FIVE-MEMBERED-RING-SUBSTITUTED 1-METHYL-1H-INDENO[1,2-b]PYRIDINES

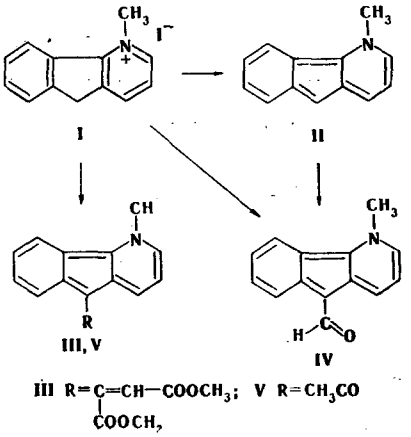
N. S. Prostakov, Keti Sudzhi,
N. M. Mikhailova, L. A. Murugova,
and V. F. Zakharov

UDC 547.836'665

1-Methyl-1H-indeno[1,2-b]pyridine and 1-methyl-1H-5-(α,β-dicarbomethoxyvinyl)-(formyl, acetyl)indeno[3,2-b]pyridines were obtained by treatment of N-methyl-4-azafluorenium iodide, as well as mixtures of it with acetylenedicarboxylic ester, dimethylformamide (DMF), and phosphorus oxychloride or acetic anhydride, with bases. 4-Azafluoronenone was used to synthesize 9-(p-methoxyphenyl)-4-azafluoren-9-ol, which was reduced to 9-(p-methoxyphenyl)-4-azafluorene, and 1-methyl-1H-5-(p-methoxyphenyl)indeno[3,2-b]pyridine was obtained from the methiodide of the latter.

The amount of information regarding five-membering-ring-substituted 1H-indenopyridines, which are nitrogen-containing pseudoazulenes that are obtained from azafluorenes, is limited. Several compounds of this type are known [1, 2]. In the present communication we describe the syntheses and properties of five-membered-ring-substituted 1-methyl-1H-indeno[1,2-b]pyridenes, which were obtained by two methods, viz., by the introduction of a substituent during the synthesis of the pseudoazulene or by prior introduction of a substituent in the C_9 position of 4-azafluorene [3, 4] with the subsequent production of a pseudoazulene.

1-Methyl-1H-indeno[1,2-b]pyridine (II) was obtained in almost quantitative yield from N-methyl-4-azafluorenium iodide (I) by treatment with a 5% solution of potassium hydroxide [2]. Without isolating pseudoazulene II, we obtained the product of its condensation with acetylenedicarboxylic ester in the presence of triethylamine, viz., 1-methyl-1H-5-(α,β-dicarbomethoxyvinyl)indeno[3,2-b]pyridine (III). 1-Methyl-1H-5-formylindeno[3,2-b]pyridine (IV) was obtained in low yield from quaternary salt I both without isolation of pseudoazulene acetylindeno[3,2-b]pyridine (V) was also obtained in low yield from iodide I and acetic anhydride in the presence of triethylamine.



Absorption at 400-700 nm is characteristic for the UV spectra of pseudoazulenes II-V (see Table 1), which is in agreement with the literature data [1]. The introduction of a substituent in the 5 position of pseudoazulene II has almost no effect on λ_{max} of the long-wave band, although azulenelike compounds should be sensitive to the effect of substituents.

A distinctive feature of the PMR spectra of pseudoazulenes II-V as compared with starting salt I is the weak-field shift of the signal of the protons of the N—CH_3 group to ∿4.75 ppm.

Patrice Lumumba Peoples' Friendship University, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1382-1386, October, 1981. Original article submitted January 4, 1981.

