208. *Trihalogenomethyl Compounds of Potential Therapeutic Interest. Part III.*[1] *The Synthesis of* 1,1,1-*Trichloromethyl Ketones.*

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Routes to 1,1,1-trichloromethyl ketones have been investigated; the method of chlorination of mercuriacetates of terminal acetylenes has been shown to be of general application.

In connection with another investigation, a number of routes to 1,1,1-trichloromethyl ketones have been investigated. The method of Myddleton, Barrett, and Seager,[2] involving conversion of terminal acetylenes into their mercuric acetate complexes (I) with subsequent chlorination of the complexes to give the ketones (II), has been used for the conversion of 3- and 4-hydroxyalk-1-ynes and a 3,4-epoxyalk-1-yne into the corresponding trichloromethyl ketones in yields of up to 53%. The reaction is not straightforward when applied to structures containing other easily chlorinated systems; for example, chlorination of the mercuric acetate complexes of 1-ethynylcyclohexan-1-ol and 1-*o*-tolyloxybut-3-yn-2-ol gave inseparable mixtures of the required 1,1,1-trichloromethyl ketones with other higher chlorinated products. The structures of the mercuric acetate

$$\underset{\text{(I)}}{R{\cdot}C(O{\cdot}Hg{\cdot}O{\cdot}CO{\cdot}Me){:}C(Hg{\cdot}O{\cdot}CO{\cdot}Me)_2} \qquad \underset{\text{(II)}}{R{\cdot}CO{\cdot}CCl_3}$$

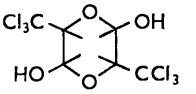
complexes have not been examined in detail but the elemental and acetyl analyses and infrared spectra of the complexes from 2-methylbut-3-yn-2-ol and 1-phenylprop-2-yn-1-ol are in accord with (I; R = Me_2CHOH) and (I; R = PhCHOH), respectively, both with one molecule of acetic acid of crystallisation and the first also with one molecule of water of crystallisation. This type of structure for the mercuric acetate complexes was originally proposed by Myddleton *et al.* and recently by Matsoyan *et al.*[3] α-Hydroxytrichloromethyl ketones obtained from α-hydroxyacetylenes were contaminated with varying amounts of the acetates of the alcohols. Prop-2-yn-1-ol gave an acetate exclusively, while secondary and tertiary alcohols gave progressively lesser proportions of acetates. Matsoyan *et al.*[3] suggested that α-acetoxy-ketones were formed by acetylation due to acetic anhydride produced when α-hydroxyacetylenes were refluxed with mercuric acetate in acetic acid.

[1] Part II, Bishop, Bowman, Campbell, and Jones, *J.*, 1963, 2381.
[2] Myddleton, Barrett, and Seager, *J. Amer. Chem. Soc.*, 1930, **52**, 4405.
[3] Matsoyan, Chukhadzhyan, and Vartanyan, *J. Gen. Chem.* (*U.S.S.R.*), 1960, **30**, 1223.

However, when we carried out the mercuration reaction in the cold in excess of ethanol or methanol, which should have removed the acetic anhydride, chlorination of the complexes still yielded acetylated materials. We feel, in view of this and because the complexes showed no *O*-acetyl carbonyl absorption in their infrared spectra, that

$Cl_3C\cdot CH(OH)\cdot CH_2\cdot CO\cdot CCl_3$ (III)

$Cl_3C\cdot C(O\cdot CO\cdot Me):C(OH)\cdot CCl_3$ (IV)


(V)

$Cl_3C\cdot CO\cdot CH_2OH$ (VI)

$Cl_3C\cdot C(OH)_2\cdot CH_2\cdot O\cdot CO\cdot Me$ (VII)

