423. *The Preparation of 4 : 4′-Bistetrahydropyranyl and of Ethane-1 : 1 : 2 : 2-tetra-acetic Acid.*

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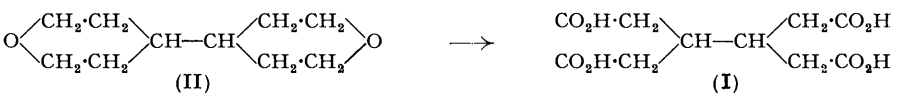
Six methods for the synthesis of ethane-1 : 1 : 2 : 2-tetra-acetic acid (I) have been investigated. Of these, the only one successful was the oxidation of 4 : 4′-bistetrahydropyranyl (II). This compound was prepared by symmetrical anodic coupling of tetrahydropyran-4-carboxylic acid.

The hitherto unknown ethane-1 : 1 : 2 : 2-tetra-acetic acid (ββ′-biscarboxymethyladipic acid) (I) was required as an intermediate in the possible synthesis of 1 : 4 : 7 : 8-tetrahydropentalene and thence of pentalene (see Blood and Linstead, *J.*, 1952, 2255). A considerable number of synthetic methods were examined, of which only that involving tetrahydropyran intermediates was successful. This is described in suitable detail below. Five unsuccessful methods are briefly outlined.

1. *Successful Process.*—By analogy with the preparation of glutaric acid itself from tetrahydropyran, it seemed possible that oxidation of 4 : 4′-bistetrahydropyranyl (II) might yield ethane-1 : 1 : 2 : 2-tetra-acetic acid (I) :

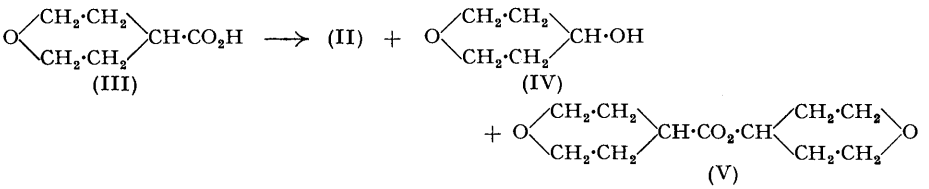


(II) (I)

Moreover, an attractively simple route to 4 : 4′-bistetrahydropyranyl was an anodic synthesis from the readily accessible tetrahydropyran-4-carboxylic acid (III). No previous study seems to have been made of the anodic behaviour of an acid of this type containing a carboxyl group directly attached to a reduced heterocyclic ring. A difficulty was clearly involved in the fact that the carboxyl group was attached to a doubly substituted carbon atom, an arrangement which is known to lead to side reactions (see, *e.g.*, Petersen, *Z. Elektrochem.*, 1906, **12**, 141).

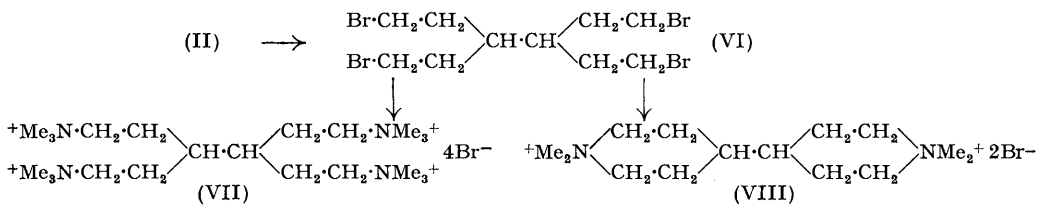
The electrolysis of (III) was studied over a considerable range of experimental conditions and with cells of diverse design. The results are detailed in the Experimental section.

The best results were obtained with quite simple experimental procedures. Three main products were identified; there was also some low-boiling material, probably a mixture of hydrogenated monocyclic pyrans arising from disproportionation of the radical corresponding to (III). The main products were 4-hydroxytetrahydropyran (IV), 4 : 4′-bistetrahydropyranyl (II), and the ester (V) derived from the alcohol (IV) and the original acid.



