SYNTHESIS OF 2-METHYL(PHENYL)-6-METHYL-7-PHENYLINDOLISINE AND 2-METHYL(PHENYL)INDOLISINO[6,7-a]INDENE

N. S. Prostakov and O. B. Baktibaev

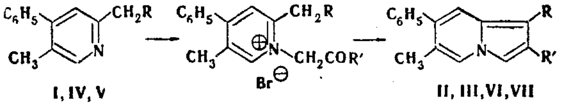
UDC 547.836'759.3.07

Substituted indolisines were obtained from 2-methyl-, 2-ethoxymethyl-, and 2-phenoxymethyl-5-methyl-4-phenylpyridines. 3-Methyl-2-azafluorene was used in the syntheses of a four-ring condensed system – substituted indolisino[6,7-a]indene.

Continuing our research on the synthesis and study of polynuclear nitrogen-containing heterocyclic compounds based on substituted pyridine bases, we have addressed ourselves to the synthesis of systems containing an indolisine ring. The starting compound for the synthesis described in this paper is 2,5-dimethyl-4-phenylpyridine (I) [1]. The transition from I to substituted indolisines was accomplished by known methods [2-4]. 2,6-Dimethyl-7-phenylindolisine (II) and 6-methyl-2,7-diphenylindolisine (III) were obtained in yields of 35.8% and 75%, respectively, by treatment of the pyridinium salt obtained from I and bromoacetone or bromoacetophenone with sodium bicarbonate.

We previously described the preparation from I of 2-ethoxymethyl- (IV) and 2-phenoxymethyl-5-methyl-4-phenylpyridine (V) [5], which are now used in the synthesis of 1-ethoxy- (VI) and 1-phenoxy-6-methyl-2,7-diphenylindolisine (VII). Strong bands of asymmetric and symmetric stretching vibrations of aliphatic groups (2975 and 2870 cm^{-1}) are observed in the IR spectrum* of VI in the high-frequency region. Bands of the deformation vibrations of the same groups are observed at 1458 and 1353 cm^{-1}. The presence of a phenyl substituent is confirmed by weak bands of the stretching vibrations of the aromatic CH bond (3030, 3060 cm^{-1}), by the presence of a band of the C = C stretching vibrations (1605 cm^{-1}), and also by the bands of out-of-plane deformation vibrations of the aromatic CH bonds (703 and 761 cm^{-1}). The intense band at 1085 cm^{-1} can be related [7] to the stretching vibration of the C–O–C group.

The IR spectrum of VII contains weak bands of the stretching vibrations of the aromatic CH bonds (3020 and 3010 cm^{-1}), a strong band of the stretching vibrations of the C = C bonds of the benzene ring (1600 cm^{-1}), and bands of the out-of-plane deformation vibrations of monosubstituted benzene rings (760, 703 cm^{-1}). The presence of a C–O–C group is confirmed by the presence of an intense band of asymmetric stretching vibrations at 1215 cm^{-1}.



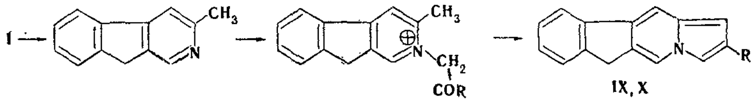
I–III R=H; IV, VI R=OEt; V, VII R=OPh; II R'=Me; III, VI, VII R'=Ph

Compound I was also used as a starting substance in the syntheses of condensed indolisine structures. The catalytic dehydrocyclization of I yields 3-methyl-2-azafluorene (VIII) [6]. The corresponding quaternary salts were obtained from VIII and bromoacetone, as well as bromoacetophenone, and the salts were then used to obtain 2-methyl (IX) and 2-phenylindolisino[6,7-a]indene (X).

---

*The IR spectra of KBr pellets of the compounds were obtained with a UR-20 spectrometer with LiF, NaCl, and KBr prisms.

Patrice Lumumba University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1395-1397, October, 1971. Original article submitted September 15, 1970.



IX R=Me; X R=Ph

The substituted indolisines (II, III, VI, and VIII) and indolisinoindenes (IX and X) are colored, crystalline substances. They are quite labile and apparently undergo profound changes on exposure to light. For example, freshly prepared benzene solutions of IX and X have a color that corresponds to the color of the crystals. (The solutions fluoresce.) However, on exposure to light, even at room temperature, the color of the solution changes comparatively rapidly and becomes black. The crystals undergo the same changes on storage and exposure to light.

