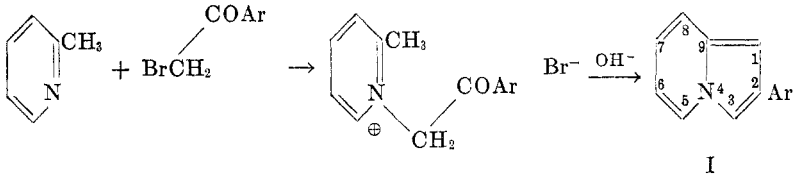
[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

2-ARYLPYRROCOLINES AND 2-ARYLPYRIMIDAZOLES

NG. PH. BUU-HOÏ, PIERRE JACQUIGNON, NG. D. XUONG, AND DENISE LAVIT

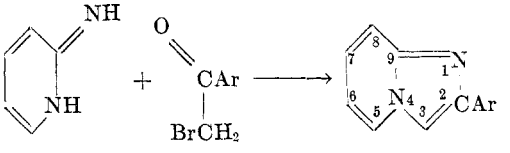
Received September 9, 1953

In the framework of investigations in the field of nitrogen-containing heterocyclic compounds, 2-arylpyrrocolines (I) and 2-arylpyrimidazoles (II) came under consideration for several reasons. From the viewpoint of cancer research, such compounds might be of interest as cocarcinogens or as potential liver poisons (1), in view of their structural analogy with 2-phenylcinchoninic acid (atophan); also, certain *Senecio* alkaloids in the molecule of which there is a tertiary nitrogen atom common to two rings (2) have recently been found carcinogenic (3). Indole in parenteral or intramedullary injection has been found to induce blood changes and lymphoadenosis (4), and this suggested the biological study of analogous compounds such as pyrimidazoles. From a purely chemical viewpoint, it has been observed that the Pfitzinger synthesis of substituted cinchoninic acids is highly sensitive toward steric hindrance (5), and it was of interest to extend these investigations to a study of the influence of steric factors in the synthesis of other nitrogenous heterocyclic compounds. The Tschitschibabin synthesis of pyrrocolines (6) from α-halogenated ketones and 2-picoline and its homologs could be outlined in the following scheme (7):



I

The Tschitschibabin synthesis of pyrimidazoles from α-halogenated ketones and 2-aminopyridine (8) could be outlined thus:

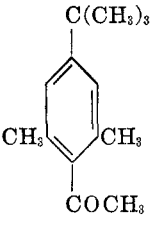


II

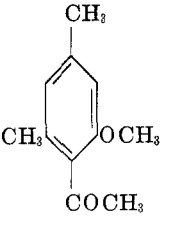
It is now shown that both syntheses, like the Pfitzinger reaction, are subject to steric hindrance.

A large number of diversely substituted ω-bromoacetophenones were condensed with α-picoline, and with 2,4- and 2,6-lutidine; the pyrrocolines thus prepared are listed in Table I; it was observed that in the case of two sterically

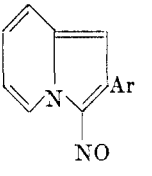
hindered ketones, 2,6-dimethyl-4-*tert*-butylacetophenone (III) and 6-methoxy-2,4-dimethylacetophenone (IV) no pyrrocoline was obtained. The same observa-



III



IV



V

tion was made in the pyrimidazole series, in which a large number of compounds, listed in Table II, could be prepared from 2-aminopyridine, and 3-methyl-, 4-methyl-, and 6-methyl-2-aminopyridine, except when the ω-bromoketones derived from III and IV were used.

The colorless 2-arylpyrrocolines readily underwent nitrosation (9) to give the corresponding, intensely green 3-nitroso-2-arylpyrrocolines (V); it was noted that, as a rule, 2-arylpyrrocolines showed high melting points, except when there was a substituent in *ortho* position on the aryl group.

Acknowledgment. This work is part of a cancer research scheme financially aided by the United States Public Health Service (Department of Health, Education, and Welfare); the authors express their thanks to the authorities concerned.

