166. *Researches on Acetylenic Compounds. Part XXXI. Some Qualitative and Quantitative Aspects of the Reppe Carboxylation Reaction.*

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As a necessary preliminary to an investigation of the mechanism of the Reppe carboxylation reaction, the degree of specificity of the various participants in the reaction has been investigated, and the stoicheiometry of the process examined.

This reaction was originally formulated by Reppe (see Copenhaver and Bigelow, " Acetylene Chemistry," Reinhold, 1949, p. 252) as follows :

$$4RC\equiv CR + Ni(CO)_4 + 2HX + 4HY \longrightarrow 4H\cdot CR{=}CR\cdot CO_2Y + NiX_2 + H_2$$

where HX and HY are respectively an acid, and a compound containing active hydrogen, *e.g.* ethanol. In preliminary investigations (Part XXII; Jones, Shen, and Whiting, *J.*, 1950, 230; *q.v.* for references to earlier work) certain anomalies were encountered, and it was therefore concluded that speculation about the mechanism of the reaction was useless until more information was available concerning the range of conditions under which it takes place and the molecular ratios of the reactants and products. The present paper deals with attempts to gain such information, to discover aspects suitable for further investigation, and to find which of the available procedures is most useful for future preparative applications.

Carboxylation reactions so far investigated fall into two classes. In the first (" type I "; *e.g.*, with phenylacetylene) a vigorous exothermic reaction, during which the nickel carbonyl is apparently consumed as fast as it is added, occurs after a period of quiescence; none of the acetylenic compound can be recovered. In the second ("type II"; *e.g.*, with 1-ethynyl*cyclo*hexyl acetate) no obvious reaction occurs, but after the reagents have been kept together at 70—80° for 20 minutes a small yield of the expected product is obtained; much of the starting material is recoverable. The latter class, and the catalysed reactions discussed in the preceding paper, were excluded from the present investigations.

The results of applying the reaction to a wide range of acetylenes under approximately uniform conditions have already been described (Part XXII, *loc. cit.*; Part XXIX, *J.*, 1951, 48). The effects of variations in the reaction conditions and the other components employed are discussed below.

(a) *Induction Period and Reaction Temperature.*—The length of the induction period varies with the acetylenic compound used, the solvent and acid employed, and the temperature; it is apparently fairly constant provided that these factors are not varied. The temperature is usually chosen so as to make the induction period conveniently short. For example, for most acetylenic compounds in aqueous-ethanolic acetic acid—"standard conditions" (see Part XXII, *loc. cit.*)—it is about one minute at 70—75°; $\beta\gamma$-acetylenic alcohols, however, require 6—10 minutes even at 80°, while acetylene itself in acetone and concentrated hydrochloric acid reacts readily even at 40°.

(b) *Solvent.*—The nature of the solvent employed appears to be relatively unimportant. Successful—*i.e.*, "type I"—reactions have been observed with phenylacetylene and acetic acid in methanol, ethanol, *iso*propanol, *tert.*-butanol, *n*-butanol, acetone, dioxan, ethyl acetate, pyridine, and anisole. Longer induction periods were observed with *tert.*-butanol, acetone, and especially anisole than with ethanol, while pyridine has a specific effect in reducing the induction period (see previous paper), though its use did not make it possible to effect the reaction at 20°. When primary alcohols were used as solvents a small proportion of the acid formed was esterified, presumably by catalysis by the acetic acid present. In the few cases where this proportion was unusually large (*e.g.*, 5-bromopent-1-yne, diphenylacetylene) the explanation is likely to be prolonged heating during the removal of nickel carbonyl, or an unusually large rate constant for esterification, rather than direct participation of the alcohol in the carboxylation reaction (see below). From a preparative point of view it is desirable to minimise this esterification, as it is always difficult to separate the pure ester from the neutral by-products of the reaction by distillation. Alkaline hydrolysis of the neutral fraction is also undesirable, as α-methylenic esters do not always give good yields of the corresponding acids, perhaps because of alkali-catalysed addition of water or methanol to the double bond; in any case the neutral fraction always contains saponifiable matter other than the expected ester, the non-crystalline acids from which impede the isolation of the main product. Accordingly, the standard conditions, *i.e.*, the use of aqueous-ethanolic acetic acid, are usually to be preferred, even when the ester is required and the use of mineral acids is not excluded, as in the synthesis of simple α-alkyl- or α-aryl-acrylic esters.

