was then shaken in a separatory funnel containing 70 ml of water and 70 ml of ether until it dissolved. The ether layer was separated and the aqueous layer was washed once with 70 ml of ether. The combined ether extracts were dried and concentrated to yield 3.34 g (80%)[8] of colorless oil. Analysis by GLC showed the oil to contain 94% 1-dodecanol and 6% 1-decanol.

Acknowledgments. One of us (A.O.C.) is grateful to Du Pont for a graduate fellowship (1973–1974). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—*cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; geraniol, 106-24-1; citronellol, 106-22-9; cyclododecanol, 1724-39-6; cyclododecanone, 830-13-7; 1-dodecanol, 112-53-8; 1-decanol, 112-30-1; calcium chloride, 10043-52-4; calcium bromide, 7789-41-5; manganous chloride, 7773-01-5; 4-*tert*-butylcyclohexanone, 98-53-3.

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(7) Camille and Henry Dreyfus Teacher–Scholar Grant recipient; Alfred P. Sloan Fellow, 1973–1975.
(8) The percent yield given is based on original amount available of desired alcohol. For example, in case IA, the amount of *trans*-4-*tert*-butylcyclohexanol available is 3.5 g (70% of 5.0 g). The yield of the purified trans epimer is 2.91 g or 84% of 3.5 g.

Diborane as a Reducing Agent. The Novel Reduction of *N*-Formylindoles and Electrophilic Substitution in Indoles

A. Chatterjee* and K. M. Biswas

Department of Chemistry, University College of Science, Calcutta 700009, India

Received September 12, 1974

Attempted reduction of *N*-formyl-3-methylindole (**1a**) and 2,3-dimethyl-*N*-formylindole (**1b**) with complex metal hydrides leads to skatole and 2,3-dimethylindole, respectively. Diborane reduction of indole derivatives has furnished interesting results.[1,2] Further studies with this reagent are now reported. Diborane reduction of **1a** gives 1,3-dimethylindole (**4a**, 49.4%) and 1,3-dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (**6a**, 35.8%). Similarly, reduction of **1b** with diorane affords 1,2,3-trimethylindole (**4b**, 52.4%) and two diastereoisomeric 1,2,3-trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (**6b**, 36.7%, and **6c**, 6.8%). This appears to be the first report on the successful reduction of an *N*-acylindole to the corresponding *N*-alkyl derivative. The formation of the indolylmethylindolines (**6**) in the diborane reduction of *N*-formylindoles (**1**) implies that electrophilic substitution takes place primarily at the 3 position of 3-substituted indoles. These results are discussed in the light of the mechanisms of diborane reduction and electrophilic substitution in 3-substituted indoles.

Indoles,[3] oxindoles,[3d,4,5] isatins,[5] indole-2-, and indole-3-carbonyl derivatives[3a,d,6-10] including indole-3-glyoxamides,[3a,f,9,11] and their *N*-methyl analogs have been reduced with diborane. However, to our knowledge, there is no report in the literature on the reduction of *N*-acylindoles with any reducing agent.[12] In the present communication a simple method is presented for the reduction of *N*-formylindoles with diborane, partly from an interest in its synthetic implications and partly to compare the reducing properties of diborane with those of lithium aluminum hydride ($LiAlH_4$).

Jackson and his coworkers demonstrated that electrophilic substitution takes place primarily at the 3 position of 3-substituted indoles.[10,13] However, recently Wolinsky and Sundeen[14] and Casnati, Dossena, and Pochini[15] claimed to have obtained evidence in favor of direct electrophilic substitution at the 2 position of 3-alkylindoles. The work reported in the present communication was undertaken also with a view to throwing further light on this subject.

