Diazaindenes (Azaindoles). Part III.[1] Reactions of Vilsmeier Reagents leading to 3-Formyl-1,6-diazaindene and -1,4-diazabenz[*f*]indene

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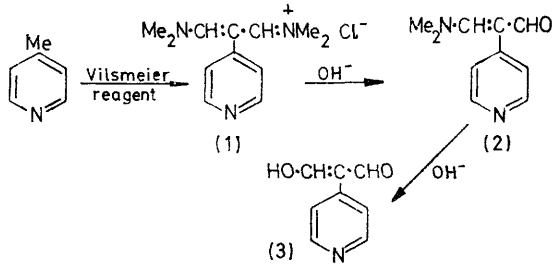
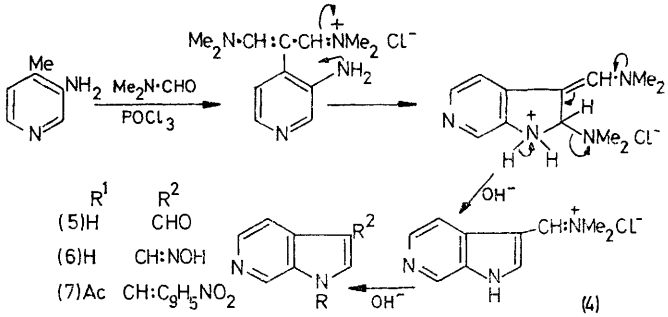
The action of the two Vilsmeier reagents from dimethylformamide and phosphoryl chloride or thionyl chloride on 2-amino-3-picoline, 3-amino-4-picoline, and 4-amino-3-picoline is reported. The first reagent with 3-amino-4-picoline gave 3-formyl-1,6-diazaindene (pyrrolo[2,3-*c*]pyridine-3-carbaldehyde) and *NN*-dimethyl-*N'*-(4-methyl-3-pyridyl)formamidine, and with 3-amino-2-methylquinoline yielded 3-formyl-1,4-diazabenz[*f*]-indene(pyrrolo[3,2-*b*]quinoline-3-carbaldehyde). Some modifications of the aldehydes were investigated; 3-(*NN*-dimethylaminomethyl)-1,6-diazaindene was prepared.

CERTAIN 3-substituted indoles have important biological activity. The synthesis of diazaindene analogues of these compounds might be approached by either (i) electrophilic substitution of the parent diazaindene, or (ii) direct synthesis of an appropriately substituted diazaindene from monocyclic starting materials. The applicability of the first approach is limited by the lack of efficient routes to some of the parent diazaindenes.[2] An investigation of one example of the second type of approach which yielded 3-substituted 1,6-diazaindenes and 3-substituted 1,4-diazabenz[*f*]indenes is reported here.



Arnold[3] has shown that the reaction of 4-methylpyridine with the Vilsmeier reagent from phosphoryl chloride and dimethylformamide gives an intermediate [presumably (1)], which is susceptible to nucleophilic attack and gives, on hydrolysis, β-dimethylamino-α-(4-pyridyl)acraldehyde (2), and this, on more vigorous hydrolysis, yields β-hydroxy-α-(4-pyridyl)acraldehyde (3). It seemed possible that the reaction of certain aminopicolines with the Vilsmeier reagent would give a species which might undergo intramolecular nucleophilic attack by the vicinal amino-group to yield an intermediate [*e.g.* (4)], which would then be expected to give 3-formyl-1,6-diazaindene (5) on hydrolysis.



	R^1	R^2
(5)	H	CHO
(6)	H	CH:NOH
(7)	Ac	CH:$C_9H_5NO_2$
(8)	Ac	CN
(9)	H	CN
(10)	H	Me
(11)	H	CH_2NH_2
(12)	H	CH_2NMe_2

3-Amino-4-methylpyridine reacted with the Vilsmeier reagent (from phosphoryl chloride and dimethylformamide) to give a sparingly soluble, yellow solid which contained chloride ion. This solid was hygroscopic

[1] Part II, A. H. Kelly and J. Parrick, *J. Chem. Soc.* (*C*), 1970, 303.

