[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

Acylization of Pyrryl Carboxylic Esters[1,2]

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The reaction of concentrated or fuming sulfuric acid with pyrroles containing a carbethoxy group was first recognized by Fischer and Walach[4] in 1925, using Knorr's pyrrole, 2,4-dimethyl-3,5-dicarbethoxypyrrole. These investigators found that the carbethoxy group in the 3 or β position was changed to a carboxyl group by dissolving the pyrrole in the acid and warming to 35° for approximately thirty minutes, then pouring the solution over ice. Fischer referred to this reaction as hydrolysis, but the concept of a true hydrolysis taking place in concentrated sulfuric acid is so difficult to grasp that it seems reasonable to seek an alternative explanation. Treffers and Hammett[5] have found that 2,4,6-trimethylbenzoic acid forms an acyl ion in sulfuric acid. The assumption that it is this reaction which Fischer observed and utilized in the pyrrole series seems most likely.

The hypothesis that acyl ions can form in the pyrrole series was tested by examining the freezing point depression in sulfuric acid solution.[6] Newman, Kuivila and Garrett have shown that esters which form acyl ions should give a van't Hoff "*i* factor" of 5 due to the formation of alkyl sulfuric ester, acyl ion, two bisulfate ions and hydronium ion. It was found that Knorr's pyrrole gives a van't Hoff factor of 3.5, indicating incomplete acylization. This is consistent with Fischer's observation that a temperature of 35° is desirable for preparative purposes instead of 10–11° that is used for the freezing point measurements.

As a further check on the hypothesis of acyl ion formation, the β-acid formed by the action of sulfuric acid on Knorr's pyrrole was dissolved in 100% sulfuric acid and poured into methanol. About one-third of the recovered product was found to be esterified, in agreement with the hypothesis of incomplete acylization.

It is evident that the balance between steric and electronic factors which was found by Hammett to control acylization in the benzene series must be altered in the pyrrole series. Assuming that all interior angles in pyrrole are equal, the exterior angle between the ring and a substituent would be 126° in the pyrrole system as against 120° in the benzene system, thus giving rise to decreased steric hindrance in the former case. Pyrrole is a very weak base which is stable in aqueous solution to approximately *p*H 1 and, on further acidification, decomposes without the formation of a stable salt.[7] The small tendency of the pyrryl nitrogen to salt formation will be still further diminished by the substitution of the electron-attracting carbethoxy group in the ring. On the other hand, the nitrogen atom of the pyrrole ring is a facile donor of electrons to the carbons, an effect which Treffers and Hammett showed to favor the formation of acyl ions. If this latter tendency were carried too far, however, cation formation would take place on the ring instead of on the carbethoxy group. This would result in a decrease in electron density instead of an increase and acylization would then be hindered. Examples of these effects can be found among substituted pyrroles.

Chart I shows a series of ester reactions with sulfuric acid, together with transformations to prove the structures of the resulting products.

Substitution of the 2-methyl group in Knorr's pyrrole by carboxyl gives compound I. This change makes a 60–65° increase in temperature necessary to bring about the reaction of acylization, indicated by the formation of compound IV. The use of fuming sulfuric instead of concentrated sulfuric lowered the reaction temperature by 20°. The course of this reaction was checked by the conversion of compound V to VI. Analysis demonstrates that the ethyl group, not the methyl, is lost, showing reaction in the α position. The increase in reaction temperature brought about by the substitution of an electron-attracting carboxyl group is consistent with Hammett's finding that such groups hinder the formation of acyl ions. This is confirmed by the observation that the "*i*" value for this substance is 2.5 instead of 5.

The esterification of compound I yields compound II. Because of the additional alkyl group, II should be more basic and hence more reactive than I. Compound II was found to react at 20° lower temperature than compound I, yielding compound III.

The fact that acylization takes place in the α position instead of the β is remarkable, since there is only one group adjacent to the α position, which thus has considerably less steric facilitation of the reaction than the β position. This peculiarity of the pyrrole system is even more striking in the case of compound VII, in which neither ester group has two adjacent groups. The reaction of conversion to compound VIII appears to take place quite readily as the corresponding reaction of Knorr's pyrrole, in which the hydrogen of position 2 is substituted by a methyl. The fact that the reaction occurs at all with compound VII

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[1] Studies in the Pyrrole Series, XXI; Paper XX, Corwin and Straughn, THIS JOURNAL, **70**, 1416 (1948).

