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Synthesis of Pyridoxine. II. The Preparation of Pyrrole Derivatives

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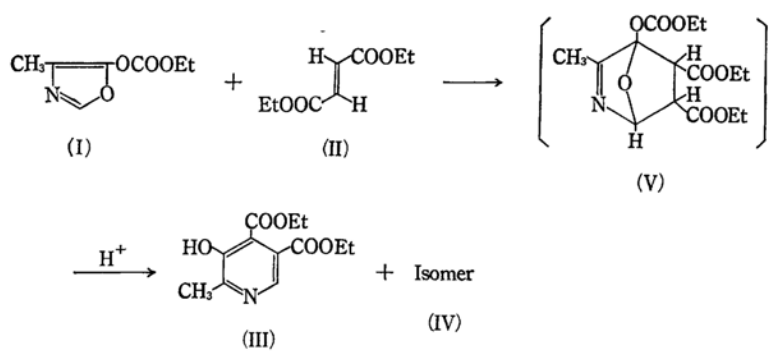
A new method for the synthesis of 2-acetyl-3, 4-diethoxycarbonylpyrrole and its derivatives by the Diels-Alder reaction is described, and the reaction mechanism of their formation is discussed.

In the previous paper,[1] we reported that 5-ethoxycarbonyloxy-4-methyloxazole (I) reacted with diethyl fumarate (II) to give 4, 5-diethoxycarbonyl-3-hydroxy-2-methylpyridine (III). Investigating this reaction furthermore, we found an isomer of III was produced as by product. The isomer III was also obtained by treatment of the intermediate (V), shown in Scheme 1, in the aftermentioned reaction, with ethanolic hydrochloric acid only in 10—20% yield, but the yield of IV was increased to 50—60%, when the ethanolic hydrochloric acid was replaced by aqueous hydrochloric acid as shown in Table 1.

In this paper, we will confirm the structure of IV as 2-acetyl-3, 4-diethoxycarbonylpyrrole and discuss the reaction mechanism. Although the synthesis of pyridine derivatives by the Diels-Alder reaction has been reported by a number of workers,[2] the formation of pyrrole derivatives as described here has never been noticed.

The compound IV is a weakly acidic substance and insoluble in both diluted hydrochloric acid and sodium bicarbonate solution. An ultraviolet (UV) spectrum of IV had absorption maxima at 281 mμ ($\log \varepsilon = 4.712$) in ethanol. The nuclear magnetic resonance (NMR) spectrum of IV had two triplets at δ 1.31 and 1.40 (6H), a singlet at 2.41 (3H), two quartets at 4.26 and 4.42 (4H), a doublet at 7.53 (H) and a broad peak at about 10.50 (H) (ppm, $CDCl_3$). On treatment with D_2O, the doublet at δ 7.53 due to an aromatic proton collapsed to a singlet, which indicated



Scheme 1.

The products from the Diels-Alder reaction.

