N-Functionally Substituted Pyrroles

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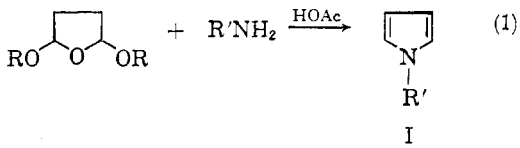
Received January 29, 1962

5-Keto-9*H*-pyrrolo[1,2-*a*]indole has been prepared in three steps starting with methyl anthranilate and 2,5-diethoxytetrahydrofuran. Through the condensation of certain amino acid derivatives with 2,5-diethoxytetrahydrofuran, several new substituted pyrroles have been prepared. These have been converted by polyphosphoric acid cyclization to derivatives of the pyrrolo[1,2-*a*]pyrrole ring system. The preparation of a *N*-pyrrolylthiophene from the corresponding aminothiophene is described.

In 1952 Clauson-Kaas and Tyle[1a] described an excellent general method for the preparation of *N*-substituted pyrroles through reaction of 2,5-dialkoxytetrahydrofurans with primary amines (equation 1). In succeeding communications, Clauson-



(1)

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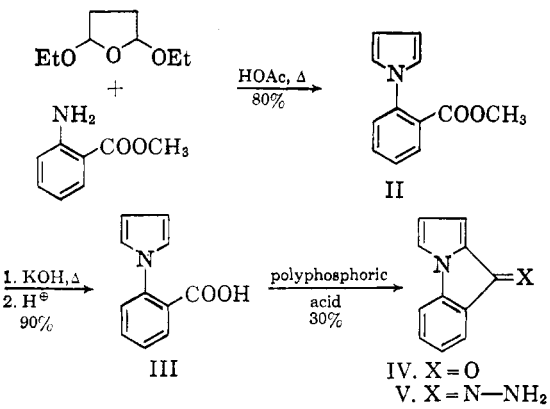
Kaas and co-workers employed a variety of simple aliphatic and aromatic primary amines together with more highly substituted cyclic acetals to obtain the corresponding *N*-substituted pyrroles in good yields. This general reaction appeared to us to invite wider exploitation since it enables the simple, direct replacement of sufficiently basic —NH_2 by the 1-pyrrolyl group, providing other factors (stereochemistry and stability of functional groups) are favorable. In particular, where R′ (equation 1) is suitably substituted with other functional groups, it opens a way to polycyclic structures containing a pyrrole ring. This report describes the preparation of a number of pyrrolo[1,2-*a*]pyrrole derivatives as well as a simple, three-step synthesis of derivatives of the pyrrolo[1,2-*a*]indole ring system from methyl anthranilate and 2,5-diethoxytetrahydrofuran.

The requisite 2,5-dialkoxytetrahydrofurans were synthesized by the Danish workers by electrolytic alkoxylation of furan and its derivatives and subsequent catalytic reduction of the resulting 2,5-dialkoxy-2,5-dihydrofuran.[1b] A more convenient route to the latter compounds is described in a recently published procedure for the preparation of 2,5-dimethoxy-2,5-dihydrofuran from furan, bromine, and methanol.[2]

We have employed the Clauson-Kaas reaction in a facile synthesis of the heterocyclic ketone 9-keto-9*H*-pyrrolo[1,2-*a*]indole[3-5] according to the following scheme



The condensation of 2,5-diethoxytetrahydrofuran with methyl anthranilate proceeds in good yield (80%) and affords 1-[2-methoxycarbonylphenyl]-pyrrole, II. Hydrolysis of II with potassium hydroxide–ethylene glycol and acidification provide the new acid, III (90%). Cyclization of the latter in hot (70°) polyphosphoric acid gives a mixture from which the ketone, IV, can be isolated in 32% yield by chromatography on neutral alumina. IV is a normal ketone for it readily forms the hydrazone, V. IV has previously been prepared by Shirley, *et al.*,[5] and by Huisgen and Laschtuvka[4] who designated it "fluorazon." The former isolated the ketone as a minor by-product from the carbonation of lithiated 1-phenylpyrrole. These authors used the mucic acid pyrrole synthesis in their studies and, interestingly, reported that the application of this method to the preparation of the pyrrole II failed. The present scheme appears to offer the preferred route to the pyrrolo[1,2-*a*]indole ring system. Moreover, it should be possible to prepare ring-substituted derivatives of known structure by choice of properly substituted amine and acetal components in the initial condensation step.

