The hydrochlorides listed in the footnotes to Table I were prepared by dissolving the bases in dry ether and adding slowly with stirring an ether solution containing slightly more than two equivalents of hydrogen chloride. The salts were purified by recrystallization from an anhydrons alcohol ether mixture. They proved to be somewhat hygroscopic and consequently most of the compounds were submitted as the bases for pharmacological testing.

N,**N**-**Bis**-(2-diethylaminoethyl)-anilines (II).—A suspension of 0.3 mole of the primary aromatic amine, 0.7 mole (120 g.) of 2-diethylaminoethyl chloride hydrochloride, 1.2 moles (166 g.) of anhydrous potassium earbonate, 2 g. of copper bronze powder and 350 ml. of benzene was heated under reflux with stirring as described above for twenty-four hours. An additional 0.3 mole (52 g.) of 2-diethylaminoethyl chloride hydrochloride was then added and the stirring and heating were continued for an additional twelve hours. The reaction mixture was then cooled, aqueous sodium hydroxide was added and the mixture was extracted with char as described in the preceding

section. The ether extracts were dried, the ether was removed, and the residue was fractionated. A forerun consisting largely of the N-(2-diethylaminoethyl)-aniline distilled first, followed by the higher boiling N,N-bis-(2diethylaminoethyl)-aniline.

We are indebted to Mr. S. M. Nagy and Mrs. C. K. Fitz for analyses.

Summary

A number of N-(2-diethylaminoethyl)-anilines (1) and N,N-bis-(2-diethylaminoethyl)-anilines (11) have been prepared by the alkylation of primary aromatic amines with diethylaminoethyl chloride. These compounds have been tested for activity in avian malaria.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY OF PURDUE UNI-VERSITY]

The Condensation of Aldehydes and Amines with Nitrogenous Five-atom Ring Systems¹

BY G. BRYANT BACHMAN AND LOWELL V. HEISEY²

The condensation of aldehydes and amines with compounds containing an active hydrogen atom has proved to be a widely applicable method of introducing aminomethyl groups.³

As applied to heterocyclic compounds, three types of active hydrogen atoms may be involved: (1) those directly attached to the nucleus, as in antipyrine¹ and indole⁵; (2) those attached to the α -carbon of an alkyl group attached to the ring, as in α -picoline⁶ and quinaldine⁷; and (3) those attached to side chains where the activation is provided by some group other than the ring, as in 2-acetothienone⁸ or 2-acetylfuran.⁸

The published observations on Mannich bases derived from each of these types are rather limited in scope and the behaviors of many of the simpler ring systems under the usual conditions of the condensation are unknown. We have undertaken to prepare a series of compounds of type (1) for the purpose of studying the generality of the reaction in the heterocyclic series, of determining the most active hydrogen in various ring systems, and of studying the pharmacological activity of these types of nitrogeneous material.

Pyrrole condenses with formaldehyde and secondary amines according to the equation

(1) Read before the Organic Section at the Atlantic City meeting of the American Chemical Society, April, 1946.

(2) From the M S, thesis of Lowell V, Heisey, Purdue University, October, 1941.

(3) For a review see Blicke, "The Mannich Reaction," Vol. I, Chapter 19, of "Organic Reactions," R. Adams, editor-in-chief, John Wiley and Soas, Inc., New York, N. Y., 1942.

- (1) Manuich and Krosche, Arch. Pharm., 250, 647 (1912).
- (5) Kuhn and Stein, Ber., 79, 567 (1937).
- (6) Tseon Heon Feb. Compt. revid., 192, 1242 (1931).
- (7) Kermael, and Muir, J. Chem. Soc., 3089 (1931).
- (8) 1 evve and Nisbet, *ibid.*, 1053 (1938),



With dimethyl- or diethylamine colorless, highboiling liquids are obtained which are stable only under vacuum in sealed containers. These liquids possess strong, characteristic and rather pleasant odors. The products from the higher aliphatic amines, such as di-*n*-butylamine, decompose on attempted vacuum distillation.

While only disubstituted products are obtained with aliphatic amines under various conditions, piperidine and morpholine readily give either mono or disubstituted pyrroles according to the ratio of reactants used. These products are white, crystalline, relatively stable solids and are formed in 85-95% yields. N-Methylaniline and thialdine do not react.

