Azafulvenes. 2.[1] Formation of Iminium Salt from Pyrrole- and Indolecarbaldehyde and Its Reaction with Bases

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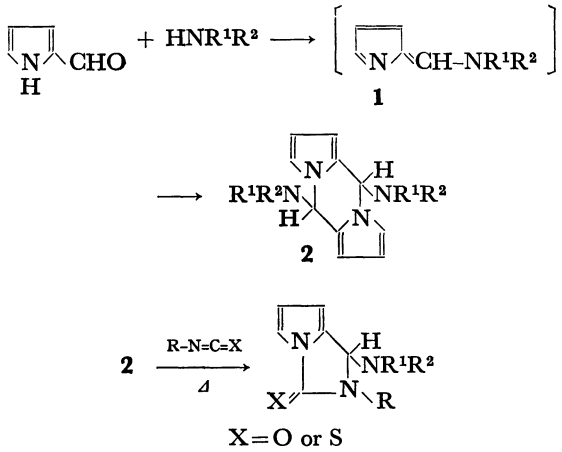
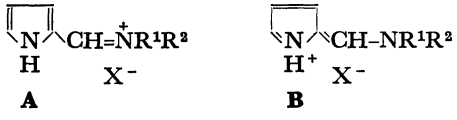
Pyrrole- and indolecarbaldehyde reacted with secondary ammonium perchlorate to produce the corresponding iminium perchlorate, which did not afford azafulvene, but instead its dimer, in good yield by deprotonation. These results indicate that the iminium perchlorate from pyrrole- and indolecarbaldehyde appears to be a convenient precursor of azafulvene.

In a preceding communication, the authors have reported that attempts to isolate 6-amino-1-azafulvene (**1**) from the reactions of pyrrole-2-carbaldehyde with secondary amines were unsuccessful because of a tendency to dimerize thermally. It has also been described that the thermal decomposition of dimer **2** regenerated **1** which was trapped as the corresponding [6+2] cycloadducts with isocyanates and isothiocyanate.[1]



X=O or S

It is well known that an enamine can be protonated to yield a stable iminium salt[2] which is also directly obtainable by the reaction of a carbonyl compound with the secondary ammonium salt.[3] Protonation of **1** containing an enamine system in its molecular structure would probably make itself stable enough to be isolated. Although two structures, iminium salt **A** and azafulvenium salt **B**, are possible as protonated products of **1**, both of them are possible as convenient precursors of 6-amino-1-azafulvene **1**.

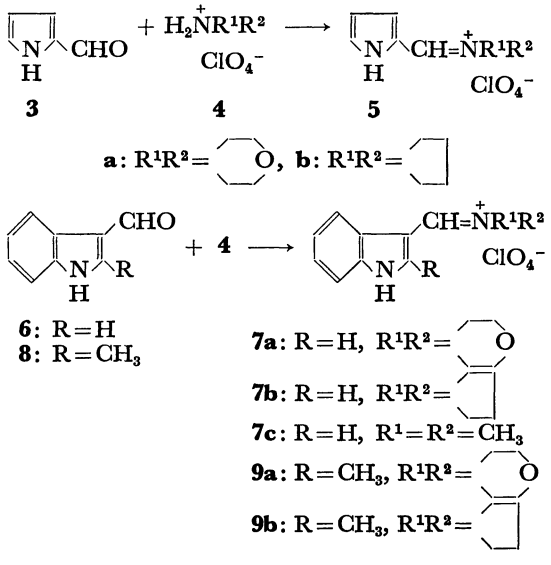


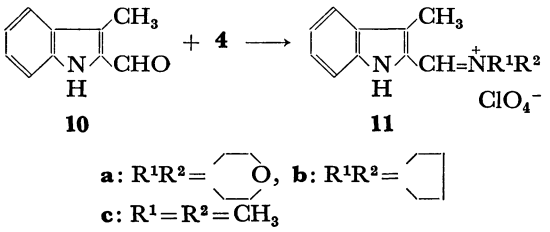
We have investigated which type of salt, iminium or azafulvenium salt, is formed from the reaction of pyrrole-2-, indole-2- and indole-3-carbaldehyde with secondary ammonium perchlorates and also examined whether these salts liberate the corresponding azafulvenes by deprotonation.

