Azaindoles. Part I. The syntheses of 5-aza- and 5,7-diazaindoles by the non-catalytic thermal indolization of 4-pyridyl- and 4-pyrimidylhydrazones respectively[1]

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The thermal indolization of a series of 4-pyridyl- and 4-pyrimidylhydrazones has been investigated. Under these conditions, isobutyraldehyde and 2-methylbutyraldehyde 4-pyridylhydrazones afford only 5-aza-2,3-dimethylindole and 5-aza-2-ethyl-3-methylindole respectively, and both ethyl methyl ketone and isobutyraldehyde 4-pyrimidylhydrazones afford only 5,7-diaza-2,3-dimethylindole. Several attempts to effect a Chichibabin amination on 5-aza-2,3-dimethyl- and 5-aza-1,2,3-trimethylindole led only to the recovery of starting material.

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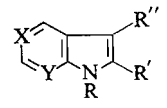
Several synthetic approaches to the 5-azaindole system have been developed (1), but that involving the acid-catalyzed Fischer indolization (2) of 4-pyridylhydrazones has either failed or only succeeded under much more drastic conditions than employed for the indolization of the corresponding phenylhydrazones (1, 2). These limitations with 4-pyridylhydrazones are caused by deactivation of the pyridine nucleus towards intramolecular electrophilic attack, one of the stages in the mechanism of the Fischer indole synthesis, both by the inductive effect of the hetero-nitrogen atom and by protonation of this atom in the acidic reaction media (2). Recently (3, 4) protonation of this nitrogen atom during such indolizations has been prevented by employing the non-catalytic thermal indolization technique (5), several 2-pyridylhydrazones (3, 4) and cyclohexanone 4-pyridylhydrazone (3) having been converted into the corresponding 7-azaindoles and 6-aza-1,2,3,4-tetrahydrocarbazole respectively by boiling in di- or triethylene glycol. We have now investigated the application of this technique to the indolization of further 4-pyridylhydrazones.

The introduction of another nitrogen atom into the aromatic ring of a pyridylhydrazone affords, amongst other possible compounds, 4-pyrimidylhydrazones, in which the second hetero-nitrogen atom further reduces the nucleophilicity of the aromatic ring. This, however, does not prevent their non-catalytic thermal indolization to 5,7-diazaindoles in the examples which have been investigated in the present studies. Although syntheses of the 5,7-diazaindole ring system (6–8) and of 5,7-diazaindole itself (7,8) have been published, these are the first reports of such syntheses using Fischer indolizations, an approach which offers a versatile preparation of 5,7-diazaindoles having alkyl or aryl substituents in the 2- and/or 3-position(s), since 4-hydrazinopyrimidine is readily available (9, see also the Experimental).

The 4-pyridylhydrazones (Table I) were prepared by addition of the appropriate carbonyl compound to an aqueous or aqueous ethanolic solution of 4-hydrazinopyridine hydrochloride (10). Attempted preparation of ethyl pyruvate 4-pyridylhydrazone by condensation of ethyl pyruvate and 4-hydrazinopyridine hydrochloride under these conditions afforded only pyruvic acid 4-pyridylhydrazone. The 4-pyrimidylhydrazones (Table II) were prepared by condensation of the appropriate carbonyl compound with 4-hydrazinopyrimidine (9) in methanolic solution.

Attempted indolization of pyruvic acid 4-pyridylhydrazone by boiling a solution of it in mono-, di-, or triethylene glycol was unsuccessful, as were the similar attempts to prepare 5-aza-2-methylindole (**1**, R = R″ = H, R′ = CH_3, X = N, Y = CH) from acetone 4-pyridylhydrazone.



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These results are analogous to those obtained from the previous unsuccessful attempts (4) to thermally indolize pyruvic acid and acetone 2-pyridylhydrazones: however, 5-aza-3-methylindole (**1**, R = R′ = H, R″ = CH_3, X = N, Y = CH) is produced by boiling a solution of

[1]Preliminary communication, P. A. Crooks and B. Robinson. Chem. Ind. London, 547 (1967).

