n.m.r. spectrum[29]: δ 1.75 (weight 8 protons), multiplet centered at 2.95 (weight 1 proton), doublet centered at 7.68 (weight 1 proton). The n.m.r. spectrum of the 2,4-DNP of 2-methylcyclopentanone has a sharp doublet centered at δ 1.28 (methyl protons). The n.m.r. spectrum of the crude product was identical in all respects with that of the 2,4-DNP of cyclopentanealdehyde. There was no trace of a doublet at δ 1.28.

Repetition of this work in which the reaction mixture was allowed to stand for 24 hr. before work-up gave the same results. However, concentration of the filtrate gave unchanged 2,4-dinitrophenylhydrazine contaminated with traces of the 2,4-DNP derivatives of VIII and IX.

If a solution of X in 50 vol. % sulfuric acid was allowed to stand at room temperature for 1 hr. before treatment with 2,4-dinitrophenylhydrazine, the product contained an unidentified compound, probably an aldol product, in addition to the 2,4-DNP of VIII, but there was no detectable amount of the 2,4-DNP of IX.

Replacement of the 50 vol. % sulfuric acid with 50 wt. % (35 vol. %) sulfuric acid gave a crude product containing 76% VIII and 24% IX as the 2,4-DNP derivatives.

Cyclopentenemethanol did not react with the usual 2,4-dinitrophenyl hydrazine reagent[19] (*ca.* 12 vol. % sulfuric acid) at room temperature, but after 45 min. on a steam bath 69% of the 2,4-DNP of VIII and 31% of the 2,4-DNP of IX were produced.

(29) The protons belonging to the 2,4-dinitrophenylhydrazine portion of the molecule are not listed.

Acknowledgment.—The author is indebted to Mr. J. B. Causey for the n.m.r. and infrared spectra and to Mr. R. W. Jarrett for the mass spectra.

Products from Attempted Vilsmeier–Haack Acylations of Pyrroles with Select Amides[1a,b]

ALDO ERMILI,[1c] ALBERT J. CASTRO,[1d] AND PHILIP A. WESTFALL[1e]

Department of Chemistry, San Jose State College, San Jose, California

Received September 21, 1964

The Vilsmeier–Haack condensation of pyrroles with chloro-, oxo-, and ethoxycarbonyl-substituted amides yields the expected ketones in some cases. However, different products result in other examples, wherein the nature of the product is influenced by that of the particular pyrrole and amide. A dialkylammonium ion is considered a rational intermediate in the reaction.

The most useful general procedure for the synthesis of pyrrole aldehydes and ketones involves the application of the Vilsmeier–Haack reaction,[2-8] in which a 2- or 3-unsubstituted pyrrole is condensed usually with an N,N-disubstituted carboxamide[9] through the action of phosphorus oxychloride. At the present time, the range of application of this reaction has been incompletely explored. In this connection the possibility of self-condensation of N,N-dialkylcarboxamides[14] and of lactams,[15] the condensation of N,N-dialkylcarboxamides with active methylene groups,[15] and the replacement of alcoholic and readily enolizable keto groups by chlorine[2] represent possible complicating features in particular cases. It is also of interest to note that, although thiophene can be converted to 2-thiophenecarboxaldehyde by condensation with N-methylformanilide without any difficulty,[16] the attempted acylation of thiophene under the conditions of the Vilsmeier–Haack reaction was reportedly[6] unsuccessful. Also, in other results related to the present discussion, ketones have been obtained in the condensation of a number of *ortho*-, *meta*-, and *para*-substituted benzanilides with dimethylaniline, whereas with the *o*-acetoxy and *o*-nitro derivatives by-product formation is dominant.[17] During the course of synthesis of pyrrole derivatives of possible biological importance, we have had occasion to investigate the application of the Vilsmeier–Haack reaction in examples which further define the scope of this reaction.

Results and Discussion

Ketones X–XVI (Table I) were readily obtained from the condensation of the appropriate pyrroles and amides. Although the optimum conditions for the synthesis of each of these was not investigated, the preparation of 2-chloroacetylpyrrole (X) was attempted a number of times using different conditions and those described in detail in the Experimental section represent the optimum found. From these results and from those obtained in the other instances where more than one trial was carried out in addition to results described in the literature,[16] it is apparent that the conditions employed in the Vilsmeier–Haack condensation can be critical. However, the yields recorded and the ease of manipulation make this method competitive

(1) (a) This investigation was supported mainly by Public Health Service Research Grant CA 06255-02 (National Cancer Institute) for which we are grateful. (b) Presented in part as paper 36 before the division of Medicinal Chemistry at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964. (c) Visiting Fulbright-Hays Research Scholar from Italy. (d) To whom requests for reprints should be sent. (e) National Science Foundation Undergraduate Research Participant (NSF-GE 2934).

(2) O. Bayer, "Methoden der Organischen Chemie," Vol. VII (1), E. Müller, Ed., 4th Ed., G. Thieme Verlag, Stuttgart, 1954, p. 29.

(3) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Syn.*, **36**, 74 (1956).