$Cl_3C\cdot CHR\cdot CHR'\cdot CO\cdot CCl_3$ (VIII)

acetylation occurred during chlorination of the complexes. No acetate formation was apparent in the preparation of 1,1,1,5,5,5-hexachloro-4-hydroxypentan-2-one, (III), which may indicate an intramolecular mechanism of acetylation during chlorination of the α-hydroxy compounds. In most cases the acetates could not be hydrolysed selectively, but hydrolysis of 1,1,1,4,4,4-hexachlorobut-2-ene-2,3-diol monoacetate [assigned structure (IV) from infrared data] and 1,1,1-trichloro-3-acetoxypropan-2-one proceeded smoothly in a boiling mixture of glacial acetic and concentrated hydrochloric acid. In the latter case, the product was the cyclic ketal (V), and not the hydroxy-ketone (VI). The infrared spectrum showed no carbonyl absorption and the molecular weight was somewhat less than twice that for the ketone. This compound was identical with that prepared by the method (acid hydrolysis of 1,1,1-trichlorodiazoacetone) of Vardar and Tüccarbasi [4] and claimed by them to be 1,1,1-trichloro-3-hydroxy-propan-2-one (VI). Treatment of 1,1,1-trichloro-3-acetoxypropan-2-one with cold water gave a hydrate formulated as (VII) because of its infrared spectrum and its ready conversion into the ketone during attempted crystallisation from light petroleum (b. p. 60—80°)–chloroform. Attempted dehydration of (III) with cold concentrated sulphuric acid gave a compound, $C_5H_3Cl_7O$. This had an infrared peak at 1745 cm.$^{-1}$ (CCl_3·CO) and was either 1,1,1,2,5,5,5- or 1,1,1,3,5,5,5-heptachloropentan-4-one (VIII; R = H, R′ = Cl or R = Cl, R′ = H) arising by the addition of hydrogen chloride (from trichloromethyl hydrolysis) across the double bond of the intermediate αβ-unsaturated ketone. The

$Cl_3C\cdot CO\cdot CH_2R$ (IX)

$Cl_3C\cdot CH(OH)\cdot CHR\cdot CO_2R'$ (X)

$Cl_3C\cdot CO\cdot CHR\cdot CO_2R'$ (XI)

$Ph\cdot CH(CO_2H)\cdot C(OH)(CCl_3)\cdot CH(CO_2H)\cdot Ph$ (XII)

preparation of 1,1,1-trichloropropan-2-one has been investigated by use of two conventional routes, as described in the Experimental section. The first route is adaptable to large-scale working but the yields (5—6% based on acetone) are much poorer than those (28—34%) obtained in the second. We have attempted to prepare 1,1,1-trichloromethyl ketones (IX) *via* the acids (X; R = Ph, R′ = H) and (X; R = Bu^n, R′ = H) and their esters (X; R = Ph, R′ = Me) and (X; R = Bu^n, R′ = Et). These were smoothly oxidised to the keto-esters (XI) but acidolysis did not give the ketones. Attempted condensation of chloral with phenylmalonic acid in the presence of pyridine [5] led only to isolation of phenylacetic acid, and not the acid (X; R = Ph, R′ = H) which was, however, readily preparable, in both diastereoisomeric forms, by use of the Ivanov reaction,[6] with phenylacetic acid and chloral. When trichloroacetyl chloride was substituted for

[4] Vardar and Tüccarbasi, *Istanbul Univ. Fak. Mecmusai*, 1953, **18A**, Ser. A, 423.
[5] Cf. von Auwers and Wissebach, *Ber.*, 1923, **56**, 735.
[6] Ivanov, Mihova, and Christova, *Bull. Soc. chim. France*, 1932, **51**, 1321; cf. Simmerman and Traxler, *J. Amer. Chem. Soc.*, 1957, **79**, 1922.

chloral, 3-hydroxy-2,4-diphenyl-3-trichloromethylglutaric acid (XII) was formed. A complex mixture of substances was only obtained when sodium phenylacetate was used in this reaction. The acid (X; R = Bu^n, R′ = H) was obtained in one of its diastereoisomeric forms by condensation of chloral with n-butylmalonic acid, catalysed by pyridine.

