

97. *Synthesis of Methyl α -Methoxyacrylate and α -Methoxyacrylonitrile : Characterisation of Methoxy-derivatives of Propionic Acid.*

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Satisfactory methods for the preparation of monomeric *α-methoxyacrylonitrile* and methyl *α-methoxyacrylate* have been worked out and, in the course of the investigation, a number of isomeric derivatives of methoxypropionic acids have been synthesised, characterised as their crystalline amides, and their constitutions established.

In the course of investigations which had as their aim the synthesis of derivatives of *α-alkoxyacrylic acids*, various dimethoxy-, methoxyhydroxy-, and methoxyhalogeno-propionic esters have been prepared and their orientations established. All these esters are readily converted, by the action of cold aqueous ammonia, into highly crystalline amides, which are thus very convenient derivatives for the purpose of characterisation.

The initial line of attack was the action of sodium methoxide on halogenopropionic esters and this revealed points of interest regarding the relative reactivity of halogen substituents in the *α*- and the *β*-position. The main product of the action of two molecular proportions of methyl-alcoholic sodium methoxide on methyl *αβ*-dichloropropionate is a liquid of relatively high boiling point which contains chlorine. Its structure has not yet been established, but it is certainly formed by the interaction of more than one molecule of the halogeno-ester. When only one molecular proportion of sodium methoxide is used, the overall result is the replacement of the *β*-chlorine atom to give *methyl α-chloro-β-methoxypropionate*, characterised as its *amide* (I), m. p. 61°. The same ester (identified as the amide) is obtained when one molecule of sodium methoxide acts upon methyl *α-chloro-β-hydroxypropionate*. If this ester is formed by a direct bimolecular replacement, the greater reactivity of the primary halide (*β*-) than of the secondary (*α*-) is in harmony with the general conclusions from the recent work of Hughes, Ingold, and their collaborators (cf. *inter alia*, Hughes, *Trans. Faraday Soc.*, 1941, 603). Treatment of *αβ*-dibromopropionic acid with two molecular proportions of sodium methoxide in dry alcohol, however, gives a highly unsaturated sodium salt (probably sodium *α-bromoacrylate*) which, with a third molecule of sodium methoxide in the presence of a little quinol and subsequent acidification, affords a highly unsaturated acid, almost halogen-free. Esterification of this with dry methyl-alcoholic silver oxide and methyl iodide gives mainly *methyl αβ-dimethoxypropionate* (II), contaminated with a little unsaturated ester, since it is converted by ammonia into *αβ-dimethoxypropionamide* * (III), m. p. 58°, identical with a specimen prepared by methylation of methyl *β-hydroxy-α-methoxypropionate* (below) and conversion of the product into the amide. The formation of the same chlorine-containing amide from both the *αβ*-dichloro- and the *α-chloro-β-hydroxy-ester* proves that (I) is the *α-chloro-β-methoxy-derivative*. Confirmation of this structure is derived from the observation that (I) is isomeric, but not identical, with *β-chloro-α-methoxypropionamide* (IV), m. p. 138°, which was synthesised in the following manner. Methyl methoxyacetate condenses with methyl formate in the presence of sodium to give the sodium derivative of methyl *α-methoxy-β-hydroxyacrylate*, which, after acidification, is reduced (without isolation) by hydrogen and a Raney-nickel catalyst (G.P. 524,086 of 1940) to methyl *α-methoxy-β-hydroxypropionate*, characterised as its *amide* (V), m. p. 71°. Treated with thionyl chloride and pyridine, this ester affords the corresponding *β-chloro-ester*, converted by aqueous ammonia into (IV).

