

203. $\alpha\alpha'$ -Di-*n*-propyl- and -butyl-glutaric Acid, and Some Derived Amido-acids.

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Some *N*-substituted glutaramic acids have been synthesised by treatment of the *meso*-anhydrides with primary amines, and their antibacterial activities *in vitro* have been determined.

PREVIOUS work¹ on $\alpha\alpha'$ -dialkylglutaric acids has now been extended to *N*-substituted $\alpha\alpha'$ -di-*n*-propyl- and -butyl-glutaramic acid.

The required dicarboxylic acids were obtained by hydrolysis and decarboxylation of the corresponding ethyl tetracarboxylates. The acids were split into their optically inactive forms, and in the case of the dipropyl acid these were identified. Some racemates of derived amic acids were prepared by condensation of aniline and *p*-chloroaniline with equimolecular amounts of the appropriate *meso*-anhydride in dry chloroform.

The amic acids were more active against *M. tuberculosis in vitro* than any of the seventeen previously tested.¹ Similar compounds, with 5—8 carbon atoms in their side chains (a total continuous chain length of 13—19 carbon atoms), might possess optimum antitubercular activity, as Barry and his co-workers² found for α -mono- and $\alpha\alpha'$ -di-alkyl-succinic acids and their half-esters and amic acids, the potencies being much reduced

¹ Evans and Roberts, *J.*, 1957, 2104.

² Barry, *Nature*, 1945, **156**, 48; 1946, **158**, 863; Barry and Twomey, *Proc. Roy. Irish Acad.*, 1947, **51**, 137; Barry and McNally, *ibid.*, p. 145.

however in presence of serum. (Monoalkylglutamic acids with side chains up to C_{16} showed little activity.³)

The amic acids were slightly active against some other bacteria and protozoa.

EXPERIMENTAL

Ethyl Nonane-4,4,6,6-tetracarboxylate.—This ester was best prepared from ethyl propane-1,1,3,3-tetracarboxylate¹ by three treatments with sodium and n-propyl iodide in dry ethanol. The red oil was distilled through a heated 15-in. column (Fenske helices), with reflux-ratio control. The viscous yellow fraction of b. p. 183—184°/1.3 mm. was cooled with solid carbon dioxide, and the ester crystallised twice from light petroleum (b. p. 40—60°), forming plates (32%), m. p. 46° (lit.,⁴ 42°) $[R_L]_D$, 104.3 (calc. 105.8) (Found: C, 60.0; H, 8.9. $C_{21}H_{36}O_8$ requires C, 60.5; H, 8.7%).

Ethyl Undecane-5,5,7,7-tetracarboxylate.—Several possible methods of preparation were tried.⁵ Best yields were obtained when the above tetraester was added to sodium (2 equiv.) in dry ethanol, followed by a little dry sodium iodide and n-butyl bromide (2.6 equiv.), and the products were worked up in ether. Two distillations, as above, gave 27% of an oil, b. p. 174—176°/1.3 mm., $[R_L]_D$, 116.2 (calc., 115.0) (Found: C, 61.7; H, 8.8. Calc. for $C_{23}H_{40}O_8$: C, 62.1; H, 9.1%).

α' -Dipropylglutaric Acid.—Hydrolysis of the nonanetetracarboxylate was much more difficult than that of the lower homologues.¹ The ester (130 g.) was heated with 50% v/v sulphuric acid (600 ml.) for 72 hr. under reflux with stirring, then cooled and diluted with water to 5 l. The mixture of tetra- and di-acids obtained by ether-extraction was heated at 200° *in vacuo*, and the resultant red-brown material crystallised four times from light petroleum (b. p. 80—100°) and twice from this solvent containing 15% of ether; this gave diacids (mixture) (57%), m. p. 76—92° (Found: C, 61.2; H, 9.2. Calc. for $C_{11}H_{20}O_4$: C, 61.1; H, 9.3%).

