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2,3,4a,9,10,10a-HEXAHYDRO-4H-NAPHTHO[2,1-b]-1,4-OXAZINES

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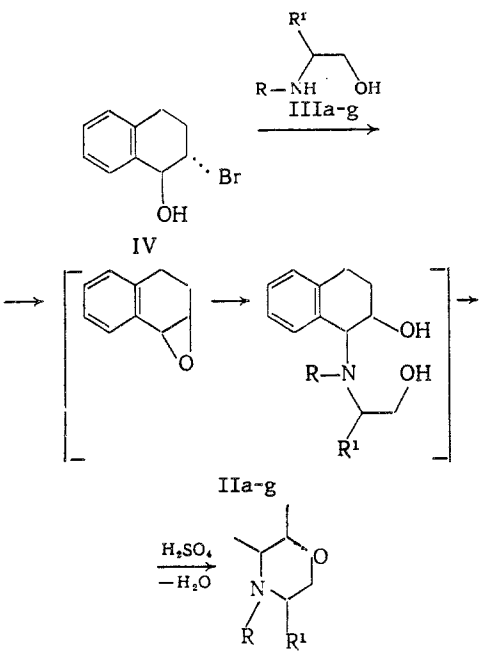
As a continuation of our search for biologically active substances in the series of tricyclic systems containing amorpholine fragment [2-4], we employed the following pattern to synthesize derivatives of naphtho[2,1-b]oxazines (Ia-c, e, f):



Ia-c, e, f

R = H (Ia, f – IIa, f), Me (Ib-IIIb).
Et (Ic-IIIc), Bu (Ie-IIIe),
i = Pr (IId, IIId) C_6H_{11} (IIg, IIIg),
R^1 = H Ia-c, e-IIIa-c, e; IId, g; IIId, g)
Et (If-IIIf)

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Hexahydronaphtho[2,1-b]oxazines I are isomers of "Naphthalanmorpholine" – 2,3,4a,5,10,10a-hexahydro-4H-naphtho[2,3-b]-1,4-oxazine – which was synthesized by Knorr in 1898, which he proposed as a cyclic structure of morpholine [7]. The morpholine ring in naphthoxazines I are joined with a tetraline fragment in position 1,2. The nitrogen atom in these compounds, just as in the indeno[2,1-b]-1,4-oxazines that we examined previously [1, 3], is located in the benzyl position. In addition, those oxazines might be considered cyclic 4-phenylbutylamines. We thought that it would be of interest not only to synthesize these compounds but also to establish the stereochemical result of cyclicizing trans-1,2,3,4-tetrahydro-2-hydroxyl-1-(2-hydroxyethylamino)naphthalines II in the presence of sulfuric acid: with the formation of a mix of both diastereoisomers [4] or only one of them [6].

The starting trans-1-amino-1,2,3,4-tetrahydro-2-naphtholes II were obtained by reacting trans-2-bromo-1,2,3,4-tetrahydro-1-naphthol IV with amino alcohols III at a 1:2 ratio. Cyclization of aminotetralols II in the presence of sulfuric acid was performed with unpurified oils of II. Moreover, the oxazines Ia-c, f that are obtained in this way contain an admixture of the starting amino alcohols III because they are readily soluble in water and are difficult to extract with ether (with the exception of compound Ie: IIIe was separated by fractional distillation). The bases IIa-e are oils that darken rapidly, so that we could not describe them. The secondary amines IIa, f were cyclicized by reaction with 60% H_2SO_4. A large excess of 70% H_2SO_4 was used for the tertiary amines. We were able to increase the yield of Ia, f by adjusting the II: 60% H_2SO_4 ratio to 1:1.8 [6].

We were not able to condense the N-isopropyl (IId) and N-cyclohexyl (IIg) derivatives of aminotetralols under the same conditions. The difficulty of cyclicizing trans-aminoindandioles with a bulky group containing a nitrogen has been noted earlier [4]. This might be due to the effect that the bulk of the substituents has an accomplishing the S_N2 transfer state. Hernestam et al. observed a similar effect that the size of the substituent at the nitrogen atom had on the progress of the reaction and the isomer composition of the resultant substituted morpholines during the cyclization of orthomorphically free N-substituted and unsubstituted 3;3'-imino-bis-(2-butanols) [15]. The yields of the naphthoxazines Ia-c, e were 35-56%, but the 3-ethyl derivative of If was obtained at a yield of only 16%. The bases of compound I constitute chromatographically homogeneous oils. Their IR spectra have absorption bands of the 1,2-substituted benzene ring and a simple ester. There are NH-group bands in the secondary amines Ia and If. The PMR spectra that were recorded on a 80-MHz spectrometer did not yield sufficient information. The proton signals $H_{(4a)}$ and $H_{(10a)}$ that might have yielded information about the configuration of the naphthoxazines were covered over. The mass spectra yielded the expected molecular weights of Ia and Ib. The spectra data indicated that decomposition entails three retro-Diels–Alder reactions.

