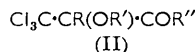
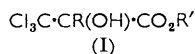


734. Trihalogenomethyl Compounds of Potential Therapeutic Interest. Part IV.*

By R. E. BOWMAN, M. D. CLOSIER, and P. J. ISLIP.

The preparation and reactions of trichloropyruvic acid and its ethyl ester have been examined. Grignard reagents with the acid and ester give moderate yields of $\beta\beta\beta$ -trichlorolactates. The ester reacted normally in the Reformatsky reaction, and condensed with active methylene compounds. Attempts to prepare α -trichloromethylsuccinic acid failed, the only product isolated being α -dichloromethylsuccinic acid.

ALTHOUGH trichloropyruvic acid was first described¹ in 1875, it has been little studied since then. The acid was prepared in the present work by the chlorination of a concentrated solution of lactic acid in water at 110°,² and was found to exist in the hydrated form (I; R = OH, R' = H). However, the anhydrous acid could be produced by refluxing a solution of the hydrate in benzene, and removing the water azeotropically.

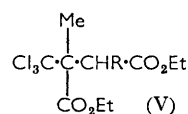
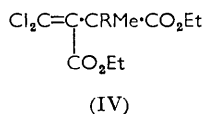
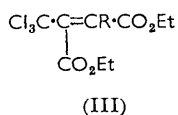


In a similar manner to pyruvic acid³ and ethyl pyruvate,⁴ both trichloropyruvic acid and ethyl trichloropyruvate (from the acid and ethyl borate) with Grignard reagents gave the substituted $\beta\beta\beta$ -trichlorolactates (I) in moderate yield.

Treatment of the acids (I; R = Me or HC≡C, R' = H) with acetyl chloride furnished the acetoxy-acids (II; R = Me or HC≡C, R' = Ac, R'' = OH), the acid chlorides of which, with ammonium hydroxide solution, gave the α -hydroxy-amides (II; R = Me or HC≡C, R' = H, R'' = NH₂). Addition of dimethylamine to the acid chloride (II; R = Me, R' = Ac, R'' = Cl) yielded *O*-acetyl- $\beta\beta\beta$ -trichloro-*NN* α -trimethyl-lactamide (II; R = Me, R' = Ac, R'' = NMe₂) which was converted into the hydroxy-amide (II; R = Me, R' = H, R'' = NMe₂) with methanolic ammonium hydroxide solution.

The α -hydroxy- and α -acetoxy-amides were found to have some activity as central nervous depressants, although this was not sufficient to be of clinical interest. In view of the activity of substituted succinimides as hypnotics and anticonvulsants, the preparation of substituted trichloromethylsuccinic acids was examined.

Ethyl trichloropyruvate was condensed with diethyl malonate and with ethyl cyanoacetate, in the presence of zinc chloride and acetic anhydride, to give the trichloro-esters (III; R = CO₂Et) and (III; R = CN), respectively.⁵



Addition of methylmagnesium iodide to the triester (III; R = CO₂Et) in the presence of cuprous chloride⁶ afforded, instead of the expected trichloro-ester (V; R = CO₂Et), a compound C₁₃H₁₈Cl₂O₆. This had ν_{max} 1592 cm.⁻¹ (=CCl₂) and λ_{max} 229 μ (ϵ 8700), and structure (IV; R = CO₂Et) was assigned to the compound on the basis of this evidence.

* Part III, Bowman, White, and Williamson, *J.*, 1964, 1086.

¹ Schreder, *Annalen*, 1875, **177**, 282.

² Skraup and Wolfschlag, G.P. 418,054/1925.

³ Peters, Griffith, Briggs, and French, *J. Amer. Chem. Soc.*, 1925, **47**, 449.

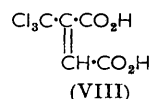
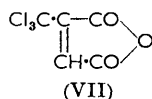
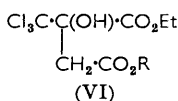
⁴ Lapkin and Golovkova, *Zhur. obshchei Khim.*, 1948, **18**, 485.

⁵ Cf. Malachowski and Czornodola, *Ber.*, 1935, **68**, 363.

⁶ Munch-Petersen, *Acta Chem. Scand.*, 1958, **12**, 2046.

