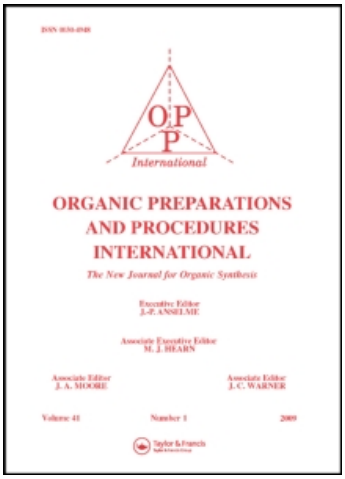

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NEW SYNTHESES OF POLYFUNCTIONAL LONG-CHAIN COMPOUNDS BY ALTERNATING FREE RADICAL ADDITIONS TO CONJUGATED OLEFINS

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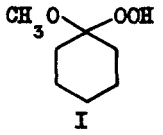
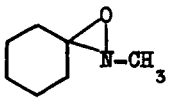
The addition to butadiene of the 5-(methoxycarbonyl)-pentyl radical generated from cyclohexanone, hydrogen peroxide and ferrous sulfate in methanol, leads to a mixture of ester isomers of C_{20} dicarboxylic acids[1]:



I

$$+ \quad Fe^{++} \longrightarrow CH_3OOC-(CH_2)_4-CH_2\cdot \quad + \quad FeOH^{++}$$

The separation of these isomers as pure products is rather difficult and was not carried out. An analogous radical[2] can be obtained from N-methylpentamethyleneoxazirane, easily obtainable from cyclohexanone and N-chloromethylamine[3]:



II

$$+ \quad Fe^{++} \quad + \quad H_2O \longrightarrow CH_3NHCO-(CH_2)_4-CH_2\cdot \quad + \quad FeOH^{++}$$

Addition of this radical to butadiene results in good yields of the diamide III, easily isolable as the pure product; a minor amount of the branched isomer IV is obtained:

$$CH_3NHCO-(CH_2)_4-CH_2\cdot + CH_2=CH-CH=CH_2 \longrightarrow CH_3NHCO-(CH_2)_5-C_4H_6\cdot$$

$$2\ CH_3NHCO-(CH_2)_5-C_4H_6\cdot \begin{cases} \nearrow (CH_3NHCO-(CH_2)_5-CH_2-CH=CH-CH_2)_2 \quad \text{III} \\ \searrow CH_3NHCO-(CH_2)_6-CH(CH=CH_2)-CH_2-CH=CH-(CH_2)_6-CONHCH_3 \quad \text{IV} \end{cases}$$

We can achieve synthetic modifications with both radicals from I and II by alternating addition to conjugated olefins. From II, acrylonitrile and butadiene, one isomer of structure V is isolated as a pure product formed through the sequence :

$$CH_3NHCO-(CH_2)_4-\dot{C}H_2 + CH_2=CH-CN \longrightarrow CH_3NHCO-(CH_2)_6-\dot{C}H-CN$$

$$CH_3NHCO-(CH_2)_6-\dot{C}H-CN + CH_2=CH-CH=CH_2 \longrightarrow CH_3NHCO-(CH_2)_6-CH(CN)-C_4H_6\bullet$$

$$2\ CH_3NHCO-(CH_2)_6-CH(CN)-C_4H_6\bullet \longrightarrow \underset{V}{(CH_3NHCO-(CH_2)_6-CH(CN)-CH_2-CH=CH-CH_2)_2}$$

Analogous products are obtained from I, acrylonitrile and butadiene; the mixture of isomers is difficult to separate in this case :

$$\underset{VI}{(CH_3OOC-(CH_2)_6-CH(CN)-C_4H_6)_2}$$

Further synthetic developments can be accomplished by oxidation of the allyl or benzyl radicals with cupric salt. From I, acrylonitrile and butadiene isomers of structure VII and VIII are obtained :

$$CH_3OOC-(CH_2)_6-CH(CN)-C_4H_6\bullet + Cu^{++} \longrightarrow CH_3OOC-(CH_2)_6-CH(CN)-C_4H_6^{+} + Cu^{+}$$

$$CH_3OOC-(CH_2)_6-CH(CN)-C_4H_6^{+} + CH_3OH \begin{cases} \longrightarrow \underset{VII}{CH_3OOC-(CH_2)_6-CH(CN)-CH_2-\underset{\displaystyle OCH_3}{\underset{|}{CH}}-CH=CH_2} \\ \longrightarrow \underset{VIII}{CH_3OOC-(CH_2)_6-CH(CN)-CH_2-\underset{\displaystyle H_3CO-CH_2}{\underset{|}{CH}}=CH} \end{cases}$$

