ISOQUINOLINE DERIVATIVES

VIII.* SYNTHESIS OF 2-ARALKYL-1,2,3,4-TETRAHYDROISOQUINOLINES

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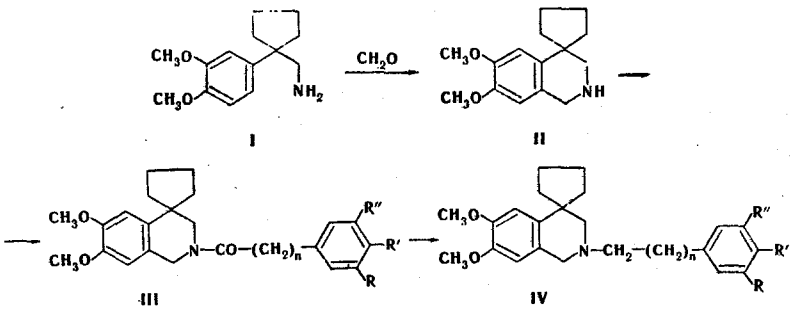
6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentane was obtained by condensation of 3,4-dimethoxyphenyl-1-(aminomethyl)cyclopentane with formalin. The corresponding amides, which were reduced to tertiary amines, were synthesized by reaction of the latter with the acid chlorides of substituted benzoic and phenylacetic acids. Substituted dibenzo[a,g]quinolizines, isoindolo[1,2-a]isoquinolines, and 1-(3,4-dimethoxyphenyl)-1-[(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolinyl)methyl]cyclopentane were synthesized, respectively, by condensation of 1-aryl(or aralkyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes and their open analog – 1-(3,4-dimethoxyphenyl)-1-(3,4-dimethoxyphenylethylaminomethyl)cyclopentane – with formalin.

In a continuation of our research on the preparation of various isoquinoline derivatives [1,2] in order to study their biological properties, we synthesized a number of N-substituted tetrahydroisoquinolines (IV and VIII) and their derivatives (VI) – analogs of isoindoloisoquinolines and berbines.



I II

III IV

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentane (II), which was obtained by condensation of 1-(3,4-dimethoxyphenyl)-1-(aminomethyl)cyclopentane (I) [2] with formalin, was used as the starting material for the synthesis of IV. The corresponding amides III (Table 1), which were converted to tertiary amines IV (Table 2) by reduction with lithium aluminum hydride, were synthesized by reaction of equimolecular amounts of II with the acid chlorides of substituted benzoic and phenylacetic acids.

The isoindoloisoquinoline and berbine (dibenzo[a,g]quinolizine) derivatives (VI) (Table 3) were synthesized by condensation of 1-aryl(or aralkyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (V) [2] with formalin in the presence of hydrochloric acid. (See following page.)

However, VIII was synthesized under the same conditions by condensation of 1-(3,4-dimethoxyphenyl)-1-{[2-(3,4-dimethoxyphenyl)ethyl]aminomethyl}cyclopentane (VII) [2] with formalin. In this case, electrophilic substitution [3] may proceed via two directions (A and B). In view of the fact that only one substance was detected by chromatography, rigorous proof of primary closing of the A type with the formation of VIII was necessary. We accomplished the alternative synthesis of this compound. The corresponding amide

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TABLE 1. 2-Aralkylcarbonyl (or arylcarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (III)