The Mannich condensation may proceed by any one or all of three different mechanisms³

(A) $R - H + CH_2O \longrightarrow R - CH_2OH$

- $RCH_2OH + R'_2NH \longrightarrow RCH_2NR'_2 + H_2O$
- (B) $R'_2NH + CH_2O \longrightarrow R'_2NCH_2OH$
- $R'NCH_2OH + R H \rightarrow RCH_2NR'_2 + H_2O$
- or (C) $R \rightarrow H + CH_2O + R'_2NH \longrightarrow RCH_2NR'_2 + H_2O$

where C represents a mechanism involving different (but unspecified) intermediates from those shown in A and B. A trimolecular reaction for C is conceivable but improbable without supporting kinetic evidence. In our experience the best vields were obtained when the amine-formaldehyde addition product was first formed and then condensed with the pyrrole, indicating that reaction mechanism B is the preferred one. Syntheses according to A and C gave poorer yields.

Pyrrole condensation products were assigned the indicated structures principally because of the recognized reactivity of the α -hydrogens in pyrrole.⁹ Supporting evidence was found in the response of these compounds to Ehrlich's test¹⁰ for free α -positions in pyrroles. The bis-(Npiperidinomethyl)- and the bis-(N-morpholinomethyl)-pyrroles gave no color (negative test) while the corresponding monosubstituted pyrroles gave the usual red color (positive test) with Ehrlich's reagent. The test was less satisfactory for the derivatives from dimethylamine and diethylamine in that the bis compounds gave a positive test. This may be explained on the basis of the relative instability of these compounds. Under the conditions of the test hydrolysis to free pyrrole undoubtedly occurs very rapidly. Finally, to be certain that substitution had not occurred at the --NH- group of the ring, 2,5bis-(N-piperidinomethyl)-pyrrole was titrated with triphenylmethylsodium according to the proced-ure of Corwin and Ellingson.¹¹ Slightly more

than one —NH— group per mole was found. Unfortunately these pyrrole bases are very sensitive to reagents. Hydrochlorides, picrates, and methiodides could be prepared, but they usually decomposed on attempted recrystallization or on standing. Catalytic hydrogenation was attempted in an extensive series of experiments employing platinum or nickel catalysts, solvents of the hydrocarbon, alcohol and organic acid types, and varying conditions of temperature and pressure. Usually the unchanged base was recovered, but at elevated temperatures the dialkylamine, from which the compound was originally prepared, and tars were obtained. Chemical reduction with hydriodic acid and red phosphorus or zinc dust and acetic acid was likewise unsuccessful. Oxidation with dichromate to maleic imides, and ring cleavage with hydroxylamine gave tars.

Although the α -positions of pyrrole are first attacked, the β -positions may be substituted by blocking the α -positions. 2,5-Dimethylpyrrole gives the 3,4-bis-(N-piperidinomethyl) derivative without difficulty. N-Methylpyrrole and Nethylpyrrole do not react under the mild conditions employed. No success attended efforts to introduce more than two aminomethyl groups into pyrrole. However the monosubstituted pyrrole bases could readily be converted into the corresponding disubstituted bases by further treatment with the secondary amine and form-

(9) Tschelinzew and Maxorow, J. Russ. Phys.-Chem. Soc., 48, 748 (1915); Chem. Zentr., 94, I, 1505 (1923).
(10) Fischer-Orth. "Die Chemie des Pyrroles," Vol. 1, Aka-

demische Verlagsgesellschaft, Leipzig, 1934, p. 66.

aldehvde. Unsymmetrical disubstituted products could probably be prepared in this manner although this was not done.

In passing from pyrrole to the diazoles certain structural changes are introduced which have a direct bearing on the mechanism of the Mannich pected to activate ring hydrogens as in pyrrole itself, while the =N- group might be expected to activate the hydrogens of an α -CH₃ group attached to the ring as in α -picoline. On the other hand, the diazole ring systems are definitely more acidic than the pyrrole ring system, and the acidity seems to reside chiefly in the --NH--group. Hence, the prediction of the point of attack in a compound like 3,5-dimethylpyrazole is difficult. An electronic analysis is complicated, and without the necessary quantitative evaluations is inconclusive. Three monosubstituted products are possible



The product actually obtained (93% yield) was a liquid which formed a rather stable solid hydrochloride. Its ease of preparation suggested that it was not III. Mannich bases from α -picoline form only slowly and at elevated temperatures. Titration with triphenylmethylsodium show no active hydrogen, thus eliminating I and III. The correct structure is therefore II. It was not possible to introduce more than one aminomethyl group into this pyrazole.

