

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

## Mannich Bases from N-Substituted Pyrroles

BY WERNER HERZ AND JOHN L. ROGERS

The Mannich reaction of N-methyl- and of N-phenylpyrrole with formaldehyde and a variety of primary and secondary amines has been investigated. The methiodides of the resulting bases are fairly active alkylating agents, as evidenced by their reaction with sodium cyanide, ethyl malonate and ethyl cyanoacetate. The alkylation of cyanide ion did not appear to involve a rearrangement of the allylic type.

Previous work<sup>1,2</sup> has shown that the alpha hydrogen atoms of pyrrole are sufficiently reactive to participate in the Mannich reaction with formaldehyde and a number of primary and secondary amines. The resulting Mannich bases resembled gramine<sup>3</sup> in their ability to alkylate a variety of substances containing active hydrogen<sup>4,5,6</sup> a property which has since been found to be common to other non-ketonic Mannich bases derived from heterocyclic nuclei.<sup>5,7</sup>

The successful results obtained with pyrrole suggested further work with N-substituted derivatives in order to study the influence of substituents in this position on the reactivity of the pyrrole nucleus and to explore synthetic routes to compounds with possible physiological activity. In the present communication the preparation of Mannich bases of substituted pyrroles is reported and their use in alkylation reactions is discussed.

The literature<sup>1</sup> records a statement that N-methyl- and N-ethyl-pyrrole do not react with formaldehyde and amines when the pyrrole derivative is added to a mixture of aldehyde and amine at 10° and the reaction mixture is then allowed to come to room temperature. However, under the conditions previously utilized by us,<sup>2</sup> *i.e.*, addition of a mixture of aldehyde and amine hydrochloride to N-methylpyrrole to prevent possible dialkylation, we observed immediate condensation of N-methylpyrrole with formaldehyde and a variety of primary and secondary amines. The yields in almost every instance exceeded the yields previously realized with pyrrole itself. Properties of the products are listed in Table I, the derivatives of N-methylpyrrole being remarkable for their comparatively large solubility in water. Further reaction of 2-(N-piperidinomethyl)-N-methylpyrrole with formaldehyde and piperidine gave the disubstituted 2,5-bis-(N-piperidinomethyl)-N-methylpyrrole in good yield, thus demonstrating the reactivity of both alpha hydrogen atoms. Disubstitution could also be carried out in one step as exemplified by the preparation of 2,5-bis-(N-dimethylaminomethyl)-N-methylpyrrole, using a slight excess of amine and formaldehyde.

In condensations involving N-phenylpyrrole, best results were achieved by carrying out the reaction in acetic acid. The yields, however, were uni-

formly lower than with N-methylpyrrole, nor could two aminomethyl groups be introduced by use of two equivalents of formaldehyde and base, although the use of excess reagents increased the yields of monosubstituted product. These results may be rationalized in terms of the electron-withdrawing power of the phenyl group which tends to reduce electron availability in the pyrrole nucleus, whereas N-methylpyrrole, in contrast, might be expected to and actually does exhibit enhanced activity compared with pyrrole.

The Mannich bases derived from N-substituted pyrroles were found to be somewhat less active as alkylating agents than those derived from pyrrole itself. Under the conditions which have been described as most favorable for alkylation in the pyrrole series,<sup>4,8</sup> *i.e.*, quaternization of the Mannich base with dimethyl sulfate in cold ethanol, no reaction was observed between 2-dimethylamino-methyl-N-methylpyrrole (I) and malonic ester. On the other hand, when the methiodides of I and of the corresponding N-phenyl analog (II) were heated at 120–130° with excess ethyl malonate or ethyl cyanoacetate, the expected condensation products were obtained in fair yield.