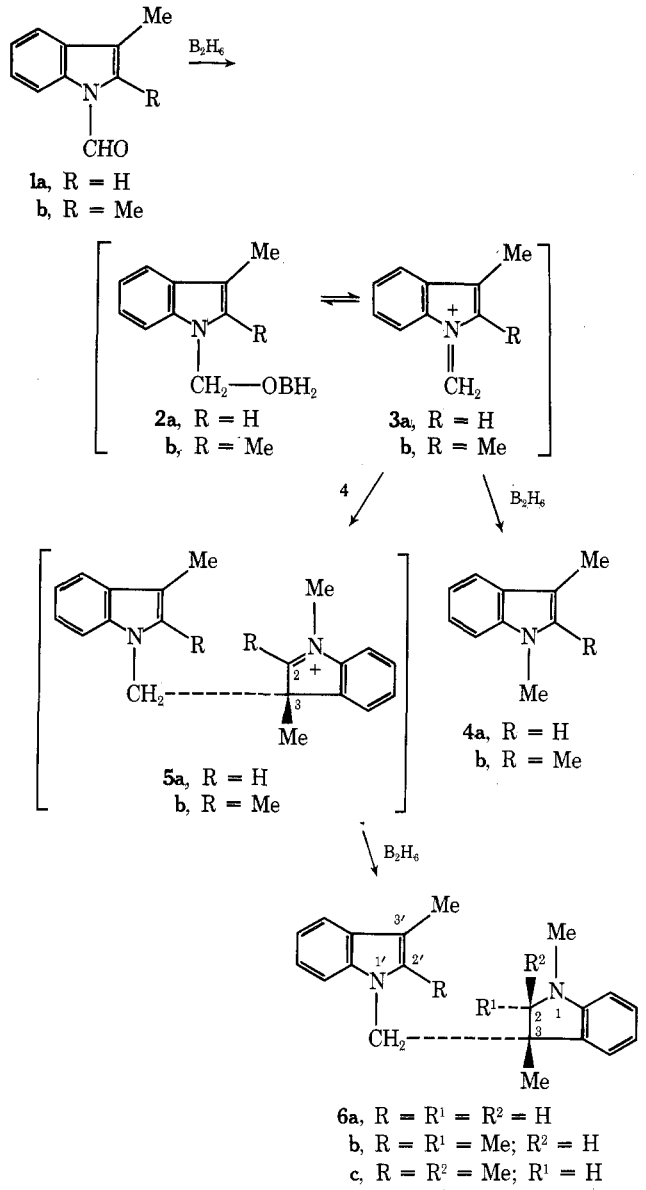
It has been observed that complex metal hydrides are unsuitable for the reduction of *N*-acylindoles,[12] presumably because of the tendency of the acyl groups of the latter to undergo cleavage under basic conditions.[12a,c,16] However, *N*-acylindoles are generally more stable in acidic than in basic media (cf. preparations of **1** by Vilsmeier–Haack method[17]). These facts and the pronounced aldehydic character of the *N*-formyl groups of **1**[17] led us to assume that diborane would be the reagent of choice for their reduction, particularly because the danger of hydrolytic cleavage would be minimum, since the reaction medium would be acidic because of the Lewis acid character of both diborane and boron trifluoride (BF_3).[18]

While attempted reduction of the *N*-formylindoles (**1**) with $LiAlH_4$ or potassium borohydride (KBH_4) under a variety of conditions always resulted in the formation of skatole and 2,3-dimethylindole, respectively,[12a] reduction of **1a** with diborane afforded 1,3-dimethylindole (**4a**) and 1,3-dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (**6a**) (Scheme I). Similarly, diborane reduction of **1b** gave 1,2,3-trimethylindole (**4b**) together with two diastereoisomeric 1,2,3-trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (**6b** and **6c**). In this connection, it may be pointed out that this appears to be the first report on the successful reduction of an *N*-acylindole.[12]

The origin of both the mono- and dimeric products in the diborane reduction of **1** may be rationalized by assuming that the intermediate (**3**) may undergo further reduction with excess diborane to give **4** (Scheme I). **3** may also undergo nucleophilic attack by the initially formed indoles (**4**) to afford the indoleninium cation (**5**), which is then reduced by excess diborane to the dimers (**6**).