Condensation of 2,5-diethoxytetrahydrofuran with β-aminopropionitrile or ethyl β-aminopropionate was readily effected to give, respectively, 1-β-cyanoethylpyrrole (VIa) and 1-β-ethoxycarbonyl-

(1)(a) N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952); (b) *ibid.*, **6**, 867 (1952).

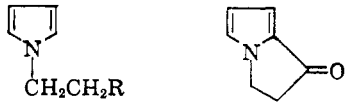
(2) D. Burness, *Org. Syn.*, **40**, 29 (1960).

(3) A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," American Chemical Society, 2nd ed., 1960, p. 316.

(4) R. Huisgen and E. Laschtuvka, *Ber.*, **60**, 81 (1960).

(5) D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

ethylpyrrole, (VIb). The former is available *via* cyanoethylation of pyrrole[6] and can be converted[7] in a Hoesch reaction to the bicyclic ketone VII

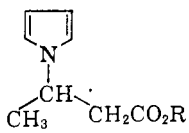


VI-a. R = CN
b. R = $CO_2C_2H_5$

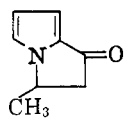
VII

which possesses the pyrrolizidine skeleton, the nucleus of the nitrogenous portion of the Senecio alkaloids. The amine–acetal condensation reaction is sufficiently versatile that it should make possible the synthesis of analogs of VII not readily available by other routes.

Ethyl β-aminobutyrate was prepared in 90% yield from ethyl acetoacetate and ammonia[8] after hydrogenation of the intermediate ethyl β-aminocrotonate.[8] Reaction of the saturated amino ester with 2,5-diethoxytetrahydrofuran gave ethyl β-(1-pyrrolyl)butyrate, VIII (R = C_2H_5), in 88% yield. Basic hydrolysis provided the corresponding acid VIII (R = H) (89%), and the latter was con-



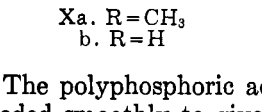
VIII



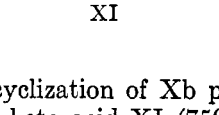
IX

verted by polyphosphoric acid to 3-methyl-1-oxo-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole, IX. The latter was isolated as a light yellow oil by chromatography on neutral alumina and characterized as the crystalline oxime.

Methyl β-aminoglutarate, obtained from ammonia and methyl acetonedicarboxylate after reduction of the intermediate methyl β-aminoglutaconate, was condensed with 2,5-diethoxytetrahydrofuran. Introduction of the pyrrole ring proceeded in excellent yield (85%) to provide methyl β-(1-pyrrolyl)glutarate, Xa. Alkaline hydrolysis gave the corresponding acid Xb (82%).



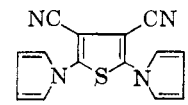
Xa. R = CH_3
b. R = H



XI

The polyphosphoric acid cyclization of Xb proceeded smoothly to give the keto acid XI (75%). The maximum yield of XI was obtained when a warm tetrahydrofuran solution of Xb was added to polyphosphoric acid. It has already been shown[1b] that diamines can be converted into di(*N*-pyrrolyl) compounds in the manner described above.

During this study, 2,5-di(*N*-pyrrolyl)-3,4-dicyanothiophene, XII, was prepared in 21% yield by reaction of 2,5-diamino-3,4-dicyanothiophene with 2,5-diethoxytetrahydrofuran in glacial acetic acid.



XII

Experimental

The 2,5-diethoxytetrahydrofuran used in these experiments was obtained from Eastman Organic Chemicals, but is no longer commercially available. However, a recently published procedure[1] describes the preparation of 2,5-dimethoxy-2,5-dihydrofuran, and this material can be readily reduced to the tetrahydro derivative.[1b]

1-[2-Methoxycarbonylphenyl]pyrrole (II).—2,5-Diethoxytetrahydrofuran (95.5 g., 0.59 mole) was added to a well stirred solution of 90 g. (0.59 mole) of methyl anthranilate in 265 ml. of glacial acetic acid. Much heat was liberated and a deep red color developed. The clear solution was heated at reflux for 1 hr., and then the acetic acid was removed by distillation at reduced pressure. Fractional distillation of the dark residue gave 95.8 g. (80%) of slightly yellow 1-[2-methoxycarbonylphenyl]pyrrole, b.p. 90–95°/2 mm. A sample which was redistilled for analysis had b.p. 110°/3 mm.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.9; H, 5.5; N, 7.3.