Proof for the structure of I, and by inference for the structure of the other Mannich bases, was furnished by a study of the alkylation of sodium cyanide with the methiodide. The nitrile which resulted on refluxing the reagents in aqueous solution was hydrolyzed to the known 2-N-methylpyrrole-acetic acid.<sup>8</sup> This result is of interest in view of the rearrangements which accompany the alkylation of sodium cyanide by other heterocyclic Mannich bases.<sup>7</sup> Since the isomeric 1,2-dimethylpyrrole-carboxylic acid was not detected, the probability of rearrangement in the present instance appears to be slight, although the formation of a small amount of the isomeric nitrile during the alkylation reaction cannot be completely excluded. Alkylation of sodium cyanide by the methiodide of II in a similar manner yielded 2-N-phenylpyrroleacetonitrile and, on hydrolysis, 2-N-phenylpyrroleacetic acid whose structures were assumed by analogy.

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### Experimental<sup>9</sup>

The following two examples illustrate general procedures for the preparation of the compounds described in Table I.

(1) G. B. Bachman and L. V. Heisey, *THIS JOURNAL*, **68**, 2496 (1946).

(2) W. Herz, K. Dittmer and S. J. Cristol, *ibid.*, **69**, 1698 (1947).

(3) (a) H. R. Snyder, C. W. Smith and J. M. Stewart, *ibid.*, **66**, 200 (1944), and many subsequent papers; (b) N. F. Albertson, S. Archer and C. M. Suter, *ibid.*, **66**, 500 (1944); **67**, 36 (1945).

(4) W. Herz, K. Dittmer and S. J. Cristol, *ibid.*, **70**, 504 (1948).

(5) N. F. Albertson, *ibid.*, **70**, 669 (1948).

(6) N. J. Leonard and E. H. Burk, *ibid.*, **72**, 2543 (1950).

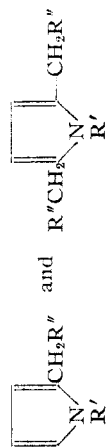
(7) H. R. Snyder and E. L. Eliel, *ibid.*, **70**, 1703, 1857, 3855 (1948); **71**, 663 (1949); E. L. Eliel and P. E. Peckham, *ibid.*, **72**, 1209 (1950).

(8) C. D. Nenitzescu and E. Solomonica, *Ber.*, **64**, 1924 (1931); F. Arndt and B. Elstert, German Patent, 650,706.

(9) Melting points are uncorrected.