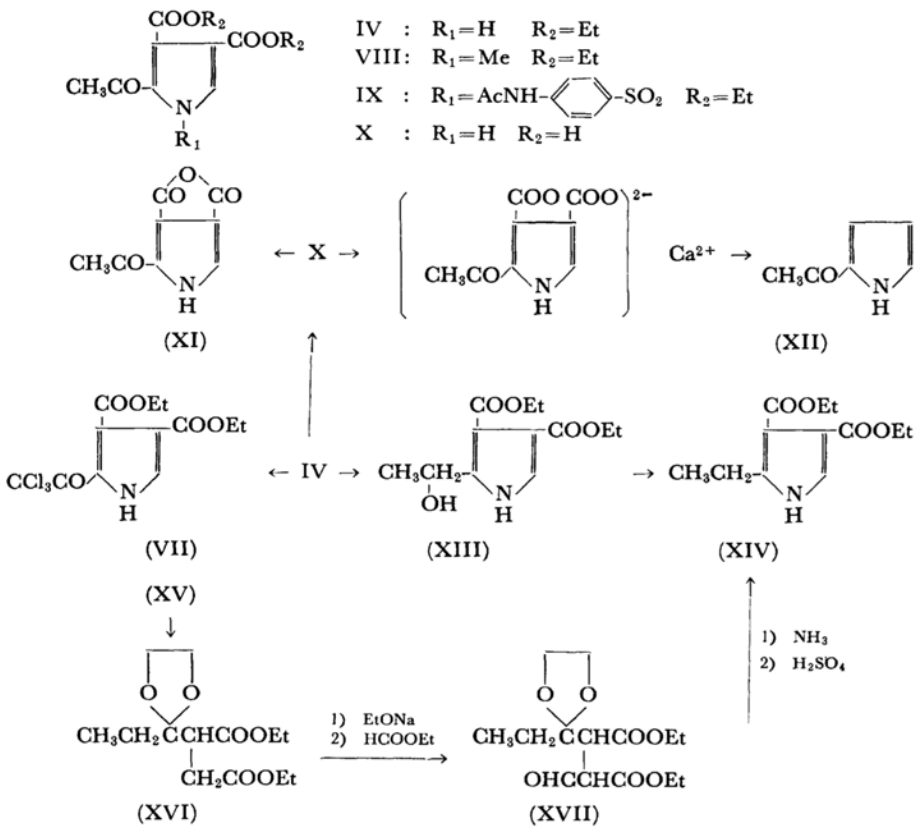
1) M. Murakami and M. Iwanami, This Bulletin, **41**, 726 (1968).

2) Kondratéva, *Izv. Akad. Nauk SSSR*, 484 (1959); E. E. Harris and R. A. Firestone, *J. Org. Chem.*, **27**, 2705 (1962); Rosche Co., Brit. Pat. 971361 (1962).

TABLE 1. THE REACTION OF 5-ETHOXYCARBONYLOXY-4-METHYL OXAZOLE (I) WITH DIETHYL FUMARATE (II)

Exp. No.	Reaction conditions: Temp. °C	Time hr	Molar ratio of II to I	Method of decomposition of adduct (V)	Products and yield, %: III*	IV
A-1	100	2	4	8 N HCl - EtOH	48.6	12.6
A-2	90	6	2	8 N HCl - EtOH	48.8	19.5
B-1	100	2	4	10% HCl - H_2O	17.4	50.0
B-2	90	6	2	10% HCl - H_2O	11.1	54.0

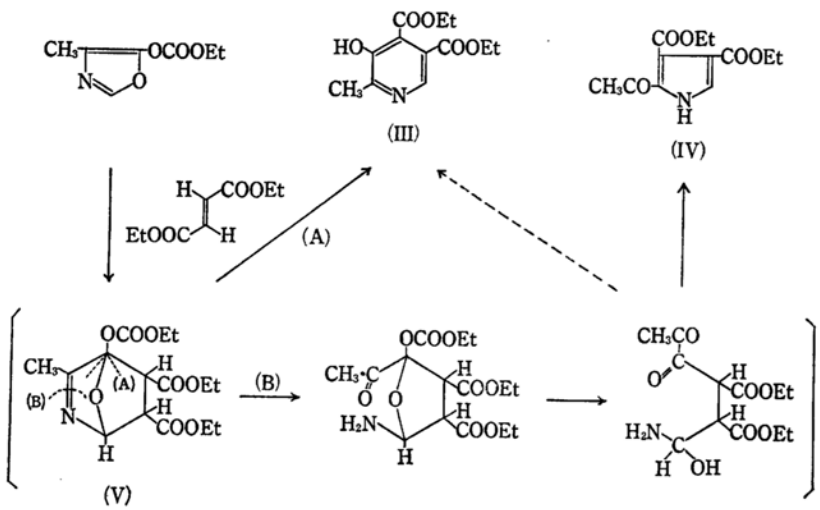
* as hydrochloride



Scheme 2.