Experimental

1,1,1-*Trichloromethyl Ketones from Acetylenes*.—The acetylenic compound (1 mole) was added to either mercuric oxide (3 moles) in acetic acid (3·2 l.) or mercuric acetate (3 moles) in acetic acid, ethanol, methanol, or chloroform (*ca.* 3 l. for each), the solvent being chosen after performing a small-scale experiment. The resulting complexes were either precipitated and were filtered off immediately, or if they failed to precipitate, were isolated by evaporation of the solvent under reduced pressure. The *complex* from 2-methylbut-3-yn-2-ol crystallised from ethyl acetate–acetic acid as colourless needles softening at 194—198° and darkening at 255—265° [Found (on sample dried for 4 hr. at 50°/1 mm.): C, 16·2; H, 2·3; Hg, 62·9; COMe (NaOH hydrolysis), 18·3. $C_{13}H_{22}Hg_3O_{11}$ requires C, 16·3; H, 2·3; Hg, 63·0; (X) 4COMe, 18·0%], $\nu_{max.}$ (Nujol) 3240s (OH), 1719w (acid CO), 1600s, 1564s (CO_2^-), 1312s cm.$^{-1}$ (C–O$^-$). The *complex* from 1-phenylprop-2-yn-1-ol was obtained as colourless crystals, m. p. 244—250° (decomp.) (Found: C, 21·0; H, 2·2; Hg, 60·9; COMe, 19·1. $C_{17}H_{20}Hg_3O_{10}$ requires C, 20·7; H, 2·05; Hg, 61·0; 4COMe, 19·4%) $\nu_{max.}$ (Nujol) 3450w (OH), 1718s (acid CO), 1600s, 1575s (CO_2^-), 1310s cm.$^{-1}$ (C–O$^-$).

The complexes were suspended in chloroform (vol. in ml., 2—4 times the weight of complex) into which chlorine was passed with stirring. When refluxing of the solvent had ceased (up to 4 hr. for 0·5 mole of complex), the mercury salts were filtered off and the filtrate washed with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, sodium thiosulphate solution, and water and then dried (Na_2SO_4). Removal of the solvent left the trichloromethyl ketones which were purified by distillation or crystallisation; with acetylenic alcohols as starting materials, the products were frequently mixtures of the corresponding alcohols and their acetates from which, in most cases, the free alcohol could be isolated by crystallisation.

The following compounds were prepared as described above.

1,1,1-*Trichloro-3-acetoxypropan-2-one* (46% from prop-2-yn-1-ol), b. p. 108—110°/20 mm., colourless rhombs from light petroleum (b. p. 60—80°), m. p. 37—39·5° (Found: C, 27·0; H, 2·4; Cl, 48·1. $C_5H_5Cl_3O_3$ requires C, 27·4; H, 2·3; Cl, 48·5%), $\nu_{max.}$ (as liquid) 3504w (trace OH), 1759s (CO), 1220s cm.$^{-1}$ (C–O). It rapidly reduced hot Fehling's solution and gave a strong carbylamine test with aniline and sodium hydroxide. Treatment of the ketol acetate (obtained as a liquid from its crystallisation liquors) with water gave rise to heat evolution and deposition of a solid which crystallised from light petroleum (b. p. 80—100°) as flat needles, of the *hydrate* of 1,1,1-trichloro-3-acetoxypropan-2-one, m. p. 104—104·5° (Found: 25·8; H, 3·0; Cl, 44·5. $C_5H_7Cl_3O_4$ requires C, 25·3; H, 3·0; Cl, 44·9%), $\nu_{max.}$ 3540w (OH), 3300m (bonded OH), 1750(CO), 1720 (bonded CO), 1217s cm.$^{-1}$ (C–O). Attempted crystallisation of this compound from light petroleum (b. p. 60—80°)–chloroform, with concentration of solvent by boiling, gave the ketol acetate, m. p. and mixed m. p. 36—38°. The ketol acetate (10 g.) in concentrated hydrochloric acid (10 ml.) and acetic acid (14 ml.) after 2·5 hr. at room temperature, scratching with a glass rod, and further storage overnight gave 2,5-dihydroxy-2,5-*bistrichloromethyl*-1,4-*dioxan* (3·45 g.), colourless hexagons, m. p. 216—218° (sintered at 110°) (from benzene–acetone) [Found: C, 20·6; H, 1·6; Cl, 58·7; 58·8; *M* (Rast), 243. $C_6H_6Cl_6O_4$ requires C, 20·3; H, 1·7; Cl, 59·9%; *M*, 354·8], pK_a, 10·3 (in 50% EtOH–H_2O), $\nu_{max.}$ (KBr) 3536s cm.$^{-1}$ (OH). This was identical with the compound made by hydrolysis of 1,1,1-trichloro-3-diazopropan-2-one.[4]

