THE SYNTHESIS OF 2-ALKYL- AND 2-ARALKYL SUBSTITUTED 2,3-DIHYDRO-1H-BENZ[de]ISOQUINOLINES

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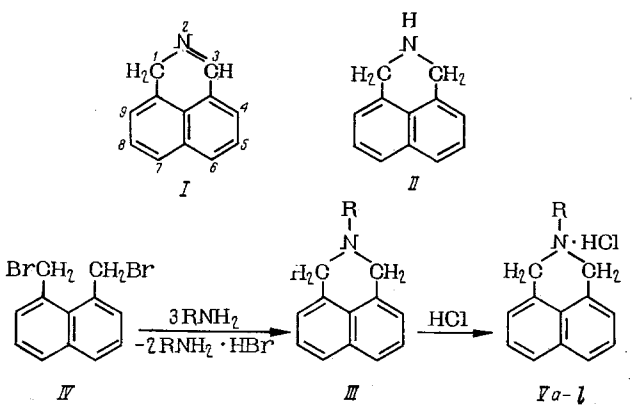
UDC 615.214.32:547.833].012.1:
542.9

Inhibitors of mitochondrial monoamine oxidase (IMO) are used for the treatment of various illnesses of the central nervous and cardio-vascular systems. Interest has been shown for some time past in IMO such as derivatives of polycyclic aromatic compounds [1] and multinuclear heterocycles [2]. However, compounds of the naphthalene series, and in particular heterocycles based on it, have practically been unexamined in this connection. Consequently it seemed of interest to investigate certain heterocyclic systems containing the naphthalene nucleus as IMO.

Among such systems constructed on the peri-positions of naphthalene, 1H-benz[de]isoquinoline (I)* is known, reported as the 2,3-dihydro derivative (II).† Certain examples of the 2,3-dihydro-1H-benz[de]isoquinoline series have been studied in a pharmacological connection [7-11].

We have synthesized a series of 2-alkyl- and 2-aralkyl-2,3-dihydro-1H-benz[de]isoquinolines, the majority of which have not been reported in the literature. The synthesis was accomplished by method [5] by the interaction of 1,8-bisbromomethylnaphthalene (IV) with the corresponding alkyl- or aralkylamine in anhydrous benzene or toluene at room temperature.



The starting dibromide (IV) was obtained from 1,8-bishydroxymethylnaphthalene by reaction with phosphorus tribromide [12] or by bromination of 1,8-dimethylnaphthalene with N-bromosuccinimide [cf.13].

Compounds (III) were isolated and purified as hydrochlorides (Va-Vl) and some were also characterized as picrates (Table 1). The hydrochlorides of 2-alkyl- and 2-aralkyl-2,3-dihydro-1H-benz[de]isoquinolines crystallized readily from absolute alcohol, melted with decomposition, and were soluble in water. Compounds (Va-Vl) were chromatographically homogeneous. The picrates of 2,3-dihydro-1H-benz[de]isoquinolines (III) were obtained directly by the interaction of hydrochlorides (V) with picric acid in alcoholic solution [cf.5]; the picrates were yellow in color and melted with decomposition.‡

* Synonyms: 2,1-peribenzisoquinoline, perinaphthazole[3,4].

† Synonyms: 2-azaperinaphthindane [5]. Derivatives of (II) are given in [6].

‡ While preparing the picrates it appeared incidentally that the compound supposedly reported [14] as 2-methyl-2,3-dihydro-1H-benz[de]isoquinoline (III, R = CH_3) seemingly had another structure, since the melting point and color of the picrate known to be 2-methyl-2,3-dihydro-1H-benz[de]isoquinoline differed substantially from the data of [14] (see Table 1).

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Translated from Khimiko-Farmatsevticheskii Zhurnal No. 3, pp. 30-33, March, 1969. Original article submitted September 5, 1968.