TABLE I

Percentage yields, melting points, and analytical data of the 4-pyridylhydrazones

4-Pyridylhydrazone of:	Yield (%)	Melting point (°C)	Molecular formula	Analysis Calculated (%) C	Calculated (%) H	Found (%) C	Found (%) H
Pyruvic acid	91*	234–236 (decomp.)	$C_8H_9N_3O_2 \cdot \frac{1}{2}H_2O$	50.5	5.25 (N:22.1)	49.8	4.6 (N:22.1)
Acetone	98†	170–171 (lit. 23)					
		170–171	$C_8H_{11}N_3$	—	—	—	—
Propionaldehyde	98‡	79–85	$C_9H_{11}N_3$	Not analyzed			
Ethyl methyl ketone	89†	125–127	$C_9H_{13}N_3$	66.25	8.0	66.25	7.8
Isobutyraldehyde	92†	108–110	$C_9H_{13}N_3$	66.25	8.0	66.05	8.1
Methyl isopropyl ketone	86†	132–134	$C_{10}H_{15}N_3$	67.8	8.45	67.65	8.55
2-Methylbutyraldehyde	93‡	81–84	$C_{10}H_{15}N_3$	Not analyzed			

*Recrystallized from aqueous ethanol.
†Recrystallized from ether.
‡Could not be recrystallized.

TABLE II

Percentage yields, melting points, and analytical data of the 4-pyrimidylhydrazones

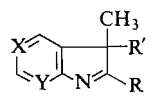
4-Pyrimidylhydrazone of:	Yield (%)	Melting point (°C)	Molecular formula	Analysis Calculated (%) C	Calculated (%) H	Found (%) C	Found (%) H
Cyclohexanone	80*	143–144	$C_{10}H_{14}N_4$	63.15	7.4	62.75	7.3
Ethyl methyl ketone	70†	109–112	$C_8H_{12}N_4$	58.85	7.3	58.35	7.2
Isobutyraldehyde	69†	120–121	$C_8H_{12}N_4$	58.85	7.3	58.75	7.2

*Recrystallized from aqueous methanol.
†Recrystallized from methanol.

propionaldehyde 4-pyridylhydrazone in diethylene glycol.

Since both cyclohexanone phenylhydrazone and 4-pyridylhydrazone have been indolized (3) in high yields using non-catalytic thermal conditions, the first attempted thermal indolization of a 4-pyrimidylhydrazone was effected on that of cyclohexanone in boiling diethylene glycol, a reaction which afforded a 32% yield of 6,8-diaza-1,2,3,4-tetrahydrocarbazole (**1**, R = H, R′ + R″ = $(CH_2)_4$, X = N, Y = CH). Boiling solutions of ethyl methyl ketone 4-pyridyl- and 4-pyrimidylhydrazones in diethylene glycol afforded only 5-aza- and 5,7-diaza-2,3-dimethylindoles (**1**, R = H, R′ = R″ = CH_3, X = N, Y = CH, and X = Y = N) respectively. These indolizations occurred as expected (2) exclusively on the methylene group of the ethyl group and not on the methyl group of the ketonic moiety.

In an attempt to extend this synthesis to the preparation of 5-aza- and 5,7-diaza-3*H*-indoles, solutions of isobutyraldehyde 4-pyridyl- and 4-pyrimidylhydrazones in monoethylene glycol were boiled, but no indolization of these compounds under these conditions could be detected, whereas in boiling diethylene glycol the hydrazones afforded only 5-aza- and 5,7-diaza-2,3-dimethylindoles (**1**, R = H, R′ = R″ = CH_3, X = N, Y = CH, and X = Y = N) respectively. Presumably, both these indoles are formed by a thermally-induced (11) Plancher rearrangement (12) of the initially-formed 5-aza- and 5,7-diaza-3,3-dimethyl-3*H*-indoles (**2**, R = H, R′ = CH_3, X = N, Y = CH, and X = Y = N) respectively. To eliminate the possibility that



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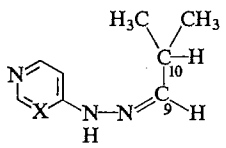
methyl group migration had occurred in the isobutyraldehyde 4-pyridyl- and 4-pyrimidylhydrazones (**3**, X = CH and N respectively) during their synthesis, the proton magnetic resonance (p.m.r.) spectra of these compounds were ex-



