

ГХТМ-14

Note

SYNTHESIS OF ISATIN *N*-MANNICH BASES*M. Jančevska and B. Stojčeva**Hemiski institut, Prirodno-matematički fakultet, Skopje, Yugoslavia*

The synthesis and identification via infrared spectra of a series of isatin *N*-Mannich bases derived from isatin, 5-methyl, 5-chloro, 5-bromo, 5-iodo and 4,5-benzoisatin as the active hydrogen component and morpholine or piperidine as the secondary amine is described.

INTRODUCTION

Considerable work has been reported on the synthesis and pharmacological activity of *C*-Mannich bases derived from compounds containing acidic hydrogen on carbon [1, 2]. However, *N*-Mannich bases, derived from compounds containing active hydrogen on a nitrogen atom have been neglected though they are also known to be physiologically active.

We became particularly interested in the synthesis of isatin and substituted-isatin *N*-Mannich bases and their identification via their infrared spectra.

EXPERIMENTAL

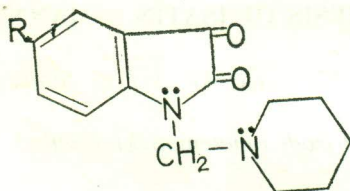
Substituted isatins (5-methylisatin, 5-chloroisatin, 5-bromoisatin, 5-iodoisatin, 4,5-benzoisatin) were prepared from the corresponding substituted anilines with chloralhydrate and hydroxylamine hydrochloride using the Sandmeyer's method [3].

Melting points were determined on a Thielle apparatus and are uncorrected. Infrared spectra from KBr discs were obtained using a Perkin-Elmer Model 521 Infrared Spectrophotometer.

Isatin N-Mannich Bases. — *N*-Mannich bases [4] were prepared by condensing equimolar portions (0.001 mol) of the components. Isatin or substituted isatins dissolved in 96% ethanol (5 ml), formalin (37% aqueous solution of formaldehyde) and the desired secondary amine, dropwise, with cooling and shaking. The reaction mixture was allowed to stand at room temperature for one to two hours. Then it was warmed on steam bath for 15 minutes. At the end of this period the content was cooled on ice or left to stand overnight in the refrigerator. An orange-red product was separated in the form of tiny needles. The product was recrystallized from ethanol or ethanol-water (1:1).

The new Mannich bases thus prepared are listed in Table. I.

TABLE I

Isatin N-Mannich Bases

No.	NR ₂	R	m.p./°C	Yield %	Formula	Analysis		Infrared ν(C=O)/cm ⁻¹
						Calcd.	Found %	
1.	piperidino	H	144—146	65	C ₁₁ H ₁₆ N ₂ O ₂	C 68,82 H 6,61 N 11,47	68,63 6,72 11,38	1725
2.	morpholino	H	186—188	70	C ₁₃ H ₁₄ N ₂ O ₃	C 63,40 H 5,74 N 11,37	63,28 5,61 11,12	1724
3.	piperidino	CH ₃	102—103	77	C ₁₅ H ₁₈ N ₂ O ₂	C 69,73 H 7,02 N 10,84	69,65 7,08 10,70	1720
4.	morpholino	CH ₃	135—136	91	C ₁₄ H ₁₆ N ₂ O ₃	C 64,59 H 6,19 N 10,76	64,48 6,07 10,70	1718
5.	piperidino	Cl	115—117	62	C ₁₄ H ₁₅ N ₂ O ₂ Cl	C 60,32 H 5,34 N 10,05	60,23 5,37 10,00	1735
6.	morpholino	Cl	138—140	65	C ₁₃ H ₁₃ N ₂ O ₃ Cl	C 55,62 H 4,68 N 9,98	55,38 4,56 9,82	1725
7.	piperidino	Br	136—138	60	C ₁₄ H ₁₅ N ₂ O ₂ Br	C 52,01 H 4,67 N 8,66	52,27 4,99 8,52	1730
8.	morpholino	Br	143—146	61	C ₁₃ H ₁₃ N ₂ O ₃ Br	C 48,02 H 4,03 N 8,61	48,12 4,08 8,38	1728
9.	morpholino	I	105—107	57	C ₁₃ H ₁₃ N ₂ O ₃ I	C 41,99 H 3,53 N 7,53	41,87 3,48 7,45	1735
10.	piperidino	4,5 - benzo	186—188	58	C ₁₇ H ₁₆ N ₂ O ₃	C 68,90 H 5,45 N 9,45	68,81 5,43 9,39	1740

RESULTS AND DISCUSSION

The recent experiments have shown that every Mannich reaction has an optimal pH value, temperature, and the duration of the experiment which is specific for a given reaction.

