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Abstract

Full Text

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COMPLETE SYNTHESIS OF LINOLEIC, LINOLENIC, ARACHIDONIC, AND DOCOSATETRAENOIC-7, 10, 13, 16 ACIDS

(Presented by Academician M. I. Kabachnik on 21 V 1962)

Higher polyenoic acids of the aliphatic series with compositions C_{18}, C_{20}, C_{22}, which perform important biological functions, belong to the group of "essential" compounds. Linoleic (I) and linolenic (II) acids are constituents of triglycerides of vegetable oils and animal fats ([1]); arachidonic (III) and docosatetraenoic-7,10,13,16 (IV) acids are components of complex lipids of the brain, liver, and other organs of animals and humans ([2]). The chemical structure of cis-, cis-, cis-, cis-docosatetraenoic-7,10,13,16 (IV), cis-, cis-, cis-, cis-eicosatetraenoic-5,8,11,14 (III), cis-, cis-, cis-octadecatrienoic-9,12,15 (II), and cis-, cis-octadecadienoic-9,12 (I) acids until recently had remained unconfirmed synthetically, although intensive work is being carried out in this direction. Within the general plan of synthetic investigations in the field of triglycerides ([3]) and phospholipids ([4]), we have developed a number of methods for the synthesis ([5]) and isolation of these acids from natural sources ([6]).

Of the routes to their synthetic preparation that we have studied, the present communication describes methods based on the use of butyne-2-diol-1,4 (V) ([7]), together with amyl bromide ([8]), 1,1,1,7-tetrachloroheptane (IX) ([9]), and 1-bromo-3-chloropropane (XXIV) ([10]). The methods developed for the synthesis of acids (I, II, III, IV) proceed through the preparation of polyynic compounds, which are selectively reduced to the corresponding derivatives with cis-configuration, as demonstrated by physicochemical constants and IR-spectral data.

By the reaction of sodium acetylide with amyl bromide, heptyne-1 (VI) is obtained; its magnesium bromide derivative is condensed with 1,4-dichlorobutyne-2 (VII), prepared from butyne-2-diol-1,4 (V), in 1-chloroundecadiyne-2,5 (VIII) ([11]). Compound (VIII), with methyl 7-iodoheptanoate (XII) by the Grignard-Wurtz method, gives methyl octadecadiynoate-9,12 (XIII). Selective hydrogenation of (XIII) and subsequent saponification of the intermediate ester (XIV) lead to cis-, cis-octadecadienoic-9,12 acid, linoleic acid (I). The methyl ester of 7-iodoheptanoic acid (XII) used in the preparation of linoleic acid (I) is obtained from 1,1,1,7-tetrachloroheptane (IX) through 7-chloroheptanoic acid (X) and its methyl ester (XI), in which the chlorine atom is replaced by iodine (Scheme 1). Condensation of methyl 7-iodoheptanoate (XII) with 1-bromoundecatriyne-2,5,8 (XXII) leads to methyl octadecatriynoate-9,12,15 (XXIII), which is saponified to cis-, cis-, cis-octadecatrienoic-9,12,15 acid, linolenic acid (II). The 1-bromoundecatriyne-2,5,8 (XXII) used in this synthesis is obtained on the basis of 4-chlorobutyn-2-ol-1 (XV) from butyne-2-diol-1,4 (V). 4-Chlorobutyn-2-ol-1 (XV), with the aid of methylmagnesium iodide, is converted into pentyn-2-ol-1 (XVI). Reaction of the corresponding bromide (XVII) with the dimagnesium bromide derivative of propargyl alcohol gives octadiyn-2,5-ol-1 (XVIII), which is converted into bromide (XIX), and in an analogous manner the chain is lengthened by three carbon atoms. The resulting undecatriyn-2,5,8-ol-1 (XX) is hydrogenated to undecatrien-2,5,8-ol-1 (XXI), and its oxy group is replaced by bromine (XXII).