It is known [3] that pyridine-2-carboxylic acid is formed by the oxidation of indolisine with potassium permanganate, and the N-oxide of the same acid is isolated on oxidation with hydrogen peroxide. We oxidized 2-phenylindolisino[6,7-a]indene (X) with potassium permanganate in acetone at room temperature and obtained 2-azafluorenone-3-carboxylic acid and benzoic acid.

EXPERIMENTAL

2,6-Dimethyl-7-phenylindolisine (II). Bromoacetone [7 g (0.054 mole)] was added at room temperature to 10 g (0.054 mole) of I. The mixture warmed up, gradually thickened, and solidified. A 0.5-g sample of the resulting pyridinium salt was dissolved in 3 ml of absolute alcohol and precipitated by the addition of ether. It was washed with dry acetone and again dissolved in 3 ml of absolute alcohol. Absolute ether was then added until the solution became turbid. Cooling (−10°) yielded 0.32 g of N-acetonyl-2,5-dimethyl-4-phenylpyridinium bromide as shiny, colorless, star-shaped crystals with mp 172.5-173°. Found: C 60.0; H 5.7; N 4.4%. $C_{16}H_{18}BrNO$. Calculated: C 60.0; H 5.7; N 4.4%. Water (80 ml) was added to 17 g (0.0768 mole) of the ground pyridinium salt, and the mixture was treated with three 50-ml portions of ether, and 9.4 g (0.112 mole) of sodium bicarbonate was added. The mixture was refluxed for 4 h, cooled, and the organic substances were extracted with ether. The residue after removal of the ether (a dark, viscous mass) was treated with ligroin to give 4.2 g (35.8%) of II as gray-green crystals with mp 177-179° (from ligroin). Compound II was quite soluble in ether, benzene, and chloroform, and slightly soluble in ligroin. Found: C 86.4; H 7.1; N 6.3%. $C_{16}H_{15}N$. Calculated: C 86.8; H 6.8; N 6.3%.

6-Methyl-2,7-diphenylindolisine (III). Bromoacetophenone [6 g (0.03 mole)] was added to 5.5 g (0.03 mole) of I, and the mixture was shaken. The mixture warmed up, thickened, and gradually solidified. The solid mass was ground, and 100 ml of water and 12 g (0.09 mole) of potassium carbonate were added. An orange precipitate formed during the addition. The mixture was refluxed for 4 h and cooled. The precipitate was removed by filtration and washed several times with cold and hot water. It was then dried in a vacuum desiccator to give 6.3 g (75.1%) of III as a dark-brown powder. Crystallization from dry ligroin yielded pale-green crystals with mp 150-150.5°. The crystals were quite soluble in benzene and slightly soluble in ligroin and alcohol. Found: C 88.7; H 6.2; N 4.9%. $C_{21}H_{17}N$. Calculated: C 89.0; H 6.0; N 4.9%.

6-Methyl-2,7-diphenyl-1-ethoxyindolisine (VI). Bromoacetophenone [2.2 g (0.011 mole)] was added to a solution of 2.5 g (0.011 mole) of IV in 30 ml of dry heptane, and the mixture was refluxed for 6 h. The liquid layer was decanted, and the dark-brown, crystalline mass was ground thoroughly and washed several times with ether. Water (80 ml) and 5 g (0.059 mole) of sodium bicarbonate were added, and the mixture was refluxed for 4 h. The solid was removed by filtration, washed several times with hot water, and dried in a vacuum desiccator to give 1.5 g (41.6%) of VI as a dark-brown powder. Two crystallizations from heptane and then from anhydrous acetone gave pale-yellow crystals of VI with mp 149.5-151.5° that were quite soluble in benzene, slightly soluble in acetone and ether, and very slightly soluble in ligroin. Found: C 84.4; H 6.7; N 4.2%. $C_{23}H_{21}NO$. Calculated: C 84.4; H 6.4; N 4.3%.

6-Methyl-2,7-diphenyl-1-phenoxyindolisine (VII). Bromoacetophenone [1.87 g (9.4 mmole)] was added to 2.6 g (9.4 mmole) of molten V with vigorous stirring, and the mixture was heated at 90-100° for 1 h. The solid mass was ground and dissolved in 30 ml of dry acetone. The compound was precipitated by the addition of absolute ether. The precipitate was removed by filtration and dried to give 3.2 g of colorless crystals of N-phenacyl-5-methyl-4-phenyl-2-phenoxymethylpyridinium bromide (apparently the hydrated form) with mp 166-167° (from acetone). Found: C 65.4; H 5.9; N 2.7%. $C_{27}H_{24}BrNO_2 \cdot H_2O$. Calculated: C 65.8; H 5.3; N 2.8%. Sodium bicarbonate [5 g (0.059 mole)] was added to a suspension of 3 g (6.3 mmole) of the pyridinium salt in 80 ml of water, and the mixture was refluxed for 4 h. The precipitate was removed by filtration, washed several times with cold and then hot water, and dried to give 2.15 g (85%) of VII as a gray powder. Two crystallizations (heptane, acetone) yielded VII as pale-green crystals with mp 148-148.5° that were quite soluble in benzene, slightly soluble in acetone, and very slightly soluble in ligroin. Found: N 3.8%. $C_{27}H_{21}NO$. Calculated: N 3.7%.

