SYNTHESIS OF INDOLES FROM PYRIDINIUM SALTS

5.* SECONDARY AMINES IN THE REACTION OF 3-NITROPYRIDINIUM SALTS WITH ACETONE

M. A. Yurovskaya, A. Z. Afanas'ev,
V. A. Chertkov, and Yu. G. Bundel'

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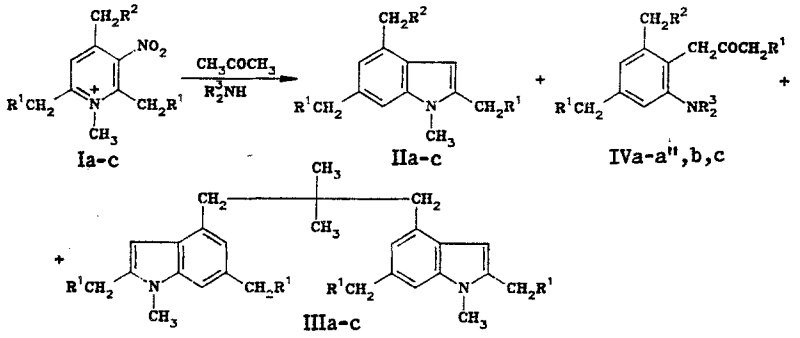
The use of secondary amines in the reaction of 3-nitropyridinium salts with acetone makes it possible to isolate stable intermediates in the formation of indoles – (o-N,N-dialkylaminobenzyl)ketones – and to observe new reaction pathways – the formation of bisindolylpropanes and p-nitroanilines.

It has been previously established that the principal products in the reaction of 3-nitropyridinium salts with ketones in the presence of primary amines are indoles [2, 3]; it was found that precisely the ketimine formed in situ or introduced into the reaction participates in the formation of the indole ring [1, 4].

The use of secondary amines in this reaction leads to a change in the direction of the process. However, the decisive factors are not only the nature of the amine but also the structure of the starting pyridinium salt.



I—IV a $R^1=R^2=H$; b $R^1=H$, $R^2=t\text{-}C_4H_9$; c $R^1=CH_3$; $R^2=H$; IV a $R^3=CH_3$, a′ $R^3=C_2H_5$; a″ $R^3=(CH_2)_5$

Just as in the case of the use of primary amines (or imines) [1, 3, 4], N-methylindoles IIa-c are among the products of the reaction of salts Ia-c. The formation of indoles IIa-c under these conditions also occurs in conformity with the previously proposed molecular design [3]. The use of secondary amines leads to new pathways of the reaction of 3-nitropyridinium salts with ketones; this decreases the yields of indoles. For example, whereas indole IIa is formed in 60% yield when a mixture of acetone with methylamine is used in the reaction with salt Ia [2] and the yield is 62% in the case of N-methylacetoneimine [1], the use of secondary amines decreases the yields of indoles to 7-16%.

Simultaneous processes involving condensation of the excess acetone (the carbonyl activity of which is substantially higher than that of acetoneimine) at the active methyl groups of the starting pyridinium salt in the presence of a more basic (than methylamine) secondary amine may also be the reason for the decrease in the yield of indole IIa. One of these condensation processes leads to the formation of 1,3-di(4-indolyl)propane IIIa.

The following signals of the protons of the alkyl chain that connects the indole rings are characteristic for the PMR spectrum of IIIa: a singlet of two gem-methyl groups at

*See [1] for Communication 4.

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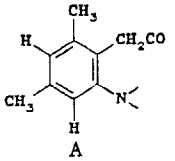
0.95 ppm (integral intensity 6H) and a singlet of protons of two CH_2 groups at 2.89 ppm (4H). In addition, signals of two equivalent indole rings and the methyl groups bonded to them, which are similar to the signals of the protons of indole IIa, appear in the spectrum. The signals of the quaternary carbon atom of the $C(CH_3)_2$ group at 37.64 ppm and the triplet of the benzyl carbon atoms (46.82 ppm) were identified in the proton-coupled ^{13}C NMR spectrum of indole IIIa. The alternative possibility of condensation of acetone at the 2-CH_3 or 6-CH_3 group was excluded on the basis of spectral data: Retention of the 2-CH_3 group follows from an analysis of the multiplicity of the signal of the 3-H proton in the PMR spectrum (q, $J_{3\text{-}H,2\text{-}CH_3}$ = 0.9 Hz) [3], and the retention of the 6-CH_3 group follows from an analysis of the fine multiplet structure of the signal of the $C_{(7)}$ atom of the indole ring, for which, in addition to the direct constant (^1J = 156.3 Hz), doublet $^3J_{C_{(7)},5\text{-}H}$ = 6.6 Hz) and quartet $^3J_{C_{(7)},6\text{-}CH_3}$ = 5.2 Hz) splittings are also observed.

The parameters of the PMR spectrum of bisindolylpropane IIIc, taking into account the presence of ethyl substituents in the 2 and 6 positions, correspond excellently to the parameters of the PMR spectrum of IIIa (see the Experimental section).

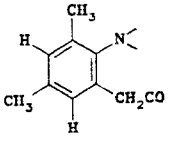
If there is a neopentyl radical in the 4 position of the starting pyridinium salt (salt Ib), the principal product becomes the corresponding indole IIb (72% yield). Such a high yield of the indole can be explained by suppression of the condensation process with respect to the sterically hindered 4-CH_2 group (in contrast to the 4-CH_3 group of salts Ia,c). The same factors are the reason for the absence of bis compounds of the III type in the reaction products.

