traces of allyl alcohol. A sample was analyzed by mass spectrometry as previously reported.[4] The remainder was diluted to 2 ml with ordinary water and then treated with excess Os_2O_6(pyridine)$_4$ and a trace of free pyridine. After standing overnight, the solution was filtered. The filtrate was dried under a stream of air to give the brown bis(pyridine) osmate ester of glycerol. This ester was reductively hydrolyzed to glycerol in water in the presence of a 2–3-fold excess of $NaHSO_3$ at room temperature for 30 min. The mixture was analyzed by measurement of the mass spectrum at m/e 61, 62, and 63 using the calculations described by Biemann.[31] Suitable blanks were run with $NaHSO_3$ alone.

Dissociation Constants for $OsO_3 \cdot L_2$.—The distribution coefficient of pyridine and 3-picoline between buffer and diethyl ether was determined at 15°. The pyridine concentration in the organic phase was measured at 256 nm after transfer to 0.1 N H_2SO_4 using ϵ 5200. 3-Picoline was measured at 263 nm (ϵ 5560). The distribution coefficient, $D = [L_0]/[L_a]$, where the subscripts refer to the organic and aqueous phases, was found to be 1.3 ± 0.02 (pyridine) and 3.3 ± 0.05 (3-picoline). When Os_2O_6(pyridine)$_4$ was equilibrated between equal volumes of buffer and ether, it was found that no detectable quantities of Os(VI) species were extracted into the organic phase, as shown by the lack of absorption in the 300–350-nm region. The degree of dissociation of the ligand from the Os(VI) species could thus be measured from the quantity of ligand in the ether phase and the distribution coefficient. The dissociation constants were calculated from the relationship

$$K = \frac{[OsO_3 \cdot L \cdot OH^-][L_a]}{[OsO_3 \cdot L_2][HO^-]}$$

using $K_w = 5 \times 10^{-15}$.[32] If we can assume no dissociation of the second ligand (see text), then

$$[OsO_3 \cdot L \cdot OH^-] = [L_a] + [L_0]$$

$$[OsO_3 \cdot L_2] = [OsO_3 \cdot L_2]_{initial} - ([L_a] + [L_0])$$

in the absence of added ligand.

Registry No.—Os–3-picoline dimer, 38641-67-7; Os–3-picoline monomer, 38669-79-3; Os–pyridine dimer, 38641-68-8; Os–pyridine monomer, 38669-80-6; Os–3-chloropyridine dimer, 38677-68-8; Os–3-chloropyridine monomer, 38669-81-7; *trans*-thymidine glycol, 38645-24-8; 1,3-dimethylthymine, 4401-71-2; *trans*-1,3-dimethylthymine glycol, 38645-26-0.

Acknowledgment.—We thank the National Science Foundation for support (GB-21267), Dr. George Serif for his help in determining the mass spectra, Mr. John Ragazzo for some of the ir spectra, and Dr. Kirk Aune for the ultracentrifugal data.

(31) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, pp 223 ff.

(32) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 640.

A Comparison of Lithium Aluminum Hydride and Diborane in the Reduction of Certain 3-Indolylglyoxamides

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The utility of lithium aluminum hydride ($LiAlH_4$) and diborane for the preparation of tryptamines from 3-indolylglyoxamides, including certain 4-trifluoromethyl derivatives, has been studied. Three distinctions in the behavior of these reducing agents toward the glyoxamides have been observed. (1) Diborane allows elaboration of the tryptamine side chain without concomitant reduction of trifluoromethyl substituents, whereas these groups are converted into methyl substituents by $LiAlH_4$ when reducing conditions are sufficiently vigorous to give the tryptamine. (2) Reduction of the glyoxamides with diborane may be accompanied by reduction of the indolic enamine triad to give indolines, an event not seen with $LiAlH_4$. (3) 1-Alkyl-3-indolylglyoxamides are converted into the corresponding tryptamines by diborane, whereas $LiAlH_4$ reduction gives 1-alkyl-3-indolylglycolamines. The formation of a 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**4**) was observed in the $LiAlH_4$ reduction of 5-methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indolylglyoxamide (**3c**). Diborane reduction of 3-indolecarboxylic acid (**16b**) and its ethyl ester **16a** gave skatole (**17**) as the major product.

Application of the Nenitzescu reaction[1] to 2-trifluoromethyl-1,4-benzoquinone and alkyl 3-aminocrotonates constitutes a convenient preparation of certain 4-trifluoromethylindoles.[2] The availability of these last substances prompted us to prepare the 4-trifluoromethyl congeners of biologically significant tryptamines, and the procedure of Speeter and Anthony[3] seemed to be the most direct way to achieve this objective. In this method an indole which is unsubstituted at the 3 position is converted into a 3-glyoxamide, reduction of which gives the tryptamine. Lithium aluminum hydride ($LiAlH_4$) is the usual reagent for this reduction, but the use of borane has been reported on one occasion.[4] In this paper we compare the effect of these two reducing agents on certain 3-indolylglyoxamides, including the 4-trifluoromethyl derivatives.

The required amides of Table I were prepared readily from 5-methoxy-2-methyl-4-trifluoromethylindole (**1**)[2] by the usual technique (see Scheme I).[3] Reduction of the N^b,N^b-dimethylglyoxamide **3c** with $LiAlH_4$ in boiling tetrahydrofuran (THF) for 48 hr gave the 4-methyltryptamine **2** and the 3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole **4**. The former product is identical with that obtained by $LiAlH_4$ reduction of 5-methoxy-2,4,N^b,N^b-tetramethyl-3-indolylglyoxamide,[5] and its formation constitutes another example of the conversion of a trifluoromethyl substituent into a methyl group by $LiAlH_4$. Such conversions were observed earlier for a 6-trifluoromethylindole,[6] another 4-trifluoromethylindole,[2] and a benzotrifluoride.[7] A

(1) C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

(2) R. Littell and G. R. Allen, Jr., *J. Org. Chem.*, **33**, 2064 (1968).

(3) M. E. Speeter and W. C. Anthony, *J. Amer. Chem. Soc.*, **76**, 6208 (1954).

(4) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968).

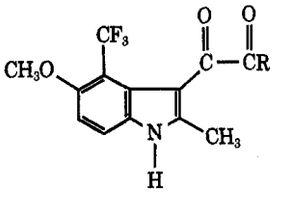
(5) G. R. Allen, Jr., V. G. DeVries, E. N. Greenblatt, R. Littell, F. J. McEvoy, and D. B. Moran, *J. Med. Chem.*, in press.

(6) A. Kalir, Z. Pelah, and D. Balderman, *Israel J. Chem.*, **5**, 101 (1967).

(7) H. J. Brabender and W. B. Wright, Jr., *J. Org. Chem.*, **32**, 4053 (1967).

