[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Proportion of Ester Anion and Amide from Esters and Sodium Amide. Carbonation of Esters. Synthesis of Malonic Acid Derivatives[1]

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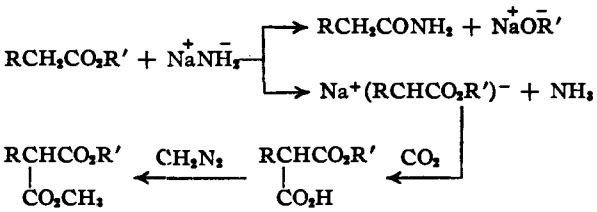
In the presence of sodium amide, carboxylic esters having α-hydrogen generally exhibit two types of reaction.[2] One type involves the reaction of the base with the carbonyl carbon of the ester to form the corresponding amide, while the other consists in the removal of the α-hydrogen of the ester to form the ester anion, which is the reactive intermediate in certain ester condensations. The ester anion may be condensed with the original ester (self-condensation) or with other carbonyl compounds. In the present investigation, various ester anions, prepared by means of sodium amide, have been carbonated to form half malonic acid esters which, in certain cases, have been esterified with diazomethane to form the corresponding methyl alkyl malonates. Obviously, the carbonation cannot be satisfactory with esters which are converted by sodium amide mainly to the corresponding amide. The reactions may be represented by Scheme A.

SCHEME A



The carbonation has been effected by adding the ester to two equivalents of sodium amide[3] in liquid ammonia, replacing the ammonia by ether and adding Dry Ice. This procedure was completed as rapidly as possible to minimize the self-condensation of the ester; however, with the acetates, some β-keto ester was usually obtained in addition to the half malonic acid ester. Although the ester was probably converted essentially completely to the ester anion or the amide, a portion of it was generally recovered. This may have been due to the insolubility of the sodium derivative in the ether in which the carbonation was carried out. With ethyl propionate and the higher esters some amide was usually obtained but, under the conditions employed, only a part of it was readily isolated. In Table I are summarized the results of carbonation, while in Table II are given the results for the esterification products.

It can be seen from Table I that the yields obtained on carbonation are 54–60% with the alkyl acetates (except with ethyl acetate), but only 31% with ethyl propionate, somewhat lower with methyl, ethyl or *n*-propyl *n*-butyrate and still lower with ethyl isovalerate. However, with *t*-butyl *n*-butyrate or *t*-butyl isovalerate the yield is almost 50%, which is more than twice that with the corresponding ethyl esters. The highest yield obtained has been with ethyl phenylacetate. It can be seen from Table II that the yields of methyl alkyl malonates, which are based on the original esters, are in general 5–12% lower than those of the corresponding half malonic acid esters from which they are obtained. Obviously the esterification proceeded in good yield.

The carbonation of esters has previously been effected in the presence of sodium triphenylmethide.[4] Since this base ionizes the α-hydrogen of esters preferentially to undergoing reaction with the carbonyl carbon, it would presumably be applicable to the carbonation of most esters having α-hydrogen. However, when the yields of carbonation products are satisfactory, sodium amide would generally be preferred, since this base is more readily available. Sodium alkoxides are not sufficiently strong to convert esters completely to their anions, which appears to be required for satisfactory carbonations. The method of carbonation is not only a convenient way to prepare half malonic acid esters but, when followed by esterification with diazomethane, it is apparently the best way to prepare pure methyl alkyl malonates. The excellent method of Wallingford, Homeyer and Jones[5] for the preparation of dialkyl malonates by carbalkoxylation of esters using sodium alkoxides does not appear applicable to the preparation of mixed alkyl malonates.

In the last column of Table I, designated "Ester Anion," are given the combined yields of half

(1) Paper XXXII on "Condensations"; paper XXXI, THIS JOURNAL, 67, 2050 (1945).

(2) In certain cases, four types of reactions might be exhibited; see Hauser, Shivers and Skell, *ibid.*, 67, 409 (1945).

