ARYL(7-INDOLIZINYL)METHANES

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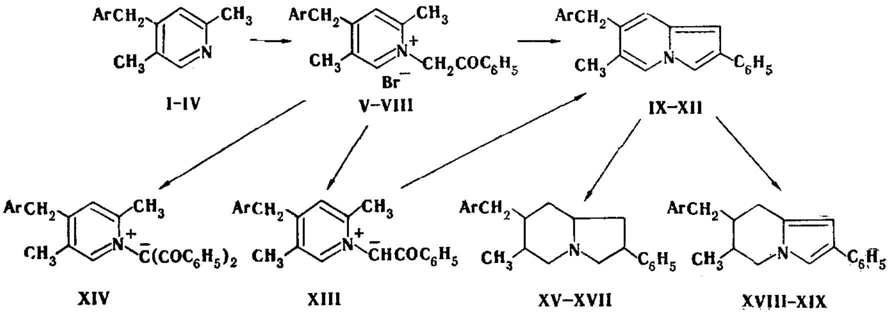
Aryl(6-methyl-2-phenyl-7-indolizinyl)methanes were obtained by quaternization of aryl(γ-pyridyl)methanes with bromoacetophenone and subsequent cyclization of the quaternary salts with 40% potassium carbonate solution (the Chichibabin method). The stable 2,5-dimethyl-4-(2,4-dimethylbenzyl)pyridinium benzoylmethylid, which was converted to an indolizine by the action of Al_2O_3, was isolated by the action of a 10% potassium carbonate solution on the corresponding quaternary salt. The ability of 3-unsubstituted indolizines to undergo protonation in both the 3 and 1 position was shown on the basis of the PMR spectra. The aryl(7-indolizinyl)methanes are selectively hydrogenated thoroughly over rhenium heptasulfide in the indolizine ring to give tetra- or octahydro derivatives without involvement of the aryl groups. Data from the IR, PMR, and mass spectra are presented.

The previously described aryl(γ-pyridyl)methanes [1, 2] were used to obtain a new group of substituted indolizines of the arylindolizinylmethane type. The products (V-VIII) of quaternization of these pyridine bases with bromoacetophenone, the subsequent conversion of which to aryl(6-methyl-2-phenyl-7-indolizinyl)methanes (IX-XII) was accomplished by treatment with 40% potassium carbonate solution [3], were obtained and characterized.



I, V, IX, XV Ar=C_6H_5; X, II, VI, XVI, XVIII Ar=3,4-$(CH_3)_2C_6H_3$; III, VII, XI, XIII, XIV Ar=2,4-$(CH_3)_2C_6H_3$; IV, VIII, XII, XVII, XIX Ar=2,4,5-$(CH_3)_3C_6H_2$

We were able to isolate 2,5-dimethyl-4-(2,4-dimethylbenzyl)pyridinium benzoylmethylid (XIII) by treatment of quaternary salt VII with 10% aqueous potassium carbonate solution. Schotten-Baumann benzoylation of quaternary salt VII leads to 2,5-dimethyl-4-(2,4-dimethylbenzyl)pyridinium dibenzoylmethylid (XIV). In contrast to previously described [3] compounds of a similar type, ylid XIII is characterized by relative stability (it is stable for a long time at room temperature). Bands at 1532 (XIII) and 1504 cm^{-1} (XIV) characteristic for pyridinium ylids [4] are present in the IR spectra of ylids XIII and XIV. Their UV spectra are in good agreement with the spectra of analogous compounds [5]. The presence of an ylid carbanion in ylid XIII was established by comparison of its PMR spectra in CF_3COOH and CF_3COOD (see Table 1). The absence of a molecular ion (M^+) peak at 343* and the presence of

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*Here and subsequently, the m/e values are presented.

