min to a cooled solution of 7,7'-dichlorobis(5-indolyl)methane (0.2 g, 0.6 mmole) in absolute bezene (30 ml) and acetic anhydride (15 ml). The product was stirred for 2 h at 0-5°C, poured onto ice, and the precipitate was filtered off. Washing with water, drying and column purification using benzene-ether (2:1) as eluent gave a yield of 0.2 g.

LITERATURE CITED

1. Dzh. Zegkhugkh, D. O. Kadzhrishvili, Sh. A. Samsoniya, N. N. Suvorov, and N. Z. Kedelashvili, Khim. Geterotsikl. Soedin., No. 8, 1062 (1988).
2. M. G. Cheshmaritashvili, Sh. A. Samsoniya, L. N. Kurkovskaya, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 1, 73 (1984).
3. G. I. Zhungietu, V. A. Budilin, and A. N. Kost, Preparative Chemistry of Indole [in Russian], Shtiintsa, Kishinev (1975), p. 116.

5-BENZOPYRIDYL-SUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES

A. A. Tolmachev, L. N. Babichenko, T. S. Chmilenko, and A. K. Sheinkman

UDC 547.833.9'832.1'753.07:543.422.25

A method of synthesis of 5-(isoquinol-1-yl)- and 5-(quinol-2-yl)-1,3,3-trimethyl-2-methyleneindolines has been developed consisting of hetarylation of 1,2,3,3-tetramethylindoline with isoquinoline and quinoline in the presence of benzoyl chloride, followed by oxidation and aromatization of N-benzoyl-1,2-dihydrobenzopyridine derivatives of 1,2,3,3-tetramethylindoline formed at the first stage to 5-benzopyridyl-substituted 2-methylene-indolines.

The Fischer base – 1,3,3-trimethyl-2-methyleneindoline – is an extremely important intermediate in the synthesis of various dyes [1-3]. Of particular interest are dyes of this type in which electron-accepting substituents are present in the 5-position of the benzene ring, which, generally, cause a considerable deepening of the color, and in several cases lead to dyes with improved properties of practical use [3].

It seemed very promising to try to use the hetarylation reaction [4] to introduce benzopyridines having electron-accepting properties into the 5-position of the Fischer base. It was found that the direct hetarylation of the Fischer base leads to the introduction of the heterocyclic residue into the CH_2 group,* rather than at the 5-position of the benzene ring, similarly as salts of an N-methylacridinium cation react with the Fischer base and other enamines [6]. Therefore, to obtain 5-hetaryl-substituted 2-methyleneindolines, we used a previously developed method of synthesis of 2-methyleneindolines, consisting in the introduction of substituents into the benzene ring of 1,2,3,3-tetramethylindoline I, followed by oxidation of the compounds obtained [7]. Indoline I was hetarylated by N-benzoylisoquinolinium and quinolinium chlorides formed in situ, and also by acridine hydrochloride. The known methods of hetarylation of dialkylanilines [8-11] served as the basis for this reaction. The hetarylation reaction proceeds most readily when indoline I is reacted with isoquinoline in the presence of benzoyl chloride. A substituted indoline II is formed directly by mixing the reagents at room temperature. The reaction proceeds with a slight warming up (50...60°C) and is concluded after 1 h. Hetarylation with acridine hydrochloride proceeds fairly rapidly with the formation of indoline III. With N-benzoylquinolinium chloride formed in situ, the hetarylation proceeds, as expected, much more slowly [8]. A maximal yield of compound IV was achieved on heating the reaction mixture without a solvent for 70 h at 70...80°C.