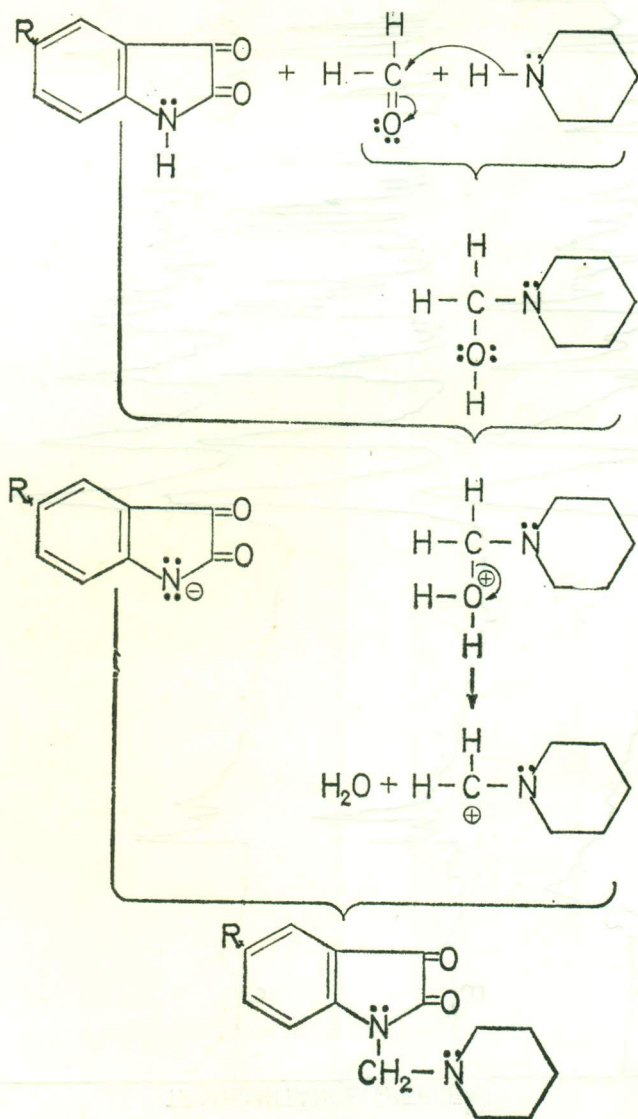


Fig. 1. The course of the Mannich reaction

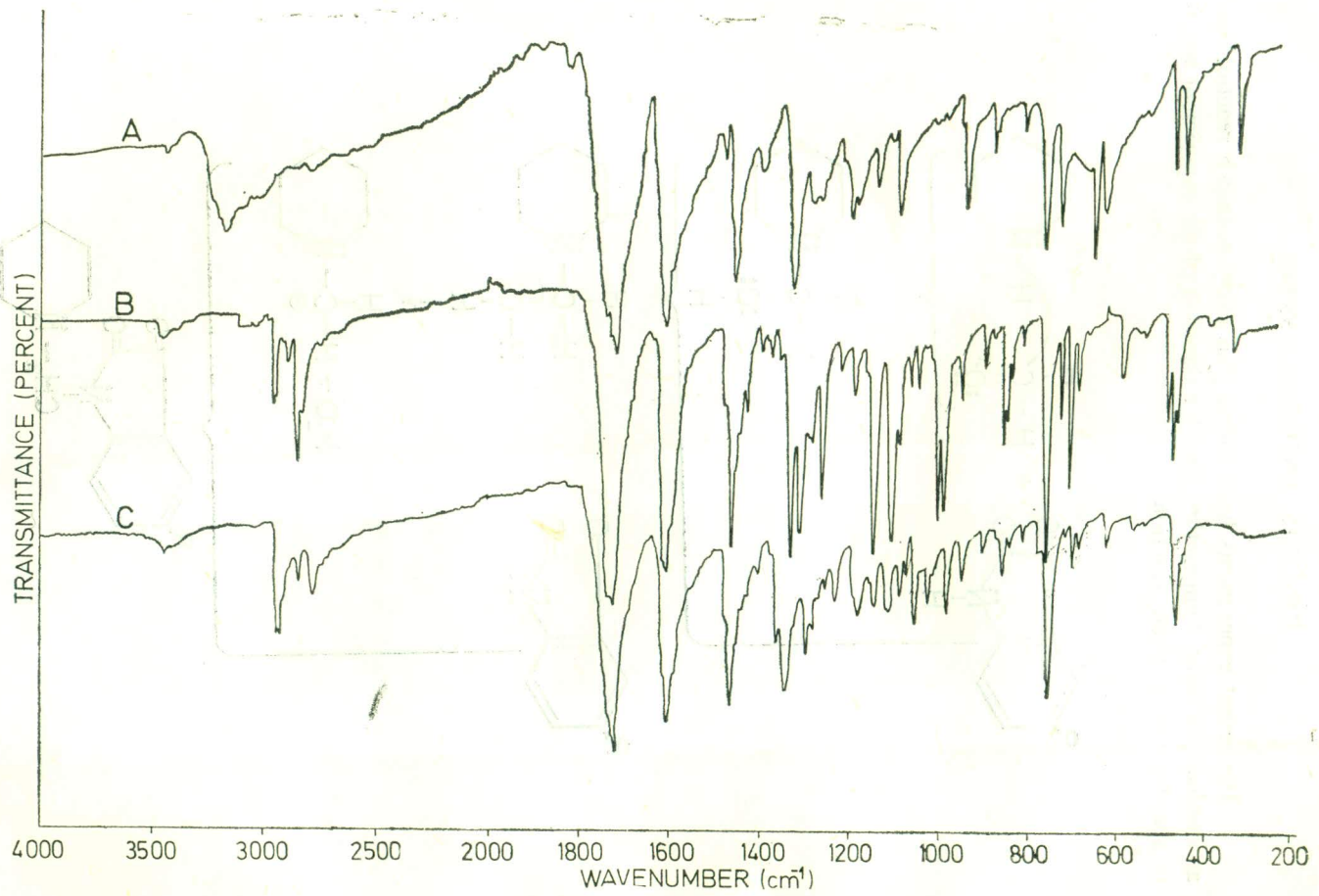


Fig. 2. Infrared spectra of isatin (A), N-morpholinomethylisatin (B), and N-piperidinomethylisatin (C).

Thus, aminoalkylation of some substituted isatins like 5-methylisatin and 4,5-benzoisatin proceeds immediately, while the reaction mixture is still cold, whereas halogen-substituted isatins need a certain period of time for the reaction to take place and its length depends on the halogen element, increasing in the order $\text{Cl} < \text{Br} < \text{I}$. In the same order falls the negative I -effect.

It was noticed that to obtain halogen-substituted isatin *N*-Mannich bases acidic medium was necessary which was attained by adding concentrated sulphuric acid.

According to the mechanism of the Mannich reaction given by Lieberman and Wagner [5] if aminoalkylation of the isatin is observed, then it is evident that the elements with more pronounced negative I -effect make the formation of isatin anion easier, which as a nucleophilic component „attacks“ the electrophilic Mannich cation derived from the secondary amine and formaldehyde. In that way the speed of condensation is increased (Fig. 1).

O'Sullivan and Sadler [6] while studying the infrared spectra of isatin and substituted isatins came to a conclusion that the NH stretching frequency depends on the nature of the substituent rather than on its position in the benzene ring. Thus, the bands move to higher frequency following the same sequence according to which the negative I -effect of the substituents ($\text{Me} > \text{Cl} > \text{Br} > \text{I}$) falls.