[2] This paper is taken from the doctoral dissertation of John Lloyd Straughn, The Johns Hopkins University.

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[4] Fischer and Walach, *Ber.*, **58**, 2820 (1925).

[5] Treffers and Hammett, THIS JOURNAL, **59**, 1708 (1937).

[6] Freezing point data reported here were obtained by Mr. Lester Kuhn. The apparatus used was essentially that of Newman, Kuivila and Garrett, *ibid.*, **67**, 704 (1945).

[7] Miller, *ibid.*, **64**, 1543 (1942).

demonstrates that electronic factors can facilitate the reaction effectively in the face of insufficient steric aid. The structure of VIII was proved by conversion to IX.

Measurements of freezing point depression confirm and strengthen this peculiarity. Compound VIII shows a van't Hoff factor of 3.3, nearly the same as Knorr's pyrrole. Since the latter, being an ester, should have a van't Hoff factor of 5, the reaction is apparently somewhat less complete for the compound which should theoretically be the more reactive. The large value for compound VIII demonstrates that acylization has taken place, however, since the substance is not affected in the α position by the sulfuric acid and, therefore, the whole of the freezing point depression observed must be due to the ionization at the β carboxyl group.

Compound X, an isomer of Knorr's pyrrole, was treated with sulfuric acid. At room temperature no acylization took place and the starting material could be recovered. At higher temperatures the pyrrole was destroyed. Compound XI was also treated with sulfuric acid and the starting material recovered unchanged. Since the electron donating character of the substituent groups in this case should make the ring even more strongly basic, we may speculate that this result is due to formation of a salt on the ring instead of on the ester group, resulting in an influence adverse to the desired reaction. Pyrrole XII was also treated with sulfuric acid. At 35° no reaction took place and the starting material could be recovered. At 50°, however, it appeared that sulfonation set in for water-soluble products were obtained which gave a qualitative test for both nitrogen and sulfur. The supposed sulfonic acid was not identified.

We conclude that the so-called "hydrolysis" of pyrrole esters in concentrated sulfuric acid solutions is really the formation of an acyl ion. This is favored in the pyrrole series by the same influences which previous workers have found effective in the benzene series, that is, by electron-donating groups and by steric crowding of the ester group affected. We have succeeded, however, in finding two pyrryl esters which have only one group adjacent to the reactive ester group and which will give the acylization reaction showing that the inherent electron-donating power of the pyrrole ring is an important factor in bringing about the reaction.

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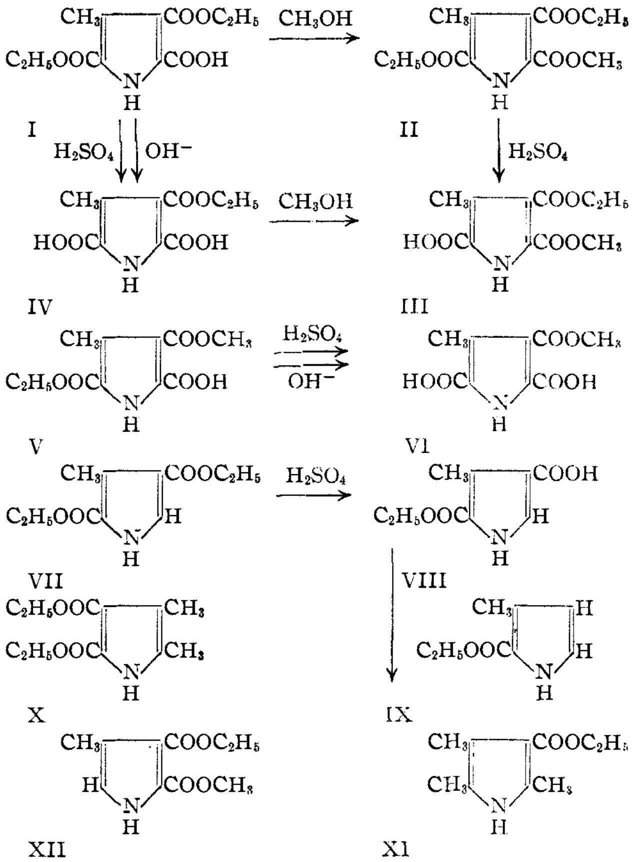
CHART I



