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Synthesis and Properties of Alkylpyrroles

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Alkylation of pyrrylmagnesium bromide with a series of alkyl halides gave in every case pyrrole, the isomeric 2- and 3-alkylpyrroles and polyalkylpyrroles. Relative amounts of the products were determined by infrared spectroscopy. Several other synthetic routes to the 2-alkylpyrroles were investigated. The acylation of pyrrylmagnesium bromide with either acyl halides or esters gave only the 2-acylpyrroles.

A very rapid and highly specialized development of pyrrole chemistry[2] followed the isolation of substituted pyrroles from the degradation of the vital pigments of hemoglobin and chlorophyll.[3] With the focus on these complex substances, the main studies of the simpler pyrrole derivatives were dictated by the requirement of the porphyrin programs. Thus one finds that the literature contains no physical properties, other than boiling points, suitable for the identification of 2- and 3-alkylpyrroles. This primitive state of affairs accounts for many of the discrepancies and apparent anomalies found in the literature. For example, one finds in the older literature[4] the conflicting claims that the alkylation of pyrrylmagnesium halides results in exclusively 2-, exclusively 3- or both 2- and 3-substitution, and three recent papers[5] have reported that the products of alkylation were the 2-isomers, failing to recognize the presence of the 3-isomers in their "2-isomer."

The development of many new chemical techniques suggested the need for a careful reinvestigation of the alkylation of pyrrylmagnesium halides and the identification of alkylpyrroles. This paper is concerned with the identification and proof of structure of the 2- and 3-alkylpyrroles which were products of the alkylation of pyrrylmagnesium bromide. The stereochemistry and mechanisms of substitution in the pyrryl anion system will be discussed in the subsequent papers of this series.

Alkylation of Pyrrylmagnesium Bromide.—In 1909, Oddo[4a] reported that the reaction of methylmagnesium iodide with pyrrole yielded methane and pyrrylmagnesium iodide. In addition he claimed that with carbon dioxide or ethyl chloroformate, the 2-carboxylate derivative of pyrrole was produced. Later he reported[4b] that pyrrylmagnesium iodide reacts with methyl iodide to produce pyrrole, 2- and 3-methylpyrrole, dimethylpyrroles and a basic material originally described as a dihydropyridine but later as a polyalkylpyrrolenine. However, these same workers claimed that alkylation with ethyl and *n*-propyl iodides gave only the 3-alkylpyrroles and polyalkylpyrroles. This was refuted by Hess and Wissing[4c] who stated that ethylation and allylation produced only the 2-alkyl and 2,5-dialkylpyrroles. Such a view has been frequently quoted in textbooks and accepted by subsequent workers[5] who report finding only 2-alkyl and 2,5-dialkylpyrroles as products of the reaction. In the present investigation it was found that all alkylations of pyrrylmagnesium halides produced comparable amounts of 2- and 3-alkylpyrroles and a mixture of polyalkylpyrroles.

In a series of experiments, pyrrylmagnesium bromide has been alkylated with a variety of alkyl halides and methyl *p*-toluenesulfonate in ethereal solutions, and in each case both 2- and 3-alkylpyrroles were identified among the products. In no instance was N-alkylation observed. The over-all extent of the reaction was determined by titration of free base in an aliquot of the reaction mixture. Distillation of the reaction products and analysis of the fractions by infrared spectroscopy, based on the properties of the pure isomers, permitted a direct determination of recovered pyrrole, 2- and 3-alkylpyrroles. The results of these analyses are presented in Table I. The high-boiling material has been reported as dialkylpyrroles. The recovery leaves much to be desired varying from 65 to 85% of the pyrrole used and efforts to improve it were not successful. For the main part, these losses can be attributed to loss in the aqueous layer and the great sensitivity of pyrroles to oxygen and acids which added to the experimental difficulties. The permissible conclusions are limited by the inadequate recovery. However, some of the gross features are undoubtedly significant.

TABLE I

ALKYLATION OF PYRRYLMAGNESIUM BROMIDE

	Products, mole %				Ratio of products	
Alkylating agent	Pyrrole	2-Alkyl	3-Alkyl	Poly-alkyl[a]	2-Alkyl/ 3-alkyl	Mono-poly
Methyl bromide	40.7	10.4	5.5	12.3	1.9	1.3
Methyl tosylate	41.2	19.6	9.2	18.7	2.1	1.5
Isopropyl bromide	26.1	16.9	11.1	12.6	1.5	2.1
sec-Butyl bromide	21.6	28.0	9.0	14.8	3.1	2.5
t-Butyl chloride	24.5	32.8	17.6	9.8	1.9	5.1
Allyl chloride	26.1	27.1	8.9	12.7	3.0	2.8

[a] Calculated as dialkylpyrrole.

(a). *In all cases both 2- and 3-alkylpyrroles were identified among the products. The ratio of 2- to*

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(1) In part abstracted from a dissertation submitted by Gerritt P. Bean in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, The Pennsylvania State University, January, 1956. A research grant from Research Corporation is gratefully acknowledged.

(2) H. Fischer and H. Orth, "Die Chemie des Pyrrole," Akademische Verlagsgessellschaft G.m.b.H., Leipzig, 1934.

