Researches on Acetylenic Compounds. Part XLIII. A New Method for the Preparation of Alkoxyacetylenes.*

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A new and very convenient method for the preparation of the alkoxyacetylenes is described. Some of their properties, including their ability to convert acids into their anhydrides under very mild conditions, are summarised.

In Part XXXVIII (Eglinton, Jones, and Whiting, *J.*, 1952, 2873) a reaction was described which involved the elimination of HX and ROH from αβ-halogeno-ethers in the presence of sodamide:

$$\mathrm{R'CH(OR){\cdot}CHXR''} \xrightarrow{\mathrm{NaNH_2}} \mathrm{R'C{\equiv}CR''}$$

This method has now been extended to the preparation of alkoxyacetylenes (R′ = OAlk, R″ = H). These are valuable synthetic agents, giving αβ-unsaturated esters by condensation with carbonyl compounds and treatment with acids, or αβ-unsaturated aldehydes when an intermediate hydrogenation stage is employed; yields are good (see Arens and van Dorp, *Nature*, 1947, **160**, 189; Clemo and Davison, *J.*, 1951, **447**; Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823; Sarett, Arth, Lukes, Beyler, Poos, Johns, and Constantin, *J. Amer. Chem. Soc.*, 1952, **74**, 4974) but these methods have been little used because of the inaccessibility of alkoxyacetylenes by present methods (Jacobs, Kramer, and Hanson, *J. Amer. Chem. Soc.*, 1942, **64**, 1223; van Dorp, Arens, and Stephenson, *Rec. Trav. chim.*, 1951, **70**, 289; Favorskii and Shchukina, *Chem. Abs.*, 1944, **38**, 300).

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* Part XLII, preceding paper.

Dimethyl chloroacetal was used for preliminary quantitative experiments, which showed that the reaction followed the expected course :

$$Cl{\cdot}CH_2{\cdot}CH(OMe)_2 + 3NH_2^- \longrightarrow \bar{C}{\equiv}C{\cdot}OMe + \bar{Cl} + \bar{O}Me + 3NH_3$$

since after 15 minutes 1, 2, and 3 mols. of sodamide had liberated 0·31, 0·61, and 0·91 mols. of ionic chlorine, respectively. After an hour the figures were substantially the same. Isolation of the very volatile product proved difficult, since if liberated from its sodium derivative by ammonium chloride it was lost on evaporation of the ammonia. On the other hand isolation of the sodium compound without acidification resulted in a series of explosions, due to its extraordinary sensitivity to air. Even when air was excluded, the dry solid underwent decomposition above about 60°. Eventually the technique described below was developed; a variant has been found satisfactory by Professor A. C. Cope and his collaborators (*Org. Synth.*, in the press). It is recommended that one of these procedures be followed exactly, since otherwise this method is hazardous. It is, however, overwhelmingly more convenient than the older routes to alkoxyacetylenes, giving in a single operation a 60% yield and being practicable on quite a large scale.

With obvious modifications this method was readily applied to the preparation of ethoxy- and butoxy-acetylenes, the requisite dibutyl chloroacetal being obtained from the methyl compound by an alcohol-interchange reaction. The bromoacetals could be substituted for the chlorine compounds, but without advantage. Attempts to convert α-bromopropionaldehyde dimethylacetal into 1-methoxyprop-1-yne, however, were unsuccessful; the main constituent of the heterogeneous product was the acetal of acraldehyde.

Some clarification of the mechanism of the acetylene-synthesis from β-halogeno-ethers described by Eglinton, Jones, and Whiting (*loc. cit.*), and further exemplified above, is now possible as a result of the work of Hill, Judge, Skell, Kantor, and Hauser (*J. Amer. Chem. Soc.*, 1952, **74**, 5599). These authors proved that when 1-octyl bromide was treated with potassamide in liquid ammonia, about 10% of the oct-1-ene (the major product) was formed by removal of one of the hydrogen atoms of the bromomethyl grouping, with hydrogen shift from the neighbouring methylene group, *i.e.*,

$$C_6H_{13}{\cdot}CH_2{\cdot}CH_2Br \xrightarrow{H_2N^-} [C_6H_{13}{\cdot}CH_2{\cdot}CH{<}] \longrightarrow C_6H_{13}{\cdot}CH{=}CH_2$$