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TABLE 1. Physicochemical and Spectral Characteristics of the Quaternary Salts of the Pyridine Bases (VI-VIII), Ylids (XIII, XIV), and Indolizines (X-XII)

Compound	mp, °C	M^+	Found, %				Empirical formula	Calc., %				IR spectra, $\nu_{C=O}$, cm^{-1}	UV spectra, λ_{max}, nm (log ε)	PMR spectrum,[a] δ, ppm	Yield, %
			C	H	Br	N		C	H	Br	N				
VI	217—218	—	68,1	6,2	18,4	3,4	$C_{24}H_{26}BrNO$	68,0	6,1	18,9	3,3	1690	202 (4,48); 250 (4,05); 280 (3,74)	8,0, s 1H(6-H); 5,86, s 2H(NCH$_2$); 3,70,s 2H(ArCH$_2$Ar^1)	96
VII	186—188	—	68,1	6,0	18,9	3,5	$C_{24}H_{26}BrNO$	68,0	6,1	18,9	3,3	1690	205 (4,54); 256 (4,40); 282 (3,64)	7,98, s 1H(6-H); 6,86, s 1H(3-H); 5,85, s 2H(NCH$_2$); 3,75, s 2H(ArCH$_2$Ar^1)	72
VIII	222—225	—	68,9	6,7	18,1	3,0	$C_{25}H_{28}BrNO$	68,8	6,4	18,3	3,2	1710	203 (4,90); 250 (4,47); 275 (3,91)	7,95, s 1H(6-H); 6,89, s 1H(3-H); 5,86, s 2H(NCH$_2$); 3,80, s 2H(ArCH$_2$Ar^1)	71
X	159—160	325	88,8	7,3	—	4,7	$C_{24}H_{23}N$	88,6	7,1	—	4,3	—	210 (4,56); 262 (4,68); 348 (3,62); 366 (3,45)	8,13, s (5-H); 5,33, s 2H(3-H); 3,75, s 2H(CH$_2$);	70
XI	175—177	325	88,3	7,3	—	4,1	$C_{24}H_{23}N$	88,6	7,1	—	4,3	—	206 (4,30); 260 (4,38); 308 (3,96); 376 (3,26)	8,13,s 1H(5-H); 5,33, s 2H(3-H); 3,77, s 2H(CH$_2$)	78
XII	193—194	339	88,1	7,7	—	4,1	$C_{25}H_{25}N$	88,5	7,4	—	4,1	—	202 (4,06); 205 (4,08); 208 (4,05); 262 (4,37); 348 (3,62); 366 (2,96)	3,71[b], s 2H(CH$_2$); 8,15, s 1H(5-H); 5,34, s 2H(3-H); 3,77, s, 2H(CH$_2$)	78
XIII	162—164	325	—	—	—	4,0	$C_{24}H_{25}NO$	—	—	—	4,1	1532[r]	203 (4,46); 226 (3,70); 250 (3,84); 416 (3,10)	7,75, s 1H(6-H); 5,62, s 2H(NCH$_2$); 3,65, s 2H(ArCH$_2$Ar^1); 5,63[c], s 1H(NCHD)	80
XIV	203—205	447	83,3	6,6	—	2,8	$C_{31}H_{29}NO_2$	83,2	6,5	—	3,1	1504[r]	203 (4,13); 224 (3,92); 242 (3,74); 282 (3,58); 320 (3,68)	7,92, s 1H(6-H); 3,68, s 2H(ArCH$_2$Ar^1)	42

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a) In CF_3COOH (hexamethyldisiloxane as the internal standard). b) In $CDCl_3$. c) CF_3COOD. d) These bands are usually assigned to ylids in the literature [4].

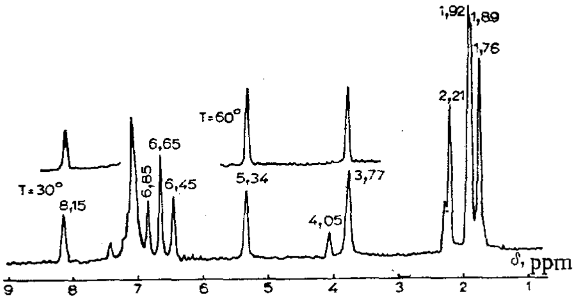

Fig. 1. PMR spectrum of 6-methyl-7-(2,4,5-trimethylbenzyl)-2-phenylindolizine.

an intense ion peak at 325 are characteristic for the mass spectrum of ylid XIII; this constitutes evidence for the ease of conversion of this ylid to an indolizine.