In an attempt to obtain the *meso*-anhydride directly,¹ some of this mixture was heated slowly to expel all the water. The anhydride, which distilled next (b. p. 300°/740 mm.), was treated to remove any unchanged acid, then thrice distilled, giving 44.9% of colourless oil, b. p. 168°/10 mm., that did not crystallise. When small portions were condensed with equimolecular amounts of recrystallised sulphanilamide in dry acetone, and with aniline or *p*-chloroaniline in dry chloroform, and the derivatives were crystallised [from ethanol-light petroleum (b. p. 80—100°) and aqueous ethanol, respectively] they gave mixed products. *E.g.*, in the last case, 0.514 g. of anhydride gave needle clusters (0.131 g.; m. p. 65—80°) and small needles (0.320 g.; m. p. 103—120°), analysis of which indicated a mixture of racemates (Found: C, 62.4; H, 7.3. Calc. for $C_{17}H_{24}ClNO_3$: C, 62.7; H, 7.4%). Hydrolysis of the remaining anhydride gave an acid of m. p. 71—93°. Evidently these α' -dialkyl-acids (except the dimethyl)^{4,6} readily form mixtures of anhydrides which distil together.

Fractional crystallisation. The unresolved acid (25.6 g.) was crystallised from glacial acetic acid until a crude high-melting form appeared. The more soluble fractions were then crystallised from light petroleum (750 ml.; b. p. 80—100°), giving twelve fractions, which varied from the low-melting form (83—85°) through mixtures to a crude high-melting acid (108—113°). Suitable manipulation of these gave, after 33 crystallisations, diamond-shaped plates (3.83 g.; m. p. 116°), and long needles (6.15 g.; m. p. 86°) of the acids. Most of the remainder gave mixtures of crystals. Since this work, Ebersson⁷ has obtained fractions of m. p. 110—112 and 81—82° by crystallisation from ethyl acetate-light petroleum (Found, for the high-melting acid: C, 60.8; H, 9.3; for the low-melting acid: C, 60.9; H, 9.1. $C_{11}H_{20}O_4$ requires C, 61.1; H, 9.3%).

Resolution. The acid of m. p. 86° (1.5 g.) was treated with (–)-brucine in warm ethanol. Vacuum-concentration gave an oil, which was washed with warm ether and gave, after further treatment, a crystalline salt. Three crystallisations from ethanol (20%) gave small colourless plates (0.803 g.), m. p. 128.5°, $[\alpha]_D^{20}$ –22.4° (4.5% in ethanol). Treatment with 0.1N-hydrochloric acid (13.6 ml.) and ether-extraction gave an acid (0.267 g.), $[\alpha]_D^{20}$ +2.70° (4.44% in

³ Roberts and Shaw, *J.*, 1950, 2842.

⁴ Guthzeit and Dressel, *Annalen*, 1890, 256, 171; Levina and Godovikov, *Zhur. obshechi Khim.*, 1954, 24, 1242.

⁵ Evans, Ph.D. Thesis. London, 1959, p. 163.

⁶ Möller, Lund Univ. Årsskrift, N.F. Ård. 2, 1919, 15, No. 6.

⁷ Ebersson, *Acta Chem. Scand.*, 1958, 12, 314.

ethanol). Concentration of the main mother-liquor gave mixtures of salts, and thence acids of negligible rotation, but 0.2 g. of an acid with $[\alpha]_D^{20} -2.3^\circ$ (4.15% in ethanol) was obtained finally. The acid of m. p. 86° was therefore the racemic form.

Similar treatment did not resolve the acid of m. p. 116° . Its brucine salt had m. p. 119° (decomp.), $[\alpha]_D^{20} -28.8^\circ$ (7.6% in ethanol).

αα'-Dibutylglutaric Acid.—This acid was obtained from the undecanetetracarboxylate by hydrolysis with ethanolic potassium hydroxide, purification of the tetra-acid through its sodium salt, decarboxylation at 200° *in vacuo* with precautions against frothing, distillation of the mixture of anhydrides (b. p. $187-190^\circ/11$ mm.), hydrolysis (18 hours' boiling with water), removal of unhydrolysed anhydride by washing of the disodium salt with ether, and acidification. It gave 19.2% of optically impure diacid.