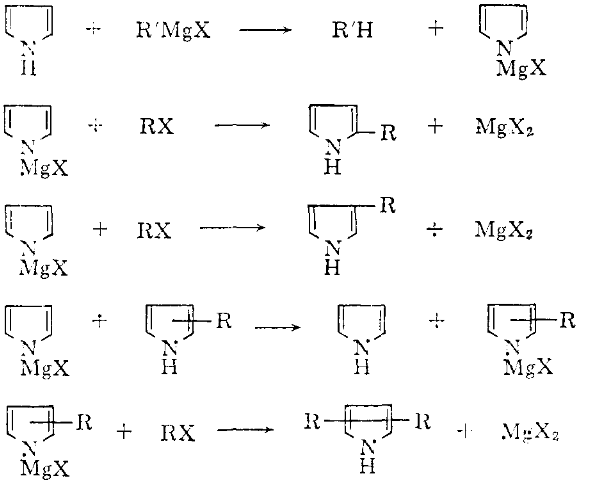
(3) F. Hoppe-Seyler, *Med. Chem. Untersuchungen*, **4**, 525 (1871); O. Piloty, J. Stock and E. Dormann, *Ann.*, **406**, 342 (1914).

(4) (a) B. Oddo, *Gazz. chim. ital.*, **39I**, 649 (1909); (b) B. Oddo and R. Mameli, *ibid.*, **43II**, 504 (1913); (c) K. Hess, *Ber.*, **46**, 3125 (1913); K. Hess and F. Wissing, *ibid.*, **47**, 1416 (1914).

(5) (a) P. Rothemund and C. Gage, *J. Am. Chem. Soc.*, **77**, 3340 (1955); (b) P. Cantor and C. VanderWerf, *ibid.*, **80**, 970 (1958); (c) K. Frisch and R. Kary, *J. Org. Chem.*, **21**, 931 (1955); U. S. Patent 2,845,435.

3-alkylpyrrole varied between 1.5 and 3, but the small variation seemed to have no obvious relation to the structure of R. (b). *t-Butyl chloride is an effective alkylating agent leading to t-butylpyrroles without accompanying olefin formation by dehydrohalogenation. It is particularly noteworthy that alkylation with tertiary alkyl halides proceeded much more rapidly than with primary alkyl halides.* (c). *Polyalkylation is an important reaction when equivalent quantities of alkylating agent are employed, thus leading to relatively poor yields of monoalkylpyrroles. Bulky R groups tend to inhibit the polyalkylation.*

The observations in this alkylation study are adequately accommodated by the equations



Evidence for this mechanistic rationalization are presented in a subsequent paper.

Separation of α- and β-Alkylpyrroles.—The α- and β-isomers of methyl, ethyl, *n*-propyl, isopropyl, allyl, *sec*-butyl and *t*-butyl pyrroles have been prepared. With the exception of the *n*-propylpyrroles, these alkylpyrroles were prepared by the alkylation of pyrrylmagnesium bromide with the appropriate alkyl halide. With vacuum fractionation through a column of greater than fifty plates efficiency, samples of the pure α- and β-isomers were separated. The quality of the separation could be followed through the infrared spectra of successive fractions since in the 12–15 μ region the α- and β-isomers were found to have non-overlapping absorption bands. As a consequence of this fortuitous non-overlapping it was possible to judge the degree of intercontamination in successive fractions through the diminution and ultimate disappearance of the contaminant's bands.

The properties of these isomers are listed in Table II. The basis of the structural assignments is indicated below.

Structural Assignments. Methylpyrroles.—Ciamician[6] described two C-methyl derivatives of pyrrole, b.p. 142–143° and 147–148°, to which he assigned the 3- and 2-methyl structures, respectively. This assignment was made possible by converting the methylpyrroles to the corresponding pyrrolecarboxylic acids by fusion with potassium hydroxide, and determining the solubility of their lead salts in water. Ciamician had found that the lead salt of 2-pyrrylcarboxylic acid was soluble in water, while the salt of 3-pyrrylcarboxylic was insoluble.

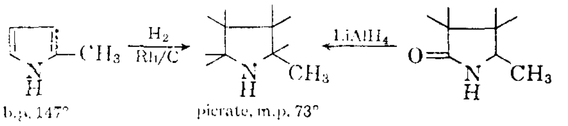
TABLE II

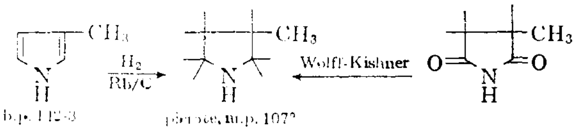
PHYSICAL PROPERTIES OF ALKYLPYRROLES

Alkylpyrrole	B.p. °C.	B.p. Mm.	n^{25}_D	Infrared[a]	
2-Methyl	84	70	1.5002	12.80	14.30
3-Methyl	80	70	1.4955	13.20	14.50
2-*n*-Propyl	92	33	1.4900	12.80	14.25
3-*n*-Propyl	90	30	1.4878	13.15	14.45
2-Isopropyl	80	25	1.4900	12.73	14.15
3-Isopropyl	90	23	1.4862	12.97	14.40
2-Allyl	68	11	1.5133	12.72	14.21
3-Allyl	74	11	1.5110	12.90	14.40
2-*sec*-Butyl	96	36	1.4897	12.77	14.13
3-*sec*-Butyl	100	36	1.4867	13.00	14.41
2-*t*-Butyl	82	20	...	12.73	14.12
3-*t*-Butyl	93	30	...	12.92	14.40

[a] Principal peaks in 12 to 15 μ region.

