Alkylation Reactions of the Pyrrole Grignard Reagent[1a]

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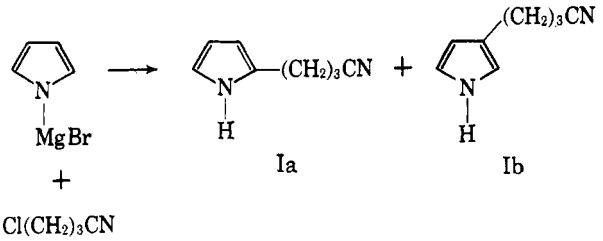
Pyrrolylmagnesium bromide and chloride react with 4-chlorobutanenitrile to yield a mixture of 2- and 3-(3-cyanopropyl)pyrrole, with the former predominant, and not 2-pyrrol-2-yl-2-pyrroline as reported in the literature. The isomer distribution is similar to that obtained in the reaction of pyrrolylmagnesium chloride with butyl chloride, heptyl chloride, and 1-chloro-4-methoxybutane. The constitution of pyrrolylmagnesium chloride in tetrahydrofuran is the same as in ethyl ether. In the alkylation with 4-chlorobutanenitrile initial complexing of the Grignard reagent with an unshared electron pair of the nitrile group occurs. Isomeric 1-, 2-, and 3-alkylpyrroles and those alkyl-substituted derivatives examined can be distinguished by their infrared absorption in the in-plane deformation region.

Pursuant to the synthesis of 2,2′-bipyrroles[2-6] it was of interest to attempt the synthesis of the parent unsubstituted bipyrrole by the dehydrogenation of the compound reported[7] as 2-pyrrol-2-yl-2-pyrroline, which was synthesized from the reaction of pyrrolylmagnesium bromide with 4-chlorobutanenitrile. Since the earlier report describing this synthesis, a number of studies[8-15] have established that the isomeric 1-pyrroline is actually to be expected. As a consequence of our examination of the pyrrole Grignard reagent–halonitrile product and the variety of observations recorded in the literature[14,16-21] for related studies we have been led to initiate an extensive investigation. In this first paper some features of the study of the reaction of the pyrrole Grignard reagent with 4-chlorobutanenitrile and associated results are described.

Results and Discussion

Product from Pyrrole Grignard Reagent and 4-Chlorobutanenitrile.—Attempts on our part to dehydrogenate this product (I), which was obtained as an oil, by heating with platinum on charcoal[22] were unsuccessful as were those with the formyl derivative (II) obtained from I *via* the Vilsmeier–Haack reaction.[23] Direct comparison of the oil (I) from the Grignard reaction with crystalline 2-pyrrol-2-yl-2-pyrroline (III), derived from the dehydrogenation of 2-pyrrol-2-ylpyrrolidine (IV), revealed that the two are indeed different. Further examination of I showed that it gives a positive Ehrlich's test for a pyrrole[24] and its infrared absorption spectrum exhibits a sharp nitrile band[25] at 4.49 μ. From the alkaline hydrolysis of I an acid was derived having the correct equivalent weight for a pyrrolylbutanoic acid (V), which was converted to a methyl ester (VI) by reaction with diazomethane. Oxidation of I gave maleimide, establishing the side chain in the 2-position. Product I must therefore be entirely, or chiefly, 2-(3-cyanopyropyl)pyrrole.

A careful gas–liquid chromatographic analysis of the pyrrole Grignard–4-chlorobutanenitrile reaction product revealed that, although the major product is 2-(3-cyanopropyl)pyrrole (Ia), it is accompanied by a second compound shown to be the isomeric 3-(3-cyanopropyl)pyrrole (Ib) (ratio 4.8:1). The identification



of the latter rests upon its infrared absorption spectrum (pyrrole NH, 2.98; pyrrole CH, 3.23; alkyl CH, 3.44 and 3.53; and C≡N, 4.46 μ), which is very much like that of the 2-isomer, and elemental analysis of the isomeric pair. Derivative II was isolated as a sharply melting solid. From the isomeric distribution in I and the expected position of formylation of Ia, II is 2-formyl-5-(3-cyanopropyl)pyrrole. No effort was made to isolate a pure compound from V and it most likely represents a mixture of 4-pyrrol-2-ylbutanoic acid and 4-pyrrol-3-ylbutanoic acid, with the former predominant. The methyl ester VI was isolated as a single fraction from a gas–liquid chromatogram. Its infrared spectrum (Table I) confirms its identity as methyl 4-pyrrol-2-ylbutanoate, the expected major product from V. The zinc and hydrochloric acid re-

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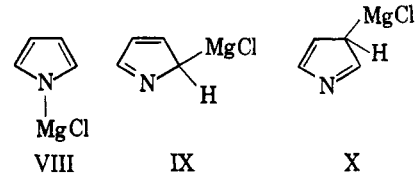
duction of I is reported[7] as yielding 2-pyrrol-2-ylpyrrolidine. Repetition of this work gave what is apparently the same amine (VII) as described earlier. However, this product is an oil, whereas the aforementioned pyrrolidine IV is a solid at room temperature, m.p. 86.3–87.8°.[13] From the method of synthesis, reported analysis and properties, and the observation that the reduction product gives a positive carbylamine test, this product must in fact be entirely 2-(4-aminobutyl)pyrrole or a mixture of mainly this compound and some 3-(4-aminobutyl)pyrrole.

It is of interest that some time ago Cloke aud coworkers[8] postulated the possible formation of a compound of the type $R(CH_2)_3CN$ from the reaction of a Grignard reagent with 4-chlorobutanenitrile, but lacked experimental support. Furthermore, these results constitute an important exception to one of the most widely accepted methods[14] for the synthesis of 2-R-1-pyrrolines in which it has been considered heretofore that apparently any Grignard reagent can be used.[16] It should be noted that the reaction of equivalent quantities of 2,3,4-trimethylpyrrolylmagnesium iodide and 4-chlorobutanenitrile yields 2-(3,4,5-trimethylpyrrol-2-yl)-1-pyrroline, whereas with an excess of the halonitrile 2,3,4-trimethyl-2(3-cyanopropyl)-2H-pyrrolenine is formed.[17] In the present study it was found that alkylation results from the reaction of equivalent quantities of pyrrolylmagnesium chloride and 4-chlorobutanenitrile or with the halonitrile in excess of the bromo Grignard reagent.