1-Bromotetradecatriyne-2,5,8 (XXIX), prepared by condensation of 1-chloroundecadiyne-2,5 (XIII) with propargyl alcohol, followed by replacement of hydroxyl by bromine in tetradecatriyn-2,5,8-ol-1 (XXVIII), intro-

$$\mathrm{ClCH_2C{\equiv}CCH_2OH} \quad (XV)$$
$$\downarrow$$
$$\mathrm{CH_3CH_2C{\equiv}CCH_2OH} \quad (XVI)$$
$$\downarrow$$
$$\mathrm{CH_3CH_2C{\equiv}CCH_2Br} \quad (XVII)$$
$$\downarrow$$
$$\mathrm{CH_2(CH_2C{\equiv}C)_2CH_2OH} \quad (XVIII)$$
$$\downarrow$$
$$\mathrm{CH_3(CH_2C{\equiv}C)_2CH_2Br} \quad (XIX)$$
$$\downarrow$$
$$\mathrm{CH_3(CH_2C{\equiv}C)_3CH_2OH} \quad (XX)$$
$$\downarrow$$
$$\mathrm{CH_3(CH_2CH{=}CH)_3CH_2OH} \quad (XXI)$$
$$\downarrow$$
$$\mathrm{CH_3(CH_2CH{=}CH)_3CH_2Br} \quad (XXII)$$

$CH_3(CH_2)_4C{\equiv}CH$ (*VI*) $HOCH_2C{\equiv}CCH_2OH$ (*V*) $Cl(CH_2)_6CCl_3$ (*IX*)

↓ ↓ ↓

$ClCH_2C{\equiv}CCH_2Cl$ (*VII*) $Cl(CH_2)_6COOH$ (*X*)

↓ ↓

$CH_3(CH_2)_3(CH_2C{\equiv}C)_2CH_2Cl$ (*VIII*) $Cl(CH_2)_6COOCH_3$ (*XI*)

↓ ↓

$J(CH_2)_6COOCH_3$ (*XII*)

↓

$CH_3(CH_2)_3(CH_2C{\equiv}C)_2(CH_2)_7COOCH_3$ (*XIII*)

↓

$CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOCH_3$ (*XIV*)

↓

$CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOH$ (*I*)

$CH_3(CH_2CH{=}CH)_3(CH_2)_7$

↓

$CH_3(CH_2CH{=}CH)_3(C$

Scheme 1

$Br(CH_2)_3Cl$ (*XXIV*)

↓

$HC{\equiv}C(CH_2)_3Cl$ (*XXV*)

↓

$HC{\equiv}C(CH_2)_3CN$ (*XXVI*)

↓

$HC{\equiv}C(CH_2)_3COOH$ (*XXVII*)

$CH_3(CH_2)_3(CH_2C{\equiv}C)_2CH_2Cl$ (*VIII*)

↓

$CH_3(CH_2)_3(CH_2C{\equiv}C)_3CH_2OH$ (*XXVIII*)

↓

$CH_3(CH_2)_3(CH_2C{\equiv}C)_3CH_2Br$ (*XXIX*)

$$HOCH_2C{\equiv}CCH_2OH \quad (V)$$
$$\downarrow$$
$$HO(CH_2)_4OH \quad (XXXII)$$
$$\downarrow$$
$$Cl(CH_2)_4Cl \quad (XXXIII)$$
$$\downarrow$$
$$J(CH_2)_4Cl \quad (XXXIV)$$
$$\downarrow$$
$$HC{\equiv}C(CH_2)_4Cl \quad (XXXV)$$
$$\downarrow$$
$$HC{\equiv}C(CH_2)_4J \quad (XXXVI)$$
$$\downarrow$$
$$HC{\equiv}C(CH_2)_4CH(COOR)_2 \quad (XXXVII)$$
$$\downarrow$$
$$HC{\equiv}C(CH_2)_4CH(COOH)_2 \quad (XXXVIII)$$
$$\downarrow$$
$$HC{\equiv}C(CH_2)_5COOH \quad (XXXIX)$$

