Fused Indoles. 2. Synthesis and Reactions of Imidazo[1,2-*a*]- and Pyrimido[1,2-*a*]-indoles

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The alkylation of 2-chloroindole-3-carboxaldehyde (**1**) and 3-acetyl-2-chloroindole (**5**) with 3-chloro-*N,N*-dimethyl-1-propylamine, 3-chloro-*N,N*-diethyl-1-propylamine and 2-chloro-*N,N*-dimethyl-1-ethylamine is described. Following alkylation, demethylation occurs and furnishes imidazo[1,2,-*a*]- and pyrimido[1,2-*a*]indoles (**3a,6,8,10**). Pyrimido-indole **3a**, on treatment with lithium aluminum hydride, furnishes the bis-indole **12**. Analogous reaction with diborane affords the reduced product **14**, while reaction with methyllithium yields the deformylated product **13**. Spectral data of the resulting compounds are also discussed.

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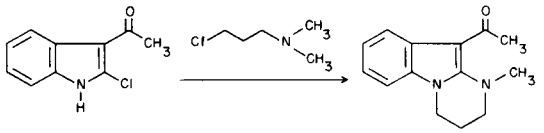
In a previous report (1), we described the utilization of 2-chloroindole-3-carboxaldehydes for the synthesis of thiazino[3,4-*b*]indoles. We now wish to communicate further observations we have made in studying the chemical behavior of these indoles.

As we have reported (1), 2-chloroindole-3-carboxaldehyde can readily be alkylated on the nitrogen atom with methyliodide in the presence of sodium hydride. We now further observe that on reaction of the preformed anion of **1a** with 3-chloro-*N,N*-dimethyl-1-propylamine (**2**), two products resulted (see Scheme I). The major product of the reaction was determined to be **3a** by nmr, mass spectral and elemental analysis. The outstanding features in the nmr spectrum of **3a** are a signal at δ 9.8 (formyl proton), and a multiplet centered at δ 8.1 (assigned to proton at position 9 in the aromatic ring). The three methylene signals of the hydrogenated pyrimidine ring are observed at δ 3.85 (t), 3.35 (m), and 2.1 (m), respectively. The protons of one N-CH_3 appear as a singlet at δ 3.25. The lack of a second nmr signal for an N-CH_3 group indicates immediately that one N-CH_3 has been lost during the transformation. The second product (**4a**) isolated from the reaction mixture proved to be the *N*-methyl derivative of the starting material **1a**. We postulate that during the reaction, intermediate **A** (Scheme I) is formed, which in turn is quarternized (intermediate **B**) and spontaneously looses methylchloride. The liberated methylchloride in a secondary reaction competes in alkylating the anion of **1a**, subsequently leading to the formation of **4a**.

Analogously, the use of 3-acetyl-2-chloroindole (1) (**5**) in this reaction afforded compound **6** in 37% yield.



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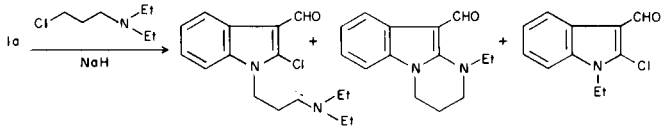
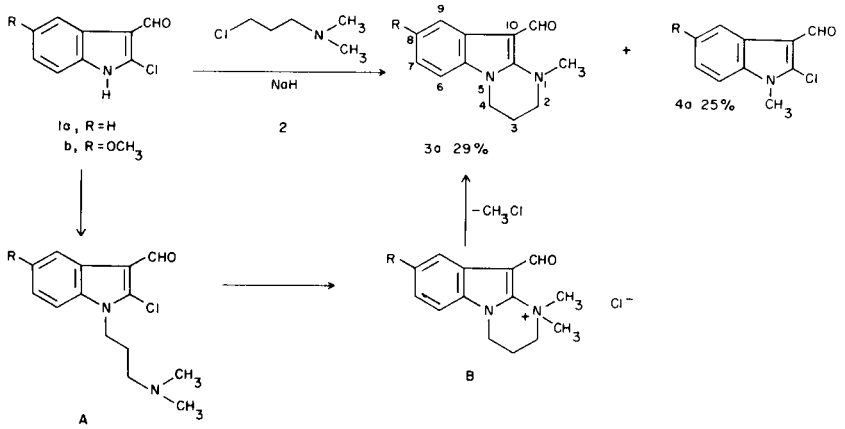
When the same reaction was attempted using **1a** and 3-chloro-*N,N*-diethyl-1-propylamine, three products were formed (2). The tricyclic product **8** was isolated in only 17% yield, the major component of the reaction being the alkylated chloroindole **7**.



