ALCOHOLYSIS AND HYDROLYSIS OF 1,3-DIKETONES AND BETA-KETO ESTERS

By Ralph Connor and Homer Adkins

A 1,3-diketone such as diacetylmethane does not undergo alcoholysis, as indicated in equation I, at temperatures obtainable in the liquid phase at atmospheric pressure unless a catalyst is used.

$$CH_3COCH_2COCH_3 + C_2H_5OH = CH_3CO_2C_2H_5 + CH_3COCH_3 \quad (I)$$
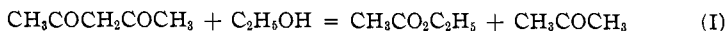
Hydrogen chloride and sodium ethoxide are active in bringing about this reaction but it is necessary to use high concentrations of the so-called catalyst in order to obtain a reasonably rapid rate of alcoholysis. For example, one hundred hours were required at $60°$ in order to completely cleave diacetylmethane even when the ratio of hydrogen chloride to diketone was 1 to 3.[1] The necessity for these high concentrations of catalyst indicates very clearly that hydrogen chloride as well as sodium ethoxide form compounds with the diketone or ester or both, to such an extent that the course of the cleavage may be profoundly modified. That the course of the reaction is modified by the environment during cleavage is further evidenced by the variation in the ratio of the two alternative modes of cleavage of an unsymmetrical 1,3-diketone as indicated in equations II and III.[2]

$$CH_3COCH_2COC_4H_9 + C_2H_5OH \longrightarrow CH_3CO_2C_2H_5 + CH_3COC_4H_7 \quad (II)$$
$$\searrow C_4H_9CO_2C_2H_5 + CH_3COCH_3 \quad (III)$$
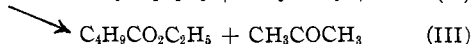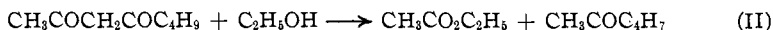
These considerations, in conjunction with the fact that no conditions were found under which β-keto esters underwent alcoholysis in the presence of hydrogen chloride, led to a search for conditions under which 1,3-diketones and β-ketonic esters would undergo alcoholysis even in the absence of any added catalyst. Conditions suitable for such an alcoholysis were suggested by the finding[3] that dehydroacetic acid showed a 70% alcoholysis at $190°$ after two hours, the product being acetoacetic ester (not acetoacetic acid as indicated in the table on p. 5195 of the paper just cited). Since dehydroacetic acid is a 1,3-diketone as well as a di-β-keto ester, this result suggests what is now known to be true, i. e., that the diketones may be split under conditions which leave β-keto esters unaffected.

Alcoholysis of 1,3-Diketones.—The alcoholysis of diacetyl- and dibenzoylmethanes and of five unsymmetrical acetylmethanes (i. e., n-valeryl, isovaleryl, trimethylacetyl, cyclohexanoyl and benzoyl) has been

[1] Adkins, Kutz and Coffman, This Journal, **52**, 3213 (1930).

[2] Kutz and Adkins, ibid., **52**, 4036 (1930).

[3] Adkins, Connor and Cramer, ibid., **52**, 5194 (1930).

studied at 150–250° under about 100 atmospheres' pressure, using (1) alcohol which had been dried over lime and sodium ethoxide, (2) alcohol which had been dried over lime only and (3) alcohol which contained 0.2% of aluminum ethoxide. A summary of the results has been given in Table I along with the results obtained by Kutz[2] in the alcoholysis of the same diketones using hydrogen chloride as a catalyst at 60° and atmospheric pressure.

TABLE I

ALCOHOLYSIS OF 1,3-DIKETONES[a]

Diketone	EtOH (Dry)[b]		EtOH (Moist)[c]		EtOH + Al(OEt)₃[d]		EtOH + HCl[e]	
	% Alcoholysis	% CH₃CO	% Alcoholysis	% CH₃CO	% Alcoholysis	% CH₃CO	% Alcoholysis	% CH₃CO
Acetyl-n-valeryl-methane	27	50	...	..	100	53	100	61
Acetyl-isovaleryl-methane	19	65	...	..	85	58	20–30	65
Acetyl-trimethyl-acetylmethane	26 (250°)	90	...	..	65	75	20–30	91
Acetylcyclo-hexanoylmethane	..	...	...	..	100	53	100	58
Acetylbenzoyl methane	43	100	100	80	100	80	100	100
Dibenzoylmethane	58	...	...	..	100	..	0	...
	9 (150°)		34 (150°)					
Diacetylmethane	13	...	100	..	...	..	100	...
	25 (250°)							