From I, acrylic acid and butadiene or α-methylstyrene, the lactones IX and X are obtainable :

$$CH_3OOC-(CH_2)_6-\underset{\displaystyle COOH}{\underset{|}{CH}}-C_4H_6^{+} \longrightarrow \underset{IX}{CH_3OOC-(CH_2)_6-\underset{\displaystyle CO-O}{\underset{|}{CH}}-CH_2-\underset{\displaystyle O}{\underset{|}{CH}}-CH=CH_2}$$

$$CH_3OOC-(CH_2)_6-\underset{\displaystyle COOH}{\underset{|}{CH}}-CH_2-\overset{+}{C}(CH_3)-C_6H_5 \longrightarrow \underset{X}{CH_3OOC-(CH_2)_6-\underset{\displaystyle CO-O}{\underset{|}{CH}}-CH_2-\underset{\displaystyle O}{\underset{|}{C}}(CH_3)-C_6H_5}$$

These are only a few examples, thus far synthetically defined, of general procedures.

These new syntheses involve several interesting theoretical aspects:

a) A correlation with the alternating effect of the radical copolymerization.

b) The reactivity of alkyl radicals from I or II towards conjugated olefins; this reactivity is higher with acrylonitrile or acrylic acid than with butadiene or α-methylstyrene owing to the prevalent nucleophilic character of the alkyl radicals and according to our previous results[4] with the radical derived from I; opposite conclusions have been reported by Kochi and Rust[5] with the same radical.

c) The different rates of oxidation by Cu^{++} of the three types of radicals involved in the reaction (alkyl, α-cyano or carboxy-alkyl and allyl or benzyl radicals).

d) The intramolecular reactivity of the allyl or benzyl cations.

Quantitative data on the reactivity of the different radicals involved and a full discussion will be published elsewhere.

Experimental

Di-N-methylamide of trans-trans-8-12-eicosadiene-1-20-dioic acid (III)

To a mixture of 10 g. of butadiene, 11 g. of ferrous sulfate heptahydrate and 50 g. of urea in 100 ml. of water, is added dropwise over a period of 15 minutes 5 g. of N-methylpentamethyleneoxazirane[3] while the mixture is stirred vigorously at -10° in a nitrogen atmosphere. The butadiene is allowed to evaporate and the mixture is acidified with sulfuric acid. The resulting precipitate is collected and washed with ether, which is used to extract the aqueous solution; 3.8 g. of Product (III), melting at 130°, is obtained; after crystallization from ethanol, m.p. 131°. After drying the ether extracts, the solvent is removed, a solid residue (2.2 g.) remains; this solid is extracted with warm ethyl acetate and the residue is crystallized from ethanol, to give an additional 0.6 g. of III.

Anal. of III. Calcd. for $C_{22}H_{40}N_2O_2$: C, 72.48; H, 11.06; N, 7.68 .
Found : C, 72.60; H, 10.92; N, 7.52 .
I.R. : 3300 cm^{-1} (NH) , 1650 cm^{-1} (C=O) , 970 cm^{-1} (CH=CH trans) .
Mol. wt. : 364 (mass spectrum) ; formula wt. of III : 364 .
The ethyl acetate and ethanol filtrates are combined and, after removal of the solvents, 1.6 g. of solid product is obtained; attempts to isolate IV by crystallization from ethyl acetate were not successful. Thin layer chromatography of the recrystallized (three times) product reveals two components, III and IV.
Analysis of the mixture : Found: C, 72.53; H, 11.15; N, 7.61 .
The I.R. spectrum posseses all the bands of III and two bands at 990 910 cm^{-1} ($CH=CH_2$). Mol. wt. : 364 (mass spectrum).

Di-N-methylamide of 8-17-dicyano-trans-trans-10-14-tetracosadiene-1-24-dioic acid (V) .