[2] R. E. Willette, *Adv. Heterocyclic Chem.*, 1968, **9**, 27.

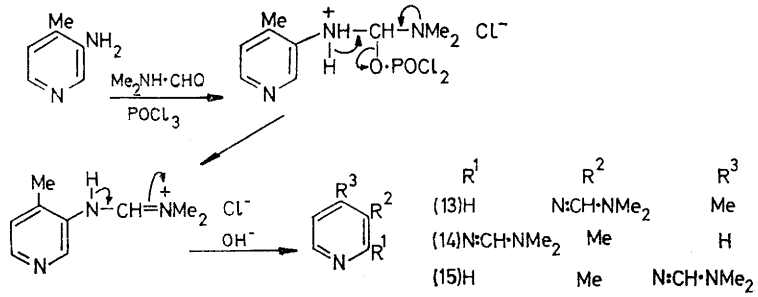
[3] Z. Arnold, *Coll. Czech. Chem. Comm.*, 1963, **28**, 863.

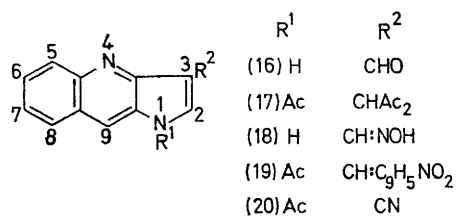
and satisfactory analytical results were not obtained. However, alkaline hydrolysis of this intermediate yielded a colourless solid, formulated as 3-formyl-1,6-diazaindene on the basis of its elemental analysis, i.r. spectrum, and reactions. The yield of the aldehyde was variable, but always low (0—20%).

Further treatment of the reaction mixture gave another yellow, hygroscopic solid, which afforded a colourless oil on alkaline hydrolysis. The oil showed parent ion and base peaks at *m/e* 163 and 44, respectively, in its mass spectrum, and a strong i.r. absorption at 1630 cm.$^{-1}$ (C:N). The oil was formulated as *NN*-dimethyl-*N'*-(4-methyl-3-pyridyl)formamidine (13), and probably arises by attack of the Vilsmeier reagent on the amino-group. The structure (13) was confirmed by the n.m.r. spectrum [τ($CDCl_3$) 7·72 (3H, s, 4-Me), 6·96 (6H, s, NMe_2), 2·59 (1H, s, CH), 2·04 (1H, s, 2-H), 2·96 (1H, d, 5-H), and 1·89 (1H, d, 6-H) ($J_{5,6}$ 5·5 Hz)].

Scott and Spedding [5] have recently reported some reactions of a type of Vilsmeier reagent prepared from thionyl chloride and dimethylformamide; aniline hydrochloride and *NN*-dimethyl-*N'*-phenylformamidine were formed on reaction with aniline. It has now been found that this Vilsmeier reagent does not give the corresponding formamidines with 3-amino-4-methyl-, 2-amino-3-methyl-, or 4-amino-3-methyl-pyridine: the aminopicoline hydrochloride and a small quantity of an unstable, unidentified product were isolated in the first case, and the aminopicoline hydrochloride and unchanged aminopicoline were isolated from the other two reaction mixtures.

Both the aldehydes (5) and (16) gave the corresponding oximes (6) and (18) and 1-acetyl azlactones (7) and (19). The 1,6-diazaindene oxime (6) was also prepared directly from the reaction mixture obtained on hydrolysis of the intermediate. Derivatives (8), (9), (10), (11), and (20) were obtained by the usual procedures. The 3-methyl-1,6-diazaindene (10) was identical with the diazaindene formed in the smaller quantity from propionaldehyde 3-pyridylhydrazone.[1] Reduction of the oxime (6) with sodium borohydride in the presence of dimethylamine gave 3-(*NN*-dimethylaminomethyl)-1,6-diazaindene (6-azagramine) (12).