TABLE I

COMPOUNDS OF THE TYPE



R'	R''	Yield, %	°C.	B.p.	Min.	n <sub>D</sub> <sup>20</sup>	Formula	Nitrogen, %		M p., °C.	Picrate Formula	Nitrogen, %	
								Calcd.	Found			Calcd.	Found
CH <sub>3</sub>	NHCH <sub>3</sub>	26 <sup>a</sup>	66	6	1.5033	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub>		22.56	22.10		C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>7</sub>	19.07	19.12
CH <sub>3</sub>	NHCH <sub>2</sub> CH <sub>3</sub>	40 <sup>a</sup>	69-70	5	1.4955	C <sub>8</sub> H <sub>14</sub> N <sub>2</sub>		20.27	20.05	93 <sup>d</sup>	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>7</sub>	19.07	19.03
CH <sub>3</sub>	N(CH <sub>2</sub> ) <sub>2</sub>	73 <sup>a</sup>	53-54	6	1.4860	C <sub>8</sub> H <sub>14</sub> N <sub>2</sub>		20.27	20.47	102.5 <sup>e</sup>	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>7</sub>	17.72	17.72
CH <sub>3</sub>	N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	77 <sup>a</sup>	75-77	6	1.4833	C <sub>10</sub> H <sub>18</sub> N <sub>2</sub>		16.85	16.99	83-84 <sup>d</sup>	C <sub>16</sub> H <sub>21</sub> N <sub>3</sub> O <sub>7</sub>	17.19	17.43
CH <sub>3</sub>	N-Piperidino	86 <sup>b</sup>	97	5	1.5115	C <sub>11</sub> H <sub>18</sub> N <sub>2</sub>		15.72	15.89	160 <sup>a,f</sup> (dec.)	C <sub>17</sub> H <sub>22</sub> N <sub>3</sub> O <sub>7</sub>	17.11	17.19
CH <sub>3</sub>	N-Morpholino	70 <sup>b</sup>	113-114	5	1.5141	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> O		15.55	15.61	137-138 <sup>a,g</sup>	C <sub>16</sub> H <sub>19</sub> N <sub>3</sub> O <sub>8</sub>	16.31	16.36
Phenyl	NHCH <sub>2</sub> CH <sub>3</sub>	22.5 <sup>b</sup>	110-112	1	1.5650	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub>		13.99	14.21	135-136 <sup>e</sup>	C <sub>19</sub> H <sub>24</sub> N <sub>3</sub> O <sub>7</sub>	16.31	16.27
Phenyl	N(CH <sub>2</sub> ) <sub>2</sub>	28 <sup>b,h</sup>	103-104	3	1.5600	C <sub>12</sub> H <sub>16</sub> N <sub>2</sub>		13.99	14.12	140.5-141 <sup>e</sup>	C <sub>19</sub> H <sub>24</sub> N <sub>3</sub> O <sub>7</sub>	14.92	14.78
Phenyl	N-Piperidino	31 <sup>b</sup>	153	3	1.5660	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub>		11.66	11.47	155.5 <sup>e</sup>	C <sub>22</sub> H <sub>28</sub> N <sub>3</sub> O <sub>7</sub>	19.29	19.58
Methyl	Bis-N(CH <sub>2</sub> ) <sub>2</sub>	78 <sup>a</sup>	87-88	3.5	1.4880	C <sub>11</sub> H <sub>21</sub> N <sub>3</sub>		21.52	21.03	169-170 <sup>a,i</sup> (dec.)	C <sub>23</sub> H <sub>27</sub> N <sub>3</sub> O <sub>14</sub>		
Methyl	Bis-N-piperidino	65 <sup>j</sup>	165-167	3		C <sub>17</sub> H <sub>29</sub> N <sub>3</sub>		15.26	15.88	198-199 <sup>e</sup>	C <sub>29</sub> H <sub>33</sub> N <sub>3</sub> O <sub>14</sub>	17.18	17.21

<sup>a</sup> Prepared by Method I. <sup>b</sup> Prepared by Method II. <sup>c</sup> This picrate could not be induced to crystallize. <sup>d</sup> Crystallized from ethanol-water by seeding at -40°. <sup>e</sup> Recrystallized from ethanol. <sup>f</sup> Decomposition point determined by immersing capillary at 157° and heating bath slowly. <sup>g</sup> This picrate appeared to decompose slowly in hot ethanol and recrystallizations were carried out as rapidly as possible. <sup>h</sup> Yield raised to 42.5% when a molar excess of formaldehyde and amine was used. <sup>i</sup> Methiodide dec. 267-268° with previous darkening above 150°. <sup>j</sup> Anal. Calcd. for C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>I<sub>2</sub>: N, 8.77. Found: N, 8.76. <sup>k</sup> Prepared from 2-N-piperidinomethyl-N-methylpyrrole by treatment with formaldehyde and piperidine in acetic acid according to Method II.

**Method I. 2-Dimethylaminomethyl-N-methylpyrrole.**—A solution of 17 g. (0.21 mole) of dimethylamine hydrochloride in 15.8 g. (0.21 mole) of 40% formalin was added, with stirring, to 16.2 g. (0.2 mole) of N-methylpyrrole at such a rate that the temperature did not exceed 60°. The mixture became homogeneous fairly rapidly. Stirring was continued for one hour after the addition was completed. After standing overnight the mixture was made alkaline with 25% sodium hydroxide solution and extracted with several portions of ether. The dried ether extracts were concentrated and distilled *in vacuo*, the fraction boiling at 50-58° (5 mm.) being collected, wt. 20.7 g. Another distillation gave material possessing the constants recorded in Table I. Like all of the other Mannich bases it decomposed slowly at room temperature and was stored in the refrigerator.

