2,5-DIMETHYL-4-PHENYLPYRIDINE IN THE SYNTHESIS OF SUBSTITUTED INDOLIZINES AND INDENO[2,1-*f*]INDOLIZINES

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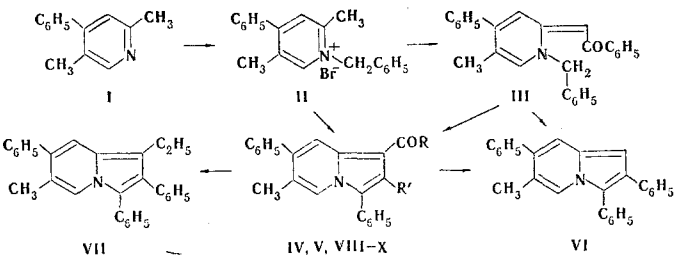
The previously unknown 1-acyl-2-aryl(alkyl)-6-methyl-3,7-diphenylindolizines, 2,3-diphenyl-1-acetyl-6-oxo-6H-indeno[2,1-*f*]indolizine, and 2-methyl-3,6-diphenyl-1-acetyl-6-hydroxy-6H-indeno[2,1-*f*]indolizine were obtained from 2,5-dimethyl-4-phenylpyridine.

α-Picoline is primarily used for the synthesis of indolizines from α-methylpyridines, while alkyl- and phenyl-substituted α-picolines are used only in individual cases [1-6]. Having a relatively practicable method for the synthesis of pyridine bases from γ-piperidones at our disposal, we decided to use some of them in the syntheses of indolizines. 2,5-Dimethyl-4-phenylpyridine (I) [7] was taken as an example for this.

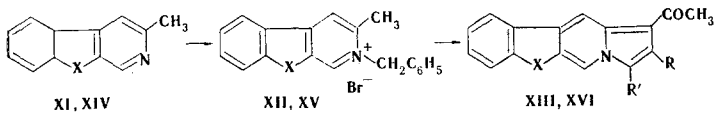
5-Methyl-4-phenyl-1-benzyl-2-phenacylidene-1,2-dihydropyridine (III) was obtained as a result of successive treatment of 1-benzyl-2,5-dimethyl-4-phenylpyridinium bromide (II) with benzoyl chloride and sodium hydroxide. Heating III with acetic, propionic, and benzoic anhydrides gave 6-methyl-2,3,7-triphenyl-1-acylindolizines (IV, V, X). Cleavage of the acetyl group in IV by heating with hydrochloric acid gave 6-methyl-2,3,7-triphenylindolizine (VI), which was also obtained by alternative synthesis by heating III with formamide, while IV was converted to 6-methyl-1-ethyl-2,3,7-triphenylindolizine (VII) by reduction with lithium aluminum hydride.

Indolizines VIII-X were obtained from II without isolation of the corresponding methylidyne derivatives.



IV R=CH_3, R′=C_6H_5; V R=C_2H_5, R′=C_6H_5; VIII R=R′=CH_3; IX R=R′=C_2H_5; X R=R′=C_6H_5

The construction of a pyrrole ring from 3-methyl-2-azafluorenone (XI) [8] was accomplished via a similar route, which made it possible to obtain 2,3-diphenyl-1-acetyl-6-oxo-6H-indeno[2,1-*f*]indolizine (XIII). The intermediately formed 2-benzyl-3-phenacylidene-2,3-dihydro-2-azafluorenone could not be isolated.



XI, XII X=CO; XIV, XV X=C(OH)C_6H_5; XIII X=CO, R=R′=C_6H_5; XVI X=C(OH)C_6H_5, R=CH_3, R′=C_6H_5

2-Methyl-3,6-diphenyl-1-acetyl-6-hydroxy-6H-indeno[2,1-*f*]indolizine (XVI) was also synthesized from 3-methyl-9-phenyl-2-aza-9-fluorenol (XIV) [9].

Benzene solutions of all of the synthesized indolizines, except XIII, fluoresce strongly.

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EXPERIMENTAL

All of the indolizines were isolated by means of column chromatography, and the purity of the compounds obtained was monitored by thin-layer chromatography on activity II aluminum oxide with ether as the eluent (acetone in the case of XVI).

1-Benzyl-2,5-dimethyl-4-phenylpyridinium Bromide (II). A mixture of 10 g (54 mmole) of I and 9.34 g (54 mmole) of benzyl bromide in 20 ml of anhydrous acetone was refluxed for 2 h and allowed to stand for 24 h. The precipitated colorless crystals were removed by filtration and washed several times with absolute ether and cold acetone to give 18.3 g (94%) of colorless prisms of II with mp 196.5-197.5° (from alcohol–acetone). Found: N 3.8%. $C_{20}H_{20}BrN$. Calculated: N 3.9%.