TABLE 1. Hydrochlorides of 2-Alkyl and 2-Aralkyl-2,3-dihydro-1H-benz[de]isoquinolines (Va-Vl)

Compound	R	Yield (in %)	Mp in °C with decomposition	Mp in °C with decomposition according to literature data	Found %		Empirical formula	Calculated %	
					Cl	N		Cl	N
Va	CH_3	87	289—90	—	16,00	6,41	$C_{13}H_{14}ClN$	16,13	6,37
			P., 190	165—6 (14)	—	13,31	$C_{19}H_{16}N_4O_7$	—	13,58
Vb	C_2H_5	42	278—90	—	14,79	6,00	$C_{14}H_{16}ClN$	15,16	5,98
Vc	n-C_3H_7	68	235—40	—	13,90	5,44	$C_{15}H_{18}ClN$	14,31	5,65
Vd	iso-C_3H_7	64	280—3	—	14,08	5,48	$C_{15}H_{18}ClN$	14,31	5,65
Ve	n-C_4H_9	61	230	238—41 (5)	—	—	$C_{16}H_{20}ClN$	—	—
Vf	tert-C_4H_9	85	250	—	13,50	5,26	$C_{16}H_{20}ClN$	13,54	5,35
			P, 220	—	—	12,34	$C_{22}H_{22}N_4O_7$	—	12,33
Vg	iso-C_5H_{11}	33	270	—	12,87	5,14	$C_{17}H_{22}ClN$	12,85	5,07
Vh	CH_2=$CHCH_2$	35	235	—	14,43	5,90	$C_{15}H_{16}ClN$	14,42	5,70
			P, 179—80	—	—	12,81	$C_{21}H_{18}N_4O_7$	—	12,77
Vi	Cyclohexyl	59	295	295 (5)	—	—	$C_{18}H_{22}ClN$	—	—
			P, 192—4	186—7 (5)	—	—	$C_{24}H_{24}N_4O_7$	—	—
Vj	$C_6H_5CH_2$	78	252—4	252, 5—4, 5 (4)	—	—	$C_{19}H_{18}ClN$	—	—
Vk	$C_6H_5CH_2CH_2$	42	284—5	—	11,06	4,34	$C_{20}H_{20}ClN$	11,4	4,52
Vl	$C_6H_5CHCH_3$	29	256	—	11,29	4,46	$C_{20}H_{20}ClN$	11,44	4,52
			P, 145—50	—	—	10,94	$C_{26}H_{22}N_4O_7$	—	11,15

Symbol: P-picrate

TABLE 2. The Dependence of the Inhibition of the Activity of Mitochondrial Monoamine Oxidase by Derivatives of 2,3-Dihydro-1H-benz[de]isoquinoline on Inhibitor Concentration

Compound	Final concentration of compounds in experiments (in M)		
	10^{-3}	10^{-4}	10^{-5}
Va	94	80	8
Vb	92	67	12
Vc	98	84	55
Vd	50	10	1
Ve	70	23	12
Vf	40	—	—
Vg	68	38	16
Vh	90	55	21
Vi	65	10	6
Vj	17	—	—
Vk	32	5	0
Vl	81	5	0

Note. Figures in the table represent degree of inhibition (as % of control experiments containing no inhibitor) of the rate of the oxidative deamination reaction of tyramine by rat liver mitochondria [16]. The results are the mean of three experiments. In control experiments it was discovered that, under standard conditions for the determination [17], on the average 4 μmole of ammonia were liberated in 45 min incubation.

Certain of the 2-alkyl-2,3-dihydro-1H-benz[de]isoquinolines investigated (especially compound Vc) caused significant inhibition of the oxidative deamination of tyramine even at a concentration of 10^{-5} M, and have been applied similarly as IMO in clinical medicine [15]. The results of the investigation of the inhibition of mitochondrial monomine oxidase by compounds (Va-Vl) are presented in Table 2.