1,1,1,4,4,4-*Hexachlorobut-2-ene-2,3-diol monoacetate* (IV) (53·7% from 1,1,1-trichlorobut-3-yn-2-ol [7]), b. p. 147—151°/20 mm., n_D^{25} 1·5056 (Found: C, 21·1; H, 1·1; Cl, 63·8. $C_6H_4Cl_6O_2$ requires C, 22·4; H, 1·2; Cl, 66·3%), $\nu_{max.}$ (Nujol) 3475w (OH), 1763s (CO), (CCl_4) 3546w (OH), 1788, 1772s cm.$^{-1}$ (CO). The anlysis and infrared spectrum show this material to be a mixture of the acetate and corresponding alcohol. Hydrolysis of the above acetate (5 g.) with glacial acetic acid (25 ml.) and concentrated hydrochloric acid (15 ml.) for 2 hr. gave 1,1,1,4,4,4-*hexachloro-3-hydroxybutan-2-one* (3·76 g.) as colourless rhombs, m. p. 69—71° [from light petroleum

[7] Shapiro, Soloway, and Freedman, *J. Amer. Chem. Soc.*, 1955, **77**, 4874.

(b. p. 40—60°)] (Found: C, 17·3; H, 0·8; Cl, 72·2. $C_4H_2Cl_6O_2$ requires C, 16·3; H, 0·8; Cl, 72·2%), $\nu_{max.}$ (CCl_4), 3564s (OH), 1763s (CO), 3564s cm.$^{-1}$ (OH).

1,1,1-*Trichloro*-3-*acetoxy*-3-*phenyl*-*propan*-2-*one* (50% from 1-phenylprop-2-yn-1-ol acetate), b. p. 157°/1·3 mm., $n_D^{21.5}$ 1·5342 (Found: C, 45·0; H, 3·3; Cl, 35·8. $C_{11}H_9Cl_3O_3$ requires C, 44·6; H, 3·0; Cl, 36·0%), $\nu_{max.}$ 3505s (OH), 1750s cm.$^{-1}$ (CO). 1-Phenylprop-2-yn-1-ol gave a mixture of the above acetate and the corresponding alcohol.

1,1,1-*Trichloro*-3-*hydroxybutan*-2-*one and its acetate* [3·76 g. (from but-3-yn-2-ol, 25·7 g.)], b. p. 106—114°/17 mm., n_D^{22} 1·4752 (Found: C, 29·9; H, 3·5. $C_4H_5Cl_3O_2$ requires C, 25·1; H, 2·6. $C_6H_7Cl_3O_3$ requires C, 30·8; H, 3·0%), $\nu_{max.}$ 3475m (OH), 1745s cm.$^{-1}$ (CO).

1,1,1-*Trichloro*-3-*hydroxy*-3-*methylbutan*-2-*one and its acetate* (from 2-methylbut-3-yn-2-ol), b. p. 87—88°/16 mm. (Found: C, 31·35; H, 3·6; Cl, 46·05. $C_5H_7Cl_3O_2$ requires C, 29·2; H, 3·4; Cl, 51·8. $C_7H_9Cl_3O_3$ requires C, 34·0; H, 3·4; Cl, 42·9%), $\nu_{max.}$ 3505 (OH), 1736 (CO), 1261 cm.$^{-1}$ (acetate C–O). A second fraction, b. p. 89—103°/16 mm., deposited, on cooling to −30°, the *alcohol* (10%) m. p. 37—39° (Found: C, 29·4; H, 3·8; Cl, 50·0%), $\nu_{max.}$ 3525s (OH), 1736s cm.$^{-1}$ (CO).

