CHEMISTRY OF POLYENIC AND POLYYNIC COMPOUNDS

COMMUNICATION 17. DIYNIC HYDROXY CARBOXYLIC ACIDS AND THEIR CHEMICAL TRANSFORMATIONS*

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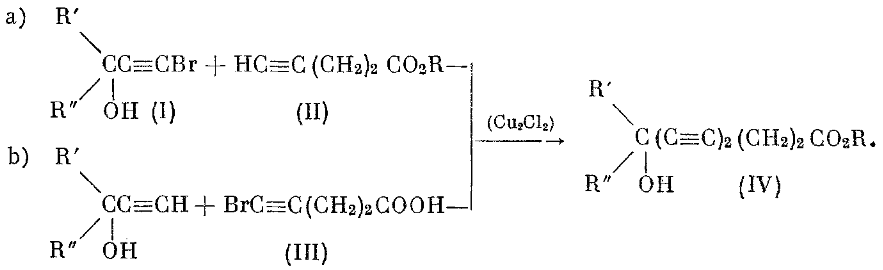
Natural polyynic compounds include those of general formula $R-(C\equiv C)_nCH_2CH_2CO_2R'$, some of which have high antibacterial activity [1-3]. Examination of the literature shows that the simplest method of synthesizing such compounds may be provided by the mixed condensation of acetylenic bromides with acetylene derivatives, which was first proposed by Chodkiewiez [4] and has been applied successfully in a number of cases [3, 5].

We considered it to be of interest to apply this reaction for the synthesis of various diynic hydroxy carboxylic acids (IV) for the purpose of studying their physiological activity and of using them in the preparation of more complex polyunsaturated compounds allied to natural products. We used the following general synthesis scheme for these compounds, in which acetylenic alcohols or their bromo derivatives (I) are condensed with methyl 4-pentynoate (II) or with 5-bromo-4-pentynoic acid (III):



The diynic hydroxy carboxylic acids obtained by these methods are listed in the table.

It will be seen from the table that the yields of condensation products are greatly affected by the amount of cuprous chloride used. Thus, in the synthesis of methyl 8-hydroxy-8-methyl-4,6-decadiynoate (V) and of methyl 8-hydroxy-4,6-decadiynoate (VII) increase in the amount of catalyst from 0.015 to 0.1 molecular proportion leads to an increase in yield by 2-2.5-fold. For the cases of 8-hydroxy-8-methyl-4,6-decadiynoic acid (VI), 9-hydroxy-4,6-decadiynoic acid (IX) and its ester (VIII), and also 8-hydroxy-9-phenyl-4,6-nonadiynoic acid (X) and its ester (XI), it was shown that the yields of these products are close in synthesis both by scheme (a) and by scheme (b). In the general case, in the choice of a method for the prepareation of diynic hydroxy carboxylic acids, the reactivity and solubility of the copper complex of the acetylene component, on the one hand, and the stability of the acetylenic bromide, on the other, must be taken into account. It is noteworthy that, when bromo derivatives of acetylenic alcohols are used, the yields of final products fall greatly as we pass from tertiary to primary alcohols, and, for example, the condensation of the bromo derivatives of 2-propyn-1-ol with methyl 4-pentynoate (expt. 11) gives methyl 8-hydroxy-4,6-octadiynoate (XII) in only 33% yield. It was shown that this arose not only from the high tendency for 3-bromo-2-propyn-1-ol to undergo oxidative side reactions [4], but the presence of an appreciable

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Functional Derivatives of Diynic Acids