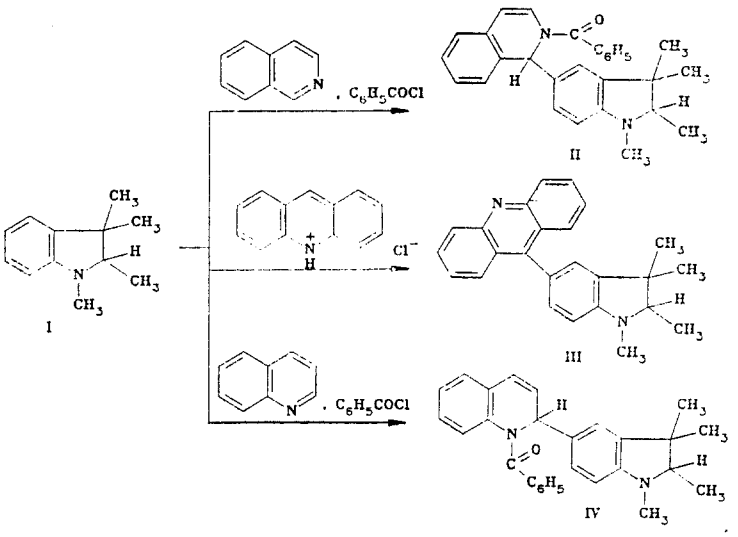
Attempts to carry out the simultaneous dehydroaromatization of 1,2-dihydroisoquinoline and indoline fragments of compound II to the corresponding isoquinoline derivative of the Fischer base X by conventional dehydroaromatizing agents were not successful. We therefore

*For a preliminary communication on this subject, see [15].

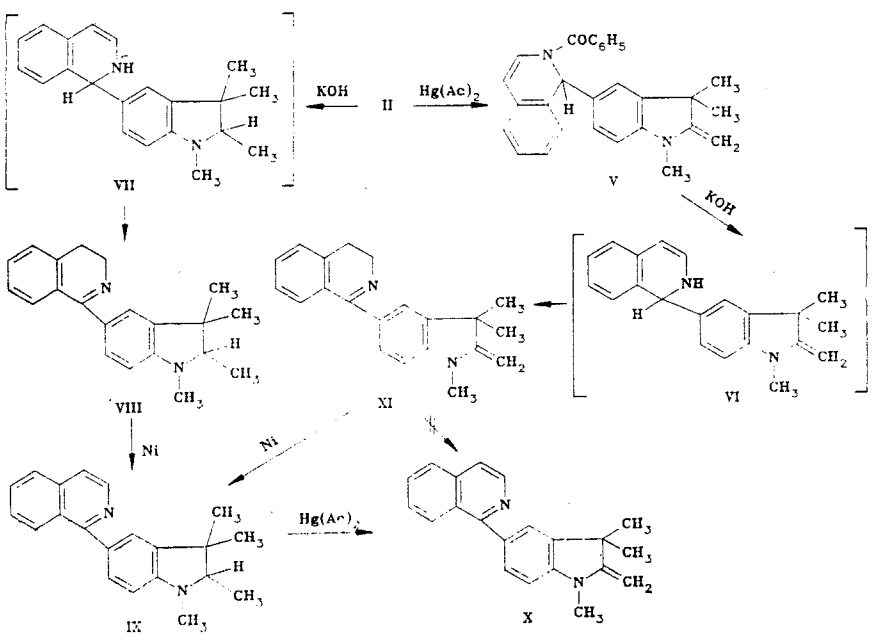
Dnepropetrovsk Construction Engineering Institute, Dnepropetrovsk 320002. Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1367-1372, October, 1989. Original article submitted March 29, 1988; revision submitted February 24, 1989.

carried out a successive dehydroaromatization of each fragment of the molecule. Conversion of 1,2,3,3-tetramethylindolines II and IX into 1,3,3-trimethyl-2-methyleneindolines V and X was effected in a fairly high yield by the action of mercuric acetate. The aromatization of the 1,2-dihydroisoquinoline fragment of compound II could not be carried out because of the strong electron-accepting influence of the N-benzoyl residue. Removal of this residue by alkaline hydrolysis in high-boiling solvents (butanol, diethylene glycol) [12] led to the formation of the isomeric 3,4-dihydroisoquinoline derivatives VIII, XI, rather than the corresponding 1,2-dihydroisoquinolines VI and VII.