5-Methyl-4-phenyl-1-benzyl-2-phenacylidene-1,2-dihydropyridine (III). A 7-g (50 mmole) sample of freshly distilled benzoyl chloride was added dropwise with vigorous stirring under nitrogen in the course of 5 min to a solution of 10 g (28 mmole) of II in 53 ml of methylene chloride and 35 ml of water. Stirring was continued for 5 min, after which 52.5 ml of 6 N sodium hydroxide was added in the course of 10 min. The color of the solution initially became yellow and then changed successively to orange, dark brown, and dark green. Stirring was continued for another 10 min, and the methylene chloride layer was separated, washed four times with 50-ml portions of cold water, and dried with magnesium sulfate. The solvent was removed by distillation to give a dark residue, which was purified by chromatography to give 9.25 g (87%) of orange plates of III with mp 177-178.5° (from alcohol). Compound III was quite soluble in methylene chloride and chloroform, only slightly soluble in benzene and ether, and practically insoluble in ligroin. Found: C 85.7; H 6.4; N 3.8%. $C_{27}H_{23}NO$. Calculated: C 85.9; H 6.1; N 3.7%.

6-Methyl-2,3,7-triphenyl-1-acetylindolizine (IV). A suspension of 1.4 g (3 mmole) of III in 10 ml of freshly distilled acetic anhydride was heated to the boiling point and shaken to dissolve III, and the solution was then refluxed for 1 h. The color of the solution changed from light green to dark green. It was then cooled to room temperature and added dropwise to 100 ml of ice water. The mixture was treated with sodium bicarbonate until it was alkaline, and the reaction products were extracted with chloroform. The extract was dried with sodium sulfate and worked up to give a dark brown residue, which was chromatographed to give 0.03 g of a dark green substance (R_f 0.92) of undetermined structure. On crystallization from benzene–hexane, this substance became almost black, and 1.03 g (84%) of IV with R_f 0.83 (ether) was isolated. Two crystallizations from alcohol gave shiny yellow needles with mp 231.5-232°. Compound IV was quite soluble in chloroform, benzene, and tetrahydrofuran, slightly soluble in alcohol, acetone, and ether, and almost insoluble in ligroin. Found: C 86.6; H 5.6; N 3.5%. $C_{29}H_{23}NO$. Calculated: C 86.7; H 5.8; N 3.5%.

6-Methyl-2,3,7-triphenyl-1-propionylindolizine (V). A solution of 1 g (2.65 mmole) of III in 10 ml of freshly distilled propionic anhydride was held at 140° for 1 h, during which the reaction mass became dark. The mixture was then cooled to room temperature and transferred to 25 ml of ice water (a dark oil separated). The aqueous mixture was treated with sodium carbonate until carbon dioxide evolution ceased, and the reaction products were extracted with chloroform. The extract was dried with magnesium sulfate, the solvent was removed by distillation, and the residue was purified by chromatography to give 0.02 g of dark green crystals (R_f 0.92) of a substance of undetermined structure and 0.49 g (44%) of V with R_f 0.81 (ether). Two crystallizations from hexane–methylene chloride gave large almost colorless plates with a yellow-green tint and mp 225-226°. Compound V was quite soluble in chloroform, methylene chloride, and benzene and only slightly soluble in hexane. Found: C 86.5; H 6.1; N 3.2%. $C_{30}H_{25}NO$. Calculated: C 86.7; H 6.1; N 3.4%.

6-Methyl-2,3,7-triphenyl-1-benzoylindolizine (X). A. A mixture of 0.76 g (2 mmole) of III and 1 g (4.4 mmole) of benzoic anhydride was held at 140° for 30 min and cooled, and the dark green residue was dissolved in 5 ml of methylene chloride. The products were separated chromatographically to give 0.02 g of VI (with mp 203-206° and R_f 0.94) followed by 0.57 g (61%) of X (R_f 0.81) as bright yellow needles with mp 214-216° (two crystallizations from hexane–methylene chloride). Found: C 87.8; H 5.4; N 2.8%. $C_{34}H_{25}NO$. Calculated: C 88.1; H 5.4; N 3.0%.

B. A mixture of 0.76 g (2.1 mmole) of II, 2.1 g (8.8 mmole) of benzoic anhydride, and 1.5 ml of freshly distilled triethylamine was heated at 140° for 1 h. On fusing, the mixture was green and then rapidly became dark. The triethylamine was removed by distillation, and the reaction products were dissolved in 4 ml of methylene chloride and separated chromatographically to give 0.01 g of VI (mp 202-205° and R_f 0.94) and 0.89 g (90%) of X with mp 214-216°.

