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Reactions of *N*- and *C*-Alkenylanilines: III.* Synthesis and Cyclization of Substituted 2-(1-Methyl-2-butenyl)anilines

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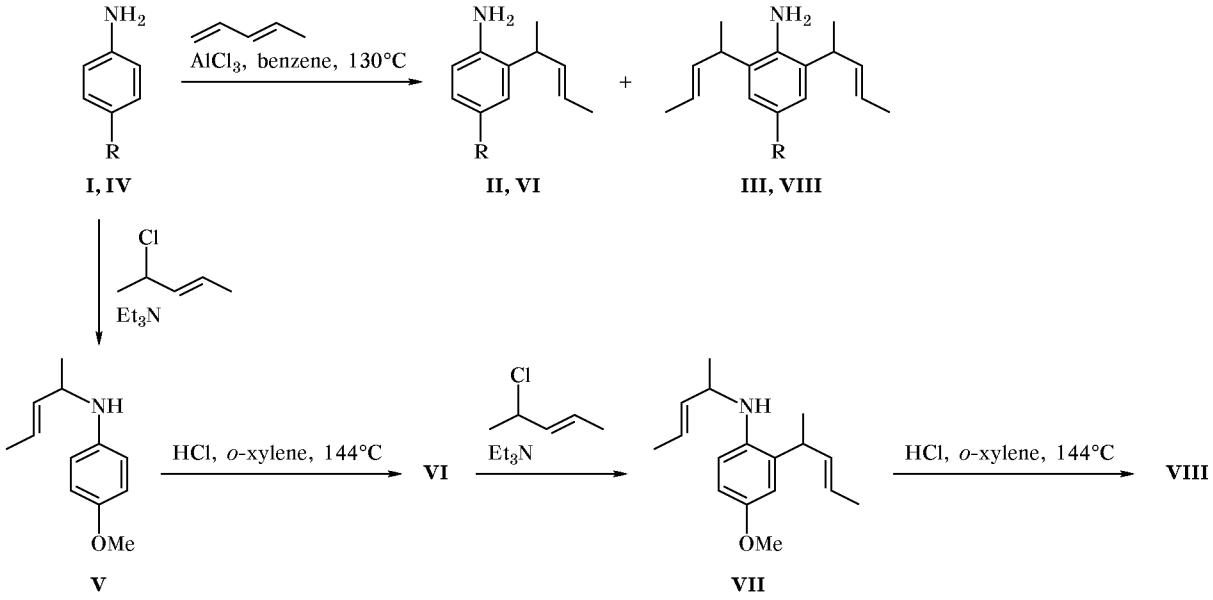
Abstract—Reactions of substituted 2-(1-methyl-2-butenyl)anilines with iodine result in cyclization and formation of 3-iodo-1,2,3,4-tetrahydroquinolines; *N*-methylsulfonyl-2-(1-methyl-2-butenyl)anilines give rise exclusively to the corresponding 2-(1-iodoethyl)-3-methyl-2,3-dihydroindoles.

2-(1-Methyl-2-butenyl)aniline derivatives, which are readily obtained from commercially available piperylene [2], exhibit biological activity [3] and are used in the synthesis of heterocyclic compounds [4]. Depending on the reagent nature, their cyclizations give dihydroindoles and aminoindans [4], mixtures of dihydroindoles with tetrahydroquinolines [5], or indoles. In continuation of our studies on heterocyclization of alkenylanilines [5], we have synthesized substituted 2-(1-methyl-2-butenyl)anilines and examined their reactions with iodine I_2.

By alkenylation of *p*-toluidine (**I**) with piperylene in benzene in the presence of $AlCl_3$ at 130°C we obtained products **II** and **III** (Scheme 1). The reaction

Scheme 1.



I, **II**, **III**, R = Me; **IV**, **VI**, **VIII**, R = OMe.

* For communication II, see [1].

