

Studies on the Kolbe Electrolytic Synthesis

III. Electrolysis of Malonamic Acids as a Preparative Route to Succinic Amides

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The preparation of some succinic amides by Kolbe electrolysis of malonamic acids is described. Configurational relationships between diastereoisomeric acids, amides, and nitriles in the 2,3-diethyl-, 2,3-diisopropyl-, and 2,3-di-(*t*-butyl)-succinic acid series have been determined.

A neopentyl rearrangement is observed in the electrolysis of *t*-butylmalonamic acid, and this has been interpreted in terms of a carbonium ion mechanism.

In the first paper of this series¹ the electrolysis of *t*-butylcyanoacetic acid was found to give, among other products, the two diastereoisomers of 2,3-di-(*t*-butyl)-succinonitrile (I), the high-melting form being isolated in 13 % yield and the low-melting one only in trace amounts (less than 0.5 % yield). It was not possible to determine the steric relationship between these dinitriles and the corresponding meso- and racemic diacid unambiguously by direct hydrolysis, since the vigorous reaction conditions necessary for effecting hydrolysis do not exclude the possibility of epimerization. Also the conversion of meso- or racemic 2,3-di-(*t*-butyl)-succinic acid into the dinitrile *via* the diamide failed, as all attempts to prepare acid chlorides from these acids resulted in the formation of the racemic anhydride. Apparently the diastereoisomers of 2,3-di-(*t*-butyl)-succinic amide are key compounds for the establishment of the configuration of (I), due to the fact that amides can be converted into acids and nitriles under relatively mild reaction conditions.

This paper is a report on the preparation of these compounds by the Kolbe electrolysis of *t*-butylmalonamic acid. The investigation has also been extended to a study of the electrolysis of some other malonamic acids, *viz.* unsubstituted, methyl-, ethyl-, isopropyl-, and diethylmalonamic acid, as no example of the Kolbe reaction with malonamic acids has been reported previously.

The electrolyses were carried out in methanolic solution under conditions specified in the experimental section. The current efficiency was in contrast

to the cases of α -cyanoacids¹ and malonic half esters² rather low, 25–35 %, and a considerable period of electrolysis often preceded the start of the Kolbe reaction. This point was easily observable, since the succinic amides formed are practically insoluble in methanol and precipitate as soon as formed at the anode. The explanation for the low current efficiency is not obvious and probably requires a deeper understanding than our present one of the primary electrode process.

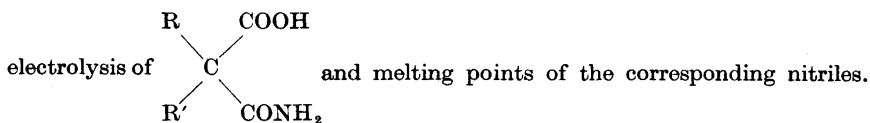
Yields and melting points of succinic amides together with steric assignments based on hydrolysis of the amides by mild methods are shown in Table 1. The last column gives melting points for the dinitriles obtained by treating the diamides with phosphorus oxychloride. In no case was epimerization observed during the hydrolytic or dehydrating process and the steric relationship between acids, amides and nitriles of the 2,3-dimethyl-, 2,3-diethyl-, 2,3-diisopropyl-, and 2,3-di-*t*-butyl-succinic acid series has thus been established. The steric assignments of the dimethyl compounds were made by Linstead and Whalley³. Their observation that racemic 2,3-dimethylsuccinic amide undergoes epimerization under relatively mild conditions, *e.g.* recrystallization from boiling water, was confirmed in this work. This behavior is rather surprising since meso- or racemic 2,3-dimethylsuccinic acid requires much more vigorous treatment in order to be interconverted^{3,4}.

