John T. Scanlan and Waldo C. Ault, for their constructive criticism during the preparation of this article.

Summary

An electronic interpretation of the reaction of olefins with organic per-acids is proposed. This is based on the assumption that the peroxide oxygen in per-acids is electrophilic, and is readily released in the presence of a nucleophilic group, such as the double bond. When electron-releasing groups are attached to, or are in close proximity to, the double bond, the reaction rate is increased because of the increased electron density of the ethylenic system, which results in an increase in the nucleophilic properties of the double bond; when electron-attracting groups are present, the reaction rate is decreased because of a decrease in the nucleophilic properties of the double bond.

The preferential oxidation of one of the double bonds in certain di-unsaturated compounds, such as isoprene, 2-methyl-2,3-butadiene, geraniol, linalyl acetate and citral is explained on the basis of an increase in the nucleophilic properties of one of the double bonds as a result of electron-releasing substituents. In methyl 2,4-hexadienoate, the 4,5-double bond, which is preferentially oxidized, has increased nucleophilic properties because of the electron-releasing methyl group attached to it, whereas the 2,3-double bond has decreased nucleophilic properties because of the electron-attracting carbomethoxy group.

Although only a small amount of experimental work is available on the use of performic acid as an oxidizing agent, it appears to react rapidly with olefins which contain one as well as two electron-releasing groups attached to the ethylenic system, whereas a slow reaction would be expected with those olefins which contain only one such group.

PHILADELPHIA 18, PA. RECEIVED FEBRUARY 3, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

The Preparation of Some Monosubstituted Derivatives of Pyrrole by the Mannich Reaction

BY WERNER HERZ, KARL DITTMER AND STANLEY J. CRISTOL

As a part of a program of synthesis and biological investigation of a number of compounds related to important biological materials, it was decided to study β-(2-pyrrole)-alanine. Since gramine, 3-dimethylaminomethylindole, and its quaternary salts have been used for the synthesis of *dl*-tryptophan,[1] it was hoped that dimethylaminomethylpyrrole would react in the same manner to give β-(2-pyrrole)-alanine. With this in mind we investigated the application of the Mannich reaction to the synthesis of various derivatives of aminomethylpyrrole. These derivatives were obtained by treating an excess of pyrrole with a solution of the various amine hydrochlorides in formalin under conditions analogous to those applied in the synthesis of gramine. Applying these conditions we found that 2-(dimethylaminomethyl)-pyrrole could be prepared in good yield by treating pyrrole with dimethylamine hydrochloride and formalin. The hydrochlorides of other secondary amines, such as diethylamine, piperidine and morpholine, were employed in the same manner.

Under the conditions used in these experiments the hydrochlorides of the primary amines, methylamine and ethylamine, condensed readily with pyrrole and formaldehyde to give the corresponding 2-(alkylmethyl)-pyrroles, although in much lower yield.

During the preparation of this manuscript a paper by Bachman and Heisey[2] appeared which describes the results obtained by the use of the Mannich reaction with nitrogenous five-atom ring systems. These workers did not employ the procedure described in this paper, but added pyrrole to a solution of the amine in formalin, so that an excess of the formaldehyde–amine complex was present. Under these conditions they were unable to obtain products from primary amines, although the yields reported by them for the Mannich reaction of pyrrole with morpholine or piperidine are higher than the yields obtained by us.

Bachman and Heisey also stated that with dimethyl- or diethylamine colorless high-boiling liquids were obtained to which they assigned the structure of 2,5-bis-(dialkylaminomethyl)-pyrroles, although the Ehrlich test[3] was positive. The compounds isolated by us from the same reactions are low-melting solids, identified as the monosubstituted 2-(dialkylaminomethyl)-pyrroles.[4]

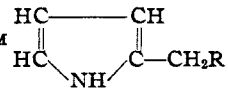
(1) Snyder and Smith, THIS JOURNAL, **66**, 350 (1944); Albertson, Archer and Suter, *ibid.*, **66**, 500 (1944); *ibid.*, **67**, 36 (1945); Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945).

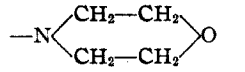
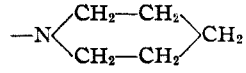
(2) Bachman and Heisey, *ibid.*, **68**, 2496 (1946).