The alcohol (IV), b. p. 91°/15 mm., was characterised as the *p*-nitrobenzoate, m. p. 69°, and the 3 : 5-dinitrobenzoate, m. p. 161°. On oxidation with chromic acid it yielded tetrahydro-4-pyrone, the 2 : 4-dinitrophenylhydrazone of which melted at 187°; and further oxidation with nitric acid gave β-carboxymethoxypropionic acid, m. p. 95°. We were at some pains to prove the structure of the alcohol conclusively because of a discrepancy in the literature. Adkins and Mozingo (*J. Amer. Chem. Soc.*, 1938, **60**, 669; cf. Blanchard and Paul, *Compt. rend.*, 1935, **200**, 1414) reported a preparation of 4-hydroxytetrahydropyran by catalytic hydrogenation of 4-pyrone over Raney nickel. Their alcohol gave a 3 : 5-dinitrobenzoate of m. p. 98—99°, for which no analytical data were given. J. W. Baker (*J.*, 1944, 296) prepared the alcohol (IV) by a Prins reaction from propylene and paraformaldehyde. He gave m. p.s of 69° for the *p*-nitrobenzoate of the alcohol, 186—187° for the 2 : 4-dinitrophenylhydrazone of the derived ketone, and 97° for carboxymethoxypropionic acid (cf. Borsche, *Ber.*, 1915, **48**, 683, who gives m. p. 93—94°). Our data tally closely with those of Baker and we confirmed the identity of our materials with his by mixed melting-point determinations of the *p*-nitrobenzoates and 2 : 4-dinitrophenylhydrazones. The dinitrobenzoate reported by Adkins and Mozingo is clearly not that of 4-hydroxytetrahydropyran.

The higher-boiling neutral products of the anodic reaction were separated by fractionation into bistetrahydropyranyl (II) and the ester (V). The dicylic ether, m. p. 67°, crystallised from the fraction of b. p. 125—135°/15 mm. It was readily soluble in organic solvents and was best purified by vacuum-sublimation. Its structure was proved as follows: Analysis corresponded to $C_{10}H_{18}O_2$. The two oxygen atoms were not acidic or ketonic. Reaction with fuming hydrogen bromide yielded 1 : 1 : 2 : 2-tetra-(2-bromoethyl)ethane (VI). This readily reacted with aliphatic amines in two ways, *viz.*, with



trimethylamine, to give the acyclic tetra-quaternary salt, ethane-1 : 1 : 2 : 2-tetra(ethyl-2-trimethylammonium) tetrabromide (VII), but with dimethylamine to give the dipiperidyl derivative (VIII). The latter reaction proceeded under mild conditions and hence probably by cyclisation of an intermediate dibromo-diamine rather than by decomposition of a tetra-salt of the type of (VII). These interesting salts are very stable and do not melt below 360°.

The formation of the tetrabromide (VI) indicates that the parent compound (II) contains two tetrahydropyran rings. In agreement with this, careful oxidation of (II) with nitric acid yielded a tetracarboxylic acid, $C_{10}H_{14}O_8$, which gave a dianhydride, $C_{10}H_{10}O_6$. To this we assign the ethanetetra-acetic acid structure (I).

The third product of the electrolysis was the ester (V). This was a viscous oil, b. p. 164°/15 mm. Its structure was shown by hydrolysis to the component acid (III) and alcohol (IV). The formation of an alcohol and an ester, such as (IV) and (V), as anodic products has many precedents.

2. *Abortive Syntheses.*—The yield of ethanetetra-acetic acid by the foregoing route was neither high nor consistent and a number of variations on the oxidation procedure failed to improve it. A search was accordingly made for an alternative synthesis. Methods examined were in brief :

(i) The action of copper on β-iodoglutaric ester in the presence of glutaconic ester (cf. Faltis and Wagner, *Annalen*, 1923, **433**, 109) ; this gave only glutaconic ester and no ethanetetra-acetic ester.

(ii) The Harries method of reduction with aluminium amalgam was applied to αγ-dicarboxyglutaconic ester, glutaconic ester, and glutaconononitrile ; all gave excellent yields of the corresponding glutaric acid derivatives and there was no appreciable formation of bimolecular material.