2-Methylindolisino[6,7-a]indene (IX). Bromoacetone [1.5 g (0.011 mole)] was added with shaking to a hot solution of 2 g (0.011 mole) of VIII in petroleum ether (70-100°). An oily layer separated immediately. The mixture was refluxed for 4 h, and the liquid portion was decanted. Water (100 ml) was added to the residue, the mixture was treated several times with ether, 5 g (0.059 mole) of sodium bicarbonate was added, and the mixture was refluxed for 4 h. The dark-green precipitate was removed by filtration, washed several times with hot water, and dried in a vacuum desiccator to give 2.03 g (83.8%) of crystals of IX (thin-layer chromatography on activity II aluminum oxide with elution by benzene gave a black spot at the start and a spot with $R_f \sim 1$), after the crystallization of which from heptane, yellow-green crystals were obtained. To purify them, a solution of the crystals in benzene was passed through a column filled with aluminum oxide. Compound IX was isolated as bright-yellow crystals, which, after recrystallization from heptane, melted above 350°. A benzene solution of IX changed color rapidly in light. Crystals of IX also darkened comparatively rapidly and were no longer soluble in benzene. The bright-yellow crystals of IX were quite soluble in benzene and slightly soluble in ligroin. Found: C 87.7; H 6.0; N 6.1%. $C_{16}H_{13}N$. Calculated: C 87.6; H 6.0; N 6.4%.

2-Phenylindolisino[6,7-a]indene (X). A mixture of 2 g (0.011 mole) of VIII and 2.2 g (0.011 mole) of bromoacetophenone in 50 ml of dry m-xylene was refluxed for 4 h. The resulting precipitate was removed by filtration, washed with ether, and dried to give 3.8 g (90.5%) of N-phenacyl-3-methyl-2-azafluorenium bromide with mp 225.5-226° (from alcohol). Found: N 3.8%. $C_{21}H_{18}BrNO$. Calculated: N 3.7%. Water (100 ml) and 5 g (0.059 mole) of sodium bicarbonate were added to 3.7 g (9.7 mmole) of the quaternary salt. Workup (see the previous experiment) yielded 2.7 g (85.2%) of X as a finely granular yellow-green powder with mp > 350° (from benzene). Purification (similar to that used for IX) with a column yielded bright-green crystals with mp 312.5-313° (benzene). Compound X was insoluble in ligroin, chloroform, ether, and ethyl acetate, and slightly soluble in benzene. Found: C 89.7; H 5.23; N 5.0%. $C_{21}H_{15}N$. Calculated: C 89.7; H 5.4; N 5.0%.

Potassium permanganate [2.2 g (13.9 mmole)] was added in portions to an emulsion of 1 g (3.5 mmole) of X in 200 ml of acetone with vigorous stirring at room temperature, and the mixture was stirred until the violet color of potassium permanganate vanished. The manganese dioxide was removed by filtration and washed thoroughly with hot water. The filtrate was evaporated to 30 ml and acidified with 50% H_2SO_4. The precipitated crystals were removed by filtration, dried, washed several times with ether, and crystallized from alcohol. A very small amount of 2-azafluorenone-3-carboxylic acid was isolated as yellow crystals with mp 219.5-220.5°. The crystals did not depress the melting point of an authentic sample. Benzoic acid was isolated from the ether solution.

LITERATURE CITED

1. N. S. Prostakov and N. N. Mikheeva, Med. Prom., No. 2, 11 (1960).
2. A. E. Chichibabin, Zh. Russk. Khim. Obshchestva, 59, 477 (1927).
3. A. E. Chichibabin and F. N. Stepanov, Zh. Russk. Khim. Obshchestva, 61, 1635 (1929).
4. V. S. Venturella, J. Pharm. Sci., 52, 868 (1963).
5. N. S. Prostakov and O. B. Baktibaev, Khim. Geterotsikl. Soedin., 1211 (1971).
6. N. S. Prostakov, D. Mat'yu, and E. N. Sedykh, Khim. Geterotsikl. Soedin., 1072 (1967).
7. K. Nakanishi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Mir, Moscow (1965), pp. 23, 30, 31, and 42.