L-leucine, m.p. 68°[13] and about 200 mg. of crude acetyl leucine, characterized by its infrared spectrum.

*Reaction of Poly-*L*-leucine with trifluoroacetic acid.* Poly-L-leucine (2.0 g.) was dissolved in 250 ml. of trifluoroacetic acid and treated as above. The reaction product was digested with ether and the material extracted by ether was distilled at 70–100° and 0.1 mm. pressure. The distillation yielded 0.4 g. of trifluoroacetyl-L-leucine, $[\alpha]^{25}_{D}$ = $-35.2°$ (c = 1.0 in water, reported $-39.4°$[13]) (11%) and a non-volatile residue (0.64 g.) with the infrared spectrum of polyleucine. The ether insoluble residue, washed with aqueous sodium bicarbonate and with water, weighed 0.90 g. and exhibited infrared absorption due to $CF_3$— groups at 1160, 1185 and 1210 cm.$^{-1}$, in addition to the bands of the polyleucine spectrum.

*Other trifluoroacetolyses.* From 2.0 g. (0.01 mol.) of *acetyl-*DL*-phenylalanine* was obtained, after 36 hr. at reflux in 60 ml. of trifluoroacetic acid, 0.95 g. of *N*-trifluoroacetyl phenylalanine, m.p. 130°[9] after recrystallization from water, plus an undetermined amount of phenylalanine.

*Acetanilide* and *acetyl-β-phenylethylamine* were both recovered quantitatively after 24 hr. at reflux in 5% solutions.

*Polyglycine* and a *copolymer of* DL*-alanine and* L*-glutamic acid* were also treated with excess trifluoroacetic acid and the reaction product extracted with organic solvents. From these extracts were isolated *N*-trifluoroacetyl glycine and *N*-trifluoroacetyl-DL-alanine, respectively.

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# β-Arylglutaconic Acids. II.[1] Imides of Certain β-Arylglutaconic and Glutaric Acids

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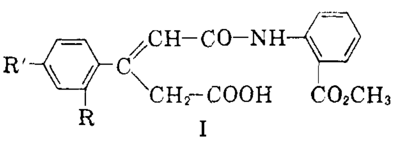
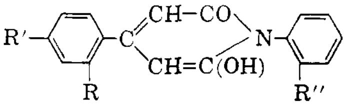
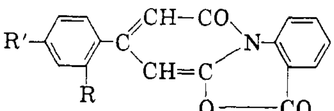
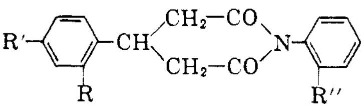
The anhydrides of β-arylglutaconic acids on treatment with equimolar quantities of methyl anthranilate in refluxing benzene solution give rise to the corresponding *cis*-semianilides (I).[1] In the present studies, the *cis*-semianilides were found to undergo dehydration when heated above 170–180° to give the corresponding imides (II) in 75–80% yield and a small quantity (5%) of a neutral substance which was later characterized as the *trans*-decarboxylation product.[3] The yield of the imides (II) was increased to 90–92% by heating at reflux temperature the β-arylglutaconic anhydrides with an excess of methyl anthranilate. The β-arylglutaconic anhydrides are in part enolic in nature, as indicated through production of a purple color with alcoholic ferric chloride solution and by the fact that they can be titrated as monobasic acids with standard alkali. The imides (II) should therefore exist partially in the enolic form. This fact was confirmed by a positive ferric chloride test and by titration with standard alkali. From the resulting alkaline solution the imides could be recovered by acidification in the cold.


I



R″
II. $CO_2CH_3$
III. $CO_2H$


IV



R″
V. $CO_2CH_3$
VI. $CO_2H$

| | R | R′ |
|---|---|---|
| In a. | H | $OCH_3$ |
| b. | $OCH_3$ | $CH_3$ |
| c. | $OCH_3$ | $OCH_3$ |

Since we were interested in studying the chemical properties of these weakly acidic compounds, imides IIa, b, and c were synthesized from (a) β-(4-methoxyphenyl)glutaconic acid,[4] (b) β-(2-methoxy-4-methylphenyl)glutaconic acid,[5] and (c) β-(2,4-dimethoxyphenyl)glutaconic acid.[6]

