

Department of Pharmaceutical Chemistry, University of Mississippi

Synthesis of Isatin-*N*-Mannich Bases

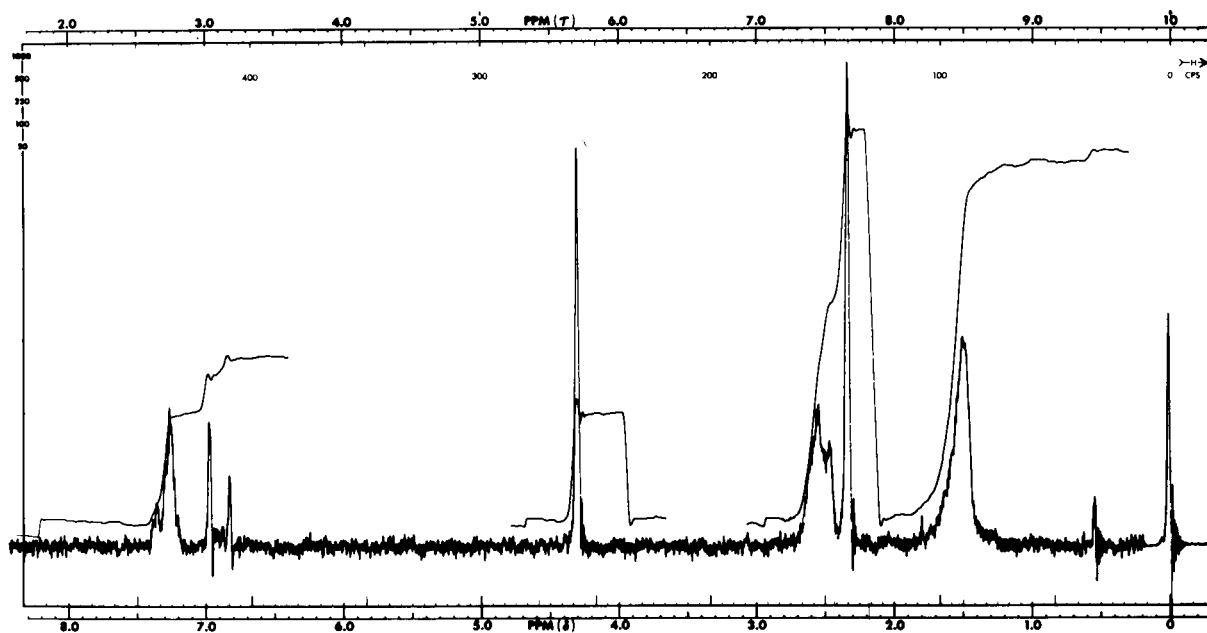
Rajendra S. Varma and W. Lewis Nobles

The synthesis of a series of isatin-*N*-Mannich bases derived from isatin, 5-methyl and 5-bromoisatins as the active hydrogen component and dimethylamine, diethylamine, morpholine, piperidine, *N*-ethylcyclohexylamine, 3-azabicyclo[3.2.2]nonane and 3-azabicyclo[3.2.1]octane as the secondary amine moiety is described. These compounds are to be screened for their pharmacological properties.

A large number of *C*-Mannich bases have been prepared and tested for analgesic, antispasmodic, anesthetic and antibacterial activity (1-9). Certain Mannich bases with complex amine moieties have shown pronounced antibacterial activity (10). Luts and Nobles (11) have reported antiinflammatory, anticonvulsant and analgesic activity in a number of β -aminoketones (Mannich Bases) and secondary and tertiary γ -aminoalcohols derived from heptamethyleneimine. Though considerable work has been reported on the synthesis and pharmacological activity of Mannich bases derived from compounds containing acidic hydrogen on carbon, only a few examples of the Mannich reaction of compounds containing an acidic hydrogen on a nitrogen atom are known (12-23) and even fewer have been evaluated for their pharmacological action. Recently it has been shown that *N*-Mannich bases derived from 3-diindolylmethane possess strong tranquilizing

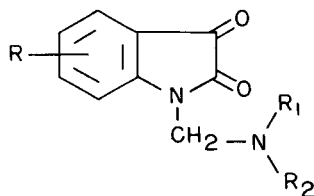
properties (24). This led us to synthesize some of the hitherto unreported *N*-Mannich bases of isatins.

Isatin-*N*-Mannich bases were prepared by condensing equimolar proportions of the appropriate isatin, secondary amine and formaldehyde, usually in the form of the 37% aqueous solution. The reaction proceeded smoothly in most of the cases in the cold but in a few cases the reaction mixture was warmed up for a few minutes to complete the reaction. It was observed especially while using 3-azabicyclo[3.2.2]nonane, hexamethyleneimine, dimethylamine and diethylamine that heating of the reaction mixture is undesirable and better yields are obtained in the cold. Sometimes heating resulted in the polymerization of the products and nothing could be isolated from the reaction mixture. It was also observed that aqueous formaldehyde gives good yields as compared to paraformaldehyde. According to Lieberman and Wagner (25) the Mannich reaction



NMR Spectrum of *N*-Piperidinomethyl-5-methylisatin

TABLE I

Isatin-*N*-Mannich Bases

R = H


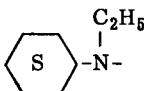

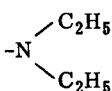

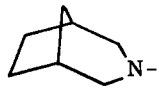
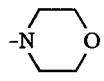
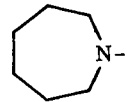