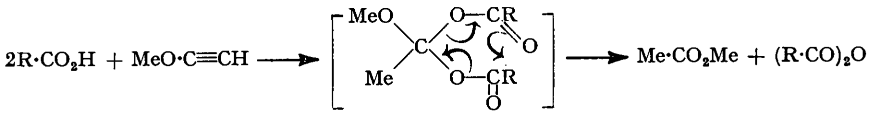
Presumably, proximity to the C–Br dipole activates a proton sufficiently for removal by H_2N^-, the synchronous separation of Br^- from the incipient carbanion lending some assistance even though an energy-rich diradical remains. Possibly (though the distortions from normal molecular dimensions are then numerous) the hydrogen-shift is concerted with the initial attack. Now, if the bromomethyl or chloromethyl group were adjacent to a carbon atom bearing an ether linkage, the main factor, proximity to the C–halogen linkage, would still operate; but RO^- might be lost simultaneously from the β-carbon atom, instead of halide ion from the α-atom. In compensation for the smaller energy gain in the ion-formation process a more stable main product, an ethylenic compound instead of a diradical, would result; or alternatively, the further complexity in the transition state implied by a simultaneous hydrogen migration would be avoided. Eglinton, Jones, and Whiting (*loc. cit.*) had assumed tacitly that when a compound $R'CHX{\cdot}CHR''{\cdot}OR$ was treated with sodamide, the only possible initial single-elimination process would give the vinyl ether $R'CH{:}CR''{\cdot}OR$, since dehydrohalogenations are easy, and dehydroalkoxylations are much more difficult to effect. Now that the work of Hill *et al.* (*loc. cit.*) has directed attention to the role of the α-substituent, a two-stage mechanism for the observed overall reaction, *i.e.*, $R'CHX{\cdot}CHR''{\cdot}OR \longrightarrow RO^- + R'{\cdot}CX{=}CHR'' \longrightarrow R'C{\equiv}CR'' + X^-$ becomes plausible and indeed preferable to the double-elimination hypothesis advanced earlier. It is supported by the contrasting effects of sodamide on the acetals of α-bromopropaldehyde and bromoacetaldehyde (see above). Secondary carbanions are less stable (and hence less easily formed, and more reactive) than primary carbanions (see *inter al.*, Gilman, Moore, and Bame, *J. Amer. Chem. Soc.*, 1941, **63**, 2479), a fact which would account for the failure of the former acetal to give 1-methoxyprop-1-yne. Competition from proton-elimination at the methyl group is not alone an adequate explanation of this result, since the propionacetal reacted much more slowly than its lower homologue, as proved by the absence, in this case, of obvious liberation of heat, and by a determination of the amount of bromide ion liberated after 30 minutes (only 0·77 mol.).

The condensation of sodiomethoxy- or sodioethoxy-acetylene with carbonyl compounds *in situ* offers an apparently attractive route to αβ-ethylenic esters, etc. This was investigated with acetone, benzaldehyde, and *cyclo*hexanone. β-Methylcrotonic acid was indeed obtained in the first place, but despite wide variations in reaction conditions, the substitution of lithium or potassium for sodium, or the preparation of sodioethoxyacetylene from pre-formed ethoxyacetylene, yields remained very low.

For alkylation *in situ*, effectively an alternative to the use of malonic ester alkylation in the synthesis of fatty acids, the presence of sodium alkoxide might well be disadvantageous. A second new route to alkoxyacetylenes from vinyl ethers was therefore sought. This involved merely the usual bromination–dehydrobromination sequence, the second reaction being effected in one operation by using sodamide (3 mols.) in liquid ammonia. Precautions were necessary to avoid the rapid reaction of the αβ-dibromo-ethers with ammonia vapour; commercially available 1 : 2-dichloroethyl ethyl ether could also be used. In this way butyl bromide was converted into hexanoic acid in 17% overall yield, which could probably be improved considerably.

