SYNTHESIS OF 2,3,4,4a,9,9a-HEXAHYDROINDENO[2,1-b]-1,4-OXAZINE DERIVATIVES

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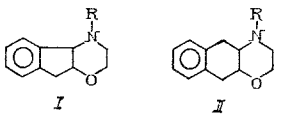
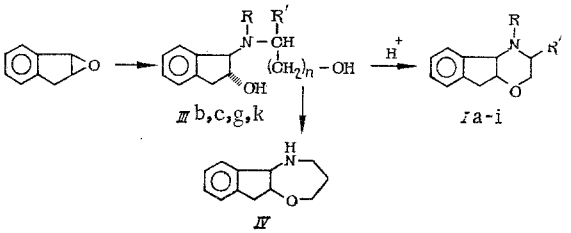
In the continuation of our search for biologically active compounds among the derivatives of C-substituted morpholines [1, 2], we synthesized 2,3,4,4a,9,9a-hexahydroindeno[2,1-b]-1,4-oxazines (I) to find how the biological activity is influenced by substitution of the middle six-membered ring in hexahydro-4H-naphtho[2,3-b]-1,4-oxazines (II), which we had already obtained [1, 2], for a five-membered ring in the derivatives of indenooxazines I. In this study we have to take into the account the difference in the distance between the nitrogen atom and the benzene ring, and the transformation of the β-phenylethylamine fragment in II into the benzylamine fragment in compounds of type I.



I II

We synthesized the required end product indenooxazines I according to the following scheme:



III b,c,g,k I a-i IV

Ia: R = H, R′ = H, $n = 1$; I, IIIb: R = CH_3, R′ = H, $n = 1$; Ic: R = C_2H_5, R′ = H, $n = 1$; Id: R = C_3H_7, R′ = H, $n = 1$; I, IIIe: R = iso-C_3H_7, R′ = H, $n = 1$; If: R = n-C_4H_9 R′ = H, $n = 1$; I, IIIg: R = $C_6H_5CH_2$, R′ = H, $n = 1$, I, IIIh: R = C_6H_{11}, R′ = H, $n = 1$; I, IIIi: R = H, R′ = C_2H_5, $n = 1$; IIIj: R = H, R′ = H, $n = 2$; IIIk: R = C_6H_5, R′ = H, $n = 1$.

The preparation of the initial 1,2-epoxyindane and its reaction with amines have been described in [3]. In contrast to the case in the above method, we used the starting materials in equimolar amounts. We found by TLC that the reaction between 1,2-epoxyindane and aminoethanol or 2-alkylaminoethanols is complete after a shorter interval of time: 30 min to 2 h, instead of 4-5 h. Some of the adducts III were isolated in the form of crystalline bases or of their hydrochlorides (Table 1).

It is convenient to obtain the end product indenooxazines I from 1,2-epoxyindane, without isolating the aminodiols III in the pure state. We treated the reaction mixture obtained as the result of the reaction between 1,2-epoxyindane and aminoalkanol with 70% sulfuric acid, and continued heating at 150-155°C for 12-20 h. We took the preparation of compounds Ia and IV as examples, and showed that the use of 60% sulfuric acid decreases the yields by 12-20%, while the use of 80% sulfuric acid is undesirable because of extensive resinification

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TABLE 1. 1-(Hydroxyalkylamino)-2-indanols (IIIb, e, g-k)

Compound	mp, °C (solvent)	Yield, %	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
IIIb	75—76 (ethyl acetate)	56,5	69,45	8,40		6,73	$C_{12}H_{17}NO_2$	69,53	8,27		6,76
IIIe	78—79 (ether—hexane)	68,7	71,20	8,90		6,09	$C_{14}H_{21}NO_2$	71,45	9,00		5,95
IIIg	163—165* (ethanol)	76,0	67,60	7,11	10,96	4,36	$C_{18}H_{22}ClNO_2$	67,60	6,94	11,09	4,38
IIIh	202—204* (ethanol)	57,0	65,26	8,31	11,48	4,52	$C_{17}H_{26}ClNO_2$	65,47	8,40	11,37	4,49
IIIi	123 (ethyl acetate)	64,2	70,79	8,54		6,32	$C_{13}H_{19}NO_2$	70,55	8,65		6,33
IIIj	93—95 (ethyl acetate)	55,8	69,52	8,26		6,77	$C_{12}H_{17}NO_2$	69,53	8,27		6,76
IIIk	146—149* (ethanol)	68,3	66,43	6,98	10,99	4,55	$C_{17}H_{20}ClNO_2$	66,77	6,59	11,59	4,58

*Hydrochloride.