Data on the configuration of the oxazines that we synthesized can be obtained by comparing our results to those obtained in [8]. One of the cis- and trans-isomers of Ia described in that article must be identical to the one that we obtained. The indicated compounds were comparable with respect to bp, bases, mp, and PMR spectra of the N-tosyl derivatives. The comparative data also support the thesis that oxazine Ia that we synthesized has a trans-configuration.

That conclusion can be applied to the remaining oxazines I as well, inasmuch as the presence of a lower alkyl on the nitrogen atom is not able to alter significantly the steric cyclization conditions. The configuration of the initial aminotetralols is retained during the formation of the ring. Moreover, the secondary hydroxyl probably attacks the carbon atom of the chain that bears the primary hydroxyl because of the latter's large spatial accessibility. The results obtained indicate that our suggested method for synthesizing the trans-naphthoxazines I is more convenient than the one described in [8].

In comparison to the naphthalane morpholine derivatives, the naphthoxazines have a less-pronounced effect on the CNS and behave as CNS depressants of the tranquilizer-type agents.*

A biochemical study of those compounds indicate that they enhance calcium ion transport across sarcolemmic muscle membranes. Oxazines Ia and Ib turned out to be the most active tranquilizer agents in this series. Compounds Ia, Ie, and Ib exhibited a noticeable effect on calcium ion transport.

*Pharmacological tests were conducted at VIZVM, Stara Zagora, by Professor R. Gakhniyan et al.

EXPERIMENTAL

Reaction control and purity of synthesized compounds was accomplished by TLC on Silufol UV-254 plates. IR spectra were recorded on a UR-20 spectrophotometer. Mass spectra were recorded on a MKh-1303 instrument with direct sample input into the ion source at an electron ionization energy of 70 eV. PMR spectra were recorded on 80 MHz Tesla–Brno and 250 MHz Bruker WM spectrophotometers (RMS was the internal standard).* The found element analysis values corresponded to the calculated ones.

Trans-1-(2-hydroxybutylamino)-1,2,3,4-tetrahydro-2-naphthol (IIf). A mixture of 9.08 g (0.04 mole) of 2-bromo-1-tetralol (IV) and 7.12 g (0.08 mole) of 2-aminobutanol (IIIf) was heated at 50°C for 1 h. TLC detected two spots in the reaction mass sample that corresponded to two stereoisomers. The reaction mixture was treated with acetone and a crystalline hydrobromide of the initial amine was filtered off. The filtrate was evaporated to dryness and the residue was recrystallized. Yield of IIf was 5.26 g (56%), mp 89-90°C (petroleum ether). IR spectrum, λ_{max}, $CHCl_3$: 3620 (OH), 3430 (OH, and HN, H bonds).

Trans-1-(2-hydroxyethylcyclohexylamino)-1,2,3,4-tetrahydro-2-naphthol (IIg). A mixture of 6.81 g (0.03 mole) of IV, 4.3 g (0.03 mole) of IIIg, and 3.10 g (0.03 mole) of Et_3N was heated on a boiling water bath for 2 h. The mixture was treated with water and ether, and the ether extracts were washed with 8% HCl, diluted, and bleached with charcoal. The acid solution was made alkaline and again extracted with an ether HCl solution. The precipitated salt was recrystallized. Yield 1.96 g (20%) of IIg. $C_{18}H_{28}ClNO_2$. mp 177-179°C (ethanol). IR spectrum, λ_{max}, petroleum jelly: 3365-3300 (OH, H bonds), 2780-2500 cm^{-1} ($\overset{+}{N}H$).

Trans-hexahydro-4H-naphth[2,1-b]-1,4-oxazines (I). A mixture of 13.62 g (0.06 mole) of IV and 0.12 mole of the corresponding ethanolamine III was heated for 1-2 h on a water bath (50-100°C) until the disappearance of the IV spot (TLC). A fivefold by volume quantity of 70% or 60% H_2SO_4 at a molar ratio of II/H_2SO_4 of 1:1.8 was added with cooling to the reaction mixture containing aminotetralol II and the hydrobromide of the initial amine (III × HBr). The mixture was heated for 20 h at 150-160°C. After the mixture was cooled it was diluted with water, bleached with activated charcoal, made alkaline, and extracted with ether. The residue was vacuum-fractionated.

Trans-2,3,4*a*,9,10,10*a*-hexahydro-4H-naphth[2,1-b]-1,4-oxazine (Ia) was obtained from IV and 7.32 g of IIIa for 2 h at 50°C and treatment with 27.4 g of 60% H_2SO_4. Yield 6.32 g (56%). mp 119-122°C/2.5 mm. IR spectrum, λ_{max}, liquid: 750 (1,2-disubstituted benzene ring), 1110 (C–O–C), 3330, 3285 cm^{-1} (NH). Mass spectrum (I rel.): 189(70), 188(61), 174(8), 161(32), 160(18), 146(14), 130(100), 117(51), 105(12), 91(14). Hydrochloride, mp 237-239°C subl. (ethanol).

