cases still moist after the experiments. The formation of the trihydroxides or of the oxide hydroxides is dependent on the amount of solution used. In the reactions

$$Ho_2O_3 + 3\,H_2O = 2\,Ho(OH)_3 \quad (1)$$

and

$$Ho_2O_3 + H_2O = 2\,HoOOH \quad (2)$$

the volume difference between product and reaction mixture is greatest for (1), and the formation of the trihydroxide is to be expected, when sufficient solution is present. Powder patterns of all products were obtained as for the tetragonal modification of holmium oxide hydroxide, and the rare earth oxide hydroxide phases were indexed, using the tetragonal unit cell parameters given in Table 1.

Single crystals of tetragonal ytterbium oxide hydroxide were prepared from a mixture of ytterbium oxide and solid sodium hydroxide. The mixture was allowed to absorb humidity from the atmosphere for a few min, and was then placed in a platinum ampoule and treated in the high-pressure belt apparatus at 50 kb and 800°C for 1 h. The sample was then slowly cooled to 600°C over a period of 30 min, followed by fast cooling to room temperature. The crystals were washed with water and dried at room temperature.

A single crystal was investigated by precession methods using Mo$K\alpha$-radiation ($\lambda = 0.7107$ Å). Photographs were taken of $hk0$, $hk1$, $hk2$, and hhl. The reflections $h00 = 2n+1$ are absent. The symmetry of the photographs are in agreement with the space group $P\bar{4}2_1m$ (No. 113). The crystal structure determination of the compound is in progress.

The present investigation shows, that high-pressure modifications of hydroxides can be obtained by hydrothermal synthesis at very high temperatures and pressures, and that a new experimental hydrothermal technique can be applied, using high-pressure belt apparatus.

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Received October 6, 1970.

Stereoselective Synthesis of Triglochinic Acid, (*E*)-2-Butene-1,2,4-tricarboxylic Acid, Derived from the Cyanogenic Glucoside Triglochinin

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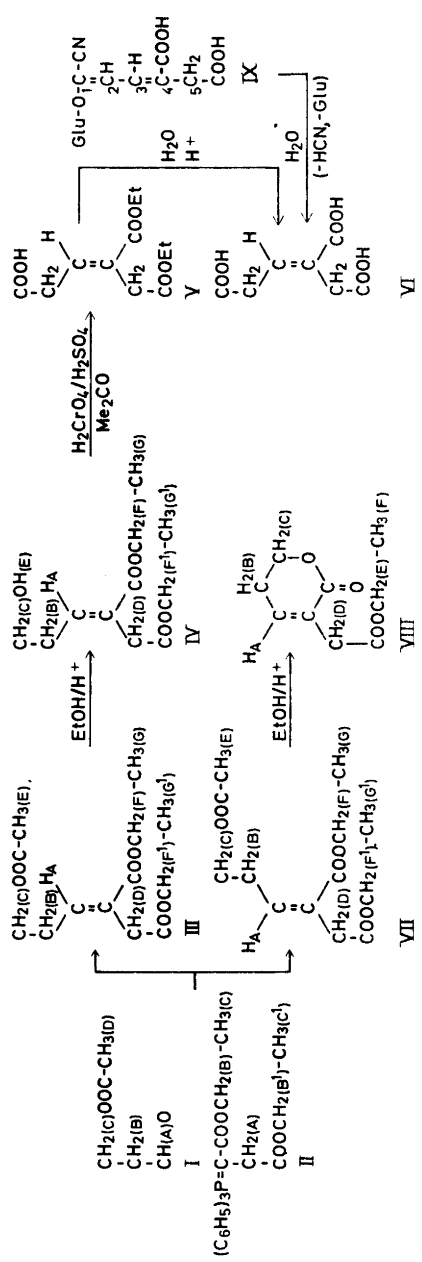
In a previous communication,[1] the isolation and constitutional assignment of a novel cyanogenic glucoside, triglochinin (IX), were described. This glucoside, unique within the group of cyanogenic glycosides in containing carboxylic functions in the aglycone,[2] was shown to decompose on enzymic or acid catalyzed hydrolysis to a hitherto unknown carboxylic acid, triglochinic acid (VI), along with glucose and HCN.[1] The (*E*)-configuration of the title compound (VI) has presently been elucidated by synthesis as depicted in the scheme below. It follows, provided the degradations of triglochinin (IX) are not accompanied with rearrangements at the 3,4-double bond, that the configuration of this double bond is (*E*). Further studies of the stereochemistry of the glucoside (IX) are in progress.