7 (23%) 8 (17%) 9

Scheme I



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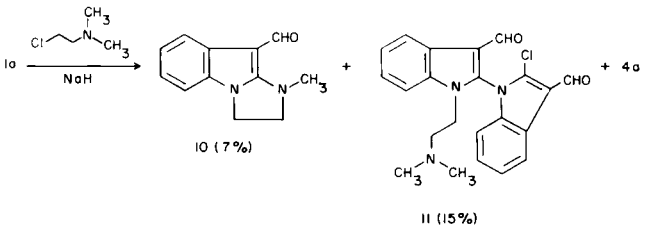
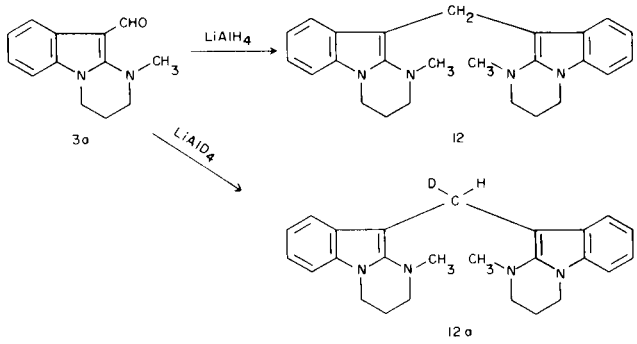
The reaction of **1a** with 2-chloro-*N,N*-dimethyl-1-ethylamine afforded three products as well (3). The tricyclic product **10** was isolated in only 7% yield. The major product, isolated in 15% yield from the reaction mixture, was assigned to have structure **11** based on the following data: its mass spectrum indicated that the highest molecular ion m/e observed was 393 (containing chlorine); the nmr spectrum exhibited two distinct aldehyde singlets at δ 10.05 and 9.95; and its elemental analysis was in full accord with the calculated values for the empirical formula of **11**.

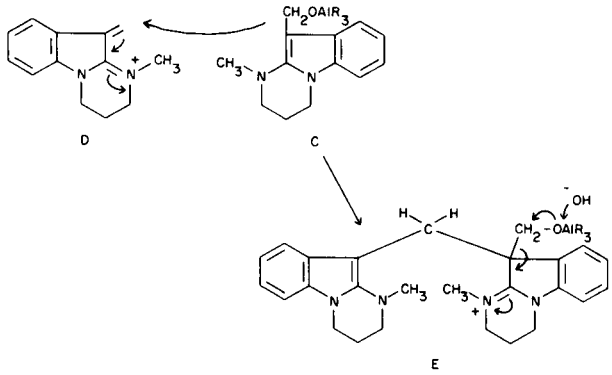


In an attempt to further elaborate the system, an investigation into the reactivity of the formyl group of these compounds (*e.g* **3a**) was undertaken. When **3a** was treated with lithium aluminum hydride, the expected 10-hydroxymethylene product was not detected. Instead, one compound could readily be isolated whose mass spectrum indicated that its highest ion m/e observed was 384. The ir spectrum showed no absorptions in the hydroxyl and carbonyl regions, while the nmr spectrum indicated the incorporation of a methylene function at δ 4.2 (s). Based on these facts and on its elemental composition, we have assigned structure **12** to this product.

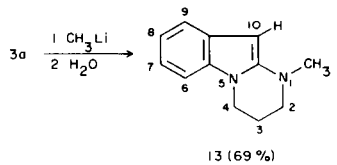


Similar treatment of **3a** lithium aluminum deuteride yielded a compound where in the mass spectrum, the highest ion m/e was observed at 385, which indicates the incorporation of only one deuterium atom. Comparison of the nmr spectra of the lithium aluminum hydride and the lithium aluminum deuteride reaction products showed that the methylene signal at δ 4.2 (in the lithium aluminum hydride product) was replaced in the lithium aluminum deuteride compound with a slightly broadened peak accounting for only one proton. This suggests that the deuterium is incorporated in the methylene bridge (structure **12a**).

