SYNTHESIS OF SUBSTITUTED INDOLIZINES FROM 1-PHENACYL-5-METHYL-4-PHENYL-2-PHENACYLIDENE-1,2-DIHYDROPYRIDINE

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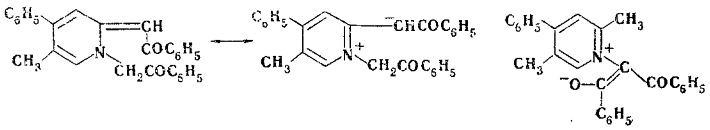
1-Phenacyl-5-methyl-4-phenyl-2-phenacylidene-1,2-dihydropyridine was obtained, and its cyclization to substituted indolizines was examined.

We have previously described [1] the transformations of 1-phenacyl-2,5-dimethyl-4-phenylpyridinium bromide (I) to substituted indolizines by the Chichibabin method [2]. New indolizines were synthesized in the present study from the same quaternary salt (I) with the isolation of the intermediate 1-phenacycl-5-methyl-4-phenyl-2-phenacylidene-1,2-dihydropyridine (II), which is formed by successive treatment of salt I with benzoyl chloride and sodium hydroxide. If one takes into account the various concepts regarding the structure of analogous compounds, the problem of the structure of dihydropyridine II cannot be considered to be definitely resolved. In conformity with [3], its structure can be dipicted by two limiting structures. According to the data in [4], II should have an ylid-like structure.



We have obtained certain information regarding the structure of II from its spectral characteristics. The bands at 700-740 cm^{-1} in its IR spectrum are related to the out-of-plane deformation vibrations of the aromatic C–H bonds. We assigned the band at 1636 cm^{-1} to the stretching vibration of the aromatic C–C bonds, inasmuch as the integral intensity of this band is $1.2 \cdot 10^4$ mole^{-1} · liter · cm^{-2}. The absorption band of the carbonyl group apparently is at 1500-1510 cm^{-1} and is overlapped by the bands of aromatic C=C bonds; this brings about a considerable increase in the intensity and broadening of the bands in this region. The assignment of the weak bands at 3080, 3060, and 3030 cm^{-1} raises some difficulty. They may be due to aromatic C–H bonds [1] and also to an enol hydroxyl group with a strong O–H...N intramolecular bond. Other hydroxy derivatives of nitrogen heterocycles also have similar spectral characteristics in the bonded hydroxyl-group region [5]. Taking this into account, one may assume the presence of a carbonyl group (benzoyl group) and a hydroxyl group with a strong hydrogen bond (the enol form of the second benzoyl group) in II.

The PMR spectrum of II does not contain the signals of a methylene group or a second methyl group. The observed signals correspond to the protons of a methyl group (δ 2.18 ppm), the α proton of the heteroring (δ 8.06 ppm), and the methlyidyne proton of the enol (δ 7.85 ppm). Two signals at 7.57 and 7.50 ppm, which are split weakly as a consequence of allylic coupling, are observed at stronger field; this makes it possible to assign them to the β proton of the heteroring and to the methylidyne proton of the phenacylidene grouping. The remaining five-proton signals are due to three phenyl groups (singlets at δ 7.35 and 7.22 ppm and a multiplet at 6.95-7.16 ppm). Thus structure II, which corresponds to the data in [4], is apparently not confirmed by the PMR spectrum. The spectral data obtained also somewhat contradict the concepts in [3]. Taking the above information into account we suppose that the most probable structure may be depicted by the enol form of methylidyne derivative II.

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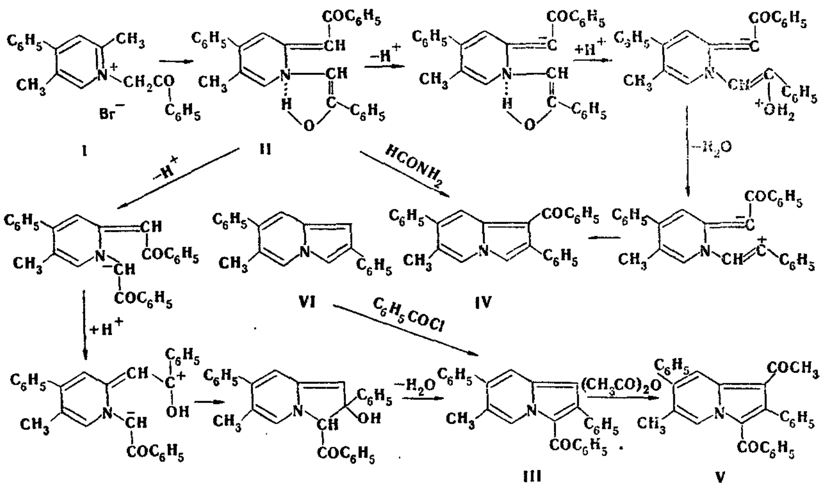
It has been established [3, 4] that the cyclization of analogous methylidyne derivatives when they are heated with acetic anhydride gives isomeric indolizines with substituents in various positions of the five-membered ring. Of compounds of the II type, we obtained 6-methyl-2,7-diphenyl-3-benzoylindolizine (III), 6-methyl-2,7-diphenyl-1-benzoylindolizine (IV), and 6-methyl-2,7-diphenyl-1-acetyl-3-benzoylindolizine (V).



