CHEMISTRY OF β-ARYL GLUTACONIC ACIDS.

Part III. Condensations with Phenolic Ethers (*Continued*).

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Introduction.

IN Part II of this series[1] a phenolic ether—*p*-cresol-ethylether—has been shown to add on to the double bond in a β-aryl-glutaconic acid to produce a ββ-diaryl-glutaconic acid. Dixit and Gokhale[2] have recently described the formation of a similar ββ-diaryl-glutaric acid in the condensation of phenol with acetone-dicarboxylic acid. In view of the stability of their compound, the structure (III) proposed by the authors seems to be untenable as such a compound would immediately lose water to form a neutral dilactone. Moreover, the condensation of dimethyl-oxalate or dimethyl-phthalate with the dimethyl ester of the glutaric acid, described by the authors to proceed in the Claisen's manner in comparison with the ββ-dimethyl-glutaric acid,[3] is quite unlikely, since the two free phenolic hydroxyls in the glutaric ester would first react with the sodium methoxide or sodium, thus inhibiting the reaction to proceed in the manner suggested. In view of this, it was thought desirable to see whether light could be thrown on the real nature of the compound in question by relating it to any of the glutaconic acids containing phenol or anisole in the β-position.

On carrying out the condensation of phenol with acetone-dicarboxylic acid under the conditions of Dixit and Gokhale,[2] a dicarboxylic acid, m.p. 235° C. (decomp.), has now been obtained, but this appears to be different from the one described by the authors, in that it does not give even a trace of the coumarin-4-acetic acid,[4] by the action of sulphuric acid, and that it did not produce any anhydride on thermal decomposition as the authors claimed to have observed, but lost carbon dioxide instead. On trying to synthesise the dicarboxylic acid, m.p. 235° C., from the known

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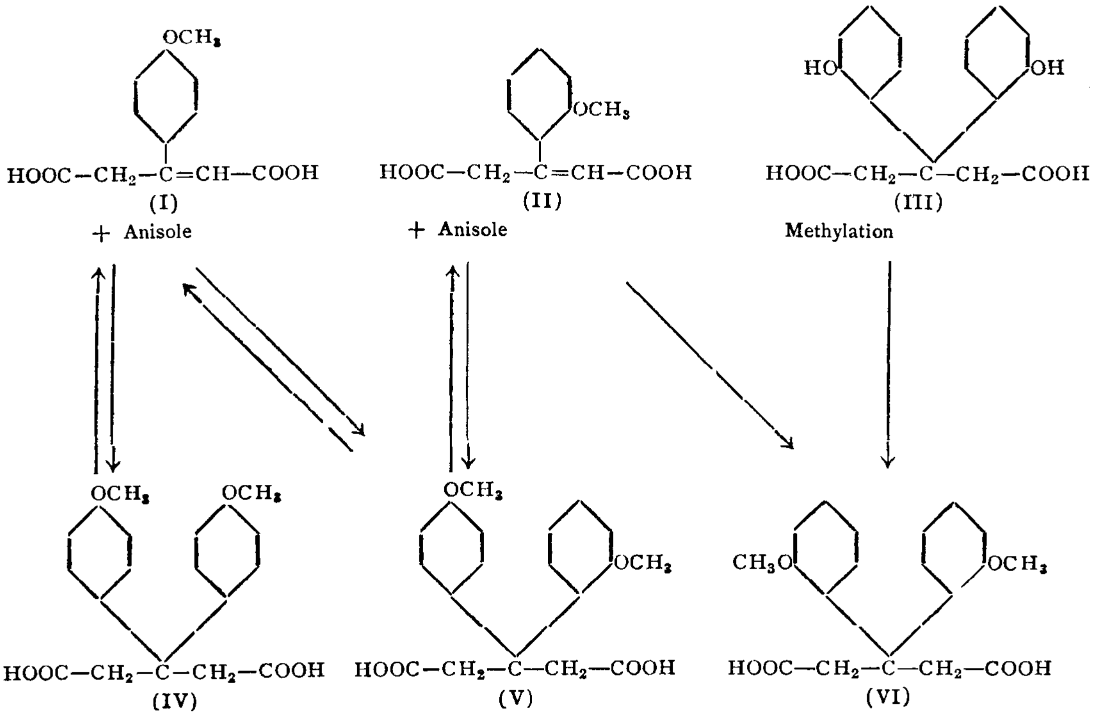
[1] Gogte, *Proc. Ind. Acad. Sci.*, (A), 1935, 1, 185–198.