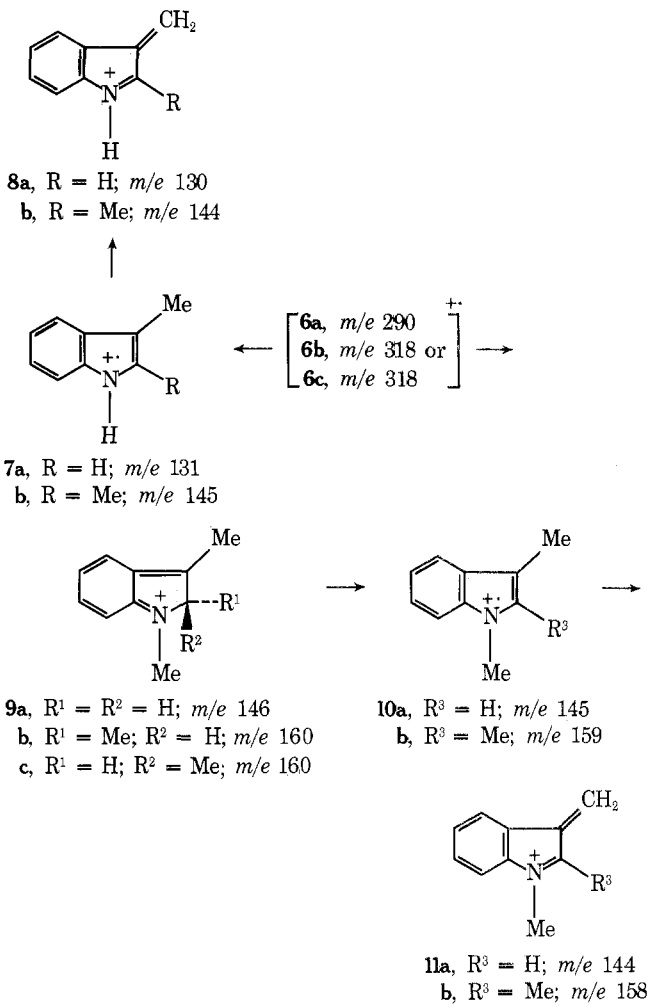
The major dimeric product was assigned the trans configuration (**6b**) on the assumption that reduction of **5** by the addition of a hydride ion at the 2 position takes place

Scheme I



predominantly trans to the bulky 3-indolylmethyl substituent.[19] Confirmation of these stereochemical assignments was obtained by examining their Dreiding models and NMR spectra. The methyl protons at the 2′ position of the cis isomer (**6c**) resonate at δ 2.00 whereas those of the trans isomer (**6b**) resonate at an unusually high field (δ 1.44). Owing to greater interaction between the two methyl groups at the 2 and 2′ positions, the trans isomer (**6b**) may preferentially exist on the average in a spatial arrangement in which the methyl protons at its 2′ position experience the shielding effect of the benzene ring of the indoline moiety, resulting in the observed upfield shift (δ 1.44). The methyl protons at the 2 position of **6b** resonate at a lower field (δ 1.44) than those of **6c** (δ 0.92). From Dreiding models it appears that the methyl protons at the 2 position of only **6b** can exist in the plane of the ring current of its indole moiety, and experience a deshielding effect, thus resulting in the observed downfield shift. On the other hand, the same protons of **6c** are shielded by the indole moiety and resonate at a higher field (δ 0.92). The methine proton at the 2 position of **6c** resonates at δ 3.52, whereas the corresponding proton of **6b** resonates at δ 3.01. Further, it appeared from the models that the methine proton at the 2 position of only **6c** lies close to the plane of the ring current

Scheme II
Mass Spectral Fragmentation Pattern of the Dimeric Products (6) Obtained in the Diborane Reduction of *N*-Formylindoles (1)

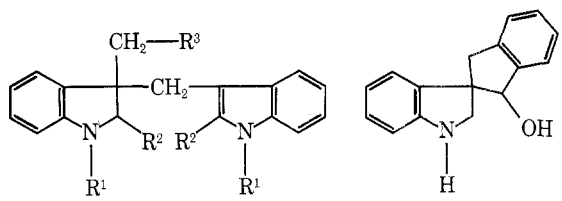


of its indole moiety. It thus experiences a deshielding effect and resonates at a lower field.