The picrate precipitated on mixing alcoholic solutions of the base and picric acid. Two recrystallizations from ethanol yielded yellow needles melting at 102.5°.

Crystals of the methiodide precipitated slowly in 96% yield from a chilled solution of 12 g. of the Mannich base in 50 ml. of absolute ethanol to which 14 g. of methyl iodide had been added cautiously. Several recrystallizations from warm, but not hot, ethanol, gave slightly colored crystals which did not have a sharp melting point. When heated up slowly in a capillary the methiodide began to darken at 140-150° and finally decomposed with gas evolution at 245°.

*Anal.*<sup>10</sup> Calcd. for C<sub>9</sub>H<sub>17</sub>N<sub>2</sub>I: C, 38.58; H, 6.12. Found: C, 38.82; H, 5.83.

**Method II. 2-Dimethylaminomethyl-N-phenylpyrrole.**—A mixture of 20 ml. of 33% aqueous dimethylamine solution and 22 ml. of acetic acid was allowed to come to room temperature and treated with 8.5 ml. of 40% formalin. The resulting solution was added dropwise to 14.3 g. (0.1 mole) of N-phenylpyrrole<sup>11</sup> with vigorous stirring. A little heat was evolved. Stirring was continued for 18 hours. The mixture was made alkaline and extracted with ether; the ether extracts were dried and distilled *in vacuo*. The fraction boiling at 100-105° (3 mm.) was collected. Redistillation yielded the material whose constants are reported in Table I. Use of two moles of dimethylamine and formaldehyde per mole of N-phenylpyrrole did not give disubstituted material but improved the yield of monosubstituted product to 42.5%.

To prepare the methiodide, 39.2 g. of the Mannich base was dissolved in 100 ml. of absolute ethanol and slowly treated with 26 g. of methyl iodide. After two days in the refrigerator, 43.2 g. of methiodide (66%) had deposited as a thick crystalline mass. The mother liquor yielded an additional 4 g. on dilution with ligroin. Although the analytical sample was recrystallized several times from absolute ethanol, its carbon content remained somewhat low. The material decomposed at 268° (previous darkening with evidence of partial fusion and resolidification at 148-150°).

*Anal.* Calcd. for C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>I: C, 49.16; H, 5.60. Found: C, 48.20; H, 5.44.

**Alkylations (A) 2-N-Methylpyrroleacetonitrile.**—A solution of 28 g. of 2-dimethylaminomethyl-N-methylpyrrole methiodide and 20 g. of sodium cyanide in 200 ml. of water was refluxed for 15 hours until the evolution of basic gases had ceased. The cooled solution was extracted with ether (a small amount of solid appeared to be insoluble), the ether extract was dried and distilled at reduced pressure. A colorless liquid, wt. 3.5 g., was collected at 85-95° (1 mm.). A second fraction, wt. 2.4 g., solidified in the side arm and receiver as the bath temperature was raised. Redistillation of fraction 1 yielded material boiling at 90-92° (1 mm.), n<sub>D</sub><sup>20</sup> 1.5188. It gave a positive Ehrlich<sup>12</sup> test and liberated ammonia on boiling with sodium hydroxide solution. The material decomposed slowly at room temperature.

*Anal.* Calcd. for C<sub>7</sub>H<sub>9</sub>N<sub>2</sub>: C, 69.97; H, 6.71. Found: C, 69.69; H, 6.39.

The second fraction melted at 144-144.5° after several recrystallizations from benzene. It was identical with the ether insoluble material isolated during the extraction. Analysis showed that partial hydrolysis of the nitrile had re-

(10) Analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

(11) H. Adkins and H. L. Coonradt, *THIS JOURNAL*, **63**, 1563 (1941).