Results and Discussion

Preparation of Iminium Perchlorate. The reactions of pyrrole-2-carbaldehyde (**3**) with morpholinium (**4a**) and pyrrolodinium perchlorate (**4b**) in ethanol under refluxing conditions produced colorless prisms, **5a** and **5b**, in 57 and 40% yields, respectively. The molecular formulae of these products agree with those of the compounds derived from the 1:1 adduct with the elimination of water. The IR spectrum of **5a** showed the characteristic band of perchlorate salt at 1100 cm^{-1} and the band assignable to >NH and $-CH=\overset{+}{N}<$ absorption at 3220 and 1640 cm^{-1}, respectively. The compound **5a** exhibited an absorption maximum at 331 nm in its UV spectrum in ethanol and no absorption in the visible region, while it has been reported by Hafner and Pfeiffer[4] that 6,6-diphenyl-1-azafulvenium fluoroborate was of a deep yellow color (λ_{max} in CH_2Cl_2: 413, 363 and 267 nm). The corroborating evidence for the structure of **5a** was afforded by its NMR spectrum in trifluoroacetic acid, which revealed signals at τ 1.59 (1H, s, $-C\underline{H}=\overset{+}{N}<$), 2.38, 2.55 and 3.28 (each 1H, m, pyrrole ring protons) and 5.72 (8H, m, morpholino methylenes). The down field shift of the α-methylene protons of morpholino moiety are based on the electron affinity of the adjacent ammonium nitrogen atom.

From the above UV and NMR data, **5a** was deduced to be, not 6-morpholino-1-azafulvenium perchlorate **B** (X=ClO_4), but 2-pyrrolylmethylenemorpholinium perchlorate **A** (X=ClO_4). The compound **5b** has already been prepared by Sonnet[5] and identified to be *N*-(2-pyrrolylmethylene)pyrrolidinium perchlorate. No formation of azafulvenium salt **B** should occur due to





a lack of the stabilizing energy of the pyrrole ring, whereas iminium salt formation does not require any loss of energy.

The reactions of indole-3-carbaldehyde (**6**) with **4a**, **4b** and dimethylammonium perchlorate (**4c**) afforded the respective colorless crystals, **7a**, **7b** and **7c**, in excellent yield which were clearly identified to be 3-indolylmethyleneammonium perchlorates on the basis of their IR, NMR and UV spectra as well as elemental analyses.

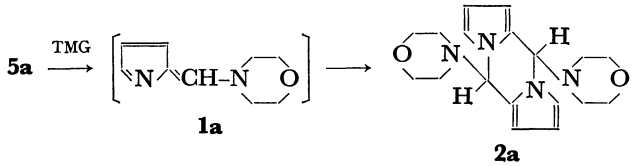
Similarly, the corresponding 3-(2-methylindolyl)-methyleneammonium perchlorates, **9a** and **9b**, were obtained on heating 2-methylindole-3-carbaldehyde (**8**) with **4a** and **4b** in ethanol.

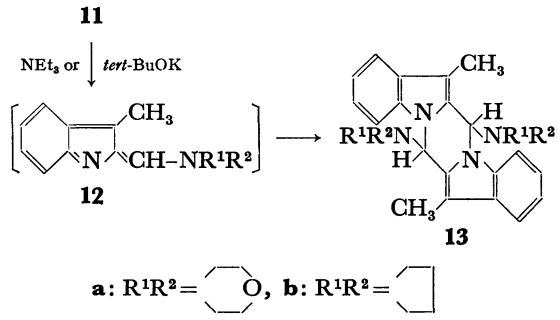
Although no reactions of 3-methylindole-2-carbaldehyde (**10**) with **4** took place during ethanol refluxing, **10** reacted with **4** to produce 2-(3-methylindolyl)-methyleneammonium perchlorate (**11**) when heated under reflux with continuous removal of the water formed in the reaction. The structures of **9** and **11** were also established by their spectroscopic results and elemental analyses.

Deprotonation of Iminium Perchlorate. For the purpose of the liberation of aminoazafulvenes, the deprotonation reactions of the iminium perchlorates, **5**, **7**, **9** and **11**, were investigated using bases such as triethylamine, tetramethylguanidine and potassium *tert*-butoxide.