TABLE I

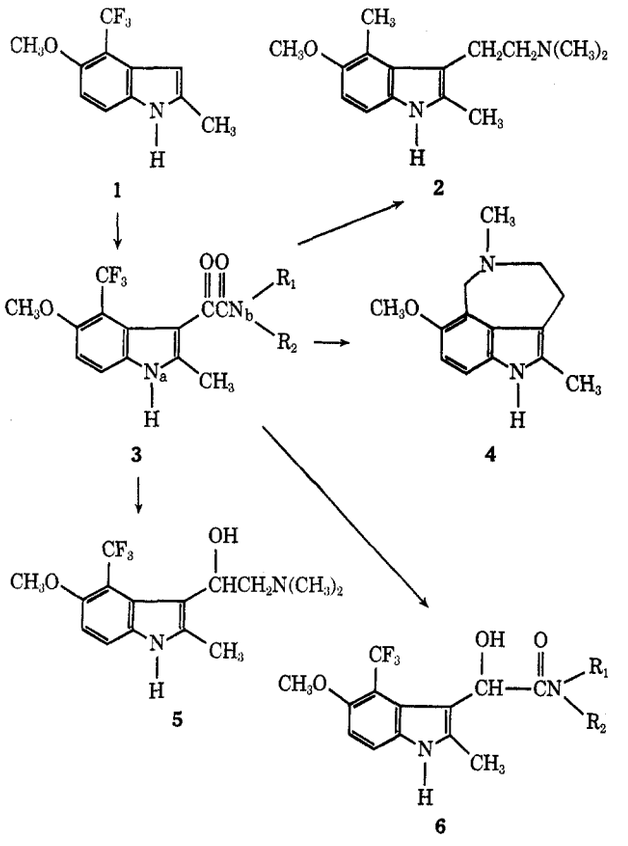
5-METHOXY-2-METHYL-4-TRIFLUOROMETHYL-3-INDOLYLGLYOXAMIDES



Registry no.	No.	R	Yield, %	Recrystn solvent	Mp, °C	Formula[a]	Analyses, % Carbon Calcd	Carbon Found	Hydrogen Calcd	Hydrogen Found	Fluorine Calcd	Fluorine Found	Nitrogen Calcd	Nitrogen Found
7664-41-7	3a	NH_2	90	MeOH	274–276 dec	$C_{13}H_{11}F_3N_2O_3$	52.00	51.85	3.69	3.64	18.98	19.06	9.33	9.21
74-89-5	3b	$NHCH_3$	75	MeOH	290–291 dec[b]	$C_{14}H_{13}F_3N_2O_3$	53.50	53.71	4.17	4.22	18.14	18.59	8.91	8.76
109-89-7	3c	$N(CH_3)_2$	80	Acetone–hexane	212–213	$C_{15}H_{15}F_3N_2O_3$	54.88	54.99	4.60	4.40	17.36	16.86	8.54	8.57
2878-14-0	3d	$NHCH_2C(CH_3)=CH_2$	75	Acetone	222–224	$C_{17}H_{17}F_3N_2O_3$	57.62	57.45	4.84	4.98	16.09	16.48	7.91	8.01
123-75-1	3e		72	Aqueous MeOH	227–229[b]	$C_{17}H_{17}F_3N_2O_3$	57.62	57.57	4.84	4.68	16.09	16.17	7.91	7.76
283-24-9	3f		64	Aqueous MeOH	262–264[b]	$C_{21}H_{23}F_3N_2O_3$[c]	61.75	61.33	5.68	5.83	13.96	14.13	6.86	6.55

[a] Except as noted the 4-trifluoromethylindolyl-3-glyoxamides had uv max 219–221, 280, 299–300 mμ (ε 25,000–30,100, 10,100–14,000, 12,600–14,100) and ir max 6.10–6.20, 6.30–6.32 μ. [b] Final purification accomplished by sublimation. [c] Uv max 219, 270, 288 mμ (ε 27,300, 14,600, 16,300).

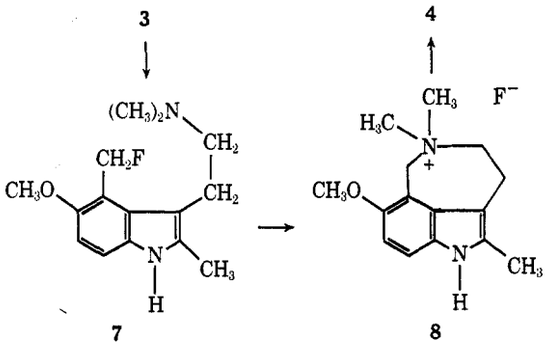
SCHEME I



recent report emphasizes that these reductions are facilitated by the presence of *o*- or *p*-amino and hydroxy functions.[8] The methoxy group in **3** presumably exerts a similar influence.

1*H*-Azepino[5,4,3-*cd*]indole (**4**) apparently results from the intramolecular quaternization of the benzyl fluoride **7**, which arises by stepwise reduction of the trifluoromethyl group in **3c**.[7] The reductive demethylation of the postulated intermediate quaternary salt **8** to give **4** (Scheme II) is amply supported in the literature. Three such examples are the conversion of

SCHEME II



strychnine methosulfate into strychnidine[9] and demethylation of two quaternary derivatives in the gelsemine class of alkaloids.[10]

Amino alcohol **5** resulted when **3c** was submitted to $LiAlH_4$ reduction under less vigorous conditions (4–16 hr, 23°). However, microanalyses on the product indicate that even these conditions are sufficient to cause partial reduction of the trifluoromethyl group. In the instance of the unsubstituted (**3a**) and N^b-methallyl (**3d**) glyoxamides, reduction with $LiAlH_4$ in boiling THF for 5–180 min gave the corresponding glycolamide **6**. Surprisingly, the pyrrolidine-derived glyoxamide **3e** suffered side-chain cleavage to regenerate **1** when exposed to $LiAlH_4$ in THF for 10 min–24 hr.

The inability to convert the 4-trifluoromethyl-3-indolylglyoxamides into the corresponding tryptamines by reduction with $LiAlH_4$ under a variety of conditions prompted us to investigate the utility of diborane for this reduction. At the outset of our study, limited

(8) N. W. Gilman and L. H. Sternbach, *Chem. Commun.*, 465 (1971).

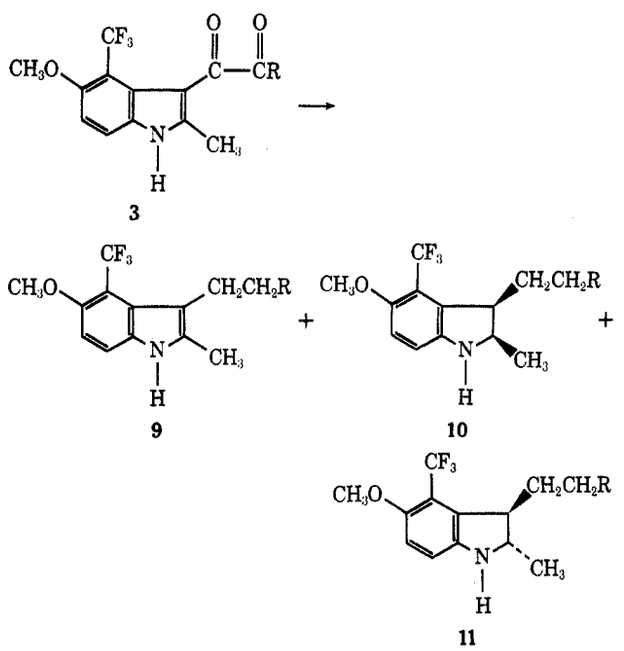
(9) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 406 (1950).