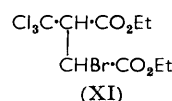
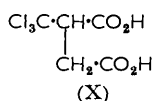
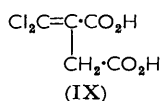
Treatment of the nitrile (III; R = CN) with methylmagnesium iodide under the same conditions yielded a product which was not homogeneous, but which evidently contained some of the dichloro-compound (IV; R = CN) [broad peak at λ_{max} , 223 $\text{m}\mu$ (ϵ 5560)].

The Reformatsky reaction between ethyl trichloropyruvate and ethyl bromoacetate in benzene afforded diethyl α -hydroxy- α -trichloromethylsuccinate (VI; R = Et) which was converted into the acid ester (VI; R = H) by acidic hydrolysis.



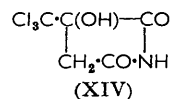
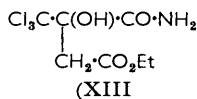
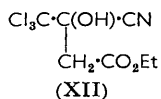
α -Trichloromethylmaleic anhydride (VII), which was obtained from the ester (VI; R = Et) by treatment with phosphorus pentoxide at 180°, was hydrolysed to α -trichloromethylmaleic acid (VIII).

Reduction of α -trichloromethylmaleic acid with phosphorus and hydriodic acid was reported⁷ to give α -trichloromethylsuccinic acid. Reduction of the anhydride (VII) under similar conditions gave α -dichloromethylenesuccinic acid (IX) instead of the expected trichloro-acid (X).



In another approach to the synthesis of α -trichloromethylsuccinic acid, diethyl maleate was treated with bromotrichloromethane under free-radical conditions.⁸ The resulting bromotrichloro-ester (XI) was reduced with phosphorus and hydriodic acid in an attempt to effect preferential reduction of the bromine atom. However, the product thus obtained was α -dichloromethylenesuccinic acid (IX), as was the case when diethyl α -trichloromethylmaleate [from the bromo-ester (XI) and triethylamine] was reduced in a similar manner. Acidic hydrolysis of the ester (XI) furnished α -trichloromethylmaleic acid as the only isolated product, *i.e.*, elimination of hydrogen bromide occurred under these conditions.

Finally, ethyl $\gamma\gamma$ -trichloro- β -cyano- β -hydroxybutyrate (XII), which was prepared from ethyl $\gamma\gamma$ -trichloroacetoacetate by the method of Burdon, Smith, and Tatlow,⁷ was converted into the amide (XIII) by hydrolysis with cold concentrated sulphuric acid. Hydrolysis of the amide with 0.1N-sodium hydroxide solution afforded α -hydroxy- α -trichloromethylsuccinimide (XIV).



EXPERIMENTAL

$\beta\beta$ -Trichloro- $\alpha\alpha$ -dihydroxypropionic Acid.—Chlorine was passed into a vigorously stirred solution of lactic acid (600 g.) in water (240 c.c.) at 110° for several days, until crystallization occurred on cooling overnight.² The solid was collected, and the filtrate chlorinated again, this process being repeated several times. The acid (432 g.) separated from chloroform as needles m. p. 102—103° (lit.,¹ 100—102°).

Ethyl Trichloropyruvate.—A solution of the above acid (30 g.) in benzene (300 c.c.) was refluxed through a phase-separator until no more water was collected. Ethyl borate (20 c.c.) was added dropwise to the cooled solution, and the mixture was refluxed for 4 hr. Repeated

⁷ Burdon, Smith, and Tatlow, *J.*, 1961, 4519.

⁸ Cf. Kharasch, U.S.P. 2,485,099/1949.

distillation of the filtered solution through a Fenske column afforded the ester (16 g.), b. p. 76.5°/10 mm., n_D^{18} 1.4844 (Found: C, 27.8; H, 2.3; Cl, 47.8. Calc. for $C_5H_5Cl_3O_3$: C, 27.4; H, 2.3; Cl, 48.5%).

$\beta\beta\beta$ -Trichlorolactates.—Ethyl trichloropyruvate (0.1 mol.), or the anhydrous acid [from the hydrate (0.1 mol.)], in ether (100 c.c.), was added to a stirred solution of the appropriate Grignard reagent * (0.3 mol.) in ether (500 c.c.) at -10° to 0° . After 1 hr. at 0° the mixture was poured on to ice and dilute hydrochloric acid, and the crude product isolated with ether, and purified by recrystallization or distillation. The products are listed in the Table.