To obtain additional evidence for these structural assignments, the low- and high-boiling isomers were converted to the known methylpyrrolidines by hydrogenation over a rhodium-on-carbon catalyst. The picrate of the pyrrolidine from the low-boiling methylpyrrole melted at 107° and the 3-methylpyrrolidine picrate (from the reduction of 2-methylsuccinimide) is reported[7] to melt at 106°. The methylpyrrolidine picrate from the high-boiling isomer melted at 67–74° and the picrate of 2-methylpyrrolidine (from the reduction of 2-methyl-5-pyrrolidone) is reported[8] to melt at 73°. Thus Ciamician's assignment is confirmed.





Allyl and Propylpyrroles.—In the past, structural assignments for these pyrroles had been made by analogy based on the respective beliefs of the authors[4bc,5b] that alkylation of pyrrylmagnesium halides produced either exclusively the 2- or 3-isomer. This is not correct for in each case careful fractionation of the products gave two fractions having relatively close boiling points, but differing in refractive indices and infrared spectra.

In the case of the products of allylation, hydrogenation of the exocyclic double bond over palladium catalyst gave the corresponding *n*-propylpyrroles which had distinctively different infrared spectra. Wolff–Kishner reduction of 2-propionylpyrrole yielded 2-*n*-propylpyrrole identical with that obtained from the lower-boiling allylpyrrole, thus providing an assignment of 2-allylpyrrole as the lower-boiling isomer and 3-allylpyrrole as the higher.

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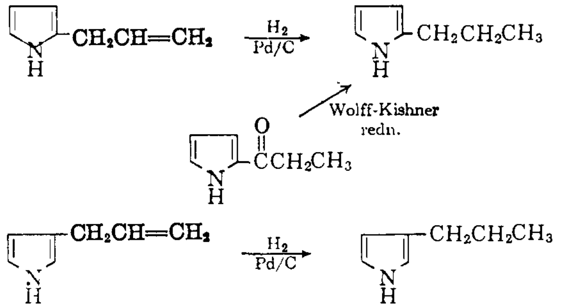
[6] G. Ciamician, *Ber.*, **14**, 1055 (1881).

[7] E. Spath and S. Prokopp, *Monatsh.*, **50**, 352 (1928).

[8] P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).



Other Alkylpyrroles.—For the three pairs of pyrroles of known structure the physical properties of the 2- and 3-isomers showed characteristic differences (boiling points, refractive indices, infrared and proton magnetic resonance spectra), the only exception being the reversal of the boiling points for the 2- and 3-methylpyrroles. The structural assignments for the isomeric C-ethyl, isopropyl, *sec*-butyl and *t*-butylpyrroles were made by analogy, employing comparisons of their physical properties.

Physical Properties of Alkylpyrroles.—The physical properties of the 2- and 3-alkylpyrroles are given in Table II.

Infared Spectra.—The infrared spectra (isooctane solvent) proved to be valuable for identification, analysis of mixtures and structural assignment. At the longer wave lengths (12 to 15 μ) each alkylpyrrole exhibited two bands, one in the 12.7 to 13.2 μ region and the other in the 14.15 to 14.50 μ region. In all cases, the two bands of the 2-isomer are shifted 0.2 to 0.4 μ shorter wave length than the bands of the 3-isomer.

Refractive Indices.—In each pair, the 2-isomer has the larger refractive index. Since the refractive index of pyrrole is $n^{25}\text{D}$ 1.5070, it is apparent that ring substitution by saturated alkyl groups produced the expected decrease in refractive index.

Boiling Points.—In each pair, with the exception of the methylpyrroles, the 3-alkylpyrrole has the higher boiling point. The unusually high boiling point of pyrrole (130°) is attributed to association through hydrogen-bonding between the nitrogen atoms. Although the molecular weight is greater, 1-methylpyrrole boils 16° lower than pyrrole, because the methyl group attached to the nitrogen prevents association. Pyrrole and 1-ethylpyrrole boil at the same temperature, but the heats of vaporization are 10.4 and 9.6 kcal./mole, respectively.[9] Thus 1-ethylpyrrole has a normal entropy of vaporization while that for pyrrole is high for a normal liquid.

A substituent at the 2-position having more than two carbon atoms can assume a conformation in which the nitrogen atom is blocked, thereby decreasing association and the boiling point. Thus for large substituents, the 2-isomer should be the lower boiling. A methyl group is too small and compact to exert an effect on association, so that 2- and 3-methylpyrrole are probably associated to the same extent.