(4) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(5) E. Ghigi and A. Drusiani, *Atti accad. sci. ist. Bologna, Classe sci. fis., Rend.*, **5**, 56 (1957); *Chem. Abstr.*, **54**, 5613*i* (1960).

(6) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).

(7) G. G. Kleinspehn and A. E. Briod, *ibid.*, **26**, 1652 (1961).

(8) M. R. de Maheas, *Bull. soc. chim. France*, 1989 (1962).

(9) In extensions of this reaction the condensations of 2-pyrrolidinone and of substituted 2-pyrrolidinones to yield pyrrolinylpyrrole and derivatives have been described.[10-12]

(10) H. Rapoport and N. Castagnoli, Jr., *J. Am. Chem. Soc.*, **84**, 2178 (1962).

(11) J. H. Atkinson, R. Grigg, and A. W. Johnson, *J. Chem. Soc.*, 893 (1964).

(12) H. Rapoport, N. Castagnoli, Jr., and K. G. Holden, *J. Org. Chem.*, **29**, 883 (1964).

(13) P. N. Edwards and G. F. Smith, "Advances in Heterocyclic Chemistry," Vol. 2, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p. 290.

(14) H. Bredereck, R. Gomper, and K. Klemm, *Chem. Ber.*, **92**, 1459 (1959).

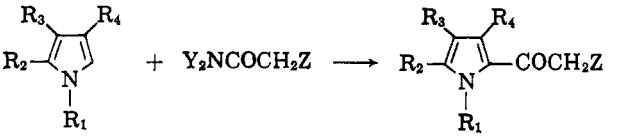
(15) H. Bredereck and K. Bredereck, *ibid.*, **94**, 2278 (1961).

(16) A. W. Weston and R. J. Michaels, Jr., *Org. Syn.* **31**, 108 (1951).

(17) R. C. Shah, R. K. Deshpande, and J. S. Chaubal, *J. Chem. Soc.*, 642 (1932).

TABLE I

KETONE SYNTHESES



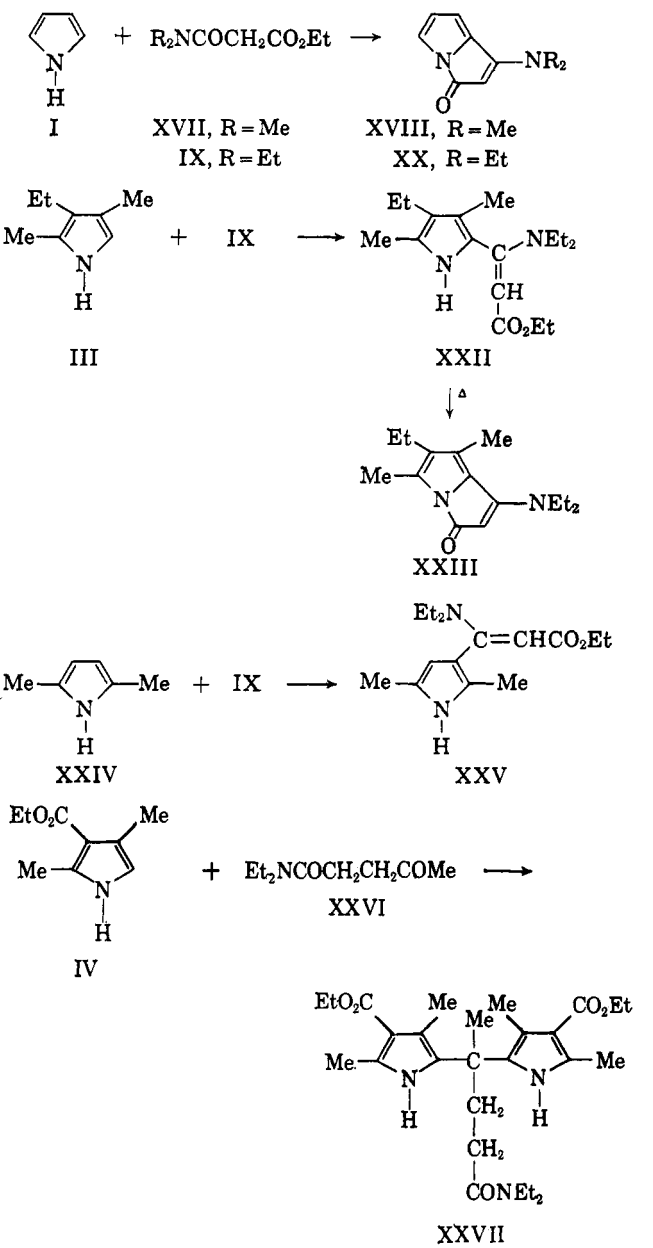
Pyrrole	R_1	R_2	R_3	R_4	Amide	Y	Z	Ketone, % yield	XIII,[a] % yield
I	H	H	H	H	V	Et	Cl	X, 54	
I	H	H	H	H	VI	Et	CH_2CO_2Et	XI, 71	
II	Me	H	H	H	VII	Me	H	XII, 40	16
II	Me	H	H	H	VIII	Et	H	XII, 59	25
III	H	Me	Et	Me	V	Et	Cl	XIV, 34	
IV	H	Me	CO_2Et	Me	V	Et	Cl	XV, 75	
IV	H	Me	CO_2Et	Me	IX	Et	CO_2Et	XVI, 61	