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amined. Both spectra showed 6-proton doublets (J = 7 and 8 c.p.s. respectively) centered at τ 8.80 and 8.87 respectively (the two equivalent methyl groups on C_{10}), a 1-proton multiplet between τ 6.90–7.90 and τ 6.97–7.82 respectively [C_{10}—H], and a 1-proton doublet (J = 6 and 5 c.p.s. respectively) centered at τ 2.84 and τ 2.77 respectively [C_9—H]. In each case signals attributable to the N—H and aromatic protons were also obtained. In both spectra, after irradiation of the C_{10}—H one-proton multiplet, the 1- and 6-proton doublets collapsed to singlets. Boiling a solution of methyl isopropyl ketone 4-pyridylhydrazone in monoethylene glycol did, however, afford 5-aza-2,3,3-trimethyl-3*H*-indole (**2**, R = R′ = CH_3, X = N, Y = CH) in which a Plancher rearrangement to an indole is impossible.

It has been claimed (4), without the evidence of physical data, that the product obtained by thermal indolization of isobutyraldehyde 2-pyridylhydrazone in boiling diethylene glycol is 7-aza-3,3-dimethyl-3*H*-indole (**2**, R = H, R′ = CH_3, X = CH, Y = N); however, this product has an almost identical melting point to that of 7-aza-2,3-dimethylindole (**1**, R = H, R′ = R″ = CH_3, X = CH, Y = N), prepared by thermal indolization of ethyl methyl ketone 2-pyridylhydrazone in boiling diethylene glycol (4). In view of this and the above mentioned rearrangements it seems probable that the compound thought (4) to be 7-aza-3,3-dimethyl-3*H*-indole is, in fact, 7-aza-2,3-dimethylindole, a possibility which has now (13) been verified as correct.

2-Methylbutyraldehyde 4-pyridylhydrazone upon indolization in boiling diethylene glycol affords only 5-aza-2-ethyl-3-methylindole (**1**, R = H, R′ = C_2H_5, R″ = CH_3, X = N, Y = CH). In this case the intermediate 5-aza-3-ethyl-3-methyl-3*H*-indole (**2**, R = H, R′ = C_2H_5, X = N, Y = CH) has also undergone thermally-induced Plancher rearrangement under the indolization conditions. The exclusive formation of **1** (R = H, R′ = C_2H_5, R″ = CH_3, X = N, Y = CH) is in accord with the observation (14) that an ethyl group has a higher migratory aptitude than a methyl group and migrates preferentially to it in a Plancher rearrangement.

It has been suggested (15) that the "essential" molecular features of a purine antimetabolite are contained in a 1-unsubstituted 5-azaindole having a 4-substituent which is capable of forming a hydrogen bond, by hydrogen donation, with a nitrogen p-electron pair of a pyrimidine nucleus. Attempts have been made to synthesize a compound having these requirements by effecting a Chichibabin reaction (16) on **1** (R = H, R′ = R″ = CH_3, X = N, Y = CH), which, by analogy with this reaction on isoquinoline which affords (17) exclusively 1-amino-isoquinoline, would be expected to afford 4-amino-5-aza-2,3-dimethylindole. However, attempted amination of 5-aza-2,3-dimethylindole with sodamide in xylene and in *N*,*N*-dimethylaniline under various conditions failed, only starting material being recoverable from such reactions [cf. the failure to aminate 7-azaindole (18)]. It appeared likely that the failure of this reaction could be caused by the heterogeneous nature of these reaction mixtures owing to the insolubility of the sodium salt of the indole which is formed and precipitated out and/or by the presence of the negative charge on the indolic nucleus of this salt which would prevent attack on the nucleus by amide anion. This salt formation was overcome by 1-methylation of **1** (R = H, R′ + R″ = CH_3, X = N, Y = CH), with sodamide and methyl iodide (19) to afford **1** (R = R′ = R″ = CH_3, X = N, Y = CH), but attempted amination of this *N*-methylated derivative with sodamide in boiling decalin or xylene or with barium amide in liquid ammonia (20) again failed and led only to the recovery of starting material.

Experimental

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. Infrared (i.r.) spectra were recorded on a Perkin–Elmer 237 spectrophotometer, ultraviolet (u.v.) spectra were measured on a Perkin–Elmer 137 spectrophotometer, and p.m.r. spectra were recorded on a Varian A 60 spectrometer in deuteriochloroform solution (unless otherwise stated) using tetramethylsilane as internal standard. Solutions were dried over anhydrous magnesium sulfate and, unless otherwise stated, solvents were removed on a steam-bath under reduced pressure (water pump).