Experimental

Esterification of 2,4-Dimethyl-3-carboxy-5-carbethoxypyrrole.—One gram of the pyrrole acid was dissolved in 22 cc. of 100% sulfuric acid and added dropwise with stirring and cooling to 100 cc. of anhydrous methanol. The solution was poured into 500 g. of an ice-water mixture and filtered. The unchanged acid was separated from the ester by sodium bicarbonate solution. Of the total solid recovered, 33% was ester and 67% was unchanged acid; melting point of ester, after crystallization from alcohol-water, 131°. Mixed m. p. with a sample melting at 134° was 133°.

A control experiment was performed by reversing the order of the mixing. The sample of pyrrole acid was ground to a paste with methanol and dissolved in a mixture of sulfuric acid and methanol. The mixture was allowed to stand for a time comparable to that used in the mixing in the preceding experiment. It was then treated in exactly the same manner. No ester was recovered, although a slight opalescence formed at the point at which ester should precipitate.

2-Carbomethoxy-3-carbethoxy-4-methyl-5-carboxypyrrole (III).[1]—A solution of 9 g. of (II)[1] in 50 ml. of 20% fuming sulfuric acid was protected from moisture and heated to 50° for thirty minutes. It was then poured over 225 g. of chopped ice in a beaker while stirring. The precipitate was filtered with suction and pressed dry. The pyrrole acid was then dissolved in methanol at 40° and sodium bicarbonate added until no more carbon dioxide was evolved. The solution was poured into five volumes of ice water and, after standing for one hour in the ice box, the unchanged ester was filtered off. This filtrate was acidified with hydrochloric acid to the congo red end-point, the pyrrole acid separated by filtration, washed with a small amount of cold water and dried in an oven at 60°. It can be crystallized from acetone-water or from acetone-hexane; m. p. 204-205°; yield, crude, 7.4 g. or 91%. Mixed m. p. with product obtained by esterification of compound IV with methanol is 204-205°.

This preparation with sulfuric acid is more sensitive to the presence of impurities than the esterification procedure reported in the previous paper.[1]

2,5-Dicarboxy-3-carbethoxy-4-methylpyrrole (IV).[1]—The procedure is essentially the same as that above. Compound (I) must be recrystallized several times before use. The reaction can be run with concentrated sulfuric acid for forty minutes at 95–100° or with 20% fuming sulfuric acid at 75°; yield 80–85%; m. p. 245–247° with decomposition.

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. Found: C, 49.65; H, 4.66.

2,5-Dicarboxy-3-carbomethoxy-4-methylpyrrole (VI).—One gram of (V) was dissolved in 5 ml. of 20% fuming sulfuric acid. The same procedure was then followed as with the preparation of compound IV; m. p. 243° with decomposition.

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. For $C_9H_9O_6N$: C, 47.58; H, 3.99. Found: C, 47.92, 48.01; H, 4.12, 4.02.

2-Carbethoxy-3-methyl-4-carboxypyrrole (VIII).—Five grams of (VII)[8] was treated with 25 ml. of concentrated sulfuric acid for forty-five minutes at 35°. The product was purified by a procedure similar to that used in the preparation of compound III; yield 3.8 g. or 97%. The pyrrole crystallizes from ethanol–water in long needles; m. p. 240° with decomposition.

Anal. Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.52. Found: C, 54.76; H, 5.61.

This substance was allowed to stand in 100% sulfuric acid and was recovered unchanged.

2-Carbethoxy-3-methylpyrrole (IX).[9]—One and one-half grams of (VIII) was heated with 6 g. of anhydrous glycerol and the distillate up to 290° collected in a distilling flask cooled with running water; 5 cc. of ethanol was added cautiously and the solution was poured into 25 cc. of ice water. On scratching the sides of the beaker the pyrrole precipitated as fine crystals which were filtered off and dried in the air; m. p. 56°. Fischer and Wiedemann[9] report 56°; mixed m. p. with material from decarboxylation of 2-carboxyl-4-methyl-5-carbethoxypyrrole,[1] 56°.