A) To a solution of 10.8 g. of butadiene , 2.7 g. of acrylonitrile and 16 g. of ferrous sulfate heptahydrate in 100 ml. of methanol, is added dropwise 6 g. of N-methylpentamethyleneoxazirane over a period of 20 minutes with stirring in a nitrogen atmosphere at -5-0° . After completion of the addition, the solution is stirred for 1 hour and then poured into water. The aqueous solution is extracted with chloroform; after drying the chloroform solution, the solvent is removed, a residue of amides remains (which in part crystallizes). The product (4.3 g.) is dissolved in 40 ml. of boiling ethyl acetate and upon cooling 1.8 g. of V crystallizes, m.p. 102°.
Anal. Calcd. for $C_{28}H_{46}N_4O_2$: C, 71.45; H, 9.85; N, 11.90 .
Found : C, 71.46; H, 9.62; N, 11.94 .
I.R. : 3300 cm^{-1} (NH) , 2250 cm^{-1} (CN), 1650 cm^{-1} (C=O), 970 cm^{-1} (CH=CH trans).
N.M.R. : vinyl protons centered at 5.5 δ (4H), CH_3-N at 2.76 and 2.84 δ (6H).
M.S. ; m/e (I%) : 470 (4), 398 (22), 289 (88), 235 (72), 73 (100),

58 (60). The molecular ion M (470) loses $\cdot CH_2-CO-NH-CH_3$ (398) and $NC-\dot{C}H-(CH_2)_6-CO-NH-CH_3$ (289). Significative ion: 235 (1/2 M) $(CH_3-NH-CO-(CH_2)_6-CH(CN)-CH_2-CH=CH-CH_2^+)$. Fragments 73 (the McLafferty rearrangement ion) and 58 ($CH_3-NH-CO^+$) are characteristic of N-methyl-amides.

Evaporation to dryness of the ethyl acetate solution leaves a viscuos product (2.5g.) , which the analytical data show to be predominantly a mixture of isomers of V.

Anal. Found : C, 70.41; H, 9.89; N, 10.66 . I.R. spectrum shows all the bands of V and two bands at 990 and 910 cm^{-1} ($CH=CH_2$) .Major fragments of M.S. are identical to that of V.

B) To a mixture of 10.8 g. of butadiene, 2.7 g. of acrylonitrile, 14 g. of ferrous sulfate heptahydrate and 50 g. of urea in 100 ml. of water, is added dropwise 6 g. of N-methylpentamethyleneoxasirane over a period of 40 minutes with vigorous stirring at -10°. The butadiene is allowed to evaporate and the mixture is acidified with sulfuric acid.

Extraction with chloroform results in 8.5 g. of product; crystallization from ethyl acetate solution leads to the separation of 1.7 g. of V , m.p. 102°.

Evaporation to dryness of the ethyl acetate solution leaves 6.8 g. of viscuos product.

Anal. Found : C, 69.21;H, 9.85; N, 12.62 . I.R. spectrum exhibits all the bands of V and two bands at 990 and 910 cm^{-1} ($CH=CH_2$). M.S. spectrum shows a weak peak at 523 (MV + 53) in addition to the major peaks of V . These analytical data indicate that the viscous product is predominantly a mixture of isomers of V, present as impurities arising from reaction of more than two moles of acrylonitrile for two moles of butadiene, as a result of the greater solubility of acrylonitrile in water.

Mixture of methyl-dicyano-C_{24}-dienedioate isomers. (VI)

10 g. of 34% hydrogen peroxide is added to 19.6 g. of cyclohexanone

while the temperature is kept below 40°. After 1 hour at room temperature the mixture is dissolved in 150 ml. of methanol which contains 20 ml. of concentrated sulfuric acid . The solution is added dropwise with stirring in a nitrogen atmosphere at -5-0° to a solution of 16.2 g. of butadiene , 15.9 g. of acrylonitrile , 28 g. of ferrous sulfate heptahydrate in 150 ml. of methanol over a period of 1 hour. After completion of addition , the solution is stirred for 30 minutes and then poured into water ; the aqueous solution is extracted with ether. The ether solution is washed with a solution of sodium bicarbonate and after removal of the solvent and excess cyclohexanone, the residue is distilled to yield 9.5 g. of product boiling at 240-250°/0.5 mm., and 4.1 g. of residue.