EXPERIMENTAL

Pyrrocoline cyclizations. The pyrrocolines were prepared by heating at 50° for 1 hour a solution of one mole of the appropriate ω-bromoketone and one mole of α-picoline, or 2,4- or 2,6-lutidine in the minimum amount of ethanol; the quaternary pyridinium or lutidinium salt obtained on cooling or after removal of solvent and addition of ether, was generally crystalline, and was taken up in a 5% aqueous solution of sodium bicarbonate. This solution was heated at 90–100° for 15 minutes, and the precipitate obtained was recrystallized from ethanol or benzene to give iridescent, colorless needles or leaflets.

Pyrimidazole cyclizations. A solution of the appropriate ω-bromoacetophenone (1 mole) and 2-aminopyridine or 3-methyl-, 4-methyl-, or 6-methyl-2-aminopyridine (1 mole) in the minimum of ethanol was gently refluxed for 1 hour; the solid obtained on evaporation of solvent was basified with an aqueous solution of hydrogen sodium carbonate, and was recrystallized from methanol or ethanol.

Nitrosation of 2-arylpyrrocolines. To a solution of one mole of the pyrrocoline in concentrated hydrochloric acid, an aqueous solution of sodium nitrite was added dropwise with stirring; the red crystalline mass of the nitroso base hydrochloride which precipitated was collected and basified with an aqueous solution of sodium carbonate, and the free *nitroso* compound was recrystallized from methanol or ethanol.

3-Nitroso-2-(2,5-dimethylphenyl)pyrrocoline crystallized from methanol as shiny green leaflets, m.p. 111–112°.

Anal. Calc'd for $C_{16}H_{14}N_2O$: N, 11.2. Found: N, 11.2.

3-Nitroso-2-(2,4-dimethylphenyl)pyrrocoline was recrystallized from methanol and had m.p. 186°.

Anal. Calc'd for $C_{16}H_{14}N_2O$: N, 11.2. Found: N, 11.0.

TABLE I

SUBSTITUTED PYRROCOLINES (I)