Expt. No.	$R_1—C≡C—Br$	$HC≡C—R_2$	Amt. of Cu_2Cl_2, mole per mole of acetylenic deriv.	Reaction product	Yield, %	B. p., °C (p, mm) or m.p., °C	n_D^{20}	Found, %		Calculated, %		Ultraviolet spectrum (in alcohol)		Infrared spectrum (in $CHCl_3$)
	R_1	R_2						C	H	C	H	λ_{max}, mμ	ε	ν, cm^{-1}
1	$C_2H_5C(CH_3)(OH)$—	—$CH_2CH_2CO_2CH_3$	0,015	(V)	53	95—96 (0,02)	1,5070	68,90	7,83	69,21	7,74	228, 241, 254	3620, 3770, 2480	1747 (—CO_2CH_3) 2281 (—C≡C—)
2	$C_2H_5C(CH_3)(OH)$—	—$CH_2CH_2CO_2CH_3$	0,1	(V)	86									
3	$C_2H_5C(CH_3)(OH)$—	—$CH_2CH_2CO_2H$	0,1	(VI)	71	106—107 *		67,80	7,46	68,02	7,27	228, 240, 254	276, 167, 270	
4	$HO_2CCH_2CH_2$—	—$C(OH)(CH_3)C_2H_5$	0,1	(VI)	65									
5	$C_2H_5CH(OH)$—	—$CH_2CH_2CO_2CH_3$	0,015	(VII)	40	110—112 (0,06)	1,5071	68,06	7,43	68,02	7,27	228, 240, 254	2435, 2480, 1413	1747, 2281
6	$C_2H_5CH(OH)$—	—$CH_2CH_2CO_2CH_3$	0,1	(VII)	80									
7	$CH_3CH(OH)CH_2$—	—$CH_2CH_2CO_2CH_3$	0,1	(VIII)	65	110—115 (0,06)	1,5151	67,65	7,23	68,02	7,27	226, 240, 265	466, 446, 265	
8	$HO_2CCH_2CH_2$—	—$CH_2CH(OH)CH_3$	0,015	(IX)	50	68 *		66,88	6,81	66,65	6,71	224,5, 240, 253, 268,5, 284,5, 303	623, 496, 335, 158, 164, 139	
9	$HO_2CCH_2CH_2$—	—$CH(OH)CH_2C_6H_5$	0,015	(X)	55	116 †		73,82	5,44	74,36	5,83	243, 255, 282,5,302	790, 606, 114, 893	
10	$C_6H_5CH_2CH(OH)$—	—$CH_2CH_2CO_2CH_3$	0,1	(XI)	55	140—150 (0,007)	1,5690	74,76	6,15	74,98	6,29	243, 257,5 279,5,295	486, 372, 272, 205	
11	$HOCH_2$—	—$CH_2CH_2CO_2CH_3$	0,1	(XII)	33	115—120 (0,08)	1,5223	65,09	5,90	65,05	5,81	230, 242, 255,5	417, 395, 221	
12	$HO_2CCH_2CH_2$—	—CH_2OH	0,015	(XIII)	40	128,5—129†		63,04	5,20	63,15	5,30	223,5,242 255,5,282 300,5	4650, 4250, 2565, 955, 808	
13	$HO_2CCH_2CH_2$—	—CH_2OH	0,1	(XIII)	40									
14	$\overline{\underline{(CH_2)_5}}C(OH)$—	—$CH_2CH_2CO_2CH_3$	0,015	(XIV)	47	120 (0,02)	1,5310	71,96	7,88	71,77	7,74	229, 241, 255	3350, 3470, 2025	1737, 2281
15	$HO_2CCH_2CH_2$—	—$CH_2CH_2CO_2CH_3$	0,1	(XV)	80	101—101,5 *		63,40	5,73	63,45	5,81	225, 238, 253, 282,5, 302	400, 314, 178, 20, 17	
16	$HO_2CCH_2CH_2$—	—$CH(OH)CH=CH_2$	0,015	(XVI)	52	82—83 *		67,97	5,68	67,40	5,66	227,5, 242, 256, 283, 302	577, 515, 321, 125, 100	1720 (—CO_2H) 2280 3018 3043 (—$CH=CH_2$)
17	$HO_2CCH=CH$—	—$CH_2CH_2CO_2CH_3$	0,1	XVII)	94	121		63,97	4,91	64,07	4,89	220, 265, 280, 298, 340	11700, 21200, 10200, 16800, 1620	

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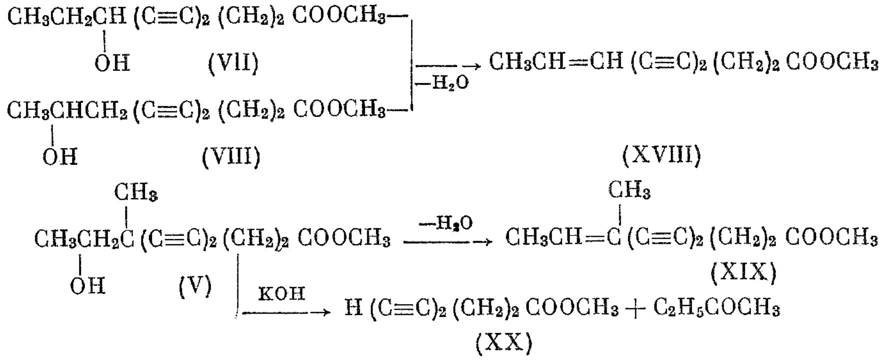
*Solvent: mixture of petroleum ether and benzene.

†Solvent: benzene.

amount of 1,3-dibromopropyne in the alcohol (as shown by gas-liquid chromatography), which is formed in the reaction of 2-propyn-1-ol with potassium hypobromite. Attempts to synthesize 8-hydroxy-4,6-octadiynoic acid (XIII) by scheme (b) (see experiments 12 and 13) also did not give good results, and the low yields in these cases are related to the high tendency for 2-propyn-1-ol to undergo symmetrical oxidative coupling [3, 4].