The realization of other pathways of the process also depends to a considerable extent on the structure of the starting pyridinium salt. For example, in the case of 3-nitropyridinium salts Ia-c, which have a 4-alkyl substituent, their reaction with acetone and secondary amines leads, in addition to indole structures II and III, to 2-aminobenzyl alkyl ketones IV.

A band of stretching vibrations of a carbonyl group of ketones at 1710 cm^{-1} is observed in the IR spectra of IVa,a″. The presence in the PMR spectra of IV of protons of NR_2[3] groups and a ketone residue and two aromatic protons (see the Experimental section) confirms the proposed structure. The problem of the mutual orientation of the substituents in the benzene ring was solved by means of the ^{13}C NMR spectra. Signals of carbon atoms of two aromatic methyl groups at 20.27 and 21.15 ppm are observed in the spectrum of IVa″. An analysis of the multiplicity of these signals in the proton-coupled ^{13}C NMR spectra showed that the first signal belongs to the CH_3 group, which has one ortho proton adjacent to it (^1J = 126.0 Hz; ^3J = 4.9 Hz). The second signal has the form of a quartet of triplets, and the direct SSCC is also 126.0 Hz; the triplet splitting J = 4.7 Hz constitutes evidence for the presence of two ortho protons adjacent to this methyl group. Thus the IVa″ molecule contains a fragment with m-oriented methyl groups and aromatic protons, and the definitive elucidation of the structure reduces to a choice between alternative structures A and B.



A



B

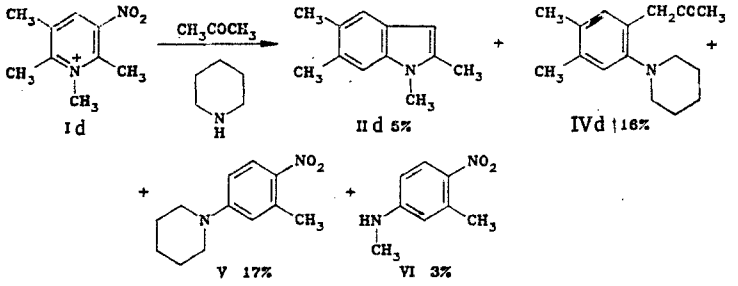
This choice was realized on the basis of an analysis of the multiplicity of the signal of the carbon atom of the CH_2 group, which is a triplet with a $^{13}C-^1H$ SSCC of 125.6 Hz. The absence of long-range couplings at a line width of 4.3 Hz indicates the absence of ortho protons adjacent to this group; this constitutes unambiguous evidence in favor of structure A.

The spectra of ketones IVa,a″,b are also in good agreement with the proposed structure.

Since Iv - ″,b are o-acetonylanilines, to ascertain whether the acetonyl residue is formed from the pyridinium salt or acetone we used salt Ic, which contains ethyl groups rather than methyl groups in the 2 and 6 positions.

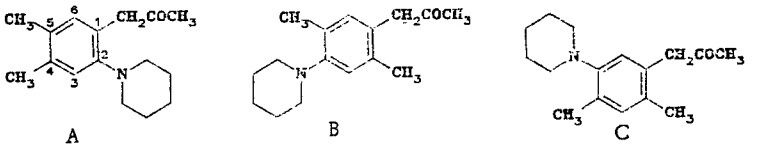
In contrast to the spectrum of IVa″, a signal of protons of an acetyl group at 2.08 ppm is absent in the aliphatic region of the PMR spectrum, and one observes (in addition to signals of protons of a piperidine ring) signals of protons of two nonequivalent ethyl groups, one aromatic CH_3 group (2.18 ppm), and a benzyl CH_2CO group (3.80 ppm). As in the case of IVa″, two broad one-proton signals at 6.78 and 6.84 ppm are present in the aromatic region of the spectrum of IVc (at 6.74 and 6.82 ppm in the case of IVa″). Thus on the basis of the PMR spectra one may draw the preliminary conclusion that the same type of substitution in the benzene ring as in acetonylaniline IVa" is retained in IVc, but a methyl ethyl ketone residue shows up in place of the acetonyl group, and an ethyl group shows up in place of one aromatic methyl group. The ^{13}C NMR spectra were used for the definitive establishment of the position of the substituents in the benzene ring. An analysis of the multiplicity of the signal of the aromatic CH_3 group indicates the presence of one ortho proton adjacent to it (^1J = 126.2 Hz; ^3J = 4.9 Hz). The multiplicity of the signal of the CH_2 group of the aromatic ethyl group (28.53 ppm) constitutes evidence for the presence of two ortho protons adjacent to it, since each of the components of the triplet (^1J = 126.7 Hz) has the form of a sextet with a normal intensity distribution (J = 4.2 Hz); this corresponds to coupling with the protons of the CH_3 groups and two ortho protons (the corresponding constants are close in value). The absence of long-range coupling of the carbon atom of the CH_2CO group (42.10 ppm, ^1J = 125.5 Hz) indicates that there are no ortho protons adjacent to it. The combination of these data makes it possible to assign the 6-methyl-4-ethyl-2-(N-piperidino)benzyl ethyl ketone structure to IVc.