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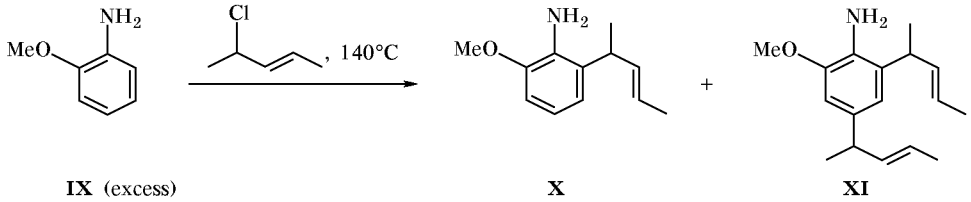
Scheme 2.



IX (excess) **X** **XI**

of *p*-anisidine (**IV**) with 2-chloro-3-pentene in triethylamine gives *N*-(1-methyl-2-butenyl)-4-methoxyaniline (**V**) [6] which undergoes Claisen rearrangement to aniline **VI** [6]. Repeated alkylation of amine **VI** with 2-chloro-3-pentene in triethylamine [6] yields N-substituted derivative **VII**. The Claisen rearrangement of the corresponding hydrochloride in *o*-xylene at 144°C leads to formation of compound **VIII** (Scheme 1).

2-Chloro-3-pentene reacts with excess *o*-anisidine (**IX**) to give both mono- and dialkylated products **X** and **XI** (Scheme 2). Due to the presence of a methoxy group in the *ortho* position, the reaction time and temperature (160°C) strongly increase, as compared to aniline [2] and alkyl-substituted anilines. Products **II**, **III**, **VI**–**VIII**, **X**, and **XI** were reported by us previously [6–9].

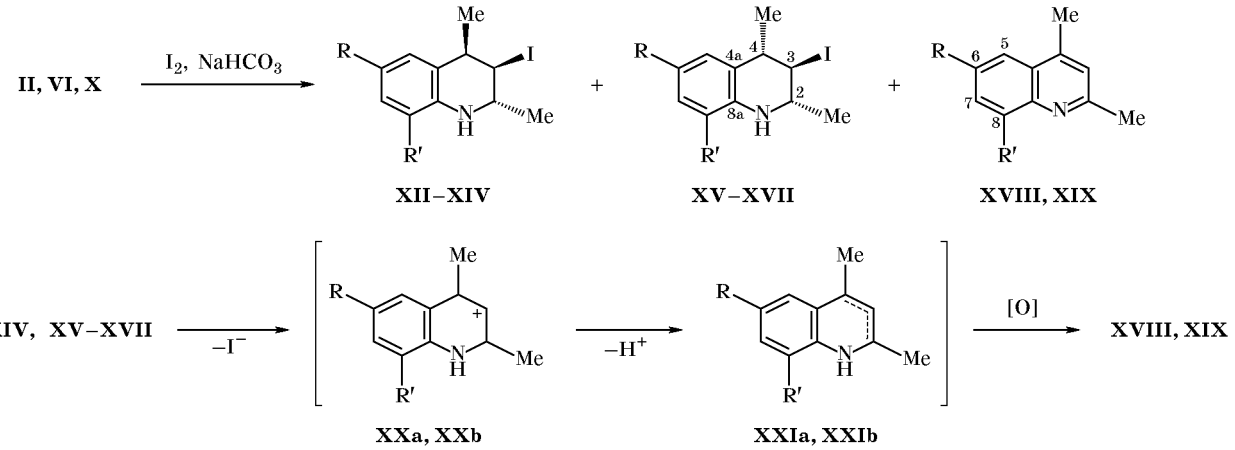
By reactions of amines **II**, **VI**, and **X** with iodine [10] we obtained stereoisomeric 3-iodo-1,2,3,4-tetrahydroquinolines **XII**–**XVII** (Scheme 3). The reactions were carried out in various solvents, but in all cases isomers **XII**–**XIV** were the major products (Table 1). From amines **II** and **VI** quinolines **XVIII** and **XIX** were obtained. Probably, the aromatization of **XII**–**XVII** involves formation of intermediate ion **XX**; elimination of a proton from the latter yields dihydroquinoline **XXI** [11] which is sensitive to oxidants.

The structure of the resulting tetrahydroquinolines suggests that the process occurs only as 6-*endo*-cyclization [12] of two possible complexes **A** and **B** (Scheme 4) in which intramolecular nucleophilic attack by the nitrogen atom is directed exclusively at the C^3 atom of the alkenyl fragment.