1-[2-Carboxyphenyl]pyrrole (III).—A solution of 13.4 g. of potassium hydroxide in 100 ml. of ethylene glycol containing 20 ml. of water was prepared by warming the stirred mixture over an open flame. After addition of 1-[2-methoxycarbonylphenyl]pyrrole (33.4 g., 0.17 mole), the mixture was emulsified by shaking and heated at 135–140° (oil bath temperature) for 3.5 hr. The dark solution was cooled, poured into a solution of 160 ml. of water and 150 ml. of 95% ethanol, and acidified with 12 *N* hydrochloric acid. After standing for 1 hr., the crude acid was removed by filtration and dried. It was obtained as a light pink crystalline solid; 28 g. (90%).

The product was dissolved in 150 ml. of chloroform, treated with charcoal, and filtered. The clear solution was concentrated to about 50 ml., and 100 ml. of methylcyclohexane was added. Filtration gave 24.9 g. (80%) of colorless needles of 1-[2-carboxyphenyl]pyrrole, m.p. 106–107°, $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ε = 7800), 287 mμ (ε = 2150).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.6; H, 4.9; N, 7.5. Found: C, 70.6; H, 4.8; N, 7.4.

9-Keto-9*H*-pyrrolo[1,2-*a*]indole ("Fluorazon"[4]) (IV).—One hundred grams of polyphosphoric acid (115%) at 70° was vigorously stirred while 10 g. (0.054 mole) of solid 1-[2-carboxyphenyl]pyrrole was added in small portions during 15 min. The dark mixture was stirred for 15–20 min., then poured into a mixture of 200 ml. of ethyl acetate and 300 ml. of water. After a 1-hr. stirring period, the organic layer was removed, and the aqueous layer was washed with two 100-ml. portions of ethyl acetate. The combined ethyl acetate extracts were successively washed with 5% sodium bicarbonate solution and saturated sodium chloride solution and were then dried over magnesium sulfate. Filtration and evaporation of the solvent provided a dark semicrystalline residue.

The crude product was dissolved in the minimum amount of chloroform and chromatographed over neutral alumina (Woelm) with chloroform as the eluent. Evaporation of the yellow eluate in a nitrogen stream gave 2.9 g. (32%) of

(6)(a) I. G. Farbenind A.-G., British Patent 457,621, *Chem. Abstr.*, **31**, 3068 (1937); (b) J. Corse, J. Bryant, and H. Shonle, *J. Am. Chem. Soc.*, **68**, 1912 (1946); (c) R. Blume and H. Lindwall, *J. Org. Chem.*, **10**, 255 (1945).

(7) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 53 (1931).

(8) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1019 (1945).

bright yellow, crystalline 9-keto-9*H*-pyrrolo[1,2-*a*]indole. Repeated crystallization from chloroform–methyl cyclohexane gave yellow plates, m.p. 121–122°, $\lambda_{max}^{C_2H_5OH}$ (mμ) 243 (sh) (ε = 25,150), 251 (ε = 31,400), 273 (ε = 8600), 277 (ε = 8780), 283 (ε = 9650), 333 (ε = 9210).

Anal. Calcd. for $C_{11}H_7NO$: C, 78.1; H, 4.2; N, 8.3. Found: C, 78.0; H, 4.3; N, 8.3.

The hydrazone of IV was prepared as follows: 1.59 g. of 85% hydrazine hydrate was added in one portion to a solution of 4.54 g. (0.027 mole) of IV in 35 ml. of absolute ethanol, and the solution was refluxed for 0.5 hr. On cooling, 3.67 g. of light yellow needles separated. These were collected, and the filtrate was concentrated to about 15 ml., whereupon an additional 0.55 g. of hydrazone separated. Treatment of the concentrated filtrate with 2 ml. of 15% hydrazine hydrate, boiling for 15 min., and cooling provided 0.17 g. of hydrazone. The total yield was 4.39 g. (89%). Two crystallizations from ethanol–water gave pale yellow needles, m.p. 171.4–172.2°.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.1; H, 5.0; N, 22.9. Found: C, 72.0; H, 4.7; N, 22.7.