Substituent	Formula	M.P., °C.	Analyses				Starting Ketone
			Calc'd		Found		
			C	H	C	H	
2-(4-Methoxyphenyl)-	$C_{15}H_{13}NO$	205	80.7	5.8	80.4	6.0	4-Methoxyacetophenone
2-(4-Ethoxyphenyl)-	$C_{16}H_{15}NO$	218	81.0	6.3	81.0	6.6	4-Ethoxyacetophenone
2-(4-Methylmercaptophenyl)-	$C_{15}H_{13}NS$	255	75.3	5.4	75.2	5.5	4-Acetylthioanisole
2-(3-Methyl-4-methoxyphenyl)-	$C_{16}H_{15}NO$	182	81.0	6.3	81.2	6.2	3-Methyl-4-methoxyacetophenone
2-(5-Methyl-2-methoxyphenyl)-	$C_{16}H_{15}NO$	86	81.0	6.3	80.9	6.4	5-Methyl-2-methoxyacetophenone
2-(3-Methyl-4-ethoxyphenyl)-	$C_{17}H_{17}NO$	200	81.3	6.8	81.0	6.8	3-Methyl-4-ethoxyacetophenone
2-(3-Chloro-4-ethoxyphenyl)-	$C_{16}H_{14}ClNO$	218	70.7	5.2	70.6	5.5	3-Chloro-4-ethoxyacetophenone
2-(3-Bromo-4-methoxyphenyl)-	$C_{15}H_{12}BrNO$	225	59.6	4.0	59.3	4.1	3-Bromo-4-methoxyacetophenone
2-(2,5-Dimethyl-4-methoxyphenyl)-	$C_{17}H_{17}NO$	124	81.3	6.8	81.2	6.8	2,5-Dimethyl-4-methoxyacetophenone
2-(3,5-Dimethyl-2-methoxyphenyl)-	$C_{17}H_{17}NO$	136	81.3	6.8	81.1	6.7	3,5-Dimethyl-2-methoxyacetophenone
2-(2-Methyl-5-isopropyl-4-methoxyphenyl)-	$C_{19}H_{21}NO$	98	81.7	7.5	81.5	7.8	2-Methyl-5-isopropyl-4-methoxyacetophenone
2-(3,4-Dimethoxyphenyl)-	$C_{16}H_{15}NO_2$	179	75.9	5.9	75.6	5.9	3,4-Dimethoxyacetophenone
2-(2,4-Dimethoxyphenyl)-	$C_{16}H_{15}NO_2$	139	75.9	5.9	75.8	5.9	2,4-Dimethoxyacetophenone
2-(2,5-Dimethoxyphenyl)-	$C_{16}H_{15}NO_2$	94	75.9	5.9	75.6	6.1	2,5-Dimethoxyacetophenone
2-(4-Phenoxyphenyl)-	$C_{20}H_{15}NO$	196	84.2	5.3	84.1	5.2	4-Phenoxyacetophenone
2-(4-Phenylmercaptophenyl)-	$C_{20}H_{15}NS$	184	79.7	4.9	79.6	5.0	4-Acetyldiphenylsulfide
2-(4-Methoxy-1-naphthyl)-	$C_{19}H_{15}NO$	173	83.5	5.5	83.2	5.6	4-Methoxy-1-acetonaphthone
2-(6-Methoxy-2-naphthyl)-	$C_{19}H_{15}NO$	210	83.5	5.5	83.5	5.8	6-Methoxy-2-acetonaphthone
2-(2,5-Dimethylphenyl)-	$C_{16}H_{15}N$	69	86.9	6.8	86.8	6.8	2,5-Dimethylacetophenone
2-(2,4-Dimethylphenyl)-	$C_{16}H_{15}N$	106	86.9	6.8	87.0	6.9	2,4-Dimethylacetophenone
2-(3,4-Dimethylphenyl)-	$C_{16}H_{15}N$	148	86.9	6.8	86.9	7.0	3,4-Dimethylacetophenone
2-(3,4-Dichlorophenyl)-	$C_{14}H_9Cl_2N$	177	64.1	3.4	63.8	3.6	3,4-Dichloroacetophenone
2-(4-Iodophenyl)-	$C_{14}H_{10}IN$	278	52.7	3.1	52.7	2.9	4-Iodoacetophenone
2-(6-Tetralyl)-	$C_{18}H_{17}N$	155	87.4	6.9	87.6	7.0	6-Acetyltetralin
2-(1-Naphthyl)-	$C_{18}H_{13}N$	110	88.9	5.3	89.2	5.2	1-Acetonaphthone
2-(2-Naphthyl)-	$C_{18}H_{13}N$	230	88.9	5.3	89.1	5.3	2-Acetonaphthone

2-(4-Fluoro-1-naphthyl)-	$C_{18}H_{12}FN$	151	82.8	4.6	82.6	4.8	4-Fluoro-1-acetonaphthone
7-Methyl-2-(2,5-dimethylphenyl)-	$C_{17}H_{17}N$	134	86.8	7.2	86.5	7.5	2,5-Dimethylacetophenone
2-(3-Pyrenyl)-	$C_{24}H_{15}N$	159	90.9	4.7	91.0	4.5	3-Acetylpyrene
2-(3-Methyl-4-fluorophenyl)-	$C_{15}H_{12}FN$	174	80.0	5.3	79.7	5.2	3-Methyl-4-fluoroacetophenone
2-(3-Phenanthryl)-	$C_{22}H_{15}N$	201	90.1	5.1	90.2	5.3	3-Acetylphenanthrene
5-Methyl-2-(4-fluorophenyl)-	$C_{15}H_{12}FN$	107	80.0	5.3	80.0	5.5	4-Fluoroacetophenone
7-Methyl-2-(4-fluorophenyl)-	$C_{15}H_{12}FN$	248	80.0	5.3	79.8	5.6	4-Fluoroacetophenone
5-Methyl-2-(4-chlorophenyl)-	$C_{15}H_{12}ClN$	111	74.5	5.0	74.3	5.3	4-Chloroacetophenone
7-Methyl-2-(4-chlorophenyl)-	$C_{15}H_{12}ClN$	287	74.5	5.0	74.3	5.1	4-Chloroacetophenone
7-Methyl-2-(3-methyl-4-fluorophenyl)-	$C_{16}H_{14}FN$	174	80.3	5.9	80.0	6.1	3-Methyl-4-fluoroacetophenone
7-Methyl-2-(3,4-dichlorophenyl)-	$C_{15}H_{11}Cl_2N$	183	65.2	4.0	65.0	4.2	3,4-Dichloroacetophenone
7-Methyl-2-(4-methoxyphenyl)-	$C_{16}H_{15}NO$	239	81.0	6.3	80.9	6.2	4-Methoxyacetophenone
7-Methyl-2-(4-methylmercaptophenyl)-	$C_{16}H_{15}NS$	283	75.9	5.9	76.2	5.9	4-Acetylthioanisole
7-Methyl-2-(2-naphthyl)-	$C_{19}H_{15}N$	237	88.7	5.8	88.4	6.0	2-Acetonaphthone
7-Methyl-2-(4-phenylmercaptophenyl)-	$C_{21}H_{17}NS$	191	80.0	5.4	79.7	5.3	4-Acetyldiphenylsulfide
7-Methyl-2-(2-thienyl)-	$C_{13}H_{11}NS$	174	73.2	5.2	73.2	5.5	2-Acetothienone

