SYNTHESIS OF SUBSTITUTED INDANO[2,1-c]PIPERIDINES

N. S. Prostakov, G. Alvarado Urbina,
M. A. Ryashentseva, and L. A. Gaivoronskaya

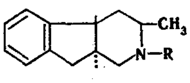
UDC 547.836.3.07

Substituted indano[2,1-c]piperidines were obtained by selective hydrogenation over Re_2S_7 and also by reduction with sodium in alcohol of 3-methyl-2-azafluorene and its derivatives. The geometrical isomers of the products were isolated and characterized.

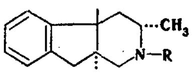
Continuing our research on the synthesis and study of polynuclear condensed nitrogen-containing compounds, we turned to the reduction of 3-methyl-2-azafluorene (I) [1] and some of its derivatives to the corresponding indano[2,1-c]piperidines. It has been reported that compounds that display antihistamine, psychotropic, and analgesic activity are found in a number of indanopiperidine derivatives [2-4]. The reduction was accomplished by catalytic hydrogenation of azafluorenes in the presence of rhenium heptasulfide [5], on which, as previously shown, selective hydrogenation of the arylpyridines to arylpiperidines occurs [6]. The method may therefore be of preparative value for the synthesis of hard-to-obtain indanopiperidines, which are formed in almost theoretical yield. The synthesis of isomeric indanopiperidines – new objects for the study of the stereochemistry of condensed nitrogen heterocycles – is an equally important result of these investigations.

The hydrogenation of (I), 3-methyl-2-azafluorenone (II), and 3-methyl-9-phenyl-2-aza-9-fluorenol (III) in methanol and ethanol is accompanied by alkylation, as a result of which the corresponding N-methyl- and N-ethyl derivatives are formed. The second peculiarity of hydrogenation under the indicated conditions consists in the fact that complete reduction of the carbonyl group and hydroxyl group, respectively, occurs along with reduction of the pyridine ring in the hydrogenation of II and III.

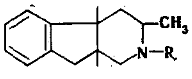
3-Methylindano[2,1-c]piperidine (IV) and its 2-methyl (V) and 2-ethyl (VI) analogs, which are formed in the hydrogenation of I, can exist in the form of four geometrical isomers (a-d).



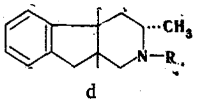
a



b



c

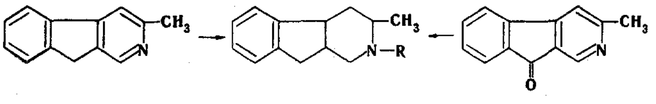


d

In this connection, one of the fundamental tasks of the present research was to establish the fact of the formation and isolation of the isomeric indanopiperidines. The reduction of II with sodium in alcohol and the catalytic hydrogenation of II were accomplished simultaneously. The similar reduction of I was described in [7]. In this case, also, the isomeric compounds were investigated and compared with the compounds that are formed in the catalytic hydrogenation. We were able to separate the mixtures of isomers by means of column chromatography on aluminum oxide.

The hydrogenation of I in benzene (hexane), methanol, and ethanol gave 2-R-3-methylindano[2,1-c]piperidines (IVa,b, R = H; Va,b, R = CH_3; VIa,b, R = C_2H_5). Compounds VIa,b were also obtained by hydrogenation of II. All of these substances are liquids. As a rule, the isomers differ significantly with respect to chromatographic mobility. Isomers IVa,b are identical to the isomers that are formed in the reduction of I with sodium in alcohol [7]. The configurational identity of isomers IV and VI was proved by alternative synthesis of VIa,b by alkylation of a mixture of isomers IVa,b, which was obtained by reduction of I with sodium in alcohol.

Patrice Lumumba University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1379-1383, October, 1973. Original article submitted December 20, 1971.