(10) (a) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, p 788. (b) A referee suggested the possibility that **8** may also function as the immediate precursor for **2** (reductive debenzylation), as well as **4** (reductive demethylation).

evidence indicated that this reagent would behave in the manner predicted by theoretical considerations. Thus, the utility of diborane for the selective reduction of a 2-acylindole-3-carboxaldehyde into a 2-acyl-3-indolylmethanol had been demonstrated by Remers and coworkers.[11] Subsequently, while our work was in progress, Biswas and Jackson reported the conversion of N^b-methyl-3-indolylglyoxamide into the corresponding tryptamine using diborane as the reducing agent.[4]

We find that this reagent reacts with the N^b,N^b-dimethylglyoxamide **3c** to give 34% of the corresponding tryptamine **9c**, which was isolated as an adduct with borane (see Scheme III). Treatment of the adduct with 1-octene in xylene liberated the tryptamine. The hydrogenolysis of the trifluoromethyl group seen in the $LiAlH_4$ reductions of **3c** is not evident with diborane. A second important distinction exists in the behavior of $LiAlH_4$ and B_2H_6 toward glyoxamide **3c**. The latter reagent also gave two indoline products, which differ only in the stereochemical relationship of the groups at the 2 and 3 positions. The major (37%) isomer is that in which the substituents are cis oriented, *e.g.*, **10c**, whereas the trans isomer **11c** constituted 10% of the reaction product. These structural assignments are based on spectral evidence, the indoline nucleus being required by the ultraviolet spectra (see Experimental Section). The geometrical relation of the 2 and 3 substituents was determined from the nmr spectra of **10a** and **11a** and appropriate decoupling experiments. The chemical shift (δ 1.35) of the 2-methyl doublet in the spectrum of the major isomer is at lower field than that (δ 1.01) in the spectrum of the minor isomer. This paramagnetic shift is characteristic of cis-oriented alkyl substituents. Decoupling experiments provided conclusive evidence. Irradiation at the 2-methyl resonance of **10c** reduced the two-proton quintet to a doublet having $J_{2,3}$ = 7.5 Hz, indicating a dihedral angle near 0° and a cis juxtaposition of the 2 and 3 hydrogens. A similar decoupling experiment with **11c** collapsed the two-proton quartet to a single line, suggesting a dihedral angle near 90°, which necessitates a trans relation of the 2 and 3 hydrogens.

SCHEME III

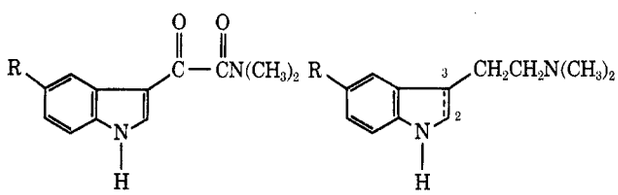


c, R = $N(CH_3)_2$
e, R = pyrrolidinyl
f, R = 3-azabicyclo[3.2.2]nonane

Reduction of the 3-azabicyclo[3.2.2]nonane-derived glyoxamide **3f** with diborane also gave a ternary mixture, nmr spectral analysis of which indicated it to contain the indole **9f** and indolines **10f** and **11f** in a ratio of 4:3:3. Separation of this mixture by partition chromatography was only partially successful; however, samples of the cis (**10f**) and trans indoline (**11f**) were isolated. The spectral properties of **10f** and **11f** were consonant with the assigned structures (see Experimental Section).

Reduction of the pyrrolidine derivative **3e** gave a mixture from which the tryptamine **9e** was isolated as the borane adduct; treatment of this adduct with 1-octene in boiling xylene then gave **9e**. The nmr spectrum of the remaining crude product indicated it to consist mostly of the cis indoline **10e**.

Extension of the borane reduction procedure to other 3-indolylglyoxamides indicates that this method for the preparation of indoline analogs of tryptamines is not general. Although reduction of *N,N*-dimethyl-3-indolylglyoxamide (**12a**) with borane gave primarily the indoline derivative **13a**, a similar reduction of the



12a, R = H
b, R = OCH_3

13a, R = H; C_2-C_3 = CH_2CH_2
b, R = OCH_3; C_2-C_3 = CH=CH

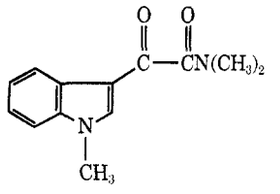
5-methoxy congener **12b** gave 73% of the tryptamine **13b**, which was isolated as the borane adduct.

The above examples illustrate two distinctions in the reduction of 3-indolylglyoxamides by $LiAlH_4$ and diborane: (1) diborane permits reduction of the glyoxamide grouping without concomitant reduction of the trifluoromethyl substituent; (2) reduction of the glyoxamide moiety with the electrophilic diborane may be accompanied by reduction of the enamine triad,[12] a side reaction not observed with the nucleophilic $LiAlH_4$. A third distinction in the behavior of these reducing agents toward 3-indolylglyoxamides has also been observed.

Thus, it has long been recognized that $LiAlH_4$ reduction of 1-alkyl-3-indolylglyoxamides, *e.g.*, **14**, affords 3-indolylhydroxylamines analogous to **5**.[3] However, diborane reduction of one such glyoxamide, **14**, efficiently reduced the side chain to the ethylamine, giving tryptamine **15a** (24%) and its 2,3-dihydro derivative **15b** (21%) as borane adducts. The isolation of **15b** constitutes the first example wherein a 1-alkylindoline has been detected among the products derived from

(11) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Amer. Chem. Soc.*, **86**, 4612 (1964).

(12) (a) J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, **28**, 421 (1963); (b) I. J. Borowitz and G. J. Williams, *ibid.*, **32**, 4157 (1967); (c) J. W. Lewis and A. A. Pearce, *J. Chem. Soc. B*, 863 (1969).



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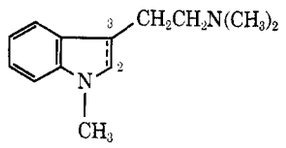
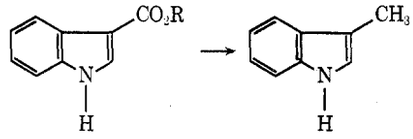


15a, $C_{2,3}$ = CH=CH
b, $C_{2,3}$ = CH_2CH_2

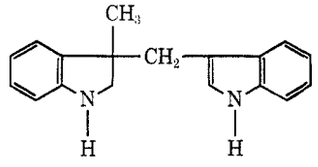
diborane reduction of a 1-alkylindole, even though earlier reports indicate that such products are not observed with 1,3-disubstituted[4] or 1,2,3-trisubstituted indoles.[13]

The susceptibility of the 3-indolylglyoxamides to reduction by diborane prompted us to study the behavior of other unstudied electrophilic indoles toward this reagent. Ethyl 3-indolylcarboxylate (**16a**) gave skatole (**17**) as the only product following treatment with diborane for 48 hr. However, a similar reduction of 3-indolecarboxylic acid (**16b**) gave **17** (49%) and the 3,3′ dimer **18** (8%). The last substance is identical



16a, R = C_2H_5
b, R = H

17



18

with one dimer which Biswas and Jackson found among the reduction products of 3-indolecarboxaldehyde,[4] and its isolation in the present instance is accommodated by their rationalization of its formation from the aldehyde.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60D spectrometer in the indicated solvent using tetramethylsilane as an internal standard. Evaporations were carried out under reduced pressure.