Indolizine XI is readily formed by passing a chloroform solution of ylid XIII through a layer of aluminum oxide. Features of the PMR spectrum of indolizine XII ($CDCl_3$) that indicate the presence of an indolizine fragment in the molecule include broad singlets at δ 6.30 and 6.83 ppm (3-H and 1-H, respectively), the absence of a pyridine ring α-H signal above 7.50 ppm, and the decrease in the number of methyl groups from five to four (δ 2.23, 2.20, and 2.12 ppm, 12H) as compared with the PMR spectrum of corresponding salt VIII. Protonation to give 3-H and 1-H cations is observed during the measurement of the PMR spectra of indolizines X-XII in CF_3COOH. In fact, two singlets of a CH_2 group of a protonated five-membered ring at δ 5.34 (3-H cation) and 4.05 ppm (1-H cation) with an overall intensity of two proton units are present in the PMR spectrum of indolizine XII (Fig. 1). The ratio of the molar concentrations of the 3-H and 1-H cations is 3:1. Irreversible conversion of the 1-H cation to the 3-H cation is observed when the solution is heated to 60°: the singlet at 4.05 ppm vanishes, and the integral intensity of the signal at 5.34 ppm increases to 2H. Lowering the temperature does not lead to restoration of the original spectral pattern. It has been noted [6] that 3-unsubstituted indolizines are protonated exclusively to give the 3-H cation. The spectra that we have described demonstrate that the possibility of the formation of appreciable amounts of the 1-H cation also exists for 3-unsubstituted indolizines.

Like the hydrogenation of aryl(γ-pyridyl)methanes [7], the hydrogenation of indolizines IX, X, and XII over rhenium heptasulfide proceeds selectively: the benzene rings are not involved, and only the nitrogen-containing ring is hydrogenated. In the case of indolizine IX we isolated a product of complete hydrogenation of the indolizine system — 6-methyl-2-phenyl-7-benzyloctahydroindolizine (XV) — whereas in the case of indolizines X and XII we isolated products of partial and complete hydrogenation — 6-methyl-2-phenyl-7-(3,4-dimethylbenzyl)-5,6,7,8-tetrahydroindolizine (XVIII), 6-methyl-2-phenyl-7-(2,4,5-trimethylbenzyl)-5,6,7,8-tetrahydroindolizine (XIX), 6-methyl-2-phenyl-7-(3,4-dimethylbenzyl)octahydroindolizine (XVI), and 6-methyl-2-phenyl-7-(2,4,5-trimethylbenzyl)octahydroindolizine (XVII), respectively. The presence in the PMR spectrum of XVIII (CCl_4) of a doublet at 1.08 ppm ($J = 6.0$ Hz, CH_3 group attached to a saturated carbon atom) and the appearance at 2.25-4.25 ppm of signals of methylene and methylidyne protons constitute evidence for hydrogenation of the pyridine ring. The retention of the pyrrole ring structure is determined by the presence in the spectrum of two one-proton signals — a broad singlet at 5.90 ppm and a doublet at 6.56 ppm ($J = 1.5$ Hz) due to β-H and α-H, respectively.

The affiliation of hydrogenation products XV and XVII with octahydroindolizines follows from the fact that their PMR spectra do not contain pyrrole ring α-H and β-H signals, whereas the ratio of the integral intensities of the signals (17:10 for XV and 26:7 for XVII) correspond to the number of aliphatic and aromatic protons.

EXPERIMENTAL

The PMR spectra in CF_3COOH, CF_3COOD, $CDCl_3$, and CCl_4 were recorded with a BS-487 spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions were measured with a Specord UV-vis spectrophotometer. The mass spectra were obtained with an MKh-1303 spectrometer. The completeness of hydrogenation of IX, X, and XIII was monitored by thin-layer chromatography (TLC) on activity II Al_2O_3 [ether—hexane (1:3)].

1-Phenacyl-2,5-dimethyl-4-[3,4-dimethyl-(VI), 2,4-dimethyl-(VII), and 2,4,5-trimethyl-(VIII)benzyl]pyridinium Bromides. As an example, we present the preparation of quaternary salt VII. A mixture of 3 g (1.33 mmole) of pyridine base III, 3.5 g (1.76 mmole) of bromoacetophenone, and 50 ml of acetonitrile was heated for 1 h, after which it was cooled, and the precipitated crystals were removed by filtration and washed with 50 ml of absolute ether to give 4 g of salt VII. Salts VI and VIII (Table 1) were similarly obtained from pyridine bases II and IV and bromoacetophenone. The compound is described in [3].