1-(β-Cyanoethyl)pyrrole (VIa. R = CN).[7]—Fourteen grams (0.2 mole) of β-aminopropionitrile was added to a gently swirled mixture of 32 g. (0.2 mole) of 2,5-diethoxytetrahydrofuran in 100 ml. of glacial acetic acid. The solution became hot and developed a red-orange color. The mixture was stirred without external heating overnight (16 hr.) and was then heated for 45 min. in an oil bath at 110–120°. The dark solution was cooled, and acetic acid was removed at a water pump. The residue was fractionally distilled through a semimicro spinning-band column to yield 12.0 g. (50%) of 1-(β-cyanoethyl)pyrrole, b.p. 101°/2 mm. (lit., b.p. 140°/20 mm.).

1-Oxo-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole (VII).[7,9]—A solution of 11.5 g. (0.096 mole) of β-(1-pyrrolyl)propionitrile in 75 ml. of anhydrous ether was cooled in an ice bath and anhydrous hydrogen chloride was passed in slowly. After 2 hr., an orange solid had appeared. The flask was stoppered and refrigerated overnight. Ether was decanted from the solid, the latter was washed once with fresh ether, and the last traces of the solvent were removed *in vacuo*. The resulting yellow crystalline solid was dissolved in 100 ml. of water and warmed on a steam bath 1 hr. The solution was extracted with 50 ml. of benzene and then heated an additional hour. After two further extractions with 50-ml. portions of benzene, the organic phase was dried over anhydrous sodium sulfate. Removal of the solvent provided 4 g. (34%) of a clear oil which crystallized on scratching. Recrystallization from petroleum ether and chloroform gave needles, m.p. 56–57.5° (lit., m.p. 54°).

1-(β-Ethoxycarbonylethyl)pyrrole (VIb. R = —$COOC_2H_5$).[7]—When a solution of 7.0 g. (0.06 mole) of ethyl β-aminopropionate in 25 ml. of glacial acetic acid was treated with 9.6 g. (0.06 mole) of 2,5-diethoxytetrahydrofuran, a vigorous exothermic reaction occurred, and the solution became light brown. After standing overnight without external heating, the solution was heated at reflux 1 hr. and then cooled. Acetic acid was removed by distillation at a water pump, and the residue was fractionally distilled to give 5.83 g. (58%) of 1-(β-ethoxycarbonylethyl)pyrrole, b.p. 52–58°/3 mm. (lit., b.p. 122°/23 mm.).

Ethyl β-Aminocrotonate.—A rapid stream of anhydrous ammonia was passed into 250 ml. of ethyl acetoacetate.[10] The temperature was held at 30–35° during the 5 hr. in which the ammonia was introduced. The reaction mixture comprised two layers. The small top layer (aqueous ammonia) was discarded, and the product was diluted with ether and dried over sodium sulfate. After distilling the ether and an intermediate fraction, the ethyl β-aminocrotonate (218 g.) distilled, b.p. 103–108°/16 mm., m.p. 33°, $n^{25}D$ 1.4982.

Ethyl β-Aminobutyrate.—A pressure vessel was charged with a solution of 129 g. (1 mole) of the ethyl β-aminocrotonate prepared above and approximately 10 g. of freshly prepared Raney nickel in 100 ml. of ethanol. The hydrogenation required 4.5 hr. at 40° and 1600 p.s.i. The catalyst was removed by filtration and the ethanol was distilled. The ethyl β-aminobutyrate, 86 ml., had b.p. 60–61°/13 mm., $n^{25}D$ 1.4233.

Anal. Calcd. for $C_6H_{13}O_2N$: Neut. equiv., 131. Found: Neut. equiv., 130.