Constitution of the Pyrrole Grignard Reagent.—Fundamental for our purpose is the constitution of the pyrrole Grignard reagent.[26,27] After the completion of an extensive study of the matter a communication[28] appeared in which the same conclusion reached by us is described. In the reported work, ethyl ether was used as a solvent, whereas tetrahydrofuran was utilized by us. The influence of the solvent on the nature of the Grignard reagent has been described recently.[29] Other features of our study are also distinctive and we wish to report briefly thereon. In this work, the preparation of the Grignard reagent and all other operations were carried out in an atmosphere of argon.[30] Tetrahydrofuran was chosen as a solvent because of the greater difficulty in handling ethyl ether and obtaining reliable concentrations. It is a matter of some interest that, whereas pyrrolylmagnesium chloride is soluble in both tetrahydrofuran and ethyl ether, pyrrolylmagnesium bromide is not readily soluble in ether; the solubility of the bromide in tetrahydrofuran was not examined. However, solutions of pyrrolylmagnesium chloride (0.105 and 0.192 *F*) in tetrahydrofuran, prepared from the reaction of pyrrole with excess filtered butylmagnesium chloride (mole ratio of pyrrole–BuMgCl, 0.259:1 and 0.481:1, respectively), exhibit no NH vibration as shown distinctly by pyrrole at 2.98 μ. The n.m.r. spectra of these show broad signals due to the 2 and 3 ring protons at δ = 6.54–6.55 and 5.82 p.p.m., respectively. The multiplicity of these could not be clearly decided, but those of a more concentrated solution (0.554 *F*, pyrrole–BuMgCl, 0.915:1) at 6.56 and 5.82 p.p.m. are clearly triplets (J = 1.6 c.p.s.). The ratio of the integrated intensities of the two signals is 1:1 and the system is therefore of the A_2X_2 type.[31] The signals due to the 2- and 3-protons of pyrrole in tetrahydrofuran are quartets centered at 6.52 and 5.92 p.p.m. (J = 2 c.p.s.) similar to the spectrum found in acetone and carbon tetrachloride.[31] The infrared and proton magnetic resonance spectra, therefore, support constitution VIII for the structure of pyrrolylmagnesium chloride in tetrahydrofuran as well as in ether.[28] The possibility of a rapid equilibrium involving IX, X, and the two



VIII IX X

alternate equivalent structures might also conceivably be consistent with the spectral data depending upon the rates of change and the nuclear spin transition times. However, this can be expunged from further consideration by the observed absence of the expected characteristic azomethine band described[14,15,32] as occurring at 6.00–6.15 μ. Bands in this region are reported[17] in the spectrum of 2,3,4-trimethyl-2-(3-cyanopropyl)-2H-pyrrolenine and 2,3,4,5-tetramethyl-2-(3-cyanopropyl)-2H-pyrrolenine, which are structurally analogous to IX. From the magnitude of the difference in electronegativity[33] of the two elements, an ionic N–Mg bond is favored with the pyrrolylmagnesium halide consequently an associated ion pair, Py^-Mg^+X, but additional supporting evidence must be obtained because of the possible variation in the electronegativity arising from the nature of other atoms bonded to a given atom and the state of hybridization of the latter. Hence, an essentially covalent bond cannot be dismissed.

The Alkylation Reaction.—Regardless of the degree of its ionic or covalent character,[34,35] the nitrogen atom of the leastwise potential tridentate pyrrolyl anion of the Grignard reagent is prevented from participating as a nucleophilic point of attack in displacement reactions with alkyl halides[36–38] as seen in the reported absence of 1-alkylation. Whereas carbon alkylation is the rule for the pyrrole Grignard reagent, nitrogen alkylation is favored for sodium and potassium derivatives of pyrrole.[34] An exception to this generalization is the formation of 2-allylpyrrole from the alkylation

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(37) P. S. Skell and G. P. Bean, *J. Am. Chem. Soc.*, **84**, 4655 (1962).

(38) *Cf.* N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963), and preceding papers.

of both pyrrolylmagnesium bromide and pyrrolylpotassium.[39] It should also be noted that, although the pyrrole Grignard reagent can be alkylated with 4-chlorobutanenitrile, attempts to synthesize 1-(3-cyanopropyl)pyrrole from pyrrolylpotassium and 4-bromobutanenitrile are described as unsuccessful.[40] Skell and Bean[37] have recently reported the formation of 2- and 3-alkylpyrroles in a ratio of 1.5–3:1, with the former the major product, from the alkylation of pyrrolylmagnesium bromide with several alkyl halides and methyl *p*-toluenesulfonate in ethyl ether. For comparative purposes in our own investigation, pyrrolylmagnesium chloride was alkylated with butyl and heptyl chlorides under the same conditions used in the alkylation with 4-chlorobutanenitrile. With the first chloride, 2- and 3-butylpyrrole were the exclusive monosubstitution products and were formed in a ratio of 3.8–4.5:1 (13–14% conversion). A small amount of dibutylpyrrole was also isolated and must have resulted from alkylation of the butylpyrrole Grignard reagent, which in turn arose from an exchange reaction[34,37,41] involving butylpyrrole and unreacted pyrrolylmagnesium chloride. Heptyl chloride also yielded only 2- and 3-heptylpyrroles as the monoalkylation products. The ratio of 2- to 3-alkylation is 5.4:1 (15%). No heptene could be detected as would be expected if elimination were to accompany substitution.[42] The analyses for isomer ratios were by means of gas–liquid chromatography. The assignment of structure of the monoalkylpyrroles rests upon the established preference for substitution at the 2-position in this type of reaction,[37] elemental analyses, and their infrared spectra (Table I) which includes NH absorption bands in the 2.98–3.01-μ region. Similarly, the dibutylpyrrole is probably the 2,5-isomer. In additional support of this assignment, it shows a distinct band at 9.68 μ similar to that found in the spectrum of 2,5-dimethylpyrrole at 9.63 μ. In contrast, 2-methyl-3-pentylpyrrole[43] exhibits bands at 8.98 and 9.35 μ and 2,4-dimethylpyrrole shows a band at 8.95 μ.