By inspection of Table 1 it is seen that the yield of coupled product follows the same general trend as for substituted succinic esters prepared by electrolysis of malonic half esters (Table 1 in Ref.²), *i.e.*, good yields are obtained from acids without β -hydrogen atoms and moderate or low yields from acids containing such atoms. This is to be expected, since the probability of hydrogen atom abstraction and disproportionation increases with increasing number of β -hydrogen atoms. Although some yields are very low, the method nevertheless competes favorably with other methods, as the starting materials are easily available. The highly substituted succinic amides cannot be prepared by other methods at all.

The nature of the by-products was not investigated except for the case of *t*-butylmalonamic acid. Here disproportionation is excluded which makes the search for possible anomalous coupling products less complicated. Anomalous carbon to nitrogen coupling has been observed for cyanoalkyl radicals generated by electrolysis of α -cyanocarboxylic acids in methanol¹ or decomposition of bisazoisobutyronitrile in inert solvents⁵⁻¹⁰, which would correspond to a possible carbon to oxygen coupling in the case of a malonamic acid.

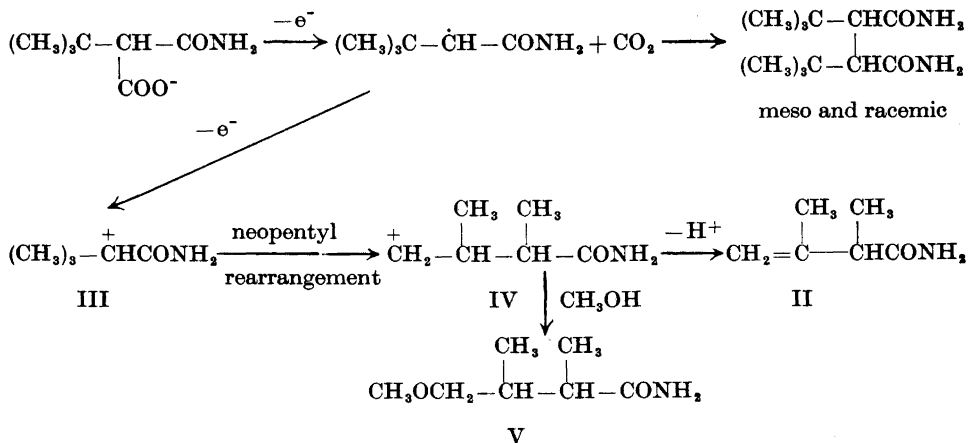
Electrolysis of *t*-butylmalonamic acid directly yielded a solid, m.p. $> 360^\circ$ with decomposition, insoluble in all the common organic solvents except boiling glacial acetic acid, boiling dimethyl formamide and boiling dimethyl sulphoxide. Fractional crystallization from glacial acetic acid gave the high- and low-melting 2,3-di-*t*-butyl-succinic amide, melting point $420-425^\circ$ and $306-313^\circ$ with decomposition, respectively. From the mother liquor a second crystalline compound was isolated, m.p. $100-102^\circ$ after two recrystallizations from ligroin. This compound, however, was not a carbon to oxygen coupling product but instead turned out to be 2,3-dimethyl-3-butenic amide (II), containing a rearranged carbon skeleton as compared with the starting material. Presumably this compound has been formed *via* the Hofer-Moest reaction

Table 1. Yields, melting points, and steric assignments of succinic amides prepared by



R,R'	Total yield of diamide, %	M.p. of diamide, °C	Steric assignment	M.p. of nitrile, °C
H,H	56	265–267 (s.c., dec.)		
CH ₃ ,H	14	302–304 » 232–236 »	meso ³ racemic ³	45–46 ³ 56–57 ³
C ₂ H ₅ ,H	24	339–340 » 247–250 »	meso racemic	45–50 56–58
<i>i</i> -C ₃ H ₇ ,H	43	395–400 » 280–283 »	meso racemic	155–156 71–73
<i>t</i> -C ₄ H ₉ ,H	55	420–425 » 306–313 »	meso racemic	89–91 181–183
C ₂ H ₅ ,C ₂ H ₅	5	199–202 »		

path,¹¹ *i.e.*, the intermediate radical has been further oxidized at the anode to a carbonium ion (III), which possesses the neopentyl structure and rearranges to the carbonium ion (IV). Proton abstraction then yields (II) and it would also be expected that (IV) should react with a solvent molecule with the formation of the methoxy amide (V). Some evidence for the formation of V was obtained by examination of the remaining material in the mother liquor.