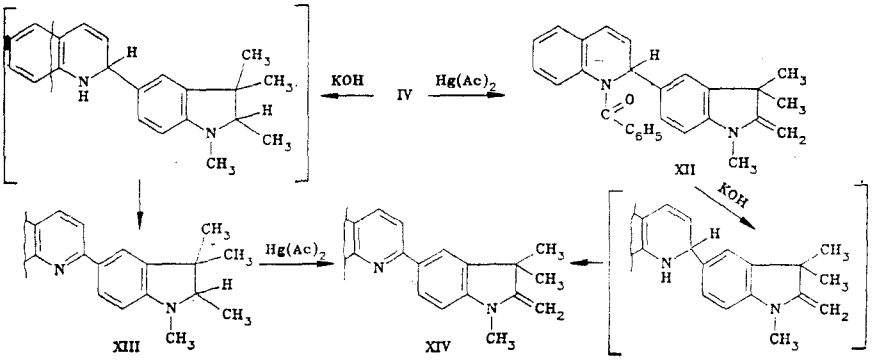
Similar rearrangements are characteristic of compounds of this type [13]. It is possible that the formation of 3,4-dihydroisoquinoline also takes place as a result of alkaline hydrolysis of other 1-aryl-2-benzoyl-1,2-dihydroisoquinolines [9], since the particular instability of 1-substituted 1,2-dihydroisoquinolines is well known [13], while compounds described as 1-aryl-1,2-dihydroisoquinolines [9] withstood even a prolonged heating with nitrobenzene. The rearrangement probably proceeds fairly rapidly since the introduction of nitrobenzene into the reaction mixture or its saturation with oxygen does not lead to the aromatization of the intermediately formed 1,2-dihydro isomers.



Dehydrogenation of 3,4-dihydroisoquinoline VIII, which we carried out on Raney nickel at high temperature [14] led to the formation of isoquinoline IX. We also obtained this compound

by the dehydrogenation of compound XI, rather than the expected indoline X, possibly as a result of the monomolecular disproportionation reaction proceeding inside the intermediately formed catalytic complex of Raney nickel and compound XI. This hypothesis is supported by the fact that carrying out this reaction in the presence of a Fischer base as a hydrogen acceptor did not lead to its reduction to indoline I.

Thus, the fact that different dehydrogenating agents – Raney nickel and mercuric acetate – must be used for the dehydroaromatization of compound II is due to the difference in the dehydrogenation mechanisms of the indoline and dihydroisoquinoline fragments as a result of the isomerization of the latter in the course of hydrolysis. In the first case, the dehydrogenation proceeds stepwise as a result of a two-electron oxidation, followed by splitting of two protons from the ring and from the methyl group and formation of anhydro-bases V and X, while in the second case, two hydrogen atoms are split off on the Raney nickel surface.



In contrast to the case of dihydroisoquinoline derivative II, alkaline hydrolysis of the dihydroquinoline derivative IV in a high boiling solvent in the presence of oxidizing agents (nitrobenzenes) led to quinoline XIII, while further oxidation of the latter with mercuric acetate gives the end product of the reaction XIV. The same compound is also formed during the primary oxidation of compound IV to 2-methyleneindoline XII by mercuric acetate and subsequent hydrolysis by potassium hydroxide in butanol or diethylene glycol in the presence of nitrobenzenes, which is probably due to the absence of isomerization of the intermediately formed 1,2-dihydroquinoline derivative into 3,4-dihydroquinoline.

