Studies on the Kolbe Electrolytic Synthesis. I. Electrolysis of Some α-Cyanocarboxylic Acids

LENNART EBERSON

Division of Organic Chemistry, Draco, Lunds Farmaceutiska AB, Lund, Sweden

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The electrolysis of cyanoacetic and *t*-butylcyanoacetic acid in methanolic solution has been studied. The results indicate that electrolytically liberated cyanoalkyl radicals undergo normal carbon to carbon coupling with the formation of a succinonitrile only to a limited extent, the dominating reaction being an abnormal carbon to nitrogen coupling yielding a keteneimine. The keteneimine is not isolated as such but in the form of its addition compound with water, an *N*-acylated glycinonitrile. This process presumably occurs *via* a nucleophilic attack of cyanocarboxylate ion on the keteneimine with subsequent protonation and transesterification by methanol, since the methyl ester of the cyanocarboxylic acid is formed during the electrolysis.

The Kolbe anodic synthesis with mono- and dialkyl hydrogen malonates has been found to give fairly good yields of the normal coupling products, 2,3-dialkyl- and tetraalkylsuccinic esters.[1,2] Apparently the presence of the carbethoxy group in the α-position does not exert any negative influence on the degree of anodic coupling. The dominating side reaction is disproportionation of the intermediate radicals with the formation of saturated and unsaturated esters containing the same carbon skeleton as the radical. This is best illustrated by the fact that electrolysis of monoethyl *t*-butylmalonate gave a mixture of *meso*- and *racemic*-di-(*t*-butyl)succinic ester in about 90% yield.[1] In this case the intermediate radical lacks hydrogen atoms on the β-carbon atom and consequently disproportionation is excluded.

Whereas the electrolysis of substituted malonic half esters is relatively well studied, literature data on the Kolbe reaction with α-cyanocarboxylic acids are very scarce.[3,4] Fichter and Schnider[5] electrolyzed equivalent amounts of cyanoacetic acid and its potassium salt in aqueous solution and demonstrated that only trace amounts of succinonitrile were formed, the reaction products being carbon dioxide, hydrogen cyanide, and formaldehyde. The work by Asano, *et al.*,[6-8] gives the only indication that α-cyanocarboxylic acids can give normal coupling products upon electrolysis. When co-electrolyzing a dialkylcyanoacetic acid and a fatty acid they could isolate a trialkylacetonitrile resulting from cross-coupling of the radicals, together with a tetraalkylsuccinonitrile.

This paper is a report of a study of the electrolysis of some α-cyanocarboxylic acids, carried out in methanolic solution where the conditions for obtaining optimum yields of coupled products are favorable.[3] For a first study, cyanoacetic and *t*-butylcyanoacetic acid were chosen since the corresponding cyanoalkyl radicals cannot disproportionate and consequently coupling must occur preponderantly.

The electrolyses were carried out with the pure acids in methanolic solution and with about one mole per cent of potassium hydroxide added. The temperature was kept below 40° and the electrolysis was discontinued when the reaction mixture showed a slightly alkaline reaction. In the case of cyanoacetic acid the solvent was evaporated at room temperature and the residue distilled directly *in vacuo*. Two main fractions were collected, one consisting of methyl cyanoacetate and one of a mixture of succinonitrile (I) and *N*-acetylglycinonitrile (II) which could not be separated by distillation. Acid hydrolysis of this mixture gave succinic acid, acetic acid, and glycine. By oxygen analysis the ratio between I and II in the second fraction was estimated to about 2:3.

The reaction mixture from the electrolysis of *t*-butylcyanoacetic acid directly deposited crystals which were identified as 2,3-di-(*t*-butyl)succinonitrile (III), m.p. 178–181° after two recrystallizations from ethyl acetate. This structure was established from elementary analyses, infrared spectrum and acid hydrolysis to *racemic*-2,3-di-(*t*-butyl)succinic anhydride. By fractional crystallization of the mother liquor a second compound was isolated which melted at 147–149° after two recrystallizations from ethyl acetate. It had an elementary analysis of *N*-(*t*-butylacetyl)-*t*-butylglycinonitrile (IV) and its infrared spectrum was consistent with this structure, showing the typical bands of the amide group and a very weak C≡N-stretching band, characteristic of nitriles with electron-attracting substituents attached to the same carbon atom as the nitrile function.[9]

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On acid hydrolysis IV gave *t*-butylacetic acid and *t*-leucine. From the residue of the fractional crystallization there was further isolated by distillation methyl *t*-butylcyanoacetate and trace amounts of a compound which according to elementary analysis and infrared spectrum was the second isomer of 2,3-di(*t*-butyl)succinonitrile, m.p. 85–90° (V).