Under analogous conditions, the reactions of anilines **III** and **VIII** with iodine gave complex mixtures of products. Judging by the ^{13}C NMR spectra, the major products were isomers **XXIIa** (**XXIIb**) and **XXIIIa** (**XXIIIb**) (Scheme 5). Presumably, the formation of compounds with *cis*-arrangement of the 4-methyl group and 3-iodine atom is preferred. We failed to isolate pure isomers, and their structure was assigned on the basis of characteristic signals from C^2 at δ_C 50.4 and 50.8 ppm and C^4 at 36.6 and 37.0 ppm, by analogy with the ^{13}C NMR spectra of tetrahydroquinolines **XII**–**XIV**.

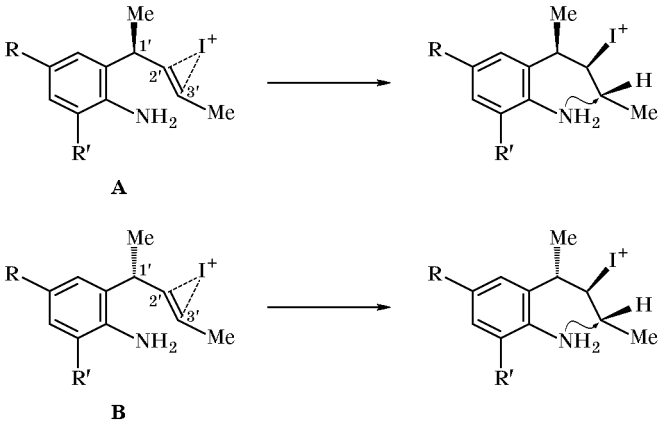
Treatment of amines **II** and **VI** with methanesulfonyl chloride gave sulfonamides **XXIV** and **XXV**; the latter reacted with iodine to afford dihydroindoles **XXVI**–**XXIX** among which *trans* isomers **XXVI** and

Scheme 3.



II, **XII**, **XV**, **XVIII**, **XXa**, **XXIa**, R = Me, R′ = H; **VI**, **XIII**, **XVI**, **XIX**, **XXb**, **XXIb**, R = OMe, R′= H; **X**, **XIV**, **XVII**, R = H, R′ = OMe.

Scheme 4.

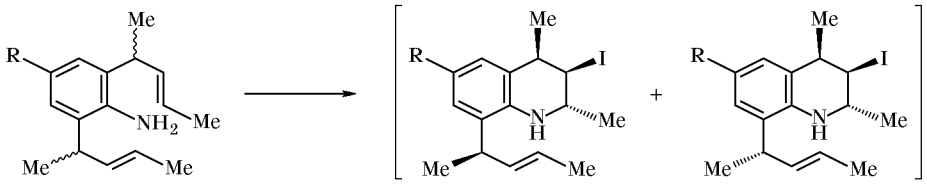


A

B

R = Me, R′ = H; R = OMe, R′ = H; R = H, R′ = OMe.

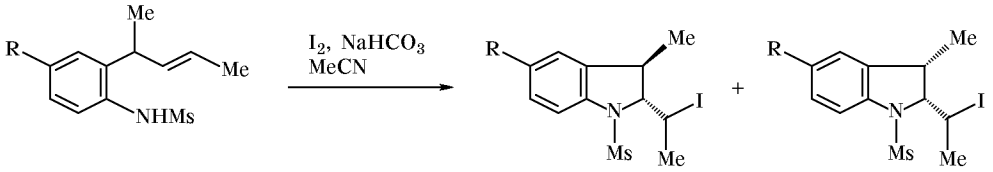
Scheme 5.



III, VIII **XXIIa, XXIIb** **XXIIIa, XXIIIb**

XXII, **XXIII**, R = Me (**a**), R = OMe (**b**).

Scheme 6.