$\beta\beta\beta$ -Trichlorolactates (I).

R	R'	B. p./mm.	M. p.	Yield (%)	Found (%)			Formula	Required (%)		
					C	H	Cl		C	H	Cl
Me	H	—	169—170 ^a	83	23.1	2.5	51.0	$C_4H_5Cl_3O_3$	23.2	2.4	51.3
HC≡C	H	—	151—153 ^b	44	27.8	1.6	48.7	$C_5H_3Cl_3O_3$	27.6	1.4	48.9
Me	Et	95—98°/10	— ^c	66	30.9	4.1	44.8	$C_8H_9Cl_3O_3$	30.6	3.9	45.2
HC≡C	Et	82—86°/0.3	45—46 ^d	23	33.8	2.8	43.1	$C_7H_7Cl_3O_3$	34.3	2.9	43.3
HC≡C·CH ₂	Et	86—90°/0.5	— ^e	24	37.2	3.6	40.9	$C_8H_5Cl_3O_3$	37.0	3.5	41.0
Me·[CH ₂] ₄ ·C≡C	Et	107—108°/0.1	— ^f	45	45.6	5.4	33.8	$C_{12}H_{17}Cl_3O_3$	45.7	5.4	33.7

^a Prisms from benzene—light petroleum (b. p. 60—80°). ^b Prisms from benzene. ^c n_D^{18} 1.4686.

^d Prisms from light petroleum (b. p. 60—80°). ^e n_D^{22} 1.4956. ^f n_D^{21} 1.4827.

O-Acetyl- $\beta\beta\beta$ -trichloro- α -methyl-lactic Acid.— $\beta\beta\beta$ -Trichloro- α -methyl-lactic acid (15 g.) was suspended in acetyl chloride (15 c.c.) and the mixture was left over night. The excess of acetyl chloride was removed *in vacuo* and the residue recrystallized from benzene to give the acid (15.8 g.) as prisms, m. p. 84—86° (Found: C, 29.1; H, 2.8; Cl, 42.4. $C_6H_7Cl_3O_4$ requires C, 28.9; H, 2.8; Cl, 42.6%). The acid chloride, prepared in the normal manner with thionyl chloride, had b. p. 103°/10 mm., n_D^{21} 1.4829 (Found: C, 26.5; H, 2.6. $C_6H_6Cl_4O_3$ requires C, 26.9; H, 2.3%).

2-Acetoxy-*2*-trichloromethylbut-*3*-ynoic Acid.—Prepared from the hydroxy-acid and acetyl chloride, the product (60%) separated from benzene—light petroleum (b. p. 60—80°) as prisms, m. p. 72—75° (Found: C, 32.5; H, 2.3; Cl, 40.5. $C_7H_5Cl_3O_4$ requires C, 32.4; H, 1.9; Cl, 41.0%). The acid chloride had b. p. 108—114°/10 mm. (Found: C, 30.6; H, 1.7. $C_7H_4Cl_4O_3$ requires C, 30.3; H, 1.5%).

$\beta\beta\beta$ -Trichloro- α -methyl-lactamide.—*O*-Acetyl- $\beta\beta\beta$ -trichloro- α -methyl-lactic acid chloride (15 g.) was added dropwise to ammonium hydroxide solution (*d* 0.9; 40 c.c.) at 0° , and the mixture stirred for 1 hr. Next day, the amide (4.1 g.) was collected and recrystallized from benzene—light petroleum (b. p. 60—80°) as prisms, m. p. 174—176° (Found: C, 22.9; H, 2.6; N, 7.2. $C_4H_6Cl_3NO_2$ requires C, 23.2; H, 2.9; N, 6.8%).

O-Acetyl- $\beta\beta\beta$ -trichloro-*NN* α -trimethyl-lactamide.—Dimethylamine (5.9 g.) was passed into a stirred solution of *O*-acetyl- $\beta\beta\beta$ -trichloro- α -methyl-lactic acid chloride (16.0 g.) in ether (100 c.c.) at 0° . After 1 hr. the filtered solution was evaporated, and the residue recrystallized from light petroleum (b. p. 60—80°) to give the amide (12.0 g.), prisms, m. p. 62—63° (Found: C, 34.9; H, 4.2; N, 5.1. $C_6H_{12}Cl_3NO_2$ requires C, 34.7; H, 4.4; N, 5.1%).