No pure compound could be isolated but the viscous, non-distillable oil after thorough drying had a methoxyl group content of about 14 %. Thus we can describe the Kolbe electrolysis of *t*-butylmalonic acid according to the reaction scheme given above.

Carbonium ion paths have been proposed in a number of cases^{11,12} as an explanation for the formation of rearranged products, alcohols and methyl ethers as by-products in the Kolbe synthesis, and the above results present further evidence for the existence of carbonium ion intermediates.

EXPERIMENTAL

Determination of melting points. Melting points were determined by the Kofler melting point microscope method unless otherwise stated. For melting point determinations of the succinic amides in sealed capillaries (abbreviated s.c.) the same procedure as used previously for substituted succinic acids² was adopted in order to obtain reproducible results. Analyses were carried out at the Department of Analytical Chemistry, University of Lund.

Preparation of the starting materials. Malonic acid was prepared according to the method given by Galat,¹³ m.p. 109–116° (decomp.) after two recrystallizations from isopropanol, lit.¹³ m.p. 110–115° (decomp.). The same method was used for the preparation of methylmalonic acid, m.p. 112–116° (decomp.) after two recrystallizations from methyl ethyl ketone, lit.¹⁴ m.p. 104–106° (decomp.). Ethyl-, isopropyl-, *t*-butyl-, and diethylmalonic acid were prepared according to a slightly modified procedure from that described by Fusco and Testa for the synthesis of ethylphenylmalonic acid¹⁵. The method here used consisted of (1) half saponification of the appropriate substituted malonic ester, (2) conversion of the half ester into the ester chloride by refluxing with a 20 % excess of thionyl chloride in absolute ether solution for 12 h, (3) treatment of the crude ester chloride with a ten-molar excess of concentrated aqueous ammonia at 5–10°, and (4) saponification of the crude ester amide by refluxing it with one equivalent of potassium hydroxide in ethanolic solution. There was obtained: ethylmalonic acid, m.p. 137–142° (decomp.) after one recrystallization from water (Found: C 45.5; H 6.7; N 10.7. Calc. for C₅H₉O₃N: C 45.8; H 6.9; N 10.7); isopropylmalonic acid, m.p. 160–163° (decomp.) after one recrystallization from water, lit.¹⁶ m.p. 158° (decomp.); *t*-butylmalonic acid, m.p. 140–147° (decomp.) after two recrystallizations from water (Found: C 52.9; H 8.3; N 8.4. Calc. for C₇H₁₃O₃N: C 52.8; H 8.2; N 8.8.); diethylmalonic acid, m.p. 144–147° (decomp.) after one recrystallization from water, lit.¹⁷ m.p. 144–145°. The purity of the malonic acids was checked by determination of the neutralization equivalent before the electrolysis experiments.

Electrolysis experiments. The electrolysis apparatus has been described elsewhere². The electrolyte consisted of the malonic acid, methanol (100 ml/0.1 mole of acid), and potassium hydroxide (1–2 mole % of the acid). A current of about 2.5 A was passed through the solution until it had a slightly alkaline reaction. In all cases this required three to four times the amount of current calculated theoretically, and it was frequently observed that the formation of the succinic amide did not start until a considerable amount of current had been passed through the electrolyte. The temperature of the solution was kept below 35°.

Succinic amide. Filtration of the chilled reaction mixture from the electrolysis of 40.0 g (0.39 mole) of malonic acid gave 13.0 g (56 %) of almost pure succinic amide, m.p. 265–267° (s.c., decomp.) after recrystallization from water, lit.¹⁸ m.p. 260° (decomp.).