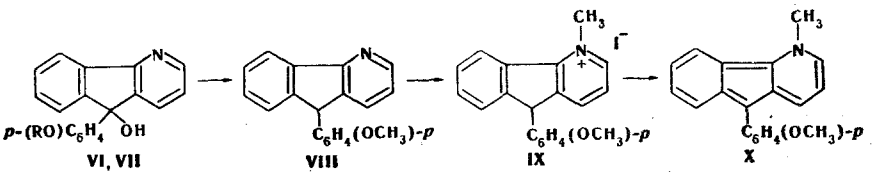
 0009-3122/81/1710-1038$07.50

TABLE 1. UV and PMR Spectra of Substituted 1-Methyl-1H-indeno[1,2-b]pyridines

Compound	λ_{max}, nm (log ε)	δ, ppm
II	230 (4,30); 274 (4,10); 425 (4,02) 312 (3,98); 570 (3,80)	4,29 (s, 3H, N—CH_3); 7,14 (s, 1H, 5-H); 7,74 (d, 1H, J=7 Hz, 6-H); 7,88 (d, 1H, J=7Hz, 9-H); 8,13 (d, 1H, J=7Hz, 2-H)
III	230 (4,48); 278 (4,44); 440 (4,71) 323 (4,66); 560 (3,40)	3,63 (s, 3H, OCH_3); 3,90 (s, 3H, OCH_3); 4,72 (s, 3H, N—CH_3); 6,04 (s, 1H, β-H); 6,84—8,50 (7H, aromatic protons)
IV	222 (4,18); 311 (3,98); 578 (3,82)	4,65 (s, 3H, N—CH_3); 6,84—8,50 (7H, aromatic protons); 9,20 (s, 1H, CH=O)
V	207 (4,32); 255 (4,00); 440 (3,90) 285 (3,97); 495 (3,70) 300 (4,10); 595 (3,73) 312 (4,18)	8,10 (d, 1H, J=7,0 Hz, 2-H; 7,69 (d, 1H, J=7,0Hz, 4-H); 8,94 (d, 1H, J=7,5 Hz, 6-H); 4,17 (s, 3H, N—CH_3); 2,62 (s, 3H, CH_3CO)
X	206 (5,02); 286 (4,22); 460 (2,81) 225 sh (4,68); 300 (4,21) 320 (4,28) 344 (4,12)	
XII	207 (4,48); 254 (4,06); 375 (2,70) 214 (4,41); 284 (4,03); 494 (3,73) 300 (4,14) 312 (4,21) 355 (2,76)	5,05 (s, 2H, 9-H); 6,62—8,45 (14H, aromatic protons)

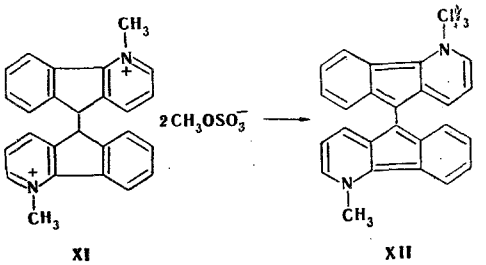
This may be a consequence of a change in the electronic structures of these compounds or may be due to the anisotropic effect of the condensed benzene ring of the azafluorene fragment.

We carried out the following successive syntheses in order to synthesize a similar five-membered-ring-substituted pseudoazulene. From 4-azafluorenone [4] and the corresponding organomagnesium compounds we obtained the previously unknown 9-(p-methoxyphenyl)- and 9-(p-ehtoxyphenyl)-4-azafluoren-9-ols (VI and VII). Azafluorenol VI was reduced with tin in hydrochloric acid and ethanol to 9-(p-methoxyphenyl)-4-azafluorene (VIII), the methiodide (IX) of which on treatment with 5% potassium hydroxide solution was converted to 1-methyl-1H-5-(p-methoxyphenyl)indeno[3,2-b]pyridine (X). Absorption in the long-wave region at 460 nm is also characteristic for the UV spectrum of this compound (see Table 1).



VI R=CH_3; VII R=C_2H_5

We made an attempt to synthesize a more complex pseudoazulene from bis(1-methyl-4-azafluorenia-9-yl) bis(methylsulfate) (XI), which was obtained from our previously described bis(4-aza-9-fluorenyl) [5].