The uv spectral data and broad mass spectral fragmentation pattern of the dimeric products (**6**), which confirm their structures, are presented in the Experimental Section and Scheme II, respectively.

In this connection, it may be pointed out that, although indole,[3a-d] N-unsubstituted alkylindoles,[3d,e] oxindole,[3d,4] *N*-methyloxindole,[4] and N-unsubstituted and *N*-methylindole-3-glyoxamides[3f] were reported to give indolines on reduction with diborane, we failed to observe any indolines, either in our present work or in our earlier studies with indole-3- and indole-2-carbonyl derivatives.[3a,6,8-11]

The electrophilic attack at the 3 position of the 3-substituted indoles (**4**) by **3** and trapping of the 3,3-disubstituted indolenines (**5**) by diborane reduction follow essentially the same mechanism as is involved in the formation of the indolylmethylindolines (**12**) in the diborane reduction of in-



12, R^1, R^2 = H or Me
R^3 = H or OH

13

dole-3-carboxaldehydes[19] and indole-3-carboxylic acid,[3f] and the spirocyclic indoline (13) in the diborane reduction of 3-(*o*-carboxybenzyl)indole.[10] Thus, our present results, though limited and not sufficient to make any firm conclusion, tend to provide support to the theory of Jackson and his coworkers.[13] Jackson's more recent observations[20] and those of others[3e,21,22] also support this theory.[13]

Experimental Section

Light petroleum refers to the fraction boiling between 60 and 80°, if not indicated otherwise. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$, if not otherwise mentioned, chemical shifts are given in δ values relative to Me_4Si, and s, d, q, and m indicate singlet, doublet, quartet, and multiplet, respectively. Mass spectra were recorded on an AEI MS-9 spectrometer. Tetrahydrofuran (THF), BF_3OEt_2, and diglyme were dried and redistilled before use.

Attempted Reduction of *N*-Formylindoles (1) with Complex Metal Hydrides. A solution of **1a**[23] (223 mg, 0.0014 mol) in dry THF (2 ml) was added dropwise to a suspension of $LiAlH_4$ (210 mg, 0.0055 mol) in dry THF (4 ml), and the mixture was refluxed for 4 hr and then left at 25° overnight. After usual work-up and crystallization of the product from light petroleum, skatole (180 mg), mp 96–97°, was obtained. Its identity was confirmed by mixture melting point determination and TLC comparison with an authentic sample. Attempted reduction of **1a** with KBH_4 in boiling absolute EtOH and of **1b**[23] with $LiAlH_4$ or KBH_4 also resulted only in the formation of skatole and 2,3-dimethylindole, respectively.[12]

Hydrolysis of *N*-Formylindoles (1). 1a[23] (160 mg) was treated with alcoholic NaOH (42 mg in 1 ml) for 45 min at 25°. After removal of EtOH, the residue was extracted with ether to give skatole (105 mg). The ether-insoluble fraction afforded sodium formate as colorless, shining needles, mp 252–253° (lit.[24] mp 253°) from absolute EtOH. Similar treatment of **1b** gave 2,3-dimethylindole and sodium formate.[25]