Meltzer and his co-workers [4] have recently investigated the reaction of the Vilsmeier reagent with 2-amino-3-methylpyrazine and obtained a high yield of 3-formyl-1,4,7-triazaindene. The product that would be formed by attack of the reagent on the amino-group was not observed. These results differ from our findings in the pyridine series, but are in accord with the expected greater nucleophilicity of an amino-group as a 3-pyridine substituent compared to that as a 2-pyrazine substituent; the latter would be expected to be more closely similar to 2- or 4-aminopyridine. This argument is supported by the observation that attempted reactions of the Vilsmeier reagent with 2-amino-3-methylpyridine and 4-amino-3-methylpyridine did not give (14) or (15), nor were diazaindene aldehydes obtained.

In contrast, 3-amino-2-methylquinoline gave a yellow solid intermediate when treated with the Vilsmeier reagent. Alkaline hydrolysis of the solid gave 3-formyl-1,4-diazabenz[*f*]indene (16), which showed i.r. absorptions at 3350 and 1655 cm.$^{-1}$ (NH and C:O respectively). This assignment was confirmed by conversion of the aldehyde into (17), which did not show these i.r. peaks, but had new absorptions at 1710 and 1750 cm.$^{-1}$ (amide and acetyl C:O respectively). The n.m.r. spectrum of the aldehyde (16) showed peaks at τ[$(CD_3)_2SO$] 1·71—2·54 (4H, m, 5-, 6-, 7-, and 8-H), 1·43 and 1·09 (each 1H, s, 2- and 9-H), —0·40 (1H, s, CHO), and —2·70br (1H, s, exchangeable, NH).

The preparation of the aldehydes by use of the Vilsmeier reagent is a useful route to certain substituted diazaindenes, but the method is not entirely satisfactory because the yields are low and suitably substituted aminopicolines are not readily accessible. It seemed possible that the thermal indolisation technique [1] might allow the direct preparation of suitably protected 3-formyldiazaindenes. Attempts were made to cause

[4] S. Klutchko, H. V. Hansen, and R. I. Meltzer, *J. Org. Chem.*, 1965, **30**, 3454.
[5] M. D. Scott and H. Spedding, *J. Chem. Soc.* (*C*), 1968, 1603.

indolisation of the model compound 4,4-dimethoxybutan-2-one phenylhydrazone to 3,3-bisdimethoxymethyl-2-formylindole. The only product isolated was 3-methyl-1-phenylpyrazole when either diethylene glycol or tetralin was used as solvent. The same product was obtained when anhydrous zinc chloride was added to the solution of the phenylhydrazone in tetralin. Similar results were obtained when 1-(1,3-dioxolan-2-yl)propan-2-one phenylhydrazone was subjected to the usual thermal indolisation conditions.

EXPERIMENTAL

Compounds were colourless, unless otherwise stated. Solutions in ether and chloroform were dried over anhydrous magnesium sulphate. U.v. and i.r. spectra were determined with Perkin-Elmer 137 and Unicam SP 200 spectrometers respectively. The u.v. spectra were determined for methanolic solutions; log ε values are quoted in parentheses. Unless otherwise stated, the i.r. spectral data are for samples prepared as potassium bromide discs. The mass and n.m.r. spectra were determined by the London University Inter-Collegiate Services.

3-*Formyl*-1,6-*diazaindene* (*Pyrrolo*[2,3-c]*pyridine*-3-*carbaldehyde*) (5).—Phosphoryl chloride (9·2 g.) was added to dry dimethylformamide (22 g.) with cooling and stirring. After 0·5 hr., this mixture was slowly added to a cooled solution of 3-amino-4-methylpyridine[6] (2·2 g.) in dimethylformamide (15 ml.). The mixture was then warmed in a flask fitted with a calcium chloride guard-tube on a boiling water-bath for 8 hr., and then cooled in an ice-bath. The yellow solid was filtered off, washed with dimethylformamide, and quickly sucked dry. The hygroscopic solid was added to potassium hydroxide solution (10%; 100 ml.) and refluxed for 3 hr. 3-*Formyl*-1,6-*diazaindene* separated during two days and gave needles (0·53 g., 19%), m.p. 217—218° (from methanol–ethyl acetate) (Found: C, 65·3; H, 4·3; N, 19·2. $C_8H_6N_2O$ requires C, 65·7; H, 4·1; N, 19·2%), $\nu_{max.}$ 3100 and 1670 cm.$^{-1}$ (NH and CO respectively), $\lambda_{max.}$ 215 (4·31), 247 (4·35), and 281 mμ (4·10). The *oxime* (6) was obtained either (*a*) from the aldehyde; m.p. 242—243° (decomp.) (from ethanol) (Found: C, 59·6; H, 4·9. $C_8H_7N_3O$ requires C, 59·6; H, 4·4%), $\nu_{max.}$ 3130—3200 cm.$^{-1}$ (OH); or (*b*) when the crude yellow solid (1 g.) from the preparation of the aldehyde, aqueous potassium hydroxide (10%, 20 ml.), and hydroxylamine hydrochloride (6 g.) were warmed on a water-bath for 3 hr. This sample (0·3 g.) had m.p. and mixed m.p. 242—243° (decomp.).