TABLE II

SUBSTITUTED PYRIMIDAZOLES (II)

Substituent	Formula	M.P., °C.	Analyses				Starting Ketone
			Calc'd		Found		
			C	H	C	H	
2-(3,4-Dimethylphenyl)-	$C_{15}H_{14}N_2$	120	81.1	6.3	80.9	6.5	3,4-Dimethylacetophenone
2-(4-Methoxyphenyl)-	$C_{14}H_{12}N_2O$	139	75.0	5.3	74.8	5.3	4-Methoxyacetophenone
2-(4-Ethoxyphenyl)-	$C_{15}H_{14}N_2O$	148	75.6	5.9	75.2	5.8	4-Ethoxyacetophenone
2-(3,4-Dichlorophenyl)-	$C_{13}H_8Cl_2N_2$	172	59.3	3.0	59.0	3.2	3,4-Dichloroacetophenone
2-(2,5-Dimethoxyphenyl)-	$C_{15}H_{14}N_2O_2$	117	70.9	5.5	70.6	5.8	2,5-Dimethoxyacetophenone
2-(2-Naphthyl)-	$C_{17}H_{12}N_2$	160	83.6	4.9	83.3	4.8	2-Acetonaphthone
2-(6-Methoxy-2-naphthyl)-	$C_{18}H_{14}N_2O$	152	78.8	5.1	78.8	5.3	6-Methoxy-2-acetonaphthone
2-(3-Methyl-4-fluorophenyl)-	$C_{14}H_{11}FN_2$	143	74.3	4.9	74.0	5.1	3-Methyl-4-fluoroacetophenone
2-(2-Methyl-5-isopropyl-4-methoxyphenyl)-	$C_{18}H_{20}N_2O$	113	77.1	7.1	77.0	7.1	2-Methyl-5-isopropyl-4-methoxyacetophenone
2-(4-β-Phenylethylphenyl)-	$C_{21}H_{18}N_2$	139	84.6	6.0	84.2	6.3	4-Acetyldibenzyl
2-(4-Methoxy-1-naphthyl)-	$C_{18}H_{14}N_2O$	131	78.8	5.1	78.5	5.3	4-Methoxy-1-acetonaphthone
7-Methyl-2-(2,5-dimethylphenyl)-	$C_{16}H_{16}N_2$	133	81.4	6.8	81.2	6.6	3,4-Dimethylacetophenone
7-Methyl-2-(4-methoxyphenyl)-	$C_{15}H_{14}N_2O$	160	75.6	5.9	75.2	6.0	4-Methoxyacetophenone
8-Methyl-2-(4-methoxyphenyl)-	$C_{15}H_{14}N_2O$	122	75.6	5.9	75.3	5.9	4-Methoxyacetophenone
7-Methyl-2-(4-methylmercaptophenyl)-	$C_{15}H_{14}N_2S$	177	70.9	5.5	70.6	5.8	4-Acetylthioanisole
7-Methyl-2-(4-ethoxyphenyl)-	$C_{16}H_{16}N_2O$	142	76.2	6.3	76.0	6.5	4-Ethoxyacetophenone
8-Methyl-2-(4-ethoxyphenyl)-	$C_{16}H_{16}N_2O$	122	76.2	6.3	75.9	6.4	4-Ethoxyacetophenone
8-Methyl-2-(4-xenyl)-	$C_{20}H_{16}N_2$	199	84.5	5.6	84.3	5.5	4-Acetyldiphenyl
7-Methyl-2-(3,4-dimethoxyphenyl)-	$C_{16}H_{16}N_2O_2$	167	71.6	6.0	71.3	6.1	3,4-Dimethoxyacetophenone
7-Methyl-2-(2,4-dimethoxyphenyl)-	$C_{16}H_{16}N_2O_2$	152	71.6	6.0	71.5	6.2	2,4-Dimethoxyacetophenone
7-Methyl-2-(5-methyl-2-methoxyphenyl)-	$C_{16}H_{16}N_2O$	119	76.2	6.3	76.0	6.4	2-Methoxy-5-methylacetophenone
7-Methyl-2-(3-bromo-4-methoxyphenyl)-	$C_{15}H_{13}BrN_2O$	160	56.8	4.1	56.6	4.1	3-Bromo-4-methoxyacetophenone
7-Methyl-2-(3-chloro-4-ethoxyphenyl)-	$C_{16}H_{15}ClN_2O$	171	67.0	5.2	66.7	5.4	3-Chloro-4-ethoxyacetophenone
8-Methyl-2-(3-chloro-4-ethoxyphenyl)-	$C_{16}H_{15}ClN_2O$	115	67.0	5.2	66.7	5.3	3-Chloro-4-ethoxyacetophenone
7-Methyl-2-(2-fluorenyl)-	$C_{21}H_{16}N_2$	229	85.1	5.4	85.0	5.7	2-Acetylfluorene