Some properties of the alkoxyacetylenes are summarised in the Experimental section; we would emphasise that, once prepared, they are stable for weeks at 0° and quite safe to handle.

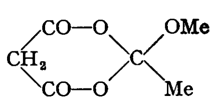
Methoxyacetylene reacted exothermically with acetic and butyric acids, giving methyl acetate and the corresponding anhydrides:

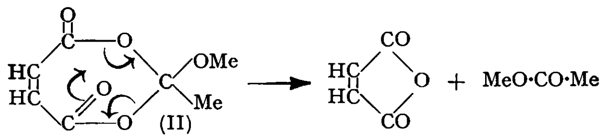


Presumably an unstable di-adduct decomposes through a cyclic transition state, in a reaction analogous to the decomposition of ethylidene diacetate into acetaldehyde and acetic anhydride (G.P. 284,996; *Chem. Zent.*, 1915, II, 294), the reaction taking place even at 0°. As no mono-adduct was obtained from an equimolecular mixture, it must be assumed that the mono-adduct is more reactive toward the acid than methoxyacetylene, as are the structurally similar keten acetals.

This method seemed to be the mildest yet devised for converting a carboxylic acid into its anhydride; heptanoic, phenylacetic, β-phenylpropionic, acrylic, chloroacetic, and trichloroacetic acids all gave their anhydrides at or below room temperature. Others were less reactive, and the use of phosphoric acid and mercuric oxide as catalysts (cf. Reppe, G.P. 588,352; 589,970) was investigated. A marked increase in reaction rate was observed in comparative experiments, crotonic and pivalic acids now reacting smoothly at room temperature. Cinnamic and palmitic acids, however, were still inert, possibly because of their insolubility.

Other acids presented points of especial interest. Formic acid reacted vigorously, even at 0°, without a catalyst, but carbon monoxide was the only product—a result which sets a lower limit to the possible stability of formic anhydride. Oxalic acid reacted similarly, though more slowly, evolving carbon monoxide and carbon dioxide. Malonic acid reacted vigorously and gave a syrupy product from which a small quantity of liquid, b. p. 85—95°/1 mm., could be separated by heating to 240°/1 mm. This appeared to be essen-


(I)


(II)

tially (I), a small proportion of enol being present, though analytical data were only approximately correct for $C_6H_8O_5$. It may perhaps have been formed by thermal depolymerisation; its properties closely resemble those of *iso*propylidene malonate (Davison and Bernhard, *J. Amer. Chem. Soc.*, 1948, **70**, 3426). Maleic acid gave an excellent yield of the anhydride; in this case the rearrangement of the initially-formed cyclic ester (II) can take place much more easily than with (I).

By this reaction the anhydride was obtained in good yield from toluene-*p*-sulphonic acid.

Work on this reaction was stopped when it was learnt that Arens and Moddermann (see *Chem. Abs.*, 1951, **45**, 6152) had discovered it independently, and in general obtained very similar results.

EXPERIMENTAL

Ethoxyacetylene.—A suspension of sodamide in liquid ammonia was prepared from sodium (38 g.) and liquid ammonia (500 ml.) in a 1-l. round-bottomed flask, clamped to the bottom of a vertical Duralumin rod (length 30″), the top of which was fixed. By using this system, the contents of the flask could be swirled very conveniently. Diethyl chloroacetal (76·5 g.; commercial) was added during 15—20 min. with manual agitation. The ammonia was evaporated in a stream of pure nitrogen. The flask was then cooled to $-70°$ (nitrogen flow maintained), and a cold ($-20°$) saturated solution of sodium chloride (325 ml.) was added as rapidly as possible, with vigorous agitation. The flask was then fitted with a still-head connected to a trap cooled to $-30°$, and the contents of the flask were slowly heated to 100°. The condensate was allowed to warm to 0° and neutralised by the addition of an aqueous slurry of sodium dihydrogen phosphate. The aqueous layer was frozen and the supernatant liquid was decanted and dried ($CaCl_2$). Distillation (15-cm. Fenske column) gave ethoxyacetylene (21·2 g., 61%), b. p. 50—52°, n_D^{20} 1·3796 (Favorskii and Shchukina, *loc. cit.*, give b. p. 50°, n_D^{20} 1·3796; Jacobs, Cramer, and Hanson, *loc. cit.*, give n_D^{20} 1·3812).