Thermal rearrangement of an initially formed 1-alkylpyrrole to a mixture of the 2- and 3-alkylpyrroles is unlikely because of the temperature reported[44,45] for such isomerizations. Also, in the present study it will be noted that the temperature of refluxing pyrrole, which was employed in the preparation of 1-butylpyrrole, is higher than that of refluxing ether, which was used in the Grignard alkylations. Moreover, any catalytic effect[46] was eliminated by refluxing an ether solution of pyrrolylmagnesium chloride with pure 1-butylpyrrole for a period close to that used in the alkylation. Careful g.l.c. analysis revealed the major components after hydrolysis to be pyrrole and 1-butylpyrrole. An insignificant amount of 2-butylpyrrole (1 part/237 parts of 1-butylpyrrole) was detectable, but it seems likely that this may have resulted from unchanged butyl chloride used in the process of preparation of pyrrolylmagnesium chloride. An extensive study of the alkylation of lithium, sodium, potassium, and dimethylanilinium salts of pyrrole with allylic halides and different solvents shows[32] that nitrogen alkylation increases with the solvation power of the medium and decreases with coordinating ability of the cation, effects explicable on the basis of increasing dissociation of the pyrrolyl–metal ion pair favoring alkylation at the 1-position. The transition state postulated can be extended for the Grignard derivative with simple alkyl halides, but the initial formation of a complex $Py^{-}RXMg^{+}X$ (ignoring representation of solvation[47]) with possible consequent important polarization of the RX bond must also be considered.[37] However, the position of alkylation is not determined by the location of the MgX moiety of the pyrrole Grignard reagent[26,27,30]; rather it is decided by the availability of an electron pair[48,49] and proceeds through a pyrrolenine.[34] The formation of 2H-pyrrolenines in the alkylation[17,50] of the pyrrole Grignard reagent results from the absence of a proton on the ring at the point of attack, which is required in the otherwise subsequent rearrangement to a pyrrole. The formation of 2,5-dibutylpyrrole in this study is an example of reaction at the unsubstituted 5-position rather than at the 2-position, which is already alkylated.[17,50,51]

Herz[52] has found that magnesium bromide catalyzes the acylation of 1-methylpyrrole with acetyl chloride. This appears to be an unlikely explanation for alkylation reactions, for, upon refluxing mixtures of 4-chlorobutanenitrile, pyrrole, and magnesium bromide etherate (10:10:1 and 9:10:11) in ether for several hours, only the starting chloronitrile and pyrrole could be detected on a gas–liquid chromatogram.

Complexes of Grignard reagents and nitriles have been described[53,54] and Swain has proposed the rapid reversible formation of such a complex to explain the mechanism of addition of Grignard reagents to nitriles.[55,56] Upon adding 4-chlorobutanenitrile to a solution of pyrrolylmagnesium chloride a precipitate is formed at once. This is different from that formed with butyl chloride. As in the reaction with pyrrolylmagnesium bromide, where the formation of an immediate precipitate was not investigated, 2- and 3-(3-cyanopropyl)pyrrole are formed. The ratio of 2- to 3-isomer found is 4.4:1 (12%). The reaction of butyl chloride, 4-chlorobutanenitrile, and pyrrole in equimolar amounts yielded only 2- and 3-(3-cyano-

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(49) The Grignard derivative of 2,4-dimethyl-3-ethoxycarbonylpyrrole, wherein an electron-attracting group is directly joined to the ring, is not alkylated under the same conditions effective with the Grignard derivative of alkylpyrroles.[50]

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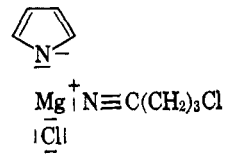
(56) Also see (a) S. J. Storfer and E. I. Becker, Abstracts, Division of Organic Chemistry, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1960, paper 148, p. 80P; (b) E. I. Becker, *Trans. N. Y. Acad. Sci.*, **25**, 513 (1963); (c) J. D. Citroen and E. I. Becker, *Can. J. Chem.*, **41**, 1260 (1963).

propyl)pyrroles (3.3:1, 10%). Furthermore, when equimolar quantities of butyl chloride, butanenitrile, and pyrrolylmagnesium chloride were allowed to react for the same period of time as in the reaction with butyl chloride alone, only a very low conversion (1.4%) to a mixture of 2- and 3-butylpyrrole (3.1:1) was observed. From these results we conclude that the reaction with the halonitrile proceeds through a complex, such as XI. The lack of a reaction with butyl



XI

chloride in the competition experiment and the slight extent of reaction in the presence of butanenitrile support this view.[57] The complex is shown as involving the p-electrons of nitrogen although a nitrile π-bond may be the participant.

In a single alkylation of pyrrolylmagnesium bromide with 4-methoxy-1-chlorobutane, which contains the potential complexing oxygen atom, a mixture of 2- and 3-(4-methoxybutyl)pyrrole (3.0:1) was obtained in a yield of 28%. Additional work on this and other phases of the problem is in progress.

Rules for Identification of Isomeric Monoalkylpyrroles and Derivatives.—Absorption in the 12–15-μ region and n.m.r. have both been employed in distinguishing between 2- and 3-alkylpyrroles.[37] The complete infrared absorption spectra of 2- and 3-methylpyrroles have been reported[58] and the absorption bands in the spectra of the two at 9.75 and 9.38 μ, respectively, have been used in the analysis of their mixtures in carbon tetrachloride and isooctane solutions.[44,59] We find that 1-, 2-, and 3-alkylpyrroles and several substituted alkyl derivatives including Ia and Ib can be distinguished with remarkable ease by examination of the strong–medium intensity bands occurring in the spectra of these in the region expected for in-plane deformations[25,59b] of the ring hydrogens. As seen in Table I, the 1-, 2-, and 3-isomers typically show bands, two (average 9.16, 9.40), three (8.95, 9.13, 9.77), and one (9.38 μ), respectively, in the region described in Table I.[60] The absence of an NH band in the 3-μ region of the spectra of 1-substituted pyrroles is, of course, an additional diagnostic feature. As expected, this band is present in the spectrum of all the 2- and 3-isomers described herein.