3-Nitroso-2-(4-methylmercaptophenyl)pyrrocoline was recrystallized from ethanol, and had m.p. 195–196°.

Anal. Calc'd for $C_{15}H_{12}N_2OS$: N, 10.4. Found: N, 10.2.

3-Nitroso-2-(4-iodophenyl)pyrrocoline was recrystallized from ethanol, and had m.p. 188°.

Anal. Calc'd for $C_{14}H_9IN_2O$: N, 8.0. Found: N, 7.7.

3-Nitroso-2-(3-methyl-4-fluorophenyl)pyrrocoline was recrystallized from methanol and had m.p. 135°.

Anal. Calc'd for $C_{15}H_{11}FN_2O$: N, 11.0. Found: N, 10.7.

SUMMARY

1. The synthesis of a large number of 2-arylpyrrocolines and 2-arylpyrimidazoles by the Tschitschibabin reaction is reported. In the case of two strongly sterically hindered ketones, neither pyrrocolines nor pyrimidazoles were obtained.

2. These compounds were found to be non-carcinogenic.

PARIS V^e^, FRANCE

REFERENCES

(1) See BUU-HOÏ, *J. Chem. Soc.*, 2882 (1949).
(2) ADAMS AND LEONARD, *J. Am. Chem. Soc.*, **66**, 257 (1944).
(3) COOK, DUFFY, AND SCHOENTAL, *Brit. J. Cancer*, **4**, 405 (1950).
(4) BÜNGELER, *Klin. Wochschr.*, 1977 (1932).
(5) BUU-HOÏ AND CAGNIANT, *Bull. soc. chim.*, **13**, 123, 134 (1946); BUU-HOÏ, *J. Chem. Soc.*, 795 (1946); BUU-HOÏ AND ROYER, *J. Chem. Soc.*, 106 (1948).
(6) TSCHITSCHIBABIN, *Ber.*, **60**, 1607 (1927).
(7) BORROWS AND HOLLAND, *Chem. Revs.*, **42**, 612 (1948); BUU-HOÏ AND HOÁN, *Rec. trav. chim.*, **68**, 454 (1949).
(8) TSCHITSCHIBABIN, *Ber.*, **58**, 1704 (1925); **59**, 2048 (1926); TSCHITSCHIBABIN AND PLASCHENKOWA, *Ber.*, **64**, 2842 (1931).
(9) BORROWS, HOLLAND, AND KENYON, *J. Chem. Soc.*, 1069, 1075, 1083 (1946).