

Synthesis of Indolines from *N*-Allylarylamines

Krzysztof Krowicki (1), Nicole Paillous, Monique Rivière and Armand Lattes

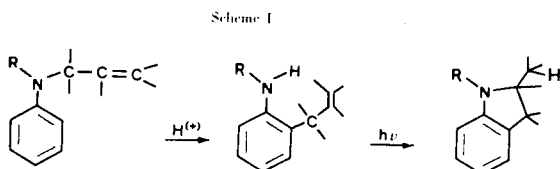
Laboratoire des Composés Azotés Polyfonctionnels, ERA au CNRS No. 264,  
Université Paul Sabatier, 118, route de Narbonne, 31077 Toulouse Cedex, France

Received September 19, 1975

A novel method of synthesis of nitrogen heterocycles is described. The acidic rearrangement of *N*-allylanilines gives 2-allylanilines which lead to indolines by photocyclization.

*J. Heterocyclic Chem.*, 13, 555 (1976).

The chemical and photochemical reactivity of allylanilines (2-5) led us to improve a new method to synthesize nitrogen heterocycles from *N*-allyl aromatic amines.

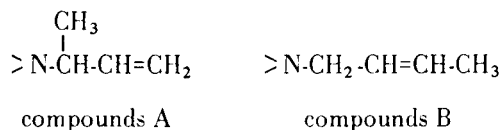


Some examples of allyl group migrations in amines, initiated by Lewis or proton acids have been reported recently. Hurd and Jenkins (6), and Schmid and coworkers (7) have prepared *ortho*-allylanilines from *N*-allylanilines using zinc chloride as a catalyst. A similar reaction was suggested by Bader and coworkers (8) for the formation of indoles from *N*-allylanilines.

In preliminary work (3,5) we reported that the thermal Claisen rearrangement of *N*-allylanilines did not occur. However, using a water-ethanol mixture as the solvent, anilines **1**, **2** and **3** (Scheme II) underwent such a rearrangement by refluxing with hydrochloric acid. In

compound **1** a modification of the ethylenic moiety was observed. This result agrees with the observations of Schmid (7) who suggests, that for reactions catalyzed by zinc chloride, a competition between the two following processes occurs: a concerted mechanism [3s, 3s] with inversion of the allyl group and an ion-pair mechanism with no inversion of the allyl group.

In order to know the parts played by the aromatic ring and by the ethylenic side chain, we studied the rearrangement of several compounds with two unsaturated chains.



a) Compounds A (**1,4,5,6,7,8**).

Using an ethanol-water mixture as the solvent and hydrochloric acid as the catalyst, the allylamines A rearranged easily into *ortho*-allylic compounds with modification of the ethylenic chain.

b) Compounds B (**9,10,11**).

For these compounds, more energetic reaction conditions were used; phosphoric acid at 150°. This acid had been used by Bader and coworkers for the synthesis of indolines (8,9). After heating for forty minutes, the yields of the *ortho*-substituted compounds, showing rearrangement of the ethylenic moiety were about 40% (Table II); other products were also obtained arising from secondary reactions of the *ortho*-substituted compounds (cyclizations or double bond migrations and polymerizations). The relative amounts of reaction products are given in Scheme III (glc, column UCON POLAR). Our results show that for the open chain compounds the reaction occurs in all cases with inversion of the allyl group.