Proton Magnetic Resonance Spectra.—In addition to the multiplet at 8.0 to 9.5 τ, characteristic of the alkyl group, the proton magnetic resonance spectra[10] of the 2- and 3-alkylpyrroles exhibit two complex multiplets at 3.3 to 3.8 τ and 4.0 to 4.5 τ. These are assigned to the ring protons, $H_{2,5}$ and $H_{3,4}$, respectively, since it is expected that the inductive unshielding effect of the nitrogen would be greater for the nearer $H_{2,5}$ and thus shift them to a lower field. Figure 1 shows that such an assignment is consistent with the observed 2:1 ratio of the areas of the peaks in the spectra of the 2- and 3-alkylpyrroles of known structures. This assignment also agrees with Abraham and Bernstein's[11] detailed analysis of the spectra of pyrrole and 2-methylpyrrole. Due to N^{14} quadrupole broadening, it is not possible to observe a peak for H_1.

Summary.—The consistency of the correlation of structure with boiling point, refractive index, infrared and proton magnetic resonance spectra suggests that in the future the assignment of structure for alkylpyrroles can be made by comparison of their physical properties.

After structural assignment from physical properties, the alkylpyrroles should be characterized by the preparation of solid derivatives. Although some polymethylpyrroles are reported to form picrates, the carboxanilides suggested by Triebs[12] appear to be the most suitable derivatives for the characterization of monoalkylpyrroles.

Other Synthetic Routes to C-Alkylpyrroles.—Due to the difficulty of separating pure alkylpyrroles from the reaction product of the alkylation of pyrrylmagnesium halides, various synthetic methods of preparing monoalkylpyrroles were investigated. One attractive route was that reported by Nenitzescu and Solomonica[13] who described the reaction of diazoacetic ester with pyrrole to produce ethyl 2-pyrrylacetate which on saponification and decarboxylation gave 2-methylpyrrole. We confirm the observations of these authors and, also, infrared analysis of a sample of methylpyrrole prepared by this method showed it to be the pure 2-isomer.

Yurev has reported many conversions of oxygen-containing heterocyclic compounds to their nitrogen and sulfur analogs by a vapor-phase catalytic method. For example, the passage of 2-methylfuran and ammonia over alumina at 450° is claimed to give 2-methylpyrrole.[14] In our hands this synthesis was unsatisfactory, since analysis of the product showed that it contained in addition to some high-boiling material, pyrrole and 2- and 3-methylpyrroles due to extensive isomerization and demethylation at the high temperature.

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(9) G. Judd, M. S. Thesis, Univ. of Portland, 1950.

(10) Proton magnetic resonance spectra were obtained with a Varian V-4300B spectrometer operating at 40 mc. Whereas the $H_{2,5}$ and $H_{3,4}$ peaks overlap in the spectrum of a neat sample of pyrrole, dilution with polar solvents causes the peaks to move apart (see J. Pople, W. Schneider and H. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 270). Therefore samples of pyrroles were studied at 25° in 20% solution of dimethyl sulfoxide with tetramethylsilane as an internal standard. The positions of the peaks are reported on Tier's τ scale.

(11) R. Abraham and H. Bernstein, *Can. J. Chem.*, **37**, 1057 (1959).

(12) A. Triebs and N. Ott, *Ann.*, **577**, 119 (1952).

(13) C. Nenitzescu and E. Solomonica, *Ber.*, **64**, 1924 (1931).

(14) Y. Yurev, *ibid.*, **69**, 440 (1936).

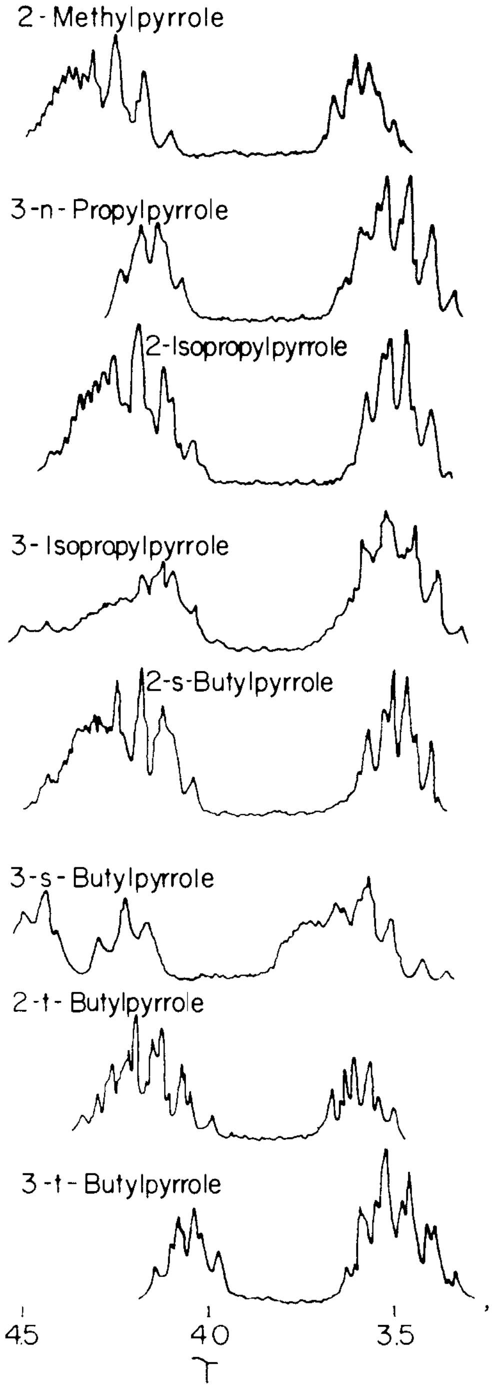

Fig. 1.—N.m.r. spectra of alkylpyrroles in DMSO at 40 mc., TMS as internal standard (10.00τ).