$$CH_3(CH_2)_3(CH_2C{\equiv}C)_4(CH_2)_3COOH \quad (XXX)$$
$$\downarrow$$
$$CH_3(CH_2)_3(CH_2CH{=}CH)_4(CH_2)_3COOH \quad (III)$$
$$\downarrow$$
$$CH_3(CH_2)_3(CH_2CH{=}CH)_4(CH_2)_3COOC_2H_5 \quad (XXXI)$$

$$CH_3(CH_2)_3(CH_2C{\equiv}C)_4(CH_2)_5COOH \quad (XL)$$
$$\downarrow$$
$$CH_3(CH_2)_3(CH_2CH{=}CH)_4(CH_2)_5COOH \quad (IV$$
$$\downarrow$$
$$CH_3(CH_2)_3(CH_2CH{=}CH)_4(CH_2)_5COOCH_3 \quad (X$$

Scheme 2

are brought into reaction with the dimagnesium bromide derivative of hexyn-5-oic acid (XXVII) in the presence of monovalent cuprous cyanide (13), converting it into eicosatetra-5,8,11,14-ynoic acid (XXX). Selective hydrogenation of (XXX) gives cis-, cis-, cis-, cis-eicosatetra-5,8,11,14-enoic, arachidonic acid (III). Hexyn-5-oic acid (XXVII) is prepared from 1-chloropentyne-4 (XXV) by reaction with sodium cyanide through the corresponding nitrile (XXVI). 1-Chloropentyne-(XXV), in turn, is obtained from 1-chloro-3-bromopropane (XXIV) with sodium acetylide (Scheme 2).

Analogously to arachidonic acid (III), from 1-bromotetradecatriyne-2,5,8 (XXIX) and octyn-7-oic acid (XXXIX), through the intermediate docosatetrayn-7,10,13,16-oic acid (XL), cis-, cis-, cis-, cis-docosatetraen-7,10,13,16-oic acid (IV) is synthesized. The starting octyn-7-oic acid (XXXIX) is obtained from butanediol-1,4 (XXXII), prepared by hydrogenation of butyne-2-diol-1,4 (V), through 1,4-dichlorobutane (XXXIII) and 1-chloro-4-iodobutane (XXXIV). With the aid of sodium acetylide, compound (XXXIV) is converted into 1-chlorohexyne-5 (XXXV), which, after replacement of chlorine by iodine, is brought into reaction with sodium malonate. The resulting 2-(hexyn-5′)-malonic ester (XXXVII) is saponified to (XXXVIII) and decarboxylated to octyn-7-oic acid (XXXIX).

The synthesized polyenoic acids (I, II, III, IV) are characterized by physico-chemical and spectral data (Table 1), and also by polybromo derivatives, the melting points of which, in a mixed sample with the corresponding bromides from natural acids, showed no depression. The acids are also characterized in the form of esters (XIV, XXIII, XXXI, XLI) and used in the synthesis of lipids —vitamins of group F.

Table 1

Physicochemical constants of the compounds

Compound	Empirical formula	M.p., °C	B.p., °C (mm)	d_4^{20}	n_D^{20}	*MR* found	*MR* calculated	Found, % C	Found, % H	Calculated, % C	Calculated, % H
I	$C_{18}H_{32}O_2F_2$	—	146–149 (0,20)	0,9059	1,4678	86,04	85,93	77,30	11,49	77,11	11,50
II	$C_{18}H_{30}O_2F_3$	—	145–148 (0,15)	0,9109	1,4711	85,30	85,46	77,59	10,85	77,66	10,86
IV	$C_{22}H_{36}O_2F_4$	—	161–164,5 (0,07)	0,9220	1,4875	103,80	103,47	79,62	11,01	79,47	10,91
VI	$C_7H_{12}F$	—	98–99,5 (756)	0,7487	1,4177	32,37	32,46	—	—	—	—
VII	$C_4H_4Cl_2F$	—	67,9–72,4 (8)	1,268	1,5048	28,53	28,34	—	—	—	—
VIII	$C_{11}H_{15}ClF_2$	—	70–72,5 (0,22)	0,9868	1,4913	53,64	53,73	72,46	8,35	72,32	8,28