By studying the rearrangement reactions of allylamines

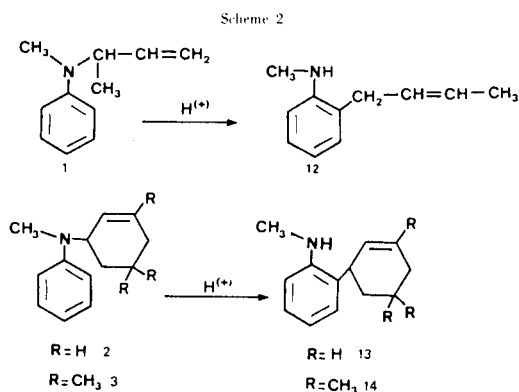
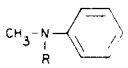
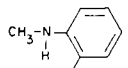
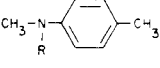
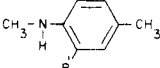
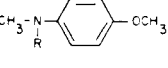
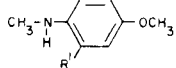
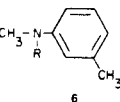
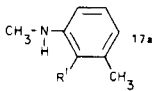
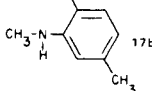
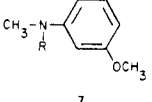
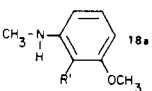
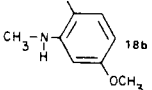
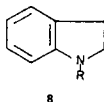
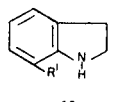


Table I

Rearrangement of *N*-Methyl-*N*-(1-methyl-2-propenyl)anilines

Starting amine (a)	Product (b)	Ir (cm <sup>-1</sup> )		Nmr (c) (δ ppm)			yield %
		ν NH	ν C=C	>C=C-CH <sub>3</sub>	-CH=CH-	aromatic H	
		3435	1670	1.65	5.45	6.70	95
		3430	1670	1.71	5.55	6.84	95
		3420	1670	1.73	5.53	6.69	92
		3420	1670	1.68	5.50	6.80	45
							45
		3420	1660	1.65	5.45	6.33 (2H) 7.13 (1H)	24
			1655	1.71	5.50	6.21 (2H) 6.91 (1H)	56
		3380	1665	1.70	5.53	6.86	90

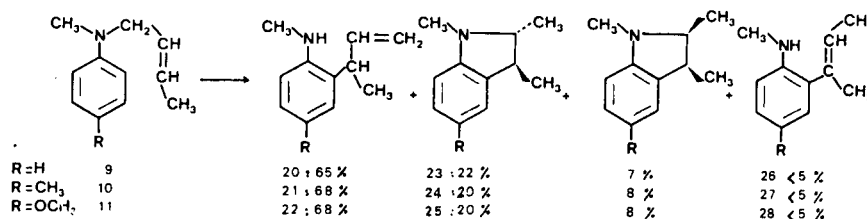
(a) R =  $\begin{array}{c} \text{-CH-CH=CH}_2 \\ | \\ \text{CH}_3 \end{array}$  (b) R' = CH<sub>2</sub>-CH=CH-CH<sub>3</sub> (c) Varian A 60, TMS as the reference and deuteriochloroform as the solvent.

we obtained a good synthetic procedure for 2-allylarlyl-*N*-methyl-2-ethylindoline. More recently, Schmid and coworkers observed an analogous reaction from *N*-methyl-2-allylaniline (10). As the yield of this heterocyclization was high, we extended it to all the compounds previously prepared.

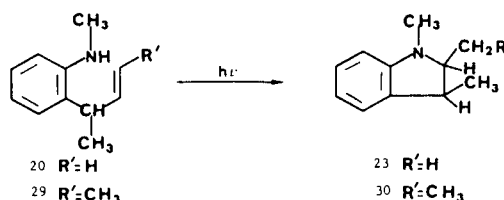
We discovered for the first time in 1971 that *N*-methyl-2-(2'-butenyl)aniline cyclized photochemically to form

*N*-methyl-2-ethylindoline. More recently, Schmid and coworkers observed an analogous reaction from *N*-methyl-2-allylaniline (10). As the yield of this heterocyclization was high, we extended it to all the compounds previously prepared.

