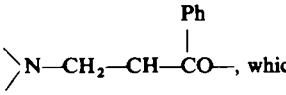
2-Methyl-2(4'-methyl-3'-oxopentyl)cyclohexanone (XI). 2-Methylcyclohexanone (22·4 g) in dry ether (25 ml) was added portionwise with stirring to a suspension of sodamide (7·8 g) in dry ether (25 ml). A suspension of the above crude methiodide (57 g) in pyridine (30 ml) was added at room temp to this preformed Na salt and the mixture stirred at room temp for 12 hr and refluxed for 1 hr. The cooled residue was flooded with water and acidified and the organic phase separated. The aqueous layer was extracted with ether and the combined ethereal extracts were washed with dil HCl, brine, dried ($MgSO_4$) and evaporated to a yellow oil which yielded the required XI as a colourless oil (3·2 g, 8%) on distillation b.p. 100—104°/0·6 mm (R_f = 45·3 min on 10% P.E.G.A. at 125°) $\nu_{C=O}^{CCl_4}$ 1712 cm^{-1}. The NMR showed a 6H doublet at τ 8·94 (J = 6 Hz) and a 3H singlet at τ 8·96.

The bis-2,4-DNP had m.p. 198–200° ($CHCl_3$–EtOH) (lit.[6] 200–201°) and the bis-semicarbazone recrystallized from MeOH as white plates m.p. 210–212°. (Found: C, 55·25; H, 8·53. $C_{15}H_{28}N_6O_2$ requires: C, 55·53; H, 8·70%).

When the experiment was repeated using the recrystallized methiodide (see above), the resultant gum showed no trace of XI on GLC examination (10% P.E.G.A. at 125°).

3-Dimethylaminomethyl-pentan-2-one (XIX). The base and its picrate were prepared as described.[14] The NMR spectrum of the base showed the following signals, τ 9·1 (3H; t), 8·5 (2H; m), 7·8 (3H; s), 7·75 (6H; s) and 7·35 (2H; m) and the picrate, τ 9·1 (3H; t), 8·3 (2H: m), 7·72 (3H; s), 7·05 (6H; s) and 6·8 (2H; m). The CH_3CO signal (τ 7·8 and 7·72) fixes the structure as XIX.

4-Dimethylamino-3-phenylbutan-2-one (XX). The base and its picrate were prepared as described,[17] and their NMR spectra showed the following signals. Base: τ 8·0 (3H; s), 7·84 (6H; s), 2·8 (5H; s) plus a multiplet at ca. τ 7·5. Picrate: τ 7·791 (3H; s), 7·04 (6H; s), 2·6 (5H; s) plus an ABX system representing



which analysed as follows ν_X τ 5·25; ν_A τ 5·9 and ν_B τ 6·63 (J_{AX} 7·6 Hz; J_{BX} −5·8 Hz; J_{AB} 13·5 Hz). The structure is confirmed by the CH_3CO signal alone (τ 8·0 and 7·91).

1-Dimethylamino-5-methylhexan-3-one (XXIII). The base and its picrate were prepared as described[4] and showed the following signals in the NMR. Base: τ 9·15 (6H; d, J = 6 Hz), ca. 8·0 (1H; m), 7·88 (6H; s), ca. 7·75 (2H; m) and 7·5 (4H; s). Picrate τ 9·1 (6H; d, J = 6 Hz), ca. 7·9 (1H; m), 7·6 (2H; d), 7·0 (6H; s) and ca. 6·7 (4H; m). The absence of a CH_3CO signal confirms structure XXIII.

6-Dimethylamino-4-oxohexanoic acid XXIV. The hydrochloride was prepared as described.[16] Its NMR (in D_2O) showed a 6H singlet at τ 7·0 and a complex multiplet in the region τ 6·4–7·5, but no CH_3CO signal. Consequently, the structure must be XXIV, rather than its isomer.

4-Dimethylamino-1,1-diphenylbutan-2-one XXVI (by W. Motherwell). The crystalline hydrochloride of the Mannich base was prepared as described,[17] and from this, the free base and its picrate[17] were obtained. These showed the following NMR signals, which confirm the structure. Base: τ 7·82 (6H; s), 7·38 (4H; m), 4·80 (1H; s), 2·73 (10H; s). Picrate τ 7·2 (6H; s), 6·68 (4H; m), 4·80 (1H; s), 2·73 (10H; s).

2-Dimethylaminoethyl-cyclopropyl ketone (XXVIII). The base and its picrate were prepared as described,[18] and showed NMR signals as follows. Base τ ca. 9·1 (4H; m) 8·1 (1H; 5 line), 7·75 (6H; s), ca. 7·4 (4H; m). Picrate τ ca. 9·0 (4H; m), 7·9 (1H, 5 line), 7·0 (6H; s), 6·6 (4H; broad t). The absence of a signal assignable to CH_3CO, confirms the suggested structure.[18]

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REFERENCES

[1] Part 1; H. L. Brown, G. L. Buchanan, A. C. W. Curran and G. W. McLay, *Tetrahedron* **24**, 4565 (1968).
[2] Preliminary report, G. L. Buchanan and A. C. W. Curran, *Chem. & Ind.* 156 (1967).
[3] G. L. Buchanan, A. C. W. Curran, J. M. McCrae and G. W. McLay, *Tetrahedron* **23**, 4729 (1967).
[4] A. Jacquier, M. Mousseron and S. Boyer, *Bull. Soc. Chim. Fr.* 1653 (1956).
[5] M. Brown and W. S. Johnson, *J. Org. Chem.* **27**, 4706 (1962).
[6] N. B. Haynes and C. J. Timmons, *J. Chem. Soc.* 224 (1966).
[7] A. M. Downes, N. S. Gill and F. Lions, *J. Am. Chem. Soc.* **72**, 3464 (1950).
[8] H. O. House and B. M. Trost, *J. Org. Chem.* **29**, 1339 (1964).

[9] E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.* 53 (1937).
[10] R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.* **73**, 724 (1951).
[11] E. D. Bergmann, D. Ginsburg and R. Pappo, *Organic Reactions* **10**, 179 (1959).
[12] B. Reichert, *Die Mannich-Reaktion* p. 121. Springer-Verlag, Berlin (1959).
[13] H. Hellmann, *Angew Chem.* **65**, 473 (1956).
[14] C. Mannich and W. Hof, *Arch. Pharm.* **265**, 595 (1927).
[15] T. A. Spencer, D. S. Watt and R. J. Friaray, *J. Org. Chem.* **32**, 1234 (1967).
[16] C. Mannich and M. Bauroth, *Ber. Dtsch. Chem. Ges.* **57**, 1108 (1924).
[17] W. Wilson and Z-Y. Kyi, *J. Chem. Soc.* 1321 (1952); L. Katz and L. S. Karger, *J. Am. Chem. Soc.* **74**, 4085 (1952); E. M. Schultz and J. B. Bicking, *Ibid.* **75**, 1128 (1953).
[18] L. J. Smith and E. R. Rogier, *Ibid.* **73**, 3840 (1951).
[19] H. M. E. Cardwell and A. E. Kilner, *J. Chem. Soc.* 2430 (1951).
[20] H. O. House, *Modern Synthetic Reactions* p. 231. Benjamin, New York (1965).
[21] E. H. Man, F. C. Frostick and C. R. Hauser, *J. Am. Chem. Soc.* **74**, 3228 (1952); H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.* **41**, 2920 (1949).
[22] H. O. House and V. Kramar, *J. Org. Chem.* **28**, 3362 (1963).