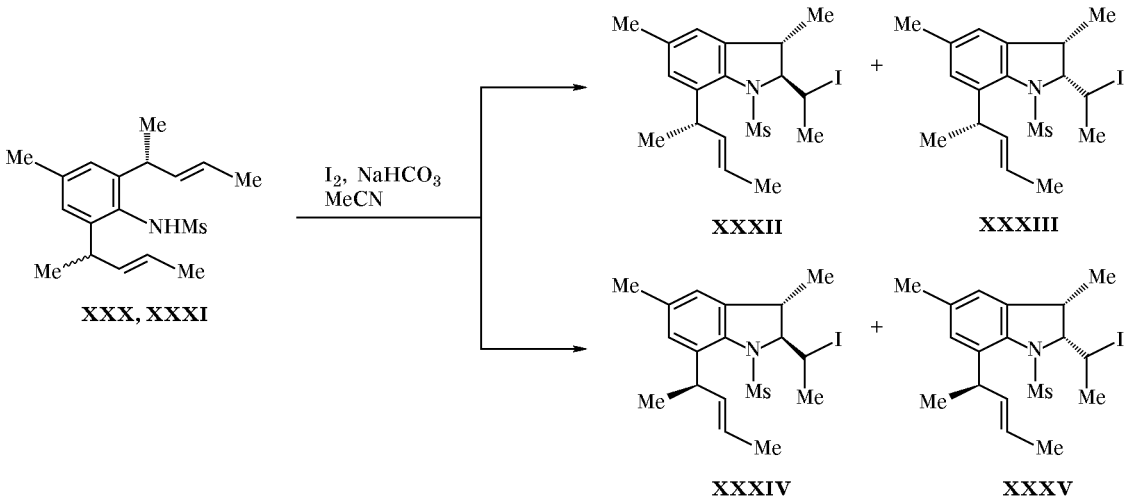
XXIV, XXV **XXVI, XXVII** **XXVIII, XXIX**

XXIV, **XXVI**, **XXVIII**, R = Me; **XXV**, **XXVII**, **XXIX**, R = OMe.

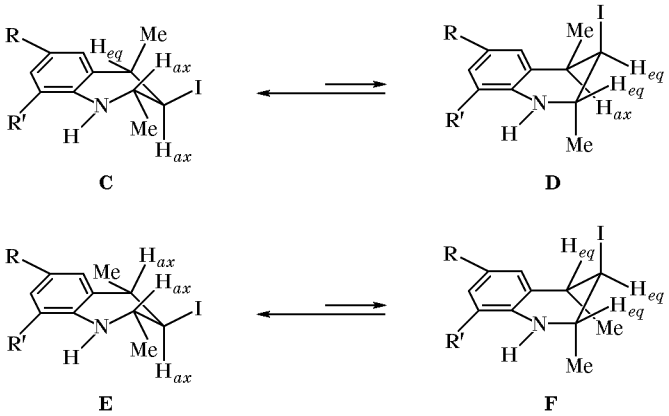
XXVII prevailed (Scheme 6). Analogous reaction with iodine of enantiomeric methanesulfonamides **XXX** and **XXXI** resulted in formation of four pairs of diastereoisomeric dihydroindoles **XXXII**–**XXXV** (Scheme 7).

The structure of the products was unambiguously proved by the data of elemental analysis and ^{1}H and ^{13}C NMR spectroscopy. The configuration of isomers **XII**–**XVII** was established on the basis of the NMR spectra. The 4-H and 2-H signals appear in the ^{1}H NMR spectra as doublets of quartets, and the 3-H signal is a doublet of doublets. The larger coupling constants for the 3-H signal of **XV**–**XVII** (10.4 and 10.3 Hz) indicates a double axial–axial interaction, i.e., these compounds are diastereoisomers with *trans,trans* arrangement of the substituents at C^2, C^3, and C^4, and the conformational equilibrium is displaced toward conformer **E** (Scheme 8). Isomers **XII**–**XIV** are characterized by different orientation of the 4-methyl group. The chemical shift of the 4-CH_3 protons changes from δ 1.69–1.72 ppm for equatorial orientation to 1.41–1.44 ppm for axial orientation. In going from the equatorial to axial isomer, the 3-H–4-H coupling constant decreases from 10.4 to

Scheme 7.



Scheme 8.