(12) Fischer-Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 66.

sulted in the formation of the amide of 2-N-methylpyrrole-acetic acid.

*Anal.* Calcd. for  $C_7H_{10}N_2O$ : C, 60.83; H, 7.29; N, 20.27. Found: C, 61.14; H, 6.85; N, 20.24.

Hydrolysis of 1.5 g. of the nitrile with 20 ml. of 80% ethanol containing 3 g. of sodium hydroxide gave a quantitative yield of 2-N-methylpyrroleacetic acid, m.p.  $113^\circ$  after recrystallization from ligroin. It did not depress the m.p. of an authentic sample.<sup>8</sup>

(B) 2-N-Phenylpyrroleacetoneitrile.—Alkylation of 12.5 g. of sodium cyanide with 20 g. of the methiodide of II in 125 ml. of water yielded 6.1 g. (57%) of colorless liquid, b.p.  $115^\circ$  (0.5 mm.),  $n_D^{25}$  1.5822, which decomposed slowly at room temperature.

*Anal.* Calcd. for  $C_{12}H_{10}N_2$ : C, 79.09; H, 5.53; N, 15.41. Found: C, 79.46; H, 5.22; N, 15.48.

Hydrolysis gave a quantitative yield of 2-N-phenylpyrroleacetic acid. The light tan crystals melted at  $113^\circ$  after three recrystallizations from benzene-ligroin.

*Anal.* Calcd. for  $C_{12}H_{11}NO_2$ : C, 71.63; H, 5.24. Found: C, 71.70; H, 5.41.

(C) Diethyl (2-N-Methylpyrrole-methyl)-malonate.—A mixture of 64 g. of malonic ester in which had been dissolved 1.84 g. of sodium and 24 g. of the methiodide of I was heated with stirring at  $120^\circ$  for 14 hours in a nitrogen atmosphere until the evolution of basic gases had ceased completely. Water was added to the dark solution and the mixture extracted with ether. The dried ether extract was distilled *in vacuo*, approximately 10 g. of material being collected at  $120$ – $140^\circ$  (1 mm.). Redistillation yielded 6.8 g. (31%) of ester, b.p.  $132$ – $138^\circ$  (1 mm.),  $n_D^{20}$  1.4818. It decomposed slowly at room temperature.

*Anal.* Calcd. for  $C_{13}H_{15}NO_4$ : C, 61.64; H, 7.56. Found: C, 61.27; H, 7.14.

The diamide was prepared by allowing 0.5 g. of the ester to stand with 10 ml. of ammonium hydroxide solutions.

White needles separated after a few days, m.p.  $215^\circ$  (dec.) from water.

*Anal.* Calcd. for  $C_9H_{12}N_2O_2$ : N, 21.53. Found: N, 21.45.

Hydrolysis of the malonate with aqueous alcoholic potassium hydroxide solution gave reddish viscous material from which a small amount of beige needles, m.p.  $144^\circ$  (dec.), could be isolated by extraction with benzene. This compound decomposed before it could be analyzed.

Attempts to alkylate ethyl cyanoacetamidoacetate resulted in highly colored tarry fractions which could not be purified satisfactorily.

(D) Ethyl (2-N-Methylpyrrole-methyl)-cyanoacetate.—From 22.6 g. of ethyl cyanoacetate containing 0.92 g. of sodium and 12 g. of methiodide there was obtained 2.3 g. (26%) of condensation product, b.p.  $130$ – $135^\circ$  (1 mm.),  $n_D^{20}$  1.5048.

*Anal.* Calcd. for  $C_{11}H_{14}N_2O_2$ : C, 64.06; H, 6.84. Found: C, 64.25; H, 6.80.

(E) Diethyl (2-N-Phenylpyrrole-methyl)-malonate.—Alkylation of 42.5 g. of malonic ester containing 1.2 g. of sodium with 17.1 g. of the methiodide of II in the usual manner gave 10.1 g. (65%) of ester, b.p.  $155$ – $156^\circ$  (0.5 mm.),  $n_D^{20}$  1.5271.