(3) In preliminary experiments with *t*-butyl acetate, two equivalents of sodium amide to one of ester produced a considerably better yield of the half malonic acid ester than did an equivalent of sodium amide; however, only an equivalent of this base is involved in the carbonation.

$$CH_3CO_2C(CH_3)_3 + \bar{N}H_2 \rightleftharpoons {}^-[CH_2CO_2C(CH_3)_3] + NH_3$$
$$^-[CH_2CO_2C(CH_3)_3] + CO_2 \longrightarrow {}^-O_2CCH_2CO_2C(CH_3)_3$$

The favorable effect of excess sodium amide may be explained in two ways. Some acetamide may be formed and this would neutralize a proportional amount of amide ion in undergoing a proton exchange to form acetamide anion, $(CH_3CONH)^-$. Since the proton exchange between the ester and the amide ion is reversible, excess amide ion should effect more completely the conversion of the ester to its anion, leaving fewer molecules of unchanged ester to acylate the ester anion. This should decrease the extent of self-condensation of the ester and thereby favor the carbonation.

(4) Baumgarten and Hauser, THIS JOURNAL, 66, 1037 (1944).

(5) Wallingford, Homeyer and Jones, *ibid.*, 63, 2056 (1941).

TABLE I

YIELDS OF MALONIC ACID HALF ESTERS

Ester	Hydrogen malonates	Yield, %[a]	Recovered ester and other products, % Ester	Other products	Ester anion, %
Ethyl acetate	Ethyl	30			
n-Propyl acetate	*n*-Propyl	54	5	*n*-Propyl acetoacetate, 4%	63
Isopropyl acetate	Isopropyl	56	*ca.* 5	Isopropyl acetoacetate,[b] 9%	70
n-Butyl acetate	*n*-Butyl	56	*ca.* 8	*n*-Butyl acetoacetate, 10%	74
t-Butyl acetate	*t*-Butyl[d]	60	20	*t*-Butyl acetoacetate[c]	87
n-Amyl acetate	*n*-Amyl	57	7	*n*-Amyl acetoacetate, 9%	73
Ethyl phenylacetate	Ethyl α-phenyl	74			>74
Ethyl propionate	Ethyl α-methyl	31			..
Methyl *n*-butyrate	Methyl α-ethyl	22		*n*-Butyramide	..
Ethyl *n*-butyrate	Ethyl α-ethyl	23	10	*n*-Butyramide	33
n-Propyl *n*-butyrate	*n*-Propyl α-ethyl	23	17	*n*-Butyramide	40
t-Butyl *n*-butyrate	*t*-Butyl α-ethyl	48	33	*n*-Butyramide	81
Ethyl isovalerate	Ethyl α-isopropyl	18	4	Isovaleramide	22
t-Butyl isovalerate	*t*-Butyl α-isopropyl	*ca.* 48	23		71

[a] Based on titration of aliquots (see general procedure). [b] Copper salt, m. p. 173–175° (Moureu and Delange, *Compt. rend.*, **134**, 46 (1902)). [c] Semicarbazone, m. p. 151–152° (Shivers, Hudson and Hauser, THIS JOURNAL, **65**, 2051 (1943)). [d] Yields up to 70% have been obtained.

TABLE II

YIELDS OF METHYL ALKYL MALONATES[a]

Malonates	B. p., °C.	Mm.	Yield, %	Analyses, % Calculated C	H	Sap. equiv.	Found C	H	Sap. equiv.
Methyl ethyl	85–87	19	25						
Methyl *n*-propyl	98–99	20	43	52.46	7.56	80.0	52.21	7.30	80.6
Methyl isopropyl	87–87.5	19	43	52.46	7.56	80.0	52.33	7.26	79.5
Methyl *n*-butyl	110.5–111	20	51	55.18	8.11	87.1	54.84	8.04	86.9
Methyl *t*-butyl	90.5–91.5	20	55	55.18	8.11	87.1	54.76	7.78	87.6
Methyl *n*-amyl	121–122.5	20	50						
Methyl *t*-butyl α-ethyl	100–100.5	20	31	59.32	8.92		59.02	8.85	
Methyl *t*-butyl α-isopropyl	100–106	20	31	61.06	9.32		60.60	9.02	

[a] These compounds, the yields of which are based on the original ester, were obtained by esterification with diazomethane of the corresponding alkyl hydrogen malonate listed in Table I.