A second distinguishing property of the isomeric pyrroles investigated by us is their behavior in gas–liquid chromatography. The 2-isomer invariably exhibits a shorter retention time than shown by the 3-isomer using silicone and Carbowax columns in different cases. We attribute this to steric interference in the sorption–desorption process involving the pyrrole NH. Upon comparison of the three monobutylpyrroles it is found that 1-butylpyrrole, lacking an NH, shows the shortest retention time, as expected. It is also shorter than that of pyrrole.

TABLE I

INFRARED ABSORPTION BANDS FOR SUBSTITUTED PYRROLES[a]

Substituent	ca. 8.9–9.8-μ region				
1-CH_3		9.16	9.42	9.57	
1-C_2H_5		9.15	9.44		
1-$CH_3(CH_2)_3$		9.18	9.41		
1-$C_6H_5CH_2$		9.16	9.36		9.69
2-CH_3[b]	8.94	9.14			9.75
2-C_2H_5	8.95	9.12		9.55	9.79
2-$CH_3(CH_2)_3$	8.94	9.13	9.34[c]		9.76
2-$N\equiv C(CH_2)_3$	8.92	9.11			9.74
2-$CH_3O_2C(CH_2)_3$	9.01	9.19			9.83
2-$CH_3O(CH_2)_4$	8.99[d]				9.77
2-$CH_3(CH_2)_6$	8.93	9.11			9.74
3-CH_3[b]			9.42		
3-$CH_3(CH_2)_3$			9.40		
3-$N\equiv C(CH_2)_3$			9.37		
3-$CH_3O(CH_2)_4$			9.34[e]		
3-$CH_3(CH_2)_6$			9.39[e]		

[a] Neat. [b] See ref. 58. [c] Weak–medium. [d] Typical ether band. [e] Deduced from the spectrum of a mixture of the 2- and 3-isomers.

Experimental

Melting points and boiling points are uncorrected. The former were determined with a Fisher-Johns or Kofler apparatus. Analyses were by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England, and the Berkeley Analytical Laboratory, Berkeley, Calif. Proton magnetic resonance spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra of the pyrrole Grignard solutions were obtained with a Beckman IR-4 spectrophotometer equipped with sodium chloride optics; the spectra of the pyrroles, with the Beckman IR-4 or IR-5 instrument. Gas–liquid chromatography was performed with a Wilkens Instrument Co. Aerograph, Model A-100-C, using in all experiments a helium flow rate of 40 ml./min. The column, supplied by the Wilkens Instrument Co., and temperature for each use is described in the text. The g.l.c. recordings were made on a Varian G-10 graphic recorder.

Pyrrole Grignard–4-Chlorobutanenitrile Condensation Product.—This was obtained as a very pale yellow (almost colorless) oil, b.p. 182–183° (7–8 mm.), lit.[7] b.p. 144–145° (5 mm.), from pyrrolylmagnesium bromide, derived from pyrrole and ethylmagnesium bromide, and 4-chlorobutanenitrile in exactly the manner described by Craig.[7] In this procedure the ratio of 4-chlorobutanenitrile to pyrrolylmagnesium bromide is 1.6:1.

A. Hydrolysis.—The condensation product, 5.0 g., was hydrolyzed by heating on a steam bath for 1 day with 53 ml. of 2.2 *N* sodium hydroxide in 80% ethanol. Evaporation, acidification, and isolation of the acidic fraction gave a reddish golden brown liquid, 3.96 g.

Anal. Calcd. for $C_8H_{11}NO_2$: neut. equiv., 153. Found: neut. equiv., 154, 157.

Distillation of a portion of the acid was apparently accompanied by decomposition. The distillate and a portion of the acid from the hydrolysis were treated separately with diazomethane.[61] The combined methylation products were distilled giving a golden liquid, b.p. 105–113° (2–3 mm.). The analytical sample obtained by g.l.c. was a pale yellow oil showing an average residence time of 6.7 min. (209°, Silicone GE SF 96 column, 5 ft. × 0.25 in.).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.22; H, 8.19; N, 8.42.

(57) An alternate possible explanation is that these results reflect the solubility of butyl chloride in the particular complex.

(58) R. E. Lancaster and C. A. VanderWerf, *J. Org. Chem.*, **23**, 1208 (1958).

(59) (a) For a review of a number of physical properties of methylpyrroles, see R. L. Hinman and S. Theodoropulos, *ibid.*, **28**, 3052 (1963). (b) A detailed study of the infrared spectra of 2-substituted pyrroles has also been reported: R. A. Jones, *Australian J. Chem.*, **16**, 93 (1963).

(60) The stray band of the 1-methyl isomer at 9.57 μ and of the 2-ethyl isomer at 9.55 μ in no way interferes with distinguishing among the three isomers in each case. The broad ether band of 2-(4-methoxybutyl)pyrrole militates against recognition of the two shorter wave-length bands, but the band at the higher wave length is still readily recognizable.

(61) "Preparation of Diazomethane from Diazald," Aldrich Chemical Co., Inc., Milwaukee, Wis.

The methyl ester gives a positive Ehrlich's test and its infrared spectrum (thin film) shows bands at 3.05 (N—H), 3.49 and 3.60 (C—H), and 5.87 μ (C=O).

