SYNTHESIS OF 2,3-DIMETHYL-6,7-BENZO-5,9-(1',2'-INDANO)-2-AZABICYCLO[3.3.1]NON-6-ENE

N. S. Prostakov and O. G. Kesarev

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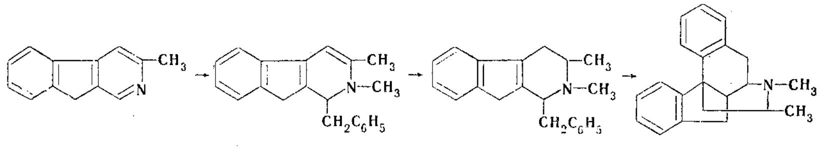
A structural analog of morphinan – 2,3-dimethyl-6,7-benzo-5,9-(1',2'-indano)-2-azabicyclo-[3.3.1]non-6-ene – was synthesized from 3-methyl-2-azafluorene.

2,3-Dimethyl-1-benzyl-1,2,3,4-tetrahydro-9H-indano[2,1-c]pyridine (III) is close in structure to alkaloids of the benzyltetrahydroisoquinoline group. The high physiological activity of analogous compounds – derivatives of partially hydrogenated indenopyridines – has been reported. For example, 2-methyl-9-phenyl-1,2,3,4-tetrahydro-9H-indeno[2,1-c]pyridine (V), which is called tephorin [1], has clearly expressed antihistamine action. 2,3-Dimethyl-6,7-benzo-5,9-(1',2'-indano)-2-azabicyclo[3.3.1]non-6-ene (IV) is the structural analog of morphinan, which has strong analgesic action [2]. 3-Methyl-2-azafluorene (I), the method for the preparation of which was previously developed by us [3], was used for the synthesis of III and IV.



I II III IV

2,3-Dimethyl-1-benzyl-1,2-dihydro-9H-indeno[2,1-c]pyridine (II) was obtained by the reaction of the methiodide of I with benzylmagnesium chloride. The absorption band at 1560 cm^{-1}, which corresponds to the pyridine ring [4] and is present in the spectrum of I, is absent in the IR spectrum of II. The sharp intense band at 705 cm^{-1} corresponds to a monosubstituted benzene ring [5], while the band at 2780 cm^{-1} is associated with the stretching vibrations of the $N-CH_3$ group in a nonaromatic heterocyclic system [6]. The hydrogenation of II to III on an Adams catalyst at room temperature and atmospheric pressure proceeds quite rapidly and selectively, and the C_3-C_4 double bond is hydrogenated, as in the hydrogenation of 1-phenylbutadiene [7,8]. The $C_{4a}-C_{9a}$ double bond, which is conjugated with the phenyl ring, is not hydrogenated. The spectral characteristics of III were compared with the characteristics of V [1], which contains all of the essential traits of the chromophore of III. As in the UV spectrum of the hydrochloride of III, there is one absorption maximum at 260 nm ($\log \varepsilon$ 3.96) in the UV spectrum of the hydrochloride of V. The characteristic absorption bands of II (705 and 2780 cm^{-1}) are retained in the IR spectrum of III. The cyclization of III to IV was accomplished by means of orthophosphoric acid (by the Grewe method [9]). Compound IV was isolated as colorless crystals with mp 130-132°. The absorption band corresponding to a monosubstituted benzene ring is absent in the IR spectrum of IV. The sharp decrease in the intensities of the absorption bands at 1600 and 1500 cm^{-1} can be explained by the absence of a double bond conjugated with the benzene ring [5]. The absorption of the $N-CH_3$ group is shifted to 2800 cm^{-1}; as previously noted [10], this also occurs for the $N-CH_3$ group in the piperidine ring. There are two absorption maxima at 266 nm ($\log \varepsilon$ 3.45) and 273 nm ($\log \varepsilon$ 3.44), which are characteristic for o-disubstituted alkylbenzenes [4], in the UV spectrum of IV (in alcohol).