4-Pyridylhydrazones

4-Hydrazinopyridine hydrochloride (4.0 g) (10) was dissolved in water (10 ml) and the appropriate aldehyde or ketone (4 ml) was added. Ninety-five percent ethanol

(8 ml) was added, if required, to effect a homogeneous reaction mixture. After standing at room temperature for 4 h, the solution was basified with sodium hydroxide solution and the liberated oil extracted with ether (2 × 20 ml). The combined ethereal extracts were washed with water (2 × 20 ml), dried, and the solvent removed to afford the 4-pyridylhydrazones as oils which completely crystallized and which were recrystallized (except propionaldehyde and 2-methylbutyraldehyde 4-pyridylhydrazones) (Table I).

In the case of acetone 4-pyridylhydrazone a precipitate, and not an oil, was formed upon basification. This was collected, washed with water until the washings were neutral, dried over P_2O_5 *in vacuo*, and recrystallized (Table I).

4-Hydrazinopyridine hydrochloride was reacted with pyruvic acid and ethyl pyruvate as above, but after standing the reaction mixture at room temperature for 4 h, the ethanol was removed and the solid which separated was collected, washed with water, dried over P_2O_5 *in vacuo*, and recrystallized (Table I).

4-Hydrazinopyrimidine

The previously published (9, 21) method for the preparation of 4-hydrazinopyrimidine from 4-hydroxypyrimidine (22) was modified as follows to afford an increase in the yield of product.

A mixture of phosphoryl chloride (50 ml) and 4-hydroxypyrimidine (22) (14 g) was boiled under reflux on an oil-bath for 40 min. The cooled reaction mixture was then shaken with sodium-dried petroleum (6 × 40 ml, b.p. 40–60°) and to the resulting brown gum was carefully added dry methanol (120 ml) dropwise. After the vigorous reaction had ceased the resulting yellow-brown solution was poured into a methanolic solution of sodium methoxide (20 g of sodium in 250 ml of dry methanol) and the resulting suspension was boiled under reflux for 30 min. After cooling, carbon dioxide was passed through the suspension until it was saturated (3 h), the mixture was filtered, the precipitate was washed with dry methanol (2 × 20 ml), and the total methanolic filtrate was evaporated to dryness on a rotating evaporator at 25°. To the residue was added dry methanol (15 ml) and the methanol was again completely evaporated at 70°, this procedure being repeated one further time. The total methanolic distillate was then evaporated at room temperature on a rotating evaporator to a volume of approximately 30 ml, hydrazine hydrate (5 ml) was added, the mixture boiled under reflux for 2 h, a further quantity of hydrazine hydrate (5 ml) was added and the boiling under reflux continued a further 2 h. The solution was left standing at room temperature overnight and the solvent evaporated to afford 4-hydrazinopyrimidine as a pale-yellow crystalline solid (6.90 g, 41%) [lit. yield 15% (9, 21)] which was used to prepare the 4-pyrimidylhydrazones below without recrystallization. A small sample was recrystallized from methanol–benzene to afford pale-yellow prisms, m.p. 133–134° (decomp.) [lit. m.p. 132–134° (9)].

4-Pyrimidylhydrazones

4-Hydrazinopyrimidine (1.6 g) was dissolved in dry methanol (10 ml) and the ketone or aldehyde (3 ml) was added. An exothermic reaction occurred, after which the solutions were left standing overnight at room temperature.

Evaporation of the solvent then left the 4-pyrimidylhydrazones (Table II) as crystalline solids which were purified by recrystallization.

5-Aza-3-methylindole

A solution of propionaldehyde 4-pyridylhydrazone (3.0 g) in diethylene glycol (30 ml) was boiled under reflux for 10 h, then cooled to room temperature, and poured into cold water (250 ml). The liberated oil was extracted with chloroform (2 × 200 ml) and the combined chloroform extracts were washed with water (2 × 300 ml), dried, and the solvent removed to afford a tan-colored solid which after recrystallization from ethanol–ether afforded light-tan prisms (1.14 g, 34.5%), m.p. 144–145°.

Anal. Calcd. for $C_8H_8N_2$: C, 72.7; H, 6.1. Found: C, 72.5; H, 6.2.