NN-*Dimethyl*-N′-(4-*methyl*-3-*pyridyl*)*formamidine* (13).—Chloroform was added to the filtrate obtained by removal of the initial precipitate in the preparation just described until precipitation of a yellow solid was complete. The solid was removed and dissolved in water, potassium carbonate solution was added (to pH 8—9), and the mixture was set aside at room temperature for 4 hr. Continuous extraction with chloroform yielded an oil which gave the *formamidine* (0·4 g.), b.p. 136—140°/0·2 mm. (Found: C, 66·7; H, 8·2. $C_9H_{13}N_3$ requires C, 66·3; H, 8·0%), $\nu_{max.}$ (film) 1630 cm.$^{-1}$ (C:N), *M* (mass spectrometry), 163. ($C_9H_{13}N_3$ requires *M*, 163).

1-*Acetyl*-3-*cyano*-1,6-*diazaindene* (1-*Acetylpyrrolo*[2,3-c]-*pyridine*-3-*carbonitrile*) (8).—Acetic anhydride (4 ml.) was added to 3-formyl-1,6-diazaindene oxime (0·8 g.) and the mixture was refluxed for 1 hr. Water was added and the precipitated *nitrile* gave needles (0·45 g.), m.p. 201—202° (from ethanol) (Found: C, 64·9; H, 4·1; N, 22·4. $C_{10}H_7N_3O$ requires C, 64·8; H, 3·8; N, 22·7%), $\nu_{max.}$ 2220 and 1722 cm.$^{-1}$ (C:N and C:O), $\lambda_{max.}$ 220 (4·45), 258 (3·57), 266 (3·59), and 287 mμ (3·76).

3-*Cyano*-1,6-*diazaindene* (*Pyrrolo*[2,3-c]*pyridine*-3-*carbonitrile*) (9).—The acetyl derivative (8) (0·3 g.) in water (10 ml.) was refluxed for 1 hr. After cooling in an ice-bath, the 3-*cyano*-1,6-*diazaindene* was collected and gave needles (0·16 g.), m.p. >300° (from ethanol) (Found: C, 66·8; H, 3·2; N, 29·9. $C_8H_5N_3$ requires C, 67·1; H, 3·5; N, 29·9%), $\nu_{max.}$ 2250 cm.$^{-1}$ (C:N), $\lambda_{max.}$ 258 (3·58), 266 (3·59), and 287 mμ (3·76).

1-*Acetyl*-3-*formyl*-1,6-*diazaindene Azlactone* {4-(1-*Acetylpyrrolo*[2,3-c]*pyridin*-3-*ylmethylene*)-2-*phenyloxazol*-5(4H)-*one*} (7).—3-Formyl-1,6-diazaindene (0·58 g.), benzoylglycine (0·72 g.), and anhydrous sodium acetate (0·16 g.) were intimately mixed. Acetic anhydride (3 ml.) was added and the mixture was heated on a water-bath for 1·5 hr. The yellow solution was poured into water (10 ml.), and the precipitated *azlactone* (0·7 g.) gave tan prisms, m.p. 241—242° (decomp.) (from glacial acetic acid) (Found: C, 68·8; H, 3·7. $C_{23}H_{15}N_3O_3$ requires C, 68·9; H, 3·9%), $\nu_{max.}$ 1777 and 1718 cm.$^{-1}$ (C:O).