[a] 1-Methyl-3-acetylpyrrole.

and in several cases superior to other procedures recorded in the literature for the synthesis of the same ketones listed in Table I. From the theoretical standpoint, the formation of 1-methyl-2-acetylpyrrole (XII) and 1-methyl-3-acetylpyrrole (XIII) in a ratio of *ca.* 2.4:1 (average) in this reaction involving electrophilic attack[6] is of interest when compared with that noted for the ratio of 1-methyl-2-nitropyrrole and 1-methyl-3-nitropyrrole, *ca.* 2:1, from the nitration of 1-methylpyrrole with nitric acid in acetic anhydride.[18] The formation of isomeric ketones in the other examples may also have occurred, but was not investigated.

The attempted synthesis of ethyl 3-oxo-3-pyrrol-2′-ylpropanoate from the condensation of N,N-dimethylethoxycarbonylacetamide (XVII) with pyrrole resulted in the formation of an orange-colored crystalline compound XVIII, which showed a single carbonyl absorption at 1710 cm.$^{-1}$ and no NH absorption. These results and the n.m.r. spectrum (Experimental) of the substance indicated that XVIII is 1-dimethylamino-3-oxo-3H-pyrrolizine. This was confirmed by direct comparison of the pyrrolizine synthesized in a like manner from N,N,N′,N′-tetramethylmalonamide (XIX) and pyrrole as reported by Anthony.[6] The condensation of N,N-diethylethoxycarbonylacetamide (IX) was found similarly to yield 1-diethylamino-3-oxo-3H-pyrrolizine (XX). The acidic hydrolysis of XVIII to 2-acetylpyrrole (XXI) has been cited[6] as evidence for its constitution. We have found that the hydrolysis of XX to 2-acetylpyrrole occurs readily under both acidic and basic conditions. When ring opening of XX was attempted by refluxing with sodium ethoxide in absolute ethanol, the starting pyrrolizine was recovered. Condensation of cryptopyrrole (III) with IX gave ethyl 3-diethylamino-3-(3,5-dimethyl-4-ethylpyrrol-2-yl)propenoate (XXII). Heating or attempted distillation of XXII was accompanied by loss of ethyl alcohol and cyclization to 1-diethylamino-3-oxo-5,7-dimethyl-6-ethyl-3H-pyrrolizine (XXIII). From 2,5-dimethylpyrrole (XXIV) and IX, ethyl 3-diethylamino-3-(2,5-dimethylpyrrol-3-yl)propenoate (XXV) was formed. When 2,4-dimethyl-3-ethoxycarbonylpyrrole (IV) was allowed to react with N,N-diethyl-4-oxopentanamide (XXVI) in the presence of phosphorus oxychloride, N,N-diethyl-4,4-di-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)pentanamide (XXVII) was produced. The attempted condensation of 1-methyl-

CHART I

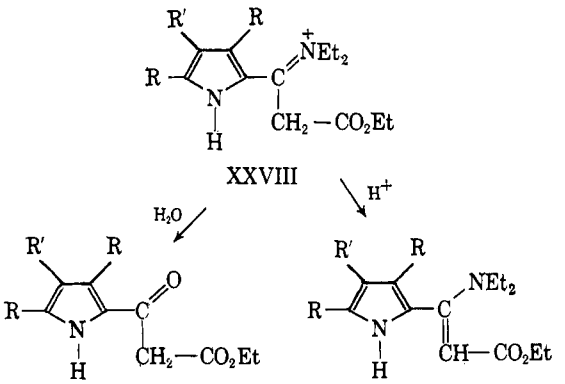


pyrrole, 1-benzylpyrrole, and 2-ethoxycarbonyl-3,5-dimethylpyrrole with N,N-diethylethoxycarbonylacetamide (IX) led to the formation of intractable

(18) H. J. Anderson, *Can. J. Chem.*, **35**, 21 (1957).

masses with the first two and recovery of the starting pyrrole in the last case.[19] (See Chart I.)

The greater ease of pyrrolizine formation in the case of pyrrole over cryptopyrrole may reflect the steric interference between the 3-methyl substituent of the cryptopyrrole ring and the amino-N-ethyl groups which opposes the proper orientation of the pyrrole NH for reaction with the ester group. At higher temperatures the energy barrier is overcome and cyclization occurs. Spectroscopic evidence has been presented[4] for the existence of a resonance species analogous to XXVIII as an intermediate in the formylation of pyrrole with N,N-dimethylformamide. Such an intermediate offers



a ready explanation for the formation of the unsaturated derivatives XXII and XXV described herein through loss of a proton, as well as the formation of a ketone (Table I) through hydrolysis. The formation of XXVII corresponds to the ready formation of *meso*-substituted dipyrrylmethanes from the acid-catalyzed condensation of ketones with 2-unsubstituted pyrroles.[20]