B. Chromic Acid Oxidation.—The condensation product, 4.0 g., in 50 ml. of glacial acetic acid was cooled in an ice bath and the solution from 8.95 g. of chromic anhydride and 20 ml. of water was added in portions with mixing. After the vigorous reaction had subsided, the resulting mixture was heated at about 60° for 10 hr. Most of the acetic acid was removed at reduced pressure, water was added, and the mixture was warmed to aid in dissolving the residue. After cooling, sodium carbonate was added until gas was no longer evolved upon further addition and the mixture was alkaline to litmus. The resulting mixture was extracted by shaking overnight with ether three times. After evaporating the ether from the combined extracts, a red oil remained. This was dissolved in a little ether and acetone, the solution was dried with magnesium sulfate, the solvents were evaporated from the dried solution, and the residual reddish golden brown oil, 0.63 g., was heated in a sublimation apparatus. An oil and some solid were collected at 0.73 mm. while the bath temperature was raised to 125°. The mixture was pressed between filter papers to remove the oil and a small quantity of cream-colored solid remained. The infrared spectrum of the solid in chloroform is identical with that of maleimide. When heated, the bulk melted in the range 84.7–91.1°, with some sublimation and preliminary melting as the temperature was raised to this range.

C. Formylation.—Using the method of Silverstein, *et al.*,[23] 2.68 g. of the Grignard–halonitrile condensation product, 3.4 g. of phosphorous oxychloride, and 1.6 g. of N,N-dimethylformamide in 4 ml. of ethylene chloride, there was obtained 1.10 g. (58%) of the aldehyde (II) as a yellow solid after crystallization from aqueous ethanol. A sample recrystallized from a mixture of ether and alcohol yielded white crystals, m.p. 61.5°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.68; H, 6.13; N, 17.45.

D. Reduction.—The product from the Grignard reaction was reduced with zinc and hydrochloric acid as described by Craig.[7] The resulting amine (VII) was obtained as a colorless liquid, b.p. 98.5–101.5° (0.50–0.52 mm.). The phenylthiourea derivative melted at 155.4–156.0° (lit.[7] m.p. 151°) after crystallization from ethyl alcohol.

Gas–liquid chromatographic analysis (10 ft. × 0.25 in. silicone column, 215°) of the product, b.p. 129–135° (0.45–0.90 mm.), from a second condensation of pyrrolylmagnesium bromide and 4-chlorobutanenitrile showed the presence of a major component with a residence time of 7 min. and a second component with a residence time of 8 min. The ratio of the two components was 4.8:1 Repeated g.l.c. separations of samples of the product from the Grignard reaction yielded pure 2-(3-cyanopropyl)pyrrole (Ia), the main component.

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.25; H, 7.82; N, 20.80.

The pure minor component, 3-(3-cyanopropyl)pyrrole (Ib), was also isolated in a quantity sufficient for determination of its infrared absorption spectrum and a mixture of the isomers (Ia–Ib, 5.6:1, g.l.c.), b.p. 120–121° (0.48–0.50 mm.), was analyzed.

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.24; H, 7.73; N, 20.94.

The condensation of pyrrolylmagnesium chloride with 4-chlorobutanenitrile was carried out in a manner like that described[7] for pyrrolylmagnesium bromide. The Grignard reagent was prepared from the reaction of 26.8 g. (0.399 mole) of pyrrole with 184 ml. of 0.218 *N* (0.401 equiv.) butylmagnesium chloride diluted with 500 ml. of ether. During the addition of the chloronitrile, 40.4 g. (0.390 mole), a fraction separated from the ether solution. This became increasingly viscous until stirring was almost impossible. The reaction mixture was stirred and refluxed for a period of 4 hr. and ether was added during this period to replace that lost through the condenser. The reaction mixture was hydrolyzed with saturated ammonium chloride solution, the ether layer was dried with sodium sulfate, and the ether was evaporated. The product was distilled under vacuum and the different fractions were examined by g.l.c. for the isomeric 3-cyanopropylpyrroles. The total yield of the isomers was calculated to be 6.56 g. (12% conversion) and the ratio of 2- to 3-alkylation product, 4.4:1.

Pyrrolylmagnesium Chloride in Tetrahydrofuran.—Butylmagnesium chloride was prepared from the reaction of equivalent quantities of butyl chloride and magnesium turnings in tetrahydrofuran in an argon atmosphere. After standing overnight, the clear solution was filtered (closed system) through a plug of glass wool into a storage flask having a rubber stopple for sample removal. The concentration of the active Grignard reagent was determined by decomposing aliquots in excess aqueous sulfuric acid and back titrating with sodium hydroxide to the phenolphthalein end point.

The exchange reaction was carried out under argon in closed reaction vessels made from 50-ml. graduated cylinders having at the top a side arm joined to a glass stopcock to which a balloon was attached for equilizing the pressure. In one experiment 9.89 mequiv. of butylmagnesium chloride and 0.172 g. (2.56 mmoles) of pyrrole were allowed to react. After the reaction was complete and the mixture had cooled to room temperature, the gold-colored solution occupied a volume of 24.5 ml. In a second experiment 11.03 mequiv. of butylmagnesium chloride and 0.3561 g. (5.31 mmoles) of pyrrole were used. The final volume was 27.6 ml. In a third experiment aliquots of the mixture from the reaction of butylmagnesium chloride and pyrrole were analyzed. The total active Grignard concentration was found to be 0.594 *N* by titration as above. The pyrrole concentration was shown to be 0.544 *M* by gas–liquid chromatographic analysis (5 ft. × 0.25 in. Apiezon column, 106°) of the solution remaining after hydrolysis of the Grignard mixture as described in the following.

In the g.l.c. analysis for pyrrole, the sample was hydrolyzed with a fixed small volume of dilute, aqueous sulfuric acid and the mixture was saturated with magnesium sulfate. The tetrahydrofuran layer that separated was removed and the aqueous layer was extracted with butyl ether. The organic phases were combined, dried with magnesium sulfate, and filtered. The magnesium sulfate was washed with a small amount of butyl ether, the filtrates were combined, the mixture was diluted to a fixed volume with more of the same solvent, and the resulting solution was analyzed. The procedure was standardized using known amounts of pyrrole in the entire process.

The transfer of samples for infrared and n.m.r. examinations were made in a plastic glove bag filled with argon.

