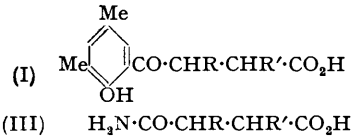
585. *Some Derivatives of Methylsuccinic Acid.*

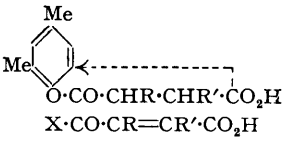
By Wesley Cocker and A. K. Fateen.

The *m*-4-xylyl hydrogen esters of methylsuccinic acid have been characterised, and the identity of the methyl-succinamic and -succinanilic acids established.

Recently (*J.*, 1951, 929), it was shown that *m*-4-xylenol reacts with methylsuccinic anhydride to yield two esters : (A), m. p. 112—113°, obtained in the larger amounts, and (B), m. p. 65°, respectively. These were rearranged to give respectively (I; R = H, R′ = Me) and (I; R = Me, R′ = H).



(I)



(II)

(III) $H_2N{\cdot}CO{\cdot}CHR{\cdot}CHR'{\cdot}CO_2H$

$X{\cdot}CO{\cdot}CR{=}CR'{\cdot}CO_2H$ (IV)

The esters (A and B) have now been shown to be 2 : 4-xylyl β-carboxy-*n*-butyrate (II; R = H, R′ = Me) and 2 : 4-xylyl β-carboxy*iso*butyrate (II; R = Me, R′ = H) respectively. The esters were converted by alcoholic ammonia into the corresponding methylsuccinamic acids (III) which were identified by comparison with the methylsuccinamic acids obtained by catalytic reduction of the corresponding mesaconamic acids (IV; R = H, R′ = Me, X = NH_2: and IV; R = Me, R′ = H, X = NH_2) (Anschutz, *Annalen*, 1907, **353**, 139). The former unsaturated amide was obtained from the corresponding ester (IV; R = H, R′ = Me, X = OEt) (the α-ester of Anschutz, *loc. cit.*), and on reduction it gave β-carboxy-*n*-butyramide (III; R = H, R′ = Me). This compound melted at 125°. The methylsuccinamic acid obtained from A melted at 106—107° but, when the higher-melting amide was seeded with the lower, the melting point of the product was 106—107°. We consider that the two amides are chemically identical, and that we have encountered two forms of β-carboxy-*n*-butyramide. Both yield correct analyses, and both yield methylsuccinic acid on hydrolysis, and the higher-melting form depresses the melting point of the methylsuccinamic acid (m. p. 127°) obtained from B.

Morrell (*J.*, 1914, **105**, 2698) mentions a somewhat similar phenomenon in the case of one of the anilides obtained from methylsuccinic anhydride. This must be β-carboxy-*n*-butyranilide (see below). Crystallised from water, it melts at 143—145°; but crystallised from ethyl acetate, it melts at 159°, reverting to 143—145° on crystallisation once more from water. However, all attempts to interchange the melting points of the amide by crystallisation were unsuccessful.

The mesaconamic acid (IV; R = Me, R′ = H, X = NH_2) was obtained from the ester-chloride ($Cl{\cdot}CO{\cdot}CMe{=}CH{\cdot}CO_2Et$) by treatment with ammonia, followed by hydrolysis of the ester-amide with methanolic potassium hydroxide, a process worked out by Anschutz (*loc. cit.*). On reduction, it yielded β-carboxy*iso*butyramide (m. p. 125°) undepressed by the amide from B, but depressed by β-carboxy-*n*-butyramide.

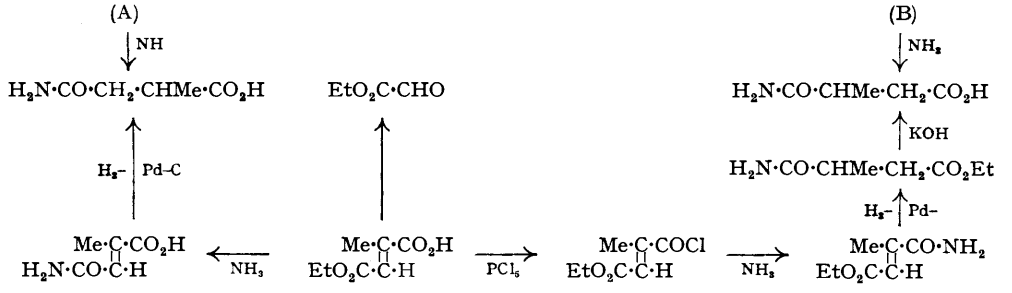
Assuming, therefore, that the mesaconamic ester (IV; R = H, R′ = Me, X = OEt) has the correct structure as given by Anschutz (*loc. cit.*), we feel justified in concluding that esters (A) and (B) have the structures suggested.