[2] Dixit and Gokhale, *J. Uni. Bombay*, 1934, 3, 80–94.

[3] Dieckmann, *Ber.*, **32**, 1230 ; Komppa, *Annalen*, **368**, 126.

[4] Limaye, *J. Ind. Chem. Soc.*, 1927, **4**, 159.

β-4-hydroxy-phenyl-glutaconic acid,[5] by condensing it with phenol (compare Part II)[1] nothing could be obtained, the glutaconic acid itself having been decomposed apparently by sulphuric acid. Presuming this instability to be due to the presence of a phenolic hydroxyl in the glutaconic acid, it was proposed to see whether the dimethoxy derivative, m.p. 158° C., of the acid m.p. 235° C. could be related by synthesis from or degradation to the β-4-methoxy-phenyl-glutaconic acid (I)[6] or the β-2-methoxy-phenyl-glutaconic acid (II), which was easily synthesised from the known coumarin-4-acetic acid[4] by hydrolysis and methylation.[7] It was observed that the latter (II) could not be made to condense with anisole at all, whereas the former (I) easily condensed with anisole to produce the dimethoxy acid, m.p. 158° C. Out of the two possible structures (IV) and (V) arising out of this synthesis, the former is the more probable as the compound lost a molecule of anisole by the action of sulphuric acid to give only the β-4-methoxy-phenyl-glutaconic acid (I). A compound of the structure (V) under these circumstances would have produced a monolactonic acid and the coumarin-4-acetic acid[4] in addition.



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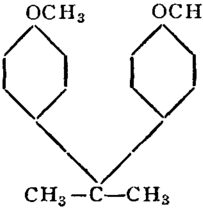
[5] Dixit, *J. Ind. Chem. Soc.*, 1931, **8**, 787.

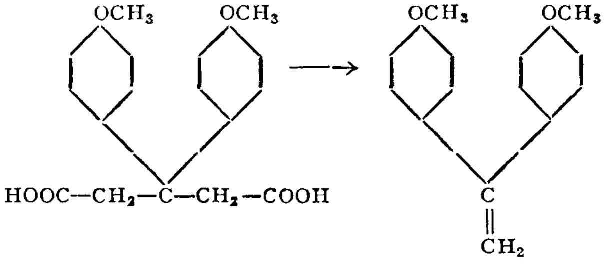
[6] Limaye and Bhave, *J. Ind. Chem. Soc.*, 1931, **8**, 137.

[7] *Cf.* Part I, *Proc. Ind. Acad. Sci.*, (A), 1934, **1**, 48–60.

To further confirm the constitution (IV) it was decided to see whether the dimethoxy acid, m.p. 158° C. could be decarboxylated to the known ββ-di-(4-methoxy-phenyl) propane (VII), m.p. 60°·5 C.[8] Dilute acids in this respect had no action on the dimethoxy acid, whereas thermal decomposition yielded its anhydride, m.p. 105°C. On heating the dimethoxy acid with lime, however, a compound melting at 140° C. and differing vastly from the expected one, was obtained. Its emperical formula ($C_{16}H_{16}O_2$) showed a loss of a molecule of acetic acid in addition to one of carbon dioxide during decarboxylation, and it was found identical with the known *unsym.* di-4-methoxyphenyl-ethylene (VIII).[9] This established conclusively the correctness of the structure (IV) for the dimethoxy acid and in consequence of the acid, m.p. 235° C. The elimination of acetic acid in the decarboxylation of organic acids is remarkable, and this along with other similar cases will be described in a separate communication.



(VII)



(IV) (VIII)

The glutaconic acids containing phenetole or *o*-cresol-methyl and ethyl ethers in the β-position have been found to condense similarly with the respective phenolic ethers, and the resulting ββ-diaryl-glutaric acids have been found to yield, when heated with lime, the corresponding αα-diaryl-ethylenes, which in the case of phenetole is known.[9] All these ββ-diaryl-glutaric acids could be obtained directly by condensing acetone-dicarboxylic acid with phenolic ethers in the presence of dilute sulphuric acid. No ββ-diaryl-glutaric acid could however be obtained from meta-cresol ethers by any of these reactions. The extension of this reaction to other phenolic ethers is in progress.