In a similar reaction, Clauson-Kaas and coworkers[15] reported the production of 2-methylpyrrole from the more reactive 2,5-dimethoxytetrahydro-2-methylfuran and ammonia at 250° over alumina. We confirm these observations. Apparently isomerization does not take place at this lower temperature as infrared analysis of the product showed that it consisted of 2-methylpyrrole and the unreacted tetrahydrofuran.

A route to other alkylpyrroles was suggested by the reports that acylation of pyrrylmagnesium halides gave only the 2-acylpyrroles.[16] If this were true, Wolff–Kishner reduction of the 2-acylpyrrole would give the corresponding 2-alkylpyrrole. In light of the fact that the alkylation of pyrrylmagnesium bromide gives 2- and 3-alkylpyrroles along with polyalkylation, it was doubted that acylation gave only the 2-acylpyrrole. However, we confirm the older claims that acylation of pyrrylmagnesium bromide with acetyl chloride, ethyl acetate or propyl propionate gives only *one* product, and Wolff–Kishner reduction of the propionylpyrrole gave 2-*n*-propylpyrrole. The 2-acetylpyrrole prepared from either acetyl chloride or ethyl acetate was identical with that prepared by Ciamician's[17] method of simply heating acetic anhydride and pyrrole.

Although a satisfactory synthesis of 3-alkylpyrroles has yet to be found, the reduction of the easily prepared 2-acylpyrroles appears to be the most convenient method of obtaining many of the 2-alkylpyrroles.

Experimental

Pyrrylmagnesium bromide was prepared by essentially the method of Oddo.[4a] To prepare 1 mole of pyrrylmagnesium bromide, 67.1 g. (1 mole) of freshly distilled pyrrole (du Pont) was slowly added to a solution of methylmagnesium bromide (from 24 g. of magnesium turnings, 1 l. of absolute ether and 60 ml. of methyl bromide). After the evolution of gas had ceased, the reaction mixture was refluxed 30 minutes. The pyrrylmagnesium bromide solution was a light brownish-green.

All reactions involving pyrrole and its compounds were conducted under an atmosphere of nitrogen.

Reaction of Methyl Bromide with Pyrrylmagnesium Bromide. Run 1.—To a 10-l. copper Grignard reactor containing 5 moles of pyrrylmagnesium bromide was added 325 ml. (6 moles) of methyl bromide. Stirring was discontinued after 2 hours and the reaction mixture allowed to stand overnight. An additional 325 ml. of methyl bromide was added the next day. On the third day, a 5-ml. aliquot was added to an excess of 0.1 *N* hydrochloric acid and the excess acid titrated. The titration indicated that 85% of the Grignard reagent had disappeared. After the addition of 4 l. of water (free of dissolved oxygen) and 30 ml. of phosphoric acid, the *p*H of the aqueous layer was 4.5. The two layers were separated and the aqueous layer extracted three times with 200-ml. portions of ether. The combined ether layers were dried over anhydrous potassium carbonate, and the ether removed by distillation. The residue (495 g.) was vacuum distilled through a 900 × 15 mm. column packed with Helipak (Podbielniak) packing. The efficiency of this column *in vacuo* was greater than 45 plates.

Fractionation of the residue gave (a) 146 g. of pyrrole, b.p. 62° (62 mm.), $n^{25}\text{D}$ 1.5072; (b) 23.15 g. of 3-methylpyrrole, b.p. 80° (70 mm.), $n^{25}\text{D}$ 1.4955; (c) 35.95 g. of 2-methylpyrrole, b.p. 84° (70 mm.), $n^{25}\text{D}$ 1.5002; (d) 33.00 g. of polymethylpyrroles, b.p. 87–75° (51–21 mm.), $n^{25}\text{D}$ 1.4943–1.5015; and (e) 49 g. of residue.

Hydrogenation of 1 g. of 3-methylpyrrole (fraction b) at 3 atm. using rhodium catalyst (Baker) gave 3-methylpyrrolidine. The picrate (from EtOH-H_2O) melted at 106.5–107° (lit. 106°). The *p*-toluenesulfonamide (from petr. ether) melted at 68.5–69.5°.

Hydrogenation of 1 g. of 2-methylpyrrole (fraction c) gave 2-methylpyrrolidine. The picrate melted at 69–74° (lit.[8] 75°). The *p*-toluenesulfonamide melted at 93–94°.

Following the procedure of Triebs,[12] 0.5-ml. samples of the methylpyrroles were heated with 0.5 ml. of phenyl isocyanate in sealed tubes for 24 hours. The resulting carboxanilides

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[15] N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952); N. Elming and N. Clauson-Kaas, *ibid.*, **6**, 870 (1952).

[16] B. Oddo, *Ber.*, **43**, 1012 (1910); W. Chelinzev and A. Terentjew, *ibid.*, **47**, 2674 (1914); W. Herz and C. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954).

[17] G. Ciamician and M. Dennstedt, *Gazz. chim. ital.*, **13**, 445 (1883).

were recrystallized from ethanol–water; 2-methylpyrrole carboxanilide, m.p. 171–174°; 3-methylpyrrole carboxanilide, m.p. 155–157°.