$\beta\beta\beta$ -Trichloro-*NN* α -trimethyl-lactamide.—The foregoing acetoxy-amide (10.0 g.) was suspended in dilute ammonium hydroxide solution (80 c.c.) and methanol was added until the solid dissolved. Next day, solvent was removed and the product (3.9 g.) was isolated with ethyl acetate as prisms, m. p. 97—99° [from benzene—light petroleum (b. p. 60—80°)] (Found: C, 31.1; H, 4.7; N, 5.8. $C_6H_{10}Cl_3NO_2$ requires C, 31.1; H, 4.4; N, 6.1%).

2-Hydroxy-*2*-trichloromethylbut-*3*-ynamide.—*2*-Acetoxy-*2*-trichloromethylbut-*3*-ynoyl chloride (11.4 g.) and ammonium hydroxide solution (*d* 0.9; 400 c.c.) at 0° furnished the amide (4.1 g.), isolated with ether, which had m. p. 167—168° (from benzene—methanol) (Found: C, 28.0; H, 2.3; N, 7.0. $C_6H_4Cl_3NO_2$ requires C, 27.7; H, 1.9; N, 6.5%).

Condensation Reactions of Ethyl Trichloropyruvate.—(a) *With diethyl malonate.* Zinc chloride

* When ethynylmagnesium bromide ^g was used, the reaction was carried out in tetrahydrofuran.

^g Jones, Skatteböl, and Whiting, *J.*, 1956, 4765.

(53.5 g.) was shaken with acetic anhydride (107 g.) until it had all dissolved. Ethyl trichloropyruvate (47.0 g.) and diethyl malonate (34.0 g.) were added, and the solution was heated on a steam-bath for 3 hr.⁵ The cooled mixture was dissolved in ether (500 c.c.), washed with water (5 × 250 c.c.), dried (Na₂SO₄), and evaporated. The tarry residue, which could not be distilled because of extensive decomposition, was dissolved in benzene, and passed through a column of activated alumina. Triethyl 3,3,3-trichloroprop-1-ene-1,1,2-tricarboxylate (25 g.), eluted with benzene, had b. p. 131—133°/0.1 mm., n_D^{23} 1.4808 (Found: C, 40.2; H, 3.9; Cl, 29.3. C₁₂H₁₅Cl₃O₆ requires C, 39.9; H, 4.2; Cl, 29.4%).

(b) *With ethyl cyanoacetate.* In a similar manner, zinc chloride (23.0 g.) and acetic anhydride (46.0 g.) with ethyl trichloropyruvate (20.0 g.) and ethyl cyanoacetate (10.0 g.) afforded diethyl 3,3,3-trichloro-1-cyanoprop-1-ene-1,2-dicarboxylate (7.0 g.), b. p. 111—115°/0.2 mm., n_D^{22} 1.4968 (Found: C, 38.2; H, 3.2; N, 4.2. C₁₀H₁₀Cl₃NO₄ requires C, 38.2; H, 3.2; N, 4.5%).

Triethyl 4,4-Dichlorobut-3-ene-2,2,3-tricarboxylate.—The foregoing triester (10.6 g.) with cuprous chloride (0.2 g.) in ether (100 c.c.) was treated with 0.65M-methylmagnesium iodide (68.5 c.c.) in ether at 20°.⁶ The mixture was stirred for 2 hr. at 20°, refluxed for 1 hr., and left overnight. Addition of water and isolation with ether furnished the dichloro-compound (5.0 g.), b. p. 122—128°/0.3 mm., n_D^{22} 1.4723 (Found: C, 45.1; H, 5.0; Cl, 21.0. C₁₃H₁₈Cl₂O₆ requires C, 45.7; H, 5.3; Cl, 20.8%), $\lambda_{\max.}$ (in ethanol) 229 m μ (ϵ 8700), $\nu_{\max.}$ 1592 cm.⁻¹ (CCl₂).