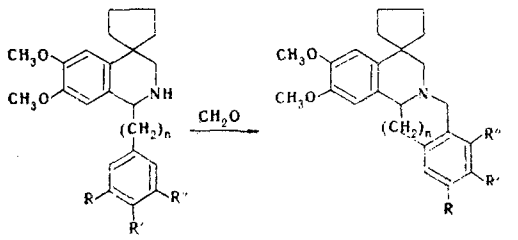
R	R′	R″	n	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
H	H	H	1	113—114	$C_{23}H_{27}NO_3$	75,4	7,2	3,8	75,6	7,4	3,8	81
H	CH_3O	H	1	Oily	$C_{24}H_{29}NO_4$	72,7	7,2	3,7	72,9	7,4	3,5	95
CH_3O	CH_3O	H	1	120—121	$C_{25}H_{31}NO_5$	70,4	7,6	3,4	70,6	7,4	3,3	84
H	H	H	0	123—124	$C_{22}H_{25}NO_3$	75,0	7,0	3,8	75,2	7,2	4,0	95
CH_3O	CH_3O	H	0	130—131	$C_{24}H_{29}NO_5$	70,3	6,9	3,3	70,1	7,1	3,4	94
CH_3O	CH_3O	CH_3O	0	144—145	$C_{25}H_{31}NO_6$	68,2	7,0	3,2	68,0	7,1	3,2	97

TABLE 2. 2-Aralkyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentane Hydrochlorides (IV)

R	R′	R″	n	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	Cl	C	H	N	Cl	
H	H	H	1	172—173	$C_{23}H_{29}NO_2 \cdot HCl$	71,2	8,0	3,7	9,3	71,2	7,8	3,6	9,1	95
H	CH_3O	H	1	202—203	$C_{24}H_{31}NO_3 \cdot HCl$	68,8	7,5	3,2	8,5	69,0	7,7	3,3	8,5	83
CH_3O	CH_3O	H	1	192—193	$C_{25}H_{33}NO_4 \cdot HCl$	67,3	7,8	3,0	8,1	67,2	7,7	3,1	7,9	75
H	H	H	0	219—220	$C_{22}H_{27}NO_2 \cdot HCl$	70,8	7,7	3,8	9,7	70,6	7,5	3,7	9,5	98
CH_3O	CH_3O	H	0	198—200	$C_{24}H_{31}NO_4 \cdot HCl$	66,8	7,6	3,4	8,3	66,4	7,4	3,2	8,1	82
CH_3O	CH_3O	CH_3O	0	197—198	$C_{25}H_{33}NO_5 \cdot HCl$	64,5	7,2	3,0	7,4	64,7	7,4	3,0	7,6	69

TABLE 3. Hydrochlorides of Substituted 5,6,13,13a-Tetrahydro-8H-dibenzo[a,g]quinolizines (VI, n = 1) and 5,6,8,12b-Tetrahydroisoindolo[1,2-a]isoquinolines (VI, n = 0)

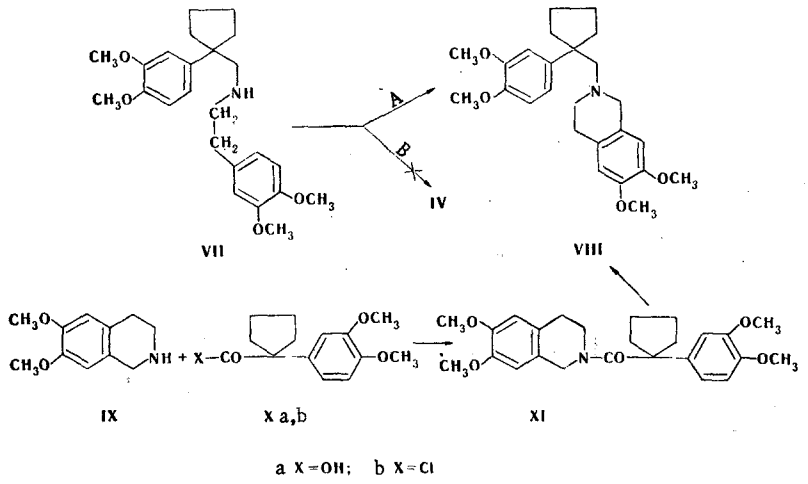
R	R′	R″	n	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	Cl	C	H	N	Cl	
H	H	H	1	185—186	$C_{23}H_{27}NO_2 \cdot HCl$	71,2	7,1	3,4	9,4	71,3	7,3	3,6	9,2	70
H	CH_3O	H	1	172—174	$C_{24}H_{29}NO_3 \cdot HCl$	69,1	7,1	3,5	8,7	69,3	7,3	3,4	8,5	62
CH_3O	CH_3O	H	1	213—214	$C_{25}H_{31}NO_4 \cdot HCl$	67,1	7,1	3,0	7,8	67,3	7,2	3,1	7,9	84
H	H	H	0	158—160	$C_{22}H_{25}NO_2 \cdot HCl$	70,9	6,9	3,8	9,4	71,0	7,0	3,7	9,5	72
CH_3O	CH_3O	H	0	225—226	$C_{24}H_{29}NO_4 \cdot HCl$	66,8	7,2	3,1	8,3	66,7	7,0	3,2	8,2	83
CH_3O	CH_3O	CH_3O	0	231—232	$C_{25}H_{31}NO_5 \cdot HCl$	64,8	7,0	2,9	7,9	65,0	6,8	3,0	7,7	76



