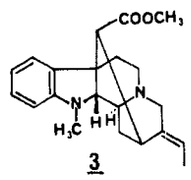
The structure of the second moiety of pleiocraline could be determined from an interpretation of the remaining carbon signals. The noise-decouple ^{13}C shifts along with the single frequency decoupled multiplicity of these signals indicated its structural resemblance (Table I) with the monomeric dihydroindole alkaloid $N_{(a)}$-methyl deacetyldeformyl-1,2-dihydroakuammiline (2β-H) (**3**). Correct assignment of the 2β-H configuration of pleiocraline **2** [C(2′) at 80.3 ppm] was made by comparison with the value available for C(2) of **3** (δ 79.1 ppm). In contrast, the C(2) resonance of the compound **4** having a 2α-H configuration was observed[9] at 70.6 ppm. The



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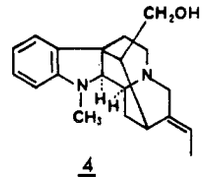

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^{13}C NMR data (see Table I) also indicate that the nature and sites of attachments between the two monomeric indole units of pleiocraline are the same as in pleiocorine (**1**). Based on these arguments, structure **2** can be assigned to pleiocraline. The stereochemistry of the linkage of the two alkaloid residues in pleiocraline is not supported or refuted by the present NMR data. Rather, the stereochemistry is the same as in