TABLE 2. 2,3,4,4a,9,9a-Hexahydroindeno[2,1-b]-1,4-oxazines (Ia-i) and 2,3,4,5,5a,10a-Hexahydroindeno[2,1-b]-1,4-oxazepine (IV)

Compound	bp, °C (mm Hg)	Yield,%	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
Ia	128,5—131,5 (4)	26,2	75,07	7,34		8,19	$C_{11}H_{13}NO$	75,40	7,48		7,99
Ib	119—123 (8)	38,0*	64,03	7,18	16,30	6,65	$C_{12}H_{16}ClNO$†	63,92	7,15	15,72	6,21
Ic	123—125 (1,7)	71,8	76,96	8,53		7,01	$C_{13}H_{17}NO$	76,80	8,43		6,89
Id	113—116 (2,5)	61,5	77,54	8,76		6,39	$C_{14}H_{19}NO$	77,38	8,81		6,45
Ie	110—113 (3)	40,6	77,35	8,69		6,10	$C_{14}H_{19}NO$	77,38	8,81		6,45
If	125—127 (3)	50,0	77,80	8,98		6,36	$C_{15}H_{21}NO$	77,88	9,10		6,05
Ig	—	43,5	—	—	11,55	5,01	$C_{16}H_{20}ClNO$†	—	—	11,74	4,64
Ih	141—142 (3)	31,3	79,11	8,95		5,72	$C_{17}H_{23}NO$	79,33	9,01		5,44
Ii	132—133 (1,4)	39,5	76,48	8,45		6,82	$C_{13}H_{17}NO$	76,80	8,43		6,89
IV	132—133 (1,4)	39,7	63,48	6,90	15,82	6,29	$C_{12}H_{16}ClNO$ †	63,92	7,15	15,72	6,21

*Yield of Ib from pure IIb is 46%.
†Hydrochloride.

TABLE 3. Mass Spectra of Indenooxazines Ib, Ig.

Compound	M^+	100% peak	m/z (intensity with respect to that of maximal peak)
Ib	189	144, 116	183 (25), 174 (22), 161 (11), 160 (36), 158 (8), 146 (13), 145 (16), 132 (23), 131 (15), 118 (25), 117 (20), 115 (30), 103 (13), 91 (8), 77 (5)
Ig	265	174	264 (9), 220 (2), 188 (3), 131 (8), 130 (8), 118 (10), 117 (21), 116 (82), 115 (48), 103 (22), 91 (93), 89 (16), 77 (15)

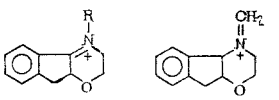
of the reaction mixture. During cyclization of purified aminodiol IIIg, a mixture of bases was obtained, from which the end product Ig was isolated by preparative chromatography. 2-Benzylaminoethanol was detected in this reaction mixture. It is possible that the elimination of the aminoalkanol is a side reaction also during the preparation of other indenooxazines I. We were unable to carry out the cyclization into indenooxazine of the aminodiol IIIk which contains a phenyl substituent attached to the nitrogen atom. When aminopropanol was used instead of alkylaminoethanols, an indenooxazepine derivative IV was obtained.

In contrast to the cyclocondensation of trans-3-(2'-hydroxyethylamino)-2-tetralol, which leads to derivatives of trans-naphthomorpholines II [4], cyclization of aminoindanediols III is not stereospecific. We found that the content of one single specific type of I in the mixture is nearly 10%; the diastereomers have not been separated.

Data on indenooxazines Ia-i and 2,3,4,5,5a,10a-hexahydro-10H-indeno[2,1-b]-1,4-oxazepine (IV) are listed in Table 2.

In the IR spectra of aminodiols III, absorption bands of a substituted benzene ring (750 cm^{-1}) and bands of the OH group in bound (3460-3430 cm^{-1}) and free states (3620-3610 cm^{-1}) are observed. On transition to indenooxazines I, the absorption bands of the OH group disappear in the IR spectra. The most intense bands in the IR spectra of indenooxazines I are observed in the 1120-1110 cm^{-1} region (C-O-C). In the spectra of Ia, Ii, and Ij, weak bands of the NH group (3330-3310 cm^{-1}) are also observed.

