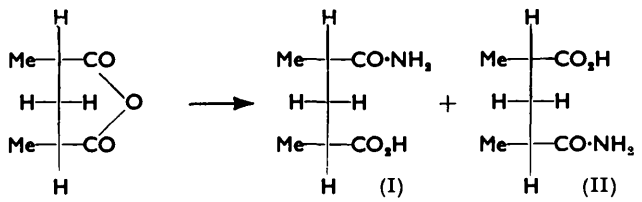
403. *Synthesis of Potential Antibacterial Agents. Part III.* Derivatives of Some αα′-Dialkylglutaric Acids.*

By D. W. S. Evans and John C. Roberts.

A number of substituted glutaramic acids have been synthesised (by treatment of the appropriate anhydrides with ammonia or primary amines), and their antibacterial activities *in vitro* have been determined.

In this paper we extend the work described in Part I [1] to derivatives of αα′-dimethyl- and αα′-diethyl-glutaric acids. All these derivatives possess, in addition to the acidic group, one of the following potential antibacterial groupings: carbamoyl, *N*-phenyl-, *N*-*p*-chlorophenyl-, *N*-*p*-sulphamoylphenyl-, *N*-2′-pyridyl-, or *N*-2′-thiazolyl-carbamoyl.

The required αα′-dialkylglutaric acids were obtained by hydrolysis and decarboxylation of the corresponding ethyl 1 : 3-dialkylpropane-1 : 1 : 3 : 3-tetracarboxylates. In order to avoid stereochemical complications in the synthesis of the dialkylglutaramic acids (see below) it was necessary to use either the racemic or the *meso*-anhydrides. We therefore chose to work, in the first instance, with the *meso*-anhydrides because they are more readily available. *meso*-αα′-Dimethylglutaric anhydride was prepared directly from the mixture of the concomitantly produced *meso*- and racemic acid by treatment with acetyl chloride.[2] A number of attempts to prepare *meso*-αα′-diethylglutaric anhydride by a direct method from the mixed acids were unsuccessful. Separation of the mixed acids into *meso*- and racemic forms was attempted by partition chromatography on a silica column,[3] but was abortive. We therefore separated the *meso*-acid by fractional crystallisation and converted it into the anhydride, a crystalline solid of low melting point (it had been reported [4] as an oil).



αα′-Dialkylglutaramic or *N*-substituted αα′-dialkylglutaramic acids were then obtained by treatment of the *meso*-anhydrides, in a dry organic solvent, with ammonia or primary amines. It should be emphasised that these derivatives are in the forms of single racemates (*e.g.*, I + II) since the *meso*-anhydride ring may open, with equal facility, in the two

* Part II, *J.*, 1952, 4935.

[1] Roberts and Shaw, *J.*, 1950, 2842.
[2] Auwers and Thorpe, *Annalen*, 1895, **285**, 327.
[3] Cf. Roberts and Selby, *J.*, 1951, 2335.
[4] (*a*) Reformatsky, *J. Russ. Phys. Chem. Soc.*, 1902, **34**, 357; (*b*) cf. Berner and Landmark, *Acta Chem. Scand.*, 1953, **7**, 1347.

possible ways. (Some *N*-substituted derivatives of glutaramic acid itself were also prepared.)

A few of the compounds investigated showed slight antibacterial activity.

Experimental

Starting Materials.—Ethyl propane-1 : 1 : 3 : 3-tetracarboxylate was prepared by Welch's method.[5] One fractionation of the crude material (through an externally heated 15" column of Fenske helices) gave a colourless oil (62% yield), b. p. 193°/9 mm. (Found : C, 54·2; H, 7·3. Calc. for $C_{15}H_{24}O_8$: C, 54·2; H, 7·3%). An alternative method [6] gave lower and variable yields. Ethyl pentane-2 : 2 : 4 : 4-tetracarboxylate was obtained by methylation of the foregoing ester; [7] two fractionations of the crude material yielded the pure ester (21% yield), b. p. 165°/1·2 mm. (Found : C, 56·4; H, 7·4. Calc. for $C_{17}H_{28}O_8$: C, 56·6; H, 7·8%). By using ethyl iodide, ethyl heptane-3 : 3 : 5 : 5-tetracarboxylate was similarly prepared : one fractional distillation and three crystallisations from light petroleum (b. p. 40—60°) gave the pure ester (33% yield), m. p. 60—61°, b. p. 194°/4 mm. (Found : C, 58·6; H, 8·2. Calc. for $C_{19}H_{32}O_8$: C, 58·7; H, 8·3%). The αα′-dialkylglutaric acids were obtained (96—97% yields) by hydrolysis and decarboxylation of the foregoing esters.[8]