Pyrrolylmagnesium Chloride with Butyl Chloride.—The butylmagnesium chloride was prepared as described above except that ethyl ether was used as the solvent. Pyrrolylmagnesium chloride was prepared from the alkylmagnesium chloride by the dropwise addition of 26.8 g. (0.399 mole) of pyrrole to a stirred solution prepared from 184 ml. of 2.18 *N* (0.401 equiv.) butylmagnesium chloride and 500 ml. of ether. After the reaction was evidently complete the mixture was stirred and refluxed for a short period and allowed to cool to room temperature. Butyl chloride, 37.0 g. (0.400 mole), was added dropwise to the pyrrolylmagnesium chloride solution during a short time and the mixture was stirred and refluxed for 4 hr. After hydrolysis with saturated aqueous ammonium chloride, the ether layer was dried with sodium sulfate and the ether was evaporated. Fractionation with a Piros–Glover spinning-band distillation unit yielded a number of fractions, which were analyzed by gas–liquid chromatography (10 ft. × 0.25 in. Carbowax 20M, 215°). The fraction boiling at 104–117° (11 mm.) showed the presence of four products having residence times of 8.6, 10.8, 14.8, and 16.3 min. Small quantities of the first three were isolated from repeated g.l.c. separations. The compound having a residence time of 8.6 min. gave a positive Ehrlich's test, showed an NH stretching vibration at 3.01 μ, and was identified as 2-butylpyrrole, $n^{25}D$ 1.4867 (lit.[38] $n^{28}D$ 1.4854).

Anal. Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.63. Found: C, 78.42; H, 10.48.

The compound having a residence time of 10.8 min. gave a positive Ehrlich's test, had an NH stretching vibration at 2.98 μ, and was 3-butylpyrrole.

Anal. Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.63. Found: C, 78.39; H, 10.60.

The compound with a residence time of 14.8 min. exhibited an NH vibration at 2.99 μ and was probably 2,5-dibutylpyrrole.

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.38; H, 11.81; N, 7.81. Found: C, 80.58; H, 11.93; N, 7.70.

The compound identified with a residence time of 16.3 min., presumably a polybutylpyrrole, was present in small concentration and was not investigated further.

The different fractions from the fractional distillation were analyzed for mono- and dibutylpyrroles by means of g.l.c. using calibrations obtained with the pure compounds. From this,

the amount of 2-butylpyrrole obtained from the alkylation reaction was 5.19 g.; 3-butylpyrrole, 1.35 g.; and dibutylpyrrole, 1.94 g. The mole ratio of 2- to 3-butylpyrrole was 3.8:1; mono- to dibutylpyrrole, 4.9:1. The conversion to monobutylpyrrole was 13%; to dibutylpyrrole, 2.7%.

The alkylation experiment was repeated, working entirely in an atmosphere of argon. Butylmagnesium chloride, 300 ml. of 1.04 *N* solution (0.312 equiv.), diluted with 500 ml. of ether, 20.9 g. (0.312 mole) of pyrrole, and 28.9 g. (0.312 mole) of butyl chloride were used. After working up the reaction mixture and evaporating the ether, the remaining liquid was analyzed by g.l.c. The mixture contained pyrrole, butyl chloride, 4.43 g. of 2-butylpyrrole, 0.98 g. of 3-butylpyrrole, 0.67 g. of dibutylpyrrole, and a small amount of a fourth reaction product, as before. The ratio of 2- to 3-butylpyrrole was 4.5:1; mono- to dibutylpyrrole, 11.8:1. The conversion to monobutylpyrrole was 14%; to dibutylpyrrole, 1.2%.

Pyrrolylmagnesium Chloride with Heptyl Chloride.—A procedure like that with butyl chloride was employed and all operations were performed in an atmosphere of argon. Pyrrolylmagnesium chloride was prepared from 350 ml. of 1.14 *N* (0.399 equiv.) butylmagnesium chloride diluted with 500 ml. of ether and 26.8 g. (0.399 mole) of pyrrole. A 53.9-g. quantity (0.400 equiv.) of heptyl chloride was used. Distillation of the reaction mixture yielded pyrrole, heptyl chloride, and 9.9 g. (15% conversion) of a mixture of 2- and 3-heptylpyrrole in a ratio of 5.4:1 (Carbowax, 220°), b.p. 106–116° (3.5–6.0 mm.).

Pure 2-heptylpyrrole was isolated through gas–liquid chromatographic separation of the isomer mixture. The pure isomer showed a residence time of *ca.* 17 min. at 220° and an NH band at 2.99 μ. 3-Heptylpyrrole showed a residence time of 22 min. at 220°.

Anal. Calcd. for $C_{11}H_{19}N$: C, 79.95; H, 11.59; N, 8.47. Found: C, 79.77; H, 11.33; N, 8.63.

A redistilled mixture of the isomers, b.p. 81–82° (0.22–0.35 mm.), was analyzed. The infrared spectrum of the mixture was like that of pure 2-heptylpyrrole with the absorption due to the 3-isomer at 9.39 μ present in the spectrum of the mixture only.

Anal. Calcd. for $C_{11}H_{19}N$: C, 79.95; H, 11.59; N, 8.47. Found: C, 79.94; H, 11.56; N, 8.59.

Pyrrolylmagnesium Chloride with 4-Chlorobutanenitrile and Butyl Chloride.—The Grignard reagent was prepared from the reaction of 26.8 g. (0.399 mole) of pyrrole and 342 ml. of 1.17 *N* (0.400 eq.) of filtered butylmagnesium chloride diluted with 500 ml. of ether. To this there was added a mixture of 40.4 g. (0.390 mole) of 4-chlorobutanenitrile and 37.0 g. (0.399 mole) of butyl chloride. As with the chloronitrile alone, a white cloudiness appeared in the reaction mixture upon the addition of each drop of the halide mixture and a gummy mass separated from the ether solution. After the addition of the halides was complete, the mixture was stirred and refluxed for a total time of 4 hr. from the start of addition of the halides. The mixture was hydrolyzed as before and dried with magnesium sulfate. The ether was evaporated and the liquid boiling as high as 127° was removed. The undistilled residue was examined for the presence of butylpyrroles by means of a g.l.c. analysis (Carbowax, 215°). No butylpyrrole could be detected. The mixture was analyzed for 2- and 3-(3-cyanopropyl)pyrrole with a silicone column as described above. The yield of the isomers was 5.23 g. (10%); the ratio of 2- to 3-alkylation, 3.3:1.