Run 2.—To a solution of pyrrylmagnesium bromide (1 mole) was added 50 ml. (0.91 mole) of methyl bromide. Every 12 hours, 15 ml. of methyl bromide was added. After 3 days, titration indicated the disappearance of 90% of the Grignard reagent. One liter of water (free of dissolved oxygen) and 12 ml. of phosphoric acid were added slowly. The aqueous layer was separated and extracted three times with ether. After drying the combined ether layers over anhydrous potassium carbonate, the ether was removed under a 20-section bubble column. The residue was vacuum distilled through a short Vigreux column. Amounts of pyrrole, 2- and 3-methylpyrroles and polymethylpyrroles were determined from the infrared spectrum of each fraction.

Reaction of Methyl Toluenesulfonate with Pyrrylmagnesium Bromide.—One-half mole (85 g.) of methyl toluenesulfonate (Monsanto practical grade) was added to a refluxing solution of 0.5 mole of pyrrylmagnesium bromide in 500 ml. of ether. After 15 minutes the reaction mixture was cooled and titration of an aliquot indicated that the reaction was complete. After hydrolysis with 1400 ml. of water (free of dissolved oxygen) and 3 ml. of phosphoric acid, the reaction product was worked up as usual. The ether was removed under a 20-section bubble column and the residue vacuum distilled. The amounts of pyrrole, 2- and 3-methylpyrroles and polymethylpyrroles were determined by infrared analysis.

Reaction of Allyl Chloride with Pyrrylmagnesium Bromide. Run. 1.—The reaction of 114 g. (1.5 moles) of allyl chloride with 1.5 moles of pyrrylmagnesium bromide was exothermic. After 15 minutes the reaction mixture was cooled in ice to room temperature, and titration of an aliquot indicated that the reaction was complete. After hydrolyzing the reaction product with 1 l. of water containing 10 ml. of phosphoric acid, the aqueous layer was separated and extracted several times with ether. The combined ether layers were dried and the ether removed under a bubble column. The residue was distilled under reduced pressure. Fractionation of the material which boiled from 63° (51 mm.) to 106° (9 mm.) through the Helipak column gave: (a) 19.3 g. of pyrrole, b.p. 55° (41 mm.), $n^{25}\mathrm{D}$ 1.5068; (b) 39.1 g. of 2-allylpyrrole, b.p. 68° (11 mm.), $n^{25}\mathrm{D}$ 1.5135; (c) 13.55 g. of 3-allylpyrrole, b.p. 74° (11 mm.), $n^{25}\mathrm{D}$ 1.5121; (d) 14.50 g. of polyalkylpyrroles, b.p. 71° (13 mm.), $n^{25}\mathrm{D}$ 1.5173; and (e) 6.0 g. of residue; 2-allypyrrole carboxanilide, m.p. 197–205°; 3-allylpyrrole carboxanilide, m.p. 113–115°.

Hydrogenation of 2-allylpyrrole (fraction b) at 3 atm. using palladium catalyst (Baker) gave 2-propylpyrrole, b.p. 92° (33 mm.), $n^{25}\mathrm{D}$ 1.4900; 2-*n*-propylpyrrole carboxanilide, m.p. 134–136°. Hydrogenation of 3-allylpyrrole (fraction c) gave 3-*n*-propylpyrrole, b.p. 90° (30 mm.), $n^{25}\mathrm{D}$ 1.4878; 3-*n*-propylpyrrole carboxanilide, m.p. 124–125°.

Run 2.—One-half mole of pyrrylmagnesium bromide was treated with 38 g. (0.5 mole) of allyl chloride as before. After 30 minutes the reaction mixture was hydrolyzed and worked up as usual. After removing the ether, the residue was vacuum distilled and the amounts of pyrrole, 2- and 3-allylpyrroles and polyallylpyrroles determined from the infrared spectrum of each fraction.

Reaction of Isopropyl Bromide with Pyrrylmagnesium Bromide.—A refluxing solution of 2 moles of pyrrylmagnesium bromide was treated with 2 moles of isopropyl bromide. After 3 hours the reaction mixture was cooled and titration indicated that only 50% of the Grignard reagent had disappeared; 6.5 hours later, only 65% had disappeared; after 24 hours, 85% had disappeared and the reaction mixture was hydrolyzed and worked up as usual. The product was vacuum distilled through a short Vigreux column and infrared spectra obtained for each fraction.

Fractionation of the combined material boiling between 52° to 90° (8 mm.) through the Helipak column gave: (a) 19.6 g. of 2-isopropylpyrrole, b.p. 80° (25 mm.), $n^{25}\mathrm{D}$ 1.4900; and (b) 9.6 g. of 3-isopropylpyrrole, b.p. 90° (23 mm.), $n^{25}\mathrm{D}$ 1.4862. From the infrared spectra of the pure isomers, the amounts of pyrrole, 2- and 3-isopropylpyrroles and polyisopropylpyrroles were calculated for the original reaction product. The carboxanilides of the isopropylpyrroles could not be crystallized.