When the carbomethoxy substituted hydroxyimides (IIa, b, and c, respectively) were boiled with strong sodium hydroxide solution (12.5*N*), they were hydrolyzed to the corresponding carboxyimides (IIIa, b, and c, respectively). Unlike the carbomethoxyimides (IIa, b, and c), these acids did not give any coloration with ferric chloride solution but did titrate as dibasic acids with standard alkali, indicating the presence of an enol group. This was further confirmed by treating the carboxyimides with acetic anhydride at reflux temperature. From the reaction mixture, neutral substances (40 to 50% yields) were isolated and after purification were characterized as the lactones (IVa, b, and c, respectively). When they were dissolved in dilute sodium hydroxide solution and the alkaline solution was neutralized, the starting carboxyimides (IIIa, b, and c, respectively) were recovered. This behavior confirms the

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[1] Prior publication, *J. Org. Chem.*, **24**, 520 (1959).

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enolic nature of the carboxyimides, and therefore allows lactonic oxazine ring formation.

In further studies, the carboxyimides of β-(2-methoxy-4-methylphenyl)glutaric acid and β-(2,4-dimethoxyphenyl)glutaric acid (VIb and c) were prepared and treated with acetic anhydride. The carboxyimides were recovered unchanged indicating the absence of enolization in the case of glutaric acid imides.

## EXPERIMENTAL

*1-(2-Carbomethoxyphenyl)-4-(4-methoxyphenyl)-6-hydroxy-2-pyridone* (IIa). A mixture of 2.2 g. (0.01 mol.) of β-(4-methoxyphenyl)glutaconic anhydride[4] and 5 ml. of methyl anthranilate was heated at reflux temperature in an oil bath for 10 min. After cooling, the red gummy solid was treated with concentrated hydrochloric acid. The solid was collected on a filter and after it had been washed with several portions of cold water, it was air dried. Two recrystallizations from 50% acetic acid gave 3.2 g. (92% yield) of IIa, m.p. 126–130°. An analytical sample was prepared by further recrystallization from ethanol, m.p. 131–132°. It was insoluble in dilute sodium bicarbonate but soluble in dilute sodium hydroxide. The pyridone was recovered from the alkaline solution by acidification with dilute hydrochloric acid.

*Anal.* Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.63; H, 5.19; N, 4.10.

*1-(2-Carboxyphenyl)-4-(4-methoxyphenyl)-6-hydroxy-2-pyridone* (IIIa). The acid (IIIa) was obtained in 63% yield by hydrolysis of the ester (IIa) with ethanolic sodium hydroxide solution. Recrystallization from ethanol gave pure IIIa, m.p. 194–195° (dec.).

*Anal.* Calcd. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; neut. equiv., 168.7. Found: C, 67.33; H, 4.75; neut. equiv., 171.0.

*1-(2-Carboxyphenyl)-4-(4-methoxyphenyl)-6-hydroxy-2-pyridone lactone* (IVa). A mixture of 6.7 g. (0.02 mol.) of IIIa and 20 ml. acetic anhydride was refluxed for 1 hr. The contents of the reaction flask was stirred into an excess of cold water (*ca.* 50 ml.) and the solid that separated was collected on a filter. It was washed with water, 5%-sodium bicarbonate solution, and again with water. The dry solid was recrystallized three times from alcohol to afford 2.6 g. (42% yield) of IVa as white needles, m.p. 85–86.5°.

*Anal.* Calcd. for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10. Found: C, 71.11; H, 4.45.

*1-(2-Carbomethoxyphenyl)-4-(2-methoxy-4-methylphenyl)-6-hydroxy-2-pyridone* (IIb). The procedure used in making this compound was the same described for IIa. From 5.8 g. (0.025 mol.) of β-(2-methoxy-4-methylphenyl)glutaconic anhydride,[5] 8.2 g. (90% yield) of IIb was obtained as dull white crystals, m.p. 175–176°.

*Anal.* Calcd. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.34; H, 5.12; N, 4.02.

*1-(2-Carboxyphenyl)-4-(2-methoxy-4-methylphenyl)-6-hydroxy-2-pyridone* (IIIb). This acid was prepared by alkaline hydrolysis of IIb. From 3.6 g. (0.01 mol.) of IIb, 1.9 g. (54% yield) of the acid (IIIb) was obtained, m.p. 214–216° (dec.).