Condensation of acetaldehyde with 1-methoxycarbonylethylidenetriphenylphosphorane (Wittig reaction) has been shown to furnish a mixture of methyl (*E*)-2-methyl-2-butenoate (methyl tiglate) and its stereoisomer (methyl angelate) in the



ratio 96.5:3.5.[3,4] Concordantly, under similar experimental conditions, the reaction between 2-formylethyl acetate (I) and 1,2-bis(ethoxycarbonyl)ethylidenetriphenylphosphorane (II) afforded a mixture of the compounds III and VII in the ratio *ca.* 97:3, estimated from the yields of IV and VIII obtained by ethanolysis of III and VII. No significant conversion of IV to VIII could be demonstrated. Further support for the stereochemical relationships is inferred from the fact that the vinylic proton (H_A) in IV resonates at a substantially lower field than that of VIII as these protons are positioned *cis* and *trans*, respectively, to the carbonyl group.[5]

Initially, much effort was exercised in order to convert IV into the corresponding aldehyde, utilizing "mild" oxidation agents normally incapable of attacking carbon-carbon double bonds. This aldehyde was then to be oxidized selectively to the desired intermediate V. Of the methods applied, oxidation with dimethylsulfoxide-*N*,*N*′-dicyclohexylcarbodiimide (Pfitzner-Moffatt oxidation [6]), with CrO_3-pyridine (Sarett's reagent [7]) and with *t*-butyl chromate [8] should be mentioned. In all cases complex mixtures resulted from which no pertinent product(s) could be isolated in spite of painstaking chromatographic work. By contrast, oxidation of IV with chromic acid in acetone at room temp. afforded V in high yield; a technique that has been employed successfully in the preparation of homoallylic steroid ketones from the parent secondary alcohols,[9] or in the conversion of 3-hexyne-1,6-diol to the corresponding diacid.[10] To the author's knowledge, however, this reagent has not been used previously for the oxidation of open chain, homoallylic, primary alcohols (see, *e.g.*, Refs. 11 and 12 for surveys).

Experimental. ^1H NMR, UV and IR spectra were recorded on JEOL JNM-C-60HL, Perkin-Elmer, type 402, and Perkin-Elmer, type 457 instruments, respectively. All δ values are relative to TMS (internal). Silica gel (Merck, 0.05–0.20 mm) used for preparative work contained 10 % H_2O.

2-Formylethyl acetate (I).[13] A column of Amberlite IRA-400 (acetate form) (200 ml) was charged with a mixture of acrolein (44.8 g, 0.8 mol) and glacial AcOH (48 g, 0.8 mol). After standing at room temp. for 17 h the reaction mixture was eluted with $MeCl_2$ (200 ml). Water (200 ml) was added to the effluent that was neutralized with $NaHCO_3$. The organic phase was separated and the aqueous layer was extracted with $MeCl_2$ (2×50 ml). The combined, dried $MeCl_2$ extracts were evaporated at reduced pressure (20°, 20 mm) and the residue was distilled from a Claisen

still to give I, 23.0 g (25 %), b.p. 71–73° (12–13 mm), (Ref. 13, b.p. 65–70° (10 mm)). ^{1}H NMR spectrum (neat), δ: 9.95, t, 1 H (H_A), J_{AB}=1.5 cps; 4.45, t, 2 H (H_C), J_{BC}=6 cps; 2.85, m, 2 H (H_B); 2.05, s, 3 H (H_D).

1,2-Bis(ethoxycarbonyl)ethylidenetriphenylphosphorane (II).[14] Triphenylphosphine HBr (14.0 g, 40 mmol) and diethyl fumarate (6.8 g, 40 mmol) were refluxed for 15 min in MeCN (20 ml). The product was dissolved in H_2O (75 ml) and washed with Et_2O (3×25 ml). The aqueous solution was treated with NaOH (2 N, 30 ml) and extracted with Et_2O (3×50 ml). Concentration of the dried Et_2O extracts gave II as a thick syrup that crystallized on seeding. Yield 14.7 g (83 %), recrystallized from Bz, m.p. 105–106° (corr.), (Ref. 14, m.p. 104–106°). ^{1}H NMR spectrum (20 % in CCl_4), δ: 8.0–7.1, m, 15 H (arom. protons); 4.1–3.5, two q, 4 H (H_B and H_{B1}); 2.78, d, 2 H (H_A), $J_{A\ Phosphorus}$=19 cps; 1.8–1.3, two t, 6 H (H_C and H_{C1}).