Experimental.

Condensation of phenol with acetone-dicarboxylic acid: *Formation of ββ-(4 : 4′-dihydroxy-diphenyl)-glutaric acid.*—An acetone-dicarboxylic acid sulphuric acid mixture prepared as usual from citric acid (50 g.) and conc. sulphuric acid (80 c.c.) was cooled in a freezing mixture and powdered ice

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[8] Dianin, *Br. Chem. Abst.*, **64**, I, 214.

[9] Gattermann, *Ber.*, 22, 1132.

(20 g.) was cautiously added, not allowing the temperature of the mixture to go above 20° C. It was further cooled to a temperature below 0° C. and phenol crystals (40 g.) were added in small portions with repeated shaking. The reaction mixture was kept at the room temperature for 20 hours and then poured on curshed ice (250 g.). The precipitate which separated after scratching and keeping overnight was filtered, dissolved in sodium carbonate solution and acidified—(16 g.). This was treated with 100 c.c. of boiling water and filtered. The insoluble portion—(3·3 g.), crystallised from alcohol in colourless silky needles, m.p. 184° C. (decomp.), and was identified as the unsubstituted coumarin-4-acetic acid by its decarboxylation to the known 4-methyl-coumarin. (Found : Eq. = 204 ; C = 64·52 per cent. ; H = 3·81 per cent. ; $C_{11}H_8O_4$ requires Eq. = 204 ; C = 64·7 per cent. ; H = 3·92 per cent.)* From the aqueous filtrates the glutaric acid separated on cooling and scratching, which was recrystallised from water (charcoal) in colourless hexagonal plates, m.p. 235° C. (decomp.), (12 g.). (Found : Eq. = 158 ; C = 64·32 per cent. ; H = 4·95 per cent. ; $C_{17}H_{16}O_6$ requires Eq. = 158 ; C = 64·56 per cent. ; H = 5·06 per cent.) The compound is very soluble in alcohol, acetic acid, and acetone, sparingly so in water and ether and insoluble in petrol, benzene and chloroform. It gives dark green colouration with ferric chloride and lost carbon dioxide at its melting point leaving behind a residue which did not melt but charred on further heating.

The *diethyl-ester* of the above crystallised from 30 per cent. methyl alcohol in colourless flat needles, m.p. 158–159° C. (Found : C = 67·58 per cent. ; H = 6·33 per cent. ; $C_{21}H_{24}O_6$ requires C = 67·74 per cent. ; H = 6·45 per cent.) The *dimethyl-ester* crystallised from methyl alcohol in colourless plates, m.p. 189° C. (Found : C = 66·02 per cent. ; H = 5·7 per cent. ; $C_{19}H_{20}O_6$ requires C = 66·28 per cent. ; H = 5·81 per cent.) *ββ-(4 : 4′-diacetoxy-diphenyl)-glutaric anhydride* was obtained by refluxing together the glutaric acid (5 g.), fused sodium acetate (7 g.) and acetic anhydride (12 c.c.) for ½ hour. It crystallised from glacial acetic acid in stout colourless needles, m.p. 204–205° C. (Found : C = 65·8 per cent. ; H = 4·6 per cent. ; $C_{21}H_{18}O_7$ requiries C = 65·96 per cent. ; H = 4·7 per cent.) *ββ′-(4 : 4′-diacetoxy-diphenyl)-glutaric acid,* obtained by refluxing the above

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* The coumarin-4-acetic acid, m. p. 172° C. (decomp.), prepared according to Limaye's method (*J. Ind. Chem. Soc.*, 1927, 4, 159) when crystallised from alcohol melted at 184° C. (decomp.) and was found identical with the above one. This thus appears to be the most simple method for the preparation of the unsubstituted coumarin-4-acetic acid, Limaye's method being tedious, requires large quantities of ether, and does not give concordant yields.

anhydride with water, crystallised from water in colourless parallelogramic plates, m.p. 188–189° C. (decomp.). (Found : C = 62·8 per cent. ; H = 4·91 per cent. ; Eq. = 197 ; $C_{21}H_{20}O_8$ requires C = 63·0 per cent. ; H = 5·00 per cent. ; Eq. = 200.) *Diethyl-ββ-(4 : 4'-diacetoxy-diphenyl)-glutarate,* prepared from the above diethyl-ester, sodium acetate and acetic anhydride, crystallised from alcohol in colourless silky needles, m.p. 135° C. (Found : C = 65·58 per cent. ; H = 6·0 per cent. ; $C_{25}H_{28}O_8$ requires C = 65·8 per cent. ; H = 6·1 per cent.)