[a] The experimental conditions for alcoholysis unless noted otherwise were as follows: 37.5 and 187.5 millimoles of diketone and ethanol, respectively, 200°, eight hours and 120 ± 30 atmospheres' pressure. [b] The ethanol was dried twice over lime. [c] The ethanol was dried over lime and aluminum ethoxide. [d] The ethanol contained 0.2% aluminum ethoxide. [e] These data were previously reported by Kutz and Adkins for alcoholysis at 60° for 100–150 hours.

The outstanding facts that emerge from these data are:

(1) Alcohol which has been dried with aluminum ethoxide was quite inactive for the alcoholysis of 1,3-diketones. For example, diacetylmethane was cleaved to the extent of only 25% after eight hours at 250°.

(2) Alcohol which contained the few tenths of one per cent. of water which was not removed by drying it twice with a good quality of lime was a rather active reagent for the cleavage of 1,3-diketones. For example, diacetylmethane was 100% cleaved after eight hours at 200° when this moist ethanol was used. This fact taken in conjunction with the inactivity of ethanol dried over aluminum ethoxide renders it open to question whether ethanol completely free of water would react at all with diketones.

(3) Aluminum ethoxide was a very active catalyst for the alcoholysis of 1,3-diketones. For example, the amount of alcoholysis, of acetylisovaleryl-
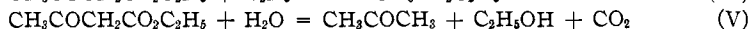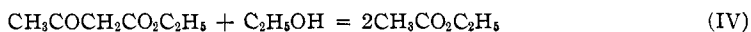
methane was more than four times as great for a given length of time in the presence of aluminum ethoxide as it was in dry ethanol.

(4) Dibenzoylmethane which was resistant to alcoholysis in the presence of hydrogen chloride at 60° and atmospheric pressure was readily cleaved at 200° either with dry ethanol or ethanol containing aluminum ethoxide. In fact the order of rate of cleavage of dibenzoyl-, acetyl-benzoyl- and diacetylmethane in dry ethanol at 200° is the reverse of that previously found for the relative rates of cleavage of the three diketones at 60° in ethanol containing hydrogen chloride.

(5) Branching of the chain adjacent to one carbonyl group decreased the rate of alcoholysis with dry ethanol just as it did with ethanol containing hydrogen chloride.

(6) The ratio of the products formed in the cleavage of an unsymmetrical 1,3-diketone was a function of the experimental conditions under which alcoholysis occurred. For example, acetylbenzoylmethane which gave only ethyl acetate and acetophenone when it was cleaved with dry ethanol or with ethanol and hydrogen chloride gave a 20% yield of ethyl benzoate and acetone when it was cleaved with moist ethanol or with ethanol containing aluminum ethoxide. In every case the acetyl cleavage was less with dry ethanol and with ethanol containing aluminum ethoxide than it was with ethanol and hydrogen chloride.

Alcoholysis of β-Keto Esters.—A study of the alcoholysis of β-keto esters is considerably more complicated than is one of the 1,3-diketones. This results from the greater stability of the keto esters and from the fact that such a keto ester may undergo condensation to compounds of the dehydroacetic acid type as well as cleavage. The cleavage reactions with water and ethanol are formulated as

$$CH_3COCH_2CO_2C_2H_5 + C_2H_5OH = 2CH_3CO_2C_2H_5 \qquad (IV)$$
$$CH_3COCH_2CO_2C_2H_5 + H_2O = CH_3COCH_3 + C_2H_5OH + CO_2 \qquad (V)$$

There is recorded in Table II a summary of experimental results obtained in subjecting various β-keto esters to the action of ethanol and butanol.

The data in Table II show clearly certain facts in regard to the alcoholysis of β-keto esters.