Experimental

Melting points, determined with a Fisher-Johns apparatus, and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-5 spectrophotometer and n.m.r. spectra were determined with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. Analyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

Pyrroles.—Pyrrole (I), 1-methylpyrrole (II), 2,5-dimethylpyrrole (XXIV), and crytopyrrole (III) were distilled commercial products. 2,4-Dimethyl-3-ethoxycarbonylpyrrole (IV) was synthesized essentially as has been described.[21]

Amides.—N,N-diethylchloroacetamide (V) was synthesized by the slow addition, during a period of about 2 hr., of a solution of 146.0 g. (2.00 moles) of anhydrous diethylamine in 100 ml. of ether to a vigorously stirred solution of 112.0 g. (1.00 mole) of chloroacetyl chloride in 300 ml. of dry ether. During this period the reaction mixture was contained in an ice-cooled flask and protected from the atmosphere with a calcium chloride tube. The mixture was stirred and cooled for an additional 2 hr. after adding the amine. The diethylamine hydrochloride, which had precipitated, was filtered from the solution and washed with dry ether. The ether fractions were combined, the solvent was evaporated, and the residue was distilled. The amide was collected as a colorless liquid, b.p. 87–89° (3 mm.) [lit.[22] b.p. 112–113° (10 mm.)], weighing 133.0 g. (89%).

N,N-Diethyl-3-ethoxycarbonylpropanamide (VI), a colorless oil, b.p. 100–104° (0.5 mm.) [lit.[23] b.p. 102–104° (0.8 mm.)], was synthesized (85%) from 3-ethoxycarbonylpropanoyl chloride[24] and diethylamine as has been reported.[23]

N,N-Dimethylacetamide (VII) and N,N-diethylacetamide (VIII) were commercial products.

N,N-Diethylethoxcarbonylacetamide (IX) was synthesized by heating 60.0 g. (0.37 mole) of ethyl malonate and 27.4 g. (0.37 mole) of diethylamine at 150° for 37 hr. in a closed stainless steel Aminco high-pressure reaction vessel following the procedure of Barré and Matte.[25] Distillation of the reaction mixture yielded 51.0 g. (73%) of the amide ester, which was collected as a colorless liquid, b.p. 86–88° (0.6 mm.) [lit.[25] b.p. 151° (12 mm.)].

N,N-Dimethylethoxycarbonylacetamide (XVII) was prepared in a manner similar to that for IX (140°, 40 hr.) from 60.0 g. (0.37 mole) of ethylmalonate and 17.0 g. (0.37 mole) of dimethylamine. The yield of colorless liquid, b.p. 110–112° (3.0 mm.), was 39.0 g. (66%).

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 53.02; H, 8.09; N, 9.08.

N,N,N',N'-Tetramethylmalonamide (XIX) was obtained from the reaction (150°, 40 hr.) of 60.0 g. (0.37 mole) of ethyl malonate and 34.0 g. (0.75 mole) of dimethylamine. The amide was obtained as a colorless liquid, b.p. 131–133° (1.5 mm.) [lit.[26] b.p. 138–140° (4 mm.)], weighing 51.0 g. (86%). Using a slight variation in procedure from ours, Lawson and Croom[26] obtained a yield of 79.5%. These results are better than those described[15] for the synthesis of this compound from malonyl chloride and dimethylamine.

N,N-Diethyl-4-oxopentanamide (XXVI) was isolated as a colorless oil, b.p. 95–97° (1.8 mm.) [lit.[27] b.p. 90–91° (0.85 mm.)] (68%), from the reaction of 4-oxopentanoyl chloride with diethylamine as described in the literature.

2-Chloroacetylpyrrole (X).—Forty-six grams (0.30 mole) of phosphorus oxychloride was added very slowly in a dropwise manner, with stirring, to 32.8 g. (0.22 mole) of N,N-diethylchloroacetamide (V). After the addition was complete, stirring was continued for an additional 15 min. Pyrrole (I) (13.4 g., 0.20 mole) was added very slowly dropwise, and the resulting mixture was allowed to stand at room temperature overnight. On the following day, it was added to 1 l. of an ice–water mixture. The solution obtained was decolorized with charcoal and filtered; 300 ml. of chloroform was added. A saturated aqueous solution of sodium carbonate was added to the stirred chloroform–aqueous mixture until it was definitely basic and the mixture was stirred for 2 hr. The chloroform layer was separated, the aqueous phase was extracted with chloroform, the chloroform fractions were combined, and the resulting solution was dried with magnesium sulfate. Upon evaporating the solvent from the dried solution and crystallization of the residue from carbon tetrachloride, there was obtained 15.4 g. (54%) of 2-chloroacetylpyrrole, m.p. 118–119° (lit.[28] m.p. 118–119°).

