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THE MANNICH REACTION: IMPROVED CONDITIONS AND APPLICATION TO 20-KETOSTEROIDS[*]

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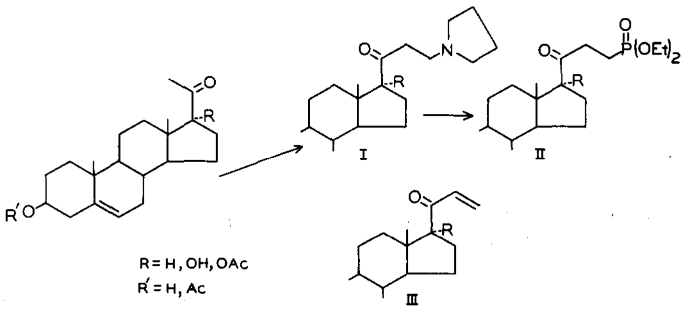
IN a program of synthesis of steroidal phosphonic acids, we had occasion to prepare the Mannich bases of certain 20-ketosteroids for conversion,[1] via the methiodides, to the corresponding 21-dialkoxyphosphinylmethyl derivatives (II).



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[1] T. C. Myers, R. G. Harvey and E. V. Jensen *J. Amer. Chem. Soc.* **77**, 3101 (1955).

When carried out in the usual manner,[2] using dimethylamine hydrochloride and paraformaldehyde in boiling ethyl or isoamyl alcohol, the Mannich reaction of 20-ketosteroids[*] was found to be very slow and accompanied by extensive decomposition of the product to form the unsaturated ketone (III). The yield of Mannich base never exceeded 50% and usually was much lower.

It was found that the desired Mannich bases (I) can be prepared in high yield by employing pyrrolidine as the amine and by carrying out the reaction in boiling 1, 2-dimethoxyethane (DME) rather than in an alcoholic solvent. Under these conditions the reaction proceeds at a satisfactory rate and formation of unsaturated ketone is minimal. A suspension of pyrrolidine hydrochloride (20 mmoles) in a solution of the steroid (12 mmoles) and paraformaldehyde (20 mmoles) in 150 ml. of DME is heated under reflux for 30 hours. The solvent is evaporated under reduced pressure and the residue poured into dilute hydrochloric acid. After extraction with ether to remove a small amount of neutral material (primarily unreacted starting ketone) the mixture is made alkaline with sodium carbonate and the Mannich

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[2] F. F. Blicke in Organic Reactions, Vol. 1, R. Adams, Ed., John Wiley & Sons, Inc., New York (1942) p. 303.

[*] To our knowledge the only example of the Mannich reaction of 20-keto steroids with yield reported is that of 3β-acetoxy-5α-pregn-16-ene-11, 20-dione with dimethylamine in acetic acid in 50% yield (T. B. Carrington, A. G. Long and A. F. Turner J. Chem. Soc. 1572 (1962)). The patent literature describes, without mention of yield, the Mannich reaction of pregnenolone with dimethylamine in isoamyl alcohol (P. L. Julian, E. W. Meyer and H. C. Printy, U. S. Patent 2, 562, 194 (1951)) and of pregnenolone acetate and certain related compounds with dimethylamine, piperidine and pyrrolidine in *t*-amyl alcohol (J. Thesing and K. Bork, German Patent 1, 107, 662 (1961)).

base extracted with ether. With pregnenolone, pregnenolone acetate and 17α-hydroxypregnenolone acetate the yield of recrystallized product is 70 to 90%, with somewhat lower yields obtained from free 17α-hydroxypregnenolone.

The reaction of 17α-hydroxypregnenolone diacetate is extremely slow even under the improved conditions. The Mannich base of this 17α-acetoxysteroid is most conveniently prepared by acetylation of the Mannich base of 17α-hydroxypregnenolone 3-acetate with acetic anhydride and pyridine for 2 hours

Table 1. Mannich Bases of 20-Ketosteroids[a]

			Methiodide	
Steroid Mannich Base	m.p.	α_D^{24}	m.p.	α_D^{24}
21-N-Pyrrolidylmethyl-[f]				
3β-Hydroxypregn-5-en-20-one	176-8		187-8	+26[d]
3β-Acetoxypregn-5-en-20-one	141-2	+8.6[b]	168-9	-2.5[d]
3β, 17α-Dihydroxypregn-5-en-20-one	194-6	-5.0[b]		
3β-Acetoxy-17α-hydroxypregn-5-en-20-one	172-3	-2.6[b]	191-2	-9.4[c]
3β, 17α-Diacetoxypregn-5-en-20-one	155-6		225-6	-45[c]
21-Dimethylaminomethyl-[f]				
3β-Hydroxypregn-5-en-20-one	136-8			
3β-Acetoxypregn-5-en-20-one	112-3	+14[b]	215-7	+14[d]
3β-Acetoxy-17α-hydroxypregn-5-en-20-one	166-7	-12[c]	236-8	

(a) All compounds listed gave satisfactory analyses for C, H and N. (b) $CHCl_3$ + 1% EtOH, (c) $CHCl_3$, (d) MeOH. (f) Chemical proof that condensation takes place at position 21 of the 17-deoxysteroids will be presented in detail elsewhere.

at room temperature. Acetylation of the 17α-hydroxyl group under these conditions represents unusual reactivity of this function,[3] apparently resulting from an influence of the pyrrolidyl moiety.

In the cases studied, the Mannich reactions with dimethylamine likewise proceeded more readily in DME than in isoamyl alcohol, but not as readily as those using pyrrolidine. The superiority of DME to alcohols as a solvent for these Mannich reactions does not appear to depend simply on its greater basicity, for similar reactions in tetrahydrofuran or in pyridine were found to take place even more slowly than those in alcohol.

The various steroidal Mannich bases, and the methiodides derived from them, are listed in Table 1. Conversion of the methiodides to the corresponding steroid phosphonic esters (II) will be described separately.

The efficacy of the modified conditions was tested with p-acetamidoacetophenone, a compound reported[4] not to undergo the Mannich reaction. Reaction of this ketone with paraformaldehyde and pyrrolidine hydrochloride in boiling DME for 16 hours furnished an essentially quantative yield of crude p-(β-N-pyrrolidylpropionyl)-acetanilide hydrochloride, recrystallized twice from ethanol to give analytically pure material, m.p. 237-238°. A similar reaction in boiling ethanol gave the same product in only 23% yield. Thus, DME would appear to be an advantageous solvent for Mannich reactions in general.

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[3] Cf. R. B. Turner J. Amer. Chem. Soc. **74**, 4220 (1952); Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler Ibid. p. 5394.

[4] C. Mannich and D. Lammering Chem. Ber. **55**, 3510 (1922).