6-Methyl-7-[3,4-dimethyl-(X), 2,4-dimethyl-(XI), and 2,4,5-trimethyl-(XII)benzyl]-2-phenylindolizines. Methods for the synthesis of indolizine XI are presented as examples. A) An 0.5-g (1.5 mmole) sample of ylid XIII was applied to a column (H = 45 cm, d = 1.8 cm) filled with activity II Al_2O_3 and eluted with chloroform. A total of 300 ml of eluate was collected and worked up to give 0.09 g (18.8%) of indolizine XI with mp 175-177° (from ligroin).

B) A mixture of 1 g (2.36 mmole) of salt VII and 7.5 ml of 40% K_2CO_3 solution was refluxed for 4 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.6 g (78%) of indolizine XI with mp 175-177° (from ligroin). Compounds X and XII (Table 1) were similarly obtained from quaternary salts VI and VIII by method B. Indolizine IX was obtained as described in [3].

2,5-Dimethyl-4-(2,4-dimethylbenzylpyridinium) Benzoylmethylid (XIII). A total of 23 ml of 10% K_2CO_3 solution (16.6 mmole) was added with vigorous stirring at 0° to a solution of 2.1 g (5 mmole) of salt VII in 35 ml of acetonitrile, after which 50 ml of water was added to the orange solution at 2-5°. The resulting orange precipitate was removed by filtration, washed with 5 ml of water at 5-10°, and dried to constant weight in a vacuum desiccator over P_2O_5 to give 1.36 g of ylid XIII (see Table 1).

2,5-Dimethyl-4-(2,4-dimethylbenzyl)pyridinium Dibenzoylmethylid (XIV). A mixture of 2.25 g (5.3 mmole) of quaternary salt VII, 10 ml of water, and 10 ml of 40% aqueous K_2CO_3 solution was shaken for 15 min, after which the resulting bright-orange crystals were extracted with 100 ml of chloroform. The chloroform extract was passed through a layer of Na_2SO_4, a solution of 0.85 g (6 mmole) of benzoyl chloride in 3 ml of chloroform and 10 ml of 20% aqueous potassium carbonate solution were added to the dried chloroform extract [theoretically containing 1.82 g (5.3 mmole) of the ylid], and the mixture was shaken for 10 min. The chloroform extract was dried with Na_2SO_4 and worked up. The residue (2.3 g) was crystallized from benzene to give 1.02 g of ylid XIV (Table 1).

Hydrogenation of the Arylindolizines. A 50-ml glass ampule with a wide neck was charged with 0.1-0.4 g (10% of the weight of the product to be hydrogenated) of Re_2S_7 and a solution of 3-3.6 g of indolizines IX, X, or XII in 15-20 ml of benzene (for UV spectroscopy), and the ampule was placed in a stainless steel rotating autoclave (150 ml) equipped with a thermocouple. The autoclave was purged with nitrogen, filled with hydrogen to a pressure of 150 atm, and heated with stirring to 250° for 30-40 min. It was then cooled, and the catalyst was removed by filtration and washed with benzene. The benzene was removed by distillation to obtain the products.

6-Methyl-2-Phenyl-7-benzyloctahydroindolizine (XV). Hydrogenation of 3 g (10 mmole) of indolizine IX with 0.3 g of Re_2S_7 at 150 atm and 250° for 4 h gave 2.87 g of product from which 1.22 g (40%) of XV with R_f 0.58 and mp 112-113° was obtained by crystallization from ligroin. UV spectrum of XV, λ_{max} (log ε): 210 (4.28), 248 (2.56), 253 (2.74), 258 (2.78), 261 (2.84), 265 (2.48), and 268 nm (2.38). Found, %: C 86.8; H 8.7; N 4.6. M 305. $C_{22}H_{27}N$. Calculated, %: C 86.6; H 8.8; N 4.6. M 305.