(c) *Water.*—The rôle played by water has already been stressed; briefly, the facts observed in the case of typical acetylenic compounds are: (i) with alcoholic solvents the free α-methylenic acid is practically the sole product when acetic acid is used, but esters are obtained in steadily increasing amount as the strength of the acid ("HX") is increased (see Table I below); (ii) whereas use of aqueous solvents commonly gives yields of 40—50%, very often 45—50%, use of anhydrous solvents with the same acetylenic compounds gives the same products in only 20—30% yields.

The conclusion drawn is that water can participate as the "HY" component in the reaction, but that alcohols cannot. In the absence of added water, side-reactions responsible for the consumption of 70—80% of the acetylenic starting material apparently lead to the formation of enough water to make possible the formation of a certain amount of the α-methylenic acid from the remainder.

(d) *Acid* ("HX") *Component.*—From the fact that both hydrochloric and acetic acids will participate in the reaction, it was at first believed that their function was merely to maintain a low pH value, and that any acid would suffice. On attempting to verify this hypothesis, however, it was found that effectiveness in the reaction is by no means merely a matter of dissociation constant. The acids which have been tested (by using aqueous ethanol as solvent and typical "reactive" acetylenes) and the results obtained are given in Table I.

The failure of quinol to react is of course not unexpected, in view of its dissociation constant, but that of the other three organic acids is surprising. The most likely explanation for this specificity is that the acid molecules, rather than hydrogen ions, participate in the main reaction.

TABLE I.

Acid.	p*K*.	Acetylene.	Exothermic reaction.	Yield of acid, %.	Yield of ester, %.
Quinol	10	Ph·C≡CH	—	0	0
$Me_3C·CO_2H$	5	do.	+	22 *	0
AcOH	4·7	do.	+	45	2
,, + 1 mol. of NaOAc	—	do.	+	50	0
$CH_2{:}CPh·CO_2H$	3·8	do.	—	(92% rec.)	13
,,	—	Bu·C≡CH	—	8	15
$H·CO_2H$	3·7	Ph·C≡CH	+	23	18
$CH_2Cl·CO_2H$	2·8	Bu·C≡CH	+	18	23
$(CO_2H)_2$	1·4	do.	—	0	0
$CCl_3·CO_2H$	<0	do.	—	0	0
,,		Ph·C≡CH	—	0	0
HCl		do.	+	5	48
H_2SO_4		do.	+	Products not isolated	
H_3PO_4		do.	+	,,	,,

* The isolation of the atropic acid formed was less complete than in other experiments (see Experimental section).

The effects of variations in the reaction components and conditions having been examined, attempts were then made to determine the true quantitative expression of the overall reaction. Here there is the difficulty that the neutral component of the reaction product has in every case proved to be a very complex mixture, from which only one known constituent (apart from the ester of the principal product) has yet been isolated; *s*-triphenylbenzene was obtained when phenylacetylene was used. The investigation was therefore limited to the determination of the ratios involving the acetylenic compound, the nickel carbonyl, and the acid component " HX " (*i.e.*, acetic acid) consumed, and the α-methylenic acid and the bivalent nickel formed. Three problems had to be solved before quantitative work was possible.

(a) *Analytical methods.* It was necessary to determine as accurately as possible the yield of α-methylenic acid formed in the reaction. Attempts to do so by alkali titration proved unsuccessful. Phenylacetylene, or, in one case, but-2-yne-1 : 4-diol diacetate, were therefore used, because the derived acids are non-volatile, readily extracted from water by ether, and easy to crystallise. By using standardised recrystallisation technique and systematically working up mother-liquors it was possible to ensure that practically all the acid formed was isolated as the pure compound, only a trace of semi-crystalline material, perhaps 1% of the total acid fraction, remaining when the final mother-liquors were evaporated.

The standard method employing dimethylglyoxime and ammonium citrate proved satisfactory for measuring the amount of bivalent nickel formed in the reaction. It was hoped that it would also be possible to work with known quantities of nickel carbonyl, and to estimate the amount which had reacted by difference; partly for this reason, and also to make it possible to test the apparatus employed, a method of oxidising the carbonyl in ethereal-alcoholic solution to the ionic state to permit its gravimetric determination was sought. Bromine water proved to be a satisfactory reagent, after dilution of the solution with carbon tetrachloride to increase its density.

(b) *Apparatus.* It was essential to use a method of effecting the reaction such that no serious loss of nickel carbonyl occurred; otherwise the danger of an accidental deficiency of the reagent would necessitate the use of a large excess of carbonyl, and errors introduced by its thermal decomposition would become significant. The apparatus devised has been illustrated (Part XXIX, *loc. cit.*); control experiments described in the Experimental section showed that, though an improvement on the apparatus previously (Part XXII, *loc. cit.*) used, it was not sufficiently reliable to permit the estimation by difference of nickel carbonyl which had reacted (This was not serious, since there is no reason to expect that this quantity would differ from the amount of divalent nickel formed, which could easily be determined.) It was, however, otherwise satisfactory.