1,1,1-*Tribromo*-3-*hydroxy*-3-*methylbutan*-2-*one and its acetate* [6·9 g. (from 2-methylbut-3-yn-2-ol, 15 g.)], b. p. 130—133°/16 mm., n_D^{20} 1·5558 (Found: Br, 69·6. $C_7H_9Br_3O_3$ requires Br, 63·0%), $\nu_{max.}$ 3600 (OH), 1754, 1730 (CO), 1222, 1205 cm.$^{-1}$ (C–O). A second fraction, b. p. 133—134°/14—16 mm., deposited the *alcohol* (6·8%), white rhombs from light petroleum (b. p. 60—80°) (Found: C, 17·8; H, 2·2; Br, 70·9. $C_5H_7Br_3O_2$ requires C, 17·7; H, 2·1; Br, 70·75%), $\nu_{max.}$ (CCl_4) 3615m (OH), 1728s cm.$^{-1}$ (CO).

1,1,1,5-*Tetrachloro*-3,4-*epoxypentan*-2-*one* (10% from 5-chloro-3,4-epoxypent-1-yne [8]), colourless plates, m. p. 27—28° (Found: C, 25·4; H, 2·05; Cl, 58·9. $C_5H_4Cl_4O_4$ requires C, 25·4; H, 1·7; Cl, 59·6%), $\nu_{max.}$ (KBr), 3040w (epoxide CH), 1763s cm.$^{-1}$ (CO).

1,1,1,5,5,5-*Hexachloro*-4-*hydroxypentan*-2-*one* (III) (15—17% from 1,1,1-trichloropent-4-yn-2-ol [9]), colourless needles from light petroleum (b. p. 60—80°), m. p. 77—79°. This was identical (infrared spectrum, mixed m. p.) with a sample prepared (with D. C. Bishop) by condensation of chloral with 1,1,1-trichloropropan-2-one in the presence of piperidine acetate or pyridine (Found: C, 19·6; H, 1·8; Cl, 69·4. $C_5H_4Cl_6O_2$ requires C, 19·5; H, 1·3; Cl, 68·9%), $\nu_{max.}$ (CCl_4) 3355s (OH), 1754s cm.$^{-1}$ (CO). The ketol (8·6 g.) was kept for 6 days in concentrated sulphuric acid (43 ml.) and the product (5·19 g.), m. p. 97—100°, was filtered off. Two crystallisations from light petroleum gave 1,1,1,2,5,5,5- or 1,1,1,3,5,5,5-*heptachloropentan*-4-*one* as needles, m. p. 113—114° (Found: C, 18·5; H, 0·8; Cl, 75·4. $C_5H_3Cl_7O$ requires C, 18·3; H, 0·9; Cl, 75·8%), $\nu_{max.}$ (Nujol) 1745m cm.$^{-1}$ (CO).

1,1,1-*Trichloropropan*-2-*one*.—(*a*) Chlorine (3,628 g.) was passed for 40 hr. into a stirred solution of acetone (870 g.) in water (4·5 l.) and concentrated hydrochloric acid (450 ml.) (cf. ref. 10). After cooling, the lower (vesicant) layer was separated and the aqueous layer was extracted with methylene chloride (1 × 2·5 l., 1 × 1·2 l.). The combined organic phases were dried ($MgSO_4$) and stirred with solid sodium hydrogen carbonate. After filtration, the solvent was distilled off and the residue fractionated through a 30 cm. Fenske column. The fractions of b. p. 117—178° were combined and re-fractionated through the column. The fraction of b. p. 134—137·5°, n_D^{20} 1·4600—1·4612, was the ketone (163·5 g.) (Found: C, 22·6; H, 1·9; Cl, 66·2. Calc. for $C_3H_3Cl_3O$: C, 22·8; H, 1·9; Cl, 65·9%).

(*b*) Diethyl malonate (224 g.) in ethanol (70 g.) and benzene (300 ml.) was added slowly to magnesium (36 g.) in benzene (110 ml.) and ethanol (10 ml.) and then allowed to react with trichloracetyl chloride (182 g.) in benzene (300 ml.) (cf. ref. 11). The next morning, the mixture was poured into 2N-sulphuric acid (750 ml.) and crushed ice (500 g.). The organic phase was separated, washed with 2N-sulphuric acid (2 × 250 ml.), then saturated sodium chloride solution (3 × 400 ml.), and dried ($MgSO_4$) and the benzene, and finally diethyl malonate (90 g.), removed (bath temp. 100—110°/0·5 mm.) to leave crude diethyl trichloroacetylmalonate (288 g.). This (269 g.) was refluxed with propionic acid (8 equiv.) and concentrated sulphuric acid (1% of the total weight) for 3 hr. The solution was then poured into water (2 l.), and light petroleum (b. p. 40—60°, 1 l.) and solid sodium hydrogen carbonate added with stirring until the mixture was neutral. After separation of the light petroleum, the aqueous phase