This product, in ether, was washed with water, dried, and recovered. After a week at room temperature it contained some crystals. After four crystallisations from light petroleum (b. p. $80-100^\circ$), with hot filtration, they gave the *dibutyl-acid*, as plates, m. p. 94° (Kögl *et al.*⁸ showed that this was a *meso*-acid; and Ebersson⁷ obtained it; neither gave an analysis) (Found: C, 64.0; H, 9.9. $C_{13}H_{24}O_4$ requires C, 63.9; H, 9.9%).

meso-αα'-Dipropylglutaric Anhydride.—The acid of m. p. 116° (1.502 g.) was heated for 3 hr. with acetyl chloride (10 ml.), the excess being then removed under a vacuum. The *anhydride* (1.22 g., 89%), b. p. $166^\circ/10$ mm., did not crystallise after five hr. at -16° (Found: C, 66.3; H, 9.2. $C_{11}H_{18}O_3$ requires C, 66.6; H, 9.2%).

meso-αα'-Dibutylglutaric Anhydride.—This was obtained similarly, but from the *meso*-dibutyl-acid (0.338 g.). The yellow residue was distilled, giving an *anhydride* (0.242 g., 77.4%), b. p. $188-190^\circ/11$ mm. (Found: C, 69.1; H, 9.8. $C_{13}H_{22}O_3$ requires C, 69.0; H, 9.8%).

N-Phenyl-αα'-dipropylglutaramic Acid.—Equimolecular amounts of the propyl *meso*-anhydride and dry freshly distilled aniline were mixed in dry chloroform, and kept for 2 hr. The resultant precipitate was thrice crystallised (from 40% ethanol) and gave the *amic acid* (63%), needles, m. p. 143.5° (Found: C, 70.0; H, 9.0; N, 4.9. $C_{17}H_{25}NO_3$ requires C, 70.1; H, 8.7; N, 4.8%).

αα'-Dibutyl-N-phenylglutaramic Acid.—Aniline (0.093 g.) and the *meso*-dibutyl-anhydride (0.226 g.) in chloroform (12 ml.) were heated on the steam-bath; evaporation then left an oil which solidified. Two crystallisations from 45% ethanol gave the *amic acid* as needles (0.236 g., 74%), m. p. 154.5° (Found: C, 71.2; H, 8.7; N, 4.3. $C_{19}H_{29}NO_3$ requires C, 71.4; H, 9.2; N, 4.4%).

N-p-Chlorophenyl-αα'-dipropylglutaramic Acid.—Similar use of *p*-chloroaniline and four crystallisations from 30% ethanol gave the *amic acid* as needles (53%), m. p. 154.5° (Found: C, 62.9; H, 7.6; Cl, 11.1; N, 4.6. $C_{17}H_{24}ClNO_3$ requires C, 62.7; H, 7.4; Cl, 10.9; N, 4.3%).

Antibiotic Properties.—The three *amic acids* were tested by standard screening methods. The *N*-phenyl derivatives were active up to 1 : 100,000 against *M. tuberculosis* H37Rv (Long's medium with 10% serum), and the *N-p*-chlorophenyl compound up to 1 : 32,000. At 1 : 1000 on blood agar, they all prevented the growth of *Cory. pyogenes* and *Haem. parapt.* The chlorophenylamide was also active against *Act. dermatonamus* and slightly against *Strept. othrix* and *Prot. vulg.* The anilic acids were slightly active against the first two of these. None showed antifungal activity (1 : 5000 on blood agar), but with protozoa each was active at 1 : 10,000, the first two being partly so at 1 : 100,000 (*E. histolytica*, strain M, in liver extract, marmite, horse serum, and rice starch, with phosphate buffer at pH 7.2).

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⁸ Kögl, Erxleben, Michaelis, and Visser, *Z. physiol. Chem.*, 1935, **235**, 181.