The formation of these reaction products (**12** and **12a**) can be explained by the following mechanism. Compound **12** is reduced to the corresponding carbinol (**C**), which after partial elimination of water, leads to the formation of the immonium compound **D**. Compound **D** in turn reacts with the remaining carbinol **C** to form the intermediate **E**, which fragments during work up to yield the product **12**.



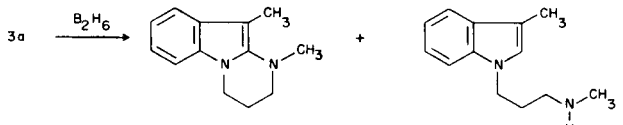
Subsequently, it was decided to treat **3a** with methyl lithium in the hope of obtaining a compound analogous to **12**, but possessing a methyl group attached to the methylene bridge. Treatment of **3a** with methyl lithium did not produce the desired product, but a pure compound was isolated in 69% yield. Based on the following data, we have tentatively assigned its structure to be **13**: the infrared spectrum lacks any carbonyl absorption. In the nmr, no incorporation of a methyl function is evident. The formyl proton in the starting material **3a** at δ 9.8 is absent while a new signal appears at δ 5.4. This signal was attributed to the proton at position 10 in compound **13**. In addition, the multiplet assigned to the proton at position 9 (of **3a**) is shifted dramatically upfield from δ 8.1 to 7.3, indicating that this proton is no longer deshielded by the formyl group. Further evidence was gathered by mass spectral studies which indicated that the highest ion m/e observed was 186. All these findings are congruent with the assignment of structure **13**.



When a similar reaction was performed and the reaction mixture was quenched with deuterium oxide, a 1:1 mixture (by nmr) of **13** and a compound analogous to **13**, but containing a deuterium atom at the 10 position, was isolated. Presently, the mechanism for the formation of compound **13** is not known.

The treatment of **3a** with diborane produced a 1:1 mixture of **14** and **15**. Separation of the two compounds could

only be achieved by the use of preparative gas chromatography and only nmr and mass spectral data were obtained. The nmr spectrum of **14** clearly exhibited the presence of two methyl groups, the N-CH_3 at δ 3.05 and the C-CH_3 at δ 2.3. In the mass spectrum, the highest ion m/e observed was 200 which corresponds to the molecular weight of **14**.



14 15

The identity of **15** was apparent from the upfield shift of the methylene adjacent to the N-CH_3 group. In the cyclic systems the methylene signal appears between δ 3.4 and 3.1; in the acyclic indoles (*e.g.* **7**), the signal is found further upfield at δ 2.55. The corresponding methylene signal of **15** also appears at δ 2.55, which is in accordance with the observations made in the spectrum of **7**. In addition, the 2-indolyl proton is clearly visible at δ 6.9, which is consistent with published results (5). In the mass spectrum, the highest ion m/e observed was 202 which corresponds to the molecular weight of **15**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrophotometer.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

1-Methyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]indole-10-carboxaldehyde (**3a**).

To a cooled solution of 14.8 g. (0.083 mole) of **1a** in 200 ml. of tetrahydrofuran was added 4.0 g. of sodium hydride (0.083 mole) (50% in mineral oil, pentane washed) in portions. The mixture was stirred at 0° for 20 minutes. Then 10.0 g. (0.083 mole) of 3-chloro-*N,N*-dimethyl-1-propylamine were added and the mixture was stirred at 70° for 72 hours. The reaction mixture was allowed to cool to room temperature and the resulting precipitate was filtered and washed with ether (compound **4a** remains in the tetrahydrofuran filtrate). The solid was triturated with 500 ml. of boiling ethyl acetate. The insoluble material was filtered off and the filtrate was concentrated to yield 4.3 g. of **3a** (29%), m.p. 183-186°; ir (Nujol): 1595 cm^{-1}; nmr (DMSO-d_6): δ 9.8 (s, 1), 8.1 (m, 1), 7.0 (m, 3), 3.85 (t, 2), 3.35 (m, 2), 3.25 (s, 3), 2.1 (m, 2); ms: (70 eV) m/e 214 (M+).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.9; H, 6.6; N, 13.1. Found: C, 72.8; H, 6.8; N, 13.2.

8-Methoxy-1-methyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]indole-10-carboxaldehyde (**3b**).