Compound	Empirical formula	M.p., °C	B.p., °C (mm)	d_4^{20}	n_D^{20}	*MR* found	*MR* calculated	Found, % C	Found, % H	Calculated, % C	Calculated, % H
X	$C_7H_{13}O_2Cl$	—	146—147 (8,5)	1,0989	1,4565	40,77	40,93	—	—	—	—
XI	$C_8H_{15}ClO_2$	—	105—106,1 (10)	1,0395	1,4426	45,53	45,66	—	—	—	—
XII	$C_8H_{15}JO_2$	—	128—129,6 (8)	1,4547	1,4938	53,98	53,50	—	—	—	—
XIII	$C_{19}H_{30}O_2F_2$	—	147—150 (0,12)	0,9566*	1,4892*	87,66	87,47	78,64	10,14	78,56	10,41
XIV	$C_{19}H_{34}O_2F_2$	—	139,2—140,5 (0,21)	0,8930	1,4609	90,42	90,66	77,67	11,45	77,52	11,63
XV	C_4H_5ClOF	—	92—94 (13)	1,2057	1,4990	25,46	25,06	—	—	—	—
XVI	C_5H_8OF	—	67—68 (27)	0,9186	1,4559	24,90	24,81	—	—	—	—
XVII	C_5H_7BrF	—	54—56 (43)	1,3931	1,5003	30,88	31,05	—	—	—	—
XVIII	$C_8H_{10}OF_2$	—	72—75 (0,23)	0,9750	1,4912	36,31	36,66	—	—	—	—
XIX	$C_8H_9BrF_2$	—	68—71 (0,42)	1,3407	1,5296	42,64	42,90	—	—	—	—

Compound	Empirical formula	M.p., °C	B.p., °C (mm)	d_4^{20}	n_D^{20}	MR found	MR calculated	Found, % C	Found, % H	Calculated, % C	Calculated, % H
XX	$C_{11}H_{12}OF_3$	27—29,5	110—112 (0,1)	—	—	—	—	82,77	7,38	82,46	7,53
XXI	$C_{11}H_{18}OF_3$	—	69—73 (0,13)	0,9185	1,4951	52,81	53,12	79,25	11,04	79,43	10,96
XXII	$C_{11}H_{17}BrF_3$	—	75—77 (0,19)	1,1678	1,5159	59,18	59,36	57,70	7,42	57,62	7,50
XXIII	$C_{19}H_{32}O_2F_3$	—	130—132 (0,14)	0,8979	1,4682	90,41	90,19	77,89	10,81	78,03	11,04
XXIV	C_3H_6BrCl	—	139—141 (754)	1,5812	1,4845	28,50	28,68	—	—	—	—
XXV	C_5H_7ClF	—	110—112 (752)	0,9648	1,4434	27,64	27,97	—	—	—	—
XXVI	C_6H_7NF	—	83,4—85 (25)	0,8916	1,4404	27,52	27,84	—	—	—	—
XXVII	$C_6H_8O_2F$	—	111—112 (14)	1,0372	1,4494	29,02	29,35	64,04	7,41	64,28	7,19
XXVIII	$C_{14}H_{18}OF_3$	28—28,8	137—138 (0,06)	—	—	—	—	83,06	8,75	83,12	8,97
XXIX	$C_{14}H_{17}BrF_3$	—	126—128 (0,04)	1,1972	1,5242	67,79	67,42	63,88	6,41	63,40	6,46

