STEREOISOMERIC 1,2,3,4,5,5a,6,10b-OCTAHYDROINDENO [1,2-c]AZEPINES

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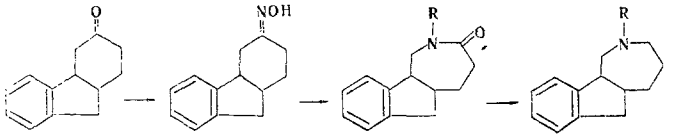
Stereoisomeric 1,2,3,4,5,5a,6,10b-octahydroindeno[1,2-c]azepines were obtained by Beckmann rearrangement of oximes. A conclusion regarding the structures of the final and intermediate products was drawn by means of establishment of the nonidentical character of the above-named azepines and one of the stereoisomeric 1,2,3,4,5,5a,6,10b-octahydroindeno[1,2-d]azepines.

As we have already indicated in our preceding communications [1, 2] we have synthesized three-ring azepine derivatives in order to study their pharmacological properties. The octahydroindeno[1,2-c]azepines (I) described in the present paper were obtained by Beckmann rearrangement of the oximes of cis- and trans-3-keto-9H-1,2,3,4,4a,9a-hexahydrofluorenes (II) [3]. The oximes (III) of both the cis- and trans ketones were obtained in the form of the two possible syn-anti isomers; this is apparently explained by the ready isomerizability of the less stable isomer.

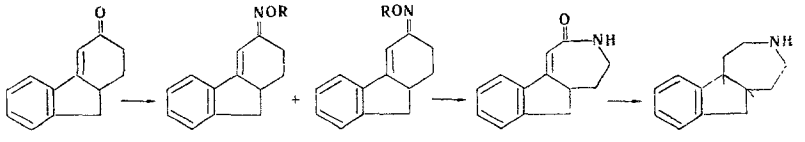


IIa,b IIIa,b IVa,b Ia,b

i—IVa — B/C-cis, b — B/C-trans, I′ R=H, I″ R=CH_3, I‴ R=C_2H_5, IV′ R=H IV″ R=CH_3, IV‴ R=CH_3CO

Rearrangement of oximes III by brief heating with polyphosphoric acid (PPA) leads to stereoisomeric 3-oxo-1,2,3,4,5,5a,6,10b-octahydro[1,2-c]azepines (IV′), which also proved to be individual substances. Lactams IV′ were methylated by dimethyl sulfate and acetylated by acetic anhydride. Stereoisomeric 1,2,3,4,5,5a,6,10b-octahydroindeno[1,2-c]azepines (I) and their N-alkyl derivatives were obtained by reduction of lactams IV with lithium aluminum hydride.

The structures of bases I (and, consequently, the structures of intermediate lactams IV and oximes III) was proved by comparison of them with one of the isomeric 1,2,3,4,5,5a,6,10b-octahydroindeno[1,2-d] azepines (V), which apparently has a trans structure. This compound was synthesized from α,β-unsaturated three-ring ketone VI, which forms two isomeric oximes; this is in all likelihood explained by the presence of a double bond in the α,β-position. The less stable (in a steric respect) isomer (VII) is apparently



VI VIIIa,b VIIa,b IX V

VII, VIII a R=H; b R=Ts

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TABLE 1. N-Substituted Stereoisomeric 3-Oxo-1,2,3,4,5,5a,6,10b-Octahydroindeno[1,2-c]azepines

Compound		mp, °C	R_f*	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
IV′	a	146	0,73	$C_{13}H_{15}NO$	77,5	7,7	6,9	77,6	7,5	7,0	92
	b	170	0,61		77,8	7,4	6,7				86
IV″	a	117	0,81	$C_{14}H_{17}NO$	78,3	7,7	6,4	78,1	7,9	6,5	73
	b	187	0,70		78,2	7,9	6,6				86
IV‴	a	94	0,87	$C_{15}H_{17}NO_2$	74,5	6,9	5,5	74,1	7,0	5,8	92
	b	111	0,79		74,3	7,0	5,4				91

* Chloroform – alcohol (9 : 1).