(iii) If acetonedicarboxylic ester could undergo a reduction analogous to that by which acetone forms pinacol, a useful dihydroxy-derivative of ethanetetra-acetic ester would result ; in practice, however, no bimolecular reduction product could be obtained by means of either aluminium amalgam or magnesium subiodide.

(iv) A double Michael addition of two molecules of ethyl malonate to ethyl muconate would yield a product with the desired carbon skeleton, but no addition could be realised in the presence of a trace of sodium ethoxide or piperidine. With two mols. of ethyl sodiomalonate, muconic ester gave only Farmer's compound (*J.*, 1922, **121**, 2017) which involves the addition of only one molecule of malonic ester.

(v) The condensation of glyoxal with certain compounds containing active methylene groups was also examined without success. West (*J. Amer. Chem. Soc.*, 1925, **47**, 2780) has shown that glyoxal condenses with two mols. of acetoacetic ester. We obtained no useful condensation between glyoxal and malonic ester, or with cyanoacetamide, although monoaldehydes yield β-alkylglutaric acids through the use of this reagent (Day and Thorpe, *J.*, 1920, **117**, 1465).

As there seemed no prospect that ethanetetra-acetic acid would become as available as the isomer, hexane-1 : 3 : 4 : 6-tetracarboxylic acid, further work on its preparation was not pursued.

Experimental

1. *Tetrahydropyran Series.*—Diethyl tetrahydropyran-4 : 4-dicarboxylate was prepared by the following improvement of Kamm and Waldo's process (*J. Amer. Chem. Soc.*, 1921, **43**, 2225). 230 Ml. of ethyl malonate were added during 15 minutes to a stirred solution of sodium (35 g.) in ethanol (375 ml.). 2 : 2′-Dichlorodiethyl ether (180 ml.) was then added, and the mixture boiled under reflux for 24 hours. A further similar amount of sodium ethoxide solution was then added, after which refluxing was continued for another 48 hours. Most of the ethanol was then distilled off, water added, and the product isolated by means of ether. The extract was washed with dilute acid, and sodium hydrogen carbonate solution, then dried, and the ester distilled (yield : 225 g., 63%), b. p. 120—125°/4 mm. From this, tetrahydropyran-4-carboxylic acid was prepared (yield 85%) by Braun and Kohler's method (*Ber.*, 1917, **50**, 1657).

Electrolysis of tetrahydropyran-4-carboxylic acid. The preferred cell consisted of a simple water-cooled cylindrical vessel containing a cylindrical smooth platinum cathode and a spiral of platinum wire as anode. A layer of light petroleum (b. p. 60—80°) was used to cover the electrolyte. More complex cells with double compartments, mechanical stirring, and mercury cathodes gave no improvement. The chief factors affecting the formation of the desired bistetrahydropyranyl were current density at the anode, concentration, and proportion of alkali. The best results were obtained with c.d. 1 amp./cm.^{2} and a charge of 60 g. of acid, 60 g. of water, and 4 g. of potassium hydroxide. Electrolysis was continued until the electrolyte became alkaline. The product was isolated by continuous extraction with ether, and fractionally distilled. Peak fractions boiled at 87—97°/15 mm. (A), 127—137°/15 mm. (B), and 164—170°/15 mm. (C). These yielded 4-hydroxytetrahydropyran (IV), 4 : 4′-bistetrahydropyranyl (II), and the ester (V), respectively. The yields varied somewhat ; that of pure bistetrahydropyranyl was usually 18—20%, and that of the two other products about the same.

