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

BY J. J. LICARI,[1,2] L. W. HARTZEL,[2] GREGG DOUGHERTY AND F. R. BENSON[2]

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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.

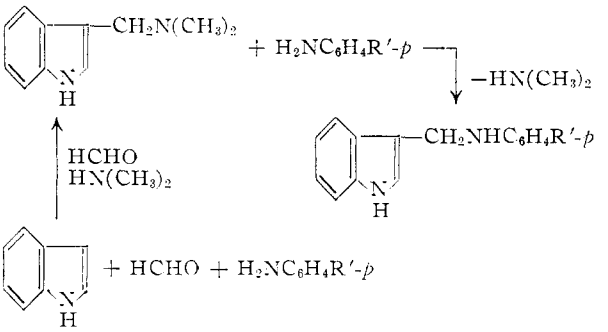
Although primary aliphatic amines are widely used in the Mannich reaction, the use of primary aromatic amines has been little explored and there are in the literature but few instances of their successful use. One of the earliest uses involved acetone, aniline hydrochloride and benzaldehyde and gave 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. Amâl[7] was unable to prepare the Mannich bases from aniline or *p*-aminobenzenesulfonic acid. Studies with 2-methylfuran[8] have shown this compound to react readily 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 paper[9] describes a number of new Mannich reactions in which N-heterocycles with a labile hydrogen were found to condense as

$$\underset{\text{I}}{RH} + HCHO + H_2NR' \longrightarrow \underset{\text{II}}{RCH_2NHR'} + H_2O$$

Fifteen Mannich bases[10] were prepared where I, the N-heterocycle, was indole, benzotriazole, 5,6-dimethylbenzotriazole or v-triazole, and R′ was the naphthyl, phenyl or *p*-$SO_2NH_2$, $NO_2$, $CO_2H$ or $OCH_3$ substituted phenyl group. Two of these compounds, $N^4$-(3-indolemethyl)-sulfanilamide and 3-(*p*-carboxyanilinomethyl)-indole, also were obtained in 5% yield by the displacement of the dimethylamino group of gramine (3-dimethylaminomethylindole).




where R′ = $CO_2H$ or $SO_2NH_2$

Reactions all proceeded at room temperature or lower in methanol–water or ethanol–water medium of *p*H 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 *p*H 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 formaldehyde and 1 mole of *p*-aminobenzoic 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, $ArN{=}CH_2$, 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.

(1) E. I. du Pont de Nemours Co. Fellow, Princeton University.

(2) Formerly associated with Remington-Rand, Inc., Norwalk, Conn.

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(9) This work was initiated at Remington-Rand, Inc., and continued at Princeton University.

(10) The anilinomethyl, *p*-$CO_2H$, *p*-$C_2H_5OOC$, *p*-$CH_3O$ and *p*-$O_2N$-anilinomethyl derivatives of 5,6-dimethylbenzotriazole and the *p*-carboxyanilinomethyl 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.

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TABLE I: REACTIONS PERFORMED: RH + HCHO + $H_2NR'$ →

| No. | R | R' | Compound isolated | M.p.,[a] °C. | Carbon, % Found | Carbon, % Calcd. | Hydrogen, % Found | Hydrogen, % Calcd. | Nitrogen, % Found | Nitrogen, % Calcd |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Indole | *p*-$O_2NC_6H_5$ | Bis-(4-nitroanilino)-methane[b] | 233–234 | 54.65 | 54.20 | 4.02 | 4.20 | ... | ... |
| 2 | Indole | *o*-$O_2NC_6H_5$ | Bis-(2-nitroanilino)-methane[c] | 196 | ... | ... | ... | ... | ... | ... |
| 3 | Indole | *p*-$H_2NSO_2C_6H_5$ | $N^4$-(3-Indolemethyl)-sulfanilamide[d] | 180–183 | 60.00 | 59.78 | 4.90 | 5.02 | ... | ... |
| 4 | Indole | *p*-$CO_2HC_6H_5$ | 3-(*p*-Carboxyanilinomethyl)-indole | 168–169 | 72.15 | 72.17 | 5.66 | 5.30 | ... | ... |
| 5 | Benzotriazole | *p*-$O_2NC_6H_5$ | 1-(*p*-Nitroanilinomethyl)-benzotriazole | 208–209 | 57.92 | 58.00 | 3.84 | 4.10 | ... | ... |
| 6 | Benzotriazole | *p*-$H_2NC_6H_5$ | 1-($N^4$-Sulfanilamidomethyl)-benzotriazole[e] | 182–183 | 52.00 | 51.47 | 4.17 | 4.32 | ... | ... |
| 7 | Benzotriazole | *p*-$CO_2HC_6H_5$ | 1-(*p*-Carboxyanilinomethyl)-benzotriazole[f] | 204–205 | 63.07 | 62.65 | 4.06 | 4.51 | 20.89 | 20.89 |
| 8 | Benzotriazole | $C_6H_5$ | 1-(Anilinomethyl)-benzotriazole | 138–139 | 69.58 | 69.59 | 5.36 | 5.39 | 25.49 | 24.98 |
| 9 | 5,6-Dimethylbenzotriazole | *p*-$CO_2HC_6H_5$ | 1-(*p*-Carboxyanilinomethyl)-5,6-dimethylbenzotriazole | 248–250 (cor.) | 65.10 | 64.85 | 5.22 | 5.44 | 18.80 | 18.91 |
| 10 | 5,6-Dimethylbenzotriazole | *p*-$CH_3OC_6H_5$ | 1-(*p*-Methoxyanilinomethyl)-5,6-dimethylbenzotriazole | 133 (cor.) | 68.20 | 68.06 | 6.24 | 6.43 | 20.20 | 19.85 |
| 11 | 5,6-Dimethylbenzotriazole | *p*-$O_2NC_6H_5$ | 1-(*p*-Nitroanilinomethyl)-5,6-dimethylbenzotriazole | 222 (cor.) | 60.30 | 60.59 | 4.90 | 5.09 | 23.10 | 23.56 |
| 12 | 5,6-Dimethylbenzotriazole | $C_6H_5$ | 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-(α-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-(β-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-dimethylbenzotriazole | 176–178 (cor.) | 69.00 | 69.12 | 7.30 | 7.17 | 23.70 | 23.71 |
| 16 | 5,6-Dimethylbenzotriazole | *p*-$CO_2C_2H_5C_6H_5$ | 1-(*p*-Carbethoxyanilinomethyl)-5,6-dimethylbenzotriazole | 174 (cor.) | 66.30 | 66.65 | 5.88 | 6.22 | 16.80 | 17.23 |
| 17 | *v*-Triazole | *p*-$CO_2HC_6H_5$ | N-[4-(*v*-Triazolyl-1′)-methylamino]-benzoic acid | 181.5 (cor.) | 55.50 | 55.04 | 4.56 | 4.62 | 25.90 | 25.68 |

[a] All melting points are by capillary and uncorrected, except where specified. [b] Melting point reported in literature[13] is 232°; molecular weight, calcd. for $C_{13}H_{12}N_4O_4$ 288; found, 271. [c] Melting point reported in literature[13] is 195°. [d] Sulfur analysis, calcd. 10.60; found, 10.40. [e] Yield was 78%. [f] Yield was 82%.

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

or

$2ArNH_2 + HCHO \longrightarrow ArNHCH_2NHAr + H_2O$

$ArNHCH_2NHAr \longrightarrow ArN{=}CH_2 + ArNH_2$

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 was added dropwise to a well-stirred ice-cold solution containing 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 temperature, 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. 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 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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