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1,2,3,9a-TETRAHYDRO-1-AZAFLUORENES

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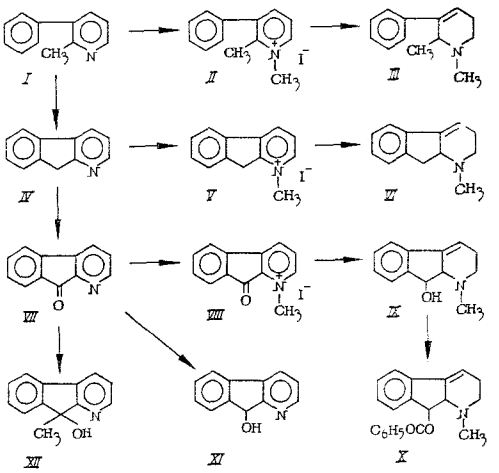
Some partially hydrogenated indenopyridines possess quite high physiological activity [1-4]. One compound of this type, used as an antiallergic drug, is teforine (2-methyl-9-phenyl-1,2,3,4-tetrahydroindano[2,3-c]pyridine tartrate [5]). Of the partially hydrogenated indenopyridines isomeric with respect to the position of the nitrogen atom, 1,2,3-9a-tetrahydro-1-azafluorenes have received virtually no attention (although they may be regarded as cyclic analogs of drugs of the amphetamine series). This is due to the lack of practicable methods for the preparation of starting materials for their synthesis, in particular 1-azafluorene. We have developed a method for the preparation of 1-azafluorene [6] by the catalytic dehydrocyclization of 2-methyl-3-phenylpyridine (I), which has enabled a study to be undertaken of its conversion, by the sodium borohydride reduction of quaternary salts of 1-azafluorene and the corresponding ketone, into partially hydrogenated 1-azafluorenes.

The methiodide of the pyridine base I (II) was first reduced. 1,2-Dimethyl-3-phenyl-1,2,5,6-tetrahydropyridine was isolated both as the free base and the hydrochloride. The PMR spectrum of (III) displayed a doublet signal for the methyl group at C_2 (δ = 0.85 ppm), and a multiplet of integral intensity one proton unit at δ = 5.70 ppm, assigned to the vinyl proton. Such multiplet signals are evidence of the location of the doublet bond between C_3 and C_4.



Sodium borohydride reduction of 1-azafluorene methiodide (V) [obtained from 1-azafluorene (IV)] gave 1-methyl-1,2,3,9a-tetrahydro-1-azafluorene (VI). The position of the double bond in its nitrogen-containing ring is apparently the same as in (III). Only signals due to the protons of the $=NCH_3$ group, and one vinyl proton at δ = 5.90 ppm, are seen in its PMR spectrum. Sodium borohydride reduction of 1-azafluorenol methiodide (VIII) [obtained from 1-azafluorenone (VII)] gives both pyridine ring and carbonyl group reduction products. 1-Methyl-9-hydroxy-

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1,2,3,9a-tetrahydro-1-azafluorene (IX) was isolated as comparatively high-melting crystals. Its IR spectrum showed a broad, intense band due to the associated hydroxyl group (3150 cm^{-1}), and a medium intensity band for the vinyl moiety (1685 cm^{-1}). The PMR spectrum of (IX) displayed two doublet signals for the protons at C_9 and C_{9a} (δ = 4.95 and 2.27 ppm, respectively). Their spin–spin coupling constant (J = 6.0 Hz), indicates that they are in the cis-configuration.

Mass spectrometric studies of (III), (VI), and (IX) confirmed their structures. Thus, sodium borohydride reduction of salts (II), (V), and (VIII) in methanol gave in all cases a tetrahydropyridine fragment with a double bond.

For pharmacological tests, the alcohol (IX) was converted into 1-methyl-9-benzoyloxy-1, 2,3,9a-tetrahydro-1-azafluorene (X), isolated as the free base and hydrochloride. For the same purposes, sodium borohydride reduction of the ketone (VII) afforded 1-azafluoren-9-ol (XI), and reaction with methyllithium gave 9-methyl-1-azafluoren-9-ol (XII). The structures of (X-XII) were confirmed by their elemental analyses, PMR, IR, and mass spectra.

In view of the fact that the structures of (VI), (IX), and (X) contain features reminiscent of amphetamine and the alkaloid ephedrine, the effects of their hydrochlorides on the central nervous system was studied using tests which detect psycho- and neurotropic activity [7]. In mice, all the drugs exhibited mild stimulant effects. (The drugs were administered intramuscularly.) They increased spontaneous motor activity, responses to irritation, and in high subtoxic doses inhibited tremor and clonic convulsions. In doses of 10-20% of the LD_{50}, the drugs shortened the effects of hexenal (by 23-60%), and enhanced the effects of apomorphine (by 16-170%) and arecoline (by 14%). The hydrochlorides of (VI) and (IX) were moderately toxic (their LD_{50} values were 75 and 100 mg/kg, respectively). The least toxic was (X) hydrochloride (LD_{50} around 300 mg/kg).