Similar results were obtained with benzimidazole which gave stable crystalline condensation products with formaldehyde and either piperidine, morpholine or diethylamine. The substituent dialkylaminomethyl group attached itself to the ring nitrogen as shown by titration with triphenvlmethylsodium. Benzotriazole condensed readily with formaldehyde and piperidine or 2-methylpiperidine, but these products were rather unstable. They hydrolyzed in hot water and with triphenylmethylsodium showed 1.23 and 1.14 moles, respectively, of active hydrogen per mole of product. No condensations whatever were obtained with imidazole, 2-ethylimidazole, 2-methyl-4,5-diphenylimidazole, 2-ethylbenzimidazole, 1-phenylbenzimidazole,12 3-ethyl-5-chloro-

⁽¹¹⁾ Corwin and Ellingson, THIS JOURNAL, 64, 2098 (1942).

⁽¹²⁾ This compound was prepared by refluxing a aminodipheuylamine with formic acid for several hours. Our product melted at 89.5° although Fischer and Rigand, Ber., 34, 4204 (1901), reported 97°. Anal. Caled. for C13H10N2: C, 80.4; H, 5.19. Found: C, 80.4, 80.6; H, 5.24, 5.40.

	Wie1.1	1)			
Active H compd.	Amine	Aldehyde	Solvent	76 Y	solvent
Pyrrole (1)	(CH ₃) ₂ NH (2)	$CH_2O(2)$	$H_2O(3)$	48	
	(CH ₃) ₂ NH·HC1 (2)	CH ₂ O (2)	$H_{2}O(3)$	Tar	
	$(C_2H_5)_2NH$ (2)	$CH_2O(2)$	H_2O (3)	30	· · · ·
	$(C_2H_5)_2NH(2)$	$CH_2O(1)$	H_2O (1.5)	20	
	$C_{5}H_{10}NH(1)$	$CH_2O(1)$	AcOH $(1)^a$	85	Hexane
	$C_5H_{10}NH(2)$	CH_2O 2)	$H_{2}O(3)$	89	Acetone
	$C_{5}H_{10}NH$ (4)	$CH_2O(4)$	$H_{2}O(6)$	69	
	$O(CH_2CH_2)_2NH(1)$	$CH_2O(1)$	AcOH $(1)^a$	95	Hexane
	$O(CH_2CH_2)_2NH$ (2)	$CH_2O(2)$	AcOH $(1)^a$	95	Ether
	$C_6H_5NHCH_3$ (2)	$CH_2O(2)$	$H_{2}O(3)$	Tar	
	$C_{5}H_{10}NH$ (1)	$CH_{3}CHO(1)$	None	Tar	
	$C_{6}H_{4}$ N=CH-NH (2)	$CH_2O(2)$	CH ₃ OH (40)	95	Water
2,5-Dimethylpyrrole (1)	$C_{5}H_{10}NH(2)$	CH ₂ O (2)	Ether (4)	73	Hexane
3,5-Dimethylpyrazole (1)	$C_{5}H_{10}NH(1)$	$CH_2O(1)$	Ether (4)	93	Hexane
Benzimidazole (1)	$C_{5}H_{10}NH$ (1)	$CH_2O(1)$	CH ₃ OH (40)	97	Hexane
	$O(CH_2CH_2)_2NH(1)$	$CH_2O(1)$	CH ₃ OH (40)	97	Acetone
	$(C_2H_5)_2NH$ (1)	$CH_2O(1)$	CH ₃ OH (40)	74	
Benzotriazole (1)	$C_{5}H_{10}NH(1)$	$CH_2O(1)$	CH ₃ OH (40)	92	Hexane
	$C_{6}H_{12}NH$ (1)	$CH_2O(1)$	CH ₃ OH (40)	90	Hexane

	TABLE I				
MANNICH	BASES	FROM	PYRROLES	AND	Azoles

1,2,4-triazole,¹³ or 1-phenylbenzotriazole. It is probable that many of these condensations would occur at elevated temperatures. Thus imidazole is known to condense with formaldehyde in the 2 and 4(5) positions at 120° . In the presence of secondary amines a Mannich base would undoubtedly form under these conditions.

Attempts to use pyrrole as the amine component in a Mannich reaction were unsuccessful. Condensations with formaldehyde and acetophenone, acetone, 2-butanone, 1-nitropropane or 2-nitropropane gave tars or liquids which decomposed on attempted vacuum distillation. Benzimidazole condensed abnormally with formaldehyde and 2-nitropropane and with formaldehyde and pyrrole to form 1-hydroxymethylbenzimidazole. 2-Ethylbenzimidazole was less reactive and apparently did not condense with formaldehyde and 2-nitropropane or 2-butanone.

Numerous attempts to use primary amines instead of secondary amines and to use higher aldehydes instead of formaldehyde were all unsuccessful in that no readily purified, individual products were obtained. Polymeric substances and tars were frequently formed.