Our results show that for preparative purposes it is more convenient to use methyl 4-pentynoate (II, R = CH_3) as acetylene component and conduct the synthesis by scheme (a), for in this case not only are the yields of the final products somewhat higher, but their isolation and purification are found to be more convenient, which is very important for compounds of relatively low stability. For example, in the reaction of the ester (II) with 5-bromo-2-(trans)-penten-4-ynoic acid [3] we obtained a quantitative yield of the monomethyl ester (XVII), which on treatment with diazomethane readily gave dimethyl 2-(trans)-decen-4,6-diynoate, m. p. 56°, corresponding (in analysis and infrared and ultraviolet spectra) to the natural product isolated from the culture liquid of Polyporus anthracophilus [6]. As would be expected, of the products obtained, 8-hydroxy-9-decen-4,6-diynoic acid (XVI) is particularly unstable; in a short time at room temperature it is converted into an insoluble red polymer. Methyl hydrogen 4,6-decadiyndioate (XV) is also unstable to keeping. However, at low temperature all the hydroxy diynic compounds are relatively stable and can be kept for a long time.

By the dehydration of the methyl esters (VII) and (VIII) we synthesized dihydromatricaric ester (XVIII), a natural polyyne which has been isolated from Matricaria inodora [7] and whose isomers have been synthesized in low yields by the condensation of cis- and trans-3-penten-1-ynes with methyl 4-pentynoate [8].



$$\left.\begin{array}{l} \underset{\substack{|\\ OH}}{CH_3CH_2CH}(C{\equiv}C)_2(CH_2)_2COOCH_3 \quad (VII) \\ CH_3\underset{\substack{|\\ OH}}{CH}CH_2(C{\equiv}C)_2(CH_2)_2COOCH_3 \quad (VIII) \end{array}\right] \xrightarrow[-H_2O]{} \underset{(XVIII)}{CH_3CH{=}CH(C{\equiv}C)_2(CH_2)_2COOCH_3}$$

$$\underset{(V)}{CH_3CH_2\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ OH}}{C}}(C{\equiv}C)_2(CH_2)_2COOCH_3} \xrightarrow{-H_2O} \underset{(XIX)}{CH_3CH{=}\overset{\substack{CH_3\\ |}}{C}(C{\equiv}C)_2(CH_2)_2COOCH_3}$$

$$(V) \xrightarrow{KOH} \underset{(XX)}{H(C{\equiv}C)_2(CH_2)_2COOCH_3} + C_2H_5COCH_3$$

It was found that, when boiled with p-toluenesulfonic acid in benzene, the methyl ester (VII) gives a 46% yield of a dehydration product which corresponds in elemental analysis and ultraviolet spectrum to dihydromatricaric ester (XVIII). Analysis by gas-liquid chromatography* showed that the product contained not less than 90% of one of the stereoisomers. The dehydration of the methyl ester (VIII) went much less satisfactorily; in this case we could isolate (XVIII) only in about 15% yield. As would be expected, the methyl ester (V) was dehydrated most readily of all, and an 82% yield was obtained of methyl 8-methyl-8-decen-4,6-diynoate (XIX), the simplest synthetic analog of natural dihydromatricaric ester. On the gas-liquid chromatogram this product gives only one peak, but this fact cannot be cited as an indication of its steric homogeneity.

We showed also that, when heated in presence of KOH, the methyl ester (V) behaves like previously described diynic alcohols [4, 9] and is broken down with elimination of butanone and formation of methyl 4,6-heptadiynoate (XX), an important starting substance for the synthesis of various natural polyynes.

EXPERIMENTAL

Bromo derivatives of acetylenic alcohols (I) were prepared by a known procedure [10] at 0° by the use of excess of potassium hypobromite.

4-Pentynoic acid (II, R = H) and its methyl ester (II, R = CH_3). A solution of 3-chloropropyne [11] in 100 ml of alcohol was added at 25-30° to a solution of sodiomalonic ester prepared from 1.1 g-atoms of sodium, 192 g of malonic ester, and 700 ml of absolute alcohol. The mixture was kept for six hours at room temperature and then heated for 5-6 h at 50-60°. After the usual treatment and distillation we obtained a 56% yield of diethyl

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*Analyses by gas-liquid chromatography were conducted on a "Rau" chromatograph, column length 1 m 20 cm, Apiezon L, 150°, argon 50 ml/min.