4-Tosyl Derivative of Ia (I, R = Ts, R^1 = H). A mixture of 1.9 g of Ia, 2 g of toluene sulfoxochloride and 40 ml of 10% NaOH was heated for 20 min on a boiling water bath with stirring. The product was filtered, washed with ethanol, and recrystallized.

Trans-4-methyl-2,3,4*a*,9,10,10*a*-hexahydro-4H-naphth[2,1-b]-1,4-oxazine (Ib) was obtained from IV and 9 g of IIIb for 1 h at 50°C and treated with 60 ml of 70% H_2SO_4. Yield 6.05 g (50%), mp 119-121°C/2.4 mm. IR spectrum, λ_{max}, liquid: 755 (1,2-disubstituted benzene ring), 1100 cm^{-1} (C–O–C). PMR spectrum, δ, ppm, CCl_4: 7.32 (m, 4H, arom.), 1.41-5.50 (m, 10H, saturated shell), 2.95 pp (s, 3H, –N–CH_3). Mass spectrum (I rel.): 203(50), 202(15), 146(14), 130(100), 129(52), 128(41), 117(23), 116(17), 115(31), 91(10). Hydrochloride $C_{13}H_{18}ClNO$. mp 244-246°C, subl. (ethanol–ether).

Trans-4-ethyl-2,3,4*a*,9,10,10*a*-hexahydro-4H-naphth[2,1-b]-1,4-oxazine (Ic) was obtained from IV and 10.68 g of IIIc, 1 h at 50°C and then treated with 68 ml of 70% H_2SO_4. Yield 4.50 g (35%). bp 124-124.5°C/3 mm. Hydrochloride. $C_{14}H_{20}ClNO$. mp 261-262°C (ethanol–ether). IR spectrum, ν_{max}, liquid: 755 (1,2-disubstituted benzene ring), 1104 cm^{-1} (C–O–C).

Trans-4-butyl-2,3,4*a*,9,10,10*a*-hexahydro-4H-naphth[2,1-b]-1,4-oxazine (Ie) was obtained from IV and 14.05 g of IIIe, 1 h at 100°C, and then treated with 80 ml of 70% H_2SO_4. The resultant mixture of Ie and IIIe was then easily separated by fractional distillation. Yield 6.35 g (55%), IR spectrum, ν_{max}, liquid: 750 (1,2-disubstituted benzene ring), 1100 cm^{-1} (C–O–C). Hydrochloride $C_{16}H_{24}ClNO$. mp 216-218°C (ethanol–ether).

*The PMR spectrum of Ia (250 MHz) was obtained and interpreted by Professor St. Spasov (Institute of Organic Chemistry, Bulgarian Academy of Sciences), to whom the authors express their gratitude.

Trans-3-ethyl-2,3,4α,9,10,10α-hexahydro-4H-naphth[2,1-b]-1,4-oxazine (If) was obtained from IV and 10.68 g of IIIf, 1 h at 100°C. A 100-ml portion of water was added to the reaction mixture and IIf was extracted with ether. The extract was dried and evaporated. A 17.5-g portion of 60% H_2SO_4 was added to the residue (14 g). Yield 2.05 g (16%). bp 100-106°C/3 mm. IR spectrum, ν_{max}, liquid: 750 (1,2-disubstituted benzene ring), 1100 (C—O—C), 3330 cm^{-1} (NH). Hydrochloride. $C_{14}H_{20}ClNO$, mp 241-245°C (ethanol—ether).

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CHOLINOLYTIC ACTIVITY OF PIPERIDINOBUTINE ESTERS OF CERTAIN CARBOXYLIC ACIDS

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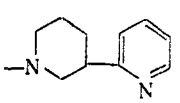
The well-known muscarine choline receptor antagonists (M-CR) constitute analogs of agonists that incorporate large hydrophobic radicals, i.e., the antagonists are "weighted" analogs of the agonists [1]. The muscarine antagonists apparently interact not only at the active center (recognition center) of the M-CR, but outside it as well. A well-known muscarine agonist is (acetoxy-2-inyl)trimethylammonium (IP-59) [2]. In our own work we investigated the muscarinolytic activity of its "weighted" analogs, namely the piperidino- and anabasinobutine esters of acetic, thioacetic, and thiobenzoic acids. The indicated acetic acid derivatives were obtained by the following synthesis pattern:

$$HOCH_2C{\equiv}CH \xrightarrow{CH_2O,\ HR} \underset{\text{I, II}}{HOCH_2C{\equiv}CCH_2R} \rightarrow$$

$$\rightarrow \underset{\text{III, IV}}{CH_3C(O)OCH_2C{\equiv}CCH_2R},$$

where R - N-piperidyl (I, III) or


(II, IV)

We synthesized 4-hydroxybutinylpiperidine (I) and 4-hydroxybutinylanabasine (II) by the aminomethylation of propargylic alcohol in the presence of catalytic quantities of CuCl. When these synthesized compounds were reacted with acetyl bromide in the presence of triethylamine they formed N-(4-acetoxybut-2-inyl)piperidine (III) and N-(4-acetoxybuty-2-inyl)-anabasine (IV).

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