SYNTHESIS AND PHARMACOLOGICAL CHARACTERISTICS OF SOME ACETYLENIC DIOLS

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It is known that hydroxyl-containing compounds including α-glycols, possess narcotic, sedative, and antispasmodic activity [4, 5]. Information on the biological activity of acetylenic δ-diols is absent from the literature, however.

The present work describes the synthesis and pharmacological activity of primary– and secondary–tertiary acetylenic δ-glycols (I-IV) and the diacetylenic diols V and VI.

The acetylenic diols I-IV were obtained by condensation of ketones with butyne-1-ol-4, or pentyn-1-ol-4 according to the scheme:

$$R^1R^2C{=}O + HC{\equiv}CCH_2CH(R^3)OH \xrightarrow{KOH} \underset{I-IV}{R^1R^2C(OH)C{\equiv}CCH_2CH(R^3)OH}$$

I: $R^1 = R^2 = R^3 = CH_3$; II: $R^1 = CH_3$, $R^2 = C_3H_7$, $R^3 = H$;
III: $R^1 = CH_3$, $R^2 = C_4H_9$, $R^3 = H$; IV: $R^1 = C_2H_5$, $R^2 = C_2H_5CH(CH_3)CH_2$, $R_3 = H$

EXPERIMENTAL CHEMISTRY

1,1-Diphenyl-2,4-pentadiyne-1,7-diol–$(C_6H_5)_2C(OH)(C{\equiv}C)_2CH_2CH_2OH$ (V). This was synthesized by the interaction of 1-bromo-1-butyn-4-ol with diphenylethynyl carbinol under the conditions of Khodkevich-Kad'o [3], and 1,1,6,6-tetraphenyl-2,4-hexadiyn-1,6-diol $(C_6H_5)_2C(OH)C{\equiv}CC{\equiv}CC(OH)C_6H_5)_2$ (VI) by the method of [2].

3-Methyl-5-ethyl-6-nonyn-5,9-diol (IV). To a suspension of 24 g (0.4 mole) of KOH in 200 ml of ether was added dropwise over one-half hour 8 g (0.11 mole) of butyn-1-ol-4, and then 23.8 g (0.18 mole) of ethylamyl ketone over 2 h at room temperature. The reaction mixture was stirred for 3 h and kept overnight at room temperature. The following day the complex was decomposed with ice water, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether layer was washed with 5% aqueous acetic acid and dried with $MgSO_4$. The residue after removal of the ether was distilled to give bp 121-123°C (1 mm), 15 g (68%) of glycol IV, n_D^{20} 1.4672. Found, %: C 72.53; H 11.24. $C_{12}H_{22}O_2$. Calculated, %: C 72.68; H 11.11. IR spectrum, ν, cm^{-1}: 2240 (C≡C), 3400 (OH).

The constants for the glycols I-III are given in [1, 6].

EXPERIMENTAL PHARMACOLOGY

The experiments were carried out on white mice and rats. Acute toxicity was determined on mice by recording results (mortality) after 24 h, and calculation of the LD_{50} according to G. N. Pershin.

The influence of these diols on the central nervous system was judged by the change in approximate spontaneous motor activity (open field), muscle tone, and central mechanism of motion coordination (horizontal motionless and rotating rod).

The analgesic activity was estimated by the change in the pain sensitivity threshold of mice, determined by the "hot plate" method.

Antiinflammatory activity was carried out on the inflammation produced by subplanar injection in the rear paw of the rats of 0.1 ml of 1% agar solution, with oncometric registration of the dynamic volume of the paw.

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TABLE 1. Antiinflammatory Activity of Acetylenic Diols

Compound	LD_{50}, mg/kg	Dose, mg/kg	Increase in volume of paws after introduction of agar, % of initial	
			after 3 h	after 5 h
I	312	100	100±10,4	104±10,2
II	410	100	53±5,6*	60±6,1*
III	541	100	56±6,9*	45±5,5 †
IV	344	68	97±6,8	103±10,2
V	250	100	38±3,7 †	42±3,4 †
		50	54±4,6*	61±8,7*
		25	73±4,6	70±5,5
VI	3000	100	32±4,5 †	42±8,00†
		50	73±10,0	82±13,1
Amidopirin (Aminopyrine)	344	100	42±4,4 †	69±4,9
Control	—	—	92±4,3	88±4,3

*$P < 0.01$.

†$P < 0.001$.

All of the test compounds were introduced intraperitoneally in doses equal to 0.1 LD_{50} in a constant volume of starch paste 30 min after beginning the studies on neutrotropic and analgesic activity, and in inflammation experiments, 1 h after the agar injection.

The results of this study showed that the LD_{50} of these compounds injected intraperitoneally into mice varied between 250-541 mg/kg, except for VI.

In toxic doses, the diols produce an incremental depression of motor activity, disturbing motor coordination, and destroying the mice after an average of 16-24 h.

At a dose of 0.1 LD_{50}, these materials (except for compound I) lowered orientational and motor activities, did not change the motor coordination and muscle tone, and did not act as analgesics.

In experiments on rats, it was shown that compounds II, III, V, and VI possessed antiinflammatory activity (see Table 1). The diol activity is indicated by comparison with aminopyrine; they suppress agar inflammation at a dose of 0.2 LD_{50}, except for compound VI (effective at a dose of 0.03 LD_{50}), while amidopyrine is effective only at a dose of 0.3 LD_{50}, giving only three hours of control. The true nature of the antiinflammatory effect of the diols is emphasized by their dependence on the dose.

The results of these studies show that acetylenic diols possess sedative and antiinflammatory activity. The basis of the antiinflammatory activity of diols I-VI is found in their distinct differences in chemical structure. Thus, in the acetylenic δ-glycols it is noted that the antiexudative action is strengthened by changing the radical R^2 from CH_3 to C_4H_9. An analogous relationship of hypnotic activity to structure of the hydrocarbon radical was observed earlier for the case of the acetylenic alcohols [4]. Favorable pharmacological properties also are obtained by introduction of a second triple bond, and by substitution of the aliphatic radicals of the tertiary carbon atom by phenyl radicals.

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