In the analysis of the structures of benzyl ketones IV it is apparent that they are formed via the same formal scheme as the corresponding indoles II [3], but the formation of a pyrrole ring becomes impossible because of replacement of the secondary amino group ($NHCH_3$) by a tertiary amino group (NR_2^3). Thus the use of secondary amines enabled us to not only detect intermediates in the formation of indoles (o-aminobenzyl ketones) but also to demonstrate that the formation of the benzene ring is the first stage in the process. In addition, it now becomes clear that the nitro group is eliminated not in the aromatization of the pyrrole ring, as proposed by Gromov and Bundel' [2] but rather in earlier stages of the process.



The absence of an alkyl substituent in the 4 position of salt Id does not have a fundamental effect on realization of the processes involved in the formation of the indoles and 2-aminobenzyl ketones. As in the case of salts Ia-c, the reaction of salt Id leads to the formation of indole IId [1] and 4,5-dimethyl-2-(N-piperidino)benzyl methyl ketone (IVd).

An analysis of the multiplicity of the signals in the proton-coupled ^{13}C NMR spectra of IVd makes it possible to conclude that both aromatic CH_3 groups and the CH_2 group of the acetonyl fragment have one ortho proton in their vicinity. This follows from the long-range $^3J_{CH}$ SSCC, which are equal in this case to 5.2, 5.2, and 4.0 Hz, respectively. On the basis of these data we can restrict ourselves to three possible structures of the benzyl ketones:

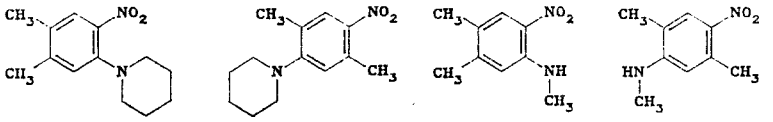


The multiplet structure of the strong-field signal of the aromatic methylidyne carbon atom (121.45 ppm) is a doublet (J = 152.6 Hz) of quartets (J = 5.1 Hz); this enables us to exclude structure C from consideration, since the corresponding signal in its spectrum should have the form of a doublet of triplets. The multiplet structure of the second methylidyne carbon atom (131.61 ppm) corresponds to a doublet (J = 152.7 Hz) of sextets (J = 5.0 Hz); this also corresponds to structures A and B and contradicts structure C, for which the signal should have the form of a doublet of septets. The multiplicities of the signals of the quaternary carbon atoms at 128.73 (q, J = 6.1 Hz), 131.06 (complex multiplet), and 134.97ppm (complex multiplet) make it possible to unequivocally choose structure A. In fact, for structure A one should observe two signals with a complex multiplet structure (the $C_{(5)}$ and $C_{(4)}$ atoms), and the signal of the $C_{(1)}$ atom can have the form of a quartet due to splitting by the 3-H proton and the protons of the CH_2 group of the acetonyl residue with close SSCC [5, 6]. In structure B the signals of the $C_{(1)}$ and $C_{(2)}$ atoms also should have a complex multiplet structure, but the signal of the $C_{(5)}$ atom cannot be a quartet, since for it one should observe large constants of spin-spin coupling [5, 6] with both the protons of the closest CH_3 group and with the 3-H proton.

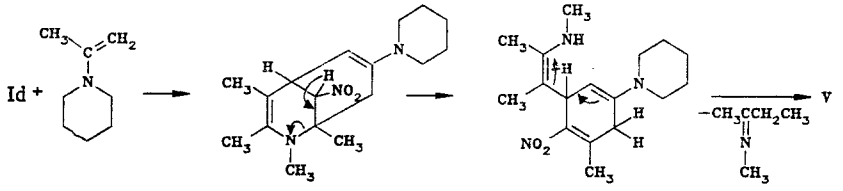
Thus even in the absence of a substituent in the 4 position of starting salt Id benzyl ketone IVd is formed via the same formal scheme as benzyl ketones IVa-c from the 4-substituted salts.

The specific characteristics of the reaction of 4-unsubstituted salt Id consist in the fact that, in addition to IId and IVd, p-nitroanilines V and VI are also formed. This reaction pathway is not realized when a 4-alkyl substituent is present in starting salt I.

It is known that 3-nitropyridinium salts that contain α-methyl groups are capable of undergoing recyclization to o- and p-nitroanilines under the influence of primary and secondary amines [7]. Via this reaction salt Id should have reacted with piperidine to give nitroanilines with the structures

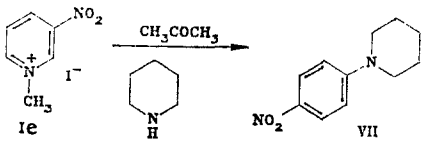


However, nitroanilines V and VI, which have one less methyl group in the benzene ring, are formed in our case when the reaction is carried out in the presence of acetone. These unexpected results are explainable if it is assumed that a molecule of acetone participates in the construction of the benzene ring with the elimination of the $C_{(5)}$–$C_{(6)}$ fragment of a molecule of the starting pyridinium salt in the form of methyl ethyl ketone N-methylimine.