TABLE 2. N-Substituted Stereoisomeric 1,2,3,4,5,5a,6,10b-Octahydroindeno[1,2-c]azepines

Compound		R_f*	Empirical formula	Found, %			Calculated, %			Hydrochloride			Yield, %
				C	H	N	C	H	N	mp, °C	Cl, % found	Cl, % calc.	
I′	a	0,47	$C_{13}H_{17}N$	83,6	8,9	7,3	83,4	9,1	7,5	144	15,2	15,9	82
	b	0,32		83,2	8,9	7,6				198	15,1		79
I″	a	0,55	$C_{14}H_{19}N$	83,0	9,8	7,2	83,6	9,4	7,00	123	14,2	14,9	90
	b	0,48		83,7	9,4	6,6				183	14,3		93
I‴	a	0,63	$C_{15}H_{21}N$	83,6	9,6	6,8	83,7	9,8	6,5	138	13,8	14,1	92
	b	0,51		83,5	9,8	6,3				204	13,6		93

* Hexane – acetone – alcohol (30 : 3 : 1).

somewhat stabilized in this case because of the formation of a hydrogen bond with the olefinic proton attached to $C_{(4)}$.

It is known that the olefinic proton of syn-oximes of α,β-unsaturated ketones resonates at a weaker field than the same proton of the anti isomers [4-6]. A comparison of the PMR spectra of the oximes that we obtained showed that high-melting isomer VII, which is less soluble in alcohol and is formed in lower yield, is the syn-oxime (the signal of the olefinic proton is at 7.33 ppm). The signal of the same proton in the spectrum of the anti isomer (VIII), which is formed in higher yield, is at 6.5 ppm.

The established impossibility of the migration of the olefinic carbon atom during Beckmann rearrangement in the anti-cyclohexenone oxime system [6-8] was also ascertained by us in an attempt to realize the rearrangement of anti-oxime VIII. The rearrangement of syn-oxime VII was accomplished by refluxing its tosylate in methanol. The IR spectrum of the compound obtained (IX) contains bands of a conjugated double bond (1640), an amide carbonyl group (1670), and an amide imino group (3350 cm^{-1}), while the UV spectrum contains absorption corresponding to the benzylideneacetone chromophore (λ_{max} 244 and 257; λ_{min}, 234 nm). Lactam IX was reduced with lithium aluminum hydride. Inasmuch as the reduction of α,β-unsaturated carbonyl compounds with metal hydrides usually does not lead to saturation of the C=C bond, the reduction product, without isolation in pure form, was then reduced with sodium in boiling butyl alcohol; this gave azepine V, the IR spectrum of which does not contain the absorption bands of a conjugated double bond and of an amide carbonyl group. Chromatography in a thin layer showed that base V is an individual substance, apparently with a trans structure, with R_f 0.39, which does not coincide with any of the R_f values of the isomeric octahydroindeno[1,2-c]azepines (R_f cis 0.47, R_f trans 0.32). The hydrochloride of V, which has the elemental composition of hydrochlorides I′, melts at 178° (as compared with mp 144° for I′a and 198° for I′b). Thus, the nonidentical character of base V and any of bases I′ may apparently serve as a confirmation of our proposed structure for the latter.

EXPERIMENTAL

The IR spectra of chloroform solutions were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions were recorded with an SF-4 spectrophotometer. The PMR spectra of dimethyl sulfoxide (DMSO) solutions were recorded with a Varian T-60 spectrometer with an operating frequency of 60 MHz and tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was carried out on activity II aluminum oxide.

Oximes (III) of cis- and trans-3-Keto-9H-1,2,3,4,4a,9a-hexahydrofluorenes. A mixture of 3.7 g (0.02 mole) of ketone II (a or b), 1.7 g (0.025 mole) of hydroxylamine hydrochloride, 2 g (0.025 mole) of sodium acetate, 40 ml of alcohol, and 20 ml of water was refluxed for 5 h.

cis-Oxime (IIIa). The yield of this compound, with mp 68° and R_f 0.68 [chlorform–alcohol (9:1), development with iodine vapors], was 3.9 g (98%). Found: C 77.6; H 7.5; N 6.9%. $C_{13}H_{15}NO$. Calculated: C 77.6; H 7.5; N 7.0%.

