546. *Acetals of Glutardialdehyde. The Preparation of* 1 : 1 : 5 : 5-*Tetraethoxy-* and 1 : 1 : 5 : 5-*Tetra*-n-*butoxy-pentanes.**

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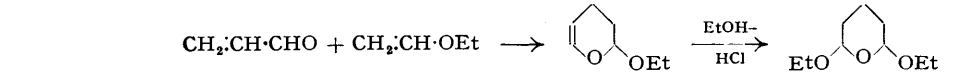
Reaction of glutardialdoxime with ethyl nitrite and treatment of the product with ethanolic hydrogen chloride and calcium chloride yielded, contrary to Baudart's findings (*Bull. Soc. chim.*, 1944, **11**, 336), only a minor amount of 1 : 1 : 5 : 5-tetraethoxypentane, the main products being ethyl 4 : 4-diethoxybutane-1-carboxylate and 2 : 6-diethoxytetrahydropyran. The last was synthesized from acraldehyde and ethyl vinyl ether, by way of 6-ethoxy-Δ^2-dihydropyran, and was converted into 1 : 1 : 5 : 5-tetraethoxypentane by reaction with excess of ethanolic hydrogen chloride. 1 : 1 : 5 : 5-Tetra-*n*-butoxypentane was similarly obtained from acraldehyde and *n*-butyl vinyl ether by way of 6-*n*-butoxy-Δ^2-dihydropyran and 2 : 6-di-*n*-butoxytetrahydropyran.

The only reported synthesis of an acetal of glutardialdehyde is that of the bisdiethyl acetal, 1 : 1 : 5 : 5-tetraethoxypentane (Baudart, *Bull. Soc. chim.*, 1944, **11**, 336), in which pyridine is converted into glutardialdoxime by way of 1 : 4-dihydropyridine by Shaw's method (*J.*, 1925, 215; 1937, 301): the dioxime is decomposed with ethyl nitrite at 0°, and the unstable glutardialdehyde produced is converted directly into its bisdiethyl acetal. No elementary analyses are recorded, however, for the product.

An acetal of glutardialdehyde was required for another investigation and the preparation of the bisdiethyl acetal was therefore attempted along the above lines. The decomposition of the dioxime with ethyl nitrite, however, invariably proved troublesome. Initiation of the reaction was difficult and seemed to depend very much on the moisture content of the oxime. When the latter had been dried in an oven (at 105°) the reaction was always more difficult to start than when the dioxime was air-dried, even though the melting point was not altered. Addition of a small amount of water and warming to 5—10° proved helpful in ensuring a fairly rapid commencement of the reaction, which then proceeded satisfactorily at about 0°. Treatment of the crude dialdehyde solution thus obtained with ethanolic hydrogen chloride and calcium chloride and isolation of the products, however, always gave rise to two main fractions, the amounts and proportions of which were very variable.

The lower-boiling fraction was shown to be the hitherto unknown 2 : 6-diethoxytetrahydropyran by elementary analyses, molecular-weight determinations, absence of aldehyde, ester, lactone, and hydroxyl groups, determination of oximation equivalent, conversion into glutardialdehyde bis-2 : 4-dinitrophenylhydrazone, and conversion into 1 : 1 : 5 : 5-tetraethoxypentane by excess of ethanolic hydrogen chloride. Its infra-red absorption spectrum was also compatible with the above formulation. It was synthesized by treating acraldehyde with ethyl vinyl ether under pressure (cf. B.P. Appln. 14678/48 to N.V. de Bataafsche Petroleum Maatschappij), to form 6-ethoxy-Δ^2-dihydropyran (subsequently prepared by Longley and Emerson, *J. Amer. Chem. Soc.*, 1950, **72**, 3079) which was then treated with ethanol in the presence of hydrogen chloride:



The higher-boiling fraction was shown to be ethyl 4 : 4-diethoxybutane-1-carboxylate containing a little 1 : 1 : 5 : 5-tetraethoxypentane. Alkaline hydrolysis, followed by acid hydrolysis, yielded 3-formylpropane-1-carboxylic acid, which was characterized as its 2 : 4-dinitro- and *p*-nitro-phenylhydrazones, identical with synthetic samples obtained from authentic 3-formylpropane-1-carboxylic acid. The latter was prepared from *cyclo*pentanone by Treibs's method (*Ber.*, 1939, **72**, 1194). A little glutardialdehyde, which was characterized as its bis-2 : 4-dinitrophenylhydrazone, was also formed in the acid hydrolysis.