Ethyl 4-Oxo-4-pyrrol-2'-ylbutanoate (XI).—This compound was prepared by the method described in the literature[3] for the synthesis of 2-formylpyrrole using 22.1 g. (0.11 mole) of N,N-diethyl-3-ethoxycarbonylpropanamide (VI), 6.7 g. (0.10 mole) of pyrrole (I), and corresponding amounts of the other reagents described in the literature. The yield of white crystalline ester, m.p. 65–65.5° (lit.[29] m.p. 69–70°), after crystallizing from aqueous ethyl alcohol was 13.7 g. (71%).

The infrared spectrum of a carbon tetrachloride solution of the ester shows NH (3280, 3460), ketone carbonyl (1645), and ester carbonyl (1740 $cm.^{-1}$) bands. The n.m.r. spectrum of a deuteriochloroform solution of the ester shows signals for pyrrole NH (δ = 10.22 p.p.m., low broad, relative intensity 1), pyrrole α'- and β-H (6.98, broad, 2), pyrrole β'-H (6.24, broad, 1), and for the other types of protons: ester ethyl methylene (4.14, quartet, 2), side-chain methylenes (2.72, 3.17, triplets, 2,2), and ester ethyl methyl (1.24, triplet, 3).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.65; H, 6.89; N, 7.23.

This compound was readily hydrolyzed to 4-oxo-4-pyrrol-2'-ylbutanoic acid (XXXIV) as described below.

(19) A procedure like that described in the Experimental section for the synthesis of 1-dimethylamino-3-oxo-3H-pyrrolizine (XVII) was used.

(20) H. Fischer and H. Orth, "Die Chemie Des Pyrrols," Vol. 1, Akademie-Verlag G.m.b.H., Leipzig, 1934, p. 350, *et seq.*

(21) L. Knorr, *Ann.*, **236**, 322 (1886).

(22) J. V. Braun and A. Heymons, *Ber.*, **62**, 409 (1929); *cf.* F. L. Hahn and M. Loos, *Ber.*, **51**, 1442 (1918).

(23) A. W. D. Avison, *J. Appl. Chem.* (London), **1**, 469 (1951).

(24) B. Riegel and W. M. Lilienfeld, *J. Am. Chem. Soc.*, **67**, 1273 (1945).

(25) R. Barré and P. L. Matte, *Ann. ACFAS*, **7**, 81 (1941); *Chem. Abstr.* **40**, 1453[8] (1946).

(26) J. K. Lawson, Jr. and J. A. Croom, *J. Org. Chem.*, **28**, 232 (1963).

(27) A. J. Speziale and H. W. Frazier, *ibid.*, **26**, 3176 (1961).

(28) F. F. Blicke, J. A. Faust, J. E. Gearien, and R. J. Warzynski, *J. Am. Chem. Soc.*, **65**, 2465 (1943).

(29) L. Chierici and G. Serventi, *Gazz. chim. ital.*, **86**, 1278 (1956).

1-Methyl-2-acetylpyrrole (XII) and 1-Methyl-3-acetylpyrrole (XIII).—Following the procedure described[30] for the formylation of 1-methylpyrrole (II), 8.1 g. (0.10 mole) of this compound was acylated employing 17.4 g. (0.20 mole) of N,N-dimethylacetamide (VII) and 35.6 g. (0.23 mole) of phosphorus oxychloride. A minor variation from the procedure described in the literature was the use of sodium carbonate instead of sodium acetate in the hydrolysis or the reaction mixture. Fractionation of the crude product yielded 4.9 g. (40%) of 1-methyl-2-acetylpyrrole (XII), b.p. 48–49° (1.5 mm.) [lit.[31] b.p. 75–76° (15 mm.)], and 1.9 g. (16%) of 1-methyl-3-acetylpyrrole (XIII), b.p. 88–89° (1.5 mm.).

The infrared absorption spectrum of XII (neat) shows a strong band due to a carbonyl stretching vibration at 1660 cm.$^{-1}$. The n.m.r. spectrum of XII is identical with that reported[32] for 1-methyl-2-acetylpyrrole.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.50; H, 7.63; N, 11.59.

The infrared spectrum of XIII (neat) also shows a carbonyl band at 1660 cm.$^{-1}$. Its n.m.r. spectrum in deuteriochloroform shows signals for N-methyl H (δ = 3.62 p.p.m., singlet, 3), acetyl methyl H (2.32, singlet, 3), pyrrole α-H (7.21, triplet, 1), and pyrrole α'- and β'-H (6.33, doublet, 2).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.09; H, 7.52; N, 11.61.

Employing essentially the same procedure, but with 23.0 g. (0.20 mole) of N,N-diethylacetamide (VIII) instead of VII and other reagents the same as above, there was obtained 7.3 g. (59%) of XII, b.p. 48–49° (1.5 mm.), and 3.1 g. (25%) of XIII, b.p. 88–89° (1.5 mm.).