2,3-Dimethyl-4,5-dicarbethoxypyrrole (X).—Five grams of 2,3-dimethyl-4-carbethoxy-5-carboxypyrrole[10] was refluxed for one hour with 50 ml. of absolute ethanol containing 0.3 g. of dry hydrogen chloride and then poured into 250 ml. of ice water containing a small amount of sodium bicarbonate. The diester was filtered off and crystallized from very dilute ethanol; yield, 95%; m. p. 110–111°.

This compound was first prepared by Piloty and Wilke[11] by esterification with alkali and diethyl sulfate.

Action of Sulfuric Acid on 2,3-Dimethyl-4,5-decarbethoxypyrrole (X).—One gram of (X) was treated with 5 ml. of concentrated sulfuric acid for forty-five minutes at 35°. The diester was recovered unchanged. The same procedure was then followed using 15% fuming sulfuric acid at a temperature of 30°. After heating for ten minutes the solution turned black. No pyrrole could be isolated, only fine particles of a decomposition product.

Action of Sulfuric Acid on 2,4,5-Trimethyl-3-carbethoxypyrrole (XI).[12]—This pyrrole was dissolved in concentrated sulfuric acid and the solution heated for forty-five minutes at a temperature of 35°. The original pyrrole was recovered unchanged.

Action of Sulfuric Acid on 2-Carbomethoxy-3-carbethoxy-4-methylpyrrole (XII).[1]—Two hundred milligrams of (XII) was dissolved in 3 ml. of concentrated sulfuric acid. After heating the solution for forty-five minutes at a temperature of 35°, the pyrrole was recovered unchanged.

Two hundred milligrams of (XII) was dissolved in 3 ml. of fuming sulfuric acid (15%). After heating for thirty minutes on a water-bath at a temperature of 50°, the solution was poured over 30 g. of ice. When the ice had melted, the solution was saturated with salt, the precipitate filtered off, washed with acetone and crystallized from a small amount of water; m. p. 130–131° with decomposition. The substance is probably a pyrrole with a sulfonic acid group in the 5 position since a qualitative test for both nitrogen and sulfur was positive. No further attempts were made to determine the structure.

FREEZING POINT DEPRESSION MEASUREMENTS[6]

Wt., g.	Δm[13]	F. p., °C.	ΔT	"i"[13]	
2,4-Dimethyl-3,5-dicarbethoxypyrrole					
		4.040			H_2SO_4 = 74.8 g.
0.1911	0.0107	3.823	0.217	3.31	
		3.812[13]	0.228	3.48	
		3.812	0.228	3.48	
2-Carboxyl-3,5-dicarbethoxy-4-methylpyrrole (I)					
		4.227			H_2SO_4 = 73.8 g.
0.2517	0.0127	4.030	0.197	2.53	
		4.026[13]	0.201	2.58	
2-Carbethoxy-3-methyl-4-carboxylpyrrole (VIII)					
		4.112			H_2SO_4 = 73.8 g.
0.2731	0.0188	3.732	0.380	3.30	
		3.733[13]	0.379	3.29	

Summary

1. It is shown that the reaction of pyrryl carboxylic esters in strong sulfuric acid which was discovered by Fischer and Walach is actually the formation of an acyl cation, discussed by Treffers and Hammett.

2. A series of selective degradations of pyrrylcarboxylic esters is recorded in which sulfuric acid is the selective reagent.

3. It is shown that steric facilitation of the acylization reaction is not as important in the pyrrole series as in the benzene series because of the greater electronic facilitation by the ring nitrogen.

4. We have succeeded in finding two pyrryl esters which have only one adjacent group and which still give the acylization reaction.

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[8] Corwin, Bailey and Viohl, THIS JOURNAL, **64**, 1272 (1942).

[9] Fischer and Wiedemann, *Z. physiol. Chem.*, **155**, 58 (1926).

[10] Piloty and Wilke, *Ber.*, **45**, 2586 (1912).

[11] Piloty and Wilke, *ibid.*, **46**, 1602 (1913).

[12] Knorr and Hess, *ibid.*, **44**, 2762 (1911).

[13] Δm is the fraction of a gram molecular weight added. "i" is the van't Hoff factor and corresponds to the number of moles of particles in solution per mole of solute added. The successive measurements on the same sample recorded in the table were taken after about four-hour intervals to test the stability of the systems.