(c) *Stability of the nickel carbonyl.* The effects of heating known quantities of nickel carbonyl in various solvents were then examined. Decomposition in aqueous-ethanolic acetic acid at *ca.* 70° is not rapid; a pale green colour slowly developed. In neutral solvents rather more decomposition occurred, probably to nickel oxide, since a black precipitate, which gave a clear solution on addition of mineral acid, was formed.

By making reasonable estimates for the amount of nickel carbonyl added in excess of that required for the reaction, the time, and the temperature, it was concluded that in the quantitative experiments described below the amount of nickel carbonyl thermally decomposed was probably about 1% of that consumed in the carboxylation reaction. The errors in the estimation of nickel were also of this order of magnitude. No attempt has been made to assess carefully the accuracy of the ratios discussed below, but systematic errors are probably not greater than ±5%, and the precision was more than adequate for the purpose envisaged.

TABLE II.

Reactions with phenylacetylene (50 *millimols.*)

Expt. no.	Solvent.	AcOH (millimols.) used.	$\mathrm{Ni^{++}}$ (millimols.) found.	$\mathrm{CH_2{:}CPh{\cdot}CO_2H}$ obtained.*	$\frac{\mathrm{CH_2{:}CPh{\cdot}CO_2H}}{\mathrm{Ni^{++}}}$.	Remarks.
1	EtOH	33	9·33	21·8(+ 1·0)	2·45	—
2	EtOH	33	8·78	20·2(+ 1·2)	2·43	—
3	EtOH	33	9·34	21·3(+ 1·3)	2·42	—
4	EtOH + NaOAc	33	9·53	24·5	2·57	—
5	$\mathrm{Pr^iOH}$	33	9·38	22·6	2·41	—
6	$\mathrm{Bu^tOH}$	33	9·32	22·9	2·46	—
7	$\mathrm{Bu^tOH}$	33	6·33	15·5	2·45	(*a*)
8	EtOAc	33	9·92	10·2(+ 8·1)	1·84	—
9	$\mathrm{Bu^tOH}$	33	10·85	25·4	2·33	(*b*)
10	EtOH	13·2	7·72	14·7	1·90	(*c*)
11	EtOH	3·3	6·08	4·3	0·71	(*c*)
12	$\mathrm{Bu^tOH}$	13·5	7·02	7·8	1·11	(*c*)

(*a*) 6·39 millimols. of $\mathrm{Ni(CO)_4}$ used. (*b*) But-2-yne-1 : 4-diol diacetate (50 millimols.) used. (*c*) Note deficiency of acetic acid.

* The weight of atropic acid obtained by hydrolysis of the neutral fraction, shown in parentheses, was included in calculating the ratio.

Results.—A number of experiments on the carboxylation of phenylacetylene were carried out under the standard conditions; the values for the atropic acid and the bivalent nickel formed are given in Table II. The ratio of the yields of these products was reasonably constant, and very near to 2·5, provided that sufficient acetic acid was present. Use of *iso*propanol or *tert.*-butanol in place of ethanol had no effect on the ratio but the use of ethyl acetate (Expt. 8) caused extensive ester-interchange, and a low value for the ratio because of the unsatisfactory yields in the hydrolysis of the ester (see above). Particularly noteworthy is Expt. 7, in which a deficiency of nickel carbonyl was used; it was quantitatively converted into bivalent nickel, and the ratio of the products was exactly the same as in experiments in which the carbonyl was present in excess. It is also interesting to note that when a deficiency of acetic acid was used, the atropic acid formed was quite unable to replace it (contrast Expts. 1—3, and 10); the fact that the ratio then fell below 2·5 indicates that when the acetic acid had been wholly consumed in the carboxylation reaction, phenylacetylene and nickel carbonyl were able to interact with the formation of bivalent nickel but not of atropic acid. This point is further discussed below.

The ratio (α-methylenic acid formed)/(acetylene used) has, in previous discussions from a preparative standpoint, been regarded as the yield of the reaction. In the first six quantitative experiments quoted, this was 46, 42, 45, 49, 45, and 46% respectively; in a larger-scale experiment on phenylacetylene (Part XXII, *loc. cit.*) a yield of 48% is quoted; two experiments in the presence of pyridine (previous paper) gave 49% and 44% yields of atropic acid. Ethynylphenylcarbinyl and ethynylpropylcarbinyl acetates gave yields of 50% and 48% respectively (Part XXII); but-2-yne-1 : 4-diol diacetate gave yields of 53% (Part XXIX) and 51% (above); and tolan (Part XXIX) gave a combined yield (crystalline acid and ester) of 48%. These figures cover every experiment so far carried out in which approximately quantitative isolation of a pure crystalline product was possible and was attempted. While it is conceded that the isolation of such products, even in favourable circumstances, can never be an accurate method of quantitative measurement, it is considered that the above figures and the results in Table II imply that in the Reppe carboxylation reaction, two molecules of the acetylene give rise to one of the product.