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

(4) When informed of our results, Dr. Bachman in a private communication reported the following: The structures of 2,5-bis-(dimethylaminomethyl)-pyrrole and 2,5-bis-(diethylaminomethyl)-pyrrole were assigned solely on the basis of analytical data. These data are however about equally satisfactory for the corresponding monosubstituted pyrroles, whose calculated N-values lie within 0.7 of those for the disubstituted pyrroles. A re-examination of the two compounds by titration with standard acid has shown them to be the monosubstituted pyrroles and identical with the compounds described in this paper.

TABLE I

PROPERTIES OF COMPOUNDS OF THE FORM 

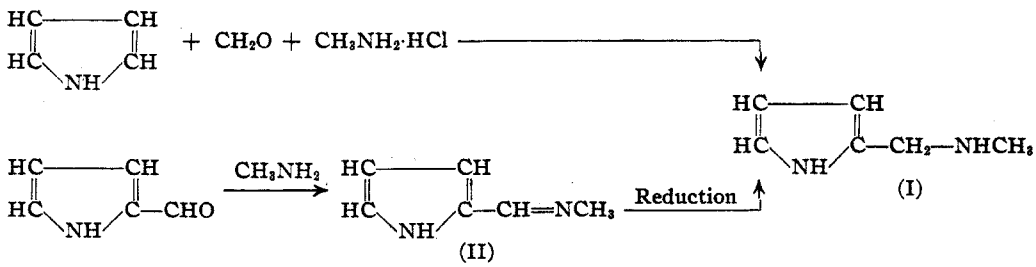
R	Yield, %	M. p., °C.	B. p. °C.	Mm.	Picrate m. p., °C.	Formula	Nitrogen, % Calcd.	Found
—NHCH$_3$	15[a]	....	84–85	11	141–142 (dec.)	$C_{12}H_{13}N_5O_7$	20.64	20.67
—NHCH$_2$CH$_3$	27	34–36[b]	94	9	138 (dec.)	$C_{13}H_{15}N_5O_7$	19.83	20.04
—N(CH$_3$)$_2$	77	64[c]	94	19	136–137 (dec.)[d]			
—N(CH$_2$CH$_3$)$_2$	40	21	108–111	8	119–120 (dec.)	$C_{15}H_{11}N_5O_7$	18.37	18.55
	25	72.5[e,f]	126–128	14	136	$C_{16}H_{17}N_5O_8$	17.71	17.59
	50	75[g]	119–121	14	152.5[g]	$C_{16}H_{19}N_5O_7$	17.80	17.77

[a] The residue polymerized in the distilling flask. [b] *Anal.* Calcd. for $C_7H_{12}N_2$: N, 22.58. Found, 22.15. [c] *Anal.* Calcd. for $C_7H_{12}N_2$: N, 22.58. Found: N, 22.16. [d] Methiodide darkens above 160°; m. p. above 350°. [e] Recrystallized from hexane. Bachman and Heisey, ref. 2, obtained this compound in higher yield. [f] *Anal.* Calcd. for $C_9H_{14}N_2O$: N, 16.85. Found: N, 16.65. [g] Mixed m. p. with piperidine picrate 120–130°.

In our experiments an excess of pyrrole was always present. Although we did not attempt to find optimum conditions for the reaction, it appears that it is essential to maintain this excess of pyrrole by the slow addition of the amine hydrochloride in 40% formalin in order to obtain monosubstituted pyrroles. In a few experiments, when the order of addition was reversed, monosubstituted products were not obtained. Even under the conditions which resulted in the formation of the monosubstituted products, comparatively large amounts of higher-boiling liquids were formed. No attempts were made to identify these high-boiling residues.

Because of difficulties encountered in the purification of the products, they were usually characterized and analyzed as their picrates. The properties of the products obtained are given in Table I. Stable picrates of 2-(morpholinomethyl)-pyrrole and 2-(piperidinomethyl)-pyrrole were obtained, contrary to the report of Bachman and Heisey.

The structure of the amine (I) formed from pyrrole, methylamine hydrochloride and formaldehyde was established by the reactions



Pyrrolalmethylamine (II), which was prepared from pyrrolealdehyde and methylamine,[5] was reduced with sodium or, in better yield, catalytically. The picrate of the resulting product was identical with the picrate of the amine obtained by the Mannich reaction. The structures of the other substances described in Table I were assumed by analogy. All of them gave a positive test with Ehrlich's reagent; a free α-position on the pyrrole nucleus is therefore indicated.