When ethyl 3,3,3-trichloro-1-cyanoprop-1-ene-1,2-dicarboxylate was treated with methylmagnesium iodide in the presence of cuprous chloride, the product, b. p. 90—95°/0.6 mm., which was evidently a mixture, could not be purified by distillation (Found: C, 42.3; H, 4.6; N, 3.1. Calc. for C₁₁H₁₃Cl₂NO₄: C, 44.9; H, 4.5; N, 4.8%), $\lambda_{\max.}$ (in ethanol) 223 m μ (ϵ 5560).

Reformatsky Reaction between Ethyl Trichloropyruvate and Ethyl Bromoacetate.—Zinc wool was washed successively with dilute alkali, dilute acid, water, ethanol, and ether, and dried at 100°. After the zinc (46.2 g.) and AnalaR benzene (2 l.) had been dried azeotropically and a crystal of iodine added, a solution of ethyl trichloropyruvate (143 g.) and ethyl bromoacetate (91 g.) in benzene (350 c.c.) was added to the boiling mixture over 3 hr. The mixture was refluxed until the zinc had all dissolved, and then decomposed by the cautious addition of *n*-hydrochloric acid (600 c.c.). Ethyl α -trichloromethyl- α -hydroxysuccinate (43 g.), isolated with benzene, had b. p. 162—166°/13 mm., n_D^{22} 1.4743 (Found: C, 35.4; H, 4.5; Cl, 34.2. C₉H₁₃Cl₃O₅ requires C, 35.1; H, 4.3; Cl, 34.6%). The ester (21.0 g.) was refluxed with concentrated hydrochloric acid (130 c.c.) for 14 hr. The solid was collected and recrystallized from ethyl acetate—light petroleum (b. p. 60—80°) to give the monoester (6.5 g.) as rods, m. p. 124—126° (Found: C, 30.1; H, 3.0; Cl, 38.1. C₇H₉Cl₃O₅ requires C, 30.1; H, 3.2; Cl, 38.1%). In another experiment the diester was refluxed with 55% hydriodic acid and red phosphorus to give the monoester, m. p. and mixed m. p. 122—124°.

α -Trichloromethylmaleic Anhydride.—A mixture of ethyl α -hydroxy- α -trichloromethylsuccinate (20 g.) and phosphorus pentoxide (20 g.) was heated at 180—200° for 1 hr. and the product (6.5 g.) was slowly distilled, b. p. 138—160°/10 mm. Redistillation afforded the anhydride, b. p. 146—152°/10 mm., n_D^{21} 1.5490 (Found: C, 28.6; H, 0.8. C₅HCl₃O₃ requires C, 27.9; H, 0.5%).

α -Trichloromethylmaleic Acid.—The last-mentioned anhydride (0.3 g.) in water (0.5 c.c.) was warmed on a steam-bath for 20 min. After removal of the water, the product separated from benzene—ethyl acetate as prisms, m. p. 147—149° (Found: C, 25.7; H, 0.8; Cl, 45.6. C₅H₃Cl₃O₄ requires C, 25.7; H, 1.3; Cl, 45.6%).

α -Dichloromethylene succinic Acid.— α -Trichloromethylmaleic anhydride (2.0 g.) was refluxed with red phosphorus (0.8 g.), hydriodic acid (*d* 1.7; 2.5 c.c.), and acetic acid (24 c.c.) for 5 hr. The mixture was diluted with water, acidified with 2*N*-sulphuric acid, and filtered. The filtrate was continuously extracted with ether for 12 hr., the organic layer dried (MgSO₄), and evaporated. Recrystallization of the residue from benzene—light petroleum (b. p. 60—80°) afforded the acid (0.5 g.), m. p. 142—144° (Found: C, 30.2; H, 1.9; Cl, 35.1. C₅H₄Cl₂O₄ requires C, 30.2; H, 2.0; Cl, 35.6%). Mixed m. p. with α -trichloromethylmaleic acid was 122—125°.

Diethyl α -Bromo- β -trichloromethylsuccinate.—Diethyl maleate (172 g.) and bromotrichloromethane (792 g.) and benzoyl peroxide (1.0 g.) was refluxed for 6 hr., more benzoyl peroxide (1.0 g.) being added after 1 hr.⁸ Repeated distillation of the solvent-free residue furnished the ester (96 g.) b. p. 108—110°/0.3 mm., n_D^{20} 1.4911 (Found: C, 29.6; H, 3.1. C₉H₁₂BrCl₃O₄ requires C, 29.2; H, 3.3%).