Some idea of the quantity of acetic acid needed for the reaction can be obtained from experiments 9, 10, and 11. Those in ethanolic solution, Nos. 9 and 10, show that more (but not much more) than one molecule of atropic acid can be obtained from one of acetic acid.

These results can be summarised in the partial equation :

$$\mathrm{10R{\cdot}C{\equiv}C{\cdot}R' + 2Ni(CO)_4 + 5H_2O + 4HX = 5R{\cdot}C(CO_2H){:}CHR' + 2NiX_2 + (5R{\cdot}C{\equiv}C{\cdot}R',3CO,4H)}$$

The last term must represent the net composition of the very complex mixture of by-products. This expression no doubt describes merely the resultant of a series of inter-related processes, but it remains essentially correct over a wide range of circumstances, provided that water and the acid used are not deficient (if either is lacking, alternative reactions evidently occur). The molecular ratio (acetylene) : (nickel carbonyl) : (α-methylenic acid) remains quite close to 10 : 2 : 5, and very far from 4 : 1 : 4, for many different acetylenes, acids, and solvents and over a wide range of relative initial concentrations. It is even evident that the acid used (in the case studied, acetic acid) can become the limiting factor, and it is then used up, in ethanolic solution at any rate, more or less according to this equation.

Allusion has been made to the formation of bivalent nickel from mixtures of nickel carbonyl and acetylenic compounds not containing an acid This reaction is easily realised; when nickel carbonyl was added to phenylacetylene in alcoholic solution at 65—70° a mildly exothermic reaction was observed and considerable quantities of dark polymeric material were obtained, from which no pure component (other than about 4% of *s*-triphenylbenzene) could be isolated by chromatography. Essentially similar results were obtained with hex-1-yne, about 35% of the product being distillable at 1 mm. (b. p. 70—140°). These two product-mixtures closely resembled the corresponding neutral fractions obtained in the normal reaction in the presence of acetic acid, and discussed briefly in Part XXII (*loc. cit.*); little, if any, of the acetylene was unchanged. It might be considered that a polymeric product of the type described is an intermediate in the normal carboxylation reaction. Such is apparently not the case; treatment of hex-1-yne with nickel carbonyl in the absence of acid to give the polymeric material, followed by addition of acetic acid, did not result in an exothermic reaction, and no acidic product was obtained.

The results described in this and the previous paper reveal the unsuspected complexity of the Reppe carboxylation reaction Further work on some of the aspects discussed is now in progress in these laboratories.

EXPERIMENTAL.

In obtaining the results shown in Table I the technique described in Part XXIX was employed; 0·02 g.-mol. of the acetylenic compound was used in the first twelve experiments. The acid fraction was isolated with ether and after being thoroughly washed with water was freed as far as possible from volatile acids; in the second experiment the pivalic acid was readily removed by sublimation at 50°/0·5 mm. The atropic acid was carefully recrystallised from light petroleum; the neutral fraction was hydrolysed with aqueous-methanolic potassium hydroxide at room temperature.

Determination of Nickel Carbonyl.—(*a*) The sample (1·2 g.) was dissolved in carbon tetrachloride (100 c.c.) and treated with bromine water in moderate excess. A steady evolution of carbon monoxide occurred; the completion of the reaction was indicated by a permanent orange-brown colour in the lower layer. The layers were separated, the lower being well washed with water, and the nickel in the upper layer and in the washings was precipitated as dimethylglyoxime complex after addition of ammonium citrate, which decomposed the excess of bromine (Vogel, " Quantitative Inorganic Analysis," Longmans, 1939, p. 499).

(*b*) The nickel carbonyl (*ca.* 1·5 g.) was treated with a solution of chromic acid (*ca.* 1·5 g.) in glacial acetic acid (20 c.c.). Slow decomposition resulted; after 2 hours the solution was diluted with water and the nickel was determined. The results obtained in control experiments are tabulated :

Expt.	Method.	$Ni(CO)_4$ used (g.).	Ni content (g.).	Ni^{++} found (g.).	Error, %.
1	*a*	2·031	0·696	0·674	−3·1
2	*a*	1·501	0·515	0·516	+0·2
3	*a*	1·409	0·484	0·486	+0·5
4	*a*	1·814	0·622	0·629	+1·1
5	*b*	0·730	0·251	0·248	−1·2

The accuracy appeared to be adequate for the rough quantitative measurements contemplated. Unfortunately, an attempt to use the convenient colorimetric method employing the oxidised dimethylglyoxime complex (Vogel, *op. cit.*, p. 213) gave inaccurate results when applied to solutions obtained by oxidising nickel carbonyl.