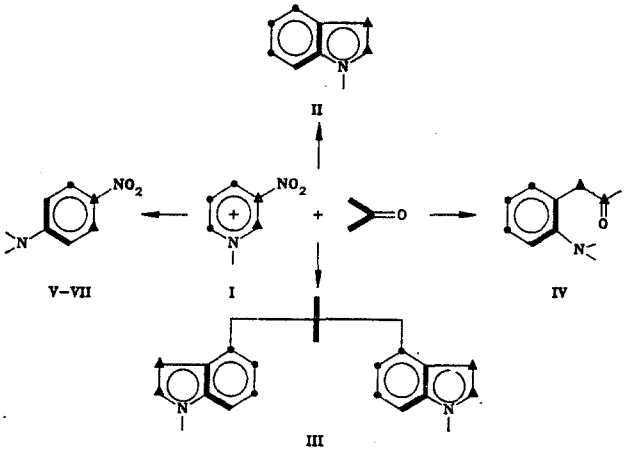


The conversion of 3,5-dinitro-2-pyridone under the influence of ketones and amines to p-nitroanilines with the participation of the three-carbon fragment of the ketone and the elimination of nitroacetamide from the starting pyridone molecule [8] serves as an analogy of this transformation of the pyridine ring. In our case, after treatment of the reaction mixture with an aqueous solution of tartaric acid and urea (for tying up the excess piperidine and removal of the nitrite ion, respectively), methyl ethyl ketone was detected (by GLC) in the distillate of the volatile components of the reaction mixture (up to 90°C); this confirms the proposed scheme.

3-Nitropyridine methiodide (Ie) evidently cannot undergo recyclization via the Kost–Sagitullin reaction [7] because of the absence of α-methyl groups. However, if our scheme is correct, in the presence of acetone methiodide Ie can be converted to a p-nitroaniline that is unsubstituted in the benzene ring. In fact, the reaction of salt Ie with acetone and piperidine leads to p-nitroaniline VII.



Thus in the case of the reactions of salts Ia-d with acetone and secondary amines it was shown that, depending on the structure of the starting salt, processes that can be represented by the following general formal scheme are realized:



The scheme graphically shows that the addition of an enamine, which acts as a 1,3-bis-C,C-nucleophile, in the 4 and 6 positions of the starting salt is necessary for the formation of indoles II and o-aminobenzyl ketones IV. However, the formation of the benzene ring of the p-nitroanilines requires the addition of the nucleophile in the 2 and 4 positions. The presence or absence of a substituent in the 4 position of starting 2,6-dialkyl-3-nitropyridinium salt I plays a substantial role in the direction of initial attack by the nucleophile. Thus on the basis of quantum-chemical calculations of the electron density in salt Ia and its anhydro base [9] it was shown that the 6 position is the most likely site of attack by the nucleophile. In the case of 4-substituted salts Ia-c the enamine evidently initially attacks the 6 position, which creates the only possibility for the formation of a benzene ring (indoles and o-aminobenzyl ketones) in the 4 position of the starting salt. However, if a substituent is absent in the 4 position of the starting pyridinium salt, then it is extremely likely that precisely this vacant position becomes the initial site of attack by the nucleophile. The subsequent formation of the benzene ring can then proceed through further attack not only in the 6 position but also in the 2 position, which we also observe when we compare the yields of the products of the reaction of salt Id.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of the compounds were recorded with T-60, Joel FX-100, and Bruker AM-360 spectrometers. Information regarding the relative intensities of the signals and data from the proton-coupled spectra were used for this assignment of the signals in the ^{13}C NMR spectra of IVa'',c,d. Data from the ^{13}C $\{^1H\}$ NMR spectra with selective decoupling of the protons were also used in the case of IVa″,d. The spectral method in [3] and the data in [10] were used to establish the structures of indoles IIb,c and IIIa. The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. Gas-liquid chromatography (GLC) was carried out with a Chrom-5 chromatograph with a 12.5-m long quartz capillary column; the carrier gas was helium, the run-off ratio was 1:60, the flow rate was 1.2 ml/min, T_{vap} was 100°C, T_{det} was 150°C, T_{therm} was 30°C, and a flame-ionization detector was used. The course of the reactions and the purity of the substances formed were monitored by TLC on Silufol in benzene–hexane (1:3) (A) and hexane–acetone (5:1) (B). The products of the reactions and the characteristics of the synthesized substances are given in Tables 1 and 2.

1,2,4,6-Tetramethyl-3-nitropyridinium iodide (Ia) was obtained by the method in [11]. PMR spectrum (d_6-DMSO): 2.52 (3H, s, 4-CH_3), 2.73 (3H, s, 6-CH_3), 2.85 (3H, s, 2-CH_3), 4.09 (3H, s, N–CH_3), 8.15 ppm (1H, s, 5-H).

TABLE 1. Products and Conditions Used to Carry Out the Reactions of 3-Nitropyridinium Salts with Acetone and Secondary Amines

Starting compounds					Reaction products					
salt	amt., mmole	amine	amt., mmole	amt. of acetone, mmole	indole	yield, %	indole	yield, %	benzyl ketone	yield, %
Ia	3,2	$(CH_3)_2NH$	16,2	50,0*	IIa	7	IIIa	5	IVa	15
Ia	5,0	$(C_2H_5)_2NH$	25,0	50,0*	IIa	11	IIIa	3	IVa′	28
Ia	5,0	$(CH_2)_5NH$	25,0	50,0	IIa	9	IIIa	9	IVa″	8
Ib	5,0	$(CH_2)_5NH$	25,0	75,0	IIb	72	—	—	IVb	14
Ic	2,5	$(CH_2)_5NH$	12,5	37,5	IIc	16	IIIc	7	IVc	9
Id†	5,0	$(CH_2)_5NH$	25,0	100,0	IId	5	—	—	IVd	16
Ie‡	2,0	$(CH_2)_5NH$	10,0	40,0	—	—	—	—	—	—

*With the addition of 5 ml of DMF.
†p-Nitroaniline V (17%) and aniline VI (3%) were isolated.
‡p-Nitroaniline VII (10%) was isolated.

