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Studies with Mannich Bases Involving N-Heterocycles and Primary Aromatic Amines

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Some novel Mannich reactions are described involving indole, benzotriazole, 5,6-dimethylbenzotriazole or v-triazole with formaldehyde and a number of primary aromatic amines. Under the conditions employed the compound isolated is usually the secondary aromatic amine. Several Mannich bases also were synthesized by N-exchange reactions between gramine and the aromatic amine. A possible mechanism for the reaction is discussed.

Although primary aliphatic amines are widely used in the Mannich reaction, the use of primary aromatic amines has been little explored and there are in the literature but few instances of their successful use. One of the earliest uses involved acetone, aniline hydrochloride and benzaldehyde and gave 1,2,6-triphenyl-4-piperidone.³ Kojic acid also undergoes the Mannich reaction with aniline, *p*toluidine or p-bromoaniline and paraformaldehyde, combining two anilinomethyl groups.⁴ Still another reaction entailing the use of primary aromatic amines is the formation of sym-2-nitro-2-alkyl-N,N-diphenyl-1,3-propanediamines from the interaction of 1-nitroalkanes, aniline and formaldehyde.5

Many others have attempted the use of primary aromatic amines but, with the exception of the above cases, have had little success. Mannich, one of the first to investigate the use of such amines,6 was unable to condense aniline with antipyrine and formaldehyde. Amål⁷ was unable to prepare the Mannich bases from aniline or paminobenzenesulfonic acid. Studies with 2-methvlfuran⁸ have shown this compound to react readilv with primary amines and formaldehyde but to give only resins when aniline was used. In general, under the usual conditions of the Mannich reaction, primary aromatic amines condense rapidly with aldehyde to give polymers and resins.

The present paper⁹ describes a number of new Mannich reactions in which N-heterocycles with a labile hydrogen were found to condense as

$$RH + HCHO + H_2NR' \longrightarrow RCH_2NHR' + H_2O$$

Fifteen Mannich bases¹⁰ were prepared where I, the N-heterocycle, was indole, benzotriazole, 5,6-dimethylbenzotriazole or v-triazole, and R' was the naphthyl, phenyl or p-SO2NH2, NO2, CO2H or OCH_3 substituted phenyl group. Two of these compounds, N4-(3-indolemethyl)-sulfanilamide and 3-(p-carboxyanilinomethyl)-indole, also were obtained in 5% yield by the displacement of the di-

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(10) The anilinomethyl, p-CO₂H, p-C₂H₅OOC, p-CH₃O and p-O₂Nanilinomethyl derivatives of 5,6-dimethylbenzotriazole and the pcarboxyanilinomethyl derivative of v-triazole were submitted to the Sloan-Kettering Institute for antitumor tests against Sarcoma 180. No significant anti-tumor activity was found for any of these compounds. methylamino group of gramine (3-dimethylaminomethylindole).



Reactions all proceeded at room temperature or lower in methanol-water or ethanol-water medium of pH 6.4 to 6.7 and, in general, gave yields of better than 40%. Compounds of type II where R is indole were unstable when heated in polar solvents and could not be crystallized in this way. Boiling in water several minutes gave a definite qualitative test for free amino group, indicating hydrolysis to the starting amino compound.

Several exceptions to the general reaction scheme were found. p-Nitroaniline with indole and formaldehyde in a medium of pH 6.7 did not give the expected 3-(p-nitroanilinomethyl)-indole, but bis-(4-nitroanilino)-methane instead. Likewise, o-nitroaniline gave a very low yield of bis-(2-nitroanilino)-methane.

Attempts to use the secondary Mannich amines as the amine compound for another Mannich condensation failed in two cases tried. v-Triazole (2 moles), 2 moles of formal dehyde and 1 mole of paminobenzoic acid did not give the expected tertiary amine but the secondary amine instead. 1-(p-Carboxyanilinomethyl)-benzotriazole (1 mole) with 1 mole each of formaldehyde and benzotriazole under the same conditions of reaction as for the formation of the secondary amines, or even after refluxing one hour in methanol, gave back the starting materials. The second hydrogen of the aromatic Mannich base is therefore much less reactive and will not undergo a further condensation.

The first step in the mechanism of these reactions may be the formation of the N-methyleneaniline Schiff base, ArN=CH2, or of the bisanilinomethane. The latter, if formed, would be expected^{11,12} to break down into the Schiff base under the slightly acid conditions employed.