1,3-Dimethylindole (4a) and 1,3-Dimethyl-3-(3′-methylindolyl-1′-methyl)indoline (6a). Diborane (0.015 mol), generated externally by the dropwise addition of a solution of $NaBH_4$ (0.85 g, 0.0225 mol) in dry diglyme (20 ml) to a magnetically stirred solution of BF_3–OEt_2 (4.47 g, 0.0312 mol) in dry diglyme (13 ml) over 35 min, was passed into a solution of **1a** (0.95 g, 0.006 mol) in dry THF (50 ml) at 0° in a slow stream of dry nitrogen. The apparatus was initially flushed with dry nitrogen, and after completion of the addition, the generator flask was heated at 60–65° for 2 hr for driving out the residual diborane into the reaction vessel. The reaction mixture, which formed a white, gelatinous precipitate within 30 min, was left overnight at 25°, and excess diborane was destroyed carefully with MeOH. After addition of a further 25 ml of MeOH, the mixture was refluxed for 2 hr, the solvents were removed, and the residue was taken up in $CHCl_3$ (50 ml). The solution was washed successively with aqueous $NaHCO_3$ (5%) and H_2O and dried ($MgSO_4$), and the solvent was distilled off under reduced pressure to give an almost colorless oil (0.94 g). TLC examination of the oil revealed it to be a mixture of two components, which were separated by chromatography on a silica gel column. Elution with light petroleum afforded 1,3-dimethylindole (**4a,** 0.43 g, 49.4%) as a colorless liquid. The picrate was obtained as pink needles (from EtOH), mp 143–144° (lit.[26] mp 142.5–143.5°). The 1,3,5-trinitrobenzene charge-transfer complex was obtained as orange-red needles (from absolute EtOH): mp 169–170° (lit.[27] mp 169°); NMR (60 MHz) δ 7.30 (m, 1, 7-H), 6.90–7.20 (m, 3, 4-, 5-, 6-H), 6.70 (s, 1, 2-H), 3.64 (s, 3, NCH_3), 2.20 (d, 3, 3-CH_3, J = 1.2 Hz), 9.03 (s, 3, ArH).

Further elution of the column with a mixture of light petroleum and ether (17:3 v/v) gave the dimer **6a** as a soft, colorless mass (0.31 g, 35.8%): ir (Nujol mull) 3000 (m), 2888 (s), 2813 (s), 2788 (s), 1610 (s, C=C), 1480 (s), 1120 (m, 1020 (m), 765 (s), 750 cm^{-1} (s); uv λ_{max} (EtOH) 223, 230, 258, 289, and 295 nm (log ϵ 4.30, 4.31, 3.80, 3.70, and 3.71); λ_{max} (concentrated H_2SO_4) 238, 243, and 294 nm (log ϵ 3.64, 3.63, and 3.70); NMR (Varian A-60) δ 7.60 (m, 1, 7-H), 6.66–6.90 (m, 3, 4-, 5-, 6-H), 2.81 (d, 1, 2-H_A, J_{AB} = 9 Hz), 3.39 (d, 1, 2-H_B, J_{AB} = 9 Hz), 2.75 (s, 3, NCH_3), 1.38 (s, 3, 3-CH_3), 7.10–7.35 (m, 4, 4′-, 5′-, 6′-, 7′-H), 6.53 (s, 1, 2′-H), 2.32 (d, 3, 3′-CH_3, J = 1.2 Hz), 4.12 (s, 2, N′CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 290 (54, M·+), 147 (59), 146 (beyond chart), 145 (beyond chart), 144 (79), 131 (100), 130 (59); mass measurement by high-resolution mass spectrometry *m/e* 290.17947 (calcd for $C_{20}H_{22}N_2$, *m/e* 290.17829); also see Scheme II. The 1,3,5-trinitrobenzene charge-transfer complex was obtained as pink needles with a metallic lustre (from MeOH), mp 133–134°.

Anal. Calcd for $C_{20}H_{22}N_2 \cdot 2C_6H_3N_3O_6$: C, 53.65; H, 3.93; N, 15.64. Found: C, 53.40; H, 3.65; N, 15.56.

1,2,3-Trimethylindole (4b) and Diastereoisomeric 1,2,3-Trimethyl-3-(2′,3′-dimethylindolyl-1′-methyl)indolines (6b and 6c). 1b[23] (1.038 g, 0.006 mol) was reduced for 4 hr with externally generated diborane (0.015 mol) following the foregoing procedure. The colorless, oily product, which indicated the presence of three components on TLC examination, was chromatographed on a column of silica gel (60–120 mesh, Chemo Synthetics). Elution with a mixture of light petroleum and benzene (17:3 v/v) afforded 1,2,3-trimethylindole (**4b,** 0.5 g, 52.4%) as a colorless oil. The picrate was obtained as dark-red needles (from benzene), mp 148–149° (lit.[28] mp 150°). The 1,3,5-trinitrobenzene charge-transfer complex was obtained as blood-red needles (from absolute EtOH): mp 170–171°; NMR (HA 100 MHz, CCl_4 + $CDCl_3$) δ 2.04 (s, 3, 3-CH_3), 2.22 (s, 3, 2-CH_3), 3.48 (s, 3, NCH_3), 6.75–7.06 (m, 4, 4-, 5-, 6-, 7-H), 8.80 (s, 3, ArH).