The structure of all the synthesized compounds II-XIV was determined by means of their IR and PMR spectra and the elemental analysis data (Table 1). In the PMR spectra of all the compounds there are characteristic signals of the $C_{(3)}(CH_3)_2$ group in the form of two singlets in the 0.9...1.2 ppm region, the signals of the $N-CH_3$ group in the form of a singlet at 2.6...3.8 ppm, proton signals of the $C_{(2)}-CH_3$ in the form of a doublet in the 1.1...1.2 ppm region, or signals of the $=CH_2$ protons in the 3.7...4.0 ppm region, as well as the signal of the $C_{(2)}$-H proton in the form of a quartet in the 2.8...3.0 ppm region. The CH_2 proton signals of the 3,4-dihydroisoquinoline ring are present in the 2.6...2.8 ppm (4-CH_2) and 3.6...3.8 ppm (3-CH_2) regions. The literature gives data, according to which the signals of these protons in analogous compounds are present in the 2.58 ppm (4-CH_2) and 3.6 ppm (3-CH_2) regions [15]. For a more convincing proof of the structure of compounds VIII and XI, we obtained a ^{13}C NMR spectrum in which a signal is observed in the region characteristic for the C=H bond (165 ppm). The signals were assigned on the basis of a comparison with the spectrum of the initial Fischer base and with the literature data. In the PMR spectra of isoquinoline derivatives IX and X there are signals characteristic for the isoquinoline protons at the 3 and 4-positions (8.55 ppm and 8.21 ppm, respectively).

EXPERIMENTAL

The IR spectra were run on a Specord 75-IR spectrophotometer (in tablets and in a thin layer) and the PMR spectra in $CDCl_3$ on a Bruker spectrometer (100 MHz), using TMS as internal standard. The course of the reaction and the purity of the compounds obtained were monitored by means of TLC on Silufol plates in ether-hexane (2:1) or ether-hexane-chloroform (3:3:1) systems. The data of the elemental analysis of compounds II-XIV for C, H, N correspond to the calculated values.

TABLE 1. Physicochemical Characteristics of Compounds II-XIV

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}	Chemical shift of protons, ppm						Yield, %
				$C_{(3)}(CH_3)_2$, s	N—CH_3, s	$C_{(2)}$—CH_3, d ($C_{(2)}$=CH_2, s	$C_{(2)}$—H, q	7′-H	aromatic and other protons	
II	$C_{28}H_{28}N_2O$	124...125	1650 (C=O)	0,95; 1,21	2,63	1,13	2,84	6,34	5,98...7,27, m, 14H	56
III	$C_{25}H_{24}N_2$	203...204	1600 (=CH)	1,12; 1,32	2,84	1,24	3,09	6,66	7,10...8,25, m, 10H	29
IV	$C_{28}H_{28}N_2O$	160...161	1630 (C=O)	0,91; 1,18	2,62	1,10	2,82	—	6,30...7,24, m, 15H	53
V	$C_{28}H_{26}N_2O$	149...150	1650 (C=O)	1,2	3,07	(3,93)	—	6,45	6,6...7,7, m, 14H	59
VIII	$C_{21}H_{24}N_2$	62...65	1500, 1600 (=CH)	0,98; 1,24	2,67	1,14	2,92	—	4-CH_2 (2,6...3,0, m, 2H); 3-CH_2 (3,6...3,8, m, 2H); 7,15...7,45, m, 6H	56
IX	$C_{21}H_{22}N_2$	46...48	1490, 1600	1,10; 1,35	2,79	1,22	3,02	6,61	4-H (8,23, d, 1H); 3-H (8,57, d, 1H); 7,4...7,8, m, 6H	81
X	$C_{21}H_{20}N_2$	88...90	1600 (=CH)	1,41	3,12	(3,93)	—	6,66	4-H (8,19, d, 1H); 3-H (8,57, d, 1H); 7,44...8,0, m, 6H	51
XI	$C_{21}H_{22}N_2$	73...75	1500, 1600 (=CH)	1,37	3,07	(3,90)	—	6,54	4-CH_2 (2,68...2,91, m, 2H); 3-CH_2 (3,7...3,9, m, 2H); 7,15...7,65, m, 6H	79
XII	$C_{28}H_{26}N_2O$	175...176	1640 (C=O)	1,13; 1,21	2,83	(3,72)	—	6,26	6,4...7,17, m, 14H	61
XIII	$C_{21}H_{22}N_2$	48...50	1500, 1600 (=CH)	1,17; 1,38	2,77	1,21	3,03	6,61	6,7...8,13, m, 8H	70
XIV	$C_{21}H_{20}N_2$	90...92	1600 (=CH)	1,44	3,09	(3,94)	—	6,64	7,4...8,16, m, 8H	35