The use of alkyl nitrites or nitrous fumes to convert oximes into the corresponding free carbonyl compounds, particularly in circumstances where mineral acids cannot be employed,

* Part of this work is described in B.P. Appln. 11,261/50.

is well known (Claisen and Manasse, *ibid.*, 1888, **21**, 2176; 1889, **22**, 526, 530; Harries, *ibid.*, 1901, **34**, 1488; von Braun and Danziger, *ibid.*, 1913, **46**, 110) but there appear to be no references to the formation of esters as by-products in this type of reaction. The ethyl 4 : 4-diethoxybutane-1-carboxylate may have arisen from partial oxidation of the intermediate glutardialdehyde, followed by esterification and acetal formation, but this oxidation could hardly have been due to atmospheric oxygen since a nitrogen atmosphere was used initially and nitrous oxide was evolved throughout the reaction of the oxime with the ethyl nitrite, thus providing a cover of inert gas.

The 2 : 6-diethoxytetrahydropyran, which may be regarded as a cyclodehydration product of the bishemiacetal of glutardialdehyde, probably arose during acetal formation from the crude glutardialdehyde solution with ethanolic hydrogen chloride and calcium chloride, thus demonstrating the relative ease of formation and stability of this ring structure. Further evidence for the stability of the compound was provided by the recovery of some unchanged material when it was treated at room temperature with a large excess of ethanol containing hydrogen chloride to convert it into the desired 1 : 1 : 5 : 5-tetraethoxypentane. The latter reaction enabled the tetraethoxy-compound to be prepared either from glutardialdoxime by a modified version of Baudart's method or from acraldehyde and ethyl vinyl ether by way of 6-ethoxy-Δ^2-dihydropyran. The latter route is more attractive as the overall yields are higher, and, as it is obviously possible to proceed in one step from the 6-ethoxy-Δ^2-dihydropyran to the tetraethoxy-compound, 1 : 1 : 5 : 5-tetraethoxypentane can thus be prepared in two stages from acraldehyde and ethyl vinyl ether.

More recently the route from acraldehyde has been used for the preparation of 1 : 1 : 5 : 5-tetra-*n*-butoxypentane. 6-*n*-Butoxy-Δ^2-dihydropyran was prepared from acraldehyde and *n*-butyl vinyl ether by the method of Longley and Emerson (*loc. cit.*) and treated with a molecular proportion of *n*-butanol in the presence of acid at 30—40°, to give 2 : 6-di-*n*-butoxytetrahydropyran in 73% yield. Ring scission with excess of butanol containing hydrogen chloride at 40° for 2 days was incomplete, about one-half of the dibutoxy-compound being recovered unchanged, but 1 : 1 : 5 : 5-tetra-*n*-butoxypentane was isolated from the product in 31% yield (65% after allowance for recovered starting material).

Experimental.

M. p.s and b. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss of Oxford.

Glutardialdoxime.—Glutardialdoxime, m. p. 175°, was prepared from pyridine by Shaw's method (*locc. cit.*). With ethanolic 2 : 4-dinitrophenylhydrazine hydrochloride solution it gave the bis-2 : 4-dinitrophenylhydrazone, as tiny brownish-yellow needles, m. p. 186—187° (from acetic acid) (Found : C, 44·85, 44·85; H, 3·35, 3·5; N, 24·3. Calc. for $C_{17}H_{16}O_8N_8$: C, 44·35; H, 3·5; N, 24·3%) (Shaw, *J.*, 1937, 301, gives m. p. 169—172°).