ββ-(4 : 4'-dimethoxy-diphenyl)-glutaric acid.—The dihydroxy-diphenyl-glutaric acid (5 g.), was methylated by dimethyl-sulphate (25 c.c.) and 25 per cent. sodium hydroxide solution (80 c.c.), on a boiling water-bath. The dimethoxy acid coming out as a sticky semi-solid mass on acidification was treated with 250 c.c. of boiling water and filtered, when it came out in colourless silky needles. When recrystallised from water it melted at 158° C. (Found : Eq. = 171·8 ; C = 66·17 per cent. ; H = 5·74 per cent. ; $C_{19}H_{20}O_6$ requires Eq. = 172 ; C = 66·28 per cent. ; H = 5·81 per cent.) *ββ-(4 : 4'-dimethoxy-diphenyl)-glutaric anhydride* was obtained by heating the dimethoxy acid at 200° C. for 1½ hours till the water evolution stopped. The residue was dissolved in boiling benzene, and the undecomposed dimethoxy acid which separated on cooling was filtered out. On removing the benzene from the filtrate the anhydride remained as an oil which solidified on keeping overnight in a vacuum desiccator over paraffin. It was washed with sodium carbonate and crystallised from methyl alcohol in colourless plates, m.p. 104–105° C. (Found : C = 69·78 per cent. ; H = 5·44 per cent. ; $C_{19}H_{18}O_5$ requires C = 69·94 per cent. ; H = 5·52 per cent). The *semi-anilide* was prepared by heating the above anhydride with aniline in benzene solution. The product separated on cooling in ice and scratching and was crystallised from methyl alcohol in colourless light plates, m.p. 187° C. (Found : C = 71·38 per cent. ; H = 5·82 per cent. ; $C_{25}H_{25}O_5N$ requires C = 71·6 per cent. ; H = 5·96 per cent.)

Synthesis of the ββ-(4 : 4'-dimethoxy-diphenyl)-glutaric acid by the condensation of β-(4-methoxy-phenyl)-glutaconic acid with anisole.—The glutaconic acid (5 g.) was dissolved in ice-cold 75 per cent. aqueous sulphuric acid (60 c.c.) and anisole (8 c.c.) was added in small portions with repeated shaking. The reaction mixture was allowed to remain overnight at the room temperature and poured over crushed ice (100 g.) when a precipitate separated on scratching and keeping overnight. It was filtered, dissolved in sodium carbonate solution, washed with ether, and the dimethoxy acid precipitated by acids. On crystallising from boiling water it melted at 158° C. and was identified by mixed m.p.

Degradation of the ββ-(4 : 4′-dimethoxy-diphenyl)-glutaric acid to the β-(4-methoxy-phenyl)-glutaconic acid.—The glutaric acid (10 g.) was dissolved in 80 per cent. sulphuric acid (50 c.c.) with slight warming, and the solution on keeping for 4 hours was poured in 150 c.c. water, when a product crystallised out on cooling in ice, scratching and keeping overnight (yield 2·5 g.). It was filtered, washed, neutralised by alkali, an excess of barium acetate solution added, and the whole boiled, when a heavy precipitate of a barium salt separated, from which the glutaconic acid was obtained by acidification. It crystalliesd from 50 c.c. of boiling water in colourless needles, m.p. 176° C. (decomp.).

Decarboxylation of the ββ-(4 : 4′-dimethoxy-diphenyl)-glutaric acid to the αα-(4 : 4′-dimethoxy-diphenyl)-ethylene.—The dimethoxy glutaric acid (1 g.) was intimately mixed with freshly ignited lime (3 g.) and placed in a hard glass test-tube supported horizontally. It was cautiously heated by a smoky flame when a red oil collected in the cooler part of the tube. On keeping at the room temperature for a few hours, the oil solidified to a yellow crystalline mass, which was scraped out, washed with methyl alcohol, and crystallised from 50 c.c. of the same solvent in colourless shining leaflets, m.p. 140° C. (0·4 g.), and was identified as the diphenyl-ethylene by mixed m.p. (Found : C = 79·9 per cent. ; H = 6·6 per cent. ; $C_{16}H_{16}O_2$ requires C = 80 per cent. ; H = 6·67 per cent.)