Ethyl β-(1-Pyrrolyl)butyrate (VIII).—Ethyl β-aminobutyrate (26.2 g., 0.2 mole) and 32 g. (0.2 mole) of 2,5-diethoxytetrahydrofuran were heated with 50 ml. of glacial acetic acid. When the reaction mixture reached a temperature of 120° distillation commenced, and the temperature dropped to 100°. Ethanol distilled from the reaction mixture followed by water and acetic acid. The bulk of the acetic acid was distilled at 25°/5 mm. The ethyl β-(1-pyrrolyl)butyrate (32 g., 88%) distilled at 73–77°/0.2 mm., $n^{25}D$ 1.4715.

β-(1-Pyrrolyl)butyric Acid (VIII. R = H).—Ethyl β-(1-pyrrolyl)butyrate (27.2 ml., 0.15 mole), 70 ml. of methanol, and 35 ml. of an aqueous solution containing 0.2 mole of sodium hydroxide was mixed to give a clear solution. The solution was allowed to stand at room temperature for 5 days, and the methanol was removed by distillation at atmospheric pressure. After part of the methanol had distilled, 100 ml. of water was added and the distillation was continued until a total of 160 ml. had distilled. To the aqueous solution in the still pot, 20 ml. of concentrated hydrochloric acid was added. The product separated as an almost colorless oily phase. The phases were separated and the aqueous solution was extracted with ether. The organic fractions were combined and the ether was distilled. Toluene was added and distilled at atmospheric pressure to dry the product. The last of the toluene was removed by heating at a pressure of 5 mm. The β-(1-pyrrolyl)butyric acid thus obtained was a yellow oil, 20.3 g. (89%).

Anal. Calcd. for $C_8H_7O_2N$: Neut. equiv., 153. Found: Neut. equiv., 155.

3-Methyl-1-oxo-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole (IX).—β-(1-Pyrrolyl)butyric acid (4.6 g.) was added to 95 g. of polyphosphoric acid (115%) and the mixture was held at 80–100° for 20 min. with vigorous stirring. The ether extractable fraction from this experiment was acid-free, indicating that the reaction had gone to completion. The keto pyrrole ($\lambda_{max}^{C_2H_5OH}$ 283 mμ) was isolated as a brown oil upon evaporation of the ether.

The crude product was placed on a column of neutral alumina (Woelm) and the neutral ketone was rapidly eluted with chloroform. Evaporation of the eluate gave 3-methyl-1-oxo-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole as a light yellow oil which did not crystallize even on cooling.

Reaction with hydroxylamine gave the oxime which crystallized from aqueous methanol as feathery needles, m.p. 151–152°.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 64.0; H, 6.68; N, 18.7. Found: C, 64.1; H, 6.72; N, 19.0.

Methyl β-Aminoglutaconate.—An approximately saturated solution was prepared by passing anhydrous ammonia into methanol cooled in ice (the solution was found by titration to be 11 *M*). To 327 ml. (2.25 moles) of methyl acetonedicarboxylate (Charles Pfizer and Co.) in a 1-l. distilling flask was added 219 ml. (2.4 moles) of the methanolic ammonia solution. When the first part of the ammonia solution was added, a bright yellow color appeared. This color disappeared upon addition of the rest of the ammonia solution. The reactants warmed considerably upon mixing, and the mixture was brought back to room temperature by cooling for a short time in an ice bath.

After standing for 3 days at room temperature, the mixture had acquired a grayish amber color with a greenish blue fluorescence. The methanol, water, and ammonia were distilled under reduced pressure. By titration this

(9) R. Adams, private communication.

(10) A. C. Cope, *et al.*, *J. Am. Chem. Soc.*, **67**, 1019 (1945).

distillate (205 ml.) was found to be 0.5 *M* in ammonia and thus represented a recovery of 0.1 mole of ammonia. The methyl β-aminoglutaconate (358 g., 92%, $n^{25}D$ 1.5067) was then distilled, b.p. 120–130°/*ca.* 1 mm., whereupon a residue of 17 g. remained. The infrared spectrum of methyl β-aminoglutaconate had four bands in the double bond region (1580, 1640, 1690, and 1760 $cm.^{-1}$) and two in the N—H stretch region (3500 and 3650 $cm.^{-1}$).

Anal. Calcd. for $C_7H_{11}O_4N$: C, 48.6; H, 6.40; N, 8.09. Found: C, 48.7; H, 6.39; N, 8.19.