High- and low-melting 2,3-dimethylsuccinic amide. The reaction mixture from the electrolysis of 54.3 g (0.46 mole) of methylmalonic acid on filtration gave high-melting 2,3-dimethylsuccinic amide (1.3 g), m.p. 302–304° (s.c., decomp.) after recrystallization from glacial acetic acid, lit.³ m.p. 301–303°.

The mother liquor was evaporated to a volume of about 70 ml and this solution after standing over night had deposited crystals of the low-melting amide, (3.4 g) m.p. 232–236° (s.c., decomp.) after recrystallization from methanol, lit.³ m.p. 223–226°. Recrys-

tallization from boiling water caused epimerization, as was also observed by Lindstead and Whalley³.

Meso-2,3-dimethylsuccinic acid. High-melting 2,3-dimethylsuccinic amide was hydrolyzed by boiling with concentrated hydrochloric acid for 2 h. *Meso-2,3-dimethylsuccinic acid* separated on cooling, m.p. 193–196° (s.c., decomp.).

Racemic 2,3-dimethylsuccinic acid. On the same treatment the lowmelting 2,3-dimethylsuccinic amide gave racemic 2,3-dimethylsuccinic acid, m.p. 129–132° (s.c., decomp.).

High- and low-melting 2,3-diethylsuccinic amide. The reaction mixture from the electrolysis of ethylmalonic acid (40.0 g, 0.31 mole) on filtration directly gave the high-melting 2,3-diethylsuccinic amide (3.3 g), m.p. 339–340° (s.c., decomp.) after recrystallization from glacial acetic acid. (Found: C 55.6; H 9.1; N 16.3. Calc. for $C_8H_{16}N_2O_2$: C 55.8; H 9.4; N 16.3.)

The mother liquor was evaporated to about 75 ml and then gave the low-melting diamide (3.0 g), m.p. 247–250° (s.c., decomp.) after recrystallization from methanol. (Found: C 55.8; H 9.1; N 15.9.)

Meso-2,3-diethylsuccinic acid. High-melting 2,3-diethylsuccinic amide (0.22 g) was refluxed with concentrated hydrochloric acid (10 ml) for 8 h. On cooling *meso-2,3-diethylsuccinic acid* separated, m.p. 200–203° (decomp.), undepressed by the authentic acid².

Racemic 2,3-diethylsuccinic acid. Low-melting 2,3-diethylsuccinic amide (0.20 g) was refluxed with concentrated hydrochloric acid (5 ml) for 8 h. Racemic 2,3-diethylsuccinic acid crystallized on cooling, m.p. 130–133° (decomp.), undepressed by the authentic acid².

Meso-2,3-diethylsuccinonitrile. *Meso-2,3-diethylsuccinic amide* (1.0 g) was refluxed with phosphorus oxychloride (2.5 ml) for 5 min. The mixture was poured on ice and the crystals filtered. After drying and recrystallization from light petroleum (b.p. 30–50°) they melted at 45–50°. (Found: C 70.5; H 8.8; N 20.2. Calc. for $C_8H_{12}N_2$: C 70.6; H 8.9; N 20.6.)

Racemic 2,3-diethylsuccinonitrile. The racemic 2,3-diethylsuccinic amide on the same treatment as described for the *meso* compound yielded racemic 2,3-diethylsuccinonitrile, m.p. 56–58° after recrystallization from light petroleum (b.p. 30–50°). (Found: C 70.4; H 8.9; N 20.7. Calc. for $C_8H_{12}N_2$: C 70.6; H 8.9; N 20.6.) The mixed melting point with the *meso* nitrile was 25–40°.