Reaction of *sec*-Butyl Bromide with Pyrrylmagnesium Bromide. Run 1.—One-half mole (68 g.) of *sec*-butyl bromide was added to a refluxing solution of 0.5 mole of pyrrylmagnesium bromide. The reaction mixture was allowed to cool to room temperature after the addition was complete. After 18 hours, titration of an aliquot indicated only 52% disappearance of the Grignard reagent; after 42 hours, 78%. The reaction mixture was hydrolyzed with dilute phosphoric acid after 65 hours when titration showed the reaction to be almost complete. The ether layers were dried and distilled as usual. Infrared spectra were obtained for each fraction.

Run 2.—The reaction was repeated using 1.5 moles of *sec*-butyl bromide and pyrrylmagnesium bromide. After refluxing for 54 hours, the reaction mixture was hydrolyzed and worked up as before. Redistillation of the fraction boiling from 60° (60 mm.) to 110° (20 mm.) through the Helipak column gave (a) 44.8 g. of 2-*sec*-butylpyrrole, b.p. 79° (20 mm.), $n^{25}\mathrm{D}$ 1.4897; and (b) 9.1 g. of 3-*sec*-butylpyrrole, b.p. 100° (36 mm.), $n^{25}\mathrm{D}$ 1.4870.

Reaction of *t*-Butyl Chloride and Pyrrylmagnesium Bromide.—Two moles (185 g.) of *t*-butyl chloride was added to a refluxing solution of 2 moles of pyrrylmagnesium bromide. Three hours later, titration of an aliquot indicated that the reaction was complete. The reaction mixture was worked up as usual, and the product vacuum distilled through a short Vigreux column. Infrared spectra were obtained for each fraction.

The material boiling from 55° (13 mm.) to 83° (3 mm.) was fractionated using the Helipak column. The pure isomeric *t*-butylpyrroles were low-melting solids (*ca.* 45°). 2-*t*-Butylpyrrole boiled at 89° (30 mm.) (11.27% N), while 3-*t*-butylpyrrole boiled at 94° (30 mm.) (11.55% N); 2-*t*-butylpyrrole carboxanilide, m.p. 137–139°. A crystalline derivative could not be prepared from 3-*t*-butylpyrrole.

Reaction of Acetyl Chloride with Pyrrylmagnesium Bromide.—Thirty minutes after the addition of 78.5 g. (1 mole) of acetyl chloride to a refluxing solution of 1 mole of pyrrylmagnesium bromide, titration of an aliquot showed the reaction to be complete. The reaction mixture was hydrolyzed and worked up as before. After removal of the ether, the product was steam distilled. The residue from the steam distillation was extracted with ether and the ether solution evaporated. The infrared spectra of both the material which steam distilled and that extracted from the residue were identical.

Reaction of Ethyl Acetate with Pyrrylmagnesium Bromide.—One-quarter mole (22 g.) of ethyl acetate was added to 0.25 mole of pyrrylmagnesium bromide. After 30 minutes, the reaction mixture was hydrolyzed and worked up as before. After removing the ether by distillation, the residue crystallized. The infrared spectra of this material was identical with that obtained from the product of the reaction with acetyl chloride.

2-Acetylpyrrole.—Following the procedure of Ciamician.[17] 2-acetylpyrrole was prepared by the reaction of pyrrole and acetic anhydride. The infrared spectrum of the 2-acetylpyrrole was identical with that of the products obtained from the reaction of acetyl chloride and ethyl acetate with pyrrylmagnesium bromide.

Reaction of *n*-Propyl Propionate with Pyrrylmagnesium Bromide.—One-half mole (52 g.) of *n*-propyl propionate was added to 0.5 mole of pyrrylmagnesium bromide and refluxed 30 minutes. The reaction mixture was worked up as usual. After removal of the ether by distillation, the residue crystallized.

Twelve grams of the 2-propionylpyrrole was refluxed 1 hour with 12 g. of potassium hydroxide, 10 ml. of 85% hydrazine hydrate and 100 ml. of triethylene glycol. After removal of the water by distillation, the reaction mixture was refluxed an additional 4 hours at 175°. The product was vacuum distilled and a fraction collected at 80° (20 mm.), $n^{25}\mathrm{D}$ 1.4900. The infrared spectrum of this material was identical with that of 2-*n*-propylpyrrole prepared by the hydrogenation of 2-allylpyrrole.

2-Methylpyrrole.—Following the procedure of Nenitzescu and Solomonica,[13] 168 g. (2.5 moles) of pyrrole and 5.4 g. of bronze powder were refluxed under a nitrogen atmosphere while 134 g. (1.2 moles) of ethyl diazoacetate was slowly added. After refluxing an additional half-hour, the reaction mixture was filtered and distilled under reduced pressure. The fraction boiling at 125° (10 mm.) (70.15 g.) was distilled through a Podbielniak Mini-Cal column. The material boiling at 122° (12 mm.), $n^{25}\mathrm{D}$ 1.4933, was pure ethyl 2-pyrrylacetate.

A solution of 5.6 g. of ethyl 2-pyrrylacetate in 4.6 ml. of ethanol was refluxed 5 minutes with 9.2 g. of 1:1 aqueous potassium hydroxide solution. After diluting with an equal volume of water the *p*H was adjusted to 2.0 with hydrochloric acid and the solution extracted five times with ether. The ether solution was dried and the ether removed by distillation. The residue was distilled at atmospheric pressure. A small fraction (*ca.* 1 ml.) was collected at 140°, n^{25}_D 1.5000.