The corresponding pair of methoxy-bromopropionamides has also been obtained. Methyl *α-bromo-β-methoxypropionate*, a specimen of which was kindly supplied by Dr. E. Rothstein of this University, is converted by ammonia into *α-bromo-β-methoxypropionamide* (VI), m. p. 84°. This is isomeric with *β-bromo-α-methoxypropionamide* (VII), m. p. 135°, which was obtained by a reaction sequence similar to that used by Price, Coyne, and De Los de Tar (*J. Amer. Chem. Soc.*, 1941, 63, 2796) for the synthesis of *α-ethoxyacrylonitrile*. This paper by the American authors was published just after the corresponding synthesis of *α-methoxyacrylonitrile* (VIII) had been achieved by the present author, using a similar route. *β-Bromo-α-methoxypropionitrile*, obtained in accordance with the scheme :

$$\text{CH}_3\text{CHO} + \text{CH}_3\text{OH} + \text{HCl} \longrightarrow \text{CH}_3\text{CHCl}\cdot\text{O}\cdot\text{CH}_3 \xrightarrow{\text{BF}_3} \text{CH}_2\text{Br}\cdot\text{CHBr}\cdot\text{O}\cdot\text{CH}_3 \xrightarrow{\text{CuCN}} \text{CH}_2\text{Br}\cdot\text{CH}(\text{O}\cdot\text{CH}_3)\cdot\text{CN}$$

is converted by dry hydrogen chloride and methyl alcohol in dry ether (cf. Houben and Pfankuch, *Ber.*, 1926, 59, 2402) into the *imino-ether hydrochloride* (IX), $\text{CH}_2\text{Br}\cdot\text{CH}(\text{O}\cdot\text{CH}_3)\cdot\text{C}(\text{O}\cdot\text{CH}_3)\cdot\text{NH}_2\cdot\text{HCl}$, which readily loses methyl chloride when warmed to give the amide (VII). Decomposition of (IX) with ice affords *methyl β-bromo-α-methoxypropionate* (X).

Removal of hydrogen bromide from this ester occurs less readily than it does from the corresponding nitrile. Boiling pyridine, which readily converts the latter into the unsaturated nitrile (VIII), leaves a large proportion of the ester unchanged, but cold piperidine is effective, giving methyl *α-methoxyacrylate* (XI). This ester was prepared in an impure condition by von Auwers (*Ber.*, 1911, 44, 3523) by the action of phosphoric oxide on methyl *αα*-dimethoxypropionate (XII), obtained by condensation of methyl pyruvate with methyl orthoformate, and now characterised as *αα-dimethoxypropionamide* (XIII), m. p. 117°. Prepared by either method, the unsaturated ester is converted by ammonia into *α-methoxyacrylamide* (XIV), m. p. 109°. The same amide results from the elimination of hydrogen bromide from the bromo-methoxyamide (VII) by the action of methyl-alcoholic ammonia. Further confirmation that (VIII) is the *α-methoxy-compound* accrues from the observation that it is converted, by the action of dry hydrogen chloride and methyl alcohol in dry

* Methyl *d-αβ*-dimethoxypropionate and its amide were prepared by Frankland and Gebhard, *J.*, 1905, 87, 864.

β -hydroxy- α -methoxypropionate by refluxing with 5 c.c. of methyl iodide and dry silver oxide gave a product converted by aqueous ammonia, in small yield, into the same amide, m. p. 53–56°, raised to 55–57° by admixture with (III), m. p. 58°.