Reactions of Diethyl α -Bromo- β -trichloromethylsuccinate.—(a) *Hydrolysis.* The ester (30 g.) was refluxed with concentrated hydrochloric acid (180 c.c.) for 24 hr. The acidic fraction, isolated with ether, was recrystallized from benzene-ethyl acetate to give α -trichloromethylmaleic acid (9.8 g.), prisms, m. p. and mixed m. p. 146–148°.

(b) *Reduction with phosphorus and hydriodic acid.* The ester (22 g.), red phosphorus (2.0 g.), sodium iodide (1.0 g.), and 55% hydriodic acid (40 c.c.) were refluxed together for 15 hr., filtered, and the acidic fraction isolated from the filtrate with ethyl acetate. Recrystallization of the residue from benzene afforded α -dichloromethylsuccinic acid (4.1 g.), m. p. and mixed m. p. 137–140°.

(c) *Dehydrobromination.* The ester (25 g.) in ether (100 c.c.) was added to an ice-cooled solution of triethylamine (100 c.c.) in ether (500 c.c.), and the mixture was stirred for 6 hr. Addition of water and isolation with ether furnished *diethyl α -trichloromethylmaleate* (4.8 g.), b. p. 108–110°/0.6 mm., n_D^{20} 1.4925 (Found: C, 37.1; H, 3.9; Cl, 36.4. $C_9H_{11}Cl_3O_4$ requires C, 37.3; H, 3.8; Cl, 36.7%). This compound, hydrolysed with boiling hydrochloric acid, yielded α -trichloromethylmaleic acid, m. p. and mixed m. p. 143–145°. Reduction of the maleate (6.7 g.) with red phosphorus and hydriodic acid in the normal manner gave α -dichloromethylsuccinic acid (1.5 g.), m. p. and mixed m. p. 141–142°.

Ethyl $\gamma\gamma\gamma$ -Trichloro- β -cyano- β -hydroxybutyrate.—Potassium cyanide (13.6 g.) in water (32 c.c.) was added dropwise to an ice-cooled stirred solution of ethyl $\gamma\gamma\gamma$ -trichloroacetoacetate¹⁰ (34.3 g.) in ethanol (115 c.c.) and water (170 c.c.).⁷ After 5 hr. at 0°, 6N-sulphuric acid (112 c.c.) was added, and the product isolated with ether. The *cyanohydrin* (19.0 g.) separated from light petroleum (b. p. 60–80°) as needles, m. p. 60–62° (Found: C, 32.2; H, 2.9; N, 5.3. $C_7H_8Cl_3NO_3$ requires C, 32.3; H, 3.1; N, 5.4%).

α -Trichloromethyl- α -hydroxysuccinic Acid α -Amide β -Ethyl Ester (Ethyl 3-Carbamoyl-4,4-trichloro-3-hydroxybutyrate).—The foregoing cyanohydrin (11.0 g.) was treated with concentrated sulphuric acid (80 c.c.) and the mixture left overnight. After addition of the solution to water (2 l.), the *amide* (7.2 g.), isolated with ethyl acetate, had m. p. 130–132° (from ethyl acetate-benzene) (Found: C, 30.1; H, 3.4; N, 4.9. $C_7H_{10}Cl_3NO_4$ requires C, 30.2; H, 3.6; N, 5.0%).

α -Trichloromethyl- α -hydroxysuccinimide.—A solution of the above amide (7.0 g.) in ethanol (18 c.c.) at 60° was treated with 0.1N-sodium hydroxide solution (260 c.c.). After 2 min., the solution was acidified with 2N-hydrochloric acid, and then extracted with ether. Evaporation of the dried (Na_2SO_4) extract afforded the *imide* (2.9 g.), plates, m. p. 229–231° (from ethyl acetate-benzene) (Found: C, 26.1; H, 1.9; N, 5.9. $C_5H_4Cl_3NO_3$ requires C, 25.8; H, 1.7; N, 6.0%).

The authors are indebted to Mr. F. H. Oliver for microanalyses and to Miss E. M. Tanner for spectroscopic measurements.

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¹⁰ Broekema, van der Werf, and Arens, *Rec. Trav. chim.*, 1958, **77**, 258.