Reaction of Glutardialdoxime with Ethyl Nitrite (cf. Baudart, *loc. cit.*).—Glutardialdoxime (60 g.) and ethyl nitrite (80 g.; *Org. Synth.*, Coll. Vol. II, p. 204) were added alternately in small portions, as fast as reaction occurred, to a stirred mixture of 95% ethanol (17 c.c.), water (*ca.* 2 c.c.) and acetic acid (1·7 c.c.) which was kept under nitrogen and cooled from time to time in solid carbon dioxide–alcohol to keep its temperature at about 0°. The reaction started sluggishly after gentle warming to 5—10° but after a time proceeded quite readily at 0°. When all the reactants had been added the mixture was stirred until all the oxime had dissolved, ethanol (45 c.c.) containing anhydrous hydrogen chloride (1·5 g.) was added slowly, and then finely-powdered anhydrous calcium chloride (13·5 g.) was stirred in. The mixture was kept at 0° for 5 hours, then at room temperature for 48 hours, and extracted several times with light petroleum (b. p. 40—60°). The combined extracts were washed with water, dried (K_2CO_3), and evaporated *in vacuo*, and the oil obtained was distilled *in vacuo*, distillate (36 g.) of boiling-range 80—140°/12 mm. being collected. (The weight of crude material obtained in different experiments varied from 45 to 80% of the initial weight of glutardialdoxime.) Fractionation of this distillate through a jacketed glass column (25 × 1·5 cm.) packed with single-turn glass helices gave two main fractions : (A) 13 g., b. p. 79—80°/11 mm., n_D^{20} 1·4291, and (B) 15 g., b. p. 120—124°/13 mm., n_D^{20} 1·4220—1·4228.

Fraction (A) contained traces of an ester from which it was freed by refluxing it with alcoholic N-potassium hydroxide, dilution with water, ether-extraction, drying (Na_2SO_4), evaporation, and fractionation of the residual oil *in vacuo*. 2 : 6-*Diethoxytetrahydropyran* was obtained as a colourless liquid, b. p. 82°/13 mm., n_D^{20} 1·4290, d_4^{20} 0·9673 {Found : C, 62·15; H, 10·35%; *M* (cryoscopic in camphor), 181; oximation equiv., 91; $[M]_D^{20}$ 46·43. $C_9H_{18}O_3$ requires C, 62·05; H, 10·4%; *M*, 174; oximation equiv., 87; $[M]_D^{20}$ 46·50}, which did not react with Tollens's reagent, with boiling alcoholic N-potassium hydroxide, or with hot acetic anhydride in pyridine. Its infra-red absorption spectrum confirmed the absence of functional groups other than C–O–C. On treatment with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride solution it gave glutardialdehyde bis-2 : 4-dinitrophenylhydrazone, m. p. 186° (from acetic acid), undepressed on admixture with an authentic specimen.

Fraction (B) (sap. equiv., 233·5; oximation equiv., 193) consisted mainly (80—90%) of ethyl 4 : 4-diethoxybutane-1-carboxylate contaminated with a little 1 : 1 : 5 : 5-tetraethoxypentane. Hydrolysis of a sample (0·6 g.) of the fraction with boiling alcoholic N-potassium hydroxide solution

(10 c.c.) for 1 hour, neutralisation with N-sulphuric acid, and addition of aqueous 2 : 4-dinitrophenylhydrazine hydrochloride solution gave a precipitate which was separated into sodium hydrogen carbonate-soluble and -insoluble derivatives. The soluble derivative was *3-formylpropane-1-carboxylic acid* 2 : 4-*dinitrophenylhydrazone* and crystallised from 80—90% ethanol as small golden-yellow needles, m. p. 139—140° (after sintering at 125°) (Found : C, 44·75; H, 4·25; N, 18·8. $C_{11}H_{12}O_6N_4$ requires C, 44·6; H, 4·1; N, 18·9%), undepressed on admixture with an authentic specimen (Found : C, 44·45; H, 4·15%) prepared from 3-formylpropane-1-carboxylic acid which was synthesized from *cyclo*pentanone by Treibs's method (*loc. cit.*). The bicarbonate-insoluble derivative was glutardialdehyde bis-2 : 4-dinitrophenylhydrazone, m. p. 186° (from acetic acid), undepressed on admixture with an authentic specimen. Similar hydrolysis and treatment of the hydrolysate with *p*-nitrophenylhydrazine hydrochloride gave, as a bicarbonate-soluble derivative, 3-formylpropane-1-carboxylic acid *p*-nitrophenylhydrazone, golden-yellow crystals, m. p. 147—148°, from dilute ethanol (Harries and Tank, *Ber.*, 1908, **41**, 1708, give m. p. 148·5°). A mixed m. p. with synthetic 3-formylpropane-1-carboxylic acid *p*-nitrophenylhydrazone, prepared from authentic 3-formylpropane-1-carboxylic acid (see above), was also 147—148°.