Methoxyacetylene.—This was prepared as above from sodium (36 g.), liquid ammonia (500 ml.), and dimethyl chloroacetal (62 g.; commercial). Distillation gave methoxyacetylene (16·0 g., 57%), b. p. 22·5—23·5°/760 mm., n_D^{18} 1·3677, d_D^{18} 0·805 (Favorskii and Shostakovskii, *loc. cit.*, give b. p. 22—26°).

Dibutyl Chloroacetal.—A mixture of dimethyl chloroacetal (77·5 g.), *n*-butanol (92·5 g.), and sulphuric acid (0·1 ml.) was heated; when the theoretical quantity of methanol (50 ml.) had been collected the residue was cooled, neutralised with potassium carbonate, and distilled to give dibutyl chloroacetal (109·2 g., 84%), b. p. 71°/0·4 mm., n_D^{18} 1·4311 (Shostakovskii and Sidel'kovskaya, *Zhur. Obshchey Khim. S.S.S.R.*, 1950, **20**, 620, give b. p. 113—114°/13 mm., n_D^{20} 1·4310).

Butoxyacetylene.—Dibutyl chloroacetal (104·3 g.) was added during 1½ hr. to a suspension of sodamide [from sodium (38 g.)] in liquid ammonia (500 ml.). After a further 2½ hr. (during which more liquid ammonia was added to replace losses), a cold ($-15°$) concentrated ammonia solution (*d* 0·88; 150 ml.) was added, followed by water (200 ml.). The organic layer was separated, filtered, and distilled. After being washed with water and dried (anhydrous calcium chloride), the product was redistilled (15-cm. Fenske column), giving butoxyacetylene (21·7 g., 44%), b. p. 41—42/78 mm., $n_D^{16·5}$ 1·4067, $n_D^{4·5}$ 1·4128 (Jacobs, Cramer, and Hanson, *loc. cit.*, give b. p. 50·5°/110 mm.; Shchukina and Favorskii, *loc. cit.*, give n_D^{20} 1·4010).

n-*Hexanoic Acid.*—1 : 2-Dichloroethyl ethyl ether (13·7 g.) was added to a stirred suspension of sodamide [from sodium (7·0 g.)] in liquid ammonia (300 ml.). The resultant suspension of sodium ethoxyacetylide was treated with *n*-butyl bromide (13·3 g.) and stirred for 2 hr. After the ammonia had evaporated, water was added and the product was isolated with ether. Evaporation of the solvent gave crude 1-ethoxyhex-1-yne (5·2 g.) which could not be distilled owing to persistent foaming; it was therefore added portionwise to a mixture of ethanol (10 ml.), water (10 ml.), sulphuric acid (2N; 2 ml.), and a trace of mercuric oxide. The mixture was heated under reflux for 10 min., the excess of acid was neutralised, and a solution of sodium hydroxide (3 g.) in ethanol (10 ml.) was added; heating was continued for a further 2 hr. Isolation of the acid fraction gave *n*-hexanoic acid (2·0 g., 17%), b. p. 47°/0·03 mm., n_D^{17} 1·4187 (Simon, *Bull. Soc. chim. Belg.*, 1929, **38**, 47, gives b. p. 205°/760 mm., n_D^{15} 1·4188).