(2-propynyl)malonate [b. p. 128-129° (22 mm)], which was hydrolyzed with aqueous-alcoholic alkali and then decarboxylated by procedures described previously [12-14]. 4-Pentynoic acid (II, R = H, m. p. 57°) was obtained in 80% yield, and after methylation by the usual method a 65% yield was obtained of the corresponding methyl ester (II, R = CH_3); b. p. 53° (15 mm); n_D^{20} 1.4218 [12].

5-Bromo-4-pentynoic acid (III), m. p. 92° (from hexane), was prepared in 80% yield from the acid (II, R = H) by a known procedure [10].

Condensation of methyl 4-pentynoate (II) with bromo derivatives of acetylenic alcohols (I). A solution of 0.1 mole of the appropriate bromo acetylenic alcohol (I) in 35 ml of methanol was added dropwise with vigorous stirring to a solution of 0.1 mole of methyl 4-pentynoate (II) in 25 ml of methanol containing 0.01 mole of cuprous chloride, 0.01 mole of hydroxylamine hydrochloride, and 0.18 mole of ethylamine in the form of a 40% aqueous solution. The reaction mixture was kept for two hours at 20-25°, treated with 10% hydrochloric acid, and extracted with ether; the extract was washed with water and dried, and the reaction product was distilled. The yields and constants of the diynic hydroxy esters of type (IV) are given in the table (experiments 1-3, 5-7, 10, 11, and 14).

Condensation of acetylenic alcohols with 5-bromo-4-pentynoic acid (III). A solution of 0.04 mole of the acid (III) in 15 ml of methanol was neutralized by the addition of the corresponding amount of 40% aqueous ethylamine, and the resulting solution was added with stirring at 20-25° to a solution of 0.04 mole of the acetylenic alcohol in 10 ml of methanol containing 0.004 mole of Cu_2Cl_2, 0.004 mole of hydroxylamine hydrochloride, and 0.07 mole of ethylamine. After the above-described treatment and removal of solvent, the crystalline reaction product was recrystallized from a suitable solvent. The yields and constants of the diynic hydroxy acids obtained in this way are given in the table (experiments 4, 8, 9, 12, 13, and 16). By an analogous procedure we conducted the condensation of 5-bromo-4-pentynoic acid (III) with methyl 4-pentynoate (II, R = CH_3) (expt. 15).

Methyl 8-decen-4,6-diynoate (XVII). A solution of 1.2 g of the methyl ester (VII) in 100 ml of benzene was boiled for 90 min in presence of 0.03 g of p-toluenesulfonic acid. Water was added, and the benzene layer was carefully washed with water and dried; solvent was driven off, and the residue was chromatographed on alumina of activity II. Elution with benzene gave 0.5 g (46%) of product; b. p. 65° (0.009 mm); n_D^{20} 1.5290; λ_{max} 225, 248, 262, 277, 304 mμ (ε 3970, 8460, 12430, 9750, 2870), identical to dihydromatricaric ester [8]. Found: C 74.87; H 6.86%. $C_{11}H_{12}O_2$. Calculated: C 74.47; H 7.17%. A product with same constants, but obtained in low yield (about 15%), was also formed in the dehydration of 9-hydroxy-4,6-decadiynoic ester (VIII).

Methyl 8-methyl-8-decen-4,6-diynoate (XIX). This was prepared in 82% yield by a procedure analogous to that described above from the methyl ester (V); b. p. 65° (0.004 mm); n_D^{20} 1.5365; λ_{max} (in alcohol) 238, 250, 264, 279 mμ (ε 5600, 10760, 15720, 12480). Found: C 75.56; H 7.41%. $C_{12}H_{14}O_2$. Calculated: C 75.76; H 7.42%.

Methyl 4,6-heptadiynoate (XX). A mixture of the methyl ester (V) and 2-5% of potassium hydroxide powder was slowly distilled at 0.5 mm and 140-150° (in the bath). After redistillation we obtained a yield of about 60% of the diacetylenic ester (XX), b. p. 50° (2 mm), which, after recrystallization, had m. p. 30.3-30.8°; λ_{max} (in alcohol) 224.5, 238, 251.5, 280 mμ (ε 3490, 3660, 4000, 8070). The infrared spectrum contained absorption bands at 1737 cm^{-1} ($-CO_2CH_3$), 2258 cm^{-1} ($-C{\equiv}C-$), and 3300 cm^{-1} ($-C{\equiv}CH$). Found: C 70.58; H 5.88%. $C_8H_8O_2$. Calculated: C 70.64; H 5.81%.

SUMMARY

1. Diynic hydroxy carboxylic acids and their esters were synthesized, and some of their chemical transformations were studied.

2. Methods are proposed for the synthesis of natural dihydromatricaric ester and methyl 4,6-heptadiynoate, which is an important starting substance for the preparation of various natural polyynes.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