Conversion of 2 : 6-*Diethoxytetrahydropyran into* 1 : 1 : 5 : 5-*Tetraethoxypentane.*—Ethanol (80 c.c.) containing anhydrous hydrogen chloride (2·4 g.) was added to 2 : 6-diethoxytetrahydropyran (21 g.), and the mixture was kept for 3 days at room temperature. Ethanolic sodium ethoxide was added cautiously to the resultant deep red solution until it was just alkaline and the excess of alkali was neutralised with carbon dioxide. The ethanol was distilled off and the residual oil was distilled *in vacuo*, distillate (22 g.) of boiling-range 90—145°/19 mm. being obtained. Fractionation of this distillate *in vacuo* through the column described above gave a small fore-run of unchanged starting material and then the desired 1 : 1 : 5 : 5-tetraethoxypentane as a colourless oil (9·9 g.), b. p. 133—134°/13 mm., n_D^{20} 1·4204 (Found : C, 62·6; H, 11·15%; oximation equiv., 128. Calc. for $C_{13}H_{28}O_4$: C, 62·85; H, 11·35%; oximation equiv., 124). Baudart (*loc. cit.*) gives b. p. 97—100°/3 mm., n_D^{25} 1·4232, d^{25} 0·9009. On treatment with aqueous-alcoholic 2 : 4-dinitrophenylhydrazine sulphate solution the tetraethoxy-compound gave glutardialdehyde bis-2 : 4-dinitrophenylhydrazone, m. p. 186—187° (from acetic acid), undepressed on admixture with an authentic specimen.

Modified Preparation of 1 : 1 : 5 : 5-*Tetraethoxypentane from Glutardialdoxime.*—Glutardialdoxime (120 g.) and ethyl nitrite (160 g.) were added alternately in small portions to a stirred, cooled mixture of 95% ethanol (33 c.c.), acetic acid (3·3 c.c.), and water (10 c.c.) as described above, the resultant solution was treated with ethanol (*ca.* 80 c.c.) containing anhydrous hydrogen chloride (4 g.), and anhydrous calcium chloride (27 g.) was added. The mixture was kept at 0° for a few hours, then at room temperature for two days, neutralised with ethanolic sodium ethoxide, made slightly acid with acetic acid, evaporated to a small bulk *in vacuo*, diluted with light petroleum (b. p. 40—60°) and water, and agitated. The aqueous layer was separated and extracted again with light petroleum, and the combined extracts were dried (K_2CO_3) and distilled. The distillate (91·5 g.) of boiling range 80—160°/13 mm. was mixed with a solution of potassium hydroxide (10 g.) in ethanol (100 c.c.) and water (10 c.c.), the mixture was refluxed for 1½ hours, almost neutralised with 0·2N-sulphuric acid (added cautiously with vigorous stirring), filtered, concentrated *in vacuo*, diluted with ether and water, and agitated, and the ethereal extract was separated. Evaporation of the dried (K_2CO_3) ethereal solution gave an oil which was dissolved in ethanol (500 c.c.) containing anhydrous hydrogen chloride (15 g.), the solution was kept at room temperature for 2—3 days, neutralised with ethanolic sodium ethoxide, filtered, concentrated *in vacuo*, and extracted with light petroleum (b. p. 40—60°), and the extracts were washed with water, dried (K_2CO_3), and evaporated. The residual oil was distilled and the distillate (68·9 g.), boiling range 90—140°/12 mm., was fractionated through the column described above, yielding 2 : 6-diethoxytetrahydropyran (9·1 g.), b. p. 80°/11·5 mm., n_D^{20} 1·4295, and 1 : 1 : 5 : 5-tetraethoxypentane (38·0 g.), b. p. 133°/12 mm., n_D^{20} 1·4201, d_4^{20} 0·9135 (Found : C, 63·2; H, 11·45%; $[M]_D^{20}$ 68·82. Calc. for $C_{13}H_{28}O_4$: C, 62·85; H, 11·35%; $[M]_D^{20}$, 68·81), as colourless liquids.