The reaction was performed similar to the one described for the preparation of **3a** and the product, **3b**, was isolated in 37% yield, m.p. 198-200°; ir (Nujol): 1600 cm^{-1}; nmr (deuteriochloroform): δ 9.85 (s, 1), 7.85 (d, 1), 6.7 (m, 2), 3.8 (s, 3), 3.7 (t, 2), 3.35 (m, 2), 3.2 (s, 3), 2.1 (m, 2).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6; N, 11.5. Found: C, 68.8; H, 6.9; N, 11.1.

Methyl 1,2,3,4-tetrahydro-1-methylpyrimido[1,2-*a*]indol-10-yl Ketone (**6**).

The reaction was performed similar to the one described for the preparation of **3a**. The product, **6**, was isolated in 37% yield, m.p. 124-126°; ir (chloroform): 1610 cm^{-1}; nmr (deuteriochloroform): δ 7.7 (m, 1), 7.1 (m, 3), 3.9 (t, 2), 3.3 (m, 2), 3.15 (s, 3), 2.6 (s, 3), 2.1 (m, 2).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.6; H, 7.1; N, 12.3. Found: C, 73.4; H, 7.0; N, 12.1.

1-Ethyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]indole-10-carboxaldehyde (**8**).

Following the conditions described for the preparation of **3a**, 9.6 g. of **1a** and 8.0 g. of 3-chloro-*N,N*-diethyl-1-propylamine were allowed to react. The mixture was allowed to cool to room temperature and the precipitate (sodium chloride) was removed by filtration. The tetrahydrofuran was removed under reduced pressure and the resulting residue was dissolved in methylene chloride. This solution was extracted with 2*N* hydrochloric acid. The aqueous phase was made basic by addition of 2*N* sodium hydroxide and the resulting oil was extracted into methylene chloride. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel using chloroform to elute the product. Crystallization from methylene chloride/ethyl acetate furnished 2.1 g. of **8** (17%), m.p. 128-130°; ir (chloroform): 1635, 1605 cm^{-1}; nmr (deuteriochloroform): δ 9.9 (s, 1), 8.2 (m, 1), 7.0 (m, 3), 3.85-3.25 (m, 6), 2.1 (m, 2), 1.25 (t, 3).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.1; N, 12.3. Found: C, 73.4; H, 7.0; N, 12.7.

A second more polar fraction isolated from the column contained 3.7 g. of **7** (23%) (oil); ir (chloroform): 2840, 1660 cm^{-1}; nmr (deuteriochloroform): δ 10.1 (s, 1), 8.25 (m, 1), 7.3 (m, 3), 4.25 (t, 2), 2.55 (m, 6), 1.95 (m, 2), 1.0 (t, 6); ms: (70 eV) m/e 292 (M+, containing chlorine).

2,3-Dihydro-1-methyl-1*H*-imidazo[1,2-*a*]indole-9-carboxaldehyde (**10**).

The reaction and workup was performed similar to the one described for the preparation of **8**. The product, **10**, was isolated in 7% yield, m.p. 190-193°; nmr (deuteriochloroform): δ 9.9 (s, 1), 8.0 (m, 1), 6.95 (m, 3), 3.8 (s, 4), 3.05 (s, 3).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.0; N, 14.0. Found: C, 71.9; H, 6.3; N, 14.3.

2-Chloro-1′-(2-dimethylaminoethyl)-1,2′-bisindole-3,3′-dicarboxaldehyde (**11**).

This product was isolated from the reaction mixture of the preparation of **10** by column chromatography of the mother liquor in 15% yield, m.p. 180-181°; ir (chloroform): 1660 cm^{-1}; nmr (deuteriochloroform): δ 10.05 (s, 1), 9.95 (s, 1), 8.1 (m, 2), 7.4-6.6 (m, 6), 4.5 (s, 4), 2.65 (s, 6); ms: (70 eV) m/e 393 (M+, containing chlorine).

Anal. Calcd. for $C_{22}H_{20}ClN_3O_2$: C, 67.1; H, 5.1; N, 10.7; Cl, 9.0. Found: C, 66.7; H, 5.3; N, 10.3; Cl, 9.2.

10-10′-Methylenebis(1,2,3,4-tetrahydro-1-methylpyrimido[1,2-*a*]indole (**12**).