High- and low-melting 2,3-diisopropylsuccinic amide. The reaction mixture after the electrolysis of isopropylmalonic acid (104 g, 0.72 mole) was filtered. The solid (31.1 g) was practically insoluble in the common organic solvents and had a m.p. > 360°. A sample (5.0 g) of this solid was dissolved in the minimum amount of boiling glacial acetic acid (450 ml) and the solution allowed to cool. High-melting amide (2.0 g) separated, m.p. 395–400° (s.c., decomp.). (Found: C 60.0; H 9.8; N 13.7. Calc. for $C_{10}H_{20}N_2O_2$: C 60.0; H 10.0; N 14.0.)

The mother liquor was then concentrated to about 30 ml in a rotating-film evaporator at a temperature of 60°. On cooling the low-melting amide (1.8 g) crystallized, m.p. 280–283° (s.c., decomp.) after one further recrystallization from glacial acetic acid. (Found: C 60.1; H 9.9; N 14.0.)

Meso-2,3-diisopropylsuccinic acid. High-melting 2,3-diisopropylsuccinic amide (0.5 g) was suspended in a mixture of glacial acetic acid (50 ml) and concentrated hydrochloric acid (3 ml). The mixture was cooled down to 0° in an ice-bath and then sodium nitrite (2.0 g) in water (15 ml) was added with vigorous stirring. Stirring was continued for 6 h at 0° and 10 h at room temperature. Finally the reaction mixture was warmed at 90° for half an hour, after which time it was poured into water (300 ml) and stored in a refrigerator over night. The crystals (0.31 g) were filtered, m.p. 225–227° (s.c., decomp.), undepressed on admixture with *meso-2,3-diisopropylsuccinic acid*².

Racemic 2,3-diisopropylsuccinic acid. Low-melting 2,3-diisopropylsuccinic amide was treated as described for the *meso* compound with the exception that the acid (0.34 g) was obtained from the aqueous solution by continuous ether extraction for 6 h. It was recrystallized from light petroleum (b.p. 30–50°) — ethyl acetate and then had m.p. 167–168°, undepressed on admixture with racemic 2,3-diisopropylsuccinic acid².

Meso-2,3-diisopropylsuccinonitrile. *Meso-2,3-diisopropylsuccinic amide* (0.5 g) was refluxed with phosphorus oxychloride (2.0 ml) for 15 min. The solution was poured on ice and the crystals (0.39 g) were filtered, m.p. 155–156° after recrystallization from ethyl acetate. (Found: C 72.7; H 9.4; N 17.4. Calc. for $C_{10}H_{16}N_2$: C 73.1; H 9.8; N 17.1.)

Racemic 2,3-diisopropylsuccinonitrile. Racemic 2,3-diisopropylsuccinic amide (0.5 g) was refluxed with phosphorus oxychloride (2.0 ml) for 10 min. The solution was poured on ice and the crystals (0.30 g) were filtered, m.p. 71–73° after recrystallization from light petroleum (b.p. 30–50°). (Found: C 73.1; H 9.8; N 17.2.)

It was not necessary to separate the diastereoisomeric amides when preparing large amounts of the dinitriles, since these are very easily separated by fractional crystallization from ethyl acetate. In this solvent the meso nitrile is much less soluble than the racemic form.

High- and low-melting 2,3-di-(t-butyl)-succinic amide. The reaction mixture from the electrolysis of *t*-butylmalonic acid (101 g, 0.64 mole) was filtered, yielding a white solid (39.5 g), m.p. > 360°, insoluble in all of the common organic solvents except boiling glacial acetic acid, boiling dimethyl formamide, and boiling dimethyl sulphoxide. A small sample (5.0 g) was dissolved in boiling glacial acetic acid (1100 ml) and this solution upon cooling gave the high-melting amide (2.0 g), m.p. 420–425° (s.c., extensive decomposition begins at about 400°). (Found: C 62.9; H 10.8; N 12.3. Calc. for C₁₂H₂₄O₂N₂: C 63.1; H 10.7; N 12.3.)