Anal. Calcd. for $C_{28}H_{44}O_4N_2$: C, 71.15; H, 9.38; N, 5.93 .

Found : C, 70.93; H, 9.22; N, 5.88 .

I.R. : 2250 cm^{-1} (CN) , 1750 cm^{-1} (CO) , 970 cm^{-1} (CH=CH trans) , 990 and 910 cm^{-1} ($CH=CH_2$) .

M.S. ; m/e (I%) : 472 (2) , 441 (13) , 440 (7) , 409 (10) , 408 (3) , 290 (22) , 258(19) , 236 (44) , 204 (66) , 183 (23) , 151 (96) , 74 (48) , 59 (49) . The molecular ion M (472) loses $CH_3O^{\bullet}$ (441) and CH_3OH (440) . Both these fragments eliminated CH_3OH (409 and 408). Highly significative ions : 290 (M- $NC-\dot{C}H-(CH_2)_6-COOCH_3$) , 258 (290 - CH_3OH) , 236 (1/2 M $CH_3OOC-(CH_2)_6-CH(CN)-CH_2-CH=CH-CH_2^+$) , 204 (236 - CH_3OH) , 183 (the protonated complementary ion of 290) and 151 (183 - CH_3OH). Fragments 74 (the Mc Lafferty rearrangement ion) and 59 (CH_3OCO^+) are typical of aliphatic methyl esters.

Methyl esters of 8-cyano-10-methoxy-11-dodecenoic acid and 8-cyano-12-methoxy-trans-10-dodecenoic acid. (VII) and (VIII)

5 g. of 34% hydrogen peroxide is added to 9.8 g. of cyclohexanone while the temperature is kept below 40° by intermittent cooling. The mixture is maintained at room temperature for 1 hour and then dissolved in 75 ml. of methanol which contains 10 ml. of concentrated sulfuric

acid. The solution is cooled at -5° and 5.4 g. of butadiene , 15 g. of acrylonitrile , 1.2 g. of cupric sulfate pentahydrate are dissolved. A solution of 15 g. of ferrous sulfate heptahydrate in 60ml. of methanol is added dropwise with stirring in a nitrogen atmosphere at -5-0° over a period of 1 hour . After completion of the addition the solution is stirred for 30 minutes and then poured into water ; the aqueous solution is extracted with ether . The ether extract is washed with a solution of sodium bicarbonate and dried over sodium sulfate . After removal of the solvent and excess cyclohexanone, the residue is distilled to yield 1.3 g. of product boiling at 50-120°/1 mm. , 8.8 g. of product boiling at 160-180°/1mm. and 0.9 g. of residue. The main fraction is analysed by g.l.c. at 160° , using a 2 m. x 3.5 mm. column packed with 1% SE 30 on Gas Chrom P silanized . Three compounds with increasing retention times are present : VIIa (29%) , VIIb (20.2%) and VIII (50.8%) . These compounds are isolated by preparative g.l.c..

Anal. Calcd. for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43; N, 5.24.

Found for VIIa : C, 67.01; H, 9.37; N, 5.20 .

Found for VIIb : C, 67.47; H, 9.35; N, 5.14 .

Found for VIII : C, 67.18; H, 9.29; N, 5.31 .

The I.R. spectra of VIIa and VIIb are identical : 2250 cm^{-1} (CN) , 1750 cm^{-1} (CO) , 990 and 930 cm^{-1} ($CH=CH_2$) . I.R. of VIII : 2250 cm^{-1} (CN) , 1750 cm^{-1} (CO) , 975 cm^{-1} (CH=CH trans).

N.M.R. of VIIa and VIIb : CH_3O at 3.25 δ (3H) , CH_3OOC at 3.65 δ (3H), vinyl protons at 5.20-5.70 δ (3H) . N.M.R. of VIII : CH_3O at 3.25 δ (3H) , CH_3OOC at 3.65 δ (3H) , vinyl protons centered at 5.63 δ (2H).