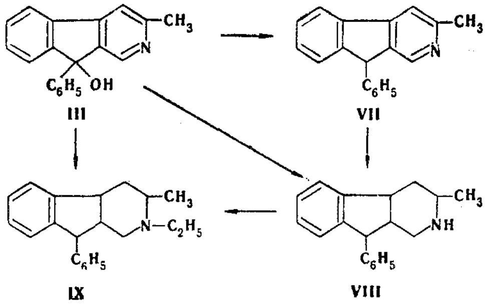
I IV–VI II

IV a,b R=H; V a,b $R=CH_3$; VI a,b $R=C_2H_5$

The analytical data on the individual isomers and their derivatives, the molecular weights (determined by mass spectrometry), and the IR and PMR spectra confirm the direction of the reaction and the structures of the compounds obtained. Bands at 1500-1620 cm^{-1}, which correspond to the pyridine ring, are absent in the IR spectra of VIa,b, Va,b, and IVa,b. In this region there are only very weak bands at 1606 and 1585 cm^{-1} (Va), 1612 and 1590 cm^{-1} (Vb), 1610 and 1585 cm^{-1} (VIa), and 1608 and 1576 cm^{-1} (VIb, in a film), which are related to the vibrations of the benzene ring. The appearance of intense bands at 2787 (Va) and 2780 cm^{-1} (Vb) confirms the presence of an $N\text{-}CH_3$ group, while the group of bands of medium intensity at 2700-2800 cm^{-1} (VIa,b) is apparently related to the $N\text{-}C_2H_5$ group [8, 9]. Singlets of $N\text{-}CH_3$ protons at δ 2.78 and 2.48 ppm are present in the PMR spectra of Va,b, while the spectrum of VIa contains a triplet (δ 1.60 ppm) and a quartet (δ 3.50 ppm) of an ethyl group.*

The formation of primarily only two isomeric indanopiperidines in all of the syntheses accomplished is apparently in conformity with principle. In the formulas of the indanopiperidine isomers presented above, fusion of the five-membered ring with the piperidine ring is realized by the trans-equatorial bonds of the latter in the case of *a* and b but by cis-equatorial and axial bonds in the case of c and d; the latter type of bonding is, of course, less likely. It can therefore be assumed that all of the isolated isomers of IV, V, and VI have the *a* and b configurations and differ with respect to the position of the methyl group attached to $C_{(3)}$. The different chromatographic mobilities of isomers *a* and b is apparently associated with a different conformation of the piperidine ring. The methyl group attached to $C_{(3)}$ is axial in isomer *a*, which has a chairlike conformation of the piperidine ring; this is thermodynamically unfavorable because of the 1–3 interaction. The piperidine ring in isomer *a* therefore apparently has the boat conformation, in which the nitrogen of the piperidine ring approaches the benzene ring, and this leads to shielding and weakening of the interaction with the adsorbent. In addition to steric factors, one must take into account the interaction of the electron pair of the nitrogen atom with the conjugated system of the π electrons of the benzene ring. We expressed similar considerations in our discussion of the structures of isomeric 3-methyl-9-benzylidene-2-azafluorenes [10].

The reduction of 3-methyl-9-phenyl-2-aza-9-fluorenol (III) [11] is accomplished by different methods.



III VII IX VIII

The hydrogenation of III in benzene and reduction of it with tin in hydrochloric acid gave 3-methyl-9-phenyl-2-azafluorene (VII), from which two isomers of 3-methyl-9-phenylindano[2,1-c]piperidine (VIII) were obtained by reduction with sodium in alcohol. However, they were isolated by direct reduction of III with sodium in alcohol. The isomers of VIII are crystalline substances; they differ considerably in chromatographic mobility.

Three isomers of 2-ethyl-3-methyl-9-phenylindano[2,1-c]piperidine (IX) were isolated in the hydrogenation of III in ethanol. Two of them are formed in the ethylation of a mixture of the isomers of VIII.

---

*The authors are grateful to V. F. Zakharov for recording the PMR spectra and participating in the interpretation of them.