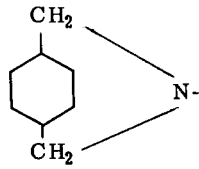
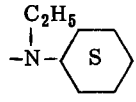


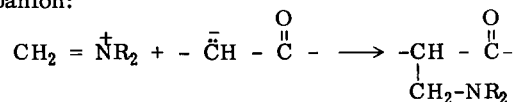
Sl. No.			M. P. °C	(d) Yield %	Molecular Formula	Analysis %	
						Calcd.	Found
1.		(f)	64-66	66	C ₁₇ H ₂₂ N ₂ O ₂	C, H, N,	71.28 7.74 9.78 70.88 7.64 9.51
2.		(b, e)	90 (a)	80	C ₁₁ H ₁₂ N ₂ O ₂	-	----- -----
3.		(f)	70 (a)	48	C ₁₃ H ₁₆ H ₂ O ₂	-	----- -----
4.		(f)	144-146 (a)	65	C ₁₄ H ₁₆ N ₂ O ₂	-	----- -----
5.		(f)	97	74	C ₁₆ H ₁₈ N ₂ O ₂	C, H, N,	71.06 6.71 10.36 71.14 6.70 10.29
6.		(e)	186-188 (a)	70	C ₁₃ H ₁₄ N ₂ O ₃	-	----- -----
7.		(b, f)	73-74	40	C ₁₅ H ₁₈ N ₂ O ₂	C, H, N,	69.74 7.02 10.84 69.35 6.86 10.87
R = 5-Bromo							
8.		(f)	136-138	77	C ₁₄ H ₁₅ BrN ₂ O ₂	C, H, N, Br,	52.01 4.67 8.66 24.73 52.27 4.99 8.56 24.81

TABLE I (Continued)

Sl. No.		M.P. °C	(d) Yield %	Molecular Formula	Analysis %		
					Calcd.	Found	
9.		(b, e)	174	76	C ₁₇ H ₁₉ BrN ₂ O ₂	C, 56.21 H, 5.27 N, 7.71	55.96 5.14 7.74
10.		(f)	> 290	40	C ₁₇ H ₂₂ BrClN ₂ O ₂ (c)	N, 6.97	6.50
R = 5-Methyl							
11.		(f)	135-136	91	C ₁₄ H ₁₆ N ₂ O ₃	C, 64.56 H, 6.19 N, 10.76	64.48 6.07 10.77
12.		(f)	102-104	77	C ₁₅ H ₁₈ N ₂ O ₂	C, 69.73 H, 7.02 N, 10.84	69.68 7.06 10.76

(a) Hellmann and Löschnann (ref. 13) report melting points for No. 2, 3, 4, 6; 90°, 71°, 146°, 187° respectively. (b) Obtained by method B, others were prepared by method A. (c) Isolated as the hydrochloride. (d) Yields are of the product after first crystallization and are based on the amount of isatin(s) used. (e) Recrystallized from chloroform-petroleum ether (60-80°). (f) Recrystallized from ethanol.

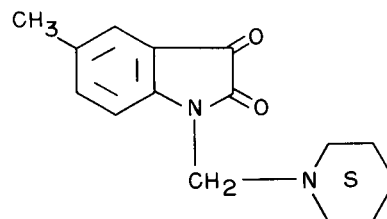
is the result of the addition of a methyleneammonium cation or a protonated dialkylaminomethanol to a carbanion:



In the case of the isatins it may be suggested that the intermediate cation attacks the nitrogen atom of isatins which has a lone pair of electrons.

NMR spectrum of the one of the *N*-Mannich bases (*N*-piperidinomethyl-5-methylisatin, I) has been studied; the results are consistent with the structure. The spectrum showed a broad peak at 1.5 δ due to the six methylene protons of the piperidine ring remote from nitrogen and a very sharp singlet at 2.34 δ due to the methyl protons at position 5. A broad peak was observed at 2.58 δ. This latter peak is

of the methylene protons (4H) of the piperidine ring adjacent to nitrogen. A sharp singlet at 4.3 δ may be assigned to two methylene protons between two nitrogen atoms and a multiplet from 6.83 to 7.36 δ is due to three aromatic protons. The infrared spectra of all compounds showed strong carbonyl absorption in the region of ~ 5.8 μ, characteristic of α-diketones (26).



I

EXPERIMENTAL (27)

Melting points were taken in open capillary tubes on a Thomas-Hoover Melting Point Apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord spectrophotometer in nujol mull. NMR spectrum was obtained in carbon tetrachloride on a Varian A-60 spectrometer using tetramethylsilane (TMS) as an internal standard.

General Procedure for Preparation of N-Mannich Bases.
Method A.

To a slurry consisting of the appropriate isatin (0.04 mole), 50% ethanol (5 ml.) and 37% formalin (5 ml.) was added the desired secondary amine (0.04 mole), dropwise, with cooling and shaking. The reaction mixture was allowed to stand at room temperature for one hour with occasional shaking after which it was warmed on a steam bath for 15 minutes. At the end of this period the contents were cooled and the product thus separated was filtered and recrystallized either from ethanol or chloroform-petroleum ether (60-80°).

Method B.

The procedure is the same as described in A except that the reaction mixture was not warmed and the product isolated in the usual way. Solid amines were dissolved in ethanol prior to addition and dimethylamine was used as the 25% aqueous solution. The results are summarized in Table I.

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- (27) Micro-analyses through the courtesy of Dr. Paul Craig, Smith Kline and French Laboratories, Philadelphia, Pa. and from Dr. Alfred Bernhardt, Max-Planck-Institute, Mülheim (Ruhr), Germany.

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