V VI

(XI), the reduction of which led to the tertiary amine (which proved to be identical to VIII), was obtained by reaction of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IX) with the acid chloride of 3,4-dimethoxyphenylcyclopentane-1-carboxylic acid (Xb). (See scheme on following page.)

The pharmacological properties of the hydrochlorides of IV, VI, and VIII were studied. In experiments on the isolated heart of a rabbit [4], it was established that all of the preparations in dilutions of $1 \cdot 10^{-6}$ and $1 \cdot 10^{-8}$ mg/ml lead to a considerable decrease in the alimentary fluid from the coronary vessels. To study the direct effect of the preparations on the tonus, amplitude, and frequency of spontaneous contractions and on the refractor period of the myocardium, we investigated the isolated spontaneously contracted auricle of the heart of a rabbit [5]. It was found that the preparations (in the same dilutions) raise the tonus of the myocardium of the auricle of the heart of the rabbit without affecting the rest of its function. In experiments on intact rats [6], it was established that the preparations do not have antiarhythmic action.



a X=OH; b X=Cl

EXPERIMENTAL

The IR spectra of mineral oil (IV) suspensions and chloroform solutions (VI and XI) were recorded with a UR-10 spectrophotometer by L. V. Khazhakyan. Thin-layer chromatography was carried out on a fixed layer of activity-II aluminum oxide. The following systems were used: A) benzene–acetone (4:1), B) chloroform–ether (1:1).

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentane (II). A 9-ml (0.06 mole) sample of 20% formalin was added dropwise with stirring to 10 g (0.04 mole) of amine I, after which the mixture was heated on a boiling-water bath for 1 h. It was then cooled, and 40 ml of benzene was added. The aqueous layer was extracted with benzene (twice with 30-ml portions), and the benzene was removed by distillation. The residue was dissolved in 10 g of 20% hydrochloric acid, and the solution was evaporated to dryness on a water bath. The crystalline residue was dissolved in 20 ml of water, and the solution was made alkaline with 20% potassium hydroxide solution to pH 10-11. The mixture was extracted with ether (twice with 30-ml portions). The ether extracts were dried with sodium sulfate, the solvent was removed by distillation, and the residue was vacuum-distilled to give 7.2 g (68%) of a product with bp 158-160° (0.5 mm), mp 62-63°, and R_f 0.79 [ascending chromatography on S paper from the Leningrad Factory in butanol–acetic acid–water (10:1:3)]. IR spectrum: 3260 cm^{-1} (NH). Found: C 73.5; H 8.3; N 5.5%. $C_{15}H_{21}NO_2$. Calculated: C 73.3; H 8.5; N 5.7%. The hydrochloride had mp 238-239° [alcohol–ether (2:1)].