λ_{max}(EtOH) 222 mμ, log ε 4.53; 275 mμ, log ε 3.39. λ_{Infl}(EtOH) 283 mμ, log ε 3.28. λ_{min}(EtOH) 245 mμ, log ε 3.04. λ_{max}(EtOH–HCl) 227.5 mμ, log ε 4.57; 284 mμ, log ε 3.34. λ_{Infl}(EtOH–HCl) 312 mμ, log ε 3.04. λ_{min} (EtOH–HCl) 246 mμ, log ε 2.92. These u.v. spectral data are similar to those reported (1) for 5-azaindole, the dissimilarities probably being caused by the bathochromic effect of the 3-methyl substituent. The p.m.r spectrum showed a 3-proton singlet at τ 7.83 [C_3—CH_3], a 1-proton singlet at τ 2.96 [C_2—H] (24), a 1-proton doublet (J = 5 c.p.s.) (ortho coupling) centered at τ 2.80 with each peak split into another doublet (J = 1.5 c.p.s.) (para coupling) [C_7—H], a 1-proton doublet (J = 5 c.p.s.) (ortho coupling) centered at τ 1.90 [C_6—H], a 1-proton doublet (J = 1.5 c.p.s.) (para coupling) centered at τ 1.25 [C_4 —H], and a broad 1-proton singlet at τ −1.36 which disappeared upon addition of D_2O (N—H).

5-Aza-2,3-dimethylindole

Ethyl methyl ketone 4-pyridylhydrazone (3.0 g) was boiled in diethylene glycol solution (30 ml) for 15 h, the reaction mixture cooled, and then poured into cold water. The resulting light-brown precipitate was collected, washed well with water followed by a little ether, and recrystallized from ethanol to afford light-tan prisms (1.41 g, 52.5%), m.p. 214–215°.

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.5; H, 6.9. Found: C, 74.15; H, 6.85.

λ_{max}(EtOH) 226 mμ, log ε 4.54; 278 mμ, log ε 3.67. λ_{Infl}(EtOH) 286 mμ, log ε 3.54. λ_{min}(EtOH) 250 mμ, log ε 3.17. λ_{max}(EtOH–HCl) 231.5 mμ, log ε 4.62; 290 mμ, log ε 3.53. λ_{Infl}(EtOH–HCl) 314 mμ, log ε 3.17. λ_{min} (EtOH–HCl) 250 mμ, log ε 3.02. The p.m.r. spectrum included two 3-proton singlets at τ 7.80 and τ 7.68 [C_3—CH_3 and C_2—CH_3 respectively] (the high-field singlet is attributed to the C_3—CH_3 protons by comparison with the τ value of the singlet caused by the protons of this group in the spectrum of 5-aza-3-methylindole quoted above), a 1-proton doublet (J = 5.5 c.p.s.) (ortho coupling) centered at τ 2.76 with each peak split into further doublets (J = 1.5 c.p.s.) (para coupling) [C_7—H], a 1-proton doublet (J = 5.5 c.p.s.) (ortho coupling) centered at τ 1.89 [C_6 —H], a 1-proton doublet (J = 1.5 c.p.s.) (para coupling) centered at τ 1.32 [C_4 —H], and a 1-proton broad singlet between τ −1.33 and τ −0.93 which disappeared upon addition of D_2O (N—H).

When this reaction was repeated using isobutyraldehyde 4-pyridylhydrazone in place of ethyl methyl ketone 4-pyridylhydrazone, 5-aza-2,3-dimethylindole (identical m.p., mixture m.p., u.v., i.r., and p.m.r. spectra with that prepared above) was produced in 14.5% yield.

5-Aza-2,3,3-trimethyl-3H-indole

A solution of methyl isopropyl ketone 4-pyridylhydrazone (3.0 g) in diethylene glycol (30 ml) was boiled under reflux under an atmosphere of nitrogen for 6 h, and the reaction mixture worked up as described above for the preparation of 5-aza-3-methylindole. Evaporation of the chloroform extract afforded a dark-brown gum from which no recognizable product could be isolated.