1,2,3,6-Tetramethyl-5-nitropyridinium perchlorate (Id) was obtained by the method in [1].

4-Methyl-2,6-diethyl-3-nitropyridine. A 10-ml sample of concentrated H_2SO_4 was added with cooling to 5.5 g (37 mmole) of 2,6-diethyl-4-methylpyridine [12], after which a mixture of 5 ml of HNO_3 (d = 1.5), 10 ml of concentrated H_2SO_4, and 10 ml of 60% oleum was added, and the resulting mixture was heated for 50 h at 105-110°C. It was then cooled and poured over ice, and the aqueous mixture was neutralized with ammonium hydroxide and extracted with benzene. The extract was dried with Na_2SO_4, the benzene was removed by distillation, and the residue was distilled in vacuo to give 4.2 g (59%) of the nitropyridine with bp 118-122°C (11 mm). PMR spectrum (CCl_4): 1.25 (6H, t, 2- and 6-CH_2CH_3), 2.22 (3H, s, 4-CH_3), 2.50 (2H, q, 6-CH_2CH_3), 2.83 (2H, q, 2-CH_2CH_3), 6.83 ppm (1H, s, 5-H).

1,4-Dimethyl-2,6-diethyl-3-nitropyridinium Methosulfate (Ic). A mixture of 3 g (9.4 mmole) or 4-methyl-2,6-diethyl-3-nitropyridine and 1.5 ml (15.8 mmole) of freshly distilled dimethyl sulfate was heated for 1.5 h at 125°C, after which it was cooled and treated with dry ether, and the precipitate was removed by filtration, washed with dry ether, and recrystallized from acetone to give 3.6 g (74%) of salt Ic with mp 155-156°C. PMR spectrum (d_6-DMSO): 1.28 (3H, t, 6-CH_2CH_3); 1.33 (3H, t, 2-CH_2CH_3); 2.53 (3H, s, 4-CH_3), 3.03 (4H, q, 2- and 6-CH_2CH_3); 3.31 (3H, s, $CH_3SO_4^-$); 4.17 (3H, s, N—CH_3); 8.08 ppm (1H, s, 5-H). Found, %: C 45.0, H 6.3. $C_{12}H_{20}N_2O_6$. Calculated, %: C 44.8, H 6.8.

2,6-Dimethyl-4-neopentylpyridine. The action of excess ammonium hydroxide on the pyrylium salt [obtained from 36 ml (0.2 mole) of diisobutylene, 88 ml (0.9 mole) of acetic anhydride, and 80 g (0.6 mole) of anhydrous $ZnCl_2$ by the method in [13]] with subsequent extraction with benzene, drying of the extract with Na_2SO_4, removal of the benzene by distillation, and distillation of the residue in vacuo gave 21.5 g (59%) of 2,6-dimethyl-4-neopentylpyridine with bp 98-100°C (20 mm) instead of the 2,4,6-trimethyl-3-tert-butylpyridine proposed by Bolle and Tomaszewski [13]. PMR spectrum (CCl_4): 0.87 [9H, s, $C(CH_3)_3$], 2.30 (2H, s, CH_2), 2.41 (6H, s, 2- and 6-CH_3), 6.62 ppm (2H, s, 3- and 5-H).

2,6-Dimethyl-4-neopentyl-3-nitropyridine. A 6-ml sample of HNO_3 (d = 1.5) and 40 ml of concentrated H_2SO_4 were added with cooling to 13 g (7.3 mmole) of 2,6-dimethyl-4-neopentylpyridine, and the mixture was heated for 60 h at 100-110°C. It was then cooled and poured over ice, and the resulting aqueous mixture was neutralized with ammonia to give 6.5 g (40%) of the nitropyridine with bp 139-141°C (14 mm) and mp 50-51°C (from aqueous methanol. PMR spectrum (d_6-DMSO): 0.92 [9H, s, $C(CH_3)_3$], 2.48 (3H, s, 6-CH_3), 2.57 (3H, s, 2-CH_3), 2.63 (2H, s, CH_2), 7.20 ppm (1H, s, 5-H).