Pharmacological Testing.—Compounds B, D, G, I and J were tested as antimalarials on ducks infected with *P. lophurae* and also as trypanocides on rats infected with *T. equiperdum* and *T. brucei*. They were inactive. Compound I showed an inconsiderable pressor action (1 mg. = 0.0005 mg. epinephrine) and no appreciable local anesthetic or analgesic action. Compound D was inactive in each of these last three tests.

Acknowledgments.—The authors are indebted to Eli Lilly and Company for financial support and pharmacological testing, and to the Barrett Division for generous supplies of pyrrole and other chemicals.

Experimental

All reactions were run under similar conditions. With pyrrole the aldehyde and the amine were mixed slowly at $0-10^\circ$, and the heterocyclic compound was then added slowly with vigorous stirring. With the azoles the formaldehyde was added to a mixture of the amine and the azole. The temperature was allowed to rise at the end of an hour and stirring continued for several hours at room temperature. Following are descriptions of typical reactions.

2,5-bis-(Diethylaminomethyl)-pyrrole.— Diethylamine (146.3 g., 2.0 moles) was stirred and maintained at 0-10° while 160 ml. of 38% formalin (2.0 moles) was added dropwise. Immediately thereafter 73.7 g. (1.1 mole) of freshly distilled pyrrole was added portionwise over a period of half an hour at 10°. The oily product began to separate very soon. The cooling bath was removed and stirring continued for several hours. The organic layer was separated and the aqueous layer was ether extracted. After drying and removing the ether the product was distilled under vacuum. Yield was 69 g. (30%) of a colorless liquid, b. p. 39.0-39.5° (1 mm.), d^{26}_{29} 0.9144, n^{26} p 1.4812, *MR* caled. 75.43, found 75.57. The liquid became brown in color and decomposed in the air within a couple of days. It could be preserved satisfactorily in evacuated tubes. The white hydrochloride, m. p. 124-127°, was prepared by passing anhydrous hydrogen chloride into a dry ethereal solution of the base at Dry Ice temperatures. It decomposed on attempted recrystallization: picrate, yellow, m. p. 112-114°; methiodide, m. p. 130°.

2,5-bis-(N-piperidinomethyl)-pyrrole.—This method utilized an organic acid as solvent. It gave better yields in some cases and poorer yields in others. Piperidine acetate was prepared from 30 g, of glacial acetic acid and 42.5 g, of piperidine. Formalin, 40 ml, of 30% solution (0.5 mole), was added to the ice-cold mixture and then enough water to facilitate stirring. Freshly distilled pyrrole, 17.4 g. (0.26 mole) was now added with stirring at 0–10°. After an hour the ice-bath was removed and the mixture alt

⁽¹³⁾ Prepared in 68% yield by boiling an alkaline solution of the diazonium chloride of 5-amino-3-ethyl-1,2.4-triazole; m. p. 101-102°. Anal. Calcd. for C₄H₈N₃Cl: N, 31.94. Found: N, 32.32, 32.44.

		ANALYSES AND	PROPERTIES OF	MANNICH	BASE	ES FROM PYRROLES AND AZOLES	
Formula	Analyses, (Calcd.	% N Found	М. р., °С.	B. p., °C. (mm.)		Product	
$C_{10}H_{19}N_3$	23.18	22.99 22.92		56-58 (2)	Α.	2,5-bis-(Dimethylaminomethyl)-pyrrole ^b	
$C_{14}H_{27}N_3$	17.70	17.60 17.50	•••••	39-40 (1)	В.	$2,5\text{-}bis\text{-}(\text{Diethylaminomethyl})\text{-}pyrrole^{c}$	
$C_{10}H_{16}N_2$	17.06	17.09 17.03	74.5-75.0		C.	2-(N-Piperidinomethyl)-pyrrole ^d	
$C_{16}H_{27}N_3$	16.08	16.14 16.19 •	96.5-97.0		D.	2,5-bis-(N-Piperidinomethyl)-pyrrole ^a	
$C_9H_{14}N_2O$	16.85	$16.58\ 16.66$	69.5 - 70.5		Е.	2-(N-Morpholinomethyl)-pyrrole ^d	
$C_{14}H_{23}N_{3}O_{2}$	15.84	15.80 15.78	86.5-87.0		F.	2,5-bis-(N-Morpholinomethyl)-pyrrole	