(E)-*Ethyl 6-acetoxy-3-ethoxycarbonyl-3-hexenoate (III)* and (Z)-*ethyl 6-acetoxy-3-ethoxycarbonyl-3-hexenoate (VII).* A solution of II (2.9 g, 6.7 mmol) in dry Bz (15 ml) was added, at room temp. during 20 min, to a continuously stirred solution of I (0.78 g, 6.7 mmol) in dry Bz (5 ml). The mixture was then refluxed for 22 h; these operations were conducted in an atmosphere of dry N_2. The orange reaction product was evaporated to dryness at reduced pressure and the residue was chromatographed on silica gel (140 g). Elution with Bz-EtOAc (9:1, v/v) afforded a mixture of III and VII as a colourless liquid, 1.31 g (72 %). The concentration of VII in this material may be estimated to *ca.* 3 %, see IV and VIII in the sequel. Thus, the following data recorded of the mixture refer to III only. ^{1}H NMR spectrum (neat), δ: 6.98, t, 1 H (H_A), J_{AB}=8 cps; 4.4–3.9, m, 6 H (H_C, H_F and H_{F1}); 3.38, broad s, 2 H (H_D); 2.55, m, 2 H (H_B); 2.00, s, 3 H (H_E); 1.25 and 1.21, two t, 6 H (H_G and H_{G1}), $J_{FG}=J_{F^1G^1}$=7.5 cps. UV spectrum: λ_{max} (MeCN) 216 nm.

(E)-*Ethyl 3-ethoxycarbonyl-6-hydroxy-3-hexenoate (IV)* and *2-ethoxycarbonylmethyl-2-penten-5-olide (VIII).* The Wittig reaction product (III and VII, 3.8 g) was treated with 1 % ethanolic HCl at room temp. for 16 h. The solution was neutralized ($NaHCO_3$), evaporated at reduced pressure and the residue chromatographed on silica gel (200 g). Irrigation with $MeCl_2$-EtOAc (8:2, v/v) furnished VIII (65.5 mg, 2.5 %) and IV (2.68 g, 83 %) as colourless oils. Renewed ethanolysis and work-up of IV (2.60 g), under conditions exactly as described above, did not reveal any lactone (VIII) in the reaction mixture (detection limit *ca.* 1 mg). IV: ^{1}H NMR spectrum (15 % in CCl_4), δ: 6.98, t, 1 H (H_A), J_{AB}=8 cps; 4.20 and 4.18, two q, 4 H (H_F and H_{F1}), $J_{FG}=J_{F1G1}$=7 cps; 3.68, t, 2 H (H_C), J_{BC}=6.5 cps; 3.32, s, 3 H (H_D and H_E); 2.39, m, 2 H (H_B); 1.28 and 1.25, two t, 6 H (H_G and H_{G1}). UV spectrum: λ_{max}(MeCN) 217 nm. VIII: ^{1}H NMR spectrum (15 % in CCl_4), δ: 6.71, broad t, 1 H (H_A); 4.35, t, 2 H (H_C), J_{BC}=6 cps; 4.10, q, 2 H (H_E), J_{EF}=7.5 cps; 3.18, broad s, 2 H (H_D); 2.48, m, 2 H (H_B); 1.25, t, 3 H (H_F). UV spectrum: λ_{max}(MeCN) 215 nm.