*Anal.* Calcd. for  $C_{18}H_{21}NO_4$ : C, 68.54; H, 6.71. Found: C, 68.34; H, 6.84.

Hydrolysis of the ester with aqueous alcoholic alkali gave a viscous oil which solidified after prolonged rubbing. Recrystallization from ethyl acetate-petroleum ether resulted in a slightly colored amorphous solid which melted at  $115$ – $116^\circ$  with decomposition. Analysis showed this to be (2-N-phenylpyrrole-methyl)-malonic acid.

*Anal.* Calcd. for  $C_{14}H_{13}NO_4$ : C, 64.86; H, 5.05. Found: C, 65.16; H, 4.98.

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## Synthesis of 2,4,8-Trimethylazulene

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2,4,8-Trimethylazulene has been synthesized. It does not appear to be identical with pyrethazulene.

In 1941 Schechter and Haller<sup>1</sup> obtained a blue azulene by zinc dust distillation of pyrethrosin<sup>2</sup> which had the formula  $C_{13}H_{14}$  and did not appear to be identical with any azulene then known. Oxidative degradation of its trinitrobenzolate with potassium permanganate yielded only acetic acid, a result which was taken to indicate the presence of three methyl groups on the azulene nucleus. On the basis of the ultraviolet spectrum which resembled that of vetivazulene<sup>3</sup> (2-isopropyl-4,8-dimethylazulene), Schechter and Haller suggested 2,4,8-trimethylazulene as a possible structure for pyrethazulene.

In the light of present-day knowledge concerning the relationship between color and constitution in the azulene series,<sup>4</sup> the presence of a 2-methyl group in a trisubstituted blue azulene is not very likely. Like vetivazulene, 2,4,8-trimethylazulene might be

expected to show a violet coloration. Moreover, the similarity of ultraviolet spectra adduced as an argument for the structural resemblance of vetivazulene and pyrethazulene has recently been shown to be of lesser importance in the identification of azulenes than visual absorption data.<sup>5</sup>

The synthesis of 2,4,8-trimethylazulene and the comparison of its physical properties with pyrethazulene therefore appeared to be of interest.<sup>6</sup> The accompanying flow sheet illustrates the method used for the synthesis of the desired azulene. Reaction of 2,4,7-trimethylindan, prepared by conventional methods, with diazoacetic ester in the manner first employed by Pfau and Plattner<sup>7</sup> for the synthesis of vetivazulene yielded a highly colored ester which after hydrolysis was simultaneously dehydrogenated and decarboxylated with palladium-charcoal. The crude azulene was converted to the trinitrobenzene complex, liberated by chromatographic adsorption and distilled. Thus purified, the violet 2,4,8-trimethylazulene boiled at

(1) M. S. Schechter and H. L. Haller, *THIS JOURNAL*, **63**, 3507 (1941).

(2) W. G. Rose and H. L. Haller, *J. Org. Chem.*, **2**, 484 (1937); M. S. Schechter and H. L. Haller, *THIS JOURNAL*, **61**, 1807 (1939).

(3) B. Susz, A. St. Pfau and Pl. A. Plattner, *Helv. Chim. Acta*, **20**, 469 (1937).

(4) Pl. A. Plattner, *ibid.*, **24**, 283E (1941); A. J. Haagen-Smit, "Fortschritte der Chemie organischer Naturstoffe," Vol. 5, Springer Verlag, Vienna, 1948, p. 40.

(5) Pl. A. Plattner and E. Heilbronner, *Helv. Chim. Acta*, **31**, 804 (1948).

(6) In the article by Schechter and Haller<sup>1</sup> announcement was made of the contemplated synthesis of 2,4,8-trimethylazulene. However, no work bearing on this problem has been published in the interim.

(7) A. St. Pfau and Pl. A. Plattner, *ibid.*, **22**, 202 (1939).