SYNTHESIS AND NEUROTROPIC ACTIVITY OF SULFUR-CONTAINING VINYLACETYLENIC CARBINOLS

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Vinylacetylenes display a wide spectrum of biological activity, and for this reason a search among compounds of this type for novel physiologically active compounds as potential drugs holds promise [4, 5].

We have now synthesized some new vinylacetylenic carbinols containing alkylthio-groups (IIIa-j), and examined their neurotropic activity.

$$CH_2{=}C(Me)C{\equiv}CH + CH_3COCH(Me)CH_2SR \longrightarrow CH_2{=}C(Me)C{\equiv}CC(OH)(Me)CH(Me)CH_2SR$$

I IIa-j IIIa-j

IIa, IIIa: R=Et; IIb, IIIb: R=Pr; IIc, IIIc R=Bu; IId, IIId R=Am; IIe, IIIe R=Am-iso; IIf, IIIf R=C_6H_{13}; IIg, IIIg: R=C_7H_{15}; IIh, IIIh: R=C_8H_{17}; IIi, IIIi: R=C_9H_{19}; IIj, IIIj; R=$C_{10}H_{21}$.

Compounds (IIIa-j) were obtained by reacting the bromomagnesium derivative of isopropenylacetylene (I) with the ketosulfides (IIa-j). The structures of (IIIa-j) were confirmed by their elemental analyses (Table 1) and their IR spectra, which showed absorption at 3420-3440 cm^{-1} (OH), 1620-1625 cm^{-1} (C=C), and 2225 cm^{-1} (C≡C).

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a UR-20 instrument (East Germany) in thin layers (10-15 μm).

Isopropenylacetylene (I) [6] and the ketosulfides (IIa-j) [1] were obtained by standard methods.

2,5,6-Trimethyl-7-alkylthiohept-1-en-3-yn-5-ols (IIIa-j). To the Grignard reagent (from 0.25 mole of EtBr) in 150 ml of dry ether was added slowly, dropwise at 5-10°C 0.25 mole of (I), diluted with an equal volume of dry ether. The mixture was stirred at 20°C for 5-6 h. To the bromomagnesium derivative of (I) was added slowly, dropwise, over 2-3 h in a solution of 0.25 mole of freshly distilled (IIa-j) in ether, and the mixture stirred for 8-12 h. It was then treated with 60 ml of saturated NH_4Cl solution, the ether layer separated, the aqueous layer extracted with ether, and the ether solution dried over $MgSO_4$. The ether was removed by distillation, and the product fractionally distilled *in vacuo* (Table 1).

EXPERIMENTAL (PHARMACOLOGY)

The working solutions of the compounds of 3.5% concentration were prepared in 10% Tween-80. Acute toxicities were measured by the intraperitoneal route in white mice of both sexes weighing 18-22 g. The test results were assessed after 24 h. Toxicities were calculated using Kerber's method [2]. The neurotropic activity of the compounds was determined by their ability in nonhypnotic doses to prolong the hypnotic effect of barbiturates, and to exert hypothermic activity [3]. It was found that (IIIa-j) were of low toxicity, the toxicity decreasing as the sulfide radical was extended by one methylene group (Table 2).

The test compounds enhanced the effects of barbiturates, activity increasing to the fourth radical in the series (IIIa-j), the hexenal sleep prolongation index then decreasing. The opposite behavior was found in studies of the hypothermic activity of the test compounds. The drugs reduced considerably the rectal temperatures of the animals. It was observed that as the length of the thioether radical was increased, the hypnotic effect of the compounds one

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TABLE 1. Properties of 2,5,6-Trimethyl-7-alkylthiohept-1-en-3-yn-5-ols (IIIa-j)

Compound	Yield, %	Bp, °C/mm Hg	Found, %			Empirical formula	Calculated, %		
			C	H	S		C	H	S
IIIa	70	1256/3	67,81	9,34	14,97	$C_{12}H_{20}OS$	67,92	9,43	15,09
IIIb	85	1202/1	68,91	9,68	14,09	$C_{13}H_{22}OS$	69,02	9,73	14,15
IIIc	64	12830/1	69,91	9,96	13,25	$C_{14}H_{24}OS$	70,00	10,00	13,33
IIId	70	1312/1	70,71	10,12	12,49	$C_{15}H_{26}OS$	70,86	10,23	12,59
IIIe	65	1135/0,5	70,76	10,10	12,51	$C_{15}H_{26}OS$	70,86	10,23	12,59
IIIf	65	1235/0,5	71,68	10,40	11,87	$C_{16}H_{28}OS$	71,64	10,44	11,94
IIIg	65	1335/0,5	72,20	10,50	11,28	$C_{17}H_{30}OS$	72,34	10,63	11,34
IIIh	75	1623/2	72,81	10,78	10,70	$C_{18}H_{32}OS$	72,97	10,81	10,81
IIIi	77	1557/1	73,44	10,90	10,22	$C_{19}H_{34}OS$	73,54	10,96	10,32
IIIj	50	1635/1	74,00	11,01	9,79	$C_{20}H_{36}OS$	74,07	11,11	9,87

TABLE 2. Neurotropic Activity of (IIIa-j)

Compound	LD_{50}, mg/kg ($M \pm m$)	Hypothermic effect (dose 1/4 of the LD_{50}) rectal temperature, °C (M±m)			Prolongation of hexobarbital sleep index
		60 min	3 h	24 h	
IIIa	425,0±18,2	36,1±0,3	35,8±0,5	35,7±0,4	1,5—2,0
IIIb	470,9±17,9	35,8±0,4	36,5±0,3	35,5±0,7	2,0—3,3
IIIc	508,4±19,9	35,5±0,3	36,7±0,4	35,0±0,8	3,4—4,8
IIId	500,0±18,3	35,6±0,4	35,3±0,5	35,0±0,7	3,8—4,6
IIIe	550,0±18,9	35,8±0,2	35,1±0,5	35,0±0,3	2,5—3,2
IIIf	567,2±19,7	36,2±0,4	36,3±0,6	34,9±0,4	2,0—3,0
IIIg	659,0±18,7	36,2±0,5	36,4±0,3	34,4±0,1	1,0—2,1
IIIh	733,4±18,3	36,5±0,2	36,6±0,4	34,2±0,2	1,0—2,0
IIIi	883,4±19,8	36,8±0,4	36,7±0,5	34,2±0,1	0,9—2,0
IIIj	900,0±20,1	36,9±0,3	36,9±0,7	34,0±0,2	0,7—1,8

Note. The temperature before administration of the drugs was 37.9 ± 0.06°C.

day following administration was enhanced (Table 2). The results were treated statistically by Oivin's method, and were found to be statistically significant.

Hence, compounds (IIIa-j) display marked neurotropic activity.

LITERATURE CITED

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