The derivatives from the isomer (IV) and authentic compound synthesis route.

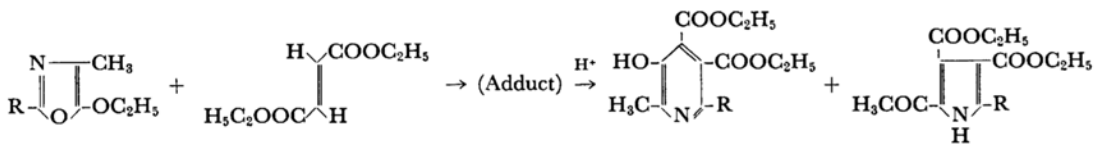
that the aromatic proton was adjacent to =NH or –OH group. The infrared (IR) spectrum of IV had the absorption bands at 3260 (=NH), 1700, 1280 (–$\overset{O}{\overset{\|}{C}}$O–) and 1670, 1360 (C=O) (cm^{-1}, KBr). The presence of an acetyl moiety was ascertained both by the formation of 2, 4-dinitrophenylhydrazone (VI) and a positive iodoform test. Chlorination of IV with phosphorus pentachloride gave the trichloro compound (VII). The NMR spectrum of VII showed no signal at δ 2.41, indicating the CH_3CO– group of IV had been chlorinated to CCl_3CO–. The reaction of IV with diazomethane gave colorless crystals (VIII). The IR spectrum of VIII showed no absorption band at 3260 cm^{-1}, suggesting the absence of =NH group. The presence of =NH group in IV was ascertained also by the formation of its *p*-acetoaminobenzenesulfonamide derivative (IX). Alkaline hydrolysis of IV gave the corresponding dicarboxylic acid (X), proving that IV is an ester. Refluxing of X in acetic anhydride yielded 2-acetyl-3, 4-dicarboxylpyrrole anhydride (XI), the structure of which was confirmed by the characteristic absorption bands of anhydride at 1850 and 1790 cm^{-1} in the IR spectrum. This fact indicated that two –COOH groups in X were situated vicinal to each other. Decarboxylation of the calcium salt of X gave 2-acetylpyrrole (XII). Reduction of IV with sodium borohydride gave a



Scheme 3.

The mechanism of pyridine and pyrrole derivatives formation in this reaction.

Table 2. The reaction of 5-ethoxy-4-methyl oxazole (XVIII) and 2, 4-dimethyl-5-ethoxy oxazole (XIX) with diethyl fumarate (II)



R	Oxazole	Method of decomposition of adduct	Products and yield, %			
			Pyridine deriv.*		Pyrrole deriv	
H	XVIII	8 N HCl - EtOH	III	80	IV	trace
H	XVIII	10% HCl - H_2O	III	30	IV	45
CH_3	XIX	10% HCl - H_2O	XX	80	XXI	10

* as hydrochloride

secondary alcohol XIII, which in turn was transformed into 3, 4-diethoxycarbonyl-2-ethylpyrrole (XIV) by hydrogenation over palladium-charcoal in methanol under acidic condition. This compound XIV was identified with the authentic sample which was prepared from diethyl propionyl succinate (XV) by the method of Kornfeld.[3] (Scheme 2)

Next we examined the NMR spectrum of the reaction mixture of the Diels-Alder reaction and noticed that there was no signal of ring proton as I, III and IV. On the basis of this result, it was presumed that V is considerably stable in the course of the Diels-Alder reaction and is decomposed only by the addition of acid to give pyridine and pyrrole derivatives. As shown in Scheme 3, V would be decomposed by two different pathes (A) and (B). When ethanolic hydrochloric acid was added to V, the oxygen bridge of V would be cleaved to III according to the process A. When aqueous hydrochloric acid was added to V, the hydrolysis of –CH=N– bond of V would predominantly occur to give IV *via* B. The reaction of 5-ethoxy-4-methyloxazole (XVIII) or 2, 4-dimethyl-5-ethoxyoxazole (XIX) with diethyl fumarate (II), or XVIII with diethyl maleate also gave the corresponding pyrrole derivatives as shown in Table 2.