The reaction was repeated in monoethylene glycol and after boiling for 6 h, the reaction mixture was cooled, poured into cold water (250 ml), and the aqueous suspension extracted with ether (3 × 150 ml). The combined ether extracts were washed with water (2 × 250 ml), dried, and the solvent removed to afford a brown oil (1.21 g) which could not be induced to crystallize and which had an u.v. spectrum (in EtOH) almost identical to that of the starting material. The aqueous phase remaining from the above ether extraction was extracted with chloroform (2 × 100 ml), the combined chloroform extracts washed with water (2 × 100 ml), dried, and the chloroform removed to afford a crystalline residue which upon sublimation [60–80° (bath temperature) at 74 mm] gave 5-aza-2,3,3-trimethyl-3*H*-indole as colorless needles (0.29 g, 10.5%), m.p. 86–87° [reported m.p. 81–81.5° (25)].

λ_{max}(EtOH) 243.5 mμ, log ε 3.56. λ_{infl}(EtOH) 299 mμ, log ε 2.78. λ_{min}(EtOH) 224 mμ, log ε 3.48. λ_{max}(EtOH–HCl) 277.5 mμ, log ε 3.85. λ_{infl}(EtOH–HCl) 308 mμ, log ε 2.94. λ_{min}(EtOH–HCl) 240 mμ, log ε 3.05. λ_{max} (conc. HCl) 256 mμ, log ε 3.84. λ_{infl}(conc. HCl) 313 mμ, log ε 2.43. λ_{min}(conc. HCl) 227 mμ, log ε 3.64. The p.m.r. spectrum showed a 6-proton singlet at τ 8.68 [C_3 $(CH_3)_2$], a 3-proton singlet at τ 7.75 [C_2 CH_3], a 1-proton doublet (J = 5 c.p.s.) (ortho coupling) centered at τ 2.75 with each peak split into further doublets (J = 1.5 c.p.s.) (para coupling) [C_7 —H], a 1-proton doublet (J = 1.5 c.p.s.) (para coupling) centered at τ 1.73 [C_4 —H], and a 1-proton doublet (J = 5 c.p.s.) (ortho coupling) centered at τ 1.70 [C_6 —H].

5-Aza-2-ethyl-3-methylindole

2-Methylbutyraldehyde 4-pyridylhydrazone (3.0 g) was indolized as described above for propionaldehyde 4-pyridylhydrazone, the boiling in diethylene glycol being continued for 16 h. The brown oil obtained by evaporation of the chloroform extract was subjected to column chromatography on alumina (grade 'H'). A light-brown band was eluted with ether, evaporation of the eluate yielding a light-brown oil which could not be crystallized and which showed no significant u.v. absorption. Elution with chloroform/ether (1:5 vol:vol) and then with chloroform, followed by evaporation of the eluates, afforded in each case a crystalline residue which after recrystallization from ethanol–ether gave light-tan prisms (0.54 g, 20%), m.p. 155–156°.

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 75.0; H, 7.55. Found: C, 75.0; H, 7.25.

λ_{max}(EtOH) 227.5 mμ, log ε 4.57; 278 mμ, log ε 3.70. λ_{infl}(EtOH) 286 mμ, log ε 3.65. λ_{min}(EtOH) 250 mμ, log ε 3.51. λ_{max}(EtOH–HCl) 232 mμ, log ε 4.65; 289 mμ, log ε 3.65. λ_{infl}(EtOH–HCl) 316 mμ, log ε 3.28. λ_{min} (EtOH–HCl) 250 mμ, log ε 3.29 (these u.v. spectral data are almost identical with those recorded for 5-aza-2,3-dimethylindole recorded above). The p.m.r. spectrum (recorded in hexadeuteriodimethylsulfoxide) showed a 3-proton triplet (J = 7 c.p.s.) and a 2-proton quartet (J = 7 c.p.s.) centered at τ 8.75 and τ 7.26 respectively [C_2 C_2H_5], a 3-proton singlet at τ 7.78 [C_3 CH_3] [cf. the value of τ 7.83 and τ 7.80 for the protons of the C_3 CH_3 groups in 5-aza-3-methylindole and 5-aza-2,3-dimethylindole respectively], a 1-proton doublet (J = 5.1 c.p.s.) (ortho coupling) centered at τ 2.75 with each peak split into a further doublet (J = 1.5 c.p.s.) (para coupling) [C_7 —H], a 1-proton doublet (J = 5.1 c.p.s.) (ortho coupling) centered at τ 1.90 [C_6 —H], a 1-proton doublet (J = 1.5 c.p.s.) (para coupling) centered at τ 1.30 [C_4 —H], and a broad singlet between τ −1.40 and τ −0.92 which disappeared upon addition of D_2O (N—H).