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EXPERIMENTAL

2,5-Dimethyl-1-benzyl-1,2-dihydro-9H-indeno[2,1-c]pyridine (II). A 2.96-g (9.2 mmole) sample of the methiodide of I (mp 237-238°) was added in the course of 5 min with vigorous stirring to an ether solution of benzylmagnesium chloride (obtained from 0.8 g of magnesium and 3.5 g of benzyl chloride in 90 ml of ether), and the mixture was refluxed for 2 h. Toluene (60 ml) was added, the ether was removed by distillation, and the mixture was refluxed for another hour. Saturated ammonium chloride solution (20 ml) was added, and the reaction products were extracted with ether. The extract was dried with sodium sulfate, and the residue (4.8 g) from the extract was chromatographed [h 78 cm, d 2.5 cm, activity II Al_2O_3 (268 g), hexane–ether (10 : 1)] to give 1.55 g (59%) of II as a yellow oil with R_f 0.87. Found,%: C 87.3; H 7.3; N 4.9. $C_{21}H_{21}N$. Calculated,%: C 87.8; H 7.3; N 4.9. The hydrochloride of II had mp 216-217° (from acetone–ether). Found,%: N 4.4. $C_{21}H_{21}N \cdot HCl$. Calculated,%: N 4.3. UV spectrum of the hydrochloride of II (in alcohol), λ_{max}, nm (log ε): 253 (4.6), 296 (4.05), shoulder.

2,3-Dimethyl-1-benzyl-1,2,3,4-tetrahydro-9H-indeno[2,1-c]pyridine (III). A 3-g (9.3 mmole) sample of the hydrochloride of II in 30 ml of alcohol was hydrogenated at room temperature and normal pressure in the presence of 0.2 g of previously reduced platinum oxide. A total of 208 ml of hydrogen (the calculated amount) was absorbed after 3.5 h. The catalyst was removed by filtration, the alcohol was removed by distillation, and the residual mixture was treated with ammonium hydroxide. The reaction products were extracted with ether, and the extract was dried with sodium sulfate and chromatographed [h 29 cm, d 1 cm, activity II Al_2O_3 (20 g), hexane–ether (10 : 1)] to give 1.8 g of III as a yellow oil with R_f 0.53. Found,%: C 87.2; H 8.0; N 4.8. $C_{21}H_{23}N$. Calculated,%: C 87.2; H 8.0; N 5.8. The hydrochloride of III had mp 213-214° (from acetone–ether). Found,%: Cl 10.8. $C_{21}H_{23}N \cdot HCl$. Calculated,%: Cl 10.9. A mixture of the hydrochlorides of II and III had mp 197-201°.

2,3-Dimethyl-6,7-benzo-5,9-(1',2'-indano)-2-azabicyclo[3.3.1]non-6-ene (IV). A mixture of 2.7 g (8.3 mmole) of the hydrochloride of III and 54 g of orthophosphoric acid was heated under nitrogen at 150° for 9 h, after which it was treated with ammonium hydroxide. The reaction products were extracted with benzene, and the extract was dried with sodium sulfate and chromatographed [h 58 cm, d 1.5 cm, activity II Al_2O_3 (95 g), ether–hexane (1 : 2)] to give 0.2 g (8%) of colorless crystals of IV with mp 130-132° and R_f 0.3. Found,%: C 87.3; H 7.5; N 5.1. $C_{21}H_{23}N$. Calculated,%: C 87.2; H 8.0; N 4.8.

The IR spectra (II and III in a liquid film, IV in a KBr pellet) were recorded with a UR-20 spectrophotometer. The UV spectra were recorded with an EPS-3T recording spectrophotometer. Thin-layer chromatography was performed in all cases on activity II Al_2O_3 with ether–hexane (3 : 1).

LITERATURE CITED

1. J. T. Plati and W. Wenner, J. Org. Chem., 20, 1412 (1955).
2. K. Fromherz, Arch. Intern. Pharmacodyn., 85, 387 (1951).
3. N. S. Prostakov, K. D. Mat'yu, and V. A. Kurichev, Khim. Geterotsikl. Soedin., 876 (1967).
4. L. A. Kozitsina and N. B. Kupletskaya, Application of UV, IR, and NMR Spectroscopy in Organic Chemistry [in Russian], VSh, Moscow (1971), pp. 166, 215.
5. K. Nakanishi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Mir, Moscow (1965), p. 31.
6. R. D. Hill and J. D. Meakins, J. Chem. Soc., 760 (1958).
7. E. D. Bergmann, Isomerism and Isomerisation of Organic Compounds, New York (1948), p. 56.
8. I. E. Muskat and B. Knapp, Ber., 64, 779 (1931).
9. R. Grewe, Naturwiss., 33, 333 (1946).
10. N. S. Prostakov, V. E. Zaitsev, N. M. Mikhailova, and N. N. Mikheeva, Zh. Obshch. Khim., 34, 463 (1964).