The initial step is deprotonation of II, which is promoted by the basic nitrogen atom in its structure. If one takes into account the fact that indolizines III and IV are formed in a ratio of 3 : 1, while V is the product of acetylation of 3-benzoylindolizine III, it can be concluded that the dominant reaction path is deprotonation of the enol hydroxyl group rather than deprotonation of the phenacylidene group of dihydropyridine II.

Indolizine III was also obtained by benzoylation of 6-methyl-2,7-diphenylindolizine (VI) [1], while IV was obtained by heating II with formamide. In the latter case, III is also formed in small amounts.

The IR spectra of indolizines III and IV are similar but not identical. The weak bands at 3030-3120 cm^{-1} are related to the vibrations of the aromatic C−H bonds, while those at 2860-2980 cm^{-1} are related to the stretching vibrations of the CH_3 group. There are bands of deformation vibrations of this group for III (IV) at 1460 (1470) and 1340 (1360) cm^{-1} and intense bands in the low-frequency region at 742 (748) and 707 (702) cm^{-1}, which are related to the vibrations of monosubstituted phenyl rings. As expected, the greatest difference is observed at 1500-1600 cm^{-1}. The bands at 1610 and 1597 cm^{-1} were well resolved for IV; the first apparently is related to the stretching vibration of the carbonyl group, inasmuch as its integral intensity is $2.9 \cdot 10^4$ mole^{-1} · liter · cm^{-2}. The bands at 1597, 1575, and 1505 cm^{-1} are related to the stretching vibrations of aromatic C=C bonds. The spectrum of indolizine III contains a single band at 1600 cm^{-1}. This band is possibly the band of a carbonyl group, inasmuch as its integral intensity is $3 \cdot 10^4$ mole^{-1} · liter · cm^{-2}. The bands at 1574 and 1507 cm^{-1} are due to the vibrations of aromatic C=C bonds. The band at 1600 cm^{-1} in the IR spectrum of indolizine V is apparently related to the vibrations of carbonyl groups; bands similar to those in the spectrum of III are also observed.

The UV spectra of indolizines III and IV are in satisfactory agreement with the UV spectra reported in [6, 7], and their mass spectra are identical.

EXPERIMENTAL

The IR spectra of KBr pellets and $CHCl_3$ solutions of the compounds were recorded with a UR-20 spectrometer. The integral intensities of the IR absorption bands were measured at 1300-1700 cm^{-1}. Chloroform solutions (0.005 M) were used for the measurements, and the layer thickness was 0.5 cm. The integral intensities were calculated by the method in [8]. The UV spectra of ethanol solutions were obtained with an EPS-3 spectrophotometer. The PMR spectra of deuterochloroform solutions were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The molecular weights were determined with an MKh-1303 mass spectrometer.

1-Phenacyl-2,5-dimethyl-4-phenylpyridinium Bromide (I). A mixture of 5.5 g (0.03 mole) of 2,5-dimethyl-4-phenylpyridine and 6 g (0.03 mole) of bromoacetophenone in 20 ml of dry acetone was refluxed for 3 h and allowed to stand for 12 h. The precipitate was removed by filtration and washed once with 5 ml of cold dry acetone and several times with absolute ether to give 11.2 g (97%) of salt I as a white powder. Two precipitations of 0.4 g of the product from acetone–alcohol (3 : 1) by the addition of absolute ether gave 0.34 g of pure salt I with mp 195-197°. Found: Br 20.8; N 3.6%. $C_{21}H_{20}BrNO$. Calculated: Br 20.8, N 3.7%.

1-Phenacyl-5-methyl-4-phenyl-2-phenacylidene-1,2-dihydropyridine (II). A 2.8-ml (27 mmole) sample of freshly distilled benzoyl chloride was added in the course of 5 min with vigorous stirring under nitrogen to a solution of 9 g (23 mmole) of salt I in a mixture of 25 ml of water and 50 ml of methylene chloride. The solution was stirred for 15 min, after which 52.5 ml of 6 N sodium hydroxide was added in the course of 10 min, and the mixture was stirred for another 30 min. The methylene chloride layer was washed several times with cold water and dried with magnesium sulfate. The solvent was removed by distillation to give 9.1 g (95%) of crude II as reddish crimson-tinted plates with mp 199-200.5° (twice from alcohol) and R_f 0.26 (KSK silica gel, benzene). Heating with activated charcoal and subsequent crystallization from alcohol did not change the color of the crystals. However, fine-grained yellow crystals with the same melting point were formed by recrystallization from benzene (heating with activated charcoal). UV spectrum, λ_{max}, nm (log ε): 255 (4.65), 390 (4.27). Found: C 83.1; H 5.7; N 3.5%. $C_{28}H_{23}NO_2$. Calculated: C 82.9; H 5.7; N 3.5%.