Upon fractional distillation of this ester, a high-boiling fraction was obtained which crystallized. This material was presumed to be one of the geometrical isomers of the aminoglutaconic ester. Accordingly, a preparation was conducted (similar to the one described above) in which some of the solid material was used to seed the reaction mixture. From this preparation, crystalline methyl β-aminoglutaconate, m.p. 50–52°, was obtained in 72% yield directly from the reaction mixture. An additional 10% crystallized from the filtrate following concentration.

Methyl β-Aminoglutarate.—Hydrogenations of methyl β-aminoglutaconate were carried out with both the distilled liquid product and with the crystalline solid. In each case, the same saturated amino ester was obtained.

A pressure vessel was charged with 93 ml. (0.64 mole) of distilled liquid methyl β-aminoglutaconate, 75 ml. of methanol, and 15 g. of an active, freshly prepared Raney nickel catalyst. This mixture was pressured with hydrogen to 2000 p.s.i. and heated at 60° for 6 hr. At the end of this time, the nickel was removed by filtration and washed with four portions of methanol. The methanol was distilled under reduced pressure. The methyl β-aminoglutarate, b.p. 81°/*ca.* 0.2 mm., $n^{25}D$ 1.4459, weighed 97 g. (87%). The infrared spectrum of this ester showed a strong absorption at 1750 $cm.^{-1}$ and a much weaker absorption at 1640 $cm.^{-1}$. In the N—H stretching region only a band at 3500 $cm.^{-1}$ was present.

Anal. Calcd. for $C_7H_{13}O_4N$: C, 48.0; H, 7.48; N, 8.00. Found: C, 48.4; H, 7.58; N, 7.99.

Methyl β-(1-Pyrrolyl)glutarate (X. R = CH_3).—To 50 ml. of acetic acid in a distillation flask was added 30.5 ml. (0.2 mole) of methyl β-aminoglutarate prepared above. The addition raised the temperature from 25° to approximately 70°. To this hot mixture 32 ml. (0.19 mole) of 2,5-diethoxytetrahydrofuran (Eastman Organic Chemicals) was added. After the mixture had stood at room temperature for approximately 20 hr., it was distilled slowly through a Vigreux column at atmospheric pressure. The ethanol formed distilled at approximately 80° and was followed by a fraction, b.p. 101–113°, which was a mixture of water and acetic acid. The remaining acetic acid was distilled to a pot temperature of 60°/10 mm. Methyl β-(1-pyrrolyl)-glutarate, 36.2 g. (85%), then distilled at approximately 120°/0.5 mm., leaving a solid residue of 6 g. The product, which solidified in the receiver, was insoluble in water, very soluble in benzene and acetone, and moderately soluble in methanol from which it could be crystallized. Thus, 32 g. was recrystallized from 150 ml. of methanol to give 27.5 g., m.p. 80–81°.

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.7; H, 6.71; N, 6.22. Found: C, 58.8; H, 6.66; N, 6.31.

β-(1-Pyrrolyl)glutaric Acid (X. R = H).—To 135 g. (0.60 mole) of methyl β-(1-pyrrolyl)glutarate and 350 ml. of methanol was added 270 ml. of an aqueous solution containing 1.8 moles of sodium hydroxide. The resulting clear solution was refluxed for 2 hr., and then methanol (390 ml.) was removed by distillation at atmospheric pressure. The aqueous solution remaining in the distillation flask was diluted with 70 ml. of water and acidified by adding 167 ml. of concentrated (12 *M*) hydrochloric acid (2.0 moles). The resulting hot solution was immediately cooled in ice and seeded with pyrrolyl glutaric acid, whereupon crystallization occurred. The solid was isolated by filtration and sucked dry. The β-(1-pyrrolyl)glutaric acid thus obtained weighed 96 g. (82%), m.p. 125–127°.

Anal. Calcd. for $C_9H_{11}O_4N$: Neut. equiv., 99. Found: Neut. equiv., 104.