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			TABLE I: REACTIONS PERFORMED: RII + HCHO + H ₂ NR	1						
No.	В	R'	Compound isolated	M.p.," °C.	Carbo Found	n % Calcd.	Hydroge Found (on. % Caled.	Nitroge Found	n, % Calcd
	Indole	<i>p</i> −O ₂ NC ₆ H ₅	$Bis-(4-nitroanilino)-methane^{b}$	233 - 234	54.65	54.20	4.02	4.20	:	:
0	Indole	0-02NC6H5	Bis-(2-nitroanilino)-methane ^c	196	:	:	:	:	:	
ಣ	Indole	p-H2NSO2C6H5	N^{4} -(3-Indolemethyl)-sulfanilamide ^d	180-183	60.00	59.78	4.90	5.02	:	•
4	Indole	p-CO ₂ HC ₆ H ₅	3-(p-Carboxyanilinomethyl)-indole	168 - 169	72.15	72.17	5.66	5.30	:	•
с,	Benzotriazole	p-O ₂ NC ₆ H ₅	1-(p-Nitroanilinomethyl)-benzotriazole	208-209	57.92	58.00	3.84	4.10	•	:
9	Benzotriazole	p-H2NC6H5	1-(N ⁴ -Sulfanilamidomethyl)-benzotriazole ^e	182-183	52.00	51.47	4.17	4.32	:	
I~	Benzotriazole	p-CO₂HC₀H₅	$1-(p-Carboxyanilinomethyl)-benzotriazole^{f}$	204 - 205	63.07	62.65	4.06	4.51	20.89	20.89
×	Benzotriazole	C ₆ H ₅	1-(Anilinomethyl)-benzotriazole	138 - 139	69.58	69.59	5.36	5.39	25.49	24.98
6	5,6-Dimethylbenzotriazole	p-CO ₂ HC ₆ H ₅	1-(p-Carboxyanilinomethyl)-5, 6-dimethylbenzotriazole	248250 (cor.)	65.10	64.85	5.22	5.44	18.80	18.91
10	5,6-Dimethylbenzotriazole	p-CH ₃ OC ₆ H ₅	1-(p-Methoxyanilinomethyl)-5, 6-dimethyl benzotriazole	133 (cor.)	68.20	68.06	6.24	6.43	20.20	19.85
11	5.6-Dimethylbenzotriazole	p-02NC6H	1-(p-Nitroanilinomethyl)-5, 6-dimethylben zotriazole	222 (cor.)	60.30	60.59	4.90	5.09	23.10	23.56
12	5.6-Dimethylbenzotriazole	C ₆ H ₅	1-(Anilinomethyl)-5,6-dimethylbenzotriazole	175.5 (cor.)	71.56	71.40	6.41	6.39	22.24	22.21
13	5,6-Dimethylbenzotriazole	$C_{10}H_7$	$1-(\alpha$ -Naphthylaminomethyl)-5,6-dimethylbenzotriazole	161.9 (cor.)	75.68	75.47	5.99	6.00	18.39	18.53
14	5,6-Dimethylbenzotriazole	$C_{10}H_7$	$1-(\beta$. Naphthylaminomethyl)-5,6-dimethylbenzotriazole	201.0 (cor.)	75.89	75.47	5.82	6.00	18.86	18.53
15	5,6-Dimethylbenzotriazole	$p-(CH_3)_2NC_6H_5$	1-(p-Dimethylaminoanilinomethyl)-5, 6-dimethylben zotriazole	176-178 (cor.)	69.00	69.12	7.30	7.17	23.70	23.71
16	5,6-Dimethylbenzotriazole	p-CO ₃ C ₃ H ₅ C ₆ H ₅	1-(p-Carbethoxyanilinomethyl)-5, 6-dimethyl benzotriazole	174 (cor.)	66.30	66.65	5.88	6.22	16.80	17.23
17	v-Triazole	p-CO ₂ HC ₆ H ₅	N-[4-(v-Triazolyl-1')-methylamino]-benzoic acid	181.5 (cor.)	55.50	55.04	4.56	4.62	25.90	25.68
a A 271.	Jl melting points are by capilla ^e Melting point reported in li	try and uncorrected iterature ¹³ is 195°.	 except where specificd. ^b Melting point reported in literature¹³; ^d Sulfur analysis, caled. 10,60; found, 10,40. ^e Yield was 78% 	is 232°; molecu	lar weigh 82%.	t, caled.	for C ₁₃	H₁₂N₄O	4 288;	found,

Step 1: $ArNH_2 + HCHO \longrightarrow ArN = CH_2 + H_2O$

$2ArNH_2 + HCHO \longrightarrow ArNHCH_2NHAr + H_2O$ $ArNHCH_2NHAr \longrightarrow ArN = CH_2 + ArNH_2$

The Schiff bases, because of their unsaturation, readily polymerize, usually to the trimer, e.g., aniline with formaldehyde in methanol-water gives the trimer, anhydroformaldehydeaniline.^{13,14} In the presence of a compound with a labile hydrogen the Schiff base reacts rapidly to give the secondary Mannich amine.

Step 2: ArN= $CH_2 + RH \longrightarrow ArNHCH_2R$

Under the reaction conditions employed and depending largely on the lability of the hydrogen of the heterocycle, it is assumed that this second step takes place faster than the trimerization of the Schiff base.

Experimental

The following procedures are representative of the syntheses performed.

 N^{4} -(3-Indolemethyl)-sulfanilamide. (a) By a Mannich Reaction.—Four milliliters of 40% aqueous formaldehyde **Reaction.**—Four milliliters of 40% aqueous formaldehyde was added dropwise to a well-stirred ice-cold solution con-taining 4.68 g. (0.04 mole) of indole and 6.88 g. (0.04 mole) of sulfanilamide in 60 cc. of methanol and 20 cc. of water. After the mixture had been stirred 30 minutes at room tem-perature, a precipitate formed. The mixture was then stirred an additional hour at room temperature, filtered, and washed with cold methanol. This solid, a mixture of the desired compound and unreacted sulfanilamide, was purified by fractional precipitation. by fractional precipitation. The crude material (5 g.) was dissolved in 60 cc. of 5% sodium hydroxide solution, collected, and reprecipitated with glacial acetic acid. A first fraction of 2.8 g. (obtained with the medium still on the alkaline side), after being washed with water, methanol, and ether, melted at 178–181°. A second fraction of 1.5 g. also was obtained.

(b) By a Gramine Replacement Reaction.-Sulfanilamide (3.4 g, 0.012 mole) and 4 g. of gramine $(0.023 \text{ mole})^{15}$ were refluxed 2 hours in 80 cc. of 95% ethanol. The solvent then was evaporated and the dry residue washed with water and dissolved in 40 cc. of 5% sodium hydroxide solution. Precipitation with glacial acetic acid gave a solid identical with the material obtained from procedure (a).

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