1,2,6-Trimethyl-4-neopentyl-3-nitropyridinium Iodide (Ib). A mixture of 6.5 g (29 mmole) of 2,6-dimethyl-4-neopentyl-3-nitropyridine and 10 ml (160 mmole) of methyl iodide was heated in a sealed ampul for 15 h at 100°C, after which the precipitate was removed by filtration and washed with ether to give 5.5 g (52%) of salt Ib with mp 183-185°C (from $CHCl_3$). PMR spectrum (d_6-DMSO): 0.92 [9H, s, $C(CH_3)_3$], 2.75 (6H, s, 2- and 6-CH_3), 2.90 (2H, s, CH_2), 4.13 (3H, s, N—CH_3), 8.10 ppm (1H, s, 5-H). Found, %: C 43.3, H 5.5. $C_{13}H_{21}IN_2O_2$. Calculated, %: C 42.8, H 5.8.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp,* °C	R_f (system)	Found, % C	Found, % H (N)	Empirical formula	Calc., % C	Calc., % H (N)
IIa	83...84 [2]	0,34 (A)					
IIb	89...90	0,45 (A)	83,7	10,7	$C_{16}H_{23}N$	83,8	10,1
IIc	37...38	0,42 (A)	83,1	9,6	$C_{14}H_{19}N$	83,5	9,5
IId	110...112 [1]	0,33 (A)					
IIIa	202...205	0,05 (A)	84,4	8,7 (7,3)	$C_{27}H_{34}N_2$	83,9	8,8 (7,3)
IIIc	115...117	0,10 (A)	84,3	9,6	$C_{31}H_{42}N_2$	84,2	9,5
IVa	77...78	0,26 (B)	76,4	8,7	$C_{13}H_{19}NO$	76,1	9,3
IVa′	Oil	0,43 (B)					
IVa′†	139...140		61,4	6,3	$C_{21}H_{27}N_5O_4$	61,0	6,5
IVa″	62...63	0,47 (B)	78,4	9,1 (6,1)	$C_{16}H_{23}NO$	78,4	9,4 (5,7)
IVb	70...71	0,54 (B)					
IVb†	190...192		64,1	7,2 (14,4)	$C_{26}H_{35}N_5O_4$	64,9	7,3 (14,4)
IVc	25...30	0,60 (B)					
IVc†	188...190		63,1	6,8 (15,4)	$C_{24}H_{31}N_5O_4$	63,6	6,8 (15,5)
IVd	43...44,5	0,47 (B)	78,4	9,2 (5,7)	$C_{16}H_{23}NO$	78,4	9,4 (5,7)
V	53...54 [16]	0,47 (B)					
VI	89...90 [17]	0,17 (B)					
VII	99...100 [8]						

*The compounds were crystallized: hexane for IIa-d, IVa,a'',d and VI, benzene–hexane for IIIa, alcohol for IIIc, and methanol for V.

†The melting points (after crystallization from methanol in the case of IVa′ and after crystallization from benzene–hexane in the case of IVb,c) and empirical formulas pertain to the 2,4-dinitrophenylhydrazones of benzyl ketones IV.

1-Methyl-3-nitropyridinium Iodide (Ie). This compound was obtained by the method in [14]. PMR spectrum (d_6-DMSO): 4.50 (3H, s, N–CH_3), 8.43 (1H, dd, J_{54} = 9 Hz, J_{56} = 6.0 Hz, 5-H), 9.40 (2H, m, 4- and 6-H), 10.1 ppm (1H, broad s, 2-H).

Reaction of 3-Nitropyridinium Salts I with Acetone and Secondary Amines (general method). The secondary amine was added dropwise with stirring to a mixture of salt I and acetone,* and the reaction mixture was maintained at room temperature for 2 days (the ratios of the reagents are given in Table 1). The excess acetone and amine were removed by distillation in vacuo, and the residue was treated with benzene and water. The benzene layer was separated, the aqueous layer was extracted with benzene, and the combined benzene extracts were washed with water, dried with Na_2SO_4, and evaporated in vacuo. The residue was chromatographed with a column packed with silica gel (40/100 μ) by successive elution with benzene–hexane (1:1) (indole fraction, II and III) and benzene–ethyl acetate in various ratios (aniline fraction, IV-VII).

Compounds IV a′, a″, c were additionally purified to remove impurities with close chromatographic mobilities by means of high-performance flash chromatography [15] on Silpearl for TLC in hexane–ethyl acetate (3:1); the column dimensions were 200 by 20 mm, the air pressure was 0.25 atm, and the charge of the mixtures was 50-100 mg.

1,4-Dimethyl-2,6-diethylindole (IIc). PMR spectrum (d_6-acetone): 1.24 (3H, t, 2-CH_2CH_3), 1.30 (3H, t, 6-CH_2CH_3), 2.42 (3H, s, 4-CH_3), 2.57-2.84 (4H, m, 2- and 6-CH_2), 3.59 (3H, s, N–CH_3), 6.13 (1H, dt, 3-H, $J_{37} = J_{3\text{-H},2\text{-}CH_2}$ = 0.9 Hz), 6.66 (1H, broad s, 5-H), 6.93 ppm (1H, broad s, 7-H). ^{13}C NMR spectrum: 13.30 (2-CH_2CH_3), 16.88 (6-CH_2CH_3), 18.68 (4-CH_3), 20.51 (2-CH_2), 29.50 (N–CH_3), 29.98 (6-CH_2), 96.73 [$C_{(3)}$], 106.11 [$C_{(7)}$], 120.75 [$C_{(5)}$], 126.93 [$C_{(4)}$], 128.94 [$C_{(8)}$], 137.59 [$C_{(6)}$], 138.73 [$C_{(9)}$], 142.43 ppm [$C_{(2)}$].

1,2,6-Trimethyl-4-neopentylindole (IIb). PMR spectrum (d_6-acetone): 0.93 [9H, s, $C(CH_3)_3$], 2.23 (3H, s, 2-CH_3), 2.36 (3H, s, 6-CH_3), 2.67 (2H, s, CH_2), 3.48 (3H, s, N–CH_3), 6.11 (1H, s, 3-H), 6.57 (1H, s, 5-H), 6.85 ppm (1H, s, 7-H). ^{13}C NMR spectrum: 12.72 (2-CH_3), 22.11 (6-CH_3), 29.43 (N–CH_3), 30.60 [$C(CH_3)_3$]; 33.35 [$C(CH_3)_3$]; 47.59 (CH_2), 99.91

*In the case of the reaction with dimethylamine salt Ia was added to a solution of dimethylamine in DMF and acetone.