trans-Oxime (IIIb). The yield of this compound, with mp 122° and R_f 0.56 (with the same system), was 3.4 g (85%). Found: C 77.5; H 7.5; N 7.0%. $C_{13}H_{15}NO$. Calculated: C 77.6; H 7.5; N 7.0%.

cis- and trans-3-Oxo-1,2,3,4,5,5a,6,10b-Octahydroindeno[1,2-c]azepines (IV'a, b). A 5-g (0.025 mole) sample of oxime III (a or b) was added to 150 g of heated (140°) polyphosphoric acid, and the mixture was heated at this temperature for 10-15 min, after which it was poured over ice. The resulting crystals were removed by filtration and recrystallized from chloroform–petroleum ether (see Table 1).

cis- and trans-2-Methyl-3-oxo-1,2,3,4,5,5a,6,10b-Octahydroindeno[1,2-c]azepines (IV" a, b). A mixture of 4 g (0.02 mole) of lactam IV', 3.8 g (0.03 mole) of dimethyl sulfate, and 40 ml of absolute benzene was refluxed for 6 h, after which excess 50% potassium carbonate solution was added, the benzene layer was separated, and the benzene was removed by distillation. The residual oil began to crystallize on trituration with absolute ether, and the solid was recrystallized from methanol (see Table 1).

cis- and trans-2-Acetyl-3-oxo-1,2,3,4,5,5a,6,10b-Octahydroindeno[1,2-c]azepines (IV"'a, b). A mixture of 5 g (0.025 mole) of lactam IV' and 50 ml of acetic anhydride was refluxed for 4h, after which the acetic anhydride was removed in vacuo, and the residue was treated with ether. The solid product was recrystallized from hexane (see Table 1).

cis- and trans-2H- and 2-Alkyl-1,2,3,4,5,5a,6,10b-Octahydroindeno[1,2-c]azepines (I). A solution of 0.01 mole of lactam IV in 15 ml of dry dioxane and 30 ml of anisole was added gradually to a solution of 0.02 mole of lithium aluminum hydride in 30 ml of absolute ether (0.03 mole of the hydride per 0.01 mole of compound was used in the case of the acetyl derivative). The mixture was refluxed for 18 h, after which it was decomposed with water. The usual workup gave a viscous uncrystallizable oil, which was purified by reprecipitation from the hydrochloride. The yields, R_f values of the bases, and the results of elementary analysis are presented in Table 2.

3-Keto-9H-1,2,3,9a-Tetrahydrofluorene Oximes (VIIa and VIIIa). A mixture of 3.9 g (0.021 mole) of ketone VI, 1.6 g (0.023 mole) of hydroxylamine hydrochloride, 1.1 g (0.026 mole) of sodium hydroxide, 26 ml of alcohol, and 13 ml of water was allowed to stand at room temperature for 2 days, after which the precipitate was removed by filtration, dried, and recrystallized from alcohol. The crystals that precipitated from the hot solution were removed by filtration and recrystallized (the syn-oxime). The anti-oxime was obtained by evaporation of the mother liquors and was also recrystallized.

syn-Oxime (VIIa). The yield of this compound, with mp 136°, was 1.6 g (38%). PMR spectrum: δ 10.46 (1H, s,* OH), 7.38 (1H, s, olefinic proton), and 7.16 ppm (4H, m, aromatic protons). Found: C 78.5; H 6.6; N 6.9%. $C_{13}H_{13}NO$. Calculated: C 78.4; H 6.5; N 7.0%.

anti-Oxime (VIIIa). The yield of this product, with mp 115°, was 2.4 g (57%). PMR spectrum: δ 10.66 (1H, s, OH), 7.26 (4H, m, aromatic protons), and 6.5 ppm (1H, s, olefinic proton), Found: C 78.6; H 6.2; N 7.1%. $C_{13}H_{13}NO$. Calculated: C 78.4; H 6.5; N 7.0%.