The IR spectra of the isomers of VIII and IX do not contain the absorption bands at 1500-1620 cm^{-1} that are characteristic for the vibrations of the pyridine ring. The weak bands in this region at 1608 and 1500 cm^{-1} (VIII) and 1604 and 1573 cm^{-1} (IX) are related to the vibrations of the benzene ring. The intense bands at 3243 and 3241 cm^{-1} (VIII) are related to the vibrations of the N−H group of the piperidine ring that is tied up in an intermolecular hydrogen bond. The bands at 2700-2800 cm^{-1} in the spectra of the isomers of IX are related to the $N-C_2H_5$ group.

EXPERIMENTAL

A mixture of a solution of the substance to be hydrogenated (1 g for 5 ml of solvent) and rhenium heptasulfide (10% of the weight of the substance) in a glass ampul was placed in a rotating autoclave. The initial hydrogen pressure was 125 atm. The experiment was carried out at 230-260° for 3 h. The catalyst was removed by filtration and washed thoroughly with the solvent, and the hydrogenation products were isolated with a chromatographic column filled with activity II aluminum oxide [ether−hexane (3 : 1)] or by distillation.

3-Methylindano[2,1-c]piperidine (IVa,b). A. A 3-g sample of I was hydrogenated in 15 ml of benzene or hexane. The residue [2.87 g; R_f 0.53; 0.40 and 0.86 (traces of the starting I) remaining after distillation of the solvent was distilled: first fraction, 95-120° (1 mm), 0.8 g, R_f 0.53; 0.40; second fraction, 120-124° (1 mm), 1.27 g, R_f 0.86, 0.53, 0.40. The first fraction was a mixture of IVa,b. Found,%: C 83.5; H 9.0; N 7.2. $C_{13}H_{17}N$. Calculated,%: C 83.5; H 9.1; N 7.4. Separation of 0.7 g of this mixture with a chromatographic column gave 0.2 g of IVa with R_f 0.53. The hydrochloride of IVa had mp 270-272° (from alcohol). Found,%: Cl 15.8; N 6.0. $C_{13}H_{17}N \cdot HCl$. Calculated,%: Cl 15.9; N 6.2. The next substance eluted was 0.35 g of IVb with R_f 0.40, bp 100-101° (1 mm), and mp 81-82°. Found,%: C 83.5; H 8.8; N 7.1. $C_{13}H_{17}N$. Calculated,%: C 83.5; H 9.1; N 7.4.

B. A 5-g (0.026 mole) sample of II, 14 g (0.6 g-atom) of sodium, and 100 ml of alcohol were used for the reduction. The reaction was carried out with vigorous refluxing of the alcohol, after which 30 ml of water and 18% hydrochloric acid were added until the mixture was acidic. The alcohol was removed by distillation, the residue was made alkaline to pH 10 with sodium hydroxide, and the reaction products were extracted with benzene. The benzene was removed from the extract by distillation, and the residue (2 g) was treated with petroleum ether. A portion (0.22 g) of the residue was insoluble in petroleum ether. The substance isolated from the petroleum ether was distilled: first fraction, 111-116° (1 mm), 0.38 g, R_f 0.53, 0.40; second fraction, 116-137° (1 mm), 0.52 g, R_f 0.78, 0.53, 0.40, 0.10; third fraction, 137-160° (1 mm), 0.28 g, R_f 0.80, 0.60, 0.40, 0.10. Crystallization of 0.3 g of the first fraction in petroleum ether gave 0.05 g of a mixture of isomers IVa,b with mp 73-74° and R_f 0.53 and 0.40. In the preparation of the picrate, 0.1 g of the first fraction gave 0.06 g of the picrate of IVb with mp 210-211° (from alcohol); IVb, isolated from the picrate, had R_f 0.40. A 0.1-g sample of the same fraction gave 0.05 g of the hydrochloride of IVa with mp 275-276° (from alcohol); IVa, isolated from the hydrochloride, had R_f 0.53. Chromatography of the second and third fractions (0.8 g) gave 0.1 g of II and 0.34 g of a mixture of IVa,b.