(1) Ethanol which has been dried over aluminum ethoxide was not an active reagent for the cleavage of β-keto esters. For example, from 51 to 68% of benzoylacetic, benzylacetoacetic and acetoacetic esters were recovered from a reaction mixture after eight to nine hours at 250°, while the remainder had chiefly undergone hydrolysis and condensation.

(2) Ethanol dried twice over lime and so containing a few tenths of one per cent. of water was an active reagent and brought about almost identically the same amount of reaction IV (acetone) as of reaction V (ethyl acetate), although of course twice as many moles of ethyl acetate as of acetone were produced.

TABLE II

ALCOHOLYSIS OF β-KETO ESTERS

Ester		Reagent		Time, hrs.	Temp., °C.	Hydrolysis, %	Alcoholysis, %	Condensation, %	Unreacted, %	Loss, % Mechanical	Loss, % Unknown
Name	m. mole	name[a]	m. mole								
Acetoacetic	385	EtOH[c]	955	3	200	19	1	6	63	5	6
Acetoacetic	385	EtOH[c]	1915	21	200	37	1	4	53	3	2
Acetoacetic	385	EtOH[d]	1915	8	200	8	4	4	71	6	7
Acetoacetic	577	EtOH[d]	2885	12	250	18	51	23	0	3	5
Acetoacetic	310	EtOH[c]	1540	8	250	42	43	0	0	17	0
Acetoacetic	577	EtOH[b]	2885	8	250	15	2	5	68	7	3
Acetoacetic	385	EtOH[d]	385	8	250	10	39	20	0	15	16
Acetoacetic	385	n-C$_4$H$_9$OH	1095	8	200	2	1	0	81	10	6
Acetoacetic	385	n-C$_4$H$_9$OH	810	8	250	7	56	15	0	8	14
Monomethyl-acetoacetic	174	EtOH[d]	870	8	250	6	57	21	0	8	8
Dimethyl-acetoacetic	158	EtOH[d]	790	8	250	0	12	4	72	12	0
Benzylaceto-acetic	100	EtOH[d]	500	10	250	13	72	14	0	1	0
Benzylaceto-acetic	100	EtOH[b]	500	9	250	24	19	0	51	5	1
Benzoylacetic	200	EtOH[d]	1000	8	250	36	47	16	0	3	0
Benzoylacetic	83	EtOH[b]	633	9	250	29	2	0	64	5	0
Malonic	319	EtOH[d]	1545	8	250	..	20	9	61	8	2

[a] Terms in this column have the same significance as in Table I. It should be noted that the hydrogen introduced into the bomb was moist, and when it was allowed to escape through dehydrite the latter gained 0.86 g. in weight.

(3)   Aluminum ethoxide was an active catalyst for alcoholysis. Since by its presence it reduces, if it does not eliminate, water from the sphere of reaction, there occurs little hydrolysis of the keto ester.

(4)   Acetoacetic ester did not undergo alcoholysis at all readily at 200° even with moist alcohol, so that a temperature of 250° was required for the ready cleavage of the keto ester.

(5)   n-Butanol was a more effective reagent for the alcoholysis of aceto-acetic ester than was ethanol, apparently because butanol was more easily and more completely dried.

(6)   Dimethylacetoacetic ester was found to be more resistant to al-coholysis than was the parent keto ester, there being only 12% cleavage after eight hours at 250°.

(7)   The two monosubstituted (methyl and benzyl) acetoacetic esters underwent alcoholysis at least as readily as the parent ester, giving good yields of the esters of acetic and propionic, and of acetic and β-phenyl-propionic acids, respectively.

(8)   Benzoylacetic ester even in the presence of aluminum ethoxide gave a high percentage of hydrolysis to acetophenone as well as alcoholysis to ethyl acetate and benzoate.

Hydrolysis of 1,3-Diketones and β-Keto Esters.—There is recorded in Table III a summary of the data obtained in subjecting various keto esters and acetylbenzoylmethane to hydrolysis. The important con-

clusions that may be drawn from the data in Table III would appear to be:

(1)   The method of cleaving β-keto esters with water or with water containing a base at 200° gave excellent yields of the corresponding ketones, with little or no acid formation.   Meerwein[4] subjected certain β-keto esters to hydrolysis at 200° in a sealed glass tube.   He obtained a 73% yield of acetophenone from benzoylacetic ester, an 88% yield of 4-phenylbutanone-2 from α-benzylacetoacetic ester and unstated amounts of ketones from five other esters which were reported as completely hydrolyzed.