9-Bis(1-methyl-1H-5-indeno[3,2-b]pyridine) (XII) was obtained by treatment of salt XI with triethylamine. The crystals of pseudoazulene XII are intensely violet. The substance has a high melting point and is insoluble in ether. These properties are probably due to the fact that a dipolar structure makes the principal contribution to the structure of XII. When it is dissolved in protic solvents, its color becomes appreciably weaker; an absorption

band at 494 nm is observed in the UV spectrum in this case. The PMR spectrum does not contain the signals of a methyl group attached to the nitrogen atom at 4 ppm that are characteristic for II-V but do contain signals in the aromatic proton region (6.62-8.45 ppm) and at 5.05 ppm (s, 2H, 5-H). On the basis of the spectral data it may be assumed that pseudoazulene XII is converted to bis(4-aza-0-fluorenyl) under these conditions [5].

Considering the instability of pseudoazulenes it may be assumed that XII undergoes protonation with subsequent demethylation in protic solvents. This is evidently a stepwise process, and its intermediate step is possibly recorded in the UV spectrum; the position of the long-wave maximum is therefore almost the same as in the case of II (see Table 1).

An intense molecular-ion peak of bis(4-aza-9-fluorenyl) with m/z 332 and an intense peak of a fragment ion with m/z 166 are observed in the mass spectrum of XII. It is possible that these ions are intermediate fragments that are formed in the fragmentation of the unstable molecular ion of XII (M^+ 360).

It must be noted that the percentage of nitrogen found in the analysis of some of the synthesized pseudoazulenes is depressed as compared with the calculated value. A similar anomaly was also observed in the analysis of the previously described pseudoazulenes of this type. Unfortunately, they cannot be recrystallized; the only method for their isolation is still chromatography. Considering their zwitterion structure it may be assumed that they form crystal hydrates.

EXPERIMENTAL

The UV spectra of solutions of the compounds in 96% ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were measured with a Perkin–Elmer Hitachi R-22 spectrometer (90 MHz) with tetramethylsilane as the internal standard. Activity II Al_2O_3 was used for column and thin-layer chromatography (TLC).

1-Methyl-1H-indeno[1,2-b]pyridine (II). A 12-ml sample of a 5% solution of potassium hydroxide was added gradually to a suspension of 1.2 g (4 mmole) of quaternary salt I (mp 249-251°C) in 15 ml of methylene chloride, and the mixture was stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with 50 ml of methylene chloride. The residue after removal of the methylene chloride by distillation was washed with water until the washings were neutral, after which it was dried *in vacuo* to give 0.7 g (96%) of pseudoazulene II as dark-blue crystals with mp 190-192°C. Found: N 6.4%. M^+ 181. $C_{13}H_{11}N$. Calculated: N 7.7%. M 181.

1-Methyl-1H-5-(α,β-dicarbomethyoxyvinyl)indeno[3,2-b]pyridine (III). A 0.9-g (6.3 mmole) sample of acetylenedicarboxylic ester and 0.9 g (9 mmole) of triethylamine were added successively to a suspension of 1 g (3.2 mmole) of salt I in 15 ml of methylene chloride, after which the dark-blue reaction mixture was stirred for 1 h. It was then chromatographed with a column (h = 34 cm, d = 2 cm) (successive elution with benzene and chloroform). Workup of the chloroform solution gave 0.52 g (50%) of III as dark-green crystals with mp 175-176.5°C (from benzene) and R_f 0.11 (chloroform). IR spectrum (mineral oil): 1720 and 1680 cm^{-1} ($COOCH_3$). Found: C 71.1; H 5.3; N 4.2%. $C_{19}N_{17}NO_4$. Calculated: C 70.9; H 5.3; N 4.3%.