3.9 Hz, while the coupling constant between 3-H and 2-H remains large (J = 7.4–7.8 Hz); these data suggest the occurrence of axial–axial interactions. Hence compounds **XII**–**XIV** are diastereoisomers with *trans,cis* arrangement of the substituents at C^2, C^3, and C^4, and the conformational equilibrium is displaced toward conformer (**C**) (Scheme 8) [13].

The methyl groups on C^2 and C^4 are characterized by different geminal coupling constants with 2-H and 4-H, respectively: $J(2\text{-H}, 2\text{-CH}_3)$ = 6.3–6.4 Hz and $J(4\text{-H}, 4\text{-CH}_3)$ = 7.3–7.4 Hz. The signals were reliably assigned on the basis of the C–H correlation spectrum, where the chemical shifts of C^2 and C^4 differ considerably from each other. In the ^{13}C NMR spectra of these compounds the greatest change of chemical shift is observed for C^4: the C^4 signal of stereoisomers **XII**–**XIV** is located in a stronger field, δ_C 36–37 ppm (conformer **C**), relative to the corresponding signal of isomers **XV**–**XVII**, δ_C 42–43 ppm (conformer **D**). This is consistent with the known data [14] on the upfield shift of signals due to 1,2-*cis*-interaction of substituents at such carbon atoms.

The iodine atom in position *3* and 2-methyl group in streoisomeric quinolines **XII**–**XIV** and **XV**–**XVII** are arranged *trans*. Presumably, the difference in the chemical shifts of C^2 is determined by orientation of the methyl group on C^4, other conditions being equal. It is known that equatorial substituents in cyclohexanes exert a stronger deshielding effect on the α- and β-carbon atoms than do the corresponding axial substituents. Therefore, the chemical shifts of C^4 and C^3 in conformer **C**, where the 4-CH_3 group occupies the axial position, are smaller than those found for conformer **E** with equatorial 4-methyl group. It is also known that the presence of an axial substituent in cyclohexane induces an upfield shift of the γ-carbon signal [15]. The C^2 and C^4 signals of 2,4-dimethyltetrahydroquinolines with *trans* arrangement of the

methyl groups appear in a stronger field relative to those of the *cis* isomer [5, 16]. Therefore, the C^2 signal of stereoisomers **XII**–**XIV** (conformer **C**) with *trans* arrangement of the 2-Me and 4-Me groups is observed at δ_C 50–51 ppm, whereas the corresponding signal of isomers **XV**–**XVII** (conformer **E**) is located in a weaker field (δ_C 53–54 ppm).

In the ^{1}H NMR spectra of *cis*-dihydroindoles **XXVIII** and **XXIX** the 2-H signal appears as a doublet of doublets at δ 4.7 ppm ($J_{2,3}$ = 8.4, $J_{2,1'}$ = 4.0 Hz). The large value of the first coupling constant indicates *cis* arrangement of 2-H and 3-H. The signal from 3-H is observed at δ 3.7 ppm as a doublet of quartets ($J_{3,2}$ = 8.4, $J_{3,3\text{-Me}}$ = 7.3 Hz). In the spectra of *trans*-isomers **XXVI** and **XXVII** the 2-H signal shifts upfield (Δδ 1.3 ppm) due to *cis*-effect of the 3-methyl group and is observed as a doublet at δ 3.4 ppm ($J_{2,3}$ = 3.0, $J_{2,1'}$ = 5.4 Hz). The low couling constant is indicative of *trans* arrangement of the 2-H and 3-H protons, their equatorial orientation, and shift of the conformational equilibrium toward conformer with axial substituents. The 3-H signal (due to *cis*-effect of the 1-iodoethyl group) appears in a stronger field (δ 3.3 ppm) as a doublet of quartets ($J_{3,2}$ = 3.0, $J_{3,2\text{-Me}}$ = 7.2 Hz).

The *trans* isomers of methanesulfonamides **XXVI** and **XXVII** are characterized by more downfield signals from C^2 and C^3, as compared to *cis* isomers **XXVIII** and **XXIX** in which *cis*-interaction of the substituents exists.