From the studies on the thermal decomposition of azonitriles[10–15] it is known that keteneimines (VI) are partially formed as intermediates by a carbon to nitrogen coupling between the cyanoalkyl radicals

$$R_2C{-}C{\equiv}N\colon + R_2C{=}C{=}\dot{N}\colon \longrightarrow$$
$$R_2C{=}C{=}N{-}C(CN)R_2 \xrightarrow{H_2O} R_2CHCONH{-}C(CN)R_2$$
VI VII

The keteneimine can be isolated as such,[12,14] or in the form of derivatives of its addition compound with water[10] which is an acylated glycinonitrile (VII) of the same type as II and IV. Evidently the same type of coupling occurs when the cyanoalkyl radicals are produced electrolytically, but the keteneimine reacts with water present in the reaction mixture to give VII. However, since in no case the water contents of the reaction components could account for the amount of VII formed, the rest of the water must originate from the esterification of the cyano acid. In both cases the methyl esters were isolated and it was also shown that the cyano acids did not undergo esterification under the conditions prevailing during the electrolyses.

Keteneimines are known to be easily attacked by nucleophilic agents.[16–18] The esterification is best pictured as a nucleophilic attack of the cyanocarboxylate ion on the carbon atom of the C=N bond followed by protonation and transesterification of VIII by methanol.

$$R_2C{=}C{=}N{-}C(CN)R_2 + R'COO^- \longrightarrow$$
$$[R_2C{=}C(OCOR'){-}\ddot{\underset{\ominus}{N}}{-}C(CN)R_2] \xrightarrow{H^+,\ CH_3OH}$$
VIII
$$R_2CH{-}CONH{-}C(CN)R_2 + R'COOCH_3 \quad\ldots\ldots(1)$$

The net result of this reaction is a consumption of one proton/molecule of methyl ester formed which is consistent with the observation that all of the acid has been used up when appreciably less than the calculated amount of current has been passed through the electrolyte.

The esterification *via* the keteneimine is formally analogous to the formation of the peptide bond in the dicyclohexylcarbodiimide synthesis.[19]

The electrolysis of monoethyl *t*-butylmalonate gave an approximately 1:1 ratio between the diastereoisomers of 2,3-di(*t*-butyl)succinic ester,[1] whereas the corresponding cyano acid yielded one form (III) preponderantly.[20] The difference between the carbethoxy and nitrile group in their effect on the isomer distribution may be explained by the appreciably larger dipole moment of the nitrile group, allowing carbon to carbon coupling only when the steric and dipole-dipole repulsion forces between the radicals have a minimum value. If this is true, the dinitrile III would have to be the *meso* form. This problem will be dealt with in a coming paper of this series.

Experimental

Electrolysis of Cyanoacetic Acid.—The electrolysis apparatus has been described elsewhere.[1] The electrolyte consisted of cyanoacetic acid (149 g., 1.75 moles), potassium hydroxide (1.0 g.), and methanol (400 ml.). By analysis of the water contents of the reagents it was calculated that the electrolyte contained altogether 1.6 g. (0.09 mole) of water.[21] A current of 3.0 amp. was passed through the solution until it had a slightly alkaline reaction (pH 8) which lasted 14 hr., corresponding to the discharge of 1.5 moles of cyanoacetic acid. During the electrolysis the temperature was kept below 40°.

The methanol was then distilled at reduced pressure and the residue distilled *in vacuo*. Two main fractions were collected, b.p. 95–105°/14 mm. (17.0 g.) and b.p. 135–142°/14 mm. (45.0 g.). The first fraction was dissolved in 50 ml. of ether and the ethereal solution was washed three times with water. Drying with Drierite and distillation yielded pure methyl cyanoacetate, b.p. 83–86°/10 mm., $n^{20}D$ 1.4175, d^{20}_4 1.1214 (12.5 g., 7%) (reported for methyl cyanoacetate,[22] $n^{20}D$ 1.4176, d^{20}_4 1.1271).