Experimental

The Diels-Alder Reaction (Pyrrole Derivatives): The Reaction of 5-Ethoxycarbonyloxy-4-methyloxazole (I) with Diethyl Fumarate (III). *A) Decomposition of the Reaction Mixture, Adduct (V), with Ethanolic Hydrochloric Acid. A-1)* A mixture of I (8.6 g) and II (34.5 g, 4 equiv.) was heated at 100°C for 2 hr. After cooling, 8 N ethanolic hydrochloric acid (50 m*l*) was added and the mixture was allowed to stand for 30 min at room temperature, then the ethanol was

3) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

removed *in vacuo*. When ether (100 ml) was added to the resulting residue, 4, 5-diethoxycarbonyl-3-hydroxy-2-methylpyridine (III) was precipitated as hydrochloride, which was collected by filtration, 7.0 g (48.6%), mp 147—148°C (decomp.).

Found: C, 49.70; H, 5.58; N, 5.07%. Calcd for $C_{12}H_{15}O_5N \cdot HCl$: C, 49.74; H, 5.57; N, 4.84%.

The mother liquor was washed with water, 5% aqueous sodium bicarbonate and water successively, and dried over anhydrous magnesium sulfate. The solvent, ether and excess II, was removed by evaporation to afford pale yellow oily residue. The residue was dissolved in a small volume of benzene and by addition of petroleum ether, 2-acetyl-3, 4-diethoxycarbonylpyrrole (IV) was precipitated. The product was recrystallized from benzene - petroleum ether to give the pale yellow crystals, mp 101—102°C (2.6 g, 12.6%).

Found: C, 57.21; H, 5.92; N, 5.48%. Calcd for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.97; N, 5.53%.

A-2) A mixture of I (2.0 g) and II (4.0 g, 2 equiv.) was heated at 90°C for 6 hr and the reaction mixture was treated as above. The yield of the hydrochloride of III was 1.65 g (48.8%) and the yield of IV was 0.6 g (19.5%).

B) Decomposition of the Adduct (V) with Aqueous Hydrochloric Acid. B-1) A mixture of I (17.0 g) and II (69.0 g, 4 equiv.) was heated at 100°C for 2 hr. After cooling, 10% aqueous hydrochloric acid (50 ml) was added to the reaction mixture and it was allowed to stand for 30 min at room temperature. The resulting solution was extracted with ether and the ether layer was washed with 5% aqueous hydrochloric acid, water, 5% aqueous sodium bicarbonate and water succesively, and dried over anhydrous magnesium sulfate. The solvent, ether and excess II, was removed by evaporation to afford pale yellow oily residue. The residue was treated as described in A-1) to give IV, yield 12.5 g (50%). The aqueous layer was neutralized with sodium bicarbonate, and was extracted with ether. After the ether solution was washed with water and dried over anhydrous magnesium sulfate, gaseous dry hydrogen chloride was bubbled into the ethereal solution. The compound III was deposited as hydrochloride, yield 5 g (17.4%).

B-2) A mixture of I (1.6 g) and II (3.2 g, 2 equiv.) was heated at 90°C for 6 hr and the reaction mixture was treated as described in B-1). The compound IV was yielded 1.27 g (54%) and III was also obtained as hydrochloride, yield 0.3 g (11.1%).

The Reaction of 5-Ethoxy-4-methyloxazole (XVIII) with Diethyl Fumarate (II). A mixture of XVIII (2.0 g) and II (5.0 g) was heated at 90°C for 1.5 hr and the reaction mixture was decomposed with 10% aqueous hydrochloric acid (5 ml). Treatment of the solution obtained according to the same method as in B-1) yielded IV, 1.8 g (45%) and III, 1.4 g (30%) as hydrochloride. When the reaction mixture was decomposed with 8 N ethanolic hydrochloric acid and the resulting solution was treated by the same method as in A-1), III was obtained as hydrochloride in the yield of 80% and IV in a trace amount.