The infrared spectra of the isatin *N*-Mannich bases (Fig. 2) show several bands characteristic for the isatin residue (e.g. those at around 1730, 1620, 1430, 1100, 770 cm^{-1}) as well as those originating from vibrations of the piperidine ring (e.g. those at around 1460, 1320, 1100, 1050, 860, 750 cm^{-1}). However, no NH stretching band is observed and, furthermore, the band at around 1405 cm^{-1} (assigned, in the spectrum of isatin, by Petrov, Naumov and Stafilov [7] to the NH bending vibration) is also missing. In the 3000—2700 cm^{-1} region, where the CH_2 stretching vibrations are expected to appear, several bands are actually present. The ones at higher frequencies belong, most probably, to the piperidine ring, whereas those at lower frequencies originate from vibrations of the CH_2 group which is not part of the ring. Taken together these spectral data seem to lend support to the conclusion that isatin *N*-Mannich bases with the proposed structure are indeed obtained.

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ИЗВОД

СИНТЕЗИ НА ИЗАТИН *N*-МАНИХОВИ БАЗИ

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Опишани се синтезите и идентификацијата со помош на инфрацрвените спектри на серија од изатин *N*-Манихови бази добиени од изатин, 5-метил-, 5-хлор-, 5-бром-, 5-јод- и 4,5-бензоизатин како активна водородна компонента и морфолин или пиперидин како секундарен амин.