The mother liquors remaining from the recrystallization of the 5-aza-2-ethyl-3-methylindole were evaporated and the p.m.r. spectrum of the residue was recorded (in hexadeuteriodimethylsulfoxide) and showed no trace of a singlet signal at ≏ τ 7.7, indicating the absence of a 2-methyl substituted 5-azaindole nucleus, since the C_2 CH_3 protons in 5-aza-2,3-dimethylindole give rise to a singlet at τ 7.68.

6,8-Diaza-1,2,3,4-tetrahydrocarbazole

Cyclohexanone 4-pyrimidylhydrazone (3.0 g) was dissolved in diethylene glycol (30 ml), the solution boiled under reflux for 5 h, and then worked up as described above for the preparation of 5-aza-3-methylindole. Evaporation of the chloroform extract afforded a light-brown oil which crystallized. Recrystallization from chloroform–ether afforded light-tan prisms (0.87 g, 32%), m.p. 233–235°.

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.4; H, 6.4. Found: C, 69.2; H, 6.45.

λ_{max}(EtOH) 232.5 mμ, log ε 4.50; 274–275 mμ, log ε 3.38; 305 mμ, log ε 3.35. λ_{min}(EtOH) 251 mμ, log ε 3.24; 290 mμ, log ε 3.33. λ_{max}(EtOH–HCl) 236–237 mμ, log ε 4.47; 292–293 mμ, log ε 3.44. λ_{infl}(EtOH–HCl) 325 mμ, log ε 3.03. λ_{min}(EtOH–HCl) 258 mμ, log ε 3.23. λ_{max}(conc. HCl) 241.5 mμ, log ε 4.50; 299.5 mμ, log ε 3.73. λ_{infl}(conc. HCl) 320–330 mμ, log ε 3.50. λ_{min}(conc. HCl) 275 mμ, log ε 3.55. The p.m.r. spectrum (recorded in hexadeuteriodimethylsulfoxide) showed two 4-proton multiplets between τ 7.93 and τ 8.46 [C_2 H_2 and C_3 H_2] and τ 7.13 and τ 7.58 [C_1 H_2 and C_4 H_2], 1-proton singlets at τ 1.37 and τ 1.25 [C_5 H and C_7 H], and a 1-proton broad singlet at τ −1.66 which disappeared upon addition of D_2O (N—H).

5,7-Diaza-2,3-dimethylindole

Ethyl methyl ketone 4-pyrimidylhydrazone (1.60 g) was dissolved in monoethylene glycol (25 ml) and the solution was boiled under reflux for 12 h. After working up as described above for the preparation of 6,8-diaza-1,2,3,4-tetrahydrocarbazole, a brown oil was obtained but all attempts to obtain a crystalline or recognizable product from this failed.

The above procedure was repeated using diethylene glycol instead of monoethylene glycol and the brown oil obtained was subjected to column chromatography on

alumina (grade 'H') using chloroform as eluant. A brown band was initially eluted which upon removal of the solvent afforded a brown gum which could not be induced to crystallize and which had no significant u.v. absorption. A deep-yellow band was then eluted, removal of the solvent from which affording a pale-yellow crystalline solid (0.15 g, 10.5%) which after recrystallization from chloroform–ether and sublimation [140–160° (bath temperature) at 0.4 mm] yielded colorless prisms, m.p. 172–173°.

Anal. Calcd. for $C_8H_9N_3$: C, 65.3; H, 6.15. Found: C, 64.55; H, 6.0.

λ_{max}(EtOH) 231.5 mμ, log ε 4.39; 274–276 mμ, log ε 3.28; 307–308 mμ, log ε 3.26. λ_{min}(EtOH) 249 mμ, log ε 3.16; 290 mμ, log ε 3.24. λ_{max}(EtOH–HCl) 235 mμ, log ε 4.38; 293 mμ, log ε 3.30. λ_{infl}(EtOH–HCl) 323 mμ, log ε 3.15. λ_{infl}(EtOH–HCl) 323 mμ, log ε 3.15. λ_{min}(EtOH–HCl) 259 mμ, log ε 3.16. λ_{max}(conc. HCl) 241 mμ, log ε 4.38; 296 mμ, log ε 3.50. λ_{infl}(conc. HCl) 320–331 mμ, log ε 3.22. λ_{min}(conc. HCl) 275 mμ, log ε 3.28. The p.m.r. spectrum showed two 3-proton singlets at τ 7.73 [C_3CH_3] and τ 7.53 [C_2CH_3], a 2-proton singlet at τ 1.23 [C_4 H and C_6 H] and a 1-proton broad singlet at τ −1.93 which disappeared upon addition of D_2O (N—H).