*Anal.* Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; neut. equiv., 175.6. Found: C, 68.18; H, 5.01; neut. equiv., 172.4.

*1-(2-Carboxyphenyl)-4-(2-methoxy-4-methylphenyl)-6-hydroxy-2-pyridone lactone* (IVb). Treatment of IIIb with acetic anhydride by the procedure outlined for IVa, gave IVb in 47% yield, m.p. 163–164.5°.

*Anal.* Calcd. for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54. Found: C, 72.19; H, 4.52.

*1-(2-Carbomethoxyphenyl)-4-(2,4-dimethoxyphenyl)-6-hydroxy-2-pyridone* (IIc). This ester was prepared from β-(2,4-dimethoxyphenyl)glutaconic anhydride[6] by the procedure used for IIa. The yield of IIc was 93%, m.p. 118–118.5°.

*Anal.* Calcd. for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02. Found: C, 65.96; H, 4.76.

*1-(2-Carboxyphenyl)-4-(2,4-dimethoxyphenyl)-6-2-hydroxy-pyridone* (IIIc). Alkaline hydrolysis of the ester (IIc) gave IIIc in 87% yield, m.p. 170–171° (dec.).

*Anal.* Calcd. for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; neut. equiv., 188.65. Found: C, 65.25; H, 4.50; neut. equiv., 185.20.

*1-(2-Carboxyphenyl)-4-(2,4-dimethoxyphenyl)-6-hydroxy-2-pyridone lactone* (IVc). This lactone was made from IIIc by treatment with acetic anhydride following the procedure used for IVa. From 3.7 g. (0.01 mol.) of the acid (IIIc), 1.7 g. (48% yield) of IVc was obtained, m.p. 152–153.5°.

*Anal.* Calcd. for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33. Found: C, 68.60; H, 4.19.

*1-(2-Carbomethoxyphenyl)-4-(2-methoxy-4-methylphenyl)-piperidine-2,6-dione* (Vb). A mixture of 2.5 g. (0.01 mol.) of β-(2-methoxy-4-methylphenyl)glutaric acid[7] and 7.5 ml. of methyl anthranilate was heated at reflux temperature for 15 min. The resulting product after processing as in the preparation of IIa, gave 3.2 g. (87% yield) of Vb, m.p. 120–121°.

*Anal.* Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76. Found: C, 68.44; H, 5.40.

It was found completely insoluble in dilute sodium bicarbonate and dilute sodium hydroxide solution and gave a negative test with ferric chloride.

*1-(2-Carboxyphenyl)-4-(2-methoxy-4-methylphenyl)-piperidine-2,6-dione* (VIb). This acid was prepared in 57% yield by the alkaline hydrolysis of Vb, m.p. 152–152.5°. It dissolved in dilute sodium bicarbonate solution with effervescence.

*Anal.* Calcd. for $C_{20}H_{19}NO_5$: neut. equiv., 353.61. Found: neut. equiv., 352.80.

*1-(2-Carbomethoxyphenyl)-4-(2,4-dimethoxyphenyl)-piperidine-2,6-dione* (Vc). This substance was prepared from β-(2,4-dimethoxyphenyl)glutaric acid[1] and methyl anthranilate by the procedure adopted for making IIa. The yield of Vc was 88%, m.p. 145–145.5°.

*Anal.* Calcd. for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52. Found: C, 65.52; H, 5.20.

*1-(2-Carboxyphenyl)-4-(2,4-dimethoxyphenyl)-piperidine-2,6-dione* (VIc). Alkaline hydrolysis of Vc gave VIc in 46% yield, m.p. 134–136°.

*Anal.* Calcd. for $C_{20}H_{19}NO_6$: neut. equiv., 369.4. Found: neut. equiv., 368.0.

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(7) D. B. Limaye and R. G. Chitre, *J. Univ. Bombay*, **4,** 101 (1935).

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# Some 2- and 4-Substituted Estrone 3-Methyl Ethers[1a,b]

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This communication describes the syntheses of several 2- and 4-substituted 1,3,5(10)-estratriene-17-one (estrone) 3-methyl ethers which were required for a biological study of the effect of substi-