Further elution of the column with more polar solvents gave only a mixture of two components, which was rechromatographed on a column of silica gel (60–100 mesh, Gouri Chemicals) in light petroleum. The first 12 fractions contained a mixture of two components (0.30 g), while the subsequent 24 fractions gave a pure compound (175 mg), which on crystallization first from light petroleum and finally from MeOH, afforded the trans dimer (**6b**) as colorless prisms: mp 123°; uv λ_{max} (EtOH) 224, 232, 260, 288, and 293 nm (log ϵ 4.36, 4.36, 3.86, 3.78, and 3.77); λ_{max} (concentrated H_2SO_4) 238, 242, and 287 nm (log ϵ 3.74, 3.71, and 3.80); NMR (Varian HA-100) δ 7.43 (m, 1, 7-H), 6.40–6.60 (m, 3, 4-, 5-, 6-H), 3.01 (q, 1, 2-H, J = 8 Hz), 2.75 (s, 3, NCH_3), 1.40 (s, 3, 3-CH_3), 1.44 (d, 3, 2-CH_3, J = 8 Hz), 6.95–7.10 (m, 4, 4′-, 5′-, 6′-, 7′-H), 1.44 (s, 3, 2′-CH_3), 2.12 (s, 3, 3′-CH_3), 3.99 (d, 1, N′CH_A, J_{AB} = 14 Hz), 4.22 (d, 1, N′CH_B, J_{AB} = 14 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 318 (28, M·+), 161 (45), 160 (beyond chart), 159 (100), 158 (84), 145 (68), 144 (73); see also Scheme II.

Anal. Calcd for $C_{22}H_{26}N_2$: C, 82.94; H, 8.23; N, 8.80. Found: C, 83.16; H, 8.15; N, 8.78.

The residue (0.3 g) of the first 12 fractions was rechromatographed on a column of silica gel (60–100 mesh, Gouri Chemicals) in light petroleum, bp 40–60°. The first seven fractions furnished the cis dimer (**6c**) as a colorless, thick liquid (40 mg): uv λ_{max} (EtOH) 223, 231, 260, 288, and 294 nm (log ϵ 4.35, 4.37, 3.86, 3.78, and 3.78); λ_{max} (concentrated H_2SO_4) 238, 242, and 286 nm (log ϵ 3.74, 3.72, and 3.79); NMR (Varian HA-100) 7.48 (m, 1, 7-H), 6.43–6.80 (m, 3, 4-, 5-, 6-H), 3.52 (q, 1, 2-H, J = 8 Hz), 2.79 (s, 3, NCH_3), 1.32 (s, 3, 3-CH_3), 0.92 (d, 3, 2-CH_3, J = 8 Hz), 7.06–7.36 (m, 4, 4′-, 5′-, 6′-, 7′-*H*), 2.00 (s, 3, 2′-CH_3), 2.23 (s, 3, 3′-CH_3), 4.15 (d, 1, N′CH_A, J_{AB} = 15 Hz), 4.32 (d, 1, N′CH_B, J_{AB} = 15 Hz); mass spectral data are recorded in Table I; see also Scheme II.

Continued elution of the column wih the same solvent gave mainly **6b** (150 mg), mp 123°, together with an approximately 1:1 mixture (50 mg) of **6b** and **6c**. Yield: **6b,** 36.7%; **6c,** 6.8% (approximate).