In the paper mentioned, Anschutz, revising his earlier views on the structure of the half-esters of mesaconic acid (Anschutz and Drugman, *Ber.*, 1897, **30**, 2649) claimed that partial hydrolysis of the diesters of mesaconic acid gives the " α-ester " (*e.g.*, ethyl β-carboxycrotonate, IV; R = H, R′ = Me, X = OEt), and that partial esterification of mesaconic acid gives a mixture in which the " α-ester " predominates.

The later paper of Anschutz is long and confusing and contains a number of printer's errors, but it appears that the half-esters were related, through their derivatives, to the known β-ester (β-carbethoxycrotonic acid; IV; R = Me, R′ = H, X = OEt) previously obtained by Cloez (*Compt. rend.*, 1890, **110**, 583) by treatment of ethyl γγ-dibromo-α-methylacetoacetate with barium carbonate. It is significant that Richter's " Organic Chemistry " (Allott, London, 1934, p. 572), in reporting Anschutz's work, interchanges the formulæ of the α- and the β-esters.

We have now identified, beyond doubt, the ester obtained by the partial hydrolysis of diethyl mesaconate as ethyl β-carboxycrotonate. This was accomplished by ozonolysis of the pure ester in sodium carbonate solution, ethyl glyoxylate being obtained and identified as its phenylhydrazone (Scheiber and Herold, *Ber.*, 1913, **46**, 1105). The claims made by Anschutz in his later paper are, therefore, correct.

The reactions we have performed are given in the scheme annexed.



When ester (A) was treated with aniline in methanol, it yielded a product which, by analogy with the corresponding amide, must be β-carboxy-*n*-butyranilide. It behaved as described by Morrell (*loc. cit.*). Its isomer, β-carboxy*iso*butyranilide, was obtained in a similar fashion from a mixture of (A) and (B), in which (B) predominated.

On theoretical grounds, the reaction of phenols, alcohols, and amines with unsymmetrical alkylsuccinic anhydrides would be expected to take place predominantly at the more electron-deficient carbonyl group, namely, the one further away from the alkyl; and with methylsuccinic anhydride, such has now been shown to be the case. It is, therefore, likely that the ester (m. p. 84—85°) obtained by Cocker, Fateen, and Lipman (*loc. cit.*) from *m*-4-xylenol and ethylsuccinic anhydride is 2 : 4-xylyl β-carboxy-*n*-valerate (II; R = H, R′ = Et).

The identity of the above *m*-4-xylyl hydrogen esters of methyl-, and ethyl-succinic acids and their *ortho*-rearrangement products in the Fries reaction (Cocker, Fateen, and Lipman, *loc. cit.*) having been established, it can be stated that rearrangement cannot take place by a process involving attack of the free carboxyl groups at the nucleus, as shown in (II).

In the Friedel–Crafts reaction between *m*-4-xylyl ethers and the above anhydrides, reaction takes place *meta* to the methoxy-group (cf. Cocker *et al.*, *J.*, 1950, 1781). At room temperature

the *meta*-position, activated by the two methyl groups, apparently offers the larger electron availability to the ion $-\overset{+}{C}O\cdot CHR\cdot CHR'\cdot CO_2H$. Some *meta*-migration may take place in the Fries rearrangement performed at 140°. The expected products of such rearrangements have not, however, been isolated, but the yield of pure *ortho*-compound never exceeded 45% of the theoretical. It is, therefore, not possible to draw any definite conclusion as to the mechanism of the Fries rearrangement of these esters, although intramolecular rearrangement involving π-complexes (Dewar, " Electronic Theory of Organic Chemistry," Oxford, 1949, p. 229) to a, possibly, thermally activated *ortho*-position, seems likely.

Experimental.

β-Carboxy-n-*butyramide* (III; R = H, R′ = Me).—The ester A (Cocker *et al.*, *J.*, 1951, 929) (11 g.) in methanol (80 c.c.) was saturated at room temperature with dry ammonia and left for 24 hours. Removal of alcohol under reduced pressure gave an oil, which was stirred with ether to remove xylenol; the residue was mixed with water and carefully acidified. The solution was then extracted continuously with ether, and the solid extract (5 g.) was crystallised several times from alcohol, from which the required *amide* was deposited as needles, m. p. 106—107° (Found : C, 45·6; H, 6·8. $C_5H_9O_3N$ requires C, 45·8; H, 6·9%).

*β-Carboxy*iso*butyramide* (III; R = Me, R′ = H) was similarly obtained from B (1·6 g.) as needles (0·58 g.), m. p. 127° (Found : C, 46·0; H, 7·0. $C_5H_9O_3N$ requires C, 45·8; H, 6·9%).

Ethyl β-carboxycrotonate (*α-Ester*) (IV; R = H, R′ = Me, X = OEt).—Mesaconic acid (*Org. Synth.*, 1931, **11**, 74) (20 g.) in anhydrous alcohol (120 c.c.) was saturated with hydrogen chloride and left overnight. Removal of solvent under reduced pressure, extraction with ether, and washing of the extract with sodium hydrogen carbonate solution yielded diethyl mesaconate (18·5 g.), b. p. 222°. The ester in alcohol (20 c.c.) was treated with a cold solution of potassium hydroxide (5·7 g.) in alcohol (68 c.c.). The solution became neutral in 45 minutes. The potassium salt which was deposited was collected and the filtrate was concentrated under reduced pressure, yielding a further quantity of the salt. The salt was dissolved in water (40 c.c.), extracted with ether to remove entrained starting ester (2·5 g.), and carefully acidified. The required ester was collected in ether, the solvent removed, and the product (12 g.; m. p. 60—66°) was crystallised from benzene as long needles, m. p. 67—68° (Anschutz, *Annalen*, 1907, **353**, 139).