The degree of inhibition did not depend upon the length of preincubation (5-60 min) of the enzyme preparation with the compounds being investigated up to the moment of introduction into the experimental substrate. Dialysis (against 500 volumes 0.005 M pH 7.4, phosphate buffer) of experiments containing mitochondrial preparations from rat liver and 2-alkyl substituted (II) (compounds Va-Vc, final concentrations 10^{-3} M in experiments prior to dialysis) completely eliminated the inhibition of the deamination reaction of tyramine.

As is evident from Table 2, an appreciable inhibiting action (at concentrations of 10^{-4} and 10^{-5} M) was shown only by alkyl- and alkenyl substituted (II) (compounds Va-Ve, Vg and Vh); cyclohexyl- and aralkyl substituted (II) (compounds Vi-Vl) were practically inactive. In the series of alkyl substituted derivatives maximal activity was associated with n-propyl (compound Vc); the transition from the saturated to the unsaturated 2-alkyl (n-C_3H_7 → CH_2 = $CHCH_2$) and also increase in branching of the alkyl radical [CH_2CH_3 → $CH(CH_3)_2$ → $C(CH_3)_3$] (compounds Vb, Vd and Vf) led to a reduction in IMO activity.

EXPERIMENTAL

1,8-Bisbromomethylnaphthalene (IV). A. This was obtained by the reaction of 1,8-bishydroxymethylnaphthalene [18] with phosphorus tribromide in benzene in the presence of pyridine according to method [12].

B. A mixture of 2 g (12.8 mmole) 1,8-dimethylnaphthalene [18], 4.55 g (25.6 mmole) N-bromosuccinimide and 40 mg benzoyl peroxide in 30 ml carbon tetrachloride was boiled for 3 h under reflux with stirring. The reaction mixture was filtered, the precipitate washed with carbon tetrachloride, and the filtrate evaporated in vacuum. The yield of unpurified 1,8-bisbromomethylnaphthalene was 3 g (75%) mp 130-131° (from benzene-hexane). According to literature data mp 130° [13].

2-Alkyl- and 2-Aralkyl-2,3-dihydro-1H-benz[de]isoquinoline Hydrochlorides (Va-Vl). A solution of 1 g (3.1 mmole) 1,8-bisbromomethylnaphthalene (IV) in anhydrous benzene or toluene (25-30 ml) was mixed with the respective primary amine (9.3 mmole), also dissolved in anhydrous benzene or toluene (5-10 ml), and kept for a day at room temperature. The starting amine hydro-bromide which had separated was filtered off, washed with benzene, and the filtrate concentrated to dryness in vacuum. The unpurified base (III) remaining (more often in the form of an oil) was treated with 10-20 ml hydrochloric acid (1:1) with heating. The hydrochloride (Va-Vl) which separated on cooling was filtered off and recrystallized from absolute ethanol.

2-Alkyl- and 2-Aralkyl-2,3-dihydro-1H-benz[de]isoquinoline Picrates. To a solution of 20 mg hydrochloride (Va-Vl) in the minimal amount of hot ethanol was added an equivalent amount of picric acid dissolved in the minimal amount of hot ethanol. After cooling the picrate was filtered off by suction and recrystallized from ethanol. The yields of product and constants of the compounds synthesized are given in Table 1.

For carrying out chromatography, the hydrochlorides (Va-Vl) were made alkaline by the addition of sodium hydroxide solution, the base (III), which separated, was extracted with ether, the extract evaporated, the residue dissolved in ethanol and chromatographed on filter FN-3 (G.D.R) paper in benzene-ethanol (19:2) as solvent system. Chromatograms were developed with iodine or Dragendorfs reagent [19] which gave orange-red, satisfactorily stable spots. All compounds (III) corresponding to hydrochlorides (Va-Vl) gave only one spot with very close R_f values (~ 0.9). On chromatography of the hydrochlorides (Va-Vl) in the same system or in butanol-acetic acid-water (4:1:5) the formation of significant "tailing" was observed.

Analogous results were obtained on thin layer chromatography on silica gel.

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