The Reaction Between Acetic Acid (2 *Mol.*) *and Methoxyacetylene* (1 *Mol.*).—Methoxyacetylene (2·8 g.) was added to frozen acetic acid (6·0 g.) during 20 min. with external cooling. The resultant mixture was stored at 0° for 1½ hr. and then at 20° for 18 hr. Careful fractionation gave methyl acetate (2·5 g., 68%), b. p. 56°, n_D^{19} 1·3628, a small intermediate fraction, and acetic anhydride (4·3 g., 85%), b. p. 71—72°/70 mm., $n_D^{18\cdot5}$ 1·3906. (Literature values are b. p. 57° and n_D^{17} 1·3639 for methyl acetate; b. p. 68°/53 mm. and n_D^{20} 1·3896 for acetic anhydride.) The methyl acetate was characterised as methyl 3 : 5-dinitrobenzoate, m. p. 109°, and the acetic anhydride as acetanilide, m. p. 114—115°, both undepressed on admixture with authentic samples.

Butyric Anhydride.—Methoxyacetylene (2·8 g.) was added to butyric acid (8·8 g.) at 10°. The reaction was only mildly exothermic. After 16 hr. at 20° distillation gave : methyl acetate (2·3 g., 62%); butyric acid (*ca.* 1·0 g.), b.p . 72—73°/18 mm., n_D^{24} 1·3990 (Found : equiv., 84. Calc. : equiv., 88); and butyric anhydride (4·8 g., 61%), b. p. 91—92°/18 mm., n_D^{25} 1·4118 (Found: equiv., 77·5. Calc. : equiv., 79). (Whitby, *J.*, 1926, 1463, gives for butyric anhydride b. p. 198°, n_D^{18} 1·4143.) The anhydride reacted vigorously with aniline to give butyranilide, m. p. 96° (Robertson, *J.*, 1919, **115**, 1220, gives m. p. 96°).

Monochloroacetic Anhydride.—Monochloroacetic acid (9·5 g.) in tetrahydrofuran (10 ml.) was treated with methoxyacetylene (2·8 g.) at 15°. The reaction was exothermic and external cooling was required. The mixture, after 18 hr. at 15—20°, was distilled to give the anhydride, b. p. 118—120° (bath temp.)/0·05 mm. (Found: equiv., 85. Calc. : equiv., 85·5), which reacted with aniline to give the anilide (yield *ca.* 90%), m. p. 136°. (Bischoff and Walden, *Ber.*, 1894, **27**, 2949, give b. p. 110°/10 mm. for monochloroacetic anhydride; Meyer, *Ber.*, 1875, **8**, 1152, gives m. p. 135° for chloroacetanilide.)

Trichloroacetic Anhydride.—Trichloroacetic acid (1·4 g.) in methylene dichloride (4 ml.) was treated with methoxyacetylene (0·5 ml.). After 20 hr. at 20°, distillation gave the anhydride (0·86 g., 64%), b. p. 128° (bath temp.)/0·02 mm., $n_D^{20\cdot5}$ 1·5078 (Fichter, Fritsch, and Miller, *Helv. Chim. Acta*, 1923, **6**, 503, give b. p. 98—100°/11 mm.).

Heptanoic Anhydride.—Heptanoic acid (1·3 g.) was treated with methoxyacetylene (0·41 g.); after 20 hr. at 20° the mixture was distilled to give heptanoic anhydride (0·81 g., 67%), b. p. 145° (bath temp.)/0·01 mm., n_D^{20} 1·4341 (Kraft and Rosing, *Ber.*, 1900, **33** ,3576, give b. p. 165°/15 mm. and Lumsden, *J.*, 1905, **87**, 93, gives n_D^{15} 1·4335 for heptanoic anhydride).

Phenylacetic Anhydride.—Methoxyacetylene (0·5 ml.) was added to phenylacetic acid (1·4 g.) in methylene dichloride (2 ml.), the mixture was set aside at 20° for 18 hr., and the solvent was then removed to give phenylacetic anhydride (1·24 g., 96%), m. p. 72—72·5° after recrystallisation from light petroleum (b. p. 60—80°). A mixture with phenylacetic acid (m. p. 76—77°) had m. p. 51—60° (Anschutz, *Ber.*, 1887, **20**, 1391, gives m. p. 72·5° for phenylacetic anhydride).