6-Methyl-2,3,7-triphenylindolizine (VI). A. A 0.5-g (1.2 mmole) sample of IV was heated in 5 ml of concentrated hydrochloric acid on a boiling-water bath for 15 min. Not all of the indolizine dissolved. The mixture was cooled to room temperature, diluted with 20 ml of cold water, and made alkaline with 5 N sodium hydroxide. The organic bases were extracted with ether, and the ether extract was dried with several crystals of magnesium sulfate for 10 min. The ether was removed by distillation to give 0.25 g (55%) of VI as large, bright yellow, star-shaped crystals with mp 206-207.5° (from alcohol–benzene). Indolizine VI was quite soluble in chloroform and benzene, slightly soluble in ether, and very slightly soluble in ligroin and carbon tetrachloride. Found: C 89.9; H 5.6; N 3.8%. $C_{27}H_{21}N$. Calculated: C 90.2; H 5.9; N 3.9%.

B. A 1.51-g (4 mmole) sample of III was stirred in 5 ml of freshly distilled formamide at 155-158° until it had all dissolved, and the solution was then heated to 200°. The dark red solution was held at 200° for 8 min, 3 ml of freshly distilled dimethylformamide was added, and the mixture was held at 200° for another 4 min. It was then slowly cooled to 100°, and 1 ml of water was added. Cooling (to −5°) for 20 h liberated an oily substance, which was extracted with methylene chloride. The extract was dried with magnesium sulfate, and the solvent was removed by distillation to give 0.61 g (42%) of VI as a light-brown oil that solidified after a certain time. Two crystallizations from hexane–methylene chloride gave yellow needles of VI with mp 205-207° and R_f 0.95. No melting-point depression was observed for a mixture of this product with the product of the deacylation of IV.

6-Methyl-1-ethyl-2,3,7-triphenylindolizine (VII). A solution of 0.5 g (1.2 mmole) of IV in 15 ml of tetrahydrofuran was added dropwise with stirring to a suspension of 0.17 g (4.5 mmole) of lithium aluminum hydride in 20 ml of freshly distilled (over lithium aluminum hydride) tetrahydrofuran, and the reaction mixture was stirred at room temperature for 1.5 h. The end of the reaction was determined by means of thin-layer chromatography on aluminum oxide. The excess lithium aluminum hydride was decomposed with methyl acetate, and the solvents were removed completely. The residue was dissolved in ether, and the ether was removed by distillation to give 0.42 g (89%) of VII as a gray-greenish powder. To purify VII, a solution of it in ether was passed twice through a column filled with aluminum oxide to give yellow-green crystals with mp 141.5-143.5° (dec.). Found: N 3.7%. $C_{29}H_{25}N$. Calculated: N 3.6%. Indolizine VII was quite soluble in chloroform, ether, tetrahydrofuran, and hexane and sparingly soluble in alcohol. Its solutions were unstable: the initial yellow color with a greenish tint rapidly became green and then Prussian blue. Compound VII could not therefore be isolated by crystallization.

2,6-Dimethyl-3,7-diphenyl-1-acetylindolizine (VIII). A suspension of 2 g (6.2 mmole) of II in 3 ml of freshly distilled acetic anhydride was heated to 140° with shaking, during which the mixture acquired a greenish color. Freshly distilled triethylamine (1.2 ml) was added, and the mixture was held at −5° for 3 days. The resulting brown precipitate was removed by filtration and washed several times with cold and then hot water. The material was then dried in a vacuum desiccator to give 1.68 g of product, which was dissolved in ether and passed through a column filled with aluminum oxide to give 1.54 g (80%) of VIII as a yellow powder (R_f 0.81). Four recrystallizations from alcohol–benzene gave VIII as light, bright yellow, star-shaped crystals with mp 172-172.5°. Compound VIII was quite soluble in chloroform and benzene and only slightly soluble in acetone, ether, and alcohol. Found: C 84.5; H 6.2; N 4.1%. $C_{24}H_{21}NO$. Calculated: C 84.9; H 6.2; N 4.1%.