malonic acid ester, β-keto ester and recovered ester. This is considered to represent the minimum percentage of ester anion formed.[6] Since, with the esters studied, amide is presumably the only additional product formed, its yield may be estimated by difference. In order to obtain more quantitative yields of the amide than was possible in the carbonation experiments, the reaction mixtures of certain esters and two equivalents of sodium amide in liquid ammonia were worked up avoiding the use of water in which the amide is somewhat soluble. The excess sodium amide was neutralized with solid ammonium chloride, the ammonia evaporated and the amide and ester taken up in benzene. The yields of these products are given in Table III. The percentage of recovered ester may be considered as a rough measure of the proportion of the ester anion, although the values are somewhat lower than the corresponding ones given in Table I. On the basis that 80% of the amide formed was isolated (see Experimental), the yield of *n*-butyramide was 50% from ethyl or *n*-propyl *n*-butyrate but only 11% from *t*-butyl *n*-butyrate, while the yield of isobutyramide from ethyl isobutyrate was 90%. From these yields of amide together with those of the ester anion given in the last column of Table I, it may be concluded that, in their reaction with sodium amide, all of the alkyl acetates (with the possible exception of ethyl acetate), ethyl phenylacetate, *t*-butyl *n*-butyrate and *t*-butyl isovalerate form mainly the corresponding ester anion. However, ethyl *n*-butyrate and probably also ethyl propionate form at least as much amide as ester anion. Ethyl isovalerate probably forms much more amide than ester anion, while ethyl isobutyrate evidently forms practically entirely the amide.

TABLE III

Ester	Amide, % yield	Ester recovered, % yield
Ethyl acetate	10	..
Ethyl *n*-butyrate	41	23[a]
n-Propyl *n*-butyrate	41	..
t-Butyl *n*-butyrate	9	50
Ethyl isobutyrate	72	0

[a] 6% of this was isolated as the β-keto ester.

The influence of structure of esters on the two

(6) Not only is there some loss in the isolation of products but, since the formation of ester anion is reversible whereas the formation of the amide is essentially irreversible, it is conceivable that in certain cases, ester anion, through reversion to the original ester might have been converted to the amide.

courses of reaction with sodium amide may be summarized by the following generalizations. (1) Substitution of an α-hydrogen of an ester by a phenyl group favors the formation of ester anion, whereas the substitution of an α-hydrogen by an alkyl group favors the formation of the amide, the effect being especially marked by the introduction of a second alkyl group as in ethyl isobutyrate. (2) Substitution of alkyl groups in the alkoxy portion of an ester favors the formation of ester anion, especially if the alkoxy portion becomes *t*-butoxy. It is of interest that generalization (1) is in agreement with what one should expect from a consideration of both the relative rates of alkaline hydrolysis of esters,[7] in which only the carbonyl carbon is involved, and of the relative rates of hydrogen–deuterium exchange with ethyl esters in the presence of ethoxide ion[8] in which only the α-hydrogen is involved. Although the rates of both the alkaline hydrolysis and the hydrogen–deuterium exchange are increased by substitution of a phenyl group for an α-hydrogen, and decreased by substitution of an alkyl group for an α-hydrogen, the effect on the hydrogen–deuterium exchange is greater. Generalization (2) is in agreement with what one should expect on the basis that the attack of a basic anion on the carbonyl carbon is hindered much more in *t*-butyl esters than in the corresponding ethyl esters (as exhibited, for example by alkaline hydrolysis[8]) whereas the attack on the α-hydrogen should be much less affected.

Experimental

Carbonation of Esters. General Procedure.—To 0.6 mole of sodium amide, prepared as described previously[9] (using a Hershberg stirrer), was added 0.3 mole of ester in 100 cc. of absolute ether over a period of two minutes. The reaction flask was then placed on a steam-bath. As the liquid ammonia evaporated, over a period of about fifteen minutes, sufficient absolute ether (about 300 cc.) was added so that the sodium derivative of the ester never went dry but was present as a pasty solid suspended in ether. When the ether began to reflux (indicating that all the liquid ammonia had evaporated) the steam-bath was removed and, while the mixture was stirred vigorously, a ten-fold excess of finely powdered Dry Ice was added. After the reaction mixture had come to room temperature, a minimum of water and an equal volume of ether were added and the homogeneous phases separated. The aqueous phase was cooled to 0°, acidified with a mixture of 100 cc. of concentrated hydrochloric acid and 50 g. of crushed ice, and the liberated malonic acid half ester extracted with ether three times or until an aliquot of the extract was found to contain essentially no titratable acid. (A blank experiment showed that no appreciable amount of hydrochloric acid was extracted by the ether under the conditions employed.) The combined ether extracts were dried over sodium sulfate, an aliquot titrated to determine the yield of half malonic acid ester and the rest treated with diazomethane as described below. The ether phase obtained from the carbonation was dried over Drierite and the solvent distilled. The residue was first distilled at atmospheric pressure to recover any original ester and then *in vacuo* to obtain any self-condensation product of the ester. The resulting residue was recrystallized to obtain the amide. The results are summarized in Table I. In the experiments with *n*-propyl, isopropyl, *n*-butyl and *n*-amyl acetates the recovered esters were obtained contaminated with the corresponding alcohols (produced by the self-condensation of the ester or by conversion of the ester to the amide), but in the other experiments the recovered esters were obtained essentially pure. The percentage recovered ester given in Table I for the experiments with *n*-propyl and *n*-amyl acetates is based on saponification equivalents of the ester–alcohol mixtures.