[8] Lespieau, *Adv. Carbohydrate Chem.*, 1946, **2**, 116.
[9] D. C. Bishop, unpublished work.
[10] Hughes, Watson, and Yates, *J.*, 1931, 3318.
[11] Bowman, *J.*, 1950, 322.

was extracted with more petroleum (1 l.), the combined organic solutions were washed with water, dried ($MgSO_4$), and the solvent was distilled off. The residue was then fractionated through a 30 cm. Fenske column to give ethyl propionate and the ketone (50·39 g.), b. p. 130—134°, n_D^{20} 1·4618.

4,4,4-*Trichloro*-3-*hydroxy*-2-*phenylbutyric Acid*.—Phenylacetic acid (109 g.) in ether (300 ml.) was added dropwise (2 hr.) with stirring to isopropylmagnesium bromide [from isopropyl bromide (246 g.) and magnesium (4·8 g.)] in ether (800 ml.), and stored at room temperature overnight. Chloral (117·6 g.) was then added (40 min.); a viscous precipitate appeared which made stirring difficult. The mixture was then warmed on a steam-bath for 4 hr. Hydrochloric acid (0·5N; 800 ml.) and water (80 ml.) were then added consecutively with stirring and cooling. 30 min. after this addition, the organic layer was separated and the aqueous layer was extracted with ether (3 × 100 ml.). The combined ether solutions were washed (H_2O; 100 ml.) dried ($MgSO_4$), and evaporated under reduced pressure. Two crystallisations from benzene gave the higher m. p. form of the *acid* (33 g.) as needles, m. p. 170—171° (softening at 168°). A sample recrystallised from benzene as colourless micro-needles had m. p. 171—173° (sintering at 168°) (Found: C, 42·7; H, 3·2; Cl, 36·85. $C_{10}H_9Cl_3O_3$ requires C, 42·4; H, 3·2; Cl, 37·5%), $\nu_{max.}$ (Nujol) 3124 (OH), 1705 cm.$^{-1}$ (CO). The filtrate from the first crystallisation of the above acid, on storage, deposited a semi-solid material (130 g.). After treatment, in sodium hydrogen carbonate solution, with charcoal and two crystallisations from benzene, the lower m. p. form of the *acid* was obtained as colourless needles (54·8 g.), m. p. 133—137°. A sample recrystallised from benzene had m. p. 133—137° (Found: C, 42·3; H, 3·3; Cl, 37·6%), $\nu_{max.}$ (Nujol) 3435 (OH), 1699 cm.$^{-1}$ (CO). Reaction of the acid of m. p. 133—137° (42·5 g.) in methanol (200 ml.) with excess of diazomethane in ether (800 ml.) gave, after evaporation of the solvents, the *methyl ester* (44·9 g.) m. p. 88—90°, which crystallised from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 90·5—91·5° (Found: C, 45·0; H, 4·1; Cl, 35·6. $C_{11}H_{11}Cl_3O$ requires C, 44·4; H, 3·7; Cl, 35·75%), $\nu_{max.}$ (Nujol) 3450m (OH), 1715s cm.$^{-1}$ (CO). The *acetate* (9·8 g.) of the higher m. p. acid was obtained by treating the acid (10 g.) in acetic anhydride (40 ml.) and acetic acid (40 ml.) with 70% perchloric acid (4 drops). It crystallised from aqueous acetic acid as colourless needles, m. p. 168—169·5° (Found: C, 43·8; H, 3·6; Cl, 32·25. $C_{12}H_{11}Cl_3O_4$ requires C, 44·3; H, 3·4; Cl, 32·7%), $\nu_{max.}$ (Nujol) 1768 (ester CO), 1715 cm.$^{-1}$ (acid CO). The *amide* (3·45 g.) of the higher m. p. acid was produced when the above acetate (6·4 g.) was refluxed with thionyl chloride (25 ml.) and the resulting acid chloride poured into ammonia (*d* 0·88, 50 ml.) to give a solid which was kept at 0° for 2 days in methanol saturated with ammonia. It crystallised from benzene as pale yellow needles, m. p. 138—140° (sintering from 125°) (Found: C, 42·8; H, 4·0; N, 4·9. $C_{10}H_{10}Cl_3NO_2$ requires C, 42·5; H, 3·6; N, 4·9%), $\nu_{max.}$ 3448, 3324, 3200 (all m) (OH and NH_2), 1675s, 1655s cm.$^{-1}$ (amide CO).