The u.v. spectra reported above for 6,8-diaza-1,2,3,4-tetrahydrocarbazole and 5,7-diaza-2,3-dimethylindole are, as would be expected, closely similar to each other but bear no resemblance to the spectrum previously reported (8) for 5,7-diazaindole (i.e. λ_{max}(pH 6.8) 271 mμ, log ε 3.60. λ_{max}(HCl) 225 mμ, log ε 4.44; 265 mμ, log ε 3.49; 299 mμ, log ε 3.18. λ_{max}(NaOH) 273 mμ, log ε 3.59), although the spectrum of 5,7-diazaindole in hydrochloric acid solution as previously reported (8) and quoted above is closely similar to those of the two 5,7-diazaindoles presently reported in ethanolic solution. Since the structures of these two 5,7-diazaindoles are definitely established by their mode of synthesis and from their p.m.r. spectra, it appears that the solvents quoted in the published (8) u.v. spectrum of 5,7-diazaindole are erroneous.

Isobutyraldehyde 4-pyrimidylhydrazone (1.6 g) was indolized in boiling diethylene glycol by a procedure analogous to that described above for the indolization of ethyl methyl ketone 4-pyrimidylhydrazone. The column was initially eluted with ether–chloroform (1:1 vol:vol) until the eluate was colorless and a brown band was subsequently eluted with chloroform. Both these eluates upon evaporation of the solvents afforded crystalline residues (total 0.23 g, 16%) which after recrystallization from chloroform–ether and sublimation [140–160° (bath temperature) at 0.4 mm] gave colorless prisms which were identical (m.p., mixture m.p., and i.r., u.v., and p.m.r. spectra) to 5,7-diaza-2,3-dimethylindole described above.

Attempted Aminations of 5-Aza-2,3-dimethylindole

After boiling mixtures of 5-aza-2,3-dimethylindole (0.50, 0.30, and 0.30 g respectively) and sodamide (0.28, 0.20, and 0.80 g respectively) in dry xylene (6 ml) for 5 h, and *N,N*-dimethylaniline (6 ml) for 1 h and 5 h respectively, the only product which could be isolated from the reaction mixtures was unchanged 5-aza-2,3-dimethylindole (0.41, 0.12, and 0.17 g respectively).

5-Aza-1,2,3-trimethylindole

To a solution of sodamide in liquid ammonia (prepared from 8.0 g of sodium in 150 ml of liquid ammonia) was added 5-aza-2,3-dimethylindole (10 g). After stirring for 1.5 h, methyl iodide (20 ml) was added dropwise with stirring over 30 min, the stirring continued for 2.5 h, the ammonia and unreacted methyl iodide removed (steam-bath), and the residue shaken with water (150 ml).

The aqueous solution was basified with sodium hydroxide solution, the precipitate extracted with chloroform (3 × 200 ml), the combined extracts washed with water (2 × 200 ml), dried, and the solvent evaporated to afford a brown oil which was distilled (b.p. 160–164° at 1.5 mm) to give a pale-yellow oil which soon completely crystallized. Recrystallization afforded 5-aza-1,2,3-trimethylindole (7.20 g, 68%) as cream-colored prisms, m.p. 69–71°.

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 75.0; H, 7.5. Found: C, 75.0; H, 7.85.

Attempted Aminations of 5-Aza-1,2,3-trimethylindole

Mixtures of 5-aza-1,2,3-trimethylindole (0.75 g) with sodamide (0.5 and 1.0 g respectively) were boiled in dry decalin (15 ml) for 1.5 h and dry xylene for 4 h respectively, and a mixture of 5-aza-1,2,3-trimethylindole (1.9 g) and barium nitrate (0.90 g) in a solution of barium amide in ammonia [prepared from barium (2.1 g), liquid ammonia (50 ml), and a trace of ignited barium oxide] was stirred for 24 h. The only product which could be isolated from all three reactions was 5-aza-1,2,3-trimethylindole (0.50, 0.46, and 1.62 g respectively).

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