Esterification of Malonic Acid Half Esters with Diazomethane. General Procedure.—To the ethereal solution of the malonic acid half esters obtained as described above was added a 10–20% excess of diazomethane prepared from nitrosomethyl urea.[10] The excess diazomethane was destroyed by adding glacial acetic acid until the reaction mixture was acidic or until the diazomethane color disappeared. The ethereal solution was dried over Drierite, the solvent distilled and the residue fractionated *in vacuo*, the malonic ester being collected. The results are summarized in Table II.

Proportion of Ester Anion and Butyramide from Butyric Esters and Sodium Amide.—To 0.6 mole of sodium amide in about 200 cc. of liquid ammonia was added during two minutes, 0.3 mole of the butyric ester dissolved in 50 cc. of absolute ether and the reaction mixture stirred for ten minutes. Sufficient liquid ammonia was then added to bring the total volume in the flask up to about 500 cc. and 1.0 mole (55 g.) of solid ammonium chloride was added carefully over a period of thirty minutes. When the vigorous reaction had subsided, the reaction flask was heated on a steam-bath until all the ammonia had evaporated. The residue was stirred and refluxed for a few minutes with 250 cc. of dry benzene, and the solid allowed to settle. While still hot, the benzene solution was decanted onto a steam-heated filter. The extraction of the residue with benzene was repeated three times or until the benzene filtrate no longer deposited crystals of the butyramide on cooling. In a blank experiment using *n*-butyramide approximately 80% of the amide was recovered under these conditions. The amide was filtered off with suction. The combined benzene filtrates were distilled and the residue fractionated, collecting recovered ester at atmospheric pressure and self-condensation product *in vacuo*. The yields are given in Table III; the melting points of the amide and the boiling points of recovered ester agreed essentially with those reported in the literature.

In a similar experiment with ethyl acetate, the residue was extracted with a mixture of three parts of benzene and one part of ethyl acetate, yielding acetamide (10%), melting at 80–80.5°.

In order to determine that all of the ester had reacted with the sodium amide, certain esters were added to equivalents of sodium amide in liquid ammonia containing a trace of sodium triphenylmethide as indicator (obtained by addition of triphenylmethane). Since the amide ion is a stronger base than the triphenylmethide ion, the color remained until all of the amide ion was neutralized. With *t*-butyl acetate the color was discharged immediately. With *t*-butyl *n*-butyrate the color disappeared within six minutes. Therefore, there is little doubt that in the experiments described above using two equivalents of sodium amide all of the ester was converted to ester anion or amide. This is also probably true for the carbonations

Summary

1. Certain esters have been carbonated using sodium amide to form half malonic acid esters, which were esterified with diazomethane to form methyl alkyl malonates.

(7) See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 211.

(8) Brown and Eberly, THIS JOURNAL, **62**, 113 (1940).

(9) Levine and Hauser, *ibid.*, **66**, 1768 (1944).

(10) Arndt, "Organic Syntheses," 2nd Coll. Vol., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 166 (Ref. 3), p. 461.

2. The proportions of ester anion and amide formed from certain esters and sodium amide have been determined. The influence of structure of esters on these courses of reaction has been discussed.

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Streptomyces Antibiotics. IV. Hydrolytic Cleavage of Streptomycin to Streptidine

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Streptomycin has been hydrolyzed in aqueous acid solution to give a basic degradation product, streptidine. Analytical data of several salts and derivatives of streptidine show that the molecular formula of streptidine is $C_8H_{18}N_6O_4$.