Fraction A on redistillation gave 4-hydroxytetrahydropyran, b. p. 91—92°/15 mm., n_D^{25} 1·4581 (Found : C, 58·9; H, 9·75. Calc. for $C_5H_{10}O_2$: C, 58·8; H, 9·8%). The 3 : 5-*dinitrobenzoate* separated from acetic acid in cream-coloured slender plates, m. p. 161° (Found : C, 48·6; H, 4·0; N, 9·55. $C_{12}H_{12}O_6N_2$ requires C, 48·7; H, 4·05; 9·5%). The *p*-nitrobenzoate, plates from light petroleum, melted at 68°, alone or mixed with a sample kindly supplied by Dr. J. W. Baker. On oxidation with aqueous chromium trioxide, the alcohol gave an 80% yield (by wt.) of tetrahydro-4-pyrone, b. p. 65°/15 mm.; its 2 : 4-dinitrophenylhydrazone formed orange plates (from ethanol), m. p. 187°, alone or in admixture with a sample from Dr. Baker. Oxidation of the alcohol (1 g.) with nitric acid (20 c.c. of 50%) yielded a solid, isolated by evaporation. On trituration and crystallisation from chloroform this gave β-carboxymethoxypropionic acid, rosettes of prisms, m. p. 95°.

Fraction C on redistillation gave tetrahydro-4-pyranyl tetrahydropyran-4-carboxylate (V), b. p. 163—165°/15 mm., n_D^{25} 1·4690. This was saponified with an excess of boiling aqueous alkali and separated in the usual way into neutral and acidic products; the former was identified as 4-hydroxytetrahydropyran by means of the 3 : 5-dinitrobenzoate, m. p. 161°, and the latter crystallised from benzene–light petroleum in prisms, m. p. 87°, alone or in admixture with authentic tetrahydropyran-4-carboxylic acid.

Fraction B slowly deposited crystals of 4 : 4′-*bistetrahydro-4-pyranyl* (II), which crystallised from water in transparent flat prisms, m. p. 67° (Found : C, 70·3; H, 10·0. $C_{10}H_{18}O_2$ requires C, 70·5; H, 10·1%). The compound sublimed at 80°/0·05 mm. in dense squat prisms.

4 : 4′-Bistetrahydropyranyl (7·0 g.) was heated in a sealed tube at 100° for 10 hours with hydrobromic acid (50 ml.; saturated at 0°). The oily tetrabromide was isolated by dilution with water and extraction with ether. 1 : 1 : 2 : 2-*Tetra*-(2-*bromoethyl*)*ethane* (VI) was obtained (yield 16·0 g.) as a pale yellow oil, b. p. 173—175°/0·05 mm., n_D^{25} 1·5608 (Found : C, 26·5; H, 3·85; Br, 69·4. $C_{10}H_{18}Br_4$ requires C, 26·2; H, 3·95; Br, 69·8%). Treatment of the tetrabromide with an excess of alcoholic trimethylamine for 3 hours at 100° yielded large cubic crystals of *ethane*-1 : 1 : 2 : 2-*tetra*(*ethyl*-2-*trimethylammonium*) *tetrabromide* (VII). This separated from methanol in small prisms, m. p. >360°, soluble in water (Found : C, 37·8; H, 8·0; N, 8·0; Br, 46·1. $C_{22}H_{54}N_4Br_4$ requires C, 38·0; H, 7·9; N, 8·1; Br, 46·1%). Addition of an excess of alcoholic dimethylamine to the tetrabromoethylethane (VI) led to an exothermic reaction and precipitation of a salt. This was separated after 48 hours and was crystallised from methanol. 1 : 1 : 1′ : 1′-*Tetramethyl*-4 : 4′-*dipiperidyl dibromide* (VIII) forms small prisms, m. p. >360° (Found : C, 43·5; H, 7·8; N, 7·3; Br, 41·1. $C_{14}H_{30}N_2Br_2$ requires C, 43·4; H, 7·8; N, 7·3; Br, 41·3%).

Ethane-1 : 1 : 2 : 2-*tetra-acetic acid* (3 : 4-*biscarboxymethyladipic acid*) (I). 4 : 4′-Bistetrahydropyranyl (2 g.) was added slowly to a stirred solution of nitric acid (15 ml.; *d* 1·42) and a trace of vanadium pentoxide, at 30° (cooling). After 3 hours the acid was removed in a vacuum-desiccator over potassium hydroxide. Trituration of the gummy product with dry ether yielded 1·0 g. of solid *ethane*-1 : 1 : 2 : 2-*tetra-acetic acid*, which crystallised from glacial acetic acid in prisms, m. p. 212—213° [Found : C, 45·5; H, 5·2%; equiv. (tetrabasic), 65·0. $C_{10}H_{14}O_8$ requires C, 45·8; H, 5·3%; equiv., 65·5]. With boiling acetic anhydride the acid yielded an *anhydride*, needles from acetic anhydride, m. p. 205—208° (decomp.) (Found : C, 53·2; H, 4·55. $C_{10}H_{10}O_6$ requires C, 53·0; H, 4·5%).