5-Methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indoleglyoxamide (3c).—The following experiment illustrates the general procedure used to prepare the glyoxamides of Table I (*cf.* footnote 3).

To a solution of 6.0 g (26.2 mmol) of 5-methoxy-2-methyl-4-(trifluoromethyl)indole in 150 ml of ether at 0° was added dropwise over 20 min 6.0 ml of oxalyl chloride. After stirring at 0° for 1 hr the bright orange solution of glyoxyl chloride was filtered. The filtrate was stirred in 600 ml of ether and saturated with gaseous dimethylamine. The resulting white solid was collected, washed with water, and dried to give 6.70 g (80%) of pale yellow powder, mp 208–210°. Characterization of this substance and the other 3-indolylglyoxamides is given in Table I.

3-(2-Dimethylaminoethyl)-5-methoxy-2,4-dimethylindole (2) Succinate and 3,4,5,6-Tetrahydro-7-methoxy-2,5-dimethyl-1*H*-azepino[5,4,3-*cd*]indole (4).—A solution of 6.5 g (20 mmol) of 5-methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indolylglyoxamide in 500 ml of THF containing 5.0 g (130 mmol) of $LiAlH_4$ was heated at reflux for 4 days. After the reaction mixture was cooled, it was treated with 32 ml of potassium sodium tartrate solution (650 mg/ml); filtration removed the inorganic salts. The solvent was evaporated, and the residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ and with water, dried over $MgSO_4$, and evaporated to give an oil which crystallized in acetone to furnish 800 mg (17%) of white powder, mp 205–207°. Several crystallizations from acetone gave the pure azepinoindole **4**: mp 213–215°; uv max 230, 288, 300 mμ (ε 27,600, 8510, 8050); nmr (DMSO-d_6) δ 2.20 (s, 3, CCH_3), 2.40 (s, 3, NCH_3), 2.83 (m, 4, $-CH_2CH_2-$), 3.68 (s, 3, OCH_3), 3.94 (s, 2, NCH_2 aryl), 6.64 (d, 1, J = 9.0 Hz, 8-H), 6.99 (d, 1, J = 9.0 Hz, 9-H), 10.48 (s, 1, NH).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17; O, 6.95; mol wt, 230.30. Found: C, 73.30; H, 8.19; N, 11.91; O, 7.48; mol wt, 230.

The filtrate from collection of the original crystalline material was evaporated to give 3.00 g of an oil. This oil was treated with a solution of 1.44 g (12 mmol) of succinic acid in 10 ml of methanol. The solution was stirred for several minutes, diluted with ether, and filtered to give 2.90 g (38%) of crystals, mp 120–124° dec. Crystallization of this material from acetone furnished pure **2** succinate as white crystals: mp 133–135°; uv max 224, 278, 297 mμ (ε 34,200, 9500, 7200); nmr (DMSO-d_6) δ 2.30 (s, 4-CH_3), 2.39 (s, $HO_2CCH_2CH_2CO_2H$), 2.46 (s, 2-CH_3), 2.50 [s, $N(CH_3)_2$], 2.84 (m, $-CH_2CH_2-$), 3.72 (s, 3, OCH_3), 6.74 (1, d, J = 9.0 Hz, 6-H), 7.00 (1, d, J = 9.0 Hz, 7-H), 9.56 (s, 2, CO_2H), 10.55 (s, 1, NH).

Anal. Calcd for $C_{15}H_{22}N_2O \cdot C_4H_6O_4$: C, 62.62; H, 7.74; N, 7.69; F, 0.00. Found: C, 62.96; H, 7.94; N, 7.53; F, 0.00.

3-(2-Dimethylamino-1-hydroxyethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole (5).—A solution of 750 mg (2.3 mmol) of 5-methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indoleglyoxamide (**3c**) in 20 ml of THF was treated with 165 mg (4.35 mmol) of $LiAlH_4$. The mixture was stirred at room temperature for 4 hr, and the excess hydride was decomposed by addition of water. The mixture was filtered, and the filtrate was evaporated. The residue was dissolved in methylene chloride; this solution was dried over magnesium sulfate and evaporated. Trituration of the residue with ether gave 400 mg (55%) of white crystals: mp 125–127°; uv max 228, 305 mμ (ε 26,900, 10,800); ir 3.00 (sh), 3.15, 6.16, 6.36 μ; nmr ($CDCl_3$, DMSO-d_6) δ 2.35 [s, 6, $N(CH_3)_2$], 2.56 (s, 3, 2-CH_3), 2.35–2.75 (underlying m, CH_2), 3.66 (s, 1, OH), 5.28 (dd, 1, $J_{1,2}$ = 10.0 Hz, $J_{1,2}$ = 3.0 Hz, CHOH), 6.80 (d, 1, J = 9.0 Hz, 6-H), 7.38 (d, 1, J = 9.0 Hz, 7-H), 10.35 (s, 1, NH).

A salt with fumaric acid was prepared by dissolution of 410 mg (1.32 mmol) of material in 2 ml of methanol and addition of 156 mg (1.35 mmol) of fumaric acid. The solid that was precipitated by addition of ether was recrystallized from methanol–ether to give crystals, mp 146–147° dec.

Anal. Calcd for $C_{15}H_{19}N_2O_2 \cdot {}^1/_2C_4H_4O_4$: C, 54.54; H, 5.65; F, 15.22; N, 7.48. Found: C, 54.97; H, 5.74; F, 13.72; N, 7.43.

5-Methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglycolamide (6a).—A solution of 1.4 g (4.65 mmol) of 5-methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglyoxamide and 600 mg (16 mmol) of $LiAlH_4$ in 140 ml of THF was heated at reflux for 5 min. Water was added, inorganic material was removed by filtration, and the filtrate was evaporated. Crystallization of the residue from acetone–hexane gave 370 mg (26%) of crystals, mp 160–162°. Two recrystallizations from the same solvents gave the analytical sample as white crystals: mp 166–167°; uv max 215, 305 mμ (ε 28,500, 11,000); ir max 3.10, 5.96, 6.16, 6.35 μ; nmr ($CDCl_3$) δ 2.36 (s, 3, 2-CH_3), 3.86 (s, 3, OCH_3), 4.12 (broad, OH), 5.45 (s, 1, CHOH), 6.85 (m, 3, NH_2, 6-H), 7.38 (d, 1, J = 8 Hz, 7-H), 10.5 (s, 1, NH).

Anal. Calcd for $C_{13}H_{13}F_3N_2O_3$: C, 51.82; H, 4.67; F, 18.85; N, 9.27. Found: C, 52.02; H, 4.41; F, 18.22; N, 9.29.

