AZAINDOLES

I. PREPARATION OF 7-AZAINDOLES BY THERMAL INDOLIZATION OF 2-PYRIDYLHYDRAZONES

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ABSTRACT

The preparation of 2-pyridylhydrazones and their thermal indolization to 2- and 3-monosubstituted and 2,3-disubstituted 7-azaindoles, and to 3,3-disubstituted and 2,3,3-trisubstituted 7-azaindolenines are described. Attempts to cause thermal indolization of two 2-(5-nitropyridyl)hydrazones were unsuccessful.

Azaindoles of the types I, II, III, and IV are of chemical interest because they contain the π-electron deficient pyridine nucleus fused to the π-electron excessive pyrrole nucleus (1), and their relationship to indole adds biochemical interest. In the cases of I and II additional similarities to purine are apparent. The biological activity of azaindoles might be expected to be similar to that of the corresponding indoles and purines but with potentially useful differences. The possible use of azaindoles as purine antimetabolites has stimulated other investigations (2), and some evidence of noteworthy biological activity of 7-azatryptophan (I*a*) is available (3). Neither the parent heterocycles nor simple derivatives of azaindoles seem to occur in nature, but the presence of the β-carboline nucleus V in certain alkaloids is well known (4).

Several investigations of azaindoles (I, II, III, and IV) have been reported by Clemo (5), Herz (6), Möller (7), and Robison (8), and currently by Albert (9) and Badger (2). Numerous 2,3-dihydroazaindole derivatives have been reported by Yakhontov and Rubtsov (10), and Ficken and Kendall (11) have prepared some azaindolenines (e.g. VI*b*). The methods employed in the preparations of azaindoles have been predominantly adaptations of standard indole syntheses and involve the formation of the pyrrole ring on the pyridine ring. For example, preparations based on the Madelung (9, 12), Fischer (8*b*, 11, 13), and Reissert (14) indole syntheses have been reported (the recent successful application of the last method (14) is in contrast to the earlier reports of failures when this technique was applied to azaindole syntheses (2, 6)). An interesting method involving photochemical ring contraction to give azaindoles has been developed (7). Synthetic approaches involving the formation of a pyridine ring on an existing pyrrole nucleus have met with only modest success (15).

7-Azaindoles have received more attention than the other azaindoles, and the parent heterocycle I is available in a good yield by a modification of the Madelung synthesis (12) and by reaction of 3-pyridylacetylene with sodamide (16), or, less readily, through the photochemical route (7*b*). The base occurs in coal tar (17) and as a pyrolysis product of nicotine (18). The 2-, 3-, 4-, 5-, and 6-methyl-7-azaindoles have been prepared by the Madelung technique (5*a*, 9, 19), and 6-amino-2,3-diphenyl-7-azaindole (I*b*) was obtained in a high yield from 2,6-diaminopyridine and benzoin in the presence of the diaminopyridine hydrochloride (20).

Probably the most useful method for the preparation of indoles is the Fischer synthesis

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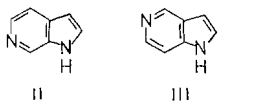
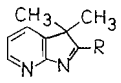
(21). However, adaptations of this technique to the synthesis of azaindoles while using the usual acid catalysts have met with only limited success: 2,3-diphenyl-7-azaindole (I*c*) (8*a*) and 6,7,8,9-tetrahydro-α-carboline (VII*b*) (8*a*, 13) were obtained in a moderate yield, and the technique has been used for the preparation of azaindolenines (VI*b*) (11).