meso-αα′-*Dimethylglutaric Anhydride.*—This was obtained from the mixture of *meso*- and racemic dimethylglutaric acids by the following modification of the method of Auwers *et al.*[2] The acid (1 g.) and acetyl chloride (2 ml.) were allowed to stand in an open tube in warm (50°) water. After the initial vigorous reaction had subsided, the tube was sealed and kept at 100° for 40 hr. The resultant brown liquid deposited a mass of needle-shaped crystals which were collected and, after having been kept *in vacuo* for 2 hr. over potassium hydroxide and phosphoric anhydride, were repeatedly recrystallised from dry ethyl acetate–light petroleum (b. p. 80—100°) to give prisms, m. p. 94—94·5° (yield 40%) (Found : C, 58·9; H, 6·9. Calc. for $C_7H_{10}O_3$: C, 59·1; H, 7·1%).

meso-αα′-*Diethylglutaric Anhydride.*—The *meso*-acid [separated by fractional crystallisation, initially from light petroleum (b. p. 80—100°), and subsequently from water [4b]] formed prisms, m. p. 119—120° (Found : C, 57·0; H, 8·2. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%). Treatment of this acid with acetyl chloride under reflux for ½ hr. led to an oil, which, when strongly cooled, deposited meso-αα′-*diethylglutaric anhydride* which recrystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 18° (67·4% yield) (Found : C, 63·3; H, 8·1. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%). It was readily soluble in ether and in benzene.

Preparation of Derivatives.—(i) *Amic acids.* Dry ammonia was passed into a solution of the anhydride (0·45 g.) in about forty times its weight of dry ether. The ether and excess of ammonia were removed. A solution of the residue in water (1 ml.) was acidified with 2N-hydrochloric acid. The clear solution was evaporated *in vacuo* at room temperature and the residue was powdered, dried, and exhaustively extracted with warm dry ethanol (5 × 5 ml.). The combined extracts were filtered, evaporated to 10 ml., and mixed with hot light petroleum (40 ml.; b. p. 80—100°). Two recrystallisations of the precipitated material yielded the pure amic acid.

(ii) N-*Phenyl- and* N-p-*chlorophenyl-glutaramic acids.* The freshly distilled amine (0·0017 mole) was added to a solution of the anhydride (0·0017 mole) in dry chloroform (10—20 ml.) and the precipitate was collected, washed with dry chloroform, and crystallised from a suitable solvent.

(iii) N-p-*Sulphamoylphenylglutaramic acids.* Equimolecular quantities of the anhydride and of recrystallised sulphanilamide were dissolved in the minimum of dry acetone. The acetone was removed on the steam-bath and the residue was recrystallised.

(iv) N-2-*Pyridylglutaramic acids.* These were prepared by a method similar to that described immediately above, but from recrystallised 2-aminopyridine and dry chloroform as solvent.

(v) N-2-*Thiazolylglutaramic acids.* Equimolecular quantities of the anhydride and of 2-aminothiazole [recrystallised from light petroleum (b. p. 100—120°)] were dissolved in a

[5] Welch, *J.*, 1931, 673.
[6] *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 290.
[7] Dressel, *Annalen*, 1890, **256**, 181.
[8] Auwers and Singhof, *Annalen*, 1896, **292**, 205.

minimum of dry chloroform. The solvent was evaporated and an ethereal solution of the residue was repeatedly extracted with 5% aqueous sodium carbonate solution. The combined aqueous extracts were acidified with 2N-hydrochloric acid, and the products were recrystallised.

Glutaramic acids. $R'NH\cdot CO\cdot CHR\cdot CH_2\cdot CHR\cdot CO_2H$.