The treatment of **5a** with tetramethylguanidine in ethanol gave pyrrole-2-carbaldehyde **3** which can be derived from the hydrolysis of the starting iminium perchlorate **5a** or 6-morpholino-1-azafulvene **1a** (NR^1R^2=N⌓O). The fact that the iminium perchlorate **5a** considerably resists hydrolysis in ethanol indicates azafulvene **1a** is formed at first in this reaction, followed by hydrolysis into **3**. Therefore, the reaction under anhydrous conditions was carried out and afforded another product **2a** which was identical to the dimer of **1a**, 5,10-dimorpholinodipyrrolo[1,2-*a*: 1′,2′-*d*]pyrazine, obtained by heating **3** with morpholine in benzene.[1]

The new compound **13a**, mp 242—243 °C (decomp.), was yielded quantitatively by the reaction of **11a** with triethylamine in benzene. The molecular formula of **13a** corresponds to the dimer of azafulvene **12a**. The NMR spectrum of **13a** in deuteriochloroform showed two methyls- and two methines-protons at τ 7.64 (6H) and 4.10 (2H) as singlets, respectively. On the basis of the spectral data, **13a** was identified to be 6,13-dihydro-5,12-



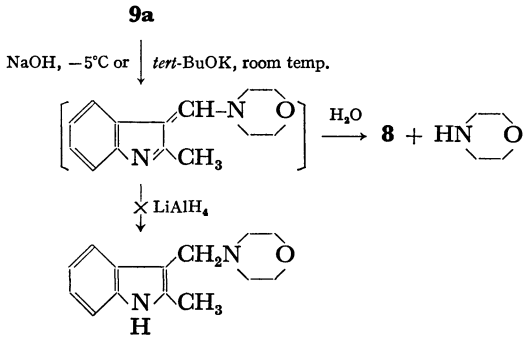


dimethyl-6,13-dimorpholinodiindolo[1,2-*a*: 1′,2′-*d*]-pyrazine.

Two isomers with the methine protons at the 6- and 13-positions of the pyrazine ring are possible for **13a**. Actually, both the *cis* and *trans* isomers have been isolated[1] in the case of the dimer of 6-(*N*-pyrrolidinyl)-1-azafulvene (**1b**), which is analogous to **13a**. The compound **13a** was determined to be the *trans* isomer because of the equivalence of the two methyls-protons and of the two methines-protons in the NMR spectrum.[1] Similarly, *trans*-6,13-dihydro-5,12-dimethyl-6,13-di(*N*-pyrrolidinyl)diindolo[1,2-*a*: 1′,2′-*d*]pyrazine (**13b**) was also obtained in excellent yield by treating **11b** with potassium *tert*-butoxide in benzene, while **11b** could not be deprotonated with triethylamine.

The above results show that 1-azafulvene is formed as an unstable intermediate[6] upon deprotonation of the corresponding iminium perchlorate and dimerized by [6+6] cycloaddition. This cyclodimerization reaction is considered to be reversible.[7] Therefore, the ease of the dimerization is attributable to the large difference between the stabilizing energies of 1-azafulvene and its dimer *via* a resonance. In particular, benzo[*b*]-1-azafulvene **12** has a tendency to change into the dimer **13** owing to the additional *o*-quinoid cyclic system in **12**.

On the other hand, benzo[*c*]-2-azafulvene, which is possible to be derived from the iminium salt **7** or **9**, is expected to be more thermally stable than benzo[*b*]-1-azafulvene. The reaction of **9a** with aqueous sodium hydroxide at −5 °C or with potassium *tert*-butoxide in benzene at room temperature gave a colorless product which was contaminated with 2-methylindole-3-carbaldehyde **8**. This moisture-sensitive product was not isolated in pure form and did not give reliable spectral data. Moreover, reduction with lithium aluminum hydride resulted in hydrolysis into **8**. The quantitative conversion of this product to **8** by the moisture in an atmosphere is explained by the guess that this water-



sensitive product is benzo[*c*]-2-azafulvene, which is thermally stable but subject to hydrolysis due to the nature of enamines.

Although similar deprotonation reactions of **7** gave products which did not include any halogen ions, the structures of these products have not yet been clarified.

Experimental

All melting points were determined using a Mitamura Riken micro melting point apparatus and are uncorrected. The IR spectra were taken in KBr disks with a Nihon Bunko IRA-1 spectrometer. The NMR spectra were obtained at 100 MHz using a Nihon Denshi JNM-MH-100 spectrometer with TMS as an internal reference. The mass spectra were determined with a Nihon Denshi JMS-06 mass spectrometer equipped with a direct inlet and at an ionization energy of 75 eV.