5-Methoxy-2-methyl-*N*-(2-methallyl)-4-(trifluoromethyl)-3-indoleglycolamide (6d).—A solution of 920 mg (2.6 mmol) of 5-methoxy-2-methyl-*N*-(2-methallyl)-4-(trifluoromethyl)-3-indoleglyoxamide and 190 mg (5 mmol) of $LiAlH_4$ in 30 ml of THF was stirred at room temperature for 3 hr. Water was added, the inorganic material was removed by filtration, and the filtrate was evaporated. Addition of ether and filtration

(13) S. A. Monti and R. R. Schmidt, *Tetrahedron*, **27**, 3331 (1971).

gave 365 mg of product, mp 164–167°. Crystallization from acetone–hexane gave the analytical sample: mp 182–183°; uv max 225, 305 mμ (ε 28,000, 11,200); ir max 3.07, 6.10, 6.35, 9.30 μ; nmr (DMSO-d_6) δ 1.70 (s, 3, C=CCH$_3$) 2.30 (s, 3, 2-CH$_3$), 3.71 (m, 2, -CH$_2$-), 4.81 (s, 2, =CH$_2$), 5.35 (d, 1, J = 5.0 Hz, CHOH), 5.55 (d, 1, J = 5.0 Hz, CHOH), 6.95 (d, 1, J = 9.0 Hz, 6-H), 7.45 (d, 1, J = 9.0 Hz, 7-H), 7.80 (t, 1, J = 6.5 Hz, NHCH$_2$), 11.30 (s, 1, NH).

Anal. Calcd for $C_{17}H_{19}F_3N_2O_3$: C, 57.30; H, 5.37; F, 15.99; N, 7.86. Found: C, 57.19; H, 5.65; F, 15.70; N, 7.93.

5-Methoxy-2-methyl-4-(trifluoromethyl)indole (1).—A solution of 710 mg (2.0 mmol) of 1-[5-methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglyoxyloyl]pyrrolidine (**3e**) and 300 mg (8 mmol) of LiAlH$_4$ in 70 ml of THF was stirred at room temperature overnight. Water was added, the inorganic precipitate was removed by filtration, and the filtrate was evaporated. Crystallization of the residue from acetone–hexane gave 110 mg (24%) of white crystals, mp 121–123°. This material was identical with known 5-methoxy-2-methyl-4-(trifluoromethyl)indole (**1**)[2] by the usual criteria. A similar reaction conducted for 10 min at room temperature gave 27% of **1**.

Reduction of 5-Methoxy-*N*,*N*,2-trimethyl-4-(trifluoromethyl)-3-indoleglyoxamide (3c) with Diborane.—A solution of 2.3 g (7.0 mmol) of **3c** in 160 ml of THF and 30 ml (30 mmol) of 1.0 *M* borane in THF was heated at reflux for 2 hr and cooled, and the excess borane was cautiously decomposed with water. After evaporation of solvent the residue was dissolved in ether, washed twice with saturated saline, dried, and evaporated. Ether was added and 750 mg (34%) of 3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole borane, mp 164–166° dec, was collected by filtration. A sample from a similar experiment with mp 166–168° dec was recrystallized from dichloromethane–hexane to give the analytical specimen: mp 180–181° dec; uv max 230, 308 mμ (ε 26,000, 11,000); ir max 3.00, 4.25–4.40, 6.17, 6.37 μ; nmr (CDCl$_3$ + DMSO-d_6) δ 2.42 (s, 3, 2-CH$_3$), 2.64 [s, 6, N(CH$_3$)$_2$], 2.64–3.33 (m, -CH$_2$CH$_2$-), 3.86 (s, 3, OCH$_3$), 6.88 (d, 1, J = 8.0 Hz, 6-H), 7.42 (d, 1, J = 8.0 Hz, 7-H), 10.4 (s, 1, NH).

Anal. Calcd for $C_{15}H_{19}F_3N_2O\cdot BH_3$: C, 57.34; H, 7.06; N, 8.92. Found: C, 57.42; H, 7.34; N, 9.01.

The filtrate from the above ether trituration was evaporated to give 1.80 g of yellow oil, which was heated at reflux temperature with 10 ml of 20% hydrochloric acid solution for 1 hr. The cooled reaction mixture was washed with ether, rendered strongly alkaline with sodium hydroxide, and extracted again with ether. The ethereal solution was washed with saline, dried, and evaporated to give 1.00 g of yellow oil. Vpc using 5% SE-30 on Chromosorb W showed this material to be a binary mixture, 22% having a retention time of 2.5 min and 78% being eluted at 3.2 min.

Chromatography on diatomaceous silica using the system heptane–ethyl acetate–methanol–water (90:10:17:4) separated the two components.[14] The product eluted at peak-hold-back volume 3.5 (V_m/V_s = 2.27) was evaporated to give 122 mg (6%) of *trans*-3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indoline (**11a**) as a colorless oil: uv max 248, 325 mμ (ε 7600, 3500); ir 3.10, 6.20 μ; nmr (CDCl$_3$) δ 1.01 (d, 3, J = 7 Hz, 2-CH$_3$), 1.73 (m, 2, -CH$_2$CH$_2$N<), 2.20 [s, 6, N(CH$_3$)$_2$], 2.39 (m, -CH$_2$CH$_2$N<), 3.12 (m, 1, 3-H), 3.46 (s, 1, NH), 3.60 (9, 1, J = 7 Hz, 2-H), 3.82 (s, 3, OCH$_3$), 6.74 (s, 2, aryl H).

Anal. Calcd for $C_{15}H_{21}F_3N_2O$: C, 59.59; H, 7.00; F, 18.85; N, 9.27. Found: C, 59.35; H, 6.68; F, 18.85; N, 8.99.

The fraction eluted at peak-hold-back volume 4.6 was evaporated to give 350 mg (17%) of *cis*-3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indoline (**10a**) as yellow crystals: mp 92–94°; uv max 248, 325 mμ (ε 7800, 3900); ir 3.20, 6.25 μ; nmr (CDCl$_3$) δ 1.33 (d, 3, J = 7 Hz, 2-CH$_3$), 1.92 (m, 2, -CH$_2$CH$_2$N<), 2.17 [s, 6, N(CH$_3$)$_2$], 2.34 (m, -CH$_2$-CH$_2$N<), 3.28 (m, 1, 3-H), 3.65 (b, 1, NH), 3.83 (s, 3, OCH$_3$), 3.90 (q, 1, 2-H), 6.68 (s, 2, aryl H).

Anal. Calcd for $C_{15}H_{21}F_3N_2O$: C, 59.59; H, 7.00; F, 18.85; N, 9.27. Found: C, 59.36; H, 6.64; F, 19.13; N, 9.20.