A study of the pesticidal properties of the compounds on cell cultures of *Chlorella*, sugar beet, and tobacco showed that the quaternary salts (II), (V), and (VIII), possessed herbicidal activity, and (VII) displayed plant growth regulant activity.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (GDR) in KBr disks, and PMR spectra on a Tesla BS 487C (Czech. SSR) of working frequency 60 MHz, internal standard tetramethylsilane. Mass spectra were obtained on an MX-1303 instrument.

2-Methyl-3-phenylpyridine Methiodide (II). A solution of 3.55 g (0.02 mole) of the pyridine (I) and 4.56 g (0.03 mole) of methyl iodide in 10 ml of methanol was boiled for 3 h. The resulting precipitate was crystallized from methanol to give 5.2 g (80%) of the salt (II) as colorless crystals, mp 197-200°C (decomp.). Found, %: N 4.1. $C_{12}H_{11}N \cdot CH_3I$. Calculated, %: N 4.5.

1,2-Dimethyl-3-phenyl-1,2,5,6-tetrahydropyridine (III). To a solution of 3 g (0.01 mole) of the salt (II) in 35 ml of methanol was added portionwise with vigorous stirring 3.8 g (0.1 mole) of sodium borohydride. Stirring was continued for 30 min at 20°C, and one hour at the boil. Water (30 ml) was added, and the mixture extracted with benzene. The residue after removal of the benzene was chromatographed (column height 20 cm, diameter 3.5 cm, aluminum oxide, eluent a 2:1 mixture of ether and hexane). There was obtained 0.55 g (30.5%); of (III) as a reddish-brown viscous liquid. PMR spectrum, δ, ppm: 0.85, doublet (3H, 2-CH_3); 2.29, singlet, (N-CH_3); 5.70, multiplet (1H, C_4-H); 7.1, multiplet (5H, aromatic protons). Mass spectrum, m/e (relative intensity, %): M^+ 187 (21), 173 (26.5), 172 (100), 169 (22), 144 (11), 129 (31), 128 (22), 115 (21), 91 (32.5), 77 (15.5). Found, %: C 83.6; H 9.0; N 7.8. $C_{13}H_{17}N$. Calculated, %: C 83.4; H 9.1; N 7.5. M 187.

Hydrochloride: mp 144-146°C (from alcohol). Found, %: C 69.9; H 7.5; N 6.1. $C_{13}H_{17}N \cdot HCl$. Calculated, %: C 70.0; H 7.6; N 6.3.

1-Azafluorene methiodide (V) was obtained in the same way as the quaternary salt (II). Yield 90%, pale yellow crystals, mp 210-212°C, (decomp., from methanol). Found, %: N 4.4. $C_{12}H_9N \cdot CH_3I$. Calculated, %: N 4.5. Literature mp [8], 205-207°C.

1-Methyl-1,2,3,9a-tetrahydro-1-azafluorene (VI). Salt (III) (1 g, 0.03 mole) was reacted with 2.2 g (0.06 mole) of sodium borohydride in 50 ml of methanol. The reaction was carried out as in the preparation of (III). There was obtained 0.35 g (59%) of the reduction product (VI) in the form of bright violet crystals, mp 49-51°C (from benzene). PMR spectrum,

δ, ppm: 2.34, singlet (3H, N=CH_3); 5.90, multiplet (1H, C_4=H). IR spectrum, ν, cm^{-1}: 1605 (C=C). Mass spectrum, m/e (relative intensity, %): M^+ 185 (82), 184 (42.5), 170 (8.5), 143 (25.5), 142 (100), 141 (42.5), 128 (17), 116 (40.5). Found, %: C 84.6; H 8.4; N 7.5. $C_{13}H_{15}N$. Calculated, %: C 84.3; H 8.1; N 7.6. M 185. Literature mp [2], 49-51°C.

1-Azafluorene methiodide (VIII) was prepared in the same way as salt (V). Yield 63%, dark red crystals, mp 193-195°C (decomp., from methanol). Found, %: C 48.4; H 3.4; N 4.1. $C_{12}H_7NO \cdot CH_3I$. Calculated, %: C 48.3; H 3.1; N 4.3. Literature mp [8], 200-201°C.