Table I
Mass Measurement of the Dimer 6c by High-Resolution Mass Spectroscopy

Fragment	Found, *m/e*	Calcd, *m/e*	For	Rel intensity
6c M·+	318.21241	318.20959	$C_{22}H_{26}N_2$	4.36
9c	160.1123	160.1123	$C_{11}H_{14}N$	100
10b	159.1046	159.1048	$C_{11}H_{13}N$	15.60
11b	158.0969	158.0969	$C_{11}H_{12}N$	10.71
	157.0885	157.0891		2.03
	156.0820	156.0813		1.25
7b	145.0884	145.0891	$C_{10}H_{11}N$	12.70
8b	144.0802	144.0813	$C_{10}H_{10}N$	10.91
	143.0730	143.0735		2.76
	142.0642	142.0656		1.18
	130.0654	130.0656		1.41

Acknowledgment. The authors wish to thank Professor A. H. Jackson, University College, Cardiff, for mass and

NMR spectra, and Professor G. W. Kenner, University of Liverpool, for high-resolution mass spectra.

Registry No.—**1a**, 31951-33-4; **1b**, 41601-98-3; **4a**, 875-30-9; **4a** 1,3,5-trinitrobenzene charge-transfer complex, 54383-93-6; **4b**, 1971-46-6; **4b** 1,3,5-trinitrobenzene charge-transfer complex, 54383-94-7; **6a**, 54383-95-8; **6a** 1,3,5-trinitrobenzene charge-transfer complex, 54383-96-9; **6b**, 54384-25-7; **6c**, 54384-26-8; skatole, 83-34-1; diborane, 19287-45-7.

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Synthesis of 4-Keto-4,5,6,7-tetrahydroindoles via Munchnone Intermediates[1]

Fred M. Hershenson

Department of Chemical Research, Searle Laboratories, Chicago, Illinois 60680

Received June 20, 1974

The amino acids, proline and pipecolinic acid, have been converted into the 4-keto-4,5,6,7-tetrahydroindoles, **5a** and **5b**, respectively, in three steps. This sequence involved the preparation of the corresponding *N*-(4-carbomethoxybutyroyl)amino acids and their subsequent reaction with acetic anhydride and dimethyl acetylenedicarboxylate, thereby yielding the pyrrole triesters, **4a** and **4b**. This latter transformation employed a 1,3-dipolar cycloaddition reaction of bicyclic munchnone derivatives generated in situ. The final step in this sequence involved a Dieckmann condensation of **4a** and **4b** using sodium hydride. The application of the sequence to acyclic amino acids was also investigated and with phenylglycine and sarcosine, the tetrahydroindoles, **15** and **16**, respectively, were obtained.

Munchnones (mesoionic oxazolium 5-oxides) have been successfully used in the preparation of pyrroles bearing simple alkyl, aryl, and/or carboalkoxy substituents.[2,3] This paper will describe the synthesis of pyrrole derivatives possessing a functionalized alkyl side chain capable of undergoing further reaction to yield 4-keto-4,5,6,7-tetrahydroindoles. In particular, this involves the reactions of *N*-(4-carbomethoxybutyroyl)amino acids with acetic anhydride and dimethyl acetylenedicarboxylate. The concept of utilizing functionalized 1,3-dipoles has recently been described by Lown and Landberg.[4]

Results and Discussion

Initially, the amino acids, proline and pipecolinic acid, were used in this study, and the reactions involving these compounds are listed in Scheme I.

Treatment of these amino acids with methyl (4-chloroformyl)butyrate in refluxing pyridine afforded the *N*-acyl amino acids, **2a** and **2b**, respectively. Attempts to carry out this acylation reaction under Schotten–Baumann conditions failed to give the desired *N*-(4-carbomethoxybutyroyl)amino acids. When pipecolinic acid was treated with methyl 4-(chloroformyl)butyrate in dilute sodium hydroxide solution, a low yield of the *N*-acyl diacid, **2c**, was obtained. **2a** and **2b** were isolated as viscous oils and were used in the next step without extensive purification, although **2b** was converted into a crystalline dicyclohexylamine salt for the purposes of characterization.

Reaction of **2a** and **2b** with acetic anhydride and dimethyl acetylenedicarboxylate furnished the tetrahydropyrrolizine **4a** and tetrahydroindolizine **4b**, respectively, as oils. The formation of these products involve the intermediacy