(14) The support is that material marketed under the trademark Celite by the Johns-Manville Co. A complete description of this technique as developed by Mr. C. Pidacks is given by M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

3-(2-Dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole (9c).—A solution of 200 mg of 3-(2-dimethylaminoethyl)-5-methoxy-2-methyl-4-(trifluoromethyl)indole borane in 2 ml of xylene and 2 ml of octene-1 was heated at reflux temperature for 4 hr, cooled, and diluted with hexane to give 80 mg of white powder. Crystallization of material from a similar experiment from acetone–hexane gave white crystals, mp 145–147°. Sublimation at 0.5 mm and 110° furnished crystals: mp 146–148°; uv max 229, 306 mμ (ε 22,500, 9300); ir 2.95, 6.13, 6.32 μ; nmr (DMSO-d_6) δ 2.2 [s, N(CH$_3$)$_2$], 2.36 (s, 2-CH$_3$), 2.08–3.00 (underlying m, CH$_2$CH$_2$), 3.82 (s, 3, OCH$_3$), 6.90 (d, 1, J = 9.0 Hz, 6-H), 7.45 (d, 1, J = 9.0 Hz, 7-H), 11.15 (s, 1, NH).

Anal. Calcd for $C_{15}H_{19}F_3N_2O$: C, 60.00; H, 6.38; F, 19.00; N, 9.33. Found: C, 60.27; H, 6.25; F, 19.27; N, 9.33.

***cis*- (10f) and *trans*-3-{2-[5-Methoxy-2-methyl-4-(trifluoromethyl)-3-indolinyl]ethyl}-3-azabicyclo[3.2.2]nonane (11f).**—A solution of 2.50 g (61.4 mmol) of 3-[5-methoxy-2-methyl-4-(trifluoromethyl)-3-indolylglyoxyloyl]-3-azabicyclo[3.2.2]-nonane (**3f**) and 20 ml of 1 *M* borane in THF was diluted with 150 ml of THF and heated at reflux temperature for 3 hr. The solution was evaporated, and the residue was distributed between ether and water. The ether layer was washed with saline, dried, and evaporated to give 2.00 g (~85%) of a yellow oil: nmr (DMSO-d_6) *inter alia* δ 1.01 (d, J = 7.0 Hz, 2-CH$_3$ in trans indoline), 1.25 (d, J = 7.0 Hz, 2-CH$_3$ in cis indoline), 2.36 (s, 2-CH$_3$, indole **9f**), 3.72 (s, OCH$_3$ of indolines), 3.82 (s, OCH$_3$ of indole **9f**), 5.52 (b, NH of indolines), 6.70, 6.79 (d, J = 9.0 Hz, 6-, 7-H of indolines), 6.93, 7.45 (d, J = 9.0 Hz, 6-, 7-H of indole), 10.95 (s, NH of indole); integration of the nmr trace indicated the ratio of **9f**:**10f**:**11f** to approximate 4:3:3.

Partial separation of material from a similar reduction was achieved by partition chromatography on diatomaceous silica using heptane–2-methoxyethanol (1:1) as the solvent system. The indoline products were eluted at peak hold-back-volumes 2.2 and 2.5 (V_m/V_s = 1.65). Isolation of pure material was achieved only after repeated rechromatography of each peak. The less polar fraction contained the trans isomer **11f**, which was sublimed to give yellow crystals: mp 113–116°; uv max 240, 320 mμ (ε 7600, 4000); ir max 2.95, 3.09, 6.20 μ; nmr (CDCl$_3$) δ 1.16 (d, J = 6.5 Hz, 2-CH$_3$), 3.80 (s, OCH$_3$), 6.70 (s, 2, aryl H), and a series of multiplets at δ 1.25–3.76.

Anal. Calcd for $C_{21}H_{29}F_3N_2O$: C, 65.93; H, 7.66; F, 14.90; N, 7.32. Found: C, 66.22; H, 7.66; F, 14.90; N, 7.32.

The more polar material was recrystallized from acetone–hexane to give the cis isomer **10f** as yellow crystals: mp 108–110°; uv max 246, 322 mμ (ε 8200, 3800); ir max 2.95, 3.10, 6.25 μ; nmr (CDCl$_3$) δ 1.40 (d, J = 6.5 Hz, 2-CH$_3$), 3.80 (s, OCH$_3$), 3.88 (q, J = 7.0 Hz, 2-H), 6.70 (s, 2, aryl H), and a series of multiplets at δ 1.25–3.77.

Anal. Found: C, 66.02; H, 7.70; F, 15.09; N, 7.28.

5-Methoxy-2-methyl-3-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)indole (9e) Borane.—A solution of 1.80 g (5.1 mmol) of 1-[5-methoxy-2-methyl-4-(trifluoromethyl)-3-indoleglyoxyolyl]-pyrrolidine (**3e**) in 140 ml of THF and 15 ml of 1.0 *M* borane in THF was heated at reflux for 4 hr and cooled, and the excess borane was decomposed with water. After evaporation of solvents, the residue was dissolved in benzene and this solution was washed with water, dried, and evaporated.

Crystallization of the crude residue from ether–hexane gave 330 mg of pale yellow powder, mp 162–164°. The mother liquor was chromatographed on 100 g of silica gel.[15] Elution with dichloromethane–hexane (9:1) gave an additional 300 mg (36% total product, mp 166–170°).

The analytical specimen was obtained from a similar experiment by crystallization from ether–hexane to give white plates: mp 174–176°; uv max 232, 308 mμ (ε 27,000, 10,000); ir max 2.99, 4.25–4.30, 6.13, 6.35 μ; nmr (CDCl$_3$ + DMSO-d_6) δ 2.00 (m, -CH$_2$CH$_2$- of pyrrolidine), 2.45 (s, 2-CH$_3$), 2.45–3.42 (m, -CH$_2$CH$_2$N, -CH$_2$NCH$_2$-), 3.85 (s, 3, OCH$_3$), 6.84 (d, 1, J = 9.0 Hz, 6-H), 7.40 (d, 1, J = 9.0 Hz, 7-H), 10.75 (s, 1, NH), and 3 H in the 1.0–3.0 region (BH$_3$).

Anal. Calcd for $C_{17}H_{24}F_3N_2O\cdot BH_3$: C, 60.00; H, 7.11; N, 8.24. Found: C, 59.91; H, 6.83; N, 8.28.

Further elution of the column with dichloromethane–ether (8:2) gave 750 mg (43%) of a mixture of the borane adducts of indolines **10e** and **11e** as a yellow oil, uv max 250, 330 mμ, ir

(15) A product of the Davison Chemical Co., Baltimore, Md., with mesh size 100–200.

max 4.20, 6.30 μ. Chromatography of this material on diatomaceous silica using a heptane–ethyl acetate–methanol–water (90:10:17:4) system gave 600 mg of oil at peak hold-back-volume 4.0 (V_m/V_s = 2.47); tlc of this material in heptane–ethyl acetate (1:1) and acetone–acetic acid–methanol–benzene (5:5:20:100) showed two spots. Partial separation was effected by preparative chromatography on silica gel using heptane–ethyl acetate (1:1). A fraction containing 240 mg was isolated as a yellow oil: uv max 246, 325 mμ (ε 8200, 3600); ir max 3.02, 4.25, 6.25 μ; nmr ($CDCl_3$) δ 1.40 (d, 3, J = 7.0 Hz, 2-CH_3), 3.80 (s, 3, OCH_3), 6.72 (s, 2, aryl H), and 1.16–4.00 (series of multiplets). This spectral data suggests the material to be the borane adduct of cis isomer **10e**.