2-Aralkylcarbonyl (or arylcarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (III) (Table 1). These compounds were obtained by condensation of equimolecular amounts of II with the acid chlorides of substituted phenylacetic and benzoic acids in the presence of pyridine as in [2]. Amides III were isolated in the form of oils and crystals [2, 7]. The crystalline amides were recrystallized from benzene–petroleum ether (1:1). The identical character of the oily and crystalline products was proved by TLC (system A). The R_f values of the amides was 0.6 ± 0.1. IR spectrum: 1640 cm^{-1} (amide CO).

2-Aralkyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes (IV) (Table 2). These compounds were obtained by reduction of amides III with lithium aluminum hydride as in [8]. The hydrochlorides of amines IV were recrystallized from alcohol–ether (1:2). The R_f value was 0.77 ± 0.03 (system B). The IR spectrum did not contain the C = O absorption band of an amide group.

Hydrochlorides of Substituted 5,6,13,13a-Tetrahydro-8H-dibenzo[a,g]quinolizines (VI, n = 1) and 9,10,-11,5,6,8,12b-Tetrahydroisoindolo[1,2-a]isoquinolines (VI, n = 0). A 2-ml sample of a 36% solution of formalin was added to a solution of 2.4 g of V in 20 ml of methanol, and the mixture was allowed to stand at room temperature for 3 days, after which 16 ml of 15% hydrochloric acid was added, and the mixture was refluxed for 30 min. The alcohol was removed by distillation, and the residual hydrochloride was recrystallized from alcohol–ether (1:2) (Table 3). R_f 0.78 ± 0.02 (system B). The IR spectrum did not contain an NH absorption band.

Hydrochloride of 1-(3,4-Dimethoxyphenyl)-1-[(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolinyl)-methyl] cyclopentane (VIII). A. This compound, with mp 183-184° [alcohol–ether (1:2)] and R_f 0.78 (system B), was obtained in 70% yield by the method described above. The IR spectrum did not contain an NH absorption band. Found: C 67.0; H 7.4; N 3.0; Cl 8.1%. $C_{25}H_{33}NO_4 \cdot HCl$. Calculated: Cl 67.1; H 7.6; N 3.1; Cl 7.9%.

B. Compound XI was reduced with lithium aluminum hydride by the method in [8] to give a product (76%) with mp 181-182° and R_f (TLC) 0.79 (system B).

1-(3,4-Dimethoxyphenyl)cyclopentane-1-carboxylic Acid (Xa). A mixture of 26 g (0.1 mole) of 1-cyano-1-(3,4-dimethoxyphenyl)cyclopentane and 22.8 g (0.4 mole) of potassium hydroxide in 80 ml of water was heated at 150° in a rocking autoclave for 24 h. Acid Xa was precipitated by the addition of 15% hydrochloric acid to give 20.3 g (74%) of a product with mp 140-141° (from benzene). Found: C 67.1; H 7.1%. $C_{14}H_{18}O_4$. Calculated: C 67.2; H 7.3%.

1-(3,4-Dimethoxyphenyl)cyclopentane-1-carboxylic Acid Chloride (Xb). A mixture of 25 g (0.1 mole) of acid Xa and 14.3 g (0.12 mole) of thionyl chloride in 200 ml of benzene was refluxed for 6 h, after which the solvent was removed by distillation, and the residue was vacuum-distilled to give 16.4 g (61%) of a product with bp 165-168° (0.5 mm). Found: Cl 13.4%. $C_{14}H_{17}ClO_3$. Calculated: Cl 13.2%.

2-(3,4-Dimethoxyphenylcyclopentanecarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XI). This compound was obtained by the method used to prepare III by condensation of equimolar amounts of IX [a] and Xb in the presence of pyridine. The product, with mp 119-120° [benzene–petroleum ether (1:1)] and R_f 0.61 (system A), was obtained in 80% yield. IR spectrum: 1630 cm^{-1} (C = O). Found: C 70.3; H 7.2; N 3.2;. $C_{25}H_{31}NO_5$. Calculated: C 70.5; H 7.3; N 3.3%.

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