2-Chloroacetyl-3,5-dimethyl-4-ethylpyrrole (XIV).—The procedure used for the synthesis of 2-chloroacetylpyrrole (X) was followed, except that the mixture was heated in a water bath at 60° for 45 min. after adding all of the pyrrole and the reaction mixture was dissolved in 150 ml. of chloroform before hydrolysis on the following day. Phosphorus oxychloride (11.5 g., 0.055 mole), 8.2 g. (0.055 mole) of N,N-diethylchloroacetamide (V), and 6.2 g. (0.050 mole) of cryptopyrrole (III) yielded 3.4 g. (34%) of 2-chloroacetyl-3,5-dimethyl-4-ethylpyrrole (XIV), m.p. 149° (lit.[33] m.p. 149°). This product was crystallized from 95% ethyl alcohol.

2-Chloroacetyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (XV).—The phosphorus oxychloride–amide complex was prepared using 5.75 g. (0.037 mole) of phosphorus oxychloride and 4.1 g. (0.025 mole) of N,N-diethylchloroacetamide (V). To this mixture, 3.45 g. (0.014 mole) of 2,4-dimethyl-3-ethoxycarbonylpyrrole (IV) dissolved in 10.0 g. of V was added. After stirring and heating at 60° for 45 min., 200 ml. of chloroform was added and the mixture was hydrolyzed as above. There was obtained 3.74 g. (75%) of 2-chloroacetyl-3,5-dimethyl-4-ethoxycarbonylpyrrole (XV), m.p. 193.0–193.5° (lit.[34] m.p. 187°), after crystallization from 95% ethyl alcohol.

This compound, like the other chloro ketones synthesized, gives a positive Beilstein test. Its n.m.r. spectrum in trifluoroacetic acid shows signals for chloroacetyl (a) and ethyl (b) methylene H superimposed in part (a, δ = 4.73 p.p.m., singlet; b, 4.57 triplet apparent adjacent to a, 4), pyrrole ring methyls H (2.68, 2.78, singlets, 3, 3), and ethyl methyl H (1.54, triplet, 3).

Ethyl 3-Oxo-3-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)propanoate (XVI).—The procedure used for the synthesis of XXII was followed using 20.3 g. (0.11 mole) of N,N-diethylethoxycarbonylacetamide (IX), 8.35 g. (0.050 mole) of 2,4-dimethyl-3-ethoxycarbonylpyrrole (IV), and 11.5 g. (0.075 mole) of phosphorus oxychloride. The procedure varied from that described for XXII in that the solid pyrrole was dissolved in a 10.0-g. portion of the total amount of amide used before adding it to the phosphorus oxychloride–amide complex. After recrystallization from a mixture of benzene and ligroin, the pale yellow-colored crystalline ester, m.p. 140.5–142° (lit.[35] m.p. 140.5–142°), weighed 8.7 g. (61%).

The infrared spectrum of a mineral oil mull of XVI exhibits an NH band (3280), ketone carbonyl band (1625), and ester carbonyl bands (1680, 1725 cm.$^{-1}$). The n.m.r. spectrum of a deuteriochloroform solution of the compound shows signals for pyrrole NH (δ = 10.83 p.p.m., low, broad, 1) and the other types of protons: ester methylenes (4.23, quartet, 4), side-chain methylene (3.80 g., singlet, 2), pyrrole methyls (2.50, 2.57, singlets, 3, 3), and ethyl methyls (1.30, multiplet, 6).

1-Dimethylamino-3-oxo-3H-pyrrolizine (XVIII).—A 23.0 g. (0.15-mole) quantity of phosphorus oxychloride was added dropwise with stirring to 17.5 g. (0.11 mole) of N,N-dimethylethoxycarbonylacetamide (XVII), which was contained in a flask cooled in an ice bath and protected from the atmosphere with a calcium chloride drying tube. After the addition of all of the phosphorus oxychloride, the mixture was removed from the ice bath and held at room temperature for 20 min. The resulting yellow solution was returned to an ice bath and 6.7 g. (0.10 mole) of pyrrole (I) was added slowly while the mixture was stirred. The reaction mixture was then stirred for 40 min. at 45–50°, cooled, and added to a mixture of crushed ice and water. The aqueous solution ultimately obtained was treated with charcoal, the mixture was filtered, and the filtrate was made basic by the addition of a saturated aqueous solution of sodium carbonate. The orange crystals that separated were collected, washed with water, and crystallized from benzene. The product, 4.5 g. (29%), melted at 142–143° (lit.[6] m.p. 143–144°). No depression of the melting point was observed when this product was mixed with an authentic sample of 1-dimethylamino-3-oxo-3H-pyrrolizine, which was synthesized from the phosphorus oxychloride condensation of N,N,N′,N′-tetramethylmalonamide (XIX) with pyrrole as has been described,[6] and the infrared spectra of the two in chloroform were identical.

The n.m.r. spectrum of this compound in deuteriochloroform shows signals for H-2 (methylidene H) (δ = 4.22, p.p.m., singlet, 1), H-5 (pyrrole α-H) (6.98, triplet, 1), H-6 and H-7 (pyrrole β- and β'-H) (6.06, multiplet, 2), and methyl H (3.12, singlet, 6).