Materials. Pyrrole-2-(**3**); mp 44—47 °C, bp 128 °C/20 Torr (lit,[8] bp 78 °C/2 Torr), indole-3-(**6**); mp 193—195 °C (lit,[9] mp 194 °C) and 2-methylindole-3-carbaldehyde (**8**); mp 201—202 °C (lit,[10] mp 202—203 °C) were prepared by the Vilsmeier reaction of the corresponding pyrroles and indoles. 3-Methylindole-2-carbaldehyde (**10**) was obtained by oxidation of 2-(3-methylindolyl)methanol with activated manganese dioxide in a 58% yield; mp 139—141 °C (lit,[11] mp 138—140 °C).

N-*(2-Pyrrolylmethylene)morpholinium Perchlorate (**5a**).* The mixture of 0.95 g (0.01 mol) of **3** and 1.88 g (0.01 mol) of **4a** was heated under reflux in 20 ml of ethanol for 1 hr. On cooling, the precipitated product was filtered and washed with a benzene–ethanol (1: 1 vol/vol) mixture giving 1.50 g (57%) of **7a**. Recrystallization from ethanol produced colorless prisms; mp 142—143 °C (decomp.). IR (KBr) cm^{-1}: 3220 (>NH), 1640 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.59 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 2.30, 2.47, 3.40 (each 1H, m, pyrrole ring protons) and 5.72 (8H, m, morpholino methylenes). UV (EtOH): 331 nm. Found: C, 40.75; H, 4.74; N, 10.43%. Calcd for $C_9H_{13}N_2O_5Cl$: C, 40.84; H, 4.95; N, 10.58%.

N-*(2-Pyrrolylmethylene)pyrrolidinium Perchlorate (**5b**).* Prepared in the same way as **5a**, starting with 0.95 g of **3** and 1.72 g of **4b** in 20 ml of ethanol. Colorless prisms from ethanol; mp 103—104 °C (decomp.). IR (KBr) cm^{-1}: 3220 (>NH), 1640 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.65 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 2.58, 2.82, 3.46 (each 1H, m, pyrrole ring protons), 6.01 and 7.77 (each 4H, m, pyrrolidinyl methylenes). UV (EtOH): 329 nm. Found: C, 43.40; H, 5.14; N, 11.19%. Calcd for $C_9H_{13}N_2O_4Cl$: C, 43.47; H, 5.27; N, 11.27%.

N-*(3-Indolylmethylene)morpholinium Perchlorate (**7a**).* A 1.45 g (0.01 mol) of **6** and 1.88 g (0.01 mol) of **4a** were refluxed in 20 ml of ethanol for 2 hr. After cooling, 2.80 g (89%) of **7a** were precipitated. Recrystallization from ethanol yielded colorless prisms; mp 242—244 °C (decomp.). IR (KBr) cm^{-1}: 3240 (>NH), 1640 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.31 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 1.64 (1H, d, 2-H of indole ring), 2.13—2.60 (4H, m, aromatic protons) and 5.66 (8H, m, morpholino methylenes). UV (EtOH): 288 nm. Found: C, 49.55; H, 4.79; N, 8.95%. Calcd for $C_{13}H_{15}N_2O_5Cl$: C, 49.61; H, 4.80; N, 8.90%.

N-*(3-Indolylmethylene)pyrrolidinium Perchlorate (**7b**).* The method used here is virtually identical with that used for **7a**: 1.45 g of **6** and 1.72 g of **4b** were refluxed for 2 hr. Colorless prisms from ethanol; mp 249—250 °C (decomp.). Yield: 2.43 g (81%). IR (KBr) cm^{-1}: 3280 (>NH), 1640 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.26 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 1.89 (1H, d, 2-H of indole ring), 2.08—2.68 (4H, m, aromatic protons), 5.95 and 7.64 (each 4H, m, pyrrolidinyl methylenes). UV (EtOH): 352 nm. Found: C, 52.07; H, 4.91; N, 9.40%. Calcd for $C_{13}H_{15}N_2O_4Cl$: C, 52.27; H, 5.06; N, 9.38%.