1-Methyl-9-hydroxy-1,2,3,9a-tetrahydro-1-azafluorene (IX). Reduction of 1 g (3 mmole) of salt (VIII) with 2.3 g of sodium borohydride in 60 ml of methanol followed by chromatographic separation (eluent 40:1) ether–methanol) gave 0.6 g (88%) of (IX) as white crystals, mp 166-168°C (decomp., from benzene). PMR spectrum, δ, ppm: 2.27, doublet (1 H, C_{9a}=H, J 6.0 Hz); 2.57, singlet (3H, CH_3); 4.95, doublet (1H, C_9=H, J = 6.0 Hz); 5.96, multiplet (1H, C_4=H). IR spectrum ν, cm^{-1}: 3150 (associated hydroxyl). Mass spectrum m/e (relative intensities, %): M^+ 201 (100) 200 (2.35), 184 (12), 183 (21.5), 182 (29.5)m 173 (37.5), 172 (59), 158 (57), 144 (98), 131 (41), 130 (41), 129 (59), 128 (63), 115 (73). Found, %: C 77.3; H 7.2; N 6.7. $C_{13}H_{15}NO$. Calculated, %: C 77.6; H 7.4; N 7.0. M 201.

Hydrochloride, mp 147-149°C (decomp., from methanol). Found, %: H 5.5. $C_{13}H_{15}NO \cdot HCl$. Calculated, %: N 5.9.

1-Methyl-9-benzoyloxy-1,2,3,9a-tetrahydro-1-azafluorene (X). To a suspension of 0.5 g (0.025 mole) of (IX) in 15 ml of 2 N potassium hydroxide was added with vigorous stirring 1 ml of freshly-distilled benzoyl chloride, and the mixture stirred for 3 h at 20°C. The reaction products were extracted with ether and dried over sodium sulfate. The residue after removal of the solvent was purified on an alumina column (eluent, a 2:1 mixture of ether and hexane) to give 0.74 g (98%) of (X) in the form of a viscous oil. PMR spectrum, δ, ppm: 2.41, singlet (3H, CH_3); 3.47, doublet (1H, C_{9a}=H, J = 6.0 Hz); 6.17 multiplet (1H, C_4=H); 6.60, doublet (1H, C_9=H, J = 6.0 Hz). Mass spectrum (relative intensities, %): M^+ 305 (4), 200 (28), 185 (49), 184 (36), 183 (100), 115 (23), 105 (66), 77 (60.5).

Hydrochloride: mp 178-181°C (decomp., from methanol). Found, %: C 70.0; H 5.5; N 4.3. $C_{20}H_{19}NO_2 \cdot HCl$. Calculated, %: C 70.2; H 5.8; N 4.1.

1-Azafluoren-9-ol (XI). To a solution of 2 g (0.011 mole) of the ketone (VII) in 50 ml of methanol was added 0.43 g (0.011 mole) of sodium borohydride, and the solution was stirred for 1 h. The mixture was poured into 100 ml of water, and the solid filtered off and recrystallized from benzene to give 1.2 g (60%) of the alcohol (XI) as pale purple crystals, mp 98-100°C. PMR spectrum, δ, ppm: 5.70, singlet (1H, C_9=H); 5.81, broadened singlet (1H, hydroxyl); 7.88, doublet of doublets (1H, C_4=H, J = 7.5 and 1.5 Hz); 8.38, doublet of doublets (1H, C_2=H, J = 5.0 and 1.5 Hz). IR spectrum, ν, cm^{-1}: 3200 (hydroxyl). Mass spectrum (relative intensities, %); M^+ 183 (66), 182 (69), 166 (6), 155 (100), 154 (53), 127 (41), 101 (28), 91.5 (20), 77 (44). Found, %: C 78.6; H 4.6; N 7.7. $C_{12}H_9NO$. Calculated %: C 78.7; H 4.9; N 7.7. M 183.

9-Methyl-1-azafluoren-9-ol (XII). To methyllithium, obtained from 0.13 g (0.019 mole) of lithium and 1.3 g (9 mmole) of methyl iodide in 50 ml of absolute ether was added portionwise with vigorous stirring at 0°C over 1 h 1 g (6 mmole) of 1-azafluorenone (VII). The ether was removed, and the residue treated with 25 ml of benzene and boiled for 3 h. The mixture was cooled, and 10 ml of water added followed by 20 ml of saturated ammonium chloride solution. The benzene layer was separated, and the aqueous layer extracted with ether (3 × 50 ml). The extracts were dried over magnesium sulfate, and the residue after removal of the solvents chromatographed on an alumina column (eluent, a 40:1 mixture of ether and methanol) to give 0.11 g (10% of azafluorenol (XII), mp 155-157°C (from benzene). Found, %: C 79.3; H 5.7; N 6.9. M^+ 197. $C_{13}H_{11}NO$. Calculated, %: C 79.2; H 5.6; N 7.1. M 197.

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