β -Bromo- α -methoxypropionitrile and Methyl β -Bromo- α -methoxypropionate.—A mixture of 200 g. of paraldehyde and 220 g. of dry methyl alcohol was cooled in a freezing mixture and saturated with dry hydrogen chloride (250 g.). The top layer (325 g.) of methyl α -chloroethyl ether was dried with calcium chloride and used without further purification. 100 C.c. of dry bromine were added dropwise with constant shaking to 199 g. of the chloro-ether at 0°. After removal of dissolved hydrogen bromide by an air stream, distillation gave a main fraction (372 g.), b. p. 67–75°/21 mm., of methyl $\alpha\beta$ -dibromoethyl ether, which was used without further purification. Redistillation gave a purer product, b. p. 67–69°/22 mm. with some loss. A solution of 196 g. of the dibromo-ether in 230 c.c. of sodium-dried ether was added to 90 g. of dry powdered cuprous cyanide in a large flask fitted with an efficient reflux condenser. The mixture was gently warmed, with constant shaking, until a brisk reaction, necessitating ice-cooling, had subsided. The mixture was then refluxed for $\frac{3}{4}$ hour and kept in the cold for 24 hours to allow separation of copper compounds. Ether from the filtrate and washings of the copper salts was distilled through a Widmer column. The dark coloured residual liquid was decanted from copper compounds which separated during concentration. Fractionation under reduced pressure gave a considerable fraction, b. p. 30–84°/15 mm., and then *β -bromo- α -methoxypropionitrile* (70 g.) was collected at 84–89°/16 mm. The pure nitrile, b. p. 54°/0.1 mm. or 94.5°/24 mm. (Found: C, 29.7; H, 3.9. C_5H_7ONBr requires C, 29.3; H, 3.7%), rapidly decomposed and was immediately converted either into the unsaturated nitrile or into the imino-ether hydrochloride. A mixture of 65 g. of the nitrile, 14 g. of dry methyl alcohol, and 350 c.c. of dry ether was saturated with dry hydrogen chloride at –10° for 3–4 hours and then kept in a refrigerator for 18 hours. Thorough washing of the separated mass of crystals with dry ether is essential to free the material from volatile halogen-containing products which are difficult to remove at later stages. The *imino-ether hydrochloride* (IX) thus obtained was almost pure (Found: C, 25.3; H, 5.3; Cl, 16.4. $C_5H_{11}O_2NClBr$ requires C, 25.8; H, 4.8; Cl, 15.3%). The chloride ion analysis was carried out on an earlier sample which may have retained traces of free hydrogen chloride.

The imino-ether hydrochloride, stirred under ether at 0°, was decomposed by gradual addition of melting ice. After complete solution had occurred, the stirring was continued at 0° for about 20 minutes to complete the decomposition (otherwise the product is contaminated with the amide) and the aqueous layer was extracted several times with ether. After removal of the solvent from the washed and dried extract through a Widmer column, fractionation of the residue gave 45 g. of *methyl β -bromo- α -methoxypropionate* (X), b. p. 49°/0.5 mm. (Found: C, 31.3; H, 4.8; Br, 40.2. $C_5H_9O_3Br$ requires C, 30.3; H, 4.6; Br, 40.6%).

The imino-ether hydrochloride readily decomposes on warming either alone or in aqueous solution to give *β -bromo- α -methoxypropionamide* (VII), m. p. 135° after crystallisation from water (Found: C, 26.6; H, 4.5; N, 7.9; Br, 44.0. $C_4H_8O_2NBr$ requires C, 26.4; H, 4.4; N, 7.7; Br, 44.0%). This amide is isomeric with *α -bromo- β -methoxypropionamide* (VI), m. p. 84° after crystallisation from ether (Found: C, 26.6; H, 4.4%), which was prepared from a specimen of methyl α -bromo- β -methoxypropionate kindly supplied by Dr. Rothstein of this University.

α -Methoxyacrylonitrile (VIII).—Freshly distilled *β -bromo- α -methoxypropionitrile* (54 g.) was added dropwise to 50 g. of boiling pyridine (dried over potassium hydroxide and distilled) under reflux, and boiling continued for 10 minutes thereafter. If the reactants are pure and dry, pyridine hydrobromide separates as a white crystalline mass from a red solution. After cooling, the pyridine hydrobromide was repeatedly extracted with boiling ether and the extracts were washed free from pyridine with 2*N*-hydrochloric acid and water. The ether was removed from the dried solution through a Widmer column, and the residue distilled. *α -Methoxyacrylonitrile* (VIII), b. p. 27.5°/15 mm. or 32.5°/23 mm., was obtained as a colourless mobile liquid (Found: C, 57.8; H, 6.5; N, 17.0. C_4H_5ON requires C, 57.8; H, 6.1; N, 16.9%).