β-*Phenylpropionic Anhydride.*—β-Phenylpropionic acid (1·50 g.) similarly gave its anhydride (0·75 g., 53%), b. p. 195° (bath temp.)/0·05 mm., n_D^{20} 1·5419; the anilide had m. p. 94—95° (Robinson and Shinoda, *J.*, 1925, **127**, 1976, give b. p. 216°/14 mm. for the anhydride. Dieckmann, Hoppe, and Stein, *Ber.*, 1904, **37**, 4627, give m. p. 96° for the anilide).

Pivalic Anhydride.—Methoxyacetylene (0·40 g.) was added to pivalic acid (1·0 g.) in ether (2 ml.) containing orthophosphoric acid (*ca.* 0·05 ml.). After 16 hr. at 20°, distillation gave pivalic anhydride (0·67 g., 75%), b. p. 103° (bath temp.)/15 mm., $n_D^{19\cdot5}$ 1·4104 (Greenwood, Whitmore, and Crooks, *J. Amer. Chem. Soc.*, 1938, **60**, 2028, give b. p. 124°/93 mm., n_D^{20} 1·4093). Treatment with aniline gave pivalanilide, m. p. 127—128° (Schwartz and Johnson, *J. Amer. Chem. Soc.*, 1931, **53**, 1005, give m. p. 128°).

Crotonic Anhydride.—Methoxyacetylene (0·5 ml.) was added portionwise to crotonic acid (0·85 g.) in methylene dichloride (2 ml.) containing a trace of mercuric oxide. After 20 hr. at 20° distillation gave the crude anhydride (0·62 g.), b. p. *ca.* 95° (bath temp.)/0·02 mm., n_D^{17} 1·466, which reacted exothermally with aniline to give crotonanilide, m. p. 115°, in good yield. (Luniak, *Ber.*, 1909, **42**, 915, gives b. p. 114°/12 mm., n_D^{20} 1·4745 for crotonic anhydride. Authenrieth and Speiss, *Ber.*, 1901, **34**, 189, give m. p. 115° for crotonanilide.)

Maleic Anhydride.—Maleic acid (1·1 g.) in methylene dichloride (3 ml.) was treated cautiously with ethoxyacetylene (1·0 ml.) in methylene dichloride (2 ml.) at 25—30°. A small amount of an insoluble white precipitate had formed after 1 hr. (polymer ?), which was discarded. Isolation gave maleic anhydride (0·88 g., 95%), m. p. 51—52° undepressed on admixture with an authentic sample of m. p. 53—54°.

*Toluene-*p*-sulphonic Anhydride.*—Methoxyacetylene (0·20 g.) was added to a suspension of toluene-*p*-sulphonic acid (0·85 g.) in methylene dichloride (5 ml.). A vigorous reaction took place and efficient cooling was required. Evaporation of the solvent and treatment with potassium hydrogen carbonate solution gave toluene-*p*-sulphonic anhydride (0·42 g., 52%), m. p. 122—124° (Meyer and Schlegl, *Monatsh.*, 1913, **34**, 573, give m. p. 122—125°).

2-*Methoxy*-2-*methyl*-4 : 6-*dioxo*-1 : 3-*dioxan.*—Methoxyacetylene (2·8 g.) in tetrahydrofuran

(5 ml.) was added to a solution of malonic acid (5·2 g.) in tetrahydrofuran (10 ml.). After 16 hr. at −5° removal of the solvent and distillation at 240° (bath temp.)/0·1 mm. yielded an oil (1·5 g.) and much acetic acid. Two redistillations gave 2-*methoxy*-2-*methyl*-4 : 6-*dioxo*-1 : 3-*dioxan* (0·45 g., 6%), b. p. 85—95° (bath temp.)/0·1 mm., n_D^{24} 1·4345. Entirely satisfactory analytical data were not obtained (Found: C, 46·4, 45·9; H, 6·15, 6·45. $C_6H_8O_5$ requires C, 45·0; H, 5·03%). Light absorption: Maximum 2430 Å, ε = 782; after excess of sodium hydroxide had been added: Maximum 2700 Å, ε = 6330.

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