The positions and splitting modes of the 2-H signal of dihydroindoles **XXVIII** and **XXIX** and of the 3-H signal of quinolines **XII**–**XIV** are similar; therefore, in order to perform a more reliable structural assignment, quinoline **XII** was treated with methanesulfonyl chloride with a view to obtain compound **XXXVI** and compare its spectral parameters with those of dihydroindole **XXVIII**. The reaction of **XII** with $MeSO_2Cl$ was carried out in pyridine (Scheme 9). It resulted in formation of a mixture of 1-methylsulfonyl-2,4,6-trimethyl-1,2,3,4-tetrahydroquinoline (**XXXVI**) and 1-methylsulfonyl-2,4,6-trimethyl-1,2-dihydroquinoline (**XXXVII**), which were identified without isolation from the mixture.

Scheme 9.

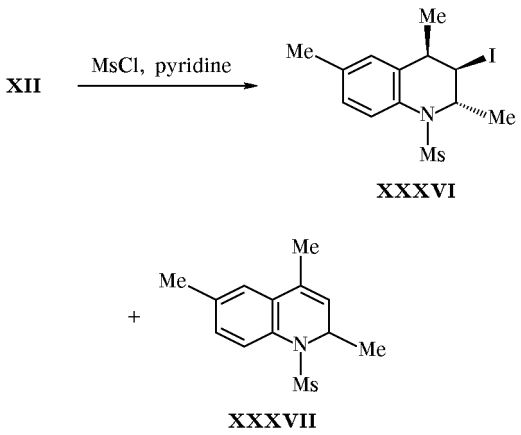


Table 1. Reactions of compounds **II**, **IV**, and **X** with iodine in the presence of $NaHCO_3$

Initial comp. no.	Solvent	Time, min	ε	*B*[a]	Molar ratio **XII**:**XV**
II	CH_2Cl_2	24	9.08	23	3:2
II	C_6H_6	48	2.28	48	4:1
II	$ClCH_2CH_2Cl$	24	10.36	40	4:3
II	CCl_4	72	2.23	0	3:1
II	MeCN	108	37.4	160	2:1
VI	$ClCH_2CH_2Cl$	72	10.36	40	[b]
X	CH_2Cl_2	45	9.08	23	[c]

[a] *B* is the solvent nucleophilicity.
[b] Molar ratio **XIII**:**XVI** = 4:3.
[c] Molar ratio **XIV**:**XVIII** = 4:1.

The ^{1}H NMR spectrum of quinoline mixture **XXXVI**/**XXXVII**, recorded by the double-resonance technique, contained 5 groups of signals in the region δ 3.7–5.8 ppm. The 2-H, 3-H, and 4-H signals of **XXXVI** were located at δ 4.1, 4.55, and 3.7 ppm, respectively. The signal from 3-H of dihydroquinoline **XXXVII** appeared at δ 5.8 ppm as a doublet (J = 5.6 Hz), and the 2-H signal was observed as a doublet of quartets at δ 4.75 ppm (J_1 = 5.6, J_2 = 7.2 Hz).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal reference. The IR spectra were measured on a UR-20 spectrometer in mineral oil. The progress of reactions was monitored by TLC on Silufol UV-254 plates; development with iodine vapor. The yields, melting points, R_f values, and elemental analyses of compounds **XII**–**XIX** and **XXIV**–**XXXI** are given in Table 2.

Reactions of compounds II, III, and VI with methanesulfonyl chloride. Methanesulfonyl chloride, 0.6 ml, was added dropwise to a solution of 3 mmol of aniline **II**, **III**, or **VI** in 4 ml of pyridine. The mixture was kept for 24 h at room temperature, 20 ml of

Table 2. Yields, melting points, R_f values, and elemental analyses of compounds **XII**–**XIX** and **XXIV**–**XXXI**