One of the first degradation reactions tried on streptomycin was hydrolytic cleavage and examination for basic cleavage products. Cleavage in acid solution was preferred in view of the strongly basic, nitrogenous nature of streptomycin. When acid hydrolysis was tried on a concentrate (500 units/mg.) of streptomycin hydrochloride or on pure streptomycin hydrochloride[1] regenerated from the helianthate, a strongly basic degradation product was formed which was readily isolated and purified as a picrate. Since the picrate of this base was obtained as readily from reaction at 120° as at 25°, the base has considerable stability in acid solution over this temperature range. This base, designated streptidine for convenience, formed an acetyl derivative. Analytical and molecular weight data showed that this derivative was an octaacetate of the molecular formula $C_{24}H_{34}N_6O_{12}$.

Streptidine was also obtained readily as a crystalline sulfate by cleavage of streptomycin in dilute aqueous or methanolic sulfuric acid solution at 25°. The practically pure streptidine sulfate crystallized directly from the reaction solution.

Streptidine was characterized as the following additional crystalline salts: dihydrochloride, carbonate, chloroplatinate, dihelianthate, di-*d*-camphorsulfonate and dihydroiodide. Analytical data on all of these salts are in agreement with the molecular formula, $C_8H_{18}N_6O_4$, for the free base.

Streptidine contains two basic groups as shown by the formation of salts containing two univalent acid ions, such as the dihydrochloride and dihydroiodide. No primary amino groups appear to be present, since streptidine failed to give nitrogen in the Van Slyke amino-nitrogen determination during a five-minute period. The presence of —OH and/or >NH groups is indicated by the infrared absorption as discussed below, and by the formation of octaacetylstreptidine. Although streptidine contains six nitrogen atoms, the absence of typical primary amino groups makes it doubtful that any of the nitrogen atoms are diacetylated. Since streptidine shows no sign of reaction with hydroxylamine, 2,4-dinitrophenylhydrazine or other carbonyl reagents, there are no free aldehydic or ketonic carbonyl groups present. There is no evidence for a carboxyl group in the molecule, and methoxyl groups are absent. Therefore, one or more of the four oxygen atoms in streptidine appears to exist as hydroxyl. Reduction of octaacetylstreptidine was attempted by a reaction with hydriodic acid and red phosphorus in a sealed tube at 160–190°; however, only streptidine dihydroiodide was isolated as a result of deacetylation.

Streptidine is optically inactive and shows only end absorption in the ultraviolet. The octaacetate, however, showed maxima $E_{1\%}$ 400 at 2200 Å. and $E_{1\%}$ 630 at 2525 Å. The infrared absorption spectrum of streptidine dihydrochloride was determined on a solid layer deposited from a methyl cellosolve suspension. Bands appeared at 2.97, 3.38 and 6.10 μ. The band at 2.97 μ is probably due to —OH and >NH groups, while the band at 6.10 μ may be due to a >C=N— bond. In the infrared, octaacetyl streptidine (solution in tetrachlorethane) showed no band at 2.97 μ but exhibited definite strong bands at 5.75 μ and 6.27 μ and a weak band at 6.48 μ. The 6.27 μ band may be due to a >C=N—bond, while the 5.75 μ band is evidently due to the ester carbonyl groups.

In the regeneration of streptomycin hydrochloride or sulfate from the helianthate,[1] there is occasionally observed some inactivation which appears to be due to the presence of excess mineral acid. Thus, a preparation of pure streptomycin helianthate treated with a small excess of hydrogen chloride in absolute methanol gave the expected yield of product, but the specific rotation of the product was −70° instead of −86° and the activity was 600 instead of 800 units/mg. From this material there was isolated streptidine picrate, m. p. 282–284° (dec.), by treating an aqueous solution with sodium picrate. Also, regeneration of streptomycin sulfate from streptomycin helianthate using methanolic sulfuric acid gave on one occasion a considerable yield of crystalline streptidine sulfate. It is therefore important that only the necessary amount of mineral acid be used in regeneration of streptomycin salts from the helianthate. The ease of hydrolysis of streptomycin

(1) Kuehl, Peck, Walti and Folkers, *Science*, **102**, 34 (1945).