1,2,3,3-Tetramethyl-5-(N-benzoyl-1,2-dihydroisoquinol-1-yl)-indoline (II). A 5.1 g portion (0.04 mole) of benzoyl chloride was added dropwise to 10.15 g (0.08 mole) of isoquinoline in 30 ml of dry benzene. A solution of 7 g (0.04 mole) of 1,2,3,3-tetramethylindoline in 20 ml of benzene was added with vigorous stirring to N-benzoylisoquinolinium chloride obtained. The temperature of the reaction mixture rose to 50...60°C. The reaction was concluded in 30...60 min. A further 30 ml of benzene was added to the solidified mass, and isoquinoline hydrochloride was filtered off. The benzene layer was washed with water (3 × 50 ml), dried over magnesium sulfate, and 100 ml of heptane was added. After 40...60 min, the precipitate formed was filtered off and recrystallized from petroleum ether. The yields and characteristics of this and other synthesized compounds are given in Table 1.

1,2,3,3-Tetramethyl-5-(acrid-9-yl)indoline (III). A. A mixture of 9.8 g (0.05 mole) of acridine hydrochloride and 4.4 g (0.025 mole) of indoline I in 50 ml of dry dimethylformamide was heated for 4 h at 50...60°C. The reaction mixture was cooled, and after adding 50 ml of water, was neutralized with ammonia and extracted with benzene. The benzene solution was dried over magnesium sulfate, the solvent was evaporated, and the residual oil was ground with hexane. The product was recrystallized from hexane.

B. A mixture of 4.9 g (0.025 mole) of acridine hydrochloride, 8.8 g (0.05 mole) of indoline I and 2.4 g (0.075 mole) of sulfur in 30 ml of dry dimethylformamide as heated for 1 h 30 min at 110...120°C. The reaction mixture was cooled, poured into water (50 ml), neutralized with ammonia, and extracted with benzene. The extract was dried over magnesium sulfate, the solvent was distilled and the residual oil was ground with hexane. The product was recrystallized from hexane.

1,2,3,3-Tetramethyl-5-(N-benzoyl-1,2-dihydroquinol-2-yl)-indoline (IV). A mixture of 10.15 g (0.08 mole) of quinoline, 5. 1 g (0.04 mole) of benzoyl chloride and 7 g (0.04 mole) of indoline I was heated for 70 h at 70...80°C. A 50 ml portion of benzene was added to the solidified reaction mixture. The solution was washed with water (3 × 50 ml), dried over magnesium sulfate and 100 ml of heptane was added. After 1...2 h, the precipitate was filtered off and recrystallized from octane.

1,3,3-Trimethyl-2-methylene-5-(N-benzoyl-1,2-dihydroisoquinol-1-yl)indoline (V) and 1,3,3-Trimethyl-2-methylene-5-(N-benzoyl-1,2-dihydroquinol-2-yl)indoline (XII). A 4 g portion (0.01 mole) of compound II (IV) was dissolved in 50 ml of acetic acid and 7 g (0.022 mole) of mercuric acetate in 100 ml of water was added. The reaction mixture was heated for 30 min on a boiling water bath, cooled, and a precipitate of mercurous monoacetate was filtered off. A large excess of sodium sulfide was added, the precipitate was centrifuged, and the filtrate was neutralized with ammonia. The precipitate that separated out was recrystallized from heptane (octane).

1,2,3,3-Tetramethyl-5-(3,4-dihydroisoquinol-1-yl)indoline (VIII) and 1,3,3-Trimethyl-2-methylene-5-(3,4-dihydroisoquinol-yl)indoline (XI). A mixture of 10 g (0.02 mole of compound II (V) and 5.6 g (0.1 mole) of potassium hydroxide in 50 ml of diethylene glycol was boiled for 1 h. The mixture was cooled, washed with 100 ml of water, and extracted with benzene. The extract was dried over magnesium sulfate, the solvent was evaporated, and the residual oil was distilled under vacuum. Compound VIII, bp 210...215°C (0.015 mm Hg). Compound XI, bp 207...209°C (0.015 mm Hg).