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TABLE III

HYDROLYSIS OF β-KETO ESTERS AND 1,3-DIKETONES

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Compound		Reagents				
Name	Milli-moles	Name	Milli-moles	Time, hrs.	Temp., °C.	Yield (%) of product(s)
Acetoacetic ester	385	Water	1945	9[b]	200	97% acetone
Benzylacetoacetic ester	114	Water	1390	8[b]	200	97% 4-phenylbutanone-2
Diethylacetoacetic ester	168	EtOH[a]	860	11	250	No cleavage
		Water	514			
Dimethylacetoacetic ester	160	Water	1600	12	250	50% Me-butanone-3
Dimethylacetoacetic ester	160	NaOH	200	10[b]	250	5% acetic and isobutyric acids;
		Water	5000			70% 2-Me-butanone-3
Diethylacetoacetic ester	310	EtOH	850	8	200	49% 3-Et-pentanone-2; 45%
		Water	2780			diethylacetoacetic ester
		NaOH	375			
Diethylacetoacetic ester	200	EtOH	1700	8	250	84%[d] 3-Et-pentanone-2; no
		Water	2780			residual ester
		NaOH	240			
Ethyl trimethylacetate	232	Water	2320	8	200	36% hydrolysis of ester
Ethyl α,α-diethyl-β-hydroxybutyrate	53	Water	1060	8	250	No hydrolysis
Acetylbenzoylmethane	37.5	Water[c]	188	8	200	76% acetic acid; 24% benzoic acid

^{a} Ethanol used as a solvent to ensure contact of reactants. ^{b} The time intervals are no doubt much longer than necessary for complete reaction as 385 m. moles of acetoacetic ester was completely hydrolyzed by 400 m. moles of water within one hour at 200°. ^{c} Cleavage was not complete after eight hours at 200°, so 555 m. moles of water was added and the mixture kept at 250° for five and one-half hours. ^{d} The amount of ethanol used rendered the isolation of the ketone more difficult and probably materially reduced the yield of ketone obtained.

(2)   The dimethyl- and diethylacetoacetic esters were quite resistant to hydrolysis even at 250°.   The diethyl ester showed no trace of hydrolysis after repeated attempts at 250°.   This resistance to hydrolysis of trisubstituted acetic acids is not limited to keto esters but was also manifested by trimethylacetic ester and especially by α,α-diethyl-β-hydroxybutyric ester, which showed no hydrolysis after eight hours at 250°.   The inactivity of these esters would appear to be the result of steric hindrance.   The resistance to hydrolysis at atmospheric pressure of the dialkylacetoacetic esters, especially those containing alkyl groups larger than methyl, was observed by Michael[5] and utilized by him in purifying dialkylacetoacetic esters.

[4] Meerwein, *Ann.*, **398**, 242 (1913).
[5] Michael, *Ber.*, **38**, 2083 (1905).

(3)   The ratio of cleavage products in the hydrolysis of acetylbenzoyl-methane with water at 250° was similar to that obtained with moist ethanol.

Experimental Part

All of the experiments on the alcoholysis of diketones and keto esters reported in this paper were carried out in the apparatus recently described[6] in glass or copper containers under a pressure of 90–150 atmospheres of hydrogen.   The diketones were from the same preparation as those used by Kutz and the reaction products, with the exceptions noted below, were analyzed as described by him.[7]   The exceptions were made in that no phenylhydrazine was used if alcoholysis was complete as evidenced by a test with ferric chloride, and in that 2,4-dinitrophenylhydrazine and benzyl alcohol were used instead of phenylhydrazine and butanol in the determination of the extent of cleavage of dibenzoylmethane.

