2-(ω-HYDROXYALKYL)-3-METHYLINDANO[2,1-c]PIPERIDINES

N. S. Prostakov, L. A. Gaivoronskaya,
G. Alvarado Urbina, Pius D. Emeruva,
and Tirio Nakanisi

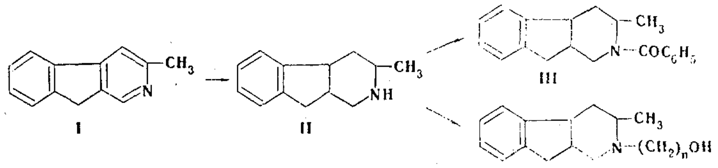
UDC 547.836:542.942.4

Two isomers of 3-methylindano[2,1-c]piperidine were isolated in the reduction of 3-methyl-2-azafluorene with sodium in alcohol. N-(ω-Hydroxyalkyl) derivatives of this heterocyclic system were obtained.

3-Methyl-2-azafluorene [1] was reduced with sodium in alcohol in order to obtain physiologically active substances and to make a systematic study of the stereochemistry of partially hydrogenated azafluorenes. Two of the four theoretically possible geometrical isomers of 3-methylindano[2,1-c]piperidine (II) were obtained – a liquid with bp 115° (1 mm) (IIa) and a crystalline substance with mp 81.5-83° (IIb). They were separated by crystallization of the hydrochlorides, column chromatography, and by isolation of IIb from the reaction mixture. Isomer IIa has greater chromatographic mobility than IIb. 2-Benzoyl-3-methylindano[2,1-c]piperidine (III) was obtained from the mixture of isomers of II by the Schotten–Baumann reaction. This same compound is also formed on treatment of II with benzoyl chloride in benzene in the presence of triethylamine. A chromatographically individual substance was isolated in both cases. The formation of one isomer of III from a mixture of isomers of II is possibly explained by the fact that both benzoyl chloride [2] and alkali [2, 3] have isomerizing action on this system.

The intense absorption bands at 1500-1620 cm^{-1} that are related to the vibrations of the pyridine ring are absent in the IR spectra of IIa and IIb, which confirms the hydrogenation of the latter to I. Only very weak bands at 1590 and 1612 cm^{-1} (for IIa in a film) as well as at 1512 and 1610 cm^{-1} (for IIb in mineral oil), which pertain to the vibrations of the benzene ring, are present in this region. The intense broad bands at 3294 (IIa in a film) and 3344 (IIa, concentrated solution in CCl_4), as well as two bands at 3220 and 3194 cm^{-1} (IIb in mineral oil), are related to the stretching vibrations of the NH group, which forms intermolecular hydrogen bonds between differently associated molecules.

3-Methylindano[2,1-c]piperidine was used to obtain 2-(ω-hydroxyalkyl)-3-methylindano[2,1-c]piperidines, which are of pharmacological interest. They were obtained by alkylation of a mixture of isomers of II with ethylene and butylene chlorohydrins in the presence of potassium iodide and carbonate. It was established by chromatography that 2-(β-hydroxyethyl)- (IV) and 2-(δ-hydroxybutyl)-3-methylindano[2,1-c]piperidines (V) are formed as two isomers, which apparently correspond to the two isomers of II. A broad band at 3420 cm^{-1}, which is related to the stretching vibrations of the OH group, which forms intermolecular hydrogen bonds, is observed in the spectrum of IV. The intense band at 1060 cm^{-1} corresponds to the stretching vibrations of the C–O bond of a primary alcohol group.



IV n=2; V n=4

Patrice Lumumba University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 666-668, May, 1972. Original article submitted January 25, 1971.

The results of a study of the stereochemistry of the isomers of II will be presented in subsequent communications.

EXPERIMENTAL

3-Methylindano[2,1-c]piperidine (II). A 55 g (2.4 g-atom) sample of sodium was added to a refluxing solution of 24 g (0.132 mole) of I in 500 ml of absolute alcohol, and the mixture was refluxed for 30 min. Water (100 ml) and 670 ml of 18% HCl (with respect to Congo red) were added, and the precipitated NaCl was removed by filtration and washed with alcohol. The alcohol was removed from the filtrate by distillation, and the residue was treated with sodium hydroxide (pH 10). The organic bases were extracted with 1200 ml of ether, and the extract was dried with magnesium sulfate and vacuum distilled: the first fraction (19.53 g) had bp 118-120° (1 mm) [R_f (ether)* 0.09 (traces), 0.39 (IIb), 0.53 (IIa)], the second fraction (2.83 g) had bp 120-131° (1 mm) [R_f 0.09 (traces), 0.39, 0.53, 0.78, 0.86 (I)], and the third fraction (1.29 g) had bp 131-154° (1 mm) [R_f 0.09, 0.39, 0.53, 0.78, 0.86]. All of the fractions gradually crystallized; according to the chromatographic characteristics, IIa and IIb are the major components of the fractions. The first fraction is a mixture of the isomers of II. Found: C 83.4; H 9.1; N 7.5%. $C_{13}H_{17}N$. Calculated: C 83.4; H 9.1; N 7.5%. Repeated crystallization of 5.9 g of the first fraction from petroleum ether (bp 38-54°) gave 0.2 g of IIb as colorless needles with mp 81.5-83° and R_f 0.39. Found: C 83.6; H 8.9; N 7.6%; mol. wt. 187.† $C_{13}H_{17}N$. Calculated: C 83.4; H 9.1; N 7.5; mol. wt. 187. The picrate of IIb had mp 210.5-211° (from alcohol). Found: N 13.4%. $C_{13}H_{17}N \cdot C_6H_3N_3O_7$. Calculated: N 13.5%. The hydrochloride of IIb had mp 282-283° (from alcohol). Found: C 69.9; H 8.0; Cl 15.8; N 6.4%. $C_{13}H_{17}N \cdot HCl$. Calculated: C 69.8; H 8.1; Cl 15.9; N 6.2%.