3-*Methyl*-1,6-*diazaindene* (10) (3-*Methylpyrrolo*[2,3-c]-*pyridine*).—3-Formyl-1,6-diazaindene semicarbazone (0·6 g.) was added to a solution of sodium (0·6 g.) in dry diethylene glycol (30 ml.) and boiled in a nitrogen atmosphere under reflux for 3 hr. The solution was poured into water (150 ml.), the pH of the mixture was adjusted to 9, and the product was extracted with chloroform. This yielded a viscous liquid which gave a solid (10) after preparative t.l.c. on Kieselgel G (development with ethanol), m.p. and mixed m.p. with an authentic sample 122—123° (lit.,[1] 122—123°).

3-*Aminomethyl*-1,6-*diazaindene* (11) (3-*Aminomethylpyrrolo*[2,3-c]*pyridine*).—3-Formyl-1,6-diazaindene oxime (3·2 g.), in warm tetrahydrofuran (250 ml.), was slowly added to a stirred solution of lithium aluminium hydride (2·0 g.) in tetrahydrofuran (80 ml.) under nitrogen. The mixture was then refluxed for 8 hr. Water (20 ml.) was added and the solid was removed. Distillation gave 3-*aminomethyl*-1,6-*diazaindene* as a yellow oil (0·5 g.), b.p. 140°/0·5 mm., which solidified; m.p. 152—154° (decomp.), $\lambda_{max.}$ 221, 261, and 295 mμ. The *picrate* (from ethanol) had m.p. 198—200° (Found: C, 45·2; H, 2·8. $C_{14}H_{12}N_6O_7$ requires C, 44·7; H, 3·1%).

3-(NN-*Dimethylaminomethyl*)-1,6-*diazaindene* {3-(NN-*Diaminomethyl*)*pyrrole*[2,3-c]*pyridine*} (12).—Potassium borohydride (0·4 g.) was slowly added to 3-formyl-1,6-diazaindene (0·5 g.), aqueous dimethylamine (60%, 2·0 ml.), and water (5 ml.), and the mixture was stirred for 4 hr. An excess of potassium carbonate was added, and extraction with chloroform then yielded an oil which slowly solidified. Sublimation of this solid (60°/1 mm.) afforded 3-(NN-*dimethylaminomethyl*)-1,6-*diazaindene* (0·3 g.), m.p. 121—123° (Found: C, 68·3; H, 7·5. $C_{10}H_{13}N_3$ requires C, 68·6; H, 7·4%), $\nu_{max.}$ 3140 and 2830 (NH and CH_3 respectively), τ[$(CD_3)_2SO$] 7·87 (6H, s, NMe_2), 6·48 (2H, s, CH_2), 2·55 (1H, s, 2-H), 2·46 (1H, d, 4-H), 1·94 (1H, d, 5-H), 1·29 (1H, s, 7-H), and −1·28br (1H, s, exchangeable, NH) ($J_{4,5}$ 6 Hz).

[6] W. Herz and D. R. K. Murty, *J. Org. Chem.*, 1960, **25**, 2242.

3-*Formyl*-1,4-*diazabenz*[f]*indene* (*Pyrrolo*[3,2-b]*quinoline*-3-*carbaldehyde*) (16).—Phosphoryl chloride (18·4 g.) was added slowly, with cooling and stirring, to dry dimethylformamide (43·8 g.). After 0·5 hr., this mixture was added to 3-amino-2-methylquinoline [7] (6·3 g.) in dimethylformamide (30 ml.) and the whole was heated on a water-bath for 5 hr. The yellow precipitate was filtered from the cold mixture, quickly sucked dry, and boiled with aqueous potassium hydroxide (10%; 60 ml.) for 3 hr. The precipitate gave 3-*formyl*-1,4-*diazabenz*[f]*indene* (2·7 g.) as prisms, m.p. 280—282° (decomp.) [from ethanol (charcoal)] (Found: C, 73·3; H, 4·1; N, 14·2. $C_{12}H_8N_2O$ requires C, 73·5; H, 4·1; N, 14·3%), $\nu_{max.}$ 3350 and 1650 cm.$^{-1}$ (NH and C:O), $\lambda_{max.}$ 280 (4·20), 329 (4·06), and 355 mμ (3·88). The yellow *oxime* (18) (from ethanol) had m.p. >300° (Found: C, 68·0; H, 4·5; N, 19·8. $C_{12}H_9N_3O$ requires C, 68·2; H, 4·3; N, 19·9%).