Instead of II, when the diethyl maleate as dienophile was reacted with XVIII, the results were similar to those mentioned before.

The Reaction of 2, 4-Dimethyl-5-ethoxyoxazole (XIX) with Diethyl Fumarate (II). A mixture of XIX (1.0 g) and II (1.35 g) was heated at 80°C for 1 hr. After removing the exeess II *in vacuo*, aqueous hydrochloric acid (20 ml) was added to the resulting mixture. After stirring for 20 min, ethanol (10 ml) was added to the solution, and homogeneous solution thus obtained was stirred for further 10 min. The solution was evaporated *in vacuo* until ethanol was largely removed and the remaining aqueous phase was extracted twice with chloroform (50 ml). The chloroform layer was washed with 5% aqueous sodium bicarbonate and water, and dried over anhydrous magnesium sulfate. The solvent was removed by evaporation to yield an oily residue. On addition of 8 N ethanolic hydrochlorio acid, the pyridine derivative, 3, 4-diethoxycarbonyl-2, 6-dimethyl-5-hydroxypyridine (XX), was precipitated as hydrochloride. After collecting the product by filtration, *n*-hexane was added to the mother liquor, 2-acetyl-3, 4-diethoxycarbonyl-5-methylpyrrole (XXI) was precipitated, which was recrystallized from benzene - *n*-hexane to afford colorless needles, mp 103—104°C. Yield 200 mg.

Found: C, 58.64; H, 6.21; N, 5.69%. Calcd for $C_{13}H_{17}O_5N$: C, 58.42; H, 6.41; N, 5.24%. IR (KBr-Wafer): 3300 (=NH); 1652 cm^{-1} (C=O)

The aqueous layer, after being extracted with chloroform, was neutralized with 5% aqueous sodium bicarbonate and extracted with ether. The extract was washed with water and dried over anhydrous magnesium sulfate. Gaseous hydrogen chloride was passed into this ethereal solution to give XX as hydrochloride, mp 150°C (decomp.). The total yield of XX as hydrochloride was 1.8 g (80%).

Found: C, 51.69; H, 6.00; N, 4.85%. Calcd for $C_{13}H_{17}O_5N \cdot HCl$: C, 51.40; H, 5.97; N, 4.61%.

The Reaction of the Isomer (IV). 2, 4-Dinitrophenylhydrazone of IV (VI). To a solution of IV (0.5 g) in 95% ethanol, 2, 4-dinitrophenylhydrazine sulfuric acid solution was added. After heating at 50°C for several min, the reaction mixture was allowed to stand overnight at room temperature. The precipitated crystals were collected and recrystallized five times from 95% ethanol. The compound VI was obtained as monohydrate of orange needles, yield 0.7 g. After drying over phosphorus pentoxide at 100°C for 6 hr *in vacuo*, VI changed into anhydrous red crystals, mp 195°C (decomp.).

Found: C, 49.84; H, 4.55; N, 16.29%. Calcd for $C_{18}H_{19}O_8N_5$: C, 49.88; H, 4.42; N, 16.16%.

3, 4-Diethoxycarbonyl-2-trichloroacetylpyrrole (VII). A mixture of IV (0.4 g), phosphorus oxychloride (5 ml) and phosphorus pentachloride (1.5 g) was heated at 120°C for 4 hr. After phosphorus oxychloride was removed, water was added to the oily residue and the mixture was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give white crystals. Recrystallization of the product from benzene afforded VII (0.2 g), needles, mp 195°C (decomp.). Found: Cl, 30.38%. Calcd for $C_{12}H_{12}O_5NCl_3$: Cl, 29.83%.