No melting-point depressions were noted for mixtures of samples of IVb, the hydrochloride of IVa, and the picrate of IVb with samples of the compounds described in [7].

2,3-Dimethylindano[2,1-c]piperidine (Va,b). A 3-g sample of I was hydrogenated in 15 ml of methanol for 6 h to give 3.15 g of hydrogenation products (R_f 0.70 and 0.47), which were separated chromatographically to give 0.67 g of Va with R_f 0.70 and bp 103-104° (1 mm). Found,%: C 83.2; H 9.9; N 6.9; mol. wt. 201. $C_{14}H_{19}N$. Calculated,%: C 83.5; H 9.5; N 7.0; mol. wt. 201. Also isolated was 0.31 g of Vb with R_f 0.47 and bp 100-101° (1 mm). Found,%: C 83.6; H 9.7; N 6.7. $C_{14}H_{19}N$. Calculated,%: C 83.6; H 9.5; N 7.0.

2-Ethyl-3-methylindano[2,1-c]piperidine (VIa,b). A. A 3-g sample of I was hydrogenated in 15 ml of ethanol to give 2.95 g of hydrogenation products [R_f 0.70; 0.30 and 0.50 (traces)], which was distilled at 117-118° (2 mm) and had R_f 0.70 and 0.30. Found,%: C 83.5; H 9.7; N 6.4. $C_5H_{21}N$., Calculated,%: C 83.7; H 9.8; N 6.5. Chromatography of 2.3 g of the products gave 0.62 g of VIa, 0.23 g of VIb, and 1.18 g of a mixture of VIa,b. Compound VIa had R_f 0.7, bp 113-114° (1 mm), n_D^{20} 1.5378 and d_4^{20} 0.9863. Found,%: C 83.5; H 10.1; N 6.4; mol. wt. 215. $C_{15}H_{21}N$. Calculated,%: C 83.7; H 9.8; N 6.5; mol. wt. 215. The picrate of VIa had mp 165-166° (from alcohol). Found,%: N 13.0. $C_{15}H_{21}N \cdot C_6H_3N_3O_7$. The hydrochloride of VIa had mp 282-283° (from methanol−ethyl acetate). Found,%: Cl 14.0; N 5.6. $C_{15}H_{21}N \cdot HCl$. Calculated,%: Cl 14.0; N 5.5.

Compound VIb had R_f 0.3 and bp 105-106° (1 mm). Found, %: C 83.3; H 10.1; N 6.4. $C_{15}H_{21}N$. Calculated, %: C 83.7; H 9.8; N 6.4. The picrate of VIb had mp 158-159° (from alcohol). Found, %: N 13.0. $C_{15}H_{21}N \cdot C_6H_3N_3O_7$. Calculated,%: N 12.7. The hydrochloride of VIb had mp 227-228° (from methanol–ethyl acetate). Found,%: Cl 14.1; N 5.3. $C_{15}H_{21}N \cdot HCl$. Calculated,%: Cl 14.0; N 5.5. Isomers VIa,b were also isolated by hydrogenation of II under similar conditions.

B. A mixture of 2.2 g (0.016 mole) of potassium carbonate, 1.7 g (0.01 mole) of ethyl iodide, and 1.3 g (0.007 mole) of a mixture of the isomers of IV in 10 ml of acetone was refluxed with vigorous stirring for 2 h. The acetone was then removed by distillation, and 16 ml of water and 18% hydrochloric acid were added until the mixture was acidic. The neutral substances were extracted with ether, and the aqueous layer was treated with sodium carbonate. The organic bases were extracted with ether, and the extract was dried with sodium sulfate. The residue (1.2 g) from the ether extract was a mixture of isomers VIa,b, according to the chromatographic data (R_f 0.70 and 0.30).