TABLE	I	

C₈H₈N₂O 18.91 18.95 19.00 141-143 G. 1-Hydroxymethylbenzimidazole $C_{18}H_{31}N_3$ 14.52 14.46 14.42 157.0-157.5H. 3,4-bis-(N-Piperidinomethyl)-2,5-dimethylpyrrole $C_{11}H_{19}N_3$ 21.7421.63 21.56 96 - 98(2)I. 3,5-Dimethyl-1-(N-piperidinomethyl)-pyrazole/ 19.53 19.20 19.28 91.5-92.5 1-(N-Piperidinomethyl)-benzimidazole^g C13H17N3 Ĩ. $C_{12}H_{15}N_{3}O$ 19.34 19.19 19.09 110.5-111.5 K. 1-(N-Morpholinomethyl)-benzimidazole^g $20.67 \quad 20.71 \quad 20.66$ 157(3)1-Diethylaminomethylbenzimidazole^h $C_{12}H_{17}N_3$ L. $25.90 \quad 25.64 \quad 25.69$ $C_{12}H_{16}N_4$ 92.5-93.5 M. 1-(N-Piperidinomethyl)-benzotriazoleⁱ 24.33 24.14 24.51 65.0 - 65.5N. 1-(N-2'-Methypiperidinomethyl)-benzotriazole $C_{13}H_{18}N_4$

^a Water, 3 moles, also present. ^b n^{26} D 1.4919, d^{26}_{26} 0.9406. ^c n^{26} D 1.4812; d^{26}_{26} 0.9144; *MR* calcd. 75.43, found 75.57; hydrochloride, m. p. 124–127°; picrate, m. p. 112–114°; methiodide, m. p. 130°. ^d Hydrochloride and picrate unstable. ^e Hydrochloride, m. p. 119–122°; picrate, m. p. 184–186°. ^f n^{26} D 1.4982; d^{26}_{26} 0.9919; hydrochloride, m. p. 238–240°. ^e Hydrochloride, decomposes before melting. ^h n^{25} D 1.5657, d^{25}_{25} 1.0710. ⁱ Hydrochloride, m. p. 167–169°.

lowed to warm to room temperature. After two hours the ice-bath was restored and the mixture was neutralized slowly with 20% sodium hydroxide solution. The oily layer which separated crystallized on standing. It was recrystallized from acetone and formed white roset-shaped groups of stout needles, m. p. $96.5-97.0^\circ$; yield 60 g. (92%); hydrochloride, m. p. $119-122^\circ$ (dec. upon recrystallization); picrate, m. p. $184-186^\circ$. 1-(N-Morpholinomethyl)-benzimidazole.—Formalin, 9.6 ml., 38% (0.12 mole), was added, dropwise, to a cooled, stimed solution of 11.8 % (0.10 mole) of benzimidazole.

1-(N-Morpholinomethyl)-benzimidazole.—Formalin, 9.6 ml., 38% (0.12 mole), was added, dropwise, to a cooled, stirred solution of 11.8 g. (0.10 mole) of benzimidazole and 9.6 g. (0.11 mole) of morpholine in 150 ml. methanol. After an hour the cooling bath was removed and stirring continued at room temperature for several hours. The solution was filtered, the ether evaporated, and the solid product recrystallized from acetone; yield, 21 g. (97%) of white platelets, m. p. 110.5- 111.5° .

Summary

The Mannich reaction has been applied to various nitrogenous five-atom ring systems. A number of new derivatives of pyrrole, pyrazole, benzimidazole and benzotriazole have been prepared and described. The variations and limitations of the reaction in the heterocyclic series are discussed.

LAFAYETTE, INDIANA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Compounds Derived from 2,2-Dimethylethylenimine

By D. Stanley Tarbell and David K. Fukushima¹

Several workers² have investigated the possibility of obtaining optically active forms due to the trivalent nitrogen atom in suitably substituted ethylenimines. The most promising approach has

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been that of Cairns,^{2b} who prepared 2,2-dimethylethylenimine (I) and obtained a crystalline urea derivative from it by the action of 1- α -phenylethyl isocyanate which, however, gave no evidence of separation into diastereoisomers on recrystallization.³

The presence of a carbonyl group on the nitrogen of the imine ring might tend to flatten the pyramidal arrangement of nitrogen valences, due to the contribution from resonance forms involving a carbon-nitrogen double bond. Therefore, in

(3) Prelog and Wieland, *Helv. Chim. Acta*, 27, 1127 (1944) [C. A., 39, 4328 (1945)] have recently reported the resolution of Trögers base, in which the asymmetry is due to trivalent nitrogen atoms.

^{(2) (}a) Adams and Cairns, THIS JOURNAL. 61, 2464 (1939); (b)
Cairns, *ibid.*, 63, 871 (1941); (c) Mole and Turner, *Chem. Ind.*, 582 (1939); (d) Meisenheimer and Chou, *Ann.*, 539, 70 (1939);
(e) Maitland, *Ann. Rept. Chem. Soc. London*, 36, 243 (1939).