Condensation of anisole with acetone-dicarboxylic acid : Formation of the ββ-(4 : 4′-dimethoxy-diphenyl)-glutaric acid.—An acetone dicarboxylic acid sulphuric acid mixture from citric acid (100 g.), sulphuric acid (160 c.c.) was diluted in cold by ice (40 g.). The whole was cooled to 0° C. and anisole (40 c.c.) was gradually added with shaking. On continuing the shaking for 2 hours, the two layers disappeared, and the reaction mixture on keeping at the room temperature for 24 hours was poured over powdered ice (500 g.), when on scratching and keeping overnight, a precipitate separated. It was filtered, dissolved in sodium carbonate solution, excess of anisole washed out with ether, and represcipitated by acids. The precipitated acids were neutralised exactly with alkalis, the solution boiled with animal charcoal, filtered, and treated with barium acetate solution in small portions, until there was no formation of any precipitate on boiling. The acids precipitated from these filtrates by mineral acids, were filtered and treated with 1·5 liters of boiling water and filtered, when the dimethoxy acid crystallised out in colourless silky needles, m.p. 158 °C. Yield 18 g.

β-(4-ethoxy-phenyl)-glutaconic acid, prepared by condensing phenetole with acetone-dicarboxylic acid, crystallised from methyl alcohol in colourless parallelogramic plates, m.p. 170 °C. (decomp.). (Found : Eq. = 125 ;

C = 62·22 per cent.; H = 5·5 per cent.; $C_{13}H_{14}O_5$ requires Eq. = 125; C = 62·4 per cent.; H = 5·6 per cent.) *Hydroxy-anhydride*, colourless silky needles from benzene, m.p. 178° C. *Semianilide*, colourless light needles from alcohol, m.p. 180° C. (decomp.).

ββ-(4 : 4′-*diethoxy-diphenyl*)-*glutaric acid*, was prepared by condensing the above glutaconic acid with phenetole in the usual manner, or by ethylating the ββ-(4 : 4′-dihydroxy-diphenyl)-glutaric acid. It crystallised from water in colourless parallelogramic plates, m.p. 157–158° C. (Found: Eq. = 186; C = 66·1 per cent.; H = 6·34 per cent; $C_{21}H_{24}O_6$ requires Eq. = 186; C = 67·4 per cent.; H = 6·45 per cent.) The *anhydride* prepared by decomposing the glutaric acid at 200° C. as usual crystallised from methyl alcohol in colourless glistening plates, m.p. 119–120° C. (Found: C = 70·98 per cent.; H = 6·12 per cent.; $C_{21}H_{22}O_5$ requires C = 71·18 per cent.; H = 6·21 per cent.). The glutaric acid, on decarboxylation with lime yielded the known αα-(4 : 4′-diethoxy-diphenyl)-ethylene, which crystallised from methyl alcohol in glistening plates, m.p. 142° C.[10]

Condensation of β-(4-*methoxy*-3-*methyl-phenyl*)-*glutaconic acid with* o-*cresol-methyl ether*: *Formation of the* ββ-(4 : 4′-*dimethoxy*-3 : 3′-*dimethyl-diphenyl*)-*glutaric acid*.—The glutaconic acid (5 g.) was condensed with *o*-cresol-methyl ether (8 c.c.) in the presence of ice-cold 80 per cent. sulphuric acid (50 c.c.) as usual. The sticky condensation product was dissolved in dilute sodium carbonate solution, washed with ether and precipitated by acids. The sticky precipitate became granular by refluxing with water, filtered, dried, dissolved in benzene and precipitated by petroleum ether. The glutaric acid thus separated was finally recrystallised from benzene in microscopic colourless flat needles, m.p. 187° C. This glutaric acid gives an insoluble barium salt in cold. (Found: Eq. = 188; C = 67·65 per cent.; H = 6·36 per cent.; $C_{21}H_{24}O_6$ requires Eq. = 186; C = 67·74 per cent.; H = 6·45 per cent.) The *anhydride* was prepared by thermal decomposition of the above glutaric acid as usual. The sticky mass solidified by rubbing with ether and crystallised from alcohol in colourless parallelogramic plates, m.p. 156° C. (Found: C = 71·07 per cent.; H = 6·14 per cent.; $C_{21}H_{22}O_5$ requires C = 71·18 per cent.; H = 6·21 per cent.) The *semianilide* prepared from the above anhydride and aniline in benzene solution, precipitated by cooling in ice and adding petroleum ether. It was filtered, refluxed with 30 per cent. methyl alcohol and crystallised from methyl alcohol in colourless parallelogramic plates, m.p. 189° C. (Found: C = 72·28 per cent.; H = 6·35 per cent.; $C_{27}H_{29}O_5N$ requires C = 72·48 per cent.; H = 6·48 per cent.)