3-Methyl-9-phenyl-2-azafluorene (VII). A. A 3-g sample of III was hydrogenated in 15 ml of benzene to give 2.86 g of reaction products [R_f 0.85, 0.44 (starting III), and 0.24 (traces)], which were separated chromatographically to give 0.63 g of VII with R_f 0.85 and mp 116-117° (from petroleum ether). Found,%: C 88.6; H 5.5; N 5.7. $C_{19}H_{15}N$. Calculated,%: C 88.8; H 5.8; N 5.5. The picrate of VII had mp 186-187° (from alcohol). Found,%: N 11.2. $C_{19}H_{15}N \cdot C_6H_3N_3O_7$. Calculated,%: N 11.5. The hydrochloride of VII had mp 214-216° (from alcohol). Found,%: Cl 12.0; N 5.1. $C_{19}H_{25}N \cdot HCl$. Calculated,%: Cl 11.9; N 4.9. Also isolated was 0.12 g of III with mp 144-147° (from benzene).

B. An 8-g (0.073 g-atom) sample of tin was added to 1 g (0.004 mole) of III in 15 ml of alcohol and 15 ml of hydrochloric acid, and the mixture was heated for 1 h and filtered. The alcohol and acid were removed from the filtrate by distillation, and 30 ml of water and sodium carbonate were added to the residue until it was alkaline. The organic bases were extracted with ether and dried with sodium sulfate to give 0.7 g of VII with mp 114-116° (from petroleum ether) and R_f 0.85.

3-Methyl-9-phenylindano[2,1-c]piperidine (VIII). A. An 8.2-g (0.36 g-atom) sample of sodium was added to a refluxing solution of 5 g (0.018 mole) of III in 60 ml of alcohol, and the mixture was refluxed for 30 min. Water (10 ml) and 150 ml of 18% hydrochloric acid were added, the alcohol was removed by distillation, and the residue was treated with sodium hydroxide until the pH was 10. The organic bases were extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation, and the residue (3.87 g) was chromatographed (column H 70 cm, d 3 cm, elution with ether) to give, as the first fraction, 2.86 g of a mixture of two isomers of VIII [R_f 0.40 and 0.10 (traces)]. Found,%: C 86.4; H 7.8; N 5.2. $C_{19}H_{21}N$. Calculated,%: C 86.5; H 8.0; N 5.3. Repeated crystallization of 2.7 g of the mixture of VIII from petroleum ether gave 0.35 g of an isomer of VIII with R_f 0.40 as colorless crystals with mp 132-133°. Found,%: C 86.3; H 8.1; N 5.1. $C_{19}H_{21}N$. Calculated,%: C 86.5; H 8.0; N 5.3. Its hydrochloride had mp 167-170° (from methanol–ethyl acetate). Found,%: Cl 11.4; N 4.3. $C_{19}H_{21}N \cdot HCl$. Calculated,%: Cl 11.6; N 4.6. The column then yielded a second fraction: 0.71 g of a second isomer of VIII with contamination by the first isomer [R_f 0.10 and 0.40 (traces)]. Crystallization of this mixture from petroleum ether gave 0.1 g of the second isomer of VIII as colorless crystals with mp 84-85° and R_f 0.10. Found,%: N 5.8. $C_{19}H_{21}N$. Calculated,%: N 5.3. Its hydrochloride had mp 128-130° (from methanol–ethyl acetate). Found,%: Cl 11.3; N 4.4. $C_{19}H_{21}N \cdot HCl$. Calculated,%: Cl 11.6; N 4.6.

B. A 1.5 g sample of VII was similarly reduced with sodium in alcohol to give 1.18 g of a mixture of isomers of VIII (R_f 0.40 and 0.10).