Indolizines III-V. A) A mixture of 0.5 g (1.2 mmole) of II and 3.5 ml of freshly distilled acetic anhydride was heated at 120° until II dissolved (with shaking), and the mixture was held at 120° for 1 h. It was then cooled and poured into 50 ml of ice water. The aqueous mixture was made alkaline with sodium bicarbonate and extracted with chloroform. The products were separated by means of column chromatography (activity II aluminum oxide, ether). Fractions with the following R_f values were isolated successively: 0.86 (0.27 g), 0.77 (0.09 g), and 0.46 (0.05 g). The first fraction was recrystallized from hexane to give bright-yellow star-shaped crystals of indolizine III with mp 135-137°. UV spectrum, λ_{max}, nm (log ε): 256 (4.48), 310 shoulder, 400 (4.21). Found: C 86.5; H 5.8; N 3.4%; M 387 $C_{28}H_{21}NO$. Calculated: C 86.8; H 5.5; N 3.6%; M 387. The second fraction was recrystallized from hexane–ether to give bright yellow plates of indolizine IV with mp 192.5-193.5°. UV spectrum, λ_{max}, nm (log ε): 255 (4.60), 286 shoulder, 390 (4.22). Found: C 86.7; H 5.9; N 3.4%; mol.wt. 387. $C_{28}H_{21}NO$. Calculated: C 86.8; H 5.5; N 3.6%; mol.wt. 387. Recrystallization of the third fraction from hexane–ether gave 0.02 g of V as brownish grains with mp 121.5-123°. Found: C 83.7; H 5.7; N 3.4%. $C_{30}H_{23}NO_2$. Calculated: C 83.9; H 5.4; N 3.3%.

B) A mixture of 1.2 g (4.2 mmole) of indolizine VI and 0.7 ml (5.9 mmole) of freshly distilled benzoyl chloride in 15 ml of dry benzene was held at room temperature for 24 h and at 50-60° for 3 h. It was then cooled to room temperature, treated with 5 ml of water, made alkaline with sodium hydroxide, and extracted with chloroform. The extract was dried with magnesium sulfate, and the solvent was removed by distillation. The dark residue was passed through a short column filled with aluminum oxide with elution with chloroform. Recrystallization of the isolated residue from hexane gave 1.13 g (69%) of III as large, yellow, star-shaped crystals (R_f 0.86, the same system as above) with mp 135-137°. No melting-point depression was observed for a mixture of this product with a sample of the material described above.

C) A suspension of 1.22 g (3 mmole) of dihydropyridine II in 2 ml of freshly distilled formamide was heated to 200° with shaking and held at that temperature for 1 min. It was then cooled to room temperature and treated with 2 ml of water. The aqueous mixture was cooled to −5°, and the dark-brown precipitate was washed several times with cold water and once with 1 ml of cold acetone. The material was vacuum dried to give 0.8 g of a yellow powder, which, according to the results of thin-layer chromatography on aluminum oxide, was a mixture of indolizines III and IV (R_f 0.86 and 0.78). The mixture was separated by chromatography to give 0.06 g of III (mp 135-137°) and 0.51 g of IV. Two crystallizations from hexane–ether gave IV as bright-yellow plates with mp 192.5-193.5°. No melting-point depression was observed for a mixture of this product with a sample of IV from experiment A.

LITERATURE CITED

1. N. S. Prostakov and O. B. Baktibaev, Khim. Geterotsikl. Soedin., 1395 (1971).
2. A. E. Chichibabin, Zh. Russk. Khim. Obshchestva, 59, 477 (1927).
3. T. Melton and D. G. Wibberley, J. Chem. Soc., C, 983 (1967).
4. F. W. Kröck and F. Kröhnke, Ber., 102, 669 (1969).
5. N. S. Prostakov, L. A. Gaivoronskaya, and G. Alvarado-Urbina, Khim. Geterotsikl. Soedin., 1087 (1971).
6. V. Bockelheide and R. S. Windgassen, J. Amer. Chem. Soc., 81, 1456 (1959).

7. T. Sasaki, K. Kanematsu, and Y. Yakimoto, J. Chem. Soc., C, 481 (1970).
8. D. A. Ramsay, J. Amer. Chem. Soc., 72, 74 (1952).