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[10] Gattermann, *Ber.*, **22**, 1132.

The above glutaric acid was degraded to the known β-(4-methoxy-3-methyl-phenyl)-glutaconic acid[11] by the action of 80 per cent. sulphuric acid as usual. The glutaconic acid was separated from the unreacted glutaric acid by its insolubility in benzene. It was crystallised from 5 per cent. acetic acid, m.p. 173° C. (decomp.). The glutaric acid was decarboxylated by heating with lime as usual to the αα-(4 : 4′-dimethoxy-3 : 3′-dimethyl-diphenyl)-ethylene, which crystallised from methyl alcohol in colourless light glistening plates, m.p. 106° C. (Found : C = 80·36 per cent. ; H = 7·32 per cent. ; $C_{18}H_{20}O_2$ requires C = 80·6 per cent. ; H = 7·46 per cent.) The glutaric acid could also be synthesised by condensing the acetonedicarboxylic acid sulphuric mixture from citric acid (25 g.), sulphuric acid (40 c.c.)—diluted with addition of ice (10 g.), with *o*-cresol-methyl ether (10 c.c.) in the usual manner. Yield 8 g.

β-(4-*ethoxy*-3-*methyl-phenyl*)-*glutaconic acid* crystallised from 40 per cent. methyl alcohol in yellowish microscopic needles, m.p. 174° C. (decomp.). The *hydroxy-anhydride* crystallised from benzene in colourless plates, m.p. 188° C. The *semianilide* crystallised from alcohol in colourless silky needles, m.p. 173°C.

ββ-(4 : 4′-*diethoxy*-3 : 3′-*dimethyl-diphenyl*)-*glutaric acid* was prepared by condensing the above glutaconic acid with *o*-cresol-ethylether in the usual manner. The sticky product was refluxed with water and crystallised from alcohol in colourless parallelogramic plates, m.p. 204° C. (decomp.). The glutaric acid gives insoluble barium salt. (Found : Eq. = 203 ; C = 68·89 per cent. ; H = 6·92 per cent. ; $C_{23}H_{28}O_6$ requires Eq. =200 ; C =69 per cent. ; H = 7 per cent.) The *anhydride* prepared by thermal decomposition at 210–220° C. crystallised from methyl alcohol in colourless glistening light plates, m.p. 104–105° C. The *semianilide* prepared from the above anhydride and aniline in benzene solution was digested with 20 per cent. methyl alcohol, and crystallised from 75 per cent. methyl alcohol in colourless rectangular plates, m.p. 155–156° C.

The glutaric acid was decarboxylated by heating with lime as usual to the αα-(4 : 4′-diethoxy-3 : 3′-dimethyl-diphenyl)-ethylene, which crystallised from methyl alcohol in light flat needles, m.p. 95–96° C. (Found : C = 80·83 per cent. ; H = 8·0 per cent. ; $C_{20}H_{24}O_2$ requires C = 81·08 per cent. ; H = 8·1 per cent.) The glutaric acid could also be prepared by condensing *o*-cresol-ethylether directly with acetone-dicarboxylic acid sulphuric acid mixture diluted with ice as usual.

The author wishes to express his thanks to Dr. P. C. Guha, D.Sc., for the encouragement given and the facilities provided while carrying on the present investigation.

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[11] Dixit, *J. Ind. Chem. Soc.*, 1931, 8, 787.