[$C_{(3)}$], 107.65 [$C_{(7)}$], 123.90 [$C_{(5)}$], 127.94 [$C_{(8)}$], 129.78 [$C_{(6)}$], 131.21 [$C_{(4)}$], 135.97 [$C_{(2)}$], 138.98 ppm [$C_{(9)}$].

2,2-Dimethyl-1,3-bis(1,3,6-trimethyl-4-indolyl)propane (IIIa). PMR spectrum ($CDCl_3$): 0.95 [6H, s, $C(CH_3)_2$], 2.34 (6H, d, 2-CH_3, $J_{CH_3,3\text{-}H}$ = 0.9 Hz), 2.44 (6H, s, 6-CH_3), 2.89 (4H, s, CH_2), 3.54 (6H, s, N-CH_3), 6.19 (2H, q, 3-H, $J_{3\text{-}H,CH_3}$ = 0.9 Hz), 6.69 (2H, s, 5-H), 6.88 ppm (2H, s, 7-H). ^{13}C NMR spectrum: 12.76 (2-CH_3), 21.88 (6-CH_3), 27.44 [$C(CH_3)_2$]; 29.27 (N-CH_3), 37.64 [$C(CH_3)_2$]; 46.82 (CH_2), 99.31 [$C_{(3)}$], 106.57 [$C_{(7)}$], 123.70 [$C_{(5)}$], 126.94 [$C_{(8)}$], 129.45 [$C_{(6)}$], 130.71 [$C_{(4)}$], 135.07 [$C_{(2)}$], 137.63 ppm [$C_{(9)}$].

2,2-Dimethyl-1,3-bis(1-methyl-2,6-diethyl-4-indolyl)propane (IIIc). PMR spectrum ($CDCl_3$): 0.93 [6H, s, $C(CH_3)_2$], 1.24 (6H, t, 2-CH_2CH_3); 1.25 (6H, t, 6-CH_2CH_3); 2.62 (4H, q, 2-CH_2), 2.63 (4H, q, 6-CH_2), 2.90 (4H, s, 4-CH_2), 3.51 (6H, s, N-CH_3), 6.15 (2H, s, 3-H), 6.68 (2H, s, 5-H), 6.85 ppm (2H, s, 7-H).

4,6-Dimethyl-2-dimethylaminobenzyl Methyl Ketone (IVa). PMR spectrum ($CDCl_3$): 2.10 (3H, s, $COCH_3$), 2.18 (3H, s, 6-CH_3), 2.25 (3H, s, 4-CH_3), 2.53 [6H, s, $N(CH_3)_2$], 3.77 (2H, s, CH_2CO), 6.80 and 6.85 ppm (2H, two s, 2- and 5-H).

4,6-Dimethyl-2-diethylaminobenzyl Methyl Ketone (IVa'). PMR spectrum ($CDCl_3$): 0.95 (6H, t, CH_2CH_3); 2.17 (6H, s, $COCH_3$, 6-CH_3), 2.30 (3H, s, 4-CH_3), 2.90 (4H, q, CH_2CH_3); 3.93 (2H, s, CH_2CO), 6.87 ppm (2H, broad s, 3- and 5-H).

4,6-Dimethyl-2-(N-piperidino)benzyl Methyl Ketone (IVa''). PMR spectrum (d_6-acetone): 1.57 (6H, m, piperidine β- and γ-H), 2.08 (3H, t, CH_3CO, $J_{CH_3COCH_2}$ = 0.4 Hz), 2.13 (3H, s, 6-CH_3), 2.23 (3H, s, 4-CH_3), 2.70 (4H, m, piperidine α-H), 3.28 (2H, broad s, CH_2CO), 6.74 (1H, s, 5-H), 6.82 ppm (1H, s, 3-H). ^{13}C NMR spectrum: 20.27 (6-CH_3), 21.15 (4-CH_3), 24.90 (piperidine γ-CH_2), 27.07 (piperidine β-CH_2), 29.07 (CH_3CO), 43.45 (CH_2CO), 54.76 (piperidine α-CH_2), 119.55 [$C_{(3)}$], 127.27 [$C_{(5)}$], 128.49 [$C_{(1)}$], 137.05 [$C_{(4)}$], 138.29 [$C_{(6)}$], 153.89 [$C_{(2)}$], 206.16 ppm (CO).

4-Methyl-6-neopentyl-2-(N-piperidino)benzyl Methyl Ketone (IVb). PMR spectrum ($CDCl_3$): 0.87 [9H, s, $C(CH_3)_3$], 1.57 (6H, m, piperidine β- and γ-H), 2.00 (3H, s, CH_3CO), 2.26 (3H, s, 4-CH_3), 2.47 (2H, s, 6-CH_2), 2.72 (4H, m, piperidine α-H), 3.67 (2H, s, CH_2CO), 6.74 (1H, s, 3-H), 6.85 ppm (1H, s, 5-H).