A sample of the second fraction (5.0 g.) was hydrolyzed by boiling with excess 20% hydrochloric acid for 2 hr. On cooling to 0° crystals deposited, m.p. 180–185°, undepressed on admixture with succinic acid. The mother liquor was continuously extracted with ether for 24 hr. and the ether solution was concentrated to about 5 ml., from which a second crystal crop of succinic acid was obtained. The total amount of succinic acid was 2.7 g., corresponding to a percentage of succinonitrile in the original mixture of about 40%.

The mother liquor from the last filtration was evaporated in a stream of air at room temperature leaving behind 0.9

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(15) G. S. Hammond, C.-H. S. Wu, O. D. Trapp, J. Warkentin, and R. T. Keys, *ibid.*, **82**, 5394 (1960).

(16) C. L. Stevens and J. C. French, *ibid.*, **75**, 657 (1953).

(17) C. L. Stevens and J. C. French, *ibid.*, **76**, 4398 (1954).

(18) R. Dijkstra and H. J. Backer, *Rec. trav. chim.*, **73**, 695 (1954).

(19) Di(*p*-tolyl)carbodiimide has been shown to react with one molecule of a carboxylic acid with the formation of a monoacyl di(*p*-tolyl)urea which then can react with a second molecule of the acid. This reaction gave the anhydride of the carboxylic acid and di(*p*-tolyl)-urea, *cf.* F. Zetzsche, E. Lüscher, and H. E. Meyer, *Ber.*, **71B**, 1088 (1938), and H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(20) It must be pointed out that the fact that III upon hydrolysis gave a compound belonging to the *racemic* series is no proof of its relative configuration. Epimerization may have occurred under the reaction conditions employed to hydrolyze the dinitrile. Of course the same difficulties are encountered in the synthesis of the dinitriles from *meso*- and *racemic*-di(*t*-butyl)succinic acid.

(21) In order to establish that the cyano acids do not undergo esterification under the electrolysis conditions, samples of the acids were stored in methanolic solution at 40° for 5 days. Aliquots were withdrawn at intervals and titrated with standard sodium hydroxide. No change in the acid contents was observed.

(22) A. Karvonen, *Ann. Acad. Sci. Fennicae* [A], **20**, No. 9, 10 (1923).

g. of acetic acid, identified by conversion into its *p*-bromophenacyl ester, m.p. 75–80°, mixed m.p. with an authentic specimen 76–81°.

The aqueous solution from the continuous ether extraction was evaporated to dryness, the remainder dissolved in a few milliliters of water and the pH adjusted to 6 by the addition of 10% aqueous potassium hydroxide. Absolute ethanol (250 ml.) was added. After standing overnight at 0°, crystals had precipitated which were filtered (1.1 g.) and identified as glycine by conversion into a 3,5-dinitrobenzoate, m.p. 172–178°, mixed m.p. with the authentic compound 171–178°. The isolation of succinic acid, acetic acid, and glycine from the hydrolysis of the fraction boiling at 135–142°/14 mm. strongly indicated that it was a mixture of succinonitrile (I) and *N*-acetylglycinonitrile (II). This was supported by a study of its infrared spectrum which displayed the general characteristics of the secondary amide and nitrile groups. The C≡N stretching band was rather strong as is the case for succinonitrile but presumably not for *N*-acetylglycinonitrile which has an electron-attracting group in the α-position to the nitrile group. In such compounds the C≡N band is very weak or wholly absent.[9] By oxygen analysis[23] the percentage of II was estimated to about 60%, in good agreement with the percentage of succinonitrile calculated from the amount of succinic acid isolated after hydrolysis. II has been described earlier as a solid melting at 77°.[24] The yields of I and II were 24 and 30%, respectively.

Electrolysis of *t*-Butylcyanoacetic Acid.—The electrolyte consisted of *t*-butylcyanoacetic acid[25] (141 g., 1.00 mole), potassium hydroxide (2.0 g.), and methanol (400 ml.). The total amount of water present was 1.1 g. (0.06 mole).[21] The electrolysis was carried out with a current of 2.5 amp., all of the cyano acid being consumed after 9.5 hr. This corresponded to the discharge of 0.85 mole of acid. Towards the end of the reaction crystals deposited which were brought into solution by warming to about 60° after the electrolysis had been discontinued. The solution was then allowed to stand overnight and the crystals were filtered, m.p. 170–177° (10.1 g.). The mother liquor was concentrated to about 250 ml. which gave a second fraction with m.p. 165–175° (3.6 g.). The two crystal crops were combined and recrystallized twice from ethyl acetate, giving pure 2,3-di(*t*-butyl)succinonitrile (12.0 g., 13%), m.p. 178–181° (III). The infrared spectrum was consistent with this structure.