2. *Unsuccessful Methods.*—The following experiments are illustrative, not exhaustive :

(i) Ethyl β-iodoglutarate, prepared from the β-bromo-ester (3·8 g.) and sodium iodide in dry acetone, was refluxed with ethyl glutaconate (3·5 g.) and freshly precipitated, dried copper (1·5 g.) in dry toluene (25 ml.). After 24 hours, 6·5 g. of ethyl glutaconate (b. p. 134—135°/16 mm.) were isolated from the product.

(ii) Tetraethyl αγ-dicarboxyglutaconate was prepared by the method of Ingold and Perrin (*J.*, 1921, **119**, 1591). 80 G. of its sodio-compound were decomposed by hydrochloric acid under ether. The ethereal layer was well washed with water and added to 20 g. of amalgamated aluminium foil covered by ether (1 l.). Water (20 ml.) was added dropwise during 3 minutes, and the mixture cooled with ice-water. After 1½ hours' stirring the alumina was removed by filtration and washed with ether. The combined ethereal solution, on distillation, yielded 68 g. (90%) of diethyl αγ-dicarbethoxyglutaconate. The very small high-boiling residue was hydrolysed : it yielded glutaric acid and not ethanetetra-acetic acid. A similar reduction of glutaconic ester gave glutaric ester (94%; b. p. 130°/11 mm., n_D^{20} 1·424). Glutaconononitrile was prepared by dehydrating β-hydroxyglutaronitrile with phosphoric oxide (Legrand, *Bull. Soc. chim. Belg.*, 1944, **53**, 166). Reaction with aluminium amalgam in the same way gave only unimolecular reduction to glutaronitrile together with some tarry material.

(iii) Ethyl acetonedicarboxylate on similar reduction with aluminium amalgam yielded 85% of low-boiling product, b. p. 117°/8 mm., n_D^{20} 1·438. There was no appreciable formation of a high-boiling pinacol. Similarly, with magnesium subiodide (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1927, **49**, 236) an 88% yield of low-boiling ester was obtained, b. p. 105°/0·8 mm., n_D^{17} 1·441. The product in both cases was presumably β-hydroxyglutaric ester but was not identified.

(iv) Malonic ester (17 g.) was added to sodium ethoxide (2 mols.; from 2·3 g. of sodium and 100 ml. of ethanol), followed by a solution of *trans-trans*-muconic ester (10 g.) in ethanol (50 ml.). After a week at room temperature the liquid was poured on ice and acid, and the product isolated in the usual way. Distillation yielded 5 g. of malonic ester and 13 g. (72%) of ethyl β-dicarbethoxymethyl-αβ-dihydromuconate, b. p. 195—205°/1 mm. (cf. Farmer, *loc. cit.*).

(v) Cyanoacetamide (8·4 g.) was dissolved in 40 ml. of warm water; 12·7 g. of glyoxal sodium bisulphite compound were then added, followed by a solution of potassium hydroxide (5·8 g.) in water (25 ml.). The mixture became homogeneous, then deep brown. Next morning, the product was freed from most of the water by vacuum-distillation, treated with 50 ml. of concentrated hydrochloric acid and 50 ml. of water, and boiled under reflux for 5 hours. Continuous ether-extraction of the product gave a small amount of gummy solid which on high-vacuum sublimation yielded a crystalline solid, m. p. 125—130°, which crystallised from chloroform. It was free from nitrogen and acid to bicarbonate (Found: C, 35·3; H, 4·9%). As it was clearly not ethanetetra-acetic acid it was not further examined.

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