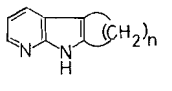
I R = R′ = R″ = H
Ia R = R″ = H, R′ = $CH_2CH(NH_2)CO_2H$
Ib R = R′ = C_6H_5, R″ = NH_2
Ic R = R′ = C_6H_5, R″ = H
Id R = R′ = CH_3, R″ = H
Ie R = C_6H_5, R′ = R″ = H
If R = R″ = H, R′ = CH_3
Ig R = R″ = H, R′ = C_2H_5
Ih R = R″ = H, R′ = C_6H_5



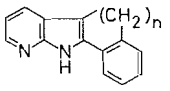
II III IV V



VIa R = H
VIb R = CH_3



VIIa n = 3
VIIb n = 4



VIIIa n = 1
VIIIb n = 2

The purely thermal indolization technique reported by Fitzpatrick and Hiser (22) appeared to offer advantages for the synthesis of azaindoles from pyridylhydrazones, since this method avoids the deactivation caused by quaternization of the pyridyl nitrogen atom. A brief study of the thermal indolization of pyridylhydrazones as part of a more general investigation of thermal indolization (23) gave encouraging results, and the application of this method to the synthesis of 7-azaindoles has been investigated in more detail.

2-Pyridylhydrazine was prepared from 2-chloropyridine (24) and then quickly converted into the 2-pyridylhydrazones of acetone, ethyl methyl ketone, isopropyl methyl ketone, acetophenone, cyclopentanone, α-indanone, α-tetralone, propionaldehyde, butyraldehyde, isobutyraldehyde, phenylacetaldehyde, pyruvic acid, and ethyl pyruvate by the usual techniques. Refluxing a solution of these 2-pyridylhydrazones in a high-boiling solvent gave the corresponding 7-azaindole in most cases (Table II). (Unless indicated in this table an inert atmosphere was not necessary to obtain the yields quoted.)

TABLE I

2-Pyridylhydrazone of:	Melting point	Formula	Calculated (%) C	Calculated (%) H	Calculated (%) N	Found (%) C	Found (%) H	Found (%) N
Cyclopentanone	91–92°	$C_{10}H_{13}N_3$	68.6	7.43		68.2	7.54	
α-Indanone	87–88°	$C_{14}H_{13}N_3$			18.8			18.5
α-Tetralone	112–114°	$C_{15}H_{15}N_3$			17.7			17.7
Propionaldehyde	54–55.5°	$C_8H_{11}N_3$	64.4	7.38		64.4	7.59	
Butyraldehyde	42–43°	$C_9H_{13}N_3$	66.3	7.97		66.5	7.99	
Phenylacetaldehyde	79–80°	$C_{12}H_{11}N_3$			19.9			19.6

NOTE: The 2-pyridylhydrazones of ethyl methyl ketone, isopropyl methyl ketone, and isobutyraldehyde were obtained only as oils and were not analyzed; those of acetone, acetophenone, pyruvic acid, and ethyl pyruvate had melting points in agreement with the literature values (25).

TABLE II

2-Pyridylhydrazone of:	Thermal indolization: Solvent*	Thermal indolization: Time (h)	Azaindole	Yield (%)	Melting point	Formula	Calculated (%): C	Calculated (%): H	Calculated (%): N	Found (%): C	Found (%): H	Found (%): N
Ethyl methyl ketone	DEG	7	I*d*	43†	137.5–138.5°	$C_9H_{10}N_2$	74.0	6.85		74.1	6.82	
Isopropyl methyl ketone	DEG (N_2)	2.5	VI*b*	5†	82–83° (77.5–78° (11*b*))	$C_{10}H_{12}N_2$			17.5			17.7
Acetophenone	TEG	4	I*e*	63†	201–202°	$C_{13}H_{10}N_2$			14.4			14.6
Cyclopentanone	DEG	9	VII*a*	67†	162.5–163.5°	$C_{10}H_{12}N_2$	75.9	6.33		75.8	6.55	
α-Indanone	DEG	7	VIII*a*	95§	266–268°	$C_{14}H_{10}N_2$			13.8			13.7
α-Tetralone	DEG (N_2)	2	VIII*b*	77‡	210–211°	$C_{15}H_{12}N_2$	81.8	5.45	12.7	81.3	5.47	12.4
Propionaldehyde	DEG (N_2)	14	I*f*	25†	126–128° (130.5–132° (19))	$C_8H_8N_2$			21.2			21.5
Butyraldehyde	DEG (N_2)	22	I*g*	37‖								
Isobutyraldehyde	DEG (N_2)	12.5	VI*a*	47‖	136–137°	$C_9H_{10}N_2$	74.0	6.85		73.6	6.92	
Phenylacetaldehyde	DEG	9	I*h*	88‡	192–5.193.5°	$C_{13}H_{10}N_2$	80.4	5.15		80.7	5.12	