6-*Ethoxy*-Δ^2-*dihydropyran.*—A mixture of acraldehyde (112 g.), ethyl vinyl ether (144 g.), and quinol (2·4 g.) was heated, in portions, in sealed tubes at 185—195° for 2½—3 hours. The pale yellow products were combined and distilled *in vacuo*, distillate (207 g.) of boiling range 30—125°/125 mm. (mainly 84—90°/125 mm.) being collected; the residue was 28 g. The distillate was fractionated *in vacuo* through a helices-packed, jacketed, glass column (35 × 2 cm.), whereupon 6-ethoxy-Δ^2-dihydropyran, was obtained as a colourless liquid (147·7 g.), b. p. 66°/52 mm., n_D^{20} 1·4420 (Found : C, 65·8; H, 9·15. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·45%) (Longley and Emerson, *loc. cit.*, subsequently found b. p. 42°/16 mm. n_D^{25} 1·4376). A test portion, on treatment with an alcoholic solution of 2 : 4-dinitrophenylhydrazine containing sulphuric acid, gave glutardialdehyde bis-2 : 4-dinitrophenylhydrazone, m. p. 185—186° (from acetic acid), undepressed on admixture with an authentic specimen.

2 : 6-*Diethoxytetrahydropyran.*—A mixture of 6-ethoxy-Δ^2-dihydropyran (128 g.) and ethanol (48 c.c.) was cooled to 0°, stirred, and treated cautiously with a solution of hydrogen chloride (0·63 g.) in absolute ethanol (10 c.c.). Heat was liberated and ice-cooling was employed. The mixture was kept at room temperature overnight, then made just alkaline by the cautious addition of concentrated ethanolic sodium ethoxide, and the excess of alkali neutralised with carbon dioxide. The product was distilled *in vacuo*, distillate of boiling-range 50°/50 mm. to 140°/12 mm. being collected; the residue was 12 g. Fractionation of the distillate through the column described above gave 2 : 6-diethoxytetrahydropyran (83·4 g.), b. p. 78—79°/11 mm., n_D^{20} 1·4297, d_4^{20} 0·9677, identical with that obtained above from glutardialdoxime.

2 : 6-*Di*-n-*butoxytetrahydropyran.*—Concentrated hydrochloric acid (0·5 c.c.; *d* 1·18) was added to a cooled, stirred mixture of *n*-butanol (29 g.) and 6-*n*-butoxy-Δ^2-dihydropyran (61 g.; Longley and Emerson, *loc. cit.*), and the resultant solution was kept at 30—40° for 22 hours. Addition of anhydrous sodium acetate (1 g.), followed by fractional distillation *in vacuo*, gave first unchanged butanol and then

the desired 2 : 6-*di*-n-*butoxytetrahydropyran* as a colourless mobile liquid (66 g., 73%), b. p. 126°/9 mm., n_D^{20} 1·4371 (Found : C, 68·1, 67·9; H, 11·7, 11·55. $C_{12}H_{26}O_3$ requires C, 67·8; H, 11·4%).

1 : 1 : 5 : 5-*Tetra*-n-*butoxypentane*.—Concentrated hydrochloric acid (3 c.c.; *d* 1·18) was added to a stirred mixture of *n*-butanol (185 g.) and 2 : 6-di-*n*-butoxytetrahydropyran (57·5 g.), and the resultant solution was kept at 40° for 2 days. The product was cooled, made slightly alkaline with a solution of sodium butoxide in butanol, and fractionated *in vacuo* to give : (i) butanol, (ii) unchanged 2 : 6-di-*n*-butoxytetrahydropyran (*ca.* 30 g.), and (iii) 1 : 1 : 5 : 5-*tetra*-n-*butoxypentane* (28·3 g.), b. p. 197·5—198·5°/9 mm., n_D^{20} 1·4343 (Found : C, 70·1, 70·15; H, 12·4, 12·2. $C_{21}H_{44}O_4$ requires C, 69·9; H, 12·3%).

Addition of a few drops of the tetrabutoxy-compound to aqueous-alcoholic 2 : 4-dinitrophenylhydrazine sulphate gave glutardialdehyde bis-2 : 4-dinitrophenylhydrazone, m. p. 186—187° (from acetic acid), undepressed on admixture with an authentic specimen.

The authors are indebted to Mr. A. R. Philpotts and Mr. W. Thain for the determination and interpretation of infra-red absorption data, to Mr. D. A. Burch for assistance with part of the experimental work, and to the Directors of the Distillers Co., Ltd., for permission to publish this work.

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