Pyrrolylmagnesium Chloride with Butyl Chloride and Butanenitrile.—The pyrrole Grignard reagent was synthesized from 26.9 g. (0.401 mole) of pyrrole and 374 ml. of 1.07 *N* (0.400 mole) butylmagnesium chloride diluted with 500 ml. of ether. A mixture of 37.1 g. (0.401 mole) of butyl chloride and 27.7 g. (0.401 mole) of butanenitrile was added dropwise. The mixture was stirred and refluxed in the usual manner and worked up as described above. The liquid distilling up to 63° (43 mm.) was removed leaving 0.67 g. of undistilled residue. This was found to be a mixture of 2- and 3-butylpyrrole (1.4%) present in a ratio of 3.1:1 by g.l.c. analysis (Carbowax, 220°). The distillate showed no butylpyrroles upon g.l.c. analysis.

Pyrrolylmagnesium Bromide with 4-Methoxy-1-chlorobutane.—Pyrrolylmagnesium bromide was prepared from 10 g. (0.15 mole) of pyrrole and the Grignard solution resulting from the reaction of excess magnesium (3.9 g., 0.16 g.-atom) with 8.72 g. (0.08 mole) of ethyl bromide in 200 ml. of ethyl ether. To the resulting mixture there was added 15.9 g. (0.13 mole) of 4-methoxy-1-chlorobutane, b.p. 140–140.3°, in a dropwise fashion. After refluxing for 3.5 hr. the mixture was treated in the usual manner. The oil remaining after removal of the ether was distilled under vacuum and analyzed by g.l.c. (10-ft. silicone column, 213°). The various fractions showed two products, the major one having a residence time of 6.6 min.; the minor, 7.6 min. Repeated g.l.c. separations yielded pure 2-(4-methoxybutyl)pyrrole, the major product.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.42; H, 9.94; N, 9.26.

A redistilled sample of the isomeric pair, b.p. 163–164° (4.5 mm.), had an infrared spectrum like that of 2-(4-methoxybutyl)-pyrrole alone, except for a band at 9.34 μ due to the presence of 3-(4-methoxybutyl)pyrrole.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.56; H, 9.81; N, 9.22.

The calculated combined yield of the two isomers was 3.46 g. (28%) and the ratio of 2-substitution to 3-substitution was 3.0:1.

Attempted Magnesium Bromide Catalyzed Alkylation of Pyrrole.—A mixture of 10.31 g. (0.100 mole) of 4-chlorobutanenitrile and 6.71 g. (0.100 mole) of pyrrole, followed by a 5-ml. ether rinse, was added to a solution of magnesium bromide prepared[62] from 0.2453 g. (0.010 g.-atom) of magnesium and 0.52 ml. (0.010 mole) of bromine in *ca.* 35–40 ml. of anhydrous ethyl ether. The magnesium bromide solution was filtered through a plug of glass wool before use. The mixture was heated and refluxed for 3 hr., washed with water, and dried with sodium sulfate; the ether was evaporated. Upon examination of the remaining liquid by means of gas–liquid chromatography (5-ft. silicone column, 202°), pyrrole and 4-chlorobutanenitrile could be detected, but there was no evidence for 2- or 3-(3-cyanopropyl) pyrrole. The isomeric cyanopropylpyrrole mixture from the Grignard reaction was easily detected under the same conditions. The same results were obtained in a similar experiment using 4-chlorobutanenitrile, pyrrole, and magnesium bromide in a mole ratio of 9:10:11.

Attempted Isomerization of 1-Butylpyrrole.—Butylmagnesium chloride (0.963 *N*) was synthesized from 5.40 g. (0.222 g.-atom) of magnesium and 20.8 g. (0.225 mole) of butyl chloride in ethyl ether. The pyrrole Grignard reagent was prepared from the reaction of 1.5324 g. (22.8 mmoles) of pyrrole and 24.3 ml. (23.4 mequiv.) of butylmagnesium chloride diluted with 24.6 ml. of ether. Some white solid, thought to be magnesium chloride, precipitated during this operation as in the alkylation experiments. A 2.8435-g. sample (23.1 mmoles) of 1-butylpyrrole and 1 ml. of ether rinse was added, and the mixture was refluxed for 3 hr. and 50 min. under argon. After standing overnight, analysis of the solution showed active Grignard and total chloride (silver nitrate, dichlorofluoroscein) to be 0.446 *N* each. The reaction mixture remaining after removal of samples for analysis was worked up essentially as in the alkylation studies and analyzed by g.l.c. (Carbowax, 209°) after removal of the bulk of the ether.

2-Pyrrol-2-yl-2-pyrroline (III).—A 2.1:1 mixture by weight of 2-pyrrol-2-ylpyrrolidine (IV)[63] and sulfur was heated. Hydrogen sulfide evolution commenced at a bath temperature of 117° and heating was continued until the temperature reached 160°. The white crystals that sublimed from the heated mixture melted at 162–166°. In a similar experiment the black reaction mass was heated at 1.16 mm. and the sublimate was recrystallized from ethyl alcohol, m.p. 162.0–162.8° (lit.[5] m.p. 162–163°).

A 0.75-g. sample of 2-pyrrol-2-pyrrolidine was heated in refluxing xylene with 0.4 g. of 5% palladium–charcoal catalyst.[5] The reaction mixture was filtered, the solvent was distilled, and the residue was sublimed at 1 mm. (bath temperature, 90–140°). After two crystallizations from ethyl alcohol the product melted at 162.0–162.8°.

Maleimide.—Pyrrole, 10 g., in 200 ml. of glacial acetic acid was oxidized with 30 g. of chromic anhydride in 40 ml. of water as described above. There was obtained 0.92 g. of crude maleimide. This was purified in portions by sublimation. For example, the white crystals, which were collected at a bath temperature of 102–113° at 0.95–1.35 mm., melted at 91.0–92.5° (lit.[64] m.p. 93°).