No.	R	R′	Solvent for recrystn.	M. p.	Yield (%)
1	Me	H	EtOH–l. p.[c]	130°	26
2	Et	H	,,	130·5	22
3	H	C_6H_5	20% EtOH	127 [a]	14
4	Me	,,	,,	158 [b]	84
5	Et	,,	25% EtOH	133	63
6	H	*p*-Cl·C_6H_4	90% EtOH	134	41
7	Me	,,	20% EtOH	179	87
8	Et	,,	,,	173·5	61
9	H	*p*-$NH_2\cdot SO_2\cdot C_6H_4$	40% EtOH	191	24
10	Me	,,	15% EtOH	182	41
11	Et	,,	40% EtOH	191·5	44
12	H	2-Pyridyl	EtOH–l. p.[c]	194·5	48
13	Me	,,	80% EtOH	153	26
14	Et	,,	,,	125·5	25
15	H	2-Thiazolyl	85% EtOH	204	58
16	Me	,,	40% EtOH	176·5	33
17	Et	,,	,,	149	33

		Found (%)					Required (%)				
No.	Formula	C	H	N	Cl	S	C	H	N	Cl	S
1	$C_7H_{13}O_3N$	52·5	8·5	8·7	—	—	52·8	8·2	8·8	—	—
2	$C_8H_{17}O_3N$	58·0	9·3	7·9	—	—	57·7	9·2	7·5	—	—
5	$C_{15}H_{21}O_3N$	68·1	7·8	5·6	—	—	68·4	8·0	5·3	—	—
6	$C_{11}H_{12}O_3NCl$	54·9	5·1	5·7	14·7	—	54·7	5·0	5·8	14·7	—
7	$C_{13}H_{16}O_3NCl$	58·2	5·8	5·3	13·5	—	57·9	6·0	5·2	13·2	—
8	$C_{15}H_{20}O_3NCl$	60·5	6·9	4·4	12·4	—	60·5	6·8	4·7	11·9	—
9	$C_{11}H_{14}O_6N_2S$	46·0	4·9	10·0	—	11·6	46·1	4·9	9·8	—	11·2
10	$C_{13}H_{18}O_6N_2S$	49·9	6·1	9·0	—	9·8	49·7	5·8	8·9	—	10·2
11	$C_{15}H_{22}O_6N_2S$	52·9	6·5	8·3	—	9·6	52·6	6·5	8·2	—	9·4
12	$C_{10}H_{12}O_3N_2$	57·3	5·9	13·3	—	—	57·7	5·8	13·5	—	—
13	$C_{12}H_{16}O_3N_2$	61·1	6 7	11·8	—	—	61·0	6·8	11·9	—	—
14	$C_{14}H_{20}O_3N_2$	63·5	7·8	10·5	—	—	63·6	7·6	10·6	—	—
15	$C_8H_{10}O_3N_2S$	45·1	5·0	12·8	—	15·2	44·9	4·7	13·1	—	15·0
16	$C_{10}H_{14}O_3N_2S$	49·8	5·8	11·8	—	13·5	49·6	5·8	11·6	—	13·2
17	$C_{13}H_{18}O_3N_2S$	53·5	6·6	10·1	—	11·5	53·3	6·7	10·4	—	11·9

[a] Balbiano *et al.*[9] give m. p. 126—127°. [b] Auwers *et al.*[10] give m. p. 157°. [c] Ethanol-light petroleum (b. p. 80—100°).

Antibiotic Properties.—None of the derivatives was active against *M. tuberculosis* H37Rv.(Long's medium with 10% serum) at 1 : 3000, except no. 15 which was, however, inactive at 1 : 9000.

No. 13 at 1 : 5000 completely inhibited the growth (on blood-agar) of *Cory. pyogenes*. Slight activity was shown by some other of the derivatives against this organism and also against *H. parapertussis*.

None of the derivatives showed any significant antiprotozoal or antifungal activity and none (of eleven which were tested) was viricidal.

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[9] Balbiano and Angeloni, *Atti R. Accad. Lincei*, 1904, [5], **13**, 146.
[10] Auwers, Oswald, and Thorpe, *Annalen*, 1895, **285**, 236.