1-Methyl-1H-5-formylindeno[3,2-b]pyridine (IV). A) A 2.16-g (9 mmole) sample of triethylamine was added to a solution of 2 g (6 mmole) of salt I in 10 ml of DMF, after which a solution of 2.1 g (7.5 mmole) of phosphorus oxychloride in 4 ml of DMF was added to the dark-blue solution at 0°C, and the mixture was stirred for 1 h. It was then heated at 80°C for 4 h, and the resulting precipitate was removed by filtration. The precipitate was treated with 25 ml of water, 10 ml of a saturated solution of sodium bicarbonate, and 50 ml of a 0.5 N solution of sodium hydroxide. The reaction products were extracted with benzene, and the benzene and DMF were removed by distillation. The residue (0.5 g) was heated in 40 ml of methanol, and the undissolved material was removed by filtration, washed with methanol, and dried *in vacuo* to give 0.1 g (8%) of formyl derivative IV as dark-crimson crystals with mp 204-205°C and R_f 0.05 (chloroform). IR spectrum (KBr pellet): 1627 cm^{-1} (CHO). Mass spectrum: M^+ 209 (100%), $[M - H]^+$ 208 (48%), $[M - CO]^+$ 181 (33%), $[M - HCO]^+$ 180 (58%), $[(M - CO) - CH_3]^+$ 166 (83%). Found: C 80.0; H 5.5; N 7.1%. M^+ 209. $C_{14}H_{11}NO$. Calculated: C 80.4; H 5.3; N 6.7%. M 209.

B) A solution of 1.6 g (0.1 mmole) of phosphorus oxychloride in 4 ml of DMF was added with stirring at 0°C to a solution of 1.05 g (5 mmole) of pseudoazulene II in 30 ml of DMF,

and the reaction mixture was stirred at room temperature for 1 h and at 50°C for 3 h. It was then cooled and treated with 35 ml of water, and the aqueous mixture was made weakly alkaline with a saturated solution of potassium carbonate and extracted with benzene. The residue (0.31 g) after removal of the benzene by distillation was crystallized from ethyl acetate–benzene (1:1) to give 0.03 g (3%) of formyl derivative IV as dark-crimson crystals with mp 206-207°C. Found: C 80.0; H 5.5; N 7.0%. M^+ 209. $C_{14}H_{11}NO$. Calculated: C 80.4; H 5.3; N 6.7%. M 209.

1-Methyl-1H-5-acetylindeno[3,2-b]pyridine (V). A mixture of 1 g (3 mmole) of iodide I, 3.6 g (30 mmole) of triethylamine, and 51 g (0.5 mole) of acetic anhydride was refluxed for 10 min, after which the excess anhydride was removed by distillation. The residue (0.18 g) was washed with ether and chromatographed (elution with chloroform) to give 0.06 g (8%) of acetyl derivative V as dark-crimson crystals with mp 127-130°C (dec.). IR spectrum (mineral oil): 1610 cm^{-1} (CO). Found: N 6.6%. M^+ 223. $C_{15}H_{13}NO$. Calculated: N 6.3%. M 223.

9-(p-Methoxyphenyl)-4-azafluoren-9-ol (VI). A 21-ml sample of an ether solution of an organomagnesium compound containing 10.4 g (4.9 mmole) of p-anisylmagnesium bromide was added gradually to a solution of 3 g (16.5 mmole) of 4-azafluorenone in 100 ml of benzene, and the mixture was refluxed for 1 h. It was then decomposed with 200 ml of water and 300 ml of a saturated solution of ammonium chloride. The ether–benzene solution was separated, and the aqueous solution was extracted repeatedly with ether. The combined extracts were dried with magnesium sulfate, and the residue (13.32 g) after removal of the solvents was crystallized from heptane to give 2.54 g (53%) of azafluorenol VIII with mp 182-185.C. Found: C 78.7; H 5.6; N 5.1%. M^+ 289. $C_{19}H_{17}NO_2$. Calculated: C 78.9; H 5.2; N 4.9%. M 289.