*DEG = diethylene glycol; TEG = triethylene glycol.
†Crystallized from petroleum ether (b.p. 60–80°).
‡Crystallized from ethanol.
§Crystallized from acetone.
‖Obtained as an oil, b.p. 90–110° at 0.5 mm.
NOTE: Liquid 3-ethyl-7-azaindole (I*g*) yielded a picrate by reaction with ethanolic picric acid. Recrystallization from ethanol gave yellow needles, m.p. 221–222.5°.
Anal. Calcd. for $C_{15}H_{11}N_5O_7$: C, 48.0; H, 3.47. Found: C, 47.8; H, 3.57.

Several attempts were made to cause indolization of acetone 2-pyridylhydrazone under a variety of conditions; in no case was an azaindole isolated, but the pyridylhydrazone was recovered in some experiments. This result is in marked contrast to the fairly ready thermal indolization of acetone phenylhydrazone (22). All attempts to obtain an azaindole from the 2-pyridylhydrazones of pyruvic acid and ethyl pyruvate were unsuccessful.

2-(5-Nitropyridyl)hydrazine, prepared from 2-chloro-5-nitropyridine, gave the nitropyridylhydrazones on reaction with cyclohexanone and ethyl methyl ketone. Again, all attempts to cause indolization failed, though extensive decomposition did occur. In this connection it is interesting that cyclohexanone *p*-nitrophenylhydrazone gives only a poor yield of 6-nitro-1,2,3,4-tetrahydrocarbazole by a purely thermal technique (23) but gives a high yield when both an elevated temperature and an acidic medium are used (24).

These results are in agreement with the idea that protonation of the hydrazino nitrogen atom is not essential in the Fischer indole synthesis but may be necessary for success when indolization is difficult (21). However, when pyridylhydrazones are used, the acidic reaction medium deactivates the nucleus for the electrophilic cyclization stage of the reaction, thus making the purely thermal method particularly useful in this series, though not successful, in the examples examined, where the pyridyl nucleus contains an electron-withdrawing nitro substituent, nor when enehydrazine formation is difficult (as is presumably the case for acetone 2-pyridylhydrazone).

EXPERIMENTAL

2-Pyridylhydrazones

Equimolecular quantities of 2-pyridylhydrazine (25) and the aldehyde or ketone were warmed on a water bath for 30 min, and then benzene was added and the water removed by azeotropic distillation. The hydrazones (Table I) were obtained in a crystalline form (except those from ethyl methyl ketone, isopropyl methyl ketone, and isobutyraldehyde) either directly or after distillation under reduced pressure.

Indolization Procedure

In a typical experiment the hydrazone (3 g) was dissolved in a suitable solvent (30 ml) and the mixture boiled under reflux. After the mixture was cooled, it was poured into ice water and the oil crystallized. Recrystallization (charcoal) gave colorless crystals (Table II). (Analytical samples were sublimed under reduced pressure.)

2-(5-Nitropyridyl)hydrazine

Hydrazine hydrate (98%, 4 g) was added to 2-chloro-5-nitropyridine (3.2 g) (26) dissolved in ethanol (100 ml) and the mixture refluxed gently for 8 h. After the mixture was cooled, the solid was filtered off and crystallized from a large volume of ethanol as yellow prisms (2.1 g), m.p. 199–200° (27).

2-(5-Nitropyridyl)hydrazones

The aforementioned hydrazine and a small excess of the ketone were mixed in ethanol and then heated on a boiling water bath for 1 h.

Ethyl methyl ketone 2-(5-nitropyridyl)hydrazone was crystallized from a small volume of ethanol as yellow needles, m.p. 92–93°.

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 52.0; H, 5.78. Found: C, 52.3; H, 5.53.

Cyclohexanone 2-(5-nitropyridyl)hydrazone was crystallized from ethanol as yellow needles, m.p. 114–116°.

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 55.5; H, 5.99. Found: C, 55.2; H, 6.17.

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