6-Methyl-4-ethyl-2-(N-piperidino)benzyl Ethyl Ketone (IVc). PMR spectrum ($CDCl_3$): 1.03 (3H, t, $COCH_2CH_3$, J = 7.4 Hz), 1.22 (3H, t, 4-CH_2CH_3, J = 7.6 Hz), 1.63 (6H, m, piperidine β- and γ-H), 2.18 (3H, s, 6-CH_3), 2.41 (2H, q, $COCH_2CH_3$, J = 7.4 Hz), 2.57 (2H, q, 4-CH_2CH_3, J = 7.6 Hz), 2.72 (4H, m, piperidine α-H), 3.80 (2H, s, 1-CH_2CO), 6.79 (1H, broad s, 3-H), 6.84 ppm (1H, broad s, 5-H). ^{13}C NMR spectrum: 7.89 ($COCH_2CH_3$); 15.18 (4-CH_2CH_3); 20.10 (6-CH_3), 24.07 (piperidine γ-CH_2), 26.30 (piperidine β-CH_2), 28.38 (4-CH_2CH_3); 34.47 ($COCH_2CH_3$); 41.95 (1-CH_2CO); 53.98 (piperidine α-CH_2), 117.69 [$C_{(3)}$], 125.35 [$C_{(5)}$], 127.48 [$C_{(1)}$], 137.38 [$C_{(6)}$], 143.00 [$C_{(4)}$], 152.98 [$C_{(2)}$], 209.79 ppm (CO).

4,5-Dimethyl-2-(N-piperidino)benzyl Methyl Ketone (IVd). PMR spectrum (d_6-acetone): 1.45-1.65 (6H, m, piperidine β- and γ-H), 2.01 (3H, s, $COCH_3$); 2.15 and 2.17 (6H, two s, 4- and 5-CH_3), 2.71 (4H, m, piperidine α-H), 3.61 (2H, s, CH_2CO); 6.90 and 6.93 ppm (2H, two s, 3- and 6-H). ^{13}C NMR spectrum: 18.13 and 18.64 (4- and 5-CH_3), 23.96 (piperidine γ-CH_2), 26.01 (piperidine β-CH_2), 27.78 ($COCH_3$); 45.92 (CH_2CO), 53.49 (piperidine α-CH_2), 121.45 [$C_{(3)}$], 128.73 [$C_{(1)}$], 131.06 [$C_{(5)}$], 131.61 [$C_{(6)}$], 134.97 [$C_{(4)}$], 150.03 [$C_{(2)}$], 204.42 ppm (CO).

N-(3-Methyl-4-nitrophenyl)piperidine (V). PMR spectrum (d_6-DMSO): 1.53 (6H, m, piperidine β- and γ-H), 2.50 (3H, s, CH_3), 3.40 (4H, m, piperidine α-H), 6.77 (2H, m, 2- and 6-H), 7.93 ppm (1H, d, J_{56} = 9.6 Hz, 5-H).

N-Methyl-3-methyl-4-nitroaniline (VI). PMR spectrum ($CDCl_3$): 2.30 (3H, s, 3-CH_3), 2.90 (3H, d, N-CH_3, J = 4.8 Hz), 5.70 (1H, broad signal, NH), 6.25-6.50 (2H, m, 2- and 6-H), 8.00 ppm (1H, dd, 5-H, J_{52} = 2 Hz, J_{56} = 8.2 Hz).

N-(4-Nitrophenyl)piperidine (VII). PMR spectrum (d_6-DMSO): 1.67 (6H, m, piperidine β- and γ-H), 3.47 (4H, m, piperidine α-H), 6.97 (2H, d, 2- and 6-H, J_{ortho} = 9.6 Hz), 8.03 ppm (2H, d, 3- and 5-H, J_{ortho} = 9.6 Hz).

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BISPYRAZOLE[3,4-b:4',3'-e]PYRAZINES AS SELF-CONDENSATION PRODUCTS FROM 4,5-DIAMINOPYRAZOLES

V. D. Orlov, Kh. Kiroga, and N. N. Kolos

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Bispyrazolo[3,4-b:4',3'-e]pyrazines have been obtained by self-condensation of 4,5-diaminopyrazoles and their structures confirmed by independent synthesis. The spectral data for these compounds is discussed.

We have recently shown [1] that refluxing a toluene solution of 4,5-diamino-3-methyl-1-phenylpyrazole (Ia) leads to self-condensation and formation of 3,5-dimethyl-1,7-diphenylpyrazolo[3,4-b:4',3'-e]pyrazine (IIa). Evidence for similar reactions has only been reported for 5,6-diamino-1,3-dimethyluracil [2].

The aim of this work was an investigation of the self-condensation of diaminopyrazoles to bispyrazolopyrazines which are of interest as luminophores.

It has been shown that diamines Ib,c like Ia, form the bispyrazolopyrazines IIa-c in 40-60% yields when heated for 1-2 h in toluene whereas diamine Id remains unchanged (route A). In methanol diamines Ia,b take part in a cross-ring 4,5-interaction (route B) to form compounds IIIa,b whereas IIc,d are unchanged under these conditions. Prolonged refluxing (15 h) of IIIa in ethylene glycol led to compound IV. The reaction mixture also contained compound IIa, but the mechanism of its formation is not clear. Separation of this mixture was difficult hence IIa and IV were identified by comparison of their R_f values and electronic absorption spectra with standard samples.

A. M. Gorko State University, Kharkov 310077.

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