Comp. no.	Yield, %	R_f or mp, °C	Found, %					Formula	Calculated, %				
			C	H	I	N	S		C	H	I	N	S
XII	37	0.4[a]	47.67	4.86	41.87	4.92		$C_{12}H_{16}IN$	48.00	5.33	42.00	4.67	
XIII	33	0.4[a]	44.98	4.71	39.58	4.14		$C_{12}H_{16}INO$	45.44	5.08	40.01	4.42	
XIV	53	110[b]	45.07	4.81	39.63	4.02		$C_{12}H_{16}INO$	45.44	5.08	40.01	4.42	
XV	30	0.5[a]	47.82	5.40	40.00	4.92		$C_{12}H_{16}IN$	48.00	5.33	42.00	4.67	
XVI	29	0.4[a]	44.98	4.65	39.58	4.42		$C_{12}H_{16}INO$	45.44	5.08	40.01	4.42	
XVII	12	0.4[a]	44.98	4.65	39.58	4.42		$C_{12}H_{16}INO$	45.44	5.08	40.01	4.42	
XVIII	20	125[b]	83.85	7.32		7.78		$C_{12}H_{13}N$	84.21	7.60		8.19	
XIX	26	0.3[c]	76.77	6.64		7.11		$C_{12}H_{13}NO$	76.98	7.00		7.48	
XXIV	91	0.5[c]	61.24	7.27		5.15	12.25	$C_{13}H_{19}NO_2S$	61.63	7.56		5.53	12.64
XXV	88	0.6[c]	57.54	6.74		4.85	11.51	$C_{13}H_{19}NO_3S$	57.97	7.11		5.20	11.90
XXVI	42	119–120[d]	40.87	4.33	32.98	3.24	8.03	$C_{13}H_{18}INO_2S$	41.17	4.78	33.46	3.69	8.45
XXVII	43	116–117[d]	39.15	4.21	31.73	3.08	8.11	$C_{13}H_{18}INO_3S$	39.50	4.59	32.11	3.54	7.69
XXVIII	12	121–122[d]	40.87	4.33	33.07	3.24	8.15	$C_{13}H_{18}INO_2S$	41.17	4.78	33.46	3.69	8.45
XXIX	11	0.4[c]	39.16	4.18	31.86	3.32	7.94	$C_{13}H_{18}INO_3S$	39.50	4.59	32.11	3.54	7.69
XXX, **XXXI**	90		67.32	8.47		4.01	9.62	$C_{18}H_{27}NO_2S$	67.32	8.24		4.36	9.97

[a] Eluent CCl_4.
[b] From $CHCl_3$.
[c] Eluent $CHCl_3$.
[d] From 2-propanol.

water was added, and the mixture was stirred for 30 min and treated with 40 ml of chloroform. The organic phase was separated, washed with 20 ml of a 10% aqueous solution of $NaHCO_3$ and 20 ml of water, and dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the residue was passed through a thin layer of silica gel usig carbon tetrachloride as eluent to isolate a mixture of stereoisomeric *N*-methylsulfonyl-2,6-bis(1-methyl-2-butenyl)-4-methylanilines **XXVIII** and **XXIX** as a light yellow oily substance.

Cyclization of alkenylanilines II, VI, and X. A mixture of 10 mmol of aniline **II**, **VI**, or **X**, 1.5 g of $NaHCO_3$, and 0.51 g of I_2 in 10 ml of appropriate solvent (Table 1) was shaken for 24–130 h at 20°C, the progress of the reaction being monitored by TLC (eluent hexane–methanol, 9.8 : 0.2). When the reaction was complete, the mixture was diluted with 50 ml of methylene chloride, and the precipitate was filtered off and washed with methylene chloride (3×10 ml). The organic phase was treated with a 5% aqueous solution of $Na_2S_2O_3$ (3×10 ml) and water (20 ml), dried over Na_2SO_4, and evaporated under reduced pressure. Carbon tetrachloride was added to the residue, and the crystalline product (quinoline **XVIII** or **XX**) was filtered off, washed with CCl_4, and dried under reduced pressure. The filtrate was evaporated to a minimal volume, and the residue was subjected to chromatography on silica gel (10 g, eluent CCl_4) to isolate compounds **XII**–**XVII**.

The cyclization of *N*-methylsulfonyl derivatives XXIV and XXV was performed in a similar way. After treatment with $Na_2S_2O_3$ and drying over Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was recrystallized from 8 ml of isopropyl alcohol to isolate dihydroindole **XXVI** or **XXVII**. The mother liquor was evaporated under reduced pressure, the residue was dissolved in 1 ml of methylene chloride, and the solution was applied to a column charged with 3 g of silica gel. Using carbon tetrachloride as eluent, *cis*-dihydroindole **XXVIII** or **XXIX** was isolated.

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