4-Methoxy-1-chlorobutane.—To a heated and stirred solution of 492 g. (4 moles) of 1,4-dichlorobutane in 500 ml. of anhydrous methanol, there was added dropwise a solution derived from 23 g. (1 g.-atm.) of sodium and 310 ml. of anhydrous methanol. An additional 20 ml. of methanol was added as a rinse; the mix-

(62) W. E. Doering and C. R. Noller, *J. Am. Chem. Soc.*, **61**, 3436 (1939).
(63) D. W. Fuhlage and C. A. VanderWerf, *ibid.*, **80**, 6249 (1958).
(64) F. Wrede and A. Rothhaas, *Z. physiol. Chem.*, **222**, 203 (1933).

ture was refluxed for 4 hr. and allowed to stand overnight. The copious precipitate of sodium chloride was removed by filtration and washed with methanol, the filtrates were combined, and the mixture was distilled. The fraction boiling at 141–146° was mixed with 50 ml. of concentrated sulfuric acid, with cooling. The 1,4-dichlorobutane, which remained undissolved, was separated and the sulfuric acid layer was washed with petroleum ether. The sulfuric acid layer was added to a mixture of ice and water, whereupon 4-methoxy-1-chlorobutane separated from solution. The chloro ether was washed successively with water and aqueous sodium bicarbonate, dried with magnesium sulfate, and distilled. The product was collected in two fractions, b.p. 139–140° and 140–140.3° (lit.[65] b.p. 140°).

Pyrroles.—The 1-methylpyrrole used was the redistilled Ansul Chemical Co. product, b.p. 111.5° (lit.[66] b.p. 112–112.5°).

1-Ethylpyrrole was kindly synthesized by Mr. Merrill T. Hugo from the reaction of ethyl iodide in ether with pyrrolylpotassium. The product was refluxed over sodium and redistilled, b.p. 128.2–128.3° (lit.[67] b.p. 129–130°).

1-Butylpyrrole was prepared from butyl chloride and pyrrolylpotassium in refluxing pyrrole. The product boiled at 68–73° (20 mm.), lit.[38] b.p. 76–77° (24 mm.), and the redistilled compound boiled at 170°.

1-Benzylpyrrole was obtained from the reaction of benzyl chloride with pyrrolylpotassium in refluxing pyrrole. The distilled product was refluxed over sodium and redistilled, b.p. 244–245° (lit.[68] b.p. 247°).

(65) H. Normant, *Compt. rend.*, **221**, 909 (1930).
(66) A. Pictet, *Ber.*, **37**, 2792 (1904).
(67) C. U. Zanetti, *ibid.*, **22**, 2515 (1889).

2-Ethylpyrrole, b.p. 163–166° (lit.[69] b.p. 163–165°), was synthesized (54%) by the Huang-Minlon modification[70,71] of the Wolff–Kishner reduction of 2-acetylpyrrole,[72] for which we are grateful to Mr. Benjamin F. Crouse.

2,4-Dimethylpyrrole, b.p. 160.0–160.5° (lit.[73] b.p. 160–165°), was synthesized by Fischer's procedure.[73]

2,5-Dimethylpyrrole was obtained from the Aldrich Chemical Co. and redistilled, b.p. 166.0° (lit.[74] b.p. 165°).

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Demjanov Rearrangement of 1-Methylcyclohexanemethylamine

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1-Methylcyclohexanemethylamine has been prepared and characterized. The Demjanov rearrangement of this amine has been investigated, yielding as products 1-methylcycloheptanol (67%), 1-ethylcyclohexanol (11%), 1-methylcycloheptene (3.8%), methylenecycloheptane (1.3%), 1-ethylcyclohexene (2.8%), and ethylidenecyclohexane (0.25%). The composition of the product alcohols and cycloalkenes were determined by gas chromatography and n.m.r. spectroscopy. Isolation of 1-methylcycloheptanol using a spinning-band column has been successful, but attempts to separate others have failed. An improved synthesis of pivalic acid from *t*-butyl alcohol is presented.

The effect of alkyl or aryl substitution at the aminomethyl carbon atom, or at a ring carbon atom in a position other than the 1-position on the Demjanov ring expansion of cycloalkanemethylamines is well known.[1] Few investigators, however, have attempted to study the substitution effect at C-1, and the available information[2] is limited to three- and five-membered rings. This work has been undertaken to see whether substitution of the methyl group for the hydrogen atom on the 1-carbon atom in cyclohexanemethylamine would facilitate ring expansion, as compared with the unsubstituted amine.[3] 1-Methylcyclohexanemethylamine (I) is new; hence its preparation and properties also are described. It may be regarded as a cyclic neoalkylamine.

1-Methylcyclohexanol, prepared from cyclohexanone, was converted to 1-methylcyclohexanecarboxylic acid by Koch and Haaf's method,[4] from which 1-methylcyclohexanecarboxamide and I were prepared. The over-all yield was 31%. The amine is a colorless liquid with a strong, fishy odor. Gas chromatographic analysis showed it to be pure and elemental analysis agreed with the formula $C_8H_{17}N$. Several derivatives such as ureas, amides, and imides were prepared. The n.m.r. spectrum[5] of the amine consisted of three resonances with areas in the ratio 2:12:3. These are assigned to the methylene hydrogens on the carbon to which the nitrogen atom is attached (τ 7.59, singlet), the ten ring protons and the amino group (several lines with one main peak at 8.56 and a broad base line), and the methyl group (9.17, singlet). The observed chemical shifts and relative intensities are in good agreement with the structure of the amine.

The reaction of I (25.4 g.) with nitrous acid in dilute orthophosphoric acid solution[6] yielded 1.8 g. of cycloalkenes and 20 g. of alcohols. Examination of the

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(5) The spectrum was determined at 25° without solvent by Dr. Shiro Satoh of this laboratory on a Varian Associates Model V-4311 high-resolution spectrometer with cyclohexane (τ 8.56) as an internal standard at 60 Mc. The same instrument and experimental conditions were employed throughout this work, unless noted otherwise.