Oxime p-Toluenesulfonates (VIIb and VIIIb). A solution of 2 g (0.01 mole) of p-toluenesulfonyl chloride in 5 ml of pyridine was added dropwise at 0° to a solution of 2 g (0.01 mole) of the oxime in 12 ml of pyridine, after which the mixture was allowed to stand at 0° for 2 h. It was then poured into crushed ice containing 2 ml of concentrated sulfuric acid, and the resulting precipitate was removed by filtration, washed on the filter several times with water, and dried.

syn-Tosylate (VIIb). The yield of this compound, with mp 99-100°, was 3 g (86%). Found: N 4.2; S 8.8%. $C_{20}H_{19}NO_3S$. Calculated: N 4.0; S 9.0%.

anti-Tosylate (VIIIb). The yield of this compound, with mp 121°, was 3.1 g (88%). Found: N 3.7; S 8.4%. $C_{20}H_{19}NO_3S$. Calculated: N 4.0; S 9.0%.

2-Oxo-2,3,4,5,5a,6-hexahydroindeno[1,2-d]azepine (IX). A mixture of 2.1 g (0.006 mole) of VIIb, 15 ml of methanol, and 10 ml of water was refluxed for 2 h, after which the slightly turbid solution was fil-

*Here and subsequently, s is singlet and m is multiplet.

tered, the methanol was partially removed from the filtrate by distillation, and the residue was poured into water containing 2 g of sodium hydroxide. The resulting oil was treated with ether, and the ether solution was washed with water and dried to give 1 g (84%) of cream-colored crystals with mp 205° (chloroform–petroleum ether) and R_f 0.68 [chloroform–ethanol (9:1)]. Found: C 78.6; H 6.4; N 6.9%. $C_{13}H_{13}NO$. Calculated: C 78.4; H 6.5; N 7.0%. IR spectrum: ν 1610 (benzene ring), 1640 (conjugated C=C), 1670 (amide CO), and 3350 cm^{-1} (amide NH). UV spectrum, λ_{max} (log ε): 244 (3.92) and 257 (3.97); λ_{min} 234 nm (3.40).

Tosylate VIIIb did not dissolve on refluxing in methanol. Workup gave oxime VIIIa, which melted at 115° and did not depress the melting point of the sample described above.

1,2,3,4,5,5a,6,10b-Octahydroindeno[1,2-d]azepine (V). A solution of 1.5 g (0.007 mole) of lactam IX in 15 ml of dry dioxane and 15 ml of anisole was added gradually to a solution of 0.6 g (0.015 mole) of lithium aluminum hydride in 20 ml of absolute ether, and the mixture was refluxed for 18 h. It was then worked up in the usual manner to give 1.2 g of crude product, which was dissolved in 70 ml of butyl alcohol. A 5-g (0.2 g-atom) sample of sodium was then added to the refluxing butyl alcohol solution, and the mixture was refluxed for 2 h, after which the alcohol was removed by steam distillation, and the residue was treated with ether. The ether solution was washed with water and dried. The solvent was removed by distillation, and the residual oil was purified by reprecipitation from the hydrochloride to give 0.8 g (57%) of a viscous uncrystallizable oil with R_f 0.39 [hexane–acetone–alcohol (30:3:1)]. The hydrochloride (from ether) had mp 178°. Found: C 70.0; H 7.9; Cl 15.4; N 5.8%. $C_{13}H_{18}ClN$. Calculated: C 69.8; H 8.0; Cl 15.9; N 6.3%.

LITERATURE CITED

1. A. P. Boyakhchyan, L. L. Oganesyan, and G. T. Tatevosyan, Arm. Khim. Zh., 24, 1000 (1971).
2. A. P. Boyakhchyan and G. T. Tatevosyan, Arm. Khim. Zh., 26, 44 (1973).
3. A. P. Boyakhchyan, L. L. Oganesyan, and G. T. Tatevosyan, Arm. Khim. Zh., 26, 944 (1973).
4. G. Slomp and W. J. Wechter, Chem. and Ind., 41 (1962).
5. C. W. Shoppee, M. J. Akhtar, and R. E. Lack, J. Chem. Soc., 3392 (1964).
6. T. Sato, H. Wawatsuka, and K. Amano, Tetrahedron, 27, 5381 (1971).
7. C. W. Shoppee, R. E. Lack, R. N. Mirington, and L. R. Smith, J. Chem. Soc., 5868 (1969).
8. F. Kohen, Chem. and Ind., 1378 (1966).