2-Acetyl-3, 4-diethoxycarbonyl-1-methylpyrrole (VIII). Into an ethereal solution of diazomethane which was prepared from *N*-nitrosomethyl urea (4 g), 2.0 g of IV was dissolved and the mixture was allowed to stand overnight at room temperature. VIII was deposited

from the solution as white needles, mp 117—118°C. Yield 1.4 g.

Found: C, 58.54; H, 6.35; N, 5.43%. Calcd for $C_{13}H_{17}O_5N$: C, 58.42; H, 6.41; N, 5.24%. IR (KBr-Wafer): 1660 cm^{-1} (C=O). NMR ($CDCl_3$): singlet (3H) at δ 3.90 (N–CH_3).

1-(*p*-Acetoaminobenzenesulfonyl)-2-acetyl-3,4-diethoxycarbonylpyrrole (IX). To a suspension of the sodium salt of IV (1.53 g) in anhydrous pyridine (10 m*l*), *p*-acetoaminobenzenesulfonyl chloride (1.8 g) was added at room temperature. After stirring for 2 hr, the reaction mixture was poured into water and extracted with chloroform. The extract was washed with 5% aqueous hydrochloric acid, water, 5% aqueous sodium bicarbonate and water successively, and dried over anhydrous magnesium sulfate. Evaporation of the solvent left a crude product of IX, which was recrystallized from chloroform-ether to give 1.6 g of IX mp 179—180°C. Found: C, 53.28; H, 4.82; N, 6.23%. Calcd for $C_{20}H_{22}O_8N_2S$: C, 53.33; H, 4.92; N, 26.2%.

2-Acetyl-3,4-dicarboxylpyrrole (X). The compound IV (3.0 g) was dissolved in 20% aqueous sodium hydroxide (20 m*l*) and the solution was refluxed for 1.5 hr. The reaction mixture was cooled with ice-water and then strongly acidified with conc. hydrochloric acid. The precipitated product was collected and recrystallized from water. After drying over phosphorus pentoxide at 100°C for 6 hr, 2.0 g of X was obtained as yellow platelets, mp 210°C (decomp.).

Found: C, 48.72; H, 3.66; N, 7.42%. Calcd for $C_8H_7O_5N$: C, 48.74; H, 3.58; N, 7.11%.

2-Acetyl-3,4-dicarboxylpyrrole Anhydride (XI). A mixture of X (500 mg), acetic anhydride (6 m*l*) and glacial acetic acid (2 m*l*) was heated at 140°C for 4 hr. After cooling, the solvent was removed *in vacuo*. The residue was dissolved in ether and an insoluble product was removed. The ethereal solution was evaporated to give the crude product of XI, which was recrystallized from ethyl acetate to afford pale yellow needles, mp 196—197°C (decomp.). Yield 360 mg.

Found: C, 53.62; H, 2.82; N, 8.10%, Cacld for $C_8H_5O_4N$: C, 53.64; H, 2.81; N, 7.82%. IR (KBr-Wafer): 1850, 1790 cm^{-1} (–CO–O–CO–)

2-Acetylpyrrole (XII). To an aqueous solution of X (1.0 g), calcium carbonate (0.5 g) was added and heated at 110°C. The slurry was dried up to give the calcium salt of X, which was heated over an alcohol lamp under reduced pressure (15—20 mmHg) to give dark yellow oily product. This material was fractionally distilled under the same pressure to afford pale yellow oily product, which was crystallized to give white needles of XII, mp 90—91°C. Yield 50 mg.

Found: N, 12.62%. Calcd for C_6H_7ON: N, 12.84%. IR (KBr-Wafer): 3240 (=NH), 1640 cm^{-1} (C=O).