N-*(3-Indolylmethylene)*-N,N-*dimethylammonium Perchlorate (**7c**)* The same procedure as that for **7a** using 2.9 g of **6** and 2.92 g of **4c** in 40 ml of ethanol afforded 4.44 g (78%) of **7c**; colorless prisms from ethanol; mp 217—220 °C (decomp.). IR (KBr) cm^{-1}: 3260 (>NH), 1640 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.60 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 1.96 (1H, d, 2-H of indole ring), 2.24—2.73 (4H, m, aromatic protons), 6.28 and 6.50 (each 3H, s, =$\overset{+}{N}$($C\underline{H}_3$)$_2$). Found: C, 48.82; H, 4.82; N, 10.07%. Calcd for $C_{11}H_{13}N_2O_4Cl$: C, 48.63; H, 4.82; N, 10.31%.

N-*(2-Methyl-3-indolylmethylene)morpholinium Perchlorate (**9a**).* To the stirred suspension of **8** (3.2 g, 0.02 mol) in 40 ml of ethanol was added 3.76 g (0.02 mol) of **4a** and which were refluxed for 2 hr. On cooling, **9a** (6.34 g, 98%) was filtered and recrystallized from ethanol to give colorless prisms, mp 248—249 °C (decomp.). IR (KBr) cm^{-1}: 3280 (>NH), 1640 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ 1.48 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 2.36—2.67 (4H, m, aromatic protons), 5.65 (8H, m, morpholino methylenes) and 7.23 (3H, s, -$C\underline{H}_3$). UV (EtOH): 289 nm. Found: C, 51.65; H, 5.05; N, 8.54%. Calcd for $C_{14}H_{17}N_2O_5Cl$: C, 51.15; H, 5.21; N, 8.52%.

N-*(2-Methyl-3-indolylmethylene)pyrrolidinium Perchlorate (**9b**).* The same method as that for **9a** starting from **8** (1.59 g) and **4b** (1.72 g) gave 2.31 g (74%) of **9b**; colorless prisms from ethanol; mp 238—239 °C (decomp.). IR (KBr) cm^{-1}: 3250 (>NH), 1640 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.67 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 2.21—2.78 (4H, m, aromatic protons), 5.84, 7.74 (each 4H, m, pyrrolidinyl methylenes) and 7.32 (3H, s, -$C\underline{H}_3$). UV (EtOH): 344 nm. Found: C, 54.09; H, 5.46; N, 9.04%. Calcd for $C_{14}H_{17}N_2O_4Cl$: C, 53.77; H, 5.48; N, 8.96%.

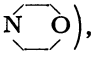
N-*(3-Methyl-2-indolylmethylene)morpholinium Perchlorate (**11a**).* A heterogeneous mixture of **10** (1.1 g, 0.069 mol), **4a** (1.3 g, 0.069 mol) and 3 drops of morpholine in 100 ml of benzene was heated under reflux for 5 hr with stirring, while water was continuously removed by means of Dean-Stark trap. The separated solid was collected by filtration, washed with a small amount of ethanol. Colorless prisms from ethanol; mp 240—242 °C (decomp.). Yield: 1.82 g (80%). IR(KBr) cm^{-1}: 3320 (>NH), 1630 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.57 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 2.26—2.90 (4H, m, aromatic protons), 5.64 (8H, m, morpholino methylenes) and 7.36 (3H, s, -$C\underline{H}_3$). Found: C, 51.20; H, 5.63; N, 8.74%. Calcd for $C_{14}H_{17}N_2O_5Cl$: C, 51.15; H, 5.21; N, 8.52%.

N-*(3-Methyl-2-indolylmethylene)pyrrolidinium Perchlorate (**11b**).* The similar procedure to that of **11a** using 1.2 g of **10**, 1.29 g of **4b** and 3 drops of pyrrolidine, but being refluxed for 10 hr, gave 2.13 g (91%) of **11b**. Recrystallization from ethanol afforded colorless prisms; mp 265—266 °C (decomp.). IR (KBr) cm^{-1}: 3320 (>NH), 1630 (-CH=$\overset{+}{N}$<) and 1100 (ClO_4). NMR (CF_3COOH) τ:1.43 (1H, s, -C$\underline{H}$=$\overset{+}{N}$<), 2.18—2.81

(4H, m, aromatic protons), 5.72, 7.68 (each 4H, m, pyrrolidinyl methylenes) and 7.33 (3H, s, $-C\underline{H}_3$). Found: C, 53.51; H, 5.84; N, 8.87%. Calcd for $C_{14}H_{17}N_2O_4Cl$: C, 53.77; H, 5.48; N, 8.96%.