Method (*a*) was readily applied to the distillates obtained when the unchanged nickel carbonyl was removed from the reaction mixture; carbon tetrachloride was added in sufficient quantity to raise the density of the organic layer to *ca.* 1·1, and the decomposition was carried out as described. It was, however, preferable to distil directly into a flask containing 100 c.c. of carbon tetrachloride and 100 c.c. of bromine water when the apparatus described in Part XXIX (*loc. cit.*) was used.

Apparatus.—The simple original apparatus (Part XXII, *loc. cit.*) was tested by heating a known weight of nickel carbonyl in alcoholic solution for 15—30 minutes at 65°, distilling over the excess of carbonyl by adding ether, and determining the nickel present, as carbonyl, in the distillate and that present in the ionic state (after addition of mineral acid, which gave a clear, pale green solution) in the reaction vessel. In these experiments the total recovery was 82, 70, and 46%, 1·5—3·5% of the carbonyl suffering decomposition. The later apparatus (Part XXIX, *loc. cit.*) was then devised; three experiments with it are tabulated below. About 2·6 g. of the carbonyl (accurately weighed into alcohol, with precautions against loss) were heated for about 30 minutes.

Expt.	Solvent (c.c.). EtOH.	H_2O.	AcOH.	Conc. HCl.	Temp.	Unchanged, %.	Decomp., %.	Total recovery, %.
1	50	—	—	—	65—70°	85·2	10·4	95·6
2	50	2	4	—	74—76	84·5	5·8	90·3
3	50	—	—	6	72—74	83·1	9·1	92·2

In Expt. 1—but not Expts. 2 and 3—a black deposit of finely-divided metal and/or oxide formed; it readily dissolved on adding mineral acid.

These results show that the apparatus is not sufficiently reliable to make possible the determination of unchanged nickel carbonyl, but would permit the use of only moderate excess of nickel carbonyl without any danger that loss through evaporation might result in a deficiency. Expt. 2, using the solvent normally employed in the carboxylation (but with a much longer reaction period, at a higher temperature), shows that thermal decomposition of the carbonyl is not an important factor.

Quantitative Experiments.—Reactions were carried out in which phenylacetylene (5·1 g., 50 millimols.), solvent (5 c.c.), acetic acid (2 c.c., 33 millimols.), and water (2 c.c., 100 millimols.) were heated to 65° and treated with a solution of nickel carbonyl (*ca.* 2 ml., 15 millimols.) in ethanol. This was added at such a rate that the temperature remained at 65—70°, to minimise losses; the end of the reaction was indicated by a sharp fall in the temperature, and addition of nickel carbonyl was stopped at this point (previous experience had shown that further addition did not increase the yield, and clearly it would lead to increased thermal decomposition). The mixture was cooled, ether (20 c.c.) was added, and the whole heated until the boiling point of the distillate reached 50°. This procedure was repeated after addition of a further 20 c.c. of ether. The reaction mixture was cooled and poured into 100 c.c. of 3% sulphuric acid; the solution was extracted with ether (3 × 75 c.c.), with care to avoid mechanical losses, and the aqueous layer was used for the gravimetric determination of nickel. The ethereal extract was washed thoroughly with saturated sodium hydrogen carbonate solution; the washings were acidified, and the acid was re-extracted with ether. The dried extract was evaporated to *ca.* 20 c.c. at atmospheric pressure, the remainder of the solvent being completely removed under reduced pressure below 60° (otherwise slight decomposition occurred). The residual solid was warmed to *ca.* 40° with 25 c.c. of light petroleum (b. p. 60—80°), and the solution cooled to 20°. Filtration gave the main crop of atropic acid, m. p. 105—106°, already practically pure. Concentration of the mother-liquors to 5 c.c. gave a second crop (*ca.* 0·1 g.), m. p. 102—105°, which was added to the first; the residue obtained on complete evaporation was only about 0·05 g. of semi-solid material, which was discarded. The neutral fraction was isolated and hydrolysed directly with dilute ethanolic potassium hydroxide solution; a small amount of acidic material was obtained which was recrystallised from benzene–light petroleum to a melting-point of at least 102°.

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