To a suspension of 90 mg. of lithium aluminum hydride in 10 ml. of tetrahydrofuran was added 0.5 g. of **3a** and the mixture was stirred at 25° for 90 minutes. Approximately 0.5 ml. of saturated sodium sulfate was added and the resulting solids were filtered off. The filtrate was evaporated under reduced pressure and the resulting oil was crystallized from methylene chloride/ether to yield 100 mg. of **12** (22%), m.p. 173-178°; ir (chloroform): 1565 cm^{-1}; nmr (deuteriochloroform): δ 7.25-6.8 (m, 8), 4.2 (s, 2), 3.95 (t, 4), 3.15 (m, 4), 3.0 (s, 6), 2.1 (m, 4); ms: (70 eV) m/e 384 (M+).

Anal. Calcd. for $C_{25}H_{28}N_4$: C, 78.1; H, 7.3; N, 14.6. Found: C, 77.8; H, 7.6; N, 14.8.

10,10′-Methylene-*d*-bis(1,2,3,4-tetrahydro-1-methylpyrimido[1,2-*a*]indole (**12a**).

The reaction was performed similar to that described for the prepara-

tion of **12**, and yielded 22% of **12a**, m.p. 167-174°; nmr (deuteriochloroform): δ 7.2-6.8 (m, 8), 4.17 (s, 1), 3.95 (t, 4), 3.15 (m, 4), 3.0 (s, 6), 2.05 (m, 4); ms: (70 eV) m/e 385 (M+).

1-Methyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]indole (**13**).

To a suspension of 5.3 g. of **3a** in 500 ml. of tetrahydrofuran, under a blanket of nitrogen, was added dropwise 16 ml. of methyllithium (5.75% in ether). The resulting solution was stirred at 25° for 3 hours. Then an additional 3 ml. of the methyllithium solution were added and the solution was stirred at 25° for an additional 2 hours. Fifteen ml. of water were added and the mixture was evaporated under reduced pressure. The residue was dissolved in methylene chloride and washed with water. Evaporation of the solvent furnished 4.3 g. of an oil, which was crystallized from ether/pentane to yield 3.2 g. of **13** (69%), m.p. 115-117°; ir (chloroform): 1575 cm^{-1}; nmr (deuteriochloroform): δ 7.3 (m, 1), 6.95 (m, 3), 5.4 (s, 1), 3.9 (t, 2), 3.1 (m, 2), 2.85 (s, 3), 2.2 (m, 2); ms: (70 eV) m/e 186 (M+).

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.4; H, 7.6; N, 15.0. Found: C, 77.4; H, 8.0; N, 14.9.

1,10-Dimethyl-1,2,3,4-tetrahydropyrimido[1,2-*a*]indole (**14**).

To a suspension of 1.0 g. of **3a** in 25 ml. of diglyme, under a blanket of nitrogen, were added dropwise, 5.0 ml. of a diborane solution (1 M in THF) and the mixture was stirred at 25° for 48 hours. The reaction mixture was poured on water and extracted into ethyl acetate. The solvent was removed under reduced pressure to yield 0.6 g. of an oil. A sample was subjected to preparative gas chromatography to furnish **14**; nmr (deuteriochloroform): δ 7.4-6.9 (m, 4), 3.9 (t, 2), 3.15 (m, 2), 3.05 (s, 3), 2.3 (s, 3), 2.1 (m, 2); ms: (70 eV) m/e 200 (M+).

The second fraction isolated from the gas chromatography was **15**; nmr (deuteriochloroform): δ 7.6 (m, 1), 7.2 (m, 3), 6.1 (d, 1), 4.15 (t, 2), 2.55 (t, 2), 2.40 (s, 3), 2.35 (d, 3), 1.95 (t, 2), 1.75 (s, broad, 1); ms: (70 eV) m/e 202 (M+).

Acknowledgement.

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REFERENCES AND NOTES

(1) G. M. Coppola and G. E. Hardtmann, *J. Heterocyclic Chem.*, **14**, 1117 (1977).

(2) The 2-chloro-1-ethylindole-3-carboxaldehyde was not isolated.

(3) The 2-chloro-1-methylindole-3-carboxaldehyde was not isolated.

(4) No attempts were made to search for further compounds in the reaction mixture.

(5) Varian NMR Spectra Catalog, Vol. 1.