Compound	Empirical formula	M.p., °C	B.p., °C (mm)	d_4^{20}	n_D^{20}	MR found	MR calculated	Found, % C	Found, % H	Calculated, % C	Calculated, % H
XXX	$C_{20}H_{24}O_2F_4$	79,8–80,5	–	–	–	–	–	81,24	8,00	81,04	8,16
XXXI	$C_{22}H_{36}O_2F_4$	–	121–122 (0,04)	0,8974	1,4719	103,70	103,92	79,35	10,95	79,47	10,91
XXXII	$C_4H_{10}O_2$	–	112–114,8 (7)	1,0230	1,4454	23,46	23,72	–	–	–	–
XXXIII	$C_4H_8Cl_2$	–	155,6–159 (759)	1,1360	1,4536	30,25	30,41	37,79	6,29	37,83	6,34
XXXIV	C_4H_8ClJ	–	64–67,5 (6)	1,7712	1,5342	38,37	38,34	–	–	–	–
XXXV	C_6H_9ClF	–	48,5–51,9 (20)	0,9679	1,4497	32,36	32,71	61,54	7,44	61,80	7,78
XXXVI	C_6H_9JF	–	77,9–81,0 (17)	1,5761	1,5255	40,51	40,65	–	–	–	–
XXXVII	$C_{13}H_{20}O_4F$	–	146–149 (12)	1,0120	1,4451	63,20	63,48	65,35	8,38	65,01	8,39
XXXVIII	$C_9H_{12}O_4F$	89–91,5	–	–	–	–	–	58,94	6,68	58,68	6,57
XXXIX	$C_8H_{12}O_2F$	–	97–100,5 (0,8)	0,9851	1,4530	38,47	38,62	68,45	8,60	68,55	8,63
XL	$C_{22}H_{28}O_2F_4$	80–81,3	–	–	–	–	–	81,61	8,46	81,44	8,70

Compound	Empirical formula	M.p., °C	B.p., °C (mm)	d_4^{20}	n_D^{20}	MR found	MR calculated	Found, % C	Found, % H	Calculated, % C	Calculated, % H
XLI	$C_{23}H_{38}O_2F_4$		128,3 – 131,9 (0,05)	0,9042	1,4764	108,10	108,20	79,70	10,97	79,71	11,05

* d_4^{25} and n_D^{25}.

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REFERENCES

1. V. Bayajan, W. Coschran, *J. Am. Oil Chem. Soc.*, **36**, 181 (1959); H. B. White, F. W. Quakkenbust, *J. Am. Oil Chem. Soc.*, **36**, 653 (1959).
2. O. S. Privett, R. P. Weber, E. Ch. Nickel, *J. Am. Oil Chem. Soc.*, **36**, 443 (1959).
3. I. K. Sarycheva, G. A. Serebrennikova et al., DAN, **135**, 617 (1960); G. A. Serebrennikova, T. K. Mitrofanova et al., DAN, **140**, 1083 (1961).
4. V. I. Shvets, N. A. Bogoslovskii et al., DAN, **140**, 851 (1961).
5. I. K. Sarycheva, G. I. Myagkova, N. A. Preobrazhenskii, ZhOKh, **29**, 2318 (1959).
6. A. A. Kraevskii, V. I. Vol' kova et al., ZhOKh, **32**, 742 (1962).
7. Yu. B. Pyatnova, L. D. Smirnov et al., ZhOKh, **32**, 142 (1962).
8. W. Reppe, *Chem. u. Technik der Acetylen-Druck-Reaktionen*, 2 Aufl., Verlag-Chemie, Weinheim, 1952, p. 3.
9. A. E. Akopyan, M. B. Ordyan, S. P. Ekmedzhyan, K. L. Kudoyan, USSR Patent, 127647. April 12, 1960.
10. A. N. Nesmeyanov, L. I. Zakharkin, *Izv. AN SSSR, OKhN*, 1955, 224.

11. N. N. Dykhanov, I. I. Korotkina, *Med. prom.*, No. 4, 26 (1957).

12. M. G. Pleshakov, I. K. Sarycheva, N. A. Preobrazhenskii, ZhOKh, **30**, 2983 (1960).

13. Yu. B. Pyatnova, I. K. Kovtun et al., ZhOKh, **32**, 138 (1962).

14. J. M. Osbond, P. G. Philpott, J. C. Wickens, *J. Chem. Soc.*, 1961, 2779.

Note: Figure translations are in progress. See original paper for figures.