Crystallization of 5.88 g of the hydrochloride of II from absolute alcohol gave 0.13 g of the hydrochloride of IIb and 0.36 g of the hydrochloride of IIa (this compound crystallized first from the solution) with mp 272-273°. Found: C 69.9; H 8.0; Cl 15.9; N 6.2%. $C_{13}H_{17}N \cdot HCl$. Calculated: C 69.8; H 8.1; Cl 15.9; N 6.2%. A mixture of the hydrochlorides of IIa and IIb had mp 230-233°.

A quantitative yield of free base IIa with bp 115° (1 mm) n_D^{20} 1.5525, and R_f 0.53 was isolated from 1.05 g (4.7 mmole) of the hydrochloride of IIa. The free base was a colorless, mobile liquid that was insoluble in water and soluble in all organic solvents. Found: C 83.6; H 9.3; N 7.6%. $C_{13}H_{17}N$. Calculated: C 83.4; H 9.1; N 7.5%.

Evaporation of the mother liquor from the crystallization gave 9.4 g of II, which was chromatographed with a column filled with 200 g of activity II Al_2O_3 and a large amount of ether to give 1.2 g of IIa, 2.9 g of IIb, and 2.2 g of a mixture of IIa and IIb.

2-Benzoyl-3-methylindano[2,1-c]piperidine (III). A 0.5 g (2.7 mmole) sample of a mixture of the isomers of II, 0.38 g (2.7 mmole) of benzoyl chloride, and 0.28 g (2.7 mmole) of triethylamine in 50 ml of anhydrous benzene was refluxed for 2 h. The triethylamine hydrochloride was removed by filtration, and the residue from removal of the benzene by distillation was heated repeatedly with petroleum ether (bp 45-73°). The extract yielded 0.72 g (92%) of III as a vitreous mass with bp 192-194° (2 mm) and R_f 0.71 [ethyl acetate–hexane (1:2); one spot shows up also in other systems on different samples of aluminum oxide]. Found: C 82.5; H 7.5; N 4.7%. $C_{20}H_{21}NO$. Calculated: C 82.5; H 7.2; N 4.8%. Compound III was also obtained from a mixture of the isomers of II via the Schotten–Baumann reaction. In some cases, III could be isolated as colorless crystals with mp 173-175° (from alcohol). Found: N 5.0%. $C_{20}H_{21}NO$. Calculated: N 4.8%.

2-(β-Hydroxyethyl)-3-methylindano[2,1-c]piperidine (IV). A mixture of 3 g (16 mmole) of II, 4 g (58 mmole) of ethylene chlorohydrin, 3.2 g (23 mmole) of potassium carbonate, and 0.3 g of potassium iodide was heated at 110° for 1 h. The reaction mass was treated with dilute 1:1 HCl (with respect to Congo red). and the neutral substances were extracted with ether. The extract was treated with alkali, and the organic bases were extracted with ether. The ether extract was dried with magnesium sulfate and vacuum distilled to give 2.23 g (60%) of IV as a viscous, colorless liquid with bp 165-169° (1 mm), n_D^{25} 1.5562, and R_f 0.65; 0.74 (ether). Found: N 5.8%; mol. wt. 231. $C_{15}H_{21}NO$. Calculated: N 6.1%; mol. wt. 231. The hydrochloride of IV had mp 223-232° (from methanol–ethyl acetate) and R_f 0.65; 0.74 (ether) as compared with mp

---

*Here and elsewhere, the R_f values are for activity V Al_2O_3.

† By mass spectrometric measurement.

268-269° (from methanol—ethyl acetate) and R_f 0.65. Found: C 67.5; H 8.3; Cl 13.1; N 5.3%. $C_{15}H_{21}NO \cdot HCl$. Calculated: C 67.3; H 8.2; Cl 13.3; N 5.2%.

2-(δ-Hydroxybutyl)-3-methylindano[2,1-c]piperidine (V). A mixture of 2.44 g (13 mmole) of II, 4.33 g (39 mmole) of 4-chloro-1-butanol [4], 5.4 g (90 mmole) of potassium carbonate, and 0.4 g of potassium iodide in 25 ml of anhydrous acetone was refluxed for 36 h (or for 3 h at 100° without a solvent) with vigorous stirring. The acetone was removed by distillation, and the residue was dissolved in 15 ml of water. The organic bases were isolated as in the case of IV to give 0.08 g of starting II and 1.56 g (46.4%) of V as a viscous liquid with bp 178-182° (1 mm) and R_f 0.60; 0.80 (ether). Found: C 78.9; H 9.9; N 5.5%. $C_{17}H_{25}NO$. Calculated: C 78.8; H 9.8; N 5.4%. The picrate of V had mp 148-151° (from alcohol). Found: N 11.3%. $C_{17}H_{25}NO \cdot C_6H_3N_3O_7$. Calculated: N 11.5%.

The IR spectra of IIa, IIb, and IV were recorded with a UR-20 spectrophotometer.

LITERATURE CITED

1. N. S. Prostakov, K. John Mathew, and V. A. Kurichev, Khim. Geterotsikl. Soedin., 876 (1967).
2. D. V. Sokolov, V. V. Sosnova, and G. S. Litvinenko, Izv. Akad. Nauk Kazakh, SSR, Ser. Khim., 17, No. 3, 63 (1967).
3. K. Isagawa et al., Nippon Kagaku Zasshi, 86, 550 (1967); Chem. Abstr., 69, 2819 (1968).
4. W. Kirner and G. Richter, J. Am. Chem. Soc., 51, 2505 (1929).