(5) Emmert, Diehl and Gollwitzer, *Ber.*, **62**, 1733 (1929).

Experimental

The following example illustrates the general procedure for the preparation of the compounds described in Table I.

2-Dimethylaminomethylpyrrole.—A solution of 85 g. (1.05 moles) of dimethylamine hydrochloride in 79 g. (1.05 moles) of 40% formalin was added slowly to 67 g. (1 mole) of pyrrole in a three-necked flask, fitted with a stirrer, reflux condenser and dropping funnel, at such a rate that the temperature did not exceed 60°. Thirty to sixty minutes was required. Stirring was continued for one and one-half hours after the addition was completed, and the mixture was allowed to stand overnight. It was then poured into 200 ml. of 25% sodium hydroxide solution and extracted with three 100-ml. portions of ether. The combined ether extracts were washed with two 20-ml. portions of water and dried over anhydrous sodium sulfate. The ether was removed, and the residue was distilled at reduced pressure, the flask being immersed in an oil-bath. The product was collected at 88–100° (19 mm.) and crystallized in the receiver in the form of long white needles which became yellowish on standing. The yield was 95 g. (77%). Almost the entire product was collected at 94° (19 mm.) when distilled a second time.

For analysis the product was redistilled in a semi-micro sublimation apparatus to give crystalline material, m. p. 63°, which discolored on standing. Recrystallization from hexane, with much loss, gave stable crystals, m. p. 64°.

2-Methylaminomethylpyrrole.—A. By following the above procedure, using 13.4 g. of pyrrole, 14.8 g. of methylamine hydrochloride and 15.8 g. of 40% formalin, 3.1 g. (15%) of product, boiling at 84–85° (11 mm.),

was obtained before the residue in the distilling flask polymerized. The picrate, prepared in the usual fashion,[6] melted at 141–142° (dec.).

B. By reducing 9 g. of 2-pyrrolalmethylamine[5] in absolute alcohol with sodium in the usual manner, 1.5 g. of very impure product boiling at 95–110° (20 mm.), was obtained; m. p. of the picrate was 139–140° (dec.).

Anal. Calcd. for $C_{12}H_{12}N_6O_7$: N, 20.64. Found: N, 20.73.

C. 1.27 g. of the Schiff base was dissolved in 20 ml. of ethanol and reduced at room temperature with hydrogen at atmospheric pressure, using 60 mg. of platinum oxide catalyst. After the calculated volume of hydrogen had been absorbed, the solution was filtered, decolorized with a little charcoal and used directly to prepare the picrate in 80% yield (based on the starting Schiff base), m. p. 140° (dec.).

Anal. Calcd. for $C_{12}H_{12}N_6O_7$: N, 20.64. Found: N, 21.18.

Mixed melting points of the picrates from A, B and C showed no depression.

(6) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 149.

Summary

The preparation of monosubstituted derivatives of pyrrole by the Mannich reaction, under conditions where excess pyrrole is treated with a mixture of formaldehyde and the hydrochlorides of a number of primary and secondary amines, is described. The structure of 2-methylaminomethylpyrrole is proved, and the properties of the compounds are given.

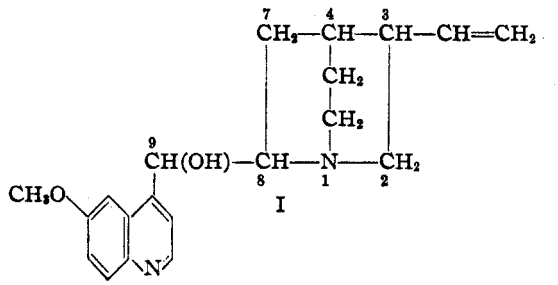
BOULDER, COLORADO RECEIVED FEBRUARY 4, 1947

[CONTRIBUTION FROM THE CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

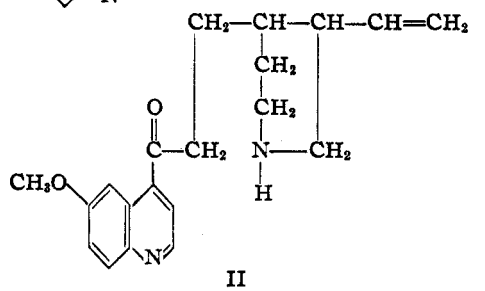
Partial Racemization of Quinine[1]