6-Methyl-2-phenyl-7-(3,4-dimethylbenzyl)octahydroindolizine (XVI) and 6-Methyl-2-phenyl-7-(3,4-dimethylbenzyl)-5,6,7,8-tetrahydroindolizine (XVIII). Hydrogenation of 3 g (9.2 mmole) of indolizine X with 0.3 g of Re_2S_7 gave 2.83 g of product, crystallization of which from hexane gave 0.05 g (1.8%) of XVI with mp 105-107°. Found, %: N 3.9. M 333. $C_{24}H_{31}N$. Calculated, %: N 4.2. M 333. The residue from the mother liquors was crystallized from ligroin to give 0.4 g (14%) of XVIII with R_f 0.64 and mp 128-130°. UV spectrum, λ_{max} (log ε): 205 (4.60), 235 (4.28), and 283 nm (4.14). Found, %: C 87.5; H 8.4; N 4.0. M 329. $C_{24}H_{27}N$. Calculated, %: C 87.5; H 8.2; N 4.3. M 329.

6-Methyl-2-phenyl-7-(2,4,5-trimethylbenzyl)octahydroindolizine (XVII) and 6-Methyl-2-phenyl-7-(2,4,5-trimethylbenzyl)-5,6,7,8-tetrahydroindolizine (XIX). Hydrogenation of 3.6 g (10.6 mmole) of indolizine XII with 0.4 g of Re_2S_7 gave 2.95 g of product, from which 0.1 g

(3.4%) of XIX with mp 107-109° was obtained by crystallization from hexane. Found, %: C 87.2; H 8.5; N 4.1. M 343. $C_{25}H_{29}N$. Calculated, %: C 87.4; H 8.5; N 4.1. M 343. Crystallization of the residue from the mother liquors from ligroin gave 0.34 g (11.5%) of XVII with R_f 0.19 and mp 113-114°. UV spectrum, λ_{max} (log ε): 203 (4.62), 220 (4.12), 262 (2.68), 266 (2.74), 269 (2.85), and 279 nm (2.80). Found, %: C 86.4; H 9.2; N 3.7. M 347. $C_{25}H_{33}N$. Calculated, %: C 86.4; H 9.5; N 4.0. M 347.

LITERATURE CITED

1. N. S. Prostakov, L. A. Gaivoronskaya, N. M. Mikhailova, and L. M. Kirillova, Zh. Obshch. Khim., 33, 2573 (1963).
2. N. S. Prostakov, V. I. Kuznetsov, V. F. Zakharov, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 8, 1077 (1976).
3. N. S. Prostakov, L. A. Gaivoronskaya, Naiga Sarata Mokhomon Kamara, V. P. Zvolinskii, A. A. Savina, Munzer Makhsida, and Viktor Ugo Opaso Karrasko, Khim. Geterotsikl. Soedin., No. 4, 506 (1970).
4. A. Henrick, E. Ritchie, and W. C. Taylor, Austral. J. Chem., 20, 2441 (1967).
5. A. Henrick, E. Ritchie, and W. C. Taylor, Austral. J. Chem., 20, 2455 (1967).
6. M. Fraser, S. McKenzie, and D. H. Reid, J. Chem. Soc., B, No. 1, 44 (1966).
7. M. A. Ryashentseva, Kh. M. Minachev, V. V. Dorogov, and N. S. Prostakov, Khim. Geterotsikl. Soedin., No. 1, 88 (1972).

MASS SPECTRA OF 2,3,4,5-TETRAHYDROPYRIMIDO[3,4-a]INDOLES

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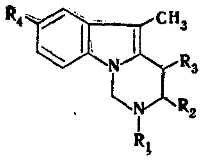
The dissociative ionization of protected 2,3,4,5-tetrahydropyrimido[3,4-a]indoles of the general formula



I-XI

under the influence of electron impact proceeds via two pathways. The first process is elimination of an R_1NCHR_2 group when $R_1 = CH_3$. The second process, which is characteristic for compounds with a formyl substituent (R_1 = CHO) or without a substituent (R_1 = H) attached to the amino nitrogen atom, is detachment of a CH_2NCHR_2 group with migration of a hydrogen atom of the amino group to the fragment ion; this is confirmed by the spectrum of the deuterium-labeled compound. The principal ion peaks (the fragment and rearranged ions) in combination with the molecular ion in the mass spectra constitute 55.0-70.0% of the total ion current. Ion peaks that characterize a methoxy group and a chloro substituent in the indole portion of the molecule are present in the mass spectra. The compositions of the ions were confirmed by the high-resolution mass spectra.

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