Methyl 2-*Phenyl*-4,4,4-*trichloroacetoacetate*.—The foregoing methyl ester (14·87 g.), in glacial acetic acid (77·7 ml.) and concentrated sulphuric acid (3·3 ml.), was cooled in water and, with stirring, treated portionwise with chromium trioxide (5·4 g.). Subsequently, the mixture was stirred for 1·25 hr., while the temperature dropped from 35°. The mixture was diluted with water (150 ml.), stirred for a few minutes, and extracted with ether (5 × 80 ml.) [or better, light petroleum (b. p. 40—60°)]. The ether solution was washed with water, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$) and the ether then evaporated. The residue gave the *keto-ester* (8·44 g.), b. p. 130—133°/0·9—1·2 mm., m. p. 34·5—36·5°, n_D^{20} 1·5358 (Found: C, 45·5; H, 3·5; Cl, 34·2. $C_{11}H_9Cl_3O_3$ requires C, 44·7; H, 3·1; Cl, 36·0%), $\nu_{max.}$ (capillary layer) 3475w (OH), 1754s (CCl_3·CO), 1730s cm.$^{-1}$ (ester CO). It gave a faint pink-green ferric reaction in ethanol.

Methyl 3-*Acetoxy*-4,4,4-*trichloro*-2-*phenylbut*-2-*enoate*.—The above keto-ester (7·8 g.) in pyridine (5·4 g.) was treated at 0° with acetyl chloride (4 g.) and the mixture stored at 0° for 2 days. The resulting solid was extracted with ether (2 × 100 ml.), and the solution washed with water, sodium hydrogen carbonate solution, 2N-hydrochloric acid, and water, dried ($MgSO_4$), and the ether evaporated to leave a solid (5·32 g.), m. p. 93—95°. Crystallisation from light petroleum (b. p. 80—100°) gave the *ester* as colourless rhombs, m. p. 94—96° (Found: C, 46·2; H, 3·2. $C_{13}H_{11}Cl_3O_4$ requires C, 46·2; H, 3·2%), $\nu_{max.}$ (Nujol) 1788s (unsat. ester CO), 1723s (ester CO), 1293, 1274, 1222 cm.$^{-1}$ (all s) (ester C–O).

2-(2,2,2-*Trichloro*-1-*hydroxyethyl*)*hexanoic Acid*.—n-Butylmalonic acid (39·89 g.) in pyridine (20 ml.) with chloral (36·7 g.) was heated (100°) for 2·75 hr. The solution was cooled, acidified with concentrated hydrochloric acid, and extracted with ether. The resulting

solution was washed with water, dried ($MgSO_4$), and the ether evaporated. Distillation of the residue gave n-hexanoic acid (10·79 g.) characterised as its *p*-phenylphenacyl ester, m. p. 65—66° (Found: C, 76·6; H, 7·25. Calc. for $C_{20}H_{22}O_3$: C, 77·4; H, 7·15%), and crystallisation of the undistilled residue from light petroleum and benzene gave the *acid* (3·07 g.), m. p. 122—125°, as colourless micro-plates (Found: C, 36·5; H, 5·3; Cl, 40·4. $C_8H_{13}Cl_3O_3$ requires C, 36·4; H, 5·0; Cl, 40·4%), $\nu_{max.}$ (Nujol) 3157m (OH), 1682 cm.$^{-1}$ (acid CO). The *ethyl ester* (30·65 g.) [prepared by benzene–ethanol esterification of a crude preparation of the acid (54·7 g.) of m. p. 95—98° (sintering from 70°)] had b. p. 104—110°/0·35 mm. (Found: C, 41·6; H, 6·3; Cl, 36·2. $C_{10}H_{17}Cl_3O_3$ requires C, 41·2; H, 5·9; Cl, 36·5%), $\nu_{max.}$ 3400s (OH), 1701s cm.$^{-1}$ (ester CO). This material was probably a mixture of the two possible diastereoisomers, since it partly crystallised. Oxidation of this ester (27·1 g.) with chromium trioxide (10 g.), as before, gave *ethyl* 2-(2,2,2-*trichloro*-1-*oxoethyl*)*hexanoate* (20·3 g.) b. p. 96°/0·45 mm., n_D^{20} 1·4632 (Found: C, 41·8; H, 5·9; Cl, 36·5. $C_{10}H_{15}Cl_3O_3$ requires C, 41·5; H, 5·2; Cl, 36·7%), $\nu_{max.}$ (capillary layer) 3475w (OH), 1754s (CCl_3)·CO, 1730s cm.$^{-1}$ (ester CO).