5-Methoxy-2-methyl-3-[2-(1-pyrrolidinyl)-ethyl]-4-(trifluoromethyl)indole (9e).—A solution of 800 mg of 5-methoxy-2-methyl-3-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)indole borane in 10 ml of xylene and 4 ml of *n*-octene-1 was heated at reflux for 3 hr, cooled, diluted with heptane, and filtered to give 510 mg of pink crystals, mp 145–150°. The product was purified by crystallization from acetone–water and sublimation at 130° to give white crystals: mp 152–154°; uv max 228, 305 mμ (ε 25,200, 10,000); ir max 2.95, 6.13, 6.32 μ; nmr (DMSO-d_6) δ 1.68 (m, 4, $-CH_2CH_2-$ of pyrrolidine), 2.36 (5,3,2-CH_3), 2.36–4.67 (underlying m, $-CH_2CH_2N<$, $-CH_2NCH_2-$), 3.81 (s, 3, OCH_3), 6.92 (d, 1, J = 9.5 Hz, 6-H), 7.47 (d, 1, J = 9.5 Hz, 7-H), 11.20 (s, 1, NH).

Anal. Calcd for $C_{17}H_{21}F_3N_2O$: C, 62.56; H, 6.49; F, 17.47; N, 8.48. Found: C, 62.87; H, 6.65; F, 17.41; N, 8.71.

3-(2-Dimethylaminoethyl)indoline (13a).—A solution of 2.16 g (10 mmol) of *N,N*-dimethyl-3-indoleglyoxamide[16] in 150 ml of THF and 40 ml of 1.0 *M* borane in THF was heated at reflux for 2.5 hr and cooled. The excess borane was cautiously decomposed with water. After evaporation of the solvents, the residue was dissolved in ether, and this solution was washed with water, dried, and evaporated to give 2.10 g of colorless oil.

The crude oil was heated at reflux temperature with 12 ml of 20% HCl for 1.5 hr. The cooled solution was washed once with ether, rendered strongly alkaline with NaOH, and extracted with ether. The ether solution was washed twice with water, dried, and evaporated to give 1.10 g of colorless oil; vpc at 142° on a 6 ft 3.8% SE-30 on Diatoport S column showed this material to be 95% **13a** (retention time 4.4 min) and 5% 3-(2-dimethylaminoethyl)indole (retention time 6.5 min; identical with that of a known sample).

Purification was effected by chromatography on diatomaceous silica using a heptane–ethyl acetate–methanol–water (90:10:17:4) solvent system. The fraction with peak hold-back-volume 3.25 (V_m/V_s = 2.44) was evaporated to give 800 mg of amber oil, uv max 242, 293 mμ (ε 5900, 2300), ir max 3.05, 6.20 μ. This material formed a picrate, mp 158–160°.

Anal. Calcd for $C_{12}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 51.55; H, 5.05; N, 16.70. Found: C, 51.28; H, 5.16; N, 16.93.

3-(2-Dimethylaminoethyl)-5-methoxyindole (13b) Borane.—A solution of 2.46 g (10 mmol) of 5-methoxy-*N,N*-dimethyl-3-indoleglyoxamide[17] in 50 ml of THF and 35 ml of 1.0 *M* borane in THF was heated at reflux temperature for 3 hr and cooled, and the excess borane was decomposed with water. After evaporation the residue was dissolved in ether, washed with water, dried, and evaporated to give 2.90 g of white plates. This material was recrystallized twice from dichloromethane–hexane to give 1.20 g of crystals: mp 124–125°; uv max 222, 278, 298, 308 mμ (ε 23,000, 5800, 4650, 3350); ir max 2.90, 4.22, 4.40, 6.15, 6.30 μ.

Anal. Calcd for $C_{13}H_{18}N_2O \cdot BH_3$: C, 67.26; H, 9.12; N, 12.07. Found: C, 67.04; H, 9.43; N, 11.97.

An additional 500 mg (73% total) of product was obtained by chromatographing the first mother liquor on 50 g of silica gel and eluting with ether–dichloromethane (1:4).

The same compound, mp 123–125°, was prepared by similar treatment of 3-(2-dimethylaminoethyl)-5-methoxyindole[17] with borane.

Reduction of 1,*N,N*-Trimethyl-3-indoleglyoxamide (14).—A solution of 2.20 g (9.6 mmol) of crude 1,*N,N*-trimethyl-3-indoleglyoxamide (**14**) (prepared in the usual way[3] from 1-methylindole, oxalyl chloride, and dimethylamine, and obtained as a homogeneous oil) and 30 ml of 1 *M* borane in THF was heated at reflux temperature for 3 hr. The usual isolation procedure gave 1.90 g of colorless oil, which was chromatographed on 100 g of silica gel. Elution with dichloromethane gave 500 mg (24%) of white crystals, mp 84–86°. Two crystallizations from ether gave pure 3-(2-dimethylaminoethyl)-1-methylindole (**15a**) borane: mp 90–92°; uv max 223, 288 mμ (ε 35,500, 5500); ir max 4.25, 4.32, 4.41, 6.15 μ; nmr ($CDCl_3$) δ 1.0–3.0 (broad, BH_3), 2.58 [s, 6, $N(CH_3)_2$], 3.06 (broadened s, 4, $-CH_2CH_2N<$), 3.62 (s, 3, NCH_3), 6.80 (s, 1, 2-H), 7.22 (m, 2, 5-, 6-, and 7-H), 7.55 (m, 1, 4-H).

Anal. Calcd for $C_{13}H_{18}N_2 \cdot BH_3$: C, 72.23; H, 9.79; N, 12.96. Found: C, 72.48; H, 9.64; N, 13.13.

Continued elution of the column with ether–dichloromethane (1:4) gave 450 mg (21%) of 3-(2-dimethylaminoethyl)-1-methylindoline (**15b**) borane as a white solid, mp 92–94°. Two recrystallizations of this solid from ether–hexane gave white crystals: mp 98–99°; uv max 250, 295 mμ (ε 12,500, 6100); ir max 2.35, 6.25 μ; nmr ($CDCl_3$) δ 1.67–2.37 (m, $-CH_2CH_2N<$), 2.65 (s, NCH_3), 2.71 [s, $-N(CH_3)_2 \cdot BH_3$], 2.71 (underlying m, 3-H), 2.89 (m, 2-CH_2), 3.20 (m, $-CH_2CH_2N<$), 6.35–7.20 (m, 4, aryl H).

Anal. Calcd for $C_{13}H_{20}N_2 \cdot BH_3$: C, 71.57; H, 10.62; N, 12.84. Found: C, 71.73; H, 10.41; N, 12.78.

3-Methylindole (17).—A solution of 2.82 g (15 mmol) of ethyl 3-indolecarboxylate (**16a**) in 50 ml of THF and 50 ml of 1.0 *M* borane in THF was heated at reflux for 48 hr. Examination of the reaction mixture by tlc and vpc showed the presence of a single product having R_f values and retention times corresponding to those of skatole.