The method of analysis of the reaction products of the alcoholysis of β-keto esters and the calculation of the yields is best presented in describing a specific experiment. Seventy-five grams (0.58 mole) of acetoacetic ester and 132.7 g. (2.88 moles) of ethanol containing 0.26 g. of aluminum ethoxide were heated for twelve hours at 250°.   The reaction products after removal from the bomb weighed 197.5 g.   The loss (10.2 g.) was in part mechanical and in part due to the escape of carbon dioxide.   The latter was identified by bubbling the gas from the bomb through a solution of barium chloride. The bomb and liner were washed out with ethanol and the combined liquid reaction products (which showed no enol test) distilled through a Widmer column having a spiral 25 cm. in length.   All except 17.0 g. distilled below 79°.   The mixture of acetone, ethanol and ethyl acetate was then analyzed for acetone by the sodium sulfite method[8] and for the ester by saponification.   The acid used in the analysis for acetone had been standardized against solutions of acetone containing ethanol and ethyl acetate.[9]   These analyses showed 5.86 g. of acetone (0.101 mole) and 51.9 g. of ethyl acetate (0.59 mole). The ketone was identified by the preparation of its 2,4-dinitrophenylhydrazone (m. p. 127–128°) and the determination of a mixed melting point (126–128°) with an authentic sample of the hydrazone of acetone.   The percentages of hydrolysis and alcoholysis were calculated on the basis of equations IV and V directly from the amounts of acetone and ethyl acetate as found by analysis.   The percentage conversion of acetoacetic ester to condensation products of b. p. above 45° (16 mm.) was calculated on the basis of its weight (17.0 g.) and the assumption that it was molecularly equivalent to acetoacetic ester.   The amount of carbon dioxide (equation V) was calculated from the amount of acetone found and deducted from the 10 g. loss found on opening the bomb.   This reduced the mechanical loss to 3% and left 5% of the acetoacetic ester unaccounted for.

This procedure for the study of the products from the alcoholysis was modified in some experiments as noted below.   (1) If any unchanged keto ester remained after alcoholysis it was separated from the other products by fractionation.   (2) Duclaux values were obtained upon the acids from the alcoholysis of α-methyl acetoacetic

6 Adkins and Cramer, THIS JOURNAL, 52, 4349 (1930); see also Ind. Eng. Chem., Anal. Ed., 4, 342 (1932).

7 Kutz and Adkins, ibid., 52, 4036 (1930).

8 Child and Adkins, ibid., 45, 3013 (1923).

9 Cf. Adkins, Semb and Bolander, ibid., 53, 1853 (1931).

ester and indicated that both propionic and acetic acids were formed. (3) The alcoholysis of α-benzylacetoacetic ester gave ethyl acetate, ethyl β-phenylpropionate and 4-phenylbutanone-2. The ethyl acetate was obtained as in the alcoholysis of acetoacetic ester but the higher boiling ester and the ketone were obtained in a fraction 104–105 (9 mm.). In general the ester was determined by saponification and the ketone by difference. In one run the analytical procedure was checked by the isolation of the ketone. (4) The alcoholysis of benzoylacetic ester also gives a mixture of esters and ketone which were determined as in the case of α-benzylacetoacetic ester, except that in this case the mixture of ester and ketone boiled at 90–95° (12 mm.).

The acetone and acetic acid obtained by the hydrolysis of acetoacetic ester were determined by titration. 4-Phenylbutanone-2 resulting from the hydrolysis of α-benzylacetoacetic ester was extracted with ether, dried over potassium carbonate and 16.4 g. distilled at 110.5–111° (13 mm.). Ethyl α,α-diethylacetoacetate after attempted hydrolysis was recovered unchanged to the extent of 95.3%.

The products from the hydrolysis of α,α-dimethylacetoacetic ester (25.5 g.) were extracted with ether, dried over sodium sulfate and fractionated. After the removal of the solvent the following fractions were obtained: (1) 75–85°, 5.3 g.; (2) 85–169° 1.9 g.; (3) 169–181° (mostly 170–179°) 9.3 g.; (4) residue, 4.2 g. A good yield of a semicarbazone of m. p. 111–112° was obtained from fraction 1; this corresponds with the melting point (112°) of the semicarbazone of methyl isopropyl ketone. The above figures indicate that approximately one-half of the keto ester was hydrolyzed to the ketone with no evidence for the formation of acids.