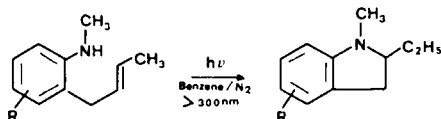
Scheme 3



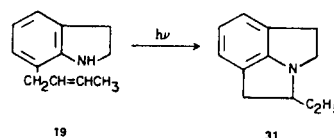
Irradiation (carried out in a nitrogen atmosphere) of *meta* or *para*-substituted *N*-methyl-2-(2'-butenyl)anilines (*E/Z* = 90/10) was performed in a benzene solution with a medium pressure mercury lamp in a pyrex vessel. The corresponding indolines were obtained in all cases with good yields as shown in Table III. The reaction is regioselective and provides preferentially a five membered ring. The isomeric 1,2-dimethyltetrahydroquinolines were only isolated in low quantities (<5%). In some cases, the *N*-methyl-2-(1'-butenyl)anilines resulting from a double bond migration were also obtained in a very poor yield.



to tricyclic compounds. Under the same conditions as above, 7-(2-but-1-enyl)indoline (19) cyclized photochemically to indoline (31). The mechanism we propose for these



The stereoselectivity of this reaction has also been investigated. By irradiating, the *N*-methyl-2-(1'-methyl-2'-propenyl)aniline (20), or *N*-methyl-2-(1'-methyl-2'-butenyl)aniline (29), two diastereoisomeric indolines 23 were obtained. In both cases, the *cis/trans* ratio was 1/3. The determination of the configuration was done by nmr on the basis of the coupling constants of the protons of the cycle ( $J_{trans} > J_{cis}$ ) (11). This method can also lead

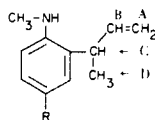


photocyclizations involves for a first step an energy transfer from the excited aniline to the double bond. The cyclization might occur in a following step. This hypothesis is based on the fact that the irradiation of the *N*-methyl-2-(2'-butenyl)aniline (*Z*) induced simultaneously a photoisomerization *Z* → *E* and a photocyclization, although the alkene moiety was not directly excited.

In conclusion, the two reactions in sequence which we propose here, appear like a very simple and suitable method for the preparation of indoline compounds.

Table II

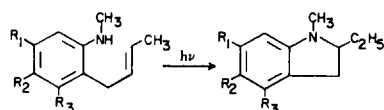
## Physical Data of



Starting amine	R	Product	Ir (cm <sup>-1</sup> )		Nmr (a) (δ ppm)					Yields
			ν NH	ν C=C	δ A (m)	δ B (m)	δ C (m)	δ D (d)	δ aromatic (m)	
9	H	20	3418	1632	5.1	6	3.4	1.41	7	45%
10	CH <sub>3</sub>	21	3415	1635	5.1	6	3.4	1.40	6.85	48%
11	OCH <sub>3</sub>	22	3410	1632	5.1	6	3.45	1.40	6.7	48%

(a) Varian A 60, TMS as the reference and deuteriochloroform as the solvent.

Table III



R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Reaction time (hours)	Yield (%)	Conversion (%)	Formula	Anal. C	Calcd./Found H	N	Nmr (b) (δ ppm)
H	H	H	3.5	85	88	C <sub>11</sub> H <sub>15</sub> N	81.94 82.09	9.38 9.54	8.69 8.79	0.9 (t, 3H) (c) 1.2-2 (m, 3H) 2.59 (s, 3H) 2.4-3.4 (m, 3H) 6.13-7.1 (m, 4H)
H	CH <sub>3</sub>	H	5.5	95.5	92	C <sub>12</sub> H <sub>17</sub> N	82.23 92.23	9.78 9.93	7.99 7.79	0.96 (t, 3H) 1.2-2.1 (m, 2H) 2.25 (s, 3H) 2.68 (s, 3H) 2.5-3.35 (m, 3H) 6.25-6.5 (1H) and 6.75-7 (2H) (m)
H CH <sub>3</sub>	H H	CH <sub>3</sub> H	5.5	77.6	90	C <sub>12</sub> H <sub>17</sub> N	82.23 82.12	9.78 9.83	7.99 8.05	0.98 (t, 3H) 1.25-2 (m, 2H) 2.28 and 2.38 (2s, 3H) 2.78 (s, 3H) 2.5-3.5 (m, 3H) 6.27-6.66 (2H) and 6.93-7.3 (1H) (m)
H	OCH <sub>3</sub>	H	5.5	89.4	95	C <sub>12</sub> H <sub>17</sub> NO	75.35 75.51	8.96 8.98	7.32 7.33	0.96 (t, 3H) 1.2-2.1 (m, 2H) 2.68 (s, 3H) 2.5-3.3 (m, 3H) 3.73 (s, 3H) 6.2-6.85 (m, 3H)
H	H	OCH <sub>3</sub>	6	77	70	C <sub>12</sub> H <sub>17</sub> NO	75.35 75.55	8.96 9.00	7.32 7.40	0.96 (t, 3H) 1.35-2.1 (m, 2H) 2.7 (s, 3H) 2.3-3.5 (m, 3H) 3.75 (s, 3H) 6.1-6.31 (2H) and 6.85-7.33 (1H) (m)
CH <sub>3</sub> O	H	H	6	71.5	70	C <sub>12</sub> H <sub>17</sub> NO	75.35 75.40	8.96 9.01	7.32 7.38	0.94 (t, 3H) 2.7 (s, 3H) 1.2-2.0 (m, 2H) 2.4-3.5 (m, 3H) 3.75 (s, 3H) 5.9-6.25 (2H) 6.28-7 (1H) (m)