1,2,3,3-Tetramethyl-5-(isoquinol-1-yl)indoline (IX). Compound VIII (6.5 g) was heated to 200°C and 10 g of a freshly prepared Raney nickel was added in small portions. A gas was thereby vigorously evolved. The reaction mixture was allowed to stand for 20...30 min at 230...250°C, then cooled, extracted with benzene, Raney nickel was filtered off, benzene was evaporated and the residual oil was distilled under vacuum at 197...200°C (0.015 mm Hg).

1,3,3-Trimethyl-2-methylene 5-(isoquinol-1-yl)indoline (X) was obtained in a similar way as compound V. The reaction product was extracted with chloroform, dried over magnesium sulfate, the solvent was distilled off, and the residual oil was distilled under vacuum at 185...188°C (0.015 mm Hg).

1,2,3,3-Tetramethyl-5-(quinol-2-yl)indoline (XIII). A mixture of 4.12 g (0.074 mole) of potassium hydroxide and 16.55 g (0.074 mole) of the sodium salt of m-nitrosulfonic acid in 100 ml of diethylene glycol was heated to 150°C. A 10 g portion (0.025 mole) of compound IV was added, and the mixture was boiled for 3 h. It was then cooled, 100 ml of water was added, and the mixture was extracted with benzene. The benzene extract was dried over magnesium sulfate, the solvent was evaporated, and the residual oil was distilled under vacuum at 208-210°C (0.015 mm Hg).

1,3,3-Trimethyl-2-methylene-5-(quinol-2-yl)indoline (XIV). A. The compound was obtained from compound XIII in a similar way as indoline X.

B. A mixture of 5 g (0.012 mole) of compound XII, 6.9 g (0.012 mole) of potassium hydroxide and 8.54 g (0.06 mole) of o-nitrophenol in 80 ml of butanol was boiled for 3 h. A 100 ml portion of water and 50 ml of methylene chloride were added to the cooled reaction mixture, the organic layer was separated, washed with an aqueous solution of ammonia and with water (3 × 50 ml), and dried over magnesium sulfate. The solvent was distilled off and the residual oil was distilled under vacuum at 180...183°C (0.05 mm Hg).

LITERATURE CITED

1. B. M. Stepanov, Introduction to the Chemistry and Technology of Organic Dyes [in Russian], Moscow (1984), p. 105.
2. L. N. Denisov and B. M. Uzhinov, Khim. Geterotsikl. Soedin., No. 6, 723 (1980).
3. The Chemistry of Synthetic Dyes [in Russian], Vol. 4, K. Venkataraman, editor, Leningrad (1975), p. 181.
4. A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 1, 3 (1974).
5. L. N. Babichenko, A. A. Tolmachev, T. S. Chmilenko, and A. K. Sheinkman, Khim. Geterotsikl. Sedin., No. 5, 709 (1988).
6. O. N. Chupakhin, V. N. Charushin, and E. O. Sidorov, Khim. Geterotsikl. Soedin., No. 5, 555 (1979).
7. A. A. Tolmachev and V. S. Tolmacheva, Khim. Geterotsikl. Soedin., No. 11, 1474 (1986).
8. A. K. Sheinkman, A. N. Prilenskaya, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 11, 1515 (1970).
9. A. K. Sheinkman, A. K. Tokarev, and S. I. Baranov, Khim. Geterotsikl. Soedin., No. 1, 82 (1971).
10. A. K. Sheinkman, S. G. Potashnikova, and S. I. Baranov, Khim. Geterotsikl. Soedin., No. 3, 562 (1969).
11. O. N. Chupakhin, V. A. Trofimov, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 12, 1674 (1970).
12. Kh. Ya. Lopatinskaya, Candidate of Chemical Sciences dissertation, Donetsk (1986).
13. Isoquinolines, G. Grethe, editor, Interscience (1981), p. 44.
14. Heterocyclic Compounds [Russian translation], Vol. 4, R. Elderfield, editor, Moscow (1955), p. 298.
15. M. D. Nair and I. S. R. Mehta, Indian J. Chem., 5, 123 (1967).