The product from the alkaline hydrolysis of α,α-dimethylacetoacetic ester was acidified with sulfuric acid, heated on a steam-bath to complete the expulsion of carbon dioxide, extracted with ether, dried over sodium sulfate and fractionated. Fraction (1) 35–75°, 1.96 g.; (2) 75–85°, 5.49 g.; (3) 85–93° (mostly 91–93°) 4.40 g.; (4) residue, 2.57 g. The residue was no more than the normal amount of liquid held back by the fractionating column and flask used. It contained 0.015 mole of acid. It thus appears that all except approximately 5% of the keto ester was converted to the ketone. The procedure in working up the product from the alkaline hydrolysis of diethylacetoacetic ester was essentially the same as that just described.

Summary

The alcoholysis and hydrolysis of a number of 1,3-diketones and β-keto esters at 150–250° under pressures in the vicinity of 100 atmospheres have been investigated. Ethanol which had been dried over aluminum ethoxide was found to be a rather inactive reagent for the alcoholysis of 1,3-diketones and β-keto esters, while ethanol containing a few tenths of one per cent. of water was a very much more active reagent. Aluminum ethoxide was found to be quite an active catalyst for alcoholysis. The keto esters were much more resistant to alcoholysis than were the diketones, the reaction of the latter proceeding approximately as rapidly at 150° as did the alcoholysis of the keto esters at 250°. α-Methyl- and α-benzylacetoacetic esters underwent alcoholysis approximately as rapidly as did the parent ester, while the dimethyl and diethylacetoacetic esters were very resistant to cleavage. Excellent yields of ketones were obtained by the hydrolysis at 200° of several β-keto esters. Dialkyl substituted β-keto esters were quite stable toward water at 200° so that they may be freed of

monoalkyl substituted β-keto esters by such a treatment. The hydrolysis of these dialkyl β-keto esters necessitates the use of alkali at 250°. The ratio of the products formed in the cleavage of unsymmetrical 1,3-diketones varied greatly with variation in the environment during cleavage.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

THE USE OF KETENE IN THE PREPARATION OF SIMPLE AND MIXED ACID ANHYDRIDES

BY CHARLES D. HURD AND MALCOLM F. DULL

Mixed acid anhydrides, R—CO—O—CO—CH₃, are generally made[1] either by refluxing the acid, RCOOH, with acetic anhydride or by the interaction[2] of any acyl chloride and sodium acetate or by reaction of the acid with acetyl chloride and pyridine. A purification procedure is essential in all of these cases. Such anhydrides as acetic propionic anhydride or acetic isovaleric anhydride are sufficiently stable to be distilled under diminished pressure, but the tendency of mixed anhydrides to disproportionate into the two symmetrical anhydrides often makes the isolation of the mixed anhydride difficult or impossible.

Ketene is an acetylating agent but it has never been considered for use in preparing mixed acetic anhydrides. Ketenes which have been added to acids to convert them into mixed anhydrides are diphenylketene and carbon suboxide.[3] Van Alphen's is the only account[4] of the reaction of ketene itself with acids. He used phenolic acids and observed acetylation of the phenolic group. No mention was made of the production of mixed anhydrides.

In the present work it has been found that ketene readily attaches itself to aliphatic or aromatic acids giving rise to mixed acetic anhydrides

$$RCOOH + CH_2{=}C{=}O \longrightarrow RCO{-}O{-}COCH_3$$
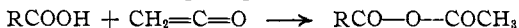
Since nothing else is formed, the purification procedure is greatly simplified. Thus, using ketene, acetic acid was quantitatively changed into acetic anhydride, n-butyric acid into acetic butyric anhydride, benzoic acid into acetic benzoic anhydride and furoic acid into acetic furoic anhydride.

Distillation of acetic benzoic anhydride or of acetic furoic anhydride, both of which were oils, gave rise to benzoic anhydride and furoic anhydride,

[1] Autenrieth, Ber., 20, 3187 (1887); 34, 168 (1901); Béhal, Ann. chim. phys., [7] 19, 274 (1900); 20, 418 (1900); Autenrieth and Thomae, Ber., 57, 423 (1924).

[2] Verkade, Rec. trav. chim., 35, 299 (1915); Kilpatrick and Kilpatrick, THIS JOURNAL, 52, 1418 (1930).

[3] Staudinger, Ann., 356, 79 (1907); Diels and Lalin, Ber., 41, 3426 (1908).

[4] Van Alphen, Rec. trav. chim., 44, 838 (1928).