1-Diethylamino-3-oxo-3H-pyrrolizine (XX).—This compound was prepared in the same manner as described for the dimethylamino derivative (XVIII) using 20.6 g. (0.11 mole) of N,N-diethylaminoethoxycarbonylacetamide (IX), 6.7 g. (0.10 mole) of pyrrole (I) and 23.0 g. (0.15 mole) of phosphorus oxychloride. After successive crystallization of the crude product from ethyl ether and ligroin (b.p. 60–110°), the resulting orange crystals weighed 5.8 g. (31%) and melted at 103.5–104°.

The infrared spectrum of this compound in carbon tetrachloride shows a strong band attributable to a carbonyl stretching vibration (1725 cm.$^{-1}$) and no band assignable to an NH stretching vibration (near 3300 cm.$^{-1}$). The n.m.r. spectrum of a deuteriochloroform solution shows signals for H-2 (δ = 4.30 p.p.m., singlet, 1), H-5 (7.03, broad multiplet, 1), H-6 and H-7 (6.10, broad, 2), methylene H (3.45 quartet, 4), and methyl H (1.29 triplet, 6).

The picrate of the pyrrolizine was prepared in the usual way in ethyl alcohol. After recrystallizing from the same solvent, the yellow crystals melted at 138–139°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 68.81; H, 7.37; N, 15.46.

Hydrolysis of the pyrrolizine was easily accomplished by warming 0.95 g. of the compound with 5.0 ml. of 1 *N* hydrochloric acid for several minutes on a steam bath. Crystals of 2-acetylpyrrole (XXI) crystallized from the heated mixture and an additional quantity was recovered upon cooling. The 2-acetylpyrrole melted at 90° (lit.[36] m.p. 90°) after recrystallizing from water. When a 0.95-g. sample of the pyrrolizine was refluxed with 30 ml. of 1 *N* aqueous potassium hydroxide solution for 1 hr. and the mixture was allowed to stand overnight, 0.50 g. (98%) of crude 2-acetylpyrrole crystallized from the mixture. The recrystallized compound melted at 90°. The infrared spectra of mineral oil mulls of the ketone from both hydrolyses are identical with that of an authentic sample of 2-acetylpyrrole. When a sample of the pyrrolizine was refluxed with excess sodium ethoxide in absolute ethanol for 1 hr. the starting pyrrolizine was recovered.

Ethyl 3-Diethylamino-3-(3,5-dimethyl-4-ethylpyrrol-2-yl)propenoate (XXII).—The general procedure described for the synthesis of the pyrrolizines was employed using 10.3 g. (0.055 mole) of N,N-diethylethoxycarbonylacetamide (IX), 6.15 g.

(30) E. E. Ryskiewicz and R. M. Silverstein, *J. Am. Chem. Soc.*, **76**, 5802 (1954).

(31) G. Ciamician and M. Dennstedt, *Ber.*, **17**, 2952 (1884).

(32) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Varian High Revolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 174.

(33) H. Fischer and M. Schubert, *Ber.*, **56**, 1202 (1923).

(34) H. Fischer, K. Schneller, and W. Zerweck, *ibid.*, **55**, 2390 (1923).

(35) E. I. Filippovich, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **30**, 3253 (1960); *Chem. Abstr.*, **55**, 21095e (1961).

(36) B. Oddo, *Ber.*, **43**, 1012 (1910).

(0.050 mole) of cryptopyrrole (III), and 11.5 g. (0.075 mole) of phosphorus oxychloride. A variation in the general procedure was that after addition of the pyrrole the mixture was allowed to stand for 3 hr. in an ice bath and at room temperature overnight. The crude solid product was treated with charcoal in hexane and 5.2 g. (36%) of light cream-colored crystals of the ester, m.p. 80–81°, were obtained.

The infrared spectrum of the ester in carbon tetrachloride shows strong bands for NH (3240 cm.$^{-1}$) and ester carbonyl (1675 cm.$^{-1}$) stretching. Its n.m.r. spectrum in deuteriochloroform shows a signal for a pyrrole NH (δ = 7.65 p.p.m., moderately broad, 1) and for the other types of protons: methylidene (4.82, singlet, 1), ester ethyl methylene (3.98, quartet, 2), aminoethyl methylene (3.18, quartet, 4), pyrrole ethyl methylene (2.40, quartet, 2), pyrrole methyls (1.92, 2.18, singlets, 3,3), and ethyl methyls (1.12, quartet, 12).

Anal. Calcd. for $C_{17}H_{28}N_2O_2$: C, 69.82; H, 9.65; N, 9.58. Found: C, 69.29; H, 9.33; N, 9.94.

1-Diethylamino-3-oxo-5,7-dimethyl-6-ethyl-3H-pyrrolizine (XXIII).—The amounts of the different reactants and the procedure were the same as described for the synthesis of ethyl 3-diethylamino-3-(3,5-dimethyl-4-ethylpyrrol-2-yl)propenoate (XXII). In this case the crude product was dissolved in ether, to aid in transfer, and after removal of the solvent the residue was distilled. The orange-colored oil collected at 180–185° (1.5 mm.) crystallized upon standing. Recrystallization from hexane yielded 8.1 g. (66%) of the pyrrolizine, m.p. 77–78°. The same compound was obtained when a sample of pure XXII was refluxed at 1.5 mm. for 1 hr., a small amount of distillate removed and the undistilled residue examined after it had crystallized upon standing.