The mother liquor was concentrated to a volume of about 200 ml and then deposited a second crystal fraction (1.1 g), m.p. 390–395° (s.c., decomp.), which according to its infra-red spectrum was a mixture of high- and low-melting amide (the separation was best followed by taking infra-red spectra of the crystal fractions). The mother liquor was further concentrated to a volume of about 30 ml and then upon slow cooling gave almost pure low-melting amide (0.9 g), m.p. 306–313° (s.c., decomp.) after one further recrystallization from glacial acetic acid. (Found: C 62.8; H 10.6; N 12.3.)

2,3-Dimethyl-3-butenic amide (II). The mother liquor from the filtration of the mixture of high- and low-melting 2,3-di-(*t*-butyl)-succinic amide was evaporated to dryness. The residue was dissolved in ether and the ether solution washed with dilute sodium carbonate solution, water and finally evaporated to dryness. The semi-solid mass was dissolved in boiling benzene (20 ml) and this solution on cooling deposited crystals (6.2 g), m.p. 94–98°, m.p. 100–102° after two recrystallizations from ligroin. According to analysis and infra-red spectrum this compound might be 2,3-dimethyl-3-butenic amide and this was confirmed by comparison with an authentic sample,¹⁹ which melted at 102–103°, mixed m.p. 100–103°.

The mother liquor from the filtration of II was freed from solvent by drying it *in vacuo* (0.1 mm Hg) at 60° over concentrated sulphuric acid for 12 h. The residue was a viscous, non-distillable oil, which had a methoxyl group analysis of 13.7 %.

Meso-2,3-di-(t-butyl)-succinic acid. High-melting 2,3-di-(*t*-butyl)-succinic amide (0.5 g) was hydrolyzed exactly in the same way as described for the high-melting diisopropyl compound. Meso-2,3-di-(*t*-butyl)-succinic acid (0.31 g) was isolated, m.p. 297–299° (s.c., decomp.), undepressed on admixture with the authentic acid².

Racemic 2,3-di-(t-butyl)-succinic anhydride. Low-melting 2,3-di-(*t*-butyl)-succinic amide (0.25 g) on treatment with nitrous acid under the same conditions as used for the high-melting amide was converted into racemic 2,3-di-(*t*-butyl)-succinic anhydride (0.13 g), m.p. 114–115°, undepressed on admixture with an authentic specimen².

Meso-2,3-di-(t-butyl)-succinonitrile. Meso-2,3-di-(*t*-butyl)-succinic amide (0.50 g) was refluxed for 5 min with phosphorus oxychloride (2.0 ml). The solution was poured on ice, the crystals were filtered and recrystallized from light petroleum (b.p. 30–50°). The compound had m.p. 89–91° and according to melting point and infra-red spectrum it was identical with the low-melting 2,3-di-(*t*-butyl)-succinonitrile obtained in trace amounts by the electrolysis of *t*-butylecyanoacetic acid¹.

Racemic 2,3-di-(t-butyl)-succinonitrile. Racemic 2,3-di-(*t*-butyl)-succinic amide (0.20 g) was refluxed for 10 min with phosphorus oxychloride (1.0 ml). The solution was poured on ice, the crystals were filtered and recrystallized from ethyl acetate. The compound melted at 181–183° and according to melting point and infra-red spectrum it was identical with the high-melting 2,3-di-(*t*-butyl)-succinonitrile obtained by electrolysis of *t*-butylecyanoacetic acid¹.

In order to prepare large amounts of meso- and racemic 2,3-di-(*t*-butyl)-succinonitrile it was found advantageous not to separate the amides before treatment with phosphorus oxychloride. The nitriles were easily separated by fractional crystallization from ethyl acetate, where the high-melting from is the less soluble one.

A grant from *Mindre Akademiska Konsistoriet*, University of Lund, is gratefully acknowledged.

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Received January 10, 1962.