(E)-*4,5-Bis(ethoxycarbonyl)-3-pentenoic acid (V).* The oxidation agent employed consisted of CrO_3 (26.72 g) and conc. H_2SO_4 (23 ml) dissolved in H_2O to a total vol. of 100.0 ml. The theoretical quantity (4.60 ml) of this reagent was added in the course of 25 min to a cooled (16–20°), vigorously stirred solution of IV (2.12 g) in Me_2CO (80 ml), whereupon the stirring was continued for further 15 min at 20°. The mixture was shaken with ice-cold $MeCl_2$–H_2O (1:1, v/v; 200 ml), the organic phase was separated and the aqueous layer was extracted with $MeCl_2$ (2×100 ml). The dried $MeCl_2$ extracts were extracted with 4 % aqueous $NaHCO_3$ (50 ml) which, in turn, was washed with $MeCl_2$ (2×50 ml). The $NaHCO_3$ solution was acidified with H_2SO_4 (4 N, 10 ml) and extracted with $MeCl_2$ (3×50 ml). Evaporation of the dried $MeCl_2$ solution yielded V as a thick syrup, 1.89 g (84 %). An aliquot (5 mg) of this product was treated with 1 % ethanolic HCl (1 ml) at room temp. for 18 h. TLC analysis (5 solvent systems) of the reaction mixture indicated the presence of one compound only, indistinguishable from triglochinic acid triethyl ester, prepared by ethanolysis of triglochinin (IX), *cf.* Ref. 1.

(E)-*2-Butene-1,2,4-tricarboxylic acid (triglochinic acid) (VI).* Hydrolysis of V (1.88 g) was effected in refluxing HCl (2 N, 40 ml) for 3 h; followed by continuous extraction with Et_2O for 16 h. Evaporation of the dried extract afforded chromatographically pure triglochinic acid, 1.41 g (97 %), recrystallized from Me_2CO-Bz, m.p. 167–168° (corr.), (Ref. 1, m.p. 160–161° (from EtOAc-$CHCl_3$)), and indistinguishable from an authentic sample (TLC, ^{1}H NMR, IR).

Acknowledgements. The author records his thanks for an institutional postdoctoral scholarship. The help of cand. pharm. Poula Nørgaard, Chemical Laboratory C, this institute, concerning pioneering research following other approaches to the preparation of the title compound is gratefully acknowledged.

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Received September 15, 1970.

Labelled Compounds of Potential Biological Interest

I. Pyrazole-4-^{3}H and 4-Methylpyrazole-3-^{3}H

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In previous studies [1,2] it was found that series of substituted pyrazoles were extremely potent inhibitors of liver alcohol dehydrogenase (LADH). 4-Bromo- and 4-iodopyrazole were the most active compounds and slightly more potent than 4-methylpyrazole. It was found [3] in our laboratories that 4-methylpyrazole was better tolerated than the two halogenated derivatives. Extended toxicity studies with 4-methylpyrazole revealed no changes in hematology, blood chemistry, urine analysis, and histopathology related to the drug treatment. The compound had thus met the criteria for commencing investigations in man.[4]

In order to carry out distribution and metabolism studies it was necessary to prepare labelled 4-methylpyrazole. For comparison we have also labelled pyrazole — another inhibitor of the ethanol oxidation.[1,2,5,6] Catalytic dehalogenation in presence of tritium appeared to be the simplest route to the labelled compounds. In trial runs the conditions were established which would cause hydrogenolysis but no hydrogenation to the pyrazolines.

Iodination of pyrazole and 4-methylpyrazole gave the desired intermediates which, on deiodination by tritium in a tritium-hydrogen gas in the presence of palladium on charcoal catalyst, furnished the labelled compounds.

The products were isolated as their oxalates and the radiochemical purity was verified by thin layer chromatography.

Experimental. Pyrazole-4-^{3}H oxalate. 4-Iodopyrazole (205 mg, 1.05 mmole) prepared according to Hüttel *et al.*[7] was dissolved in 2 ml of a solution of sodium hydroxide in 90 % ethanol (80 mg NaOH, 2 mmole) and 10 % Pd on charcoal catalyst (20 mg) was added. The mixture was hydrogenated by vigorous stirring in a H_2/T_2 mixture (20 Ci T_2) in a vacuum tritiation apparatus. Hydrogenation was complete after 20 min. The catalyst was removed by filtration, washed with ethanol and the filtrate was evaporated to dryness *in vacuo*. The residue was extracted with ether. A solution of oxalic acid in ether was added to the ether extract and the pyrazole oxalate was recrystallized from methanol-ether after dilution with 100 mg of inactive pyrazole oxalate. Yield 136 mg; m.p. 191.5–192°C (d) (uncorr.); spec. act. 8.1 mCi/mg = 1.3 Ci/mmole; activity yield 5.5 %.

Radiochemical purity was checked by thin layer chromatography on silica (Merck F-254) in a chloroform-methanol (9:1) solvent system. The product showed a single radioactive peak corresponding to the reference standard pyrazole oxalate ($R_F = 0.3$).