Reaction of 2-Methylfuran with Ammonia.—Ammonia gas was bubbled through 2-methylfuran (du Pont) and the vapor passed through a 22 × 600 mm. Pyrex tube packed with 4–8 mesh alumina. The tube was heated to 420–430° in a resistance combustion furnace. The exit vapors were condensed in a water-cooled spiral condenser and formed two layers. The lower water layer was extracted with ether and the extract was combined with the upper layer. After drying the ether solution, the ether was removed by distillation and the green residue was distilled under reduced pressure. The infrared spectrum of the distillate which was collected below 60° (30 mm.) showed the presence of pyrrole and 3-methylpyrrole in addition to 2-methylpyrrole.

Reaction of 2,5-Dimethoxytetrahydro-2-methylfuran with Ammonia.—Ammonia was bubbled through boiling 2,5-dimethoxytetrahydro-2-methylfuran (obtained from Dr. N. Elming) and the vapors passed through a 14 × 300 mm. Pyrex tube heated to 250°. The exit vapors were condensed in a trap cooled in Dry Ice. After allowing the ammonia to evaporate, the residue was vacuum distilled. The infrared spectrum of the material collected at 80–82° (72 mm.) showed it to be pure 2-methylpyrrole.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PENNA.]

The Stereochemistry of the Alkylation of Pyrrylmagnesium Bromide

BY P. S. SKELL AND G. P. BEAN

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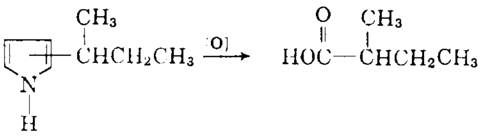
Alkylation of pyrrylmagnesium bromide with (−)-2-bromobutane gave optically active 2- and 3-*sec*-butylpyrroles. Oxidation of the pyrroles to (+)-2-methylbutyric acid indicated that the alkylation at both the 2- and 3-positions had proceeded with complete inversion of configuration.

In the previous paper[1] it was shown that the alkylation of pyrrylmagnesium halides in every case produced both the 2- and 3-alkylpyrroles in addition to pyrrole and polyalkylpyrroles. Also the nature of the alkyl halide appeared to have little effect on the position of substitution, as the ratio of 2- to 3-substitution changed only by a factor of 2 within the range of halides studied.

Since information about the steric course of the alkylation of pyrrylmagnesium halides is essential for understanding the mechanism of this substitution reaction, the alkylation with optically active 2-bromobutane was studied. No optically active alkylpyrroles have been reported; therefore the alkylation of pyrrylmagnesium bromide with an optically active halide would only indicate whether or not complete racemization had occurred unless the configuration and optical purity of alkylpyrroles can be related to a compound of known configuration and optical purity. Fortunately, the oxidation of alkylpyrroles with cold sodium permanganate produces the corresponding carboxylic acids. Therefore in the sequence PyMgBr + R*X → R*Py → R*COOH the configuration of the asymmetric carbon atom is affected only in the alkylation step.



The alkylation of pyrrylmagnesium bromide with (−)-2-bromobutane gave optically active 2- and 3-*sec*-butylpyrrole. These isomeric pyrroles were separated and oxidized to the (+)-2-methylbutyric acid (see Chart I). Since the optical purity of the two acids were identical, it follows that the steric course in both the 2- and 3-positions must be identical.

The relation of the configuration of the alkyl halide and the acid has been determined by Kenyon, Phillips and co-workers[2] (Chart II). Displacement of the tosyl group of the tosyl ester of (+)-2-butanol by cyanide ion and subsequent hydrolysis gave (−)-2-methylbutyric acid, which is a reaction which proceeds with inversion of configuration. Since 2-bromobutane and 2-butanol of the same configuration have the same sign of rotation,[3] it follows that in the alkylation of pyrrylmagnesium bromide with (−)-2-bromobutane the configuration of the asymmetric carbon must have been inverted.

CHART I

ALKYLATION OF PYRRYLMAGNESIUM BROMIDE WITH (−)-2-BROMOBUTANE

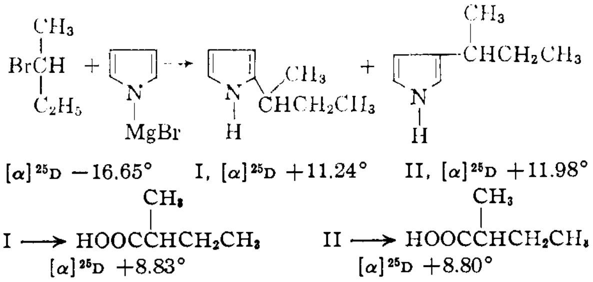
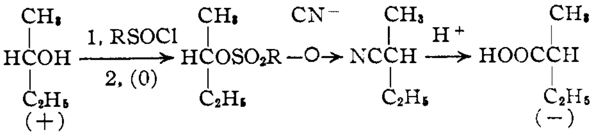


CHART II

STEREOCHEMICAL RELATIONSHIP OF 2-BUTANOL AND 2-METHYLBUTYRIC ACID



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