3-Methylindole (17) and 3-(3-Indolylmethyl)-3-methylindoline (18).—A solution of 2.42 g (15 mmol) of 3-indolecarboxylic acid (**16b**) in 100 ml of THF and 50 ml of 1 *M* borane in THF was heated at reflux for 4 hr and cooled, and the excess reagent was decomposed with water. After evaporation of the solvents, the residue, 1.6 g of malodorous oil, was dissolved in ether and extracted three times with 25-ml portions of 6 *N* HCl and the ether was dried and evaporated to give 965 mg (49%) of skatole (**17**) as white crystals, mp 75–79°. The structure was confirmed by comparison of its nmr spectrum with that of an authentic sample.

The combined acid washes were extracted with $CHCl_3$ and the $CHCl_3$ extracts were combined, washed with saturated $NaHCO_3$, dried, and evaporated to 250 mg of tan oil. This material was chromatographed on diatomaceous silica using a heptane–methanol (1:1) system. The fraction eluted at peak hold-back-volume 4.0 (V_m/V_s = 2.38) was evaporated to give 150 mg (8%) of 3-(3-indolylmethyl)-3-methylindoline (**18**) as odorless, pink crystals, mp 121–123°. Recrystallization from acetone–hexane, followed by sublimation at 115°, gave the pure sample: mp 132–134° (lit.[4] mp 132–134°); uv max 225, 284, 292 mμ (ε 29,800, 9600, 9200); ir max 2.90, 3.02, 6.08, 6.22 μ; nmr ($CDCl_3$) δ 1.33 (s, 3, CH_3), 3.00 (s, 2, $-CH_2$), 3.09 (d, 1, J = 9.0 Hz, 2-H of indoline), 3.22 (s, 1, NH of indoline), 3.50 (d, 1, J = 9.0 Hz, 2-H of indoline), 6.42–7.67 (m, 8, aryl), 7.80 (broad s, NH of indole).

Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.40; H, 6.92; N, 10.68; mol wt, 262. Found: C, 82.33; H, 6.70, N, 10.52; mol wt, 262.

Registry No.—**1,** 16052-63-4; 2 succinate, 38179-35-0; **3a,** 23340-79-6; **3b,** 23340-80-9; **3c,** 23340-81-0; **3d,** 38662-06-5; **3e,** 23340-83-2; **3f,** 23340-84-3; **4,** 38662-09-8; **5,** 38662-10-1; **5** fumarate, 38662-46-3; **6a,** 38662-11-2; **6d,** 38662-12-3; **9c,** 23340-82-1; **9c** borane, 38662-14-5; **9e,** 23340-85-4; **9e** borane, 38662-16-7; **10a,** 38662-47-4; **10e** borane, 38662-48-5; **10f,** 38677-72-4; **11a,** 38662-49-6; **11f,** 38661-77-7; **13a,** 38662-17-8; **13a** picrate, 38662-18-9; **13b** borane, 38662-23-6; **14,** 38662-19-0; **15a** borane, 38662-20-3; **15b** borane, 38662-21-4; **16a,** 776-41-0; **16b,** 771-50-6; **17,** 83-34-1; **18,** 38662-24-7; oxalyl chloride, 79-37-8; *N,N*-dimethyl-3-indoleglyoxamide, 4545-06-6; 5-methoxy-*N,N*-dimethyl-3-indoleglyoxamide, 2426-20-2; $LiAlH_4$, 16853-85-3; diborane, 19287-45-7.

(16) H. Kondo, H. Kataoka, Y. Hayashi, and T. Dodo, *Itsuu Kebkysho Nempo*, **10**, 1 (1959); *Chem. Abstr.*, **54**, 492*i* (1960).

(17) M. Julia and P. Manoury, *Bull. Soc. Chim. Fr.*, 1411 (1965).

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The Influence of Aggregate Composition on Relative Reactivities of Alkyllithiums

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Studies of the competitive metalation of indene by *tert*-butyllithium and isopropyllithium in pentane have shown that the reactions are first order in alkyllithium and that the relative reactivities of the two alkyllithiums depend upon the compositions of the aggregates in the mixture, pure *tert*-butyllithium tetramer being an order of magnitude less reactive than *tert*-butyllithium in mixed aggregates with isopropyllithium.

An important clue to the mechanism of any reaction of an organolithium compound could be the relationship of the rate of that reaction to the stabilities or inherent basicities of the organolithiums. The latter may be assumed to bear some relationship to the aqueous acidities (pK_a) of the corresponding hydrocarbons, and, in part by such an assumption, Cram[1] has combined various kinds of kinetic and equilibrium data into an internally consistent scale ("MSAD scale") of hydrocarbon acidities. We have sought correlations of MSAD acidities with the rates of the simplest possible organolithium reactions, and here report the results of some such studies on the metalation of the acidic hydrocarbon indene by two alkyllithium compounds.

In this study, a limiting amount of indene was added to a mixture of two alkyllithiums in pentane at room temperature. After a reaction period of 1–2 hr, the reaction was quenched with D_2O and the extent of deuterium incorporation in each of the resulting alkanes was determined by quantitative infrared analysis. If undeuterated alkane arose exclusively from the reaction of RLi with indene, then the relative rates of reaction of the two alkyllithiums with indene were thus determined. The determination of the relative rate constants (k/k') from the data using eq 1 requires

$$\frac{d(RLi)}{d(R'Li)} = \frac{k(RLi)^m}{k'(R'Li)^n} \quad (1)$$

assumption or prior determination of values for the exponents m and n. The literature reveals fractional orders for the very similar metalation of fluorene in benzene[2] and for metalation of triphenylmethane in THF.[3] Other reactions of alkyllithiums sometimes exhibit fractional order[4] or first order[5] or are reactions with induction periods.[5a,6]

The determination of the reaction orders m and n in a competitive study such as this one is complicated by the fact that if a fractional order arises from the commonly accepted mechanism (eq 2), and if the two

$$(RLi)_n \underset{}{\overset{K}{\rightleftharpoons}} nRLi$$
$$RLi + \text{substrate} \xrightarrow[k]{\text{slow}} \text{product} \quad (2)$$

lithium reagents in the competitive mixture have formed a statistical array of mixed aggregates, then analysis of the data using eq 1 will give constant values for k/k' only for $m = n = 1$, regardless of the fact that the rate law for reaction of an isolated RLi would be of fractional order.[7] The values of "k/k'" thus obtained will not be the ratios of rate constants for the proton-abstraction steps, but will be related to the dissociation constants of the aggregates (eq 3), where

$$\left(\frac{k}{k'}\right)_{obsd} = \left(\frac{K}{K'}\right)^{\frac{1}{n}}\left(\frac{k}{k'}\right) \quad (3)$$

K and K' are the equilibrium constants for the two alkyllithiums in the first step of mechanism 2. Competitive rate studies thus cannot be interpreted in purely kinetic terms if mechanism 2 is operative *and* if the alkyllithiums have formed a statistical mixture of aggregates.

In the present work it has been found that alkyllithiums in pentane react with indene in a process which is first order in alkyllithium, not fractional order, so that mechanism 2 is not operative here. Rather, indene apparently reacts directly with the undissociated RLi aggregate. The means by which the true first-order dependence was established was to investigate

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