9-(p-Ethoxyphenyl)-4-azafluoren-9-ol (VII). This compound was similarly obtained in 65% yield from 4-azafluorenone and p-ethoxyphenylmagnesium bromide. The shiny crystals had mp 202-203°C (from heptane). Found:C 79.0; H 5.8; N 4.6%. $C_{20}H_{17}NO_2$. Calculated: C 79.2; H 5.7; N 4.6%.

9-(p-Methoxyphenyl)-4-azafluorene (VIII). An 8-g (0.086 g-atom) sample of tin was added to a solution of 2 g (6.9 mmole) of azafluorenol VI in 70 ml of ethanol and 40 ml of hydrochloric acid, and the mixture was refluxed for 40 h. The alcohol and acid were removed by distillation, and the residue was diluted with water and saturated with sodium carbonate. The organic bases were extracted successively with ether and benzene. The combined extracts were dried with magnesium sulfate, the solvents were removed by distillation, and the residue (1.5 g) was chromatographed with a column (h = 30 cm, d = 2 cm) [elution with hexane–ether (1:1)] to give 1 g (53%) of VII with mp 106-108°C (from heptane). Found: C 83.3; H 5.6; N 4.9%. M^+ 273. $C_{19}H_{15}NO$. Calculated: C 83.5; H 5.5; N 5.1%; M 273.

N-Methyl-O-(p-methoxyphenyl)-4-azafluorenium Iodide (IX). A solution of 0.7 g (2.56 mmole) of azafluorene VII and 2.9 g (20.5 mmole) of methyl iodide in 20 ml of acetone was maintained at room temperature for 1 h, after which it was refluxed for 30 min to give 0.54 g (77%) of salt IX with mp 206-208°C (from acetone). Found: N 3.4%. $C_{19}H_{15}NO \cdot CH_3I$. Calculated: N 3.4%.

1-Methyl-1H-5-(p-methoxyphenyl)indeno[3,2-b]pyridine (X). A mixture of 0.3 g (0.7 mmole) of salt IX, 6 ml of methylene chloride, and 8 ml of 5% of sodium hydroxide was stirred until the solid material dissolved completely. The dark-blue methylene chloride solution was separated, and the methylene chloride was removed by distillation. The residue was washed with water until the washings were neutral, after which it was dried to give 0.2 g (95%) of pseudoazulene X as dark-green crystals with mp 196-198°C. Found: N 3.5%. M^+ 287. $C_{19}H_{16}NO$. Calculated: N 4.8%; M 287.

Bis(1-methyl-4-azafluoroenia-9-yl) Bis(methylsulfate) (XI). A 0.46-g (3.65 mmole) sample of dimethyl sulfate was added to a solution of 0.25 g (0.75 mmole) of bis(4-aza-9-fluorenyl) in 40 ml of benzene. After 3 days, workup gave 0.35 g (79.5%) of salt XI as colorless crystals with mp 273-275°C (dec.). Found: N 4.5%. $C_{24}H_{16}N_2 \cdot 2(CH_3O)_2SO_2$. Calculated: N 4.8%.

9-Bis(1-methyl-1H-5-indeno[3,2-b]pyridine) (XII). A 0.86-g (8.5 mmole) sample of triethylamine was added to a solution of 0.1 g (1.7 mmole) of salt XI in 8 ml of methanol, as a result of which a red-violet solution was formed. The residue after removal of the methanol by distillation was chromatographed with a column (h = 17 cm, d = 1 cm) (elution with chloroform) to give 0.02 g (32%) of pseudoazulene XII as violet crystals with mp 269-272°C and R_f 0.59 (chloroform). Found: N 7.6%. $C_{26}H_{22}N_2$. Calculated: N 7.8%.