(a) Yields determined by vpc with respect to the unreacted starting material. (b) Deuteriochloroform solution. (c) Tetrachloride solution.

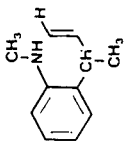
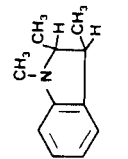
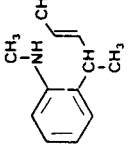
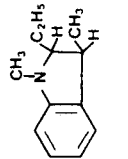
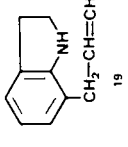
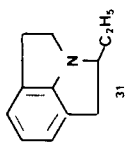
### EXPERIMENTAL

The *N*-allylamines were prepared following literature procedures (12).

Reactions with Hydrochloric Acid in Ethanol-Water Mixture.

A mixture of *N*-allylamines (20 mmoles), concentrated hydrochloric acid (1.7 ml.) and ethanol (20 ml.) was heated under reflux for 12 hours. After neutralization and extraction with ether, the solvent was evaporated and the pure rearranged amines were isolated by vacuum distillation or column chromatography (silica gel-benzene). Preparative separation of **17a** and **17b** was not

Table IV  
Preparation of 1,2,3-Trisubstituted Indolines and 2-Ethylpyrrolino[3,2,1-*hi*]indoline (31).

Starting Amines	Products	Reaction time (hours)	Yield (a) (%)	Conversion (%)	Formula	Anal. C	Anal. N	Calcd./Found N	Nmr (b) ( $\delta$ ppm)
		1.5	92	50	$C_{11}H_{15}N$	81.94 82.07	9.38 9.48	8.69 8.45	<i>trans</i> (c) 1.18-1.36 (m, 6H), 2.61 (s, 3H), 2.5-2.85 (m, 2H) $J_{2,3} = 10.0 \pm$ 0.2 Hz, 6.2-7.1 (m, 4H)
		2	65	71	$C_{12}H_{17}N$	82.23 82.36	9.78 9.89	7.99 8.06	<i>cis</i> 1.06 and 1.11 (2d, 6H), 2.6 (s, 3H), 2.73-3.6 (m, 2H) $J_{2,3} = 8 \pm$ 0.2 Hz, 6.16-7.15 (m, 4H) <i>trans</i> 0.98 (t, 3H), 1.5-2.0 (m, 2H), 1.33 (d, 3H), 2.74 (s, 3H) 2.8- 3.1 (m, 2H) $J_{2,3} = 9.2 \pm 0.2$ Hz, 6.4-7.3 (m, 4H)
		4	72	78	$C_{12}H_{15}N$	83.19 83.50	8.73 8.77	8.08 7.78	<i>cis</i> 0.95 (t, 3H), 1.5-2.0 (m, 2H), 1.16 (d, 3H), 2.8-3.1 (m, 2H) $J_{2,3} =$ 7.6 + 0.2 Hz, 2.74 (s, 3H), 6.4-7.3 (m, 4H) <i>trans</i> 1.2 (t, 3H), 1.5-2.0 (m, 2H), 2.6-3.9 (m, 7H), 6.4-7.0 (m, 3H)