Anal. Calcd. for $C_{12}H_{20}N_2$: C, 75.0; H, 10.5; N, 14,6. Found: C, 75.2; H, 10.5; N, 14.5.

The methanolic mother liquor was then successively concentrated and cooled giving three crystal fractions with m.p.'s in the range 120–140°. These were combined (40.7 g.) and recrystallized twice from ethyl acetate, giving pure *N*-(*t*-butylacetyl)-*t*-butylglycinonitrile (IV), m.p. 147–149° (32.1 g., 31%). The infrared spectrum had the bands typical of a secondary amide and a very weak band at 2240 cm.$^{-1}$ which indicated the presence of a nitrile group with an electron-attracting substituent in the α-position.[9]

Anal. Calcd. for $C_{12}H_{22}ON_2$: C, 68.5; H, 10.6; N, 13.3. Found: C, 68.6; H, 10.6; N, 13.3.

The mother liquor from the last filtration was distilled *in vacuo*, giving three fractions, b.p. 55–75°/0.2 mm. (25.5 g.), b.p. 75–100°/0.2 mm. (3.5 g.) and 100–103°/0.2 mm. (1.0 g.). At the end of the distillation the residue in the distilling flask began to decompose, giving off gaseous products which smelt strongly of formaldehyde. The first fraction was redistilled through an efficient column (about ten theoretical plates), giving pure methyl *t*-butylcyanoacetate, b.p. 97–99°/14 mm. (18.6 g., 12%).

Anal. Calcd. for $C_8H_{13}O_2N$: C, 61.9; H, 8.5; N, 9.0. Found: C, 62.2; H, 8.7; N, 9.1.

A small sample was hydrolyzed with an equivalent amount of potassium hydroxide in 90% aqueous ethanol. *t*-Butylcyanoacetic acid was isolated in 80% yield, m.p. 93–95°.

The fraction boiling at 100–103°/0.2 mm. partially solidified on standing. The crystals were freed from liquid by pressing them on a filter paper and then recrystallized from petroleum ether (b.p. 30–50°). The substance (0.05 g.) melted at 85–90° and according to analysis and infrared spectrum it was the low-melting 2,3-di(*t*-butyl)succinonitrile (V).

Anal. Calcd. for $C_{12}H_{20}N_2$: N, 14.6. Found: N, 14.4.

Acid Hydrolysis of High-Melting 2,3-Di(*t*-butyl)succinonitrile (III).—III (1.0 g.) was hydrolyzed by boiling with 4 g. of concentrated sulfuric acid, 3 ml. of glacial acetic acid, and 2 ml. of water for 20 hr. The reaction mixture was poured into 50 ml. of water and the crystals filtered. After recrystallization from aqueous acetone *racemic*-2,3-di-(*t*-butyl)succinic anhydride (0.5 g.) was obtained, m.p. 112–114°, undepressed on admixture with an authentic specimen.[1]

Acid Hydrolysis of *N*-(*t*-Butylacetyl)-*t*-butylglycinonitrile (IV).—IV (8.3 g.) was hydrolyzed by boiling with 50 ml. of 20% hydrochloric acid for 48 hr. On cooling, crystals precipitated which were dissolved by adding 150 ml. of water. The solution was continuously extracted with ether for 10 hr. and from the ethereal solution *t*-butylacetic acid was isolated by distillation, b.p. 81–82°/14 mm. (3.5 g., 76%). It was identified by conversion into its amide, m.p. 130–132°, undepressed on admixture with an authentic specimen.

The aqueous solution from the ether extraction was evaporated to dryness. The crystal mass was dissolved in a few milliliters of water and the pH was adjusted to 5.5 by the addition of 10% aqueous potassium hydroxide. Addition of acetone (250 ml.) precipitated crystals which were filtered and recrystallized from aqueous acetone. The substance (2.6 g., 50%) was identified as *t*-leucine by conversion into its formyl derivative, m.p. 207–210° (lit.,[26] 210°) and the benzoyl derivative, m.p. 159–162°, (lit.,[27] 164–165°). The infrared spectrum showed the same features as described for *t*-leucine.[28]

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(23) Analyses by the Department of Analytical Chemistry, University of Lund.

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