β-Carboxycrotonamide (IV; R = H, R′ = Me, X = NH_2).—The previous compound (1·6 g.) was dissolved in ammonia (20 c.c.; *d* 0·880), then left for 48 hours, and the solution evaporated to dryness under reduced pressure. The solid was washed with alcohol; the ammonium salt of the required amide, m. p. 174—176°, remained, from which the amide itself (1·2 g.) (Anschutz, *loc. cit.*) was obtained, m. p. 222°.

Reduction of β-carboxycrotonamide. The previous compound (0·5 g.) in glacial acetic acid (100 c.c.) with palladised charcoal (0·5 g.) was quantitatively hydrogenated at atmospheric pressure for 4 hours. Filtration and removal of solvent, under reduced pressure, gave a product (0·4 g.) which, after crystallisation from alcohol, gave needles, m. p. 124—125° (Found : C, 45·6; H, 7·1. Calc. for $C_5H_9O_3N$: C, 45·8; H, 6·9%). A mixture of this material and the amide from (A) (m. p. 106°) melted at 106—107°, but a mixture of the hydrogenation product and *β*-carboxy*iso*butyramide (m. p. 127°) melted at 104—109°.

Ethyl β-Carbamylcrotonate.—This was obtained when the acid chloride of ethyl *β*-carboxycrotonate (Anschutz, *loc. cit.*) (0·3 g.) in ether (40 c.c.) was saturated at 0° with ammonia. Ammonium chloride was collected and the solvent was removed, yielding the required amido-ester which crystallised from the ether as plates, m. p. 78°. Attempts to hydrolyse this with methanolic potassium hydroxide to *β*-carbamylcrotonic acid failed, although Anschutz (*loc. cit.*) described a successful hydrolysis.

Reduction of ethyl β-carbamylcrotonate. The above ester (0·9 g.) was reduced in alcohol with palladised charcoal and hydrogen at atmospheric pressure. The reduction was complete in 18 hours. After removal of solvent, the product was refluxed with 5% methanolic potassium hydroxide (10 c.c.) for 2 hours. Methanol was then removed, the residue was diluted and acidified, and the mixture was shaken with ether from which an oil was obtained. On being rubbed with light petroleum, it solidified and melted at 92—104°. Extraction with benzene removed methylsuccinic acid, and the residue, after one crystallisation from alcohol, gave m. p. 125°, undepressed by the amide from (B).

β-Carboxy-n-*butyranilide.*—The ester A (2·8 g.) was set aside with aniline (4 g.) in methanol (5 c.c.) for 72 hours. The mixture was distilled in steam, the clear residue was acidified, and the solid product (1·1 g.) was collected and crystallised from water as prisms, m. p. 148°. Crystallisation from ethyl acetate gave plates, m. p. 158° (cf. Morrell, *loc. cit.*) (Found : C, 64·3; H, 6·4. Calc. for $C_{11}H_{13}O_3N$: C, 63·8; H, 6·3%).

*β-Carboxy*iso*butyranilide.*—A mixture of esters A and B (1·8 g.; m. p. 70—95°) was treated with aniline as above. An oil was obtained which solidified when rubbed with light petroleum. On extraction with chloroform, *β*-carboxy-*n*-butyranilide remained undissolved, and from the solvent a product, m. p. 120—132°, was obtained which, after several crystallisations from chloroform–light petroleum, gave the desired anilide (0·06 g.), m. p. 122° (cf. Morrell, *loc. cit.*).

Ozonolysis of Ethyl β-Carboxycrotonate.—The pure ester (1·9 g.) in water (20 c.c.) containing sodium carbonate (1·3 g.) was submitted to a stream of weakly ozonised oxygen for 3·5 hours, and the solution was then shaken in hydrogen with palladised charcoal. The filtered solution was extracted once with

ether, from which a small quantity of oil was obtained. This was treated with phenylhydrazine in acetic acid and ethyl glyoxylate phenylhydrazone (50 mg.), m. p. 120—124°, was obtained. One crystallisation from dilute alcohol raised the m. p. to 128° (Scheiber and Herold, *loc .cit.*), undepressed by authentic material obtained by ozonolysis of ethyl hydrogen maleate. A large amount of starting material remained unattacked.

The authors thank the Medical Research Council of Ireland, and the Egyptian Government, for grants.

UNIVERSITY CHEMICAL LABORATORY,
TRINITY COLLEGE, DUBLIN.

[*Received, May 24th,* 1951.]