3,4-Diethoxycarbonyl-2-(α-hydroxyethyl)pyrrole (XIII). To a methanolic solution of IV (5.0 g), sodium borohydride (2.0 g) was added in portionwise at 5—10°C for 20 min. The reaction mixture was neutralized to pH 7 with 10% aqueous hydrochloric acid and methanol was largely removed, and the remaining aqueous phase was extracted with ether. After the ethereal solution was dried over anhydrous magnesium sulfate, the solvent was distilled off and the residue was recrystallized from benzene to afford white crystal of XIII, mp 109—110°C. Yield 4.5 g.

Found: C, 56.45; H, 6.65; N, 5.68%. Calcd for $C_{12}H_{17}O_5N$: C, 56.46; H, 6.71; N, 5.49%.

3,4-Diethoxycarbonyl-2-ethylpyrrole (XIV). To a methanolic solution of XIII (500 mg), conc. hydrochloric acid (0.1 m*l*) and 5% palladium charcoal (1.2 g) were added and hydrogenation was carried out at room temperature. After the reaction was over, the catalyst was filtered off and the filtrate was evaporated *in vacuo* at or below 40°C. The oily residue was extracted with ether, washed with water, 5% aqueous sodium bicarbonate and water successively, and dried over anhydrous magnesium sulfate. After removing the solvent, colorless oily residue was dissolved in a small amount of benzene, and *n*-hexane was added until the solution became turbid. The resulting mixture was allowed to stand several days in a freezer. The product XIV was crystallized as white prisms, which was recrystallized from benzene-*n*-hexane, mp 106—107°C. Yield 90 mg.

Found: C, 60.15; H, 7.10; N, 6.16%. Calcd for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.86%.

The structure of XIV was identified with an authentic sample prepared from diethylpropionyl succinate (XV).

3,4-Diethoxycarbonyl-2-ethylpyrrole (XIV) from Diethylpropionyl Succinate (XV). Diethyl-1-(α-ethylenedioxy)propyl Succinate (XVI). A mixture of diethylpropionyl succinate (XV) (10 g), ethylene glycol (10 m*l*), *p*-toluenesulfonic acid (0.7 g) and benzene (350 m*l*) was refluxed for 25 hr. The benzene solution was washed with 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and fractionally distilled under reduced pressure to give XVI, bp 115—120°C/0.3 mmHg. Yield 4 g.

Diethyl-1-(α-ethylenedioxy)propyl-2-formyl Succinate (XVII). Finely divided sodium (0.35 g) was suspended in 10 m*l* of absolute ether, and absolute ethanol (0.1 m*l*) was added with stirring. A mixture of XVI (3.5 g) and ethyl formate (1.45 g) was added dropwise to the ethereal solution during 1 hr and the reaction mixture was allowed to stand overnight. Ice and water were added to the solution, the aqueous layer was separated and acidified with 10% aqueous sulfuric acid at or below 0°C. The aqueous layer was extracted twice with ether (20 m*l*) and the extract was dried over anhydrous magnesium sulfate. After removing the solvent, the oily residue was distilled under reduced pressure at 120°C to afford XVII 0.9 g. The crude product was sufficiently pure for cyclization.

3,4-Diethoxycarbonyl-2-elthylpyrrole (XIV). A solution of crude XVII (0.75 g) in 5 m*l* of absolute ether was mixed with ammoniac ethanol (0.6 m*l*). The mixture was stirred for 10 min and evaporated under reduced pressure to remove ether and ethanol. The residual oily product was mixed with 2 m*l* of concentrated sulfuric acid keeping the temperature below 55°C. After 5 min, the sulfuric acid solution was poured onto 10 g of ice with stirring. The mixture was extracted twice with 10 m*l* of ethyl acetate and the extract was washed with 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and the solvent was evaporated. The residual product was extracted with boiling water. After cooling the extract, the deposited white crystalline product was collected and dried over phosphorus pentoxide *in vacuo*.

Recrystallization from benzene-*n*-hexane afforded XIV as white needles, mp 106—107°C. Yield 120 mg.

Found: C, 60.41; H, 7.27; N, 5.78%. Calcd for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.86%.

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