3-*Hydroxy*-2,4-*diphenyl*-3-*trichloromethylglutaric Acid*.—The Ivanov reagent [from isopropylmagnesium bromide (1 mole) and phenylacetic acid (54·5 g.) in ether (150 ml.)] was treated, with stirring at 0°, with trichloroacetyl chloride (36·4 g.) in ether (100 ml.). The formation of a heavy, oily, yellow complex made stirring difficult towards the end of the addition. The supernatant liquid was stirred at room temperature for 1 hr., the mixture treated with 5N-hydrochloric acid and water (40 ml.), and stirred for 0·5 hr. The aqueous phase was separated and extracted with ether (3 × 100 ml.). The combined ether solutions were evaporated to half the original volume and extracted with sodium hydrogen carbonate solution until the pH was *ca.* 8. The ether was then washed with water, sodium hydrogen carbonate solution, 2N-hydrochloric acid, and water until the wash pH was *ca.* 5. The ether was shaken with a mixture of charcoal and magnesium sulphate, filtered, and evaporated to give a yellow oil which yielded a solid (19·65 g.), m. p. 195—197° (decomp.) on trituration with light petroleum (b. p. 40—60°) and chloroform. Crystallisation of this solid from chloroform–ethanol gave the *glutaric acid* as micro-rhombs, m. p. 205° (decomp.) (Found: C, 51·6; H, 3·6; Cl, 25·35; Equiv. 200. $C_{18}H_{15}Cl_3O_5$ requires C, 51·8; H, 3·6; C., 25·5%; Equiv. 208·9), $\nu_{max.}$ 3440w (OH), 1682s (acid CO), 1595m, 1577 cm.$^{-1}$ (Ar system).

1-O-*Tolyloxybut*-3-*yn*-2-*ol*.—*o*-Tolyloxyacetaldehyde [12] (165·5 g.) was added to ethynylmagnesium bromide [13] [from ethylmagnesium bromide, prepared from magnesium (38·2 g.) and ethyl bromide (192 g.)] in tetrahydrofuran (500 ml.) with stirring under nitrogen at 0°. After the addition was complete, the dark solution was stirred at room temperature overnight and then decomposed with a saturated solution of ammonium chloride (1 equiv.). The inorganic salts were filtered off, the mixture evaporated to dryness, and the residue dissolved in ether and dried (Na_2SO_4). After removal of the ether, distillation gave the *butynol* (89—92 g.), b. p. 98—100°/0·5 mm., m. p. 32—33° (Found: C, 75·3; H, 7·25. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·9%), $\nu_{max.}$ (capillary layer) 3400s (OH), 3324s (≡CH), 2138w (C≡C), 1247s (O–Ar), 1123w cm.$^{-1}$ (O–C). The residue from the distillation crystallised from aqueous ethanol to give 1,6-di-o-*tolyloxyhex*-3-*yn*-2,5-*diol* (4·67 g.), m. p. 121—122° (Found: C, 73·5; H, 6·8. $C_{13}H_{22}O_4$ requires C, 73·6; H, 6·7%), $\nu_{max.}$ (Nujol) 3270, 3120m, 1248s (C–O), 747s cm.$^{-1}$ (*o*-substituted Ar).

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