*N-(3-Methyl-2-indolylmethylene)-N,N-dimethylammonium Perchlorate (**11c**).* A mixture of **10** (0.31 g), **4c** (0.28 g) and a few drops of dimethylamine was refluxed in 70 ml of benzene for 17 hr to give 0.34 g (60%) of **11c**. Colorless prisms from ethanol; mp 257 °C (decomp.). IR (KBr) cm^{-1}: 3325 (>NH), 1640 ($-CH=\overset{+}{N}<$) and 1100 (ClO_4). NMR (CF_3COOH) τ: 1.55 (1H, s, $-C\underline{H}=\overset{+}{N}<$), 2.12—2.78 (4H, m, aromatic protons), 6.06, 6.14 (each 3H, s, $=\overset{+}{N}(C\underline{H}_3)_2$) and 7.28 (3H, s, $-C\underline{H}_3$).

*The Reaction of **5a** with Tetramethylguanidine.* To the suspension of **5a** (0.27 g) in 5 ml of dry tetrahydrofuran was added 0.12 g of tetramethylguanidine which was stirred at room temperature for 10 min. The resulting solution was dried *in vacuo*, and the residue was washed with water and then dried. Recrystallization from methanol gave 0.16 g (95%) of 5,10-dihydro-5,10-dimorpholinodipyrrolo[1,2-*a*: 1′,2′-*d*]-pyrazine (**2a**), mp 190—193 °C (decomp.) (lit,[1] mp 190—193 °C (decomp.)).

*The Reaction of **11a** with Triethylamine.* 1.0 g of **11a** was suspended in 6 ml of dry benzene added to an excess of triethylamine. After refluxing for 3 hr, benzene was evaporated to give a colorless powder which was washed with water. Recrystallization from ether gave colorless needles of 6,13-dihydro-5,12-dimethyl-6,13-dimorpholinodiindolo-[1,2-*a*: 1′,2′-*d*]pyrazine (**13a**), mp 242—243 °C (decomp.). Yield 0.7 g (100%). NMR ($CDCl_3$) τ: 2.44—2.96 (8H, m, aromatic protons), 4.10 (2H, s, $>C\underline{H}-N<$), 6.38, 7.16 (each 8H, m, morpholino methylenes) and 7.64 (6H, s, $-C\underline{H}_3$). Mass (*m/e*): 456 (M^+), 370 (M^+- ), 284 (370^+- ) and 228 (M^{2+}). Found: C, 74.23; H, 6.96; N, 11.99%. Calcd for $C_{24}H_{32}N_4O_2$: C, 73.66; H, 7.06; N, 12.27%.

*The Reaction of **11b** with Potassium tert-Butoxide.* The mixture of 0.9 g of **11b**, 0.35 g of potassium *tert*-butoxide in 30 ml of dry benzene was refluxed for 5 hr. The residue obtained by evaporation was washed with water to yield 0.43 g (70%) of 6,13-dihydro-5,12-dimethyl-6,13-(*N*-pyrrolidinyl)diindolo[1,2-*a*: 1′,2′-*d*]pyrazine (**13b**), mp 204—205 °C (decomp.). Colorless prisms from ether. NMR ($CDCl_3$) τ: 2.40—3.00 (8H, m, aromatic protons), 3.76 (2H, s, $>C\underline{H}-N<$), 7.13, 8.32 (each 8H, m, pyrrolidinyl methylenes) and 7.62 (6H, s, $-C\underline{H}_3$). Mass (*m/e*): 424 (M^+), 354 (M^+- ), 284 (354^+- ) and 212 (M^{2+}). Found: C, 79.81; H, 8.16; N, 12.97%. Calcd for $C_{24}H_{32}N_4$: C, 79.20; H, 7.60; N, 13.20%.

*The Reaction of **9a** with Aqueous Sodium Hydroxide.* The suspension of 0.62 g of **9a** in 10 ml of methylene dichloride was cooled to −5 °C with ice-salt and then 10 ml of a 10% sodium hydroxide solution was added dropwise under vigorous stirring. As soon as the addition was completed, the organic layer was separated and dried with anhydrous magnesium sulfate. Evaporation of the solvent below 20 °C gave 0.40 g of colorless crystals, which were tentatively assigned to be 3-morpholinomethylene-2-methyl-3*H*-indole.

References

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