A solution of 1 c.c. of the unsaturated nitrile in 5 c.c. of dry ether and a few drops of dry methyl alcohol was saturated at 0° with dry hydrogen chloride. The solution (containing some crystalline material) was evaporated in a current of dry air under reduced pressure, and the yellow viscous mass extracted with warm dry ether. The residue from the ethereal solution crystallised after seeding. Crystallisation of the product from ether gave a saturated amide, m. p. 113°, depressed by admixture with *α -methoxyacrylamide*, m. p. 109°, but raised to 116° by admixture with *$\alpha\alpha$ -dimethoxypropionamide*, m. p. 116° (below).

Methyl α -Methoxyacrylate (XI).—A solution of 18 g. of redistilled piperidine in its own volume of dry ether was added dropwise to a solution of 39 g. of methyl *β -bromo- α -methoxypropionate* and 0.1 g. of quinol in 50 c.c. of dry ether at 0°, more ether being added as the mixture became thick with separated piperidine hydrobromide. After keeping at room temperature for 18 hours, the piperidine hydrobromide was removed by filtration. The residue from the ethereal solution, freed from piperidine and solvent as above, was distilled. *Methyl α -methoxyacrylate* (18 g.), b. p. 51.5–52°/11 mm., was obtained (Found: C, 50.9; H, 7.2; OMe, 51.3. Calc. for $C_5H_8O_3$: C, 51.7; H, 6.9; OMe, 53.4%). The ester was converted by ammonia into the same amide, m. p. and mixed m. p. 109°, as that prepared from the specimen of ester obtained from methyl *$\alpha\alpha$ -dimethoxypropionate* (XII). The latter ester, b. p. 59.5°/11 mm. (Found: C, 48.6; H, 8.6. Calc. for $C_6H_{12}O_4$: C, 48.6; H, 8.2%), was obtained by the condensation of 18 g. of methyl pyruvate with 25 g. of methyl-orthoformate in 90 c.c. of dry methyl alcohol containing 1 g. of ammonium chloride (von Auwers, *loc. cit.*). It was converted by aqueous ammonia into its *amide* (XIII), m. p. 117° after crystallisation from ether (Found: C, 45.8; H, 8.3; N, 10.95. $C_5H_{11}O_2N$ requires C, 45.1; H, 8.3; N, 10.5%). The unsaturated ester obtained by the action of phosphoric oxide on methyl *$\alpha\alpha$ -dimethoxypropionate* by von Auwers's method had b. p. 55.5°/10 mm., but, in agreement with the findings of that author, did not seem to be quite pure (Found: C, 50.5; H, 8.0; OMe, 56.2. Calc. for $C_5H_8O_3$: C, 51.7; H, 6.9; OMe, 53.4%). It was probably contaminated with a little of the unchanged dimethoxy-ester. It was, however, characterised as *α -methoxyacrylamide* (XIV), m. p. 109° after crystallisation from ether (Found: C, 47.6; H, 7.3; N, 14.1. $C_4H_7O_2N$ requires C, 47.5; H, 6.9; N, 13.9%). Ozonolysis of the unsaturated ester afforded formaldehyde, identified as its dimedon compound, m. p. and mixed m. p. 189°, but methyl oxalate could not be isolated as such. From its hydrolysis product, however, oxalic acid dihydrate, m. p. and mixed m. p. 100°, was isolated and exhibited its characteristic properties.

α -Methoxyacrylamide (0.3 g.) was treated with 0.5 g. of dry bromine, both in solution in dry carbon tetrachloride, until just coloured and the solution was evaporated to dryness on a steam-bath. The product was dissolved in dry ether and concentrated, and light petroleum (b. p. 40–60°) added. The *$\alpha\beta$ -dibromo- α -methoxypropionamide* obtained had m. p. 106° after crystallisation from benzene–light petroleum (b. p. 60–80°). It readily lost hydrogen bromide in the air and was not quite pure (Found: Br, 60.2. $C_4H_7O_2NBr_2$ requires Br, 61.3%).

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