The M.S. spectra of VIIa and VIIb are practically identical and similar to that of VIII ; m/e (I%) for VIII : 267 (0.1) , 236 (4.5) , 204 (15), 183 (4) , 151 (19) , 85 (87) , 71 (100) , 55 (50) , 41 (42). The scarce molecular ion (267) loses $\cdot OCH_3$ (236) and CH_3OH (235) . From the 236 ion loss of methanol occurs (204) . Significative fragments are : 183 ($NC-(CH_2)_7-COOCH_3$) , 151 (183 - CH_3OH) , 85 ($^+CH_2-CH=CH-CH_2-OCH_3$) , 71 ($^+CH_2-CH=CH-OCH_3$) due to previous shift of the double

bond position , 55 which is derived from 85 by loss of CH_2O as proven by the appropriate metastable ion , and 41 derived from 71 by an analogous process ;

m/e (I%) for VIIa and VIIb : 267 (0.1) , 236 (0.8) , 235 (0.4) , 204 (6) , 183 (5) , 151 (1.7) , 85 (3) , 55 (7.5) , 41 (13) . The main feature of this spectrum is the great predominance of the 71 ion; it is easily formed by the simple cleavage of the allyl C-C adjacent to the carbon atom bearing the OCH_3 group. These differ from their isomer VIII in that, according to the structures, these compounds yield the scarce 85 fragment.

Methyl ester of 8-carboxy-10-hydroxy-11-dodecenoic acid-γ-lactone.(IX)

The reaction is performed exactly as for the preparation of VII and VIII with the difference that acrylic acid is used instead of acrylonitrile. 6.9 g. of product boiling at 170-5°/0.5 mm. is obtained. G.l.c.(using the same conditions as for VII and VIII) shows 96% of IX ; a sample purified by preparative g.l.c. was analysed.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72 . Found : C, 66.02; H, 8.69 .

I.R. : 1780 cm^{-1} (CO lactone) , 1750 cm^{-1} (CO ester).

M.S. ; m/e (I%) : 223 (18) , 222 (11) , 112 (100) , 74 (42) , 59 (29). The molecular ion is missing and the fragments 223 ($M - OCH_3$) , 222 ($M - CH_3OH$) , 74 (the Mc Lafferty rearrangement ion on the methyl ester carbonyl group) and 59 (CH_3OCO^+) are typical of methyl esters . An abundant and significative ion is 112 due to loss of $CH_2=CH-(CH_2)_4-COOCH_3$ as a result of a Mc Lafferty rearrangement on the lactone carbonyl group.

Saponification of 2 g. of IX with sodium hydroxide in methanol produces 1.7 g. of the corresponding carboxylic acid , m.p. 96-7° (from ethyl acetate-petroleum ether).

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39 .Found : C, 64.96; H, 8.34

Acid equiv. Calcd. for $C_{13}H_{20}O_4$: 240. Found: at 20° 240 , at 100° 119.

M.S. : Fragmentation is very similar to that of IX . The highest mass fragment is 222 ($M - H_2O$) . The abundant and significative ion 112 must have the same structure as the corresponding fragment of IX .

Methyl ester of 8-carboxy-10-hydroxy-10-phenylundecanoic acid-γ-lactone

(X)

The reaction is performed as for the preparation of IX , using α-methylstyrene instead of butadiene : 9.6 g. of product boiling at 180-190°/1 mm. is obtained . G.l.c. (using the same conditions as for IX) shows that the sample contains 90% of the lactone X ; a sample purified by preparative g.l.c. is analysed.

Anal.Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23.Found : C, 71.36; H, 8.43.

I.R. : 1780 cm^{-1} (CO lactone) , 1750 cm^{-1} (CO ester).

M.S. ; m/e (I%) : 318 (1) , 303 (15) , 300 (3) , 271 (10) , 105 (100) . The molecular ion (318) loses $CH_3^{\bullet}$ (303) and water (300). The ion 271 is derived from 303 by loss of CH_3OH . The base peak at m/e 105 corresponds to benzoyl ion.

The corresponding acid , obtained from alkaline hydrolysis , melts at 83-4° (from ethyl acetate).

Anal.Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found : C, 71.29; H, 7.95.

Acid equiv.Calcd. : 304 . Found at 20° 304 , at 100° 150 .

M.S. : The fragmentation pattern is similar to that of its methyl ester(X).

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