Cyclization of β-(1-Pyrrolyl)glutaric Acid.—The cyclization was conducted in a 1-l., wide-mouthed Erlenmeyer flask equipped with a sturdy paddle stirrer and a thermometer and heated by a hot plate that could be raised and lowered. The β-(1-pyrrolyl)glutaric acid (49.2 g., 0.25 mole) was dissolved in 50 ml. of warm tetrahydrofuran in a small flask. The resulting solution was added with stirring to 375 g. of polyphosphoric acid (Victor Chemical Works) which had been heated to 80°. The reaction was exothermic. The mixture was maintained at 90–100° for 10 min. Water was then added cautiously (the temperature rose to 130° after about 10 ml. had been added) to give a final volume of 1320 ml. This clear, dark solution had an ultraviolet maximum at 293 mμ (ε 2670). If one assumes that this absorption is all due to the desired keto acid and that the acid has an ε of 16,500, this solution is 0.162 *M* and contains a total of 0.214 mole (86% yield). The aqueous solution was extracted with ether for 20 hr. in a continuous extractor. The ethereal extract was a clear, yellow solution with a volume of about 700 ml. It was seeded with anhydrous keto acid and refrigerated for 16 hr. The anhydrous keto acid crystallized as dense coral crystals, 19.9 g., m.p. 121–124°. The ethereal solution was extracted with aqueous alkali and the alkali was neutralized to precipitate 4.5 g. of the keto acid hydrate, m.p. *ca.* 79°. The aqueous mother liquor was extracted with ether continuously for 8 days. The ether extract was treated with aqueous alkali, and the resulting solution of the salt was acidified to yield an additional 10.4 g. of the keto acid hydrate. The total yield of keto acid (both anhydrous and hydrated) was 75%.

The aqueous solution at the end of the extraction had an ultraviolet maximum at 298 mμ (ε 242). If one assumes that the solute has a molecular extinction coefficient of 16,500, the solution is 0.015 molar. Extraction of this solution with ether failed to transfer anything to the ethereal phase, demonstrating that the compound then present is very hydrophilic and essentially non-extractable. A portion of this aqueous phase was refluxed for 16 hr. to effect the hydrolysis of any polyphosphate linkages and was again extracted with ether. No material was extracted. This indicates that the keto-pyrrole is not attached to the hydrophilic group by a hydrolytically sensitive bond.

A sample of crude hydrated keto acid was dissolved in ether and the resulting solution was treated with Darco and anhydrous magnesium sulfate. The solution was filtered through Celite and concentrated, whereupon white keto acid, m.p. 128–134°, crystallized. This material had an ultraviolet maximum in ethanol at 287 mμ (ε 18,250) with a shoulder at 250 mμ (ε 3400).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.3; H, 5.06; N, 7.82; neut. equiv., 179; carbonyl equiv., 179. Found: C, 59.9; H, 5.07; N, 7.87; neut. equiv., 180; carbonyl equiv., 205.

In ether, the ultraviolet maximum moved to a shorter wave length (283 mμ), and the extinction coefficient increased somewhat. In water, the maximum occurred at 293 mμ and had a lower extinction coefficient (ε 16,500). The infrared spectrum had absorption at 5.77 and 6.0 μ.

The partition coefficient (ether/water) for the keto acid is 0.77. The starting material, β-(1-pyrrolyl)glutaric acid, has a partition coefficient (ether/water) of 1.7. It is surprising that the keto acid is more hydrophilic than the dicarboxylic acid.

2,5-Di(*N*-pyrrolyl)-3,4-dicyanothiophene (XII).[11]—A solution of 1.6 g. (0.01 mole) of 2,5-diamino-3,4-dicyano-

(11) The authors are indebted to Dr. J. R. Roland for this experiment.

(12)(a) W. J. Middleton, U.S. Patent 2,801,908 (1957); (b) W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc.*, **80**, 2822 (1958).

thiophene[12a,b] in 10 ml. of glacial acetic acid was cooled in an ice bath, and 3.2 g. (0.02 mole) of 2,5-diethoxytetrahydrofuran was added in one portion. The cooling bath was removed, and the mixture was stirred at room temperature overnight. The dark solution was then heated at reflux for one hour and allowed to cool. The crude 2,5-di(*N*-pyrrolyl)-3,4-dicyanothiophene was filtered, washed with cold acetic acid, and dried. There was obtained 0.58 g. (22%). Recrystallization from acetic acid gave material with m.p. 164–165°.