Mass spectra of the N-methyl and N-benzyl derivatives (Ib, Ig) were obtained (Table 3). The molecular peaks of the two compounds have a fairly high intensity. Structure V can be assigned to the $(M-1)^+$ peaks, with an intensity about 50% of that of M^+. In the spectra of these two compounds, an ion peak with m/z 188 is observed, which corresponds to the cleavage of a bond in the α-position to the nitrogen atom. Structure VI can be assigned to the fragment formed.



V VI

Another characteristic course of the fragmentation is the splitting of the heterocyclic ring with the formation of an indenyl cation (m/z 116) [5] and the $C_9H_7^+$ ion (m/z 115), with the structure of ethynyltropylium or phenylcyclopropenylium cations [6]. In the spectra there are also the peak of the benzonitrile cation (m/z 103) and peaks of the ($C_6H_5CH_2^+$) and ($C_6H_5^+$) cations (m/z 91, m/z 77), which, as expected, should be most intense in the mass spectrum of Ig.

Indenooxazines I and indenooxazepine IV are cyclic analogs of 1-amino-2-indanols, among which compounds were found with a broncholytic activity [7]. In the study of the biological activity of the diastereomeric mixtures of hydrochlorides of indenooxazines I, and also of the intermediate trans-1-alkylamino-2-indanols III, we found that these compounds have antiuremic, antihistaminic (including broncholytic) and antibacterial activity [8, 9].

EXPERIMENTAL CHEMICAL PART

The course of the reaction and the purity of the compounds obtained were controlled by TLC on Silufol-254 plates. The IR spectra were run on the UR-20 spectrophotometer (GDR) in

the form of pure liquids or in mineral oil. The mass spectra were run on the MX-1303 apparatus with direct introduction of the sample into the ionic source, at an energy of the ionizing electrons of 30 eV. The melting points were determined on the Boetius apparatus (GDR). The preparative chromatography was carried out on aluminum oxide, grade II activity, according to Brockmann, using chloroform as eluant.

trans-1-(2'-Hydroxyalkylamino)-2-indanols (IIIb,e,g,h). Equimolar amounts (0.1 mole) of 1,2-epoxyindane [3] and alkanolamine are mixed, and 0.5 ml of water is added. The mixture is heated on a water bath for 1 h (for IIIb, 30 min). The course of the reaction is controlled by TLC. The product which separates out is crystallized from the solvent, as indicated in Table 1, or is converted to a hydrochloride.

Preparation of IIIi and IIIj differs from the above procedure in that the reaction is carried out in 30 ml of ethanol, and the reaction mixture is boiled for 1 h, and evaporated.

Preparation of IIIh differs in that the reaction is carried out in 30 ml of n-amyl alcohol, and the mixture is boiled for 7 h, and evaporated *in vacuo*.

Mixtures of cis- and trans-2,3,4,4a,9,9a-hexahydroindeno[2,1-b]-1,4-oxazines Ib-f, h. Equimolar amounts (0.1 mole) of 1,2-epoxyindane and alkanolamine are mixed, and 0.5 ml of water is added. The mixture is heated on a water bath for 30 min (in the case of Ie, f, h, for 1 h). The mixture is then cooled, and after the addition of 100 ml of 70% sulfuric acid, is heated under reflux at 150-155°C for 20 h (in case of Ic, for 12 h). At the end of the reaction, water is added to the mixture, which is then treated with activated charcoal, and filtered. The filtrate is made alkaline with 40% sodium hydroxide, and extracted by ether. The ethereal extracts are dried over sodium sulfate, and evaporated, and the residue is distilled *in vacuo*.

Preparation of Ia differs from the above procedure in that the starting materials are boiled for 30 min in 30 ml of n-amyl alcohol, and the solvent is evaporated *in vacuo* before the addition of sulfuric acid.

Preparation of Ii differs from the above procedure in that before the addition of sulfuric acid, the starting materials are boiled for 1 h with 30 ml of ethanol, and the solvent is evaporated.

Indenooxazine Ig. A 6.40 g portion (0.2 mole) of 1-(2'-hydroxyethylbenzylamino)-2-indanol hydrochloride (IIIg) is dissolved in 30 ml of 70% sulfuric acid, and the solution is heated for 20 h (bath at 150-155°C). After the treatment as indicated in the general procedure for the preparation of indenooxazines, 3.5 g of a mixture of bases is isolated. After separation on a column, from 1.75 g of crude product, 1.15 g of Ig was obtained, R_f = 0.85 (66% with respect to the mixture of bases).

A mixture of cis- and trans forms of 2,3,4,5,5a,10a-hexahydroindeno[2,1-b]-1,4-oxazepine IV was obtained in the same way as indenooxazine Ii (Table 2).

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