6-Methyl-2-ethyl-3,7-diphenyl-1-propionylindolizine (IX). A mixture of 2.47 g (7 mmole) of II and 5 ml of freshly distilled propionic anhydride was heated to 140° to give a dark brown solution. A 1.5 ml sample of freshly distilled triethylamine was added all at once, and the mixture was held at 140° for 1 h. It was then cooled to room temperature, and 8 g of crushed ice was added. The aqueous layer was decanted, 10 ml of water was added, and the aqueous layer was again removed by decantation. This operation was repeated twice. The residual oily substance was dissolved in chloroform, and the solution was dried with magnesium sulfate. The chloroform was removed by distillation, and the residue was dissolved in ether and chromatographed with a column filled with aluminum oxide. The second fraction (R_f 0.69) yielded 1.43 g (55%) of IX as light green needles with mp 157.5-159° (from hexane). Indolizine IX was quite soluble in chloroform, ether, and benzene and slightly soluble in hexane. Found: C 84.8; H 6.5; N 3.3%. $C_{26}H_{25}NO$. Calculated: C 85.0; H 6.5; N 3.8%.

2-Benzyl-3-methyl-9-oxofluorene-2-azonium Bromide (XII). A 2.17-g (12.7 mmole) sample of benzyl bromide was added to a solution of 2.47 g (12.7 mmole) of XI in 20 ml of anhydrous acetone at 50°, and the mixture was refluxed for 6 h and then allowed to stand for 12 h. The resulting dark green needles of XII were washed five times with 20-ml portions of ether to give 2.84 g (62%) of a product with mp 234-235° (from alcohol). Found: N 3.4%. $C_{20}H_{16}BrNO$. Calculated: N 3.8%.

2,3-Diphenyl-1-acetyl-6-oxo-6H-indeno[2,1-*f*]indolizine (XIII). A 1.66-g (11.8 mmole) sample of freshly distilled benzoyl chloride was added in the course of 3 min under nitrogen to a solution of 2.84 g (7.7 mmole) of XII in a mixture of 30 ml of water, 40 ml of methylene chloride, and 20 ml of dioxane. The mixture was allowed to stand for 5 min, after which 15 ml of 6 N sodium hydroxide was added in the course of 5 min, and the mixture was then stirred for 20 min. The mixture was initially light orange and then became almost black. The lower layer was separated, washed with four 50 ml portions of water, and dried with magnesium sulfate. The methylene chloride was removed by distillation to give 2.67 g of a black resinous substance. It was dissolved in 20 ml of freshly distilled acetic anhydride, and the solution was refluxed for 1.5 h. It was then transferred to a beaker containing 250 ml of ice water. The resinous product was washed repeatedly with cold water and triturated. The resulting black powder was removed by filtration and dried in a vacuum desiccator to give 2.26 g of material, which was then chromatographed. The fraction containing a substance with R_f 0.68 was collected to give 0.43 g (14%) of a fine orange powder. Two crystallizations from alcohol gave XIII as light-weight light orange needles with mp 230-232°. Found: C 83.9; H 4.7; N 3.2%. $C_{29}H_{18}NO_2$. Calculated: C 84.2; H 4.6; N 3.4%.

2-Benzyl-3-methyl-9-phenyl-9-hydroxyfluorene-2-azonium Bromide (XV). A 1.09-g (6.4 mmole) sample of benzyl bromide was added to a solution of 1 g (3.6 mmole) of XIV in 10 ml of dry acetone, and the mixture was heated for 3 h and allowed to stand for 12 h. The precipitated crystals were removed by filtration and washed with 5 ml of cold acetone and several times with absolute ether to give 1.06 g (65%) of XV as a colorless powder. Two recrystallizations from alcohol–acetone gave colorless needles with mp 255-258° (dec.). Found: C 69.8; H 4.9; Br 17.2; N 3.4%. $C_{26}H_{22}BrNO$. Calculated: C 70.3; H 5.0; Br 18.0; N 3.1%.

2-Methyl-3,6-diphenyl-1-acetyl-6-hydroxy-6H-indeno[2,1-*f*]indolizine (XVI). A suspension of 0.89 g (2 mmole) of XV in 3 ml of freshly distilled acetic anhydride was heated with stirring to 140°. The quaternary salt did not dissolve completely. The mixture was initially light-brown but became dark brown after 1 h. Freshly distilled triethylamine (1 ml) was added all at once, and the mixture, which became very dark, was held at 140° for 30 min. It was then cooled to room temperature, and 5 g of crushed ice was added. The oil that separated crystallized at −45° after 4 h. The brown precipitate was removed by filtration, washed several times with cold and then hot water, and dried in a vacuum desiccator to give 0.77 g of material. A solution of this material in acetone was passed through a column filled with aluminum oxide to give 0.56 g of a dark residue, which was treated with hot hexane to give 0.22 g (25%) of XVI. Subsequent crystallization from hexane (heating with activated charcoal) gave 0.18 g of XVI as large colorless needles with mp 53-57°. Compound XVI was quite soluble in ether and acetone and somewhat less soluble in hexane. Found: N 3.1%. $C_{30}H_{23}NO_2$. Calculated: N 3.2%.

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