2-Ethyl-3-methyl-9-phenylindano[2,1-c]piperidine (IX). A. A 2-g sample of III was hydrogenated in 15 ml of ethanol at an initial hydrogen pressure of 140 atm to give 2.03 g of hydrogenation products with bp 135-145° (2 mm) and R_f 0.80, 0.70, and 0.50, which are apparently a mixture of isomers of IX. Found, %: C 86.9; H 8.5; N 4.7; mol. wt. 291. $C_{21}H_{25}N$. Calculated,% : C 86.6; H 8.6; N 4.8; mol. wt., 291. Chromatographic separation of 1.3 g of this mixture gave 0.1 g of an isomer of IX with R_f 0.80. Found,%: N 5.0. $C_{21}H_{25}N$. Calculated, %: N 4.8. Its hydrochloride had mp 206-208° (from alcohol). Found,%: Cl 11.0; N 4.6. $C_{21}H_{25}N \cdot HCl$. Calculated,% : Cl 10.7; N 4.3. After this, 0.1 g of an isomer of IX with R_f 0.70 was isolated. Its hydrochloride had mp 165-167° (from alcohol). Found,%: Cl 11.0; N 4.3. $C_{21}H_{25}N \cdot HCl$. Calculated, %: Cl 10.7; N 4.3. At the end of the chromatography, 0.2 g of a third isomer of IX with R_f 0.50 was isolated. Found,%: C 86.7; H 8.6; N 4.9. $C_{21}H_{25}N$. Calculated, %: C 86.6; H 8.6; N 4.8. Its hydrochloride had mp 182-183° (from alcohol). Found,%: Cl 10.8; N 4.3. $C_{21}H_{25}N \cdot HCl$. Calculated, %: Cl 10.7; N 4.3. In addition, 0.72 g of a mixture of isomers of IX was isolated.

B. A 0.4-g sample of a mixture of the isomers of VIII was ethylated via the method used to obtain VI to give 0.37 g of a mixture of the isomers of IX with R_f 0.80 and 0.70. Found,%: C 86.5; H 8.5; N 4.8. $C_{21}H_{25}N$. Calculated,%: C 86.6; H 8.6; N 4.8.

The molecular weights were determined with an MKh-1303 mass spectrometer. The IR spectra of films (IVa,b, Va,b, and VIa,b, and each of the isomers of IX), KBr pellets (VII and VIII), and of a mineral oil suspension (VIII) were recorded with a UR-20 spectrophotometer. The PMR spectra were obtained with a Varian T-60 spectrometer. Carbon tetrachloride was used as the solvent, and the internal standard was tetramethylsilane.

LITERATURE CITED

1. N. S. Prostakov, K. D. Mat'yu, and V. A. Kurichev, Khim. Geterotsikl. Soed., 876 (1967).
2. G. Lehman, J. Pharm. Exp. Therap., 92, 249 (1948).
3. J. T. Plati and W. Wenner, J. Org. Chem., 20, 1412 (1955).
4. E. Jucker, A. Ebnoether, and J. M. Bastian, French Patent No. 2,008,984 (1970); Chem. Abstr., 73, 45,359x (1970).
5. M. A. Ryashentseva and Kh. M. Minachev, Usp. Khim., 38, 2050 (1969).
6. M. A. Ryashentseva, Kh. M. Minachev, V. V. Dorogov, and N. S. Prostakov, USSR Author's Certificate No. 287,019 (1970); Byul. Izobr., No. 35, 41 (1970); Khim. Geterotsikl. Soed., 88 (1972).
7. N. S. Prostakov, L. A. Gaivoronskaya, G. Alvarado Urbina, P. D. Émeruva, and T. Nakanishi, Khim. Geterotsikl. Soed., 666 (1972).
8. K. Nakanishi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Mir, Moscow (1965), p. 40.
9. R. D. Hill and G. D. Meakins, J. Chem. Soc., 760 (1958).
10. N. S. Prostakov, Sipeu Simo Moiz, A. T. Soldatenkov, V. P. Zvolinskii, and G. I. Cherenkova, Khim. Geterotsikl. Soed., 1398 (1971).
11. N. S. Prostakov, L. A. Gaivoronskaya, and G. Alvarado Urbina, Khim. Geterotsikl. Soed., 1087 (1971).