(a) Yields determined by vpc with respect to the unreacted starting material. (b) Deuteriochloroform solution. (c) Data from reference 11, tetrachloride solution.

possible. The composition of the mixture was determined by gas chromatography (UCON POLAR). Structures of **18a** and **18b** were determined by the Europium effect on the nmr spectra [Eu(DPM)<sub>3</sub>]. The physical data concerning *ortho*-allylamines are summarized in Table I. The amines are a mixture of the E and Z isomers (E/Z = 90/10).

Reactions with Phosphoric Acid at 150°.

A mixture of *N*-allylamines (20 mmoles) and phosphoric acid (9 g.) was heated (150°) for forty minutes under a nitrogen stream. The reaction mixture was worked up in the usual way and the products were separated by column chromatography (silica gel) with chloroform/petroleum ether (4/1) as the solvent. Yields and spectral properties are given in Table II. Isomeric indolines could not be separated. Their structures were determined by comparison with samples of *cis* and *trans* compounds previously described by us (11).

All CHN analyses agree with the proposed structures.

Irradiation of the *N*-Methyl-2-(2'-butenyl)anilines.

A solution of the *N*-methyl-2-(2'-butenyl)anilines (0,8 g., 500 ml.) in benzene was irradiated with a 450 watt medium pressure mercury lamp at room temperature, in a pyrex vessel for an average of 4-6 hours. Nitrogen was continuously bubbled through it during the course of the reaction. (If all of the oxygen had not been thoroughly displaced by this nitrogen, we find a small amount of indole present). The solvent was removed *in vacuo* and the residue purified by silica gel chromatography using benzene or a mixture of benzene with 1-10% of methanol as eluent. The *cis* and *trans*-indolines **23** or **30** were separated by preparative vpc on a UCON POLAR column at 6% of potassium hydroxide, 20' x 3/8", chromosorb 45/60 W, at 130°.

Yields and spectral properties of indolines are given in Tables III and IV.

Acknowledgement.

The authors wish to thank the "delegation generale à la recherche scientifique et technique" for partial support of this work (73.7.1718).

#### REFERENCES AND NOTES

- (1) Post Doctoral Fellow. Present address: Institute of Organic Chemistry Polish Academy of Sciences, Warszawa, ul Kasprzaka 44/52.
- (2) M. Riviere, Doctorat es Sciences, No. 391, Toulouse, (1970).
- (3) G. de Saqui-Sannes, M. Riviere and A. Lattes, *Bull. Soc. Pharm. Ouest.*, **16**, 165 (1975).
- (4) N. Paillous and A. Lattes, *Tetrahedron Letters*, 4945 (1971).
- (5) G. de Saqui-Sannes, M. Riviere and A. Lattes, *ibid.*, 2073 (1974).
- (6) C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957).
- (7) M. Schmid, H. J. Hansen and H. Schmid, *Helv. Chim. Acta.*, **56**, 105 (1973).
- (8) R. Bader, R. J. Bridgwater and P. R. Freeman, *J. Am. Chem. Soc.*, **83**, 3319 (1961).
- (9) J. E. Hyre and R. Bader, *ibid.*, **80**, 437 (1958).
- (10) U. Koch-Pomeranz, H. J. Hansen, H. Schmid, *Helv. Chim. Acta.*, **58**, 178 (1975).
- (11) M. Riviere, N. Paillous, A. Lattes, *Bull. Soc. Chim. France*, 1911 (1974).
- (12) V. L. Tweedie and J. C. Allabashi, *J. Org. Chem.*, **26**, 3676 (1961).