LITERATURE CITED

1. H. J. Timpe and A. V. El'cov, Z. Chem., 5, 172 (1975).
2. H. J. Timpe, J. Mlochowski, and Z. Szulc, Z. Chem., 19, 374 (1979).
3. N. S. Prostakov, A. V. Varlamov, G. A. Vasil'ev, O. G. Kesarev, and G. A. Urbina, Khim. Geterotsikl. Soedin., No. 1, 124 (1977).
4. N. S. Prostakov and O. G. Kesarev, Khim. Geterotsikl. Soedin., No. 12, 1671 (1977).
5. N. S. Prostakov, I. R. Vaskes, N. M. Mikhailova, and B. N. Anisimov, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 22, 920 (1979).

REACTIONS OF 2-METHYLENE-3-OXOQUINUCLIDINE WITH CARBONYL COMPOUNDS

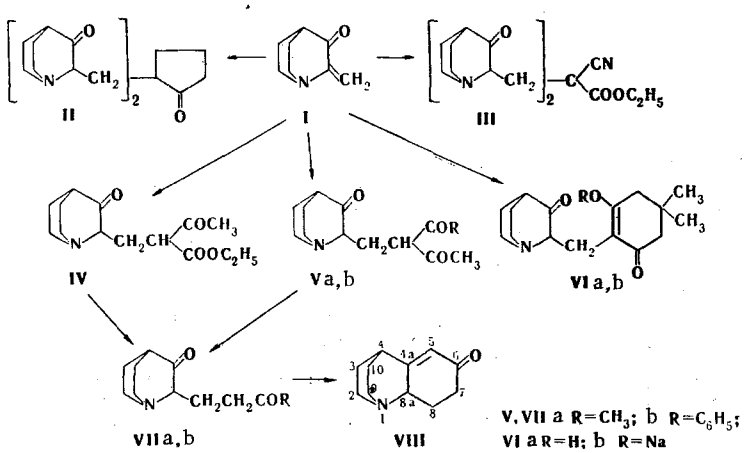
V. A. Bondarenko, E. E. Mikhlina,
T. Ya. Filipenko, K. F. Turchin,
Yu. N. Sheinker, and L. N. Yakhontov

UDC 547.834.4:541.63

The reaction of 2-methylene3-oxoquinuclidine with ketones, β-diketones, keto esters, and cyano esters was studied. Products of mono- and diaddition of the unsaturated ketone are formed in the presence of catalytic or equimolar amounts of sodium ethoxide, as well as without a catalyst (in the case of β-keto esters and β-diketones).

In a continuation of our research on the reactions of 2-methylene-3-oxoquinuclidine (I) with various nucleophilic reagents that make it possible to synthesize a number of previously unknown 2,3-disubstituted quinuclidines, including condensed systems that include a quinuclidine ring [1-3], we studied the reaction of unsaturated ketone I with carbonyl compounds, viz., ketones, β-diketones, keto esters, and cyano esters. Prior to our studies in this direction, only the reactions of ketone I with malonic ester and its C-substituted derivatives, benzyl methyl ketone, and propyl methyl ketone had been described [4].

We accomplished the reaction of 2-methylene-3-oxoquinuclidine (I) with carbonyl compounds (the Michael reaction) in the presence of catalytic or equimolar amounts of sodium ethoxide (in the case of the ketones and cyano esters), as well as without a catalyst (in the case of β-keto esters and β-diketones). In the latter case autocatalysis by the highly basic quinuclidine molecule evidently occurs. Products of mono- and diaddition of unsaturated ketone I were obtained with the indicated carbonyl compounds. Thus 2,2-bis(3-oxo-2-quinuclidinylmethyl)cyclopentanone (II) and ethyl 2,2-bis(3-oxo-2-quinuclidinylmethyl)cyanoacetate (III), respectively, were obtained in the reaction of I with cyclopentanone and cyanoacetic ester in the presence of equimolar and catalytic amounts of sodium ethoxide in ethanol at room temperature and upon heating. Monoaddition products were not isolated.



S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1387-1391, October, 1981. Original article submitted February 4, 1981.

 0009-3122/81/1710-1042$07.50