The infrared spectrum of the pyrrolizine in carbon tetrachloride shows a carbonyl stretching band (1710 cm.$^{-1}$) and no NH absorption. Its n.m.r. spectrum in deuteriochloroform shows signals for H-2 (δ = 4.36 p.p.m., singlet, 1) and for the other types of protons: aminoethyl methylene (3.42, quartet, 4), pyrrole ethyl methylene (2.32, multiplet), pyrrole methyls (2.10, 2.28, singlets) (relative intensity for foregoing three types, 8), and ethyl methyls (1.18, multiplet, 9).

Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.90; H, 8.74; N, 11.50.

Ethyl 3-Diethylamino-3-(2,5-dimethylpyrrol-3-yl)propenoate (XXV).—The same general procedure described for the synthesis of the pyrrolizines was employed using 10.3 g. (0.055 mole) of N,N-diethyl ethoxycarbonylacetamide (IX), 4.75 g. (0.050 mole) of 2,5-dimethylpyrrole (XXIV), and 8.5 g. (0.055 mole) of phosphorus oxychloride. The pale yellow-colored crystals of the ester, m.p. 132–133°, weighed 5.3 g. (40%) after crystallization from hexane.

The infrared spectrum of a carbon tetrachloride solution of the ester shows an NH band (3300 cm.$^{-1}$) and an ester carbonyl band (1675 cm.$^{-1}$). The n.m.r. spectrum of a deuteriochloroform solution of the compound shows signals for pyrrole NH (δ = 8.42 p.p.m., broad, 1), pyrrole β-H (5.58, broad, 1), and for the other types of protons: methylidene (4.79, singlet, 1), ester ethyl methylene (4.02, quartet, 2), aminoethyl methylene (3.25, quartet, 4), pyrrole methyls (2.01, 2.14, singlets, 3, 3), and ethyl methyls (1.14, sextet, 9).

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.41; H, 9.02; N, 10.51.

N,N-Diethyl 4,4-Di-(3,5-dimethyl-4-ethoxycarbonylpyrrol-2-yl)pentanamide (XXVII).—Phosphorus oxychloride (8.5 g., 0.055 mole) was added slowly to a stirred solution of 9.4 g. (0.055 mole) of N,N-diethyl-4-oxopentanamide (XXVI) in 25 ml. of anhydrous ether. The reaction mixture was protected from atmospheric moisture with a calcium chloride tube and was contained in a flask set in an ice bath. Following the addition of the phosphorus oxychloride, the mixture was stirred for 10 min. and 8.3 g. (0.050 mole) of 2,4-dimethyl-3-ethoxycarbonylpyrrole (IV) in 45 ml. of dry ether was added dropwise. The resulting mixture was refluxed for 1 hr., during which a dark oil separated from solution. The entire mixture was slowly added to a saturated aqueous solution prepared from 35 g. of sodium bicarbonate. The ether layer was separated and the aqueous layer was extracted with ether. The ether fractions were combined; the mixture was washed with water and then dried with magnesium sulfate. After evaporation of the solvent, the crude solid was crystallized from ethyl alcohol yielding 4.3 g. (36%) of white crystalline amide, m.p. 200–201°.

The infrared spectrum of a mineral oil mull of the amide shows NH (3260, 3390), amide carbonyl (1635), and ester carbonyl (1670, 1695 cm.$^{-1}$) bands. The n.m.r. spectrum of a deuteriochloroform solution of the compound shows signals due to the pyrrole NH protons (δ = 9.32 p.p.m., broad, 2) and the other types of protons: ester ethyl methylene (4.25, quartet, 4), amide ethyl methylene (3.24, quartet, 4), pentanamide chain methylenes (2.29, broad, 4), pyrrole ring methyls (2.10, 2.42, singlets, 6.6), pentanamide chain terminal methyl (1.67, singlet, 3), and ethyl methyls (1.22, multiplet, 12).

Anal. Calcd. for $C_{27}H_{41}N_3O_5$: C, 66.50; H, 8.48; N, 8.62. Found: C, 66.25; H, 8.57; N, 8.40.

4-Oxo-4-pyrrol-2′-ylbutanoic Acid (XXIX).—A mixture of 1.95 g. (0.01 mole) of ethyl 4-oxo-4-pyrrol-2′-ylbutanoate (XI) and 20 ml. of 1.5 *N* potassium hydroxide (0.030 equiv.) was refluxed for 1 hr. and the mixture was cooled and acidified with excess concentrated hydrochloric acid. The crude acid was removed by filtration and washed with a little water. Crystallization from aqueous ethyl alcohol yielded 1.51 g. (91%) of white crystalline acid, m.p. 146–147° (lit.[29] m.p. 141°).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.60; H, 5.51; N, 8.20.

Acknowledgement.—We are thankful to Mr. John P. Marsh, Jr., for his participation in initial phases of this study.