BY W. E. DOERING, GLORIA CORTES AND L. H. KNOX

Using a reaction known to effect racemization or inversion of an asymmetric secondary hydroxyl group[2,3] in general and specifically to have converted cinchonine into cinchonidine (5% yield),[4] Rabe has converted quinine to an equilibrium mixture of the four stereoisomeric alkaloids (III, IV, V and VI).[5a,5b,6]



I



II

On boiling quinine for forty-eight hours in a solution of potassium hydroxide in amyl alcohol there is isolated a mixture from which quinine (7%), quinidine (10–15%), and the two epibases (15–20% each) are obtained. From the fact that

(1) This work was carried out under Government Contract WPB-191 between the Office of Production Research and Development and the Division of War Research, Columbia University.

(2) Erlenmeyer and Hell, *Ann.*, **160**, 303 (1871); Willstätter, *Ber.*, **29**, 944 (1896).

(3) For further references, see Hückel, "Theoretische Grundlagen der organischen Chemie," Akademische Verlagsgesellschaft, Leipzig, 2nd ed., 1934, vol. I, pp. 286–288.

(4) Koenigs and Husmann, *Ber.*, **29**, 2185 (1896).

(5) (a) Rabe, Kolbe and Hochstätter, *Ann.*, **492**, 258 (1931); (b) Rabe and Höter, *J. prakt. Chem.*, **154**, 66 (1939).

(6) In molecules having structure I there are centers of asymmetry at carbon atoms 3, 4, 8 and 9. The four known isomers are all related to quinotoxine (II) and are, therefore, C.8 and C.9 epimers[7] [Pasteur, *Compt. rend.*, **36**, 26 (1853)]. Stereochemical configurations are assigned to III, IV, V, and VI on the basis of the following considerations. (1) Prelog and Zalan [*Helv. Chim. Acta*, **27**, 535 (1944)] have proved the C.7–C.8 bridge to be *cis* to the C.3 vinyl group. (2) Quinine and quinidine are C.8 epimers since they are degraded to two different C.9 desoxy alkaloids of negative and positive rotation, respectively. (3) From the specific rotation of the alkaloids (quinine, −158°; epiquinine, +43°; epiquinidine, +102°; and quinidine, +265°) application of the rule of superposition or additivity of specific rotation of individual asymmetric centers coupled with fact (2) indicates that quinine and epiquinine are epimeric at C.9, as are quinidine and epiquinidine, the two pairs differing at C.8 [for details *cf.* Henry, "The Plant Alkaloids," 3rd ed., Blakiston, London, 1939, p. 424]. (4) The direct epimerization of quinidine to epiquinidine by way of the *p*-toluene sulfonate [Sussko and Szelag, *Chem. Zentr.*, **108**, I, 464 (1937)] confirms conclusion (3). (5) The C.9 hydroxyl group and the C.3 vinyl group in quinidine react to form a cyclic ether [Henry, Solomon and Gibbs, *J. Chem. Soc.*, 592 (1937)] whereas no cyclic ether has ever been formed from quinine. Since a model of the cyclic ether can only be constructed if the C.3 and C.8 hydrogen atoms are *cis*, it follows that C.9 and the C.3 vinyl group must be *cis* in quinidine and epiquinidine, *trans* in quinine and epiquinine. (6) Woodward, *et al.*,[8] have shown that dihydroquininone is reduced catalytically predominantly to dihydroquinidine. Dihydroquininone, therefore, has the quinidine configuration at C.8 and might be named more appropriately dihydroquinidinone. If one assumes that dihydroquinidinone (dihydro IX) with the quinoline ring extended away from the quinuclidine ring is adsorbed on the catalyst in the least hindered position [Linstead, *et al.*, THIS JOURNAL, **64**, 1985 (1942)], that is, with the C.3 ethyl group away from the catalyst, reduction would lead to the isomer in which the hydroxyl group at C.9 is close to the C.3 ethyl group (the quinoline ring being oriented away from the quinuclidine ring) or to the isomer in which looking along the C.8–C.9 bond, the hydrogen, hydroxyl and quinoline ring are encountered in that order reading clockwise (the C.3 configuration arbitrarily being written as in III).

(7) Dirscherl and Thron, *Ann.*, **521**, 57 (1936).

(8) Woodward, Wendler and Brutschy, THIS JOURNAL, **67**, 1425 (1945).