1-*Acetyl*-3-*diacetoxymethyl*-1,4-*diazabenz*[f]*indene* (1-*Acetyl*-3-*diacetoxymethylpyrrolo*[3,2-b]*quinoline* (17).—The aldehyde (0·5 g.), in acetic anhydride (6·0 ml.), was refluxed for 1 hr., and then poured into water (20 ml.). The solid gave 1-*acetyl*-3-*diacetoxymethyl*-1,4-*diazabenz*[f]*indene* (0·35 g.) as needles, m.p. 163—164° [from ethanol (charcoal)] (Found: N, 8·3. $C_{18}H_{16}N_2O_5$ requires N, 8·2%), *m/e* 340 M^+ ($C_{18}H_{16}N_2O_3$ requires *M*, 340).

1-*Acetyl*-3-*formyl*-1,4-*diazabenz*[f]*indene Azlactone* {4-(1-*Acetylpyrrolo*[3,2-b]*quinolin*-3-*ylmethylene*)-2-*phenyloxazol*-5(4H)-*one*} (19).—Acetic anhydride (10 ml.) was added to an intimate mixture of the aldehyde (1·96 g.), benzoylglycine (1·8 g.), and anhydrous sodium acetate (0·5 g.), and the product was heated under reflux on a water-bath for 2 hr. On pouring the mixture into water the *azlactone* precipitated, and gave bright yellow needles (2·3 g), m.p. 265—266° (decomp.) (from glacial acetic acid) (Found: C, 72·1; H, 4·1. $C_{23}H_{15}N_3O_3$ requires C, 72·4; H, 4·1%), $\nu_{max.}$ 1701 and 1775 cm.$^{-1}$ (C:O).

1-*Acetyl*-3-*cyano*-1,4-*diazabenz*[f]*indene* (1-*Acetylpyrrolo*-[3,2-b]*quinoline*-3-*carbaldehyde*) (20).—The 3-formyl-4,4-diazabenz[*f*]indene oxime (0·4 g.), in acetic anhydride (4 ml.), was refluxed for 1 hr. and then poured into water. Crystallisation from ethanol gave the *cyano-compound* (0·27 g.) as needles, m.p. 190—191° (Found: C, 71·4; H, 4·0. $C_{14}H_9N_3O$ requires C, 71·5; H, 3·8%), $\nu_{max.}$ 2235 and 1722 cm.$^{-1}$ (C:N and C:O).

4,4-*Dimethoxybutan*-2-*one Phenylhydrazone*.—A mixture of 4,4-dimethoxybutan-2-one (5·2 g.), phenylhydrazine (3·6 g.), and benzene (100 ml.) was refluxed (with azeotropic removal of water) for 3 hr., and yielded the *phenylhydrazone* (5·9 g.) as needles from light petroleum (b.p. 60—80°), m.p. 64—65° (Found: C, 65·2; H, 8·1; N, 12·4. $C_{12}H_{18}N_2O_2$ requires C, 64·9; H, 8·1; N, 12·6%), $\nu_{max.}$ 3295, 1603, and 1117 cm.$^{-1}$ (NH, C:N, and C·O·C).

Attempted Thermal Indolisation of 4,4-*Dimethoxybutan*-2-*one Phenylhydrazone*.—A solution of 4,4-dimethoxybutan-2-one phenylhydrazone (11·3 g.), in diethylene glycol (100 ml.), was refluxed for 14 hr. under nitrogen. The mixture was poured into water; ether extraction then yielded 3-methyl-1-phenylpyrazole (4·4 g.) as an oil, b.p. 98°/2·5 mm., which solidified; m.p. 34—35° (lit.,[8] 38°).

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[7] W. Lawson, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1924, 626.

[8] I. I. Granberg and A. N. Kost, *Zhur. obshchei Khim.*, 1959, **29**, 658.