Anal. Calcd. for $C_{14}H_8N_4S$: C, 63.6; H, 3.05; N, 21.2, S, 12.1. Found: C, 63.5, H, 3.35; N, 20.4; S, 12.1.

Cyanocarbon Chemistry. XXII.[1] 3,4-Dicyano-1,2,5-triaminopyrrole and Its Derivatives

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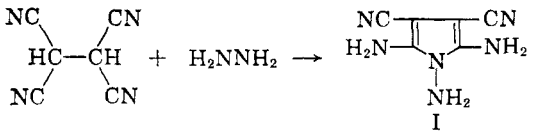
Received November 14, 1961

Tetracyanoethane and hydrazine hydrate react to form 3,4-dicyano-1,2,5-triaminopyrrole. All three amino groups in this compound condense with aldehydes to form anils. With 1,2- and 1,3-dicarbonyl compounds cyclization occurs to form pyrrolotriazines and pyrrolotriazepines, two new ring systems.

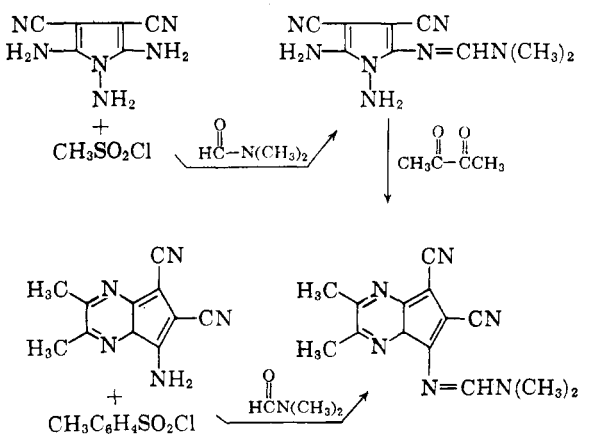
The addition of hydrazine to nitriles is a well known reaction that leads to triazoles and triazines.[2] We have found that 1,1,2,2-tetracyanoethane reacts rapidly with hydrazine hydrate in aqueous solution under mild conditions to give 3,4-dicyano-1,2,5-triaminopyrrole. This reaction is analogous to the reaction of hydrogen sulfide with tetracyanoethane to give 2,5-diamino-3,4-dicyanothiophene.[3]



I

This pyrrole is insoluble in 5% hydrochloric acid in spite of the three amino groups, and it is only slightly soluble in most organic solvents but dissolves readily in dimethylformamide.

The three amino groups can be condensed with dimethylformamide under the influence of three moles of *p*-toluenesulfonyl chloride to give a trisamidine. This reaction serves to emphasize the character of the amino groups, since only weakly basic amines undergo this reaction. For example, we observed this same reaction with 2,5-diamino-3,4-dicyanothiophene and with *p*-nitroaniline, while aniline and *p*-chloroaniline give the sulfonanilides under these conditions. The condensation of tertiary amides with the amino group of sulfonamides has been reported.[4] When only one mole of *p*-toluenesulfonyl chloride is used, a monoamidine results. This was shown to be in the 2-position for it condensed readily with bi-acetyl to give a product identical with that obtained running the condensations in reverse order.



Condensation with aromatic aldehydes gives either dianil (II) or trianil (III) derivatives, depending upon the aldehyde and the conditions. Formation of a trianil establishes that compound I has the pyrrole structure and not the alternative 3,6-diamino-1,2-dihydropyridazine structure.

There are two possible structures for the dianil. We favor the 1,2-dianil over the 2,5-dianil structure. The initial condensation would be expected to occur in the 2-position from the result with dimethylformamide and *p*-toluenesulfonyl chloride. However, when we attempted to prepare a monobenzal derivative, the only product that we isolated was the dibenzal derivative in greater than 50% yield. This was true even when the reaction was run at room temperature in dimethylformamide with acid catalysis. While it is difficult to explain why the formation of the benzal derivative should activate either the 1 or 5 amino groups, one would expect that the 5-amino would be deactivated under these circumstances and the 1-amino group

(1) Paper XXI, R. H. Boyd, *J. Chem. Phys.*, **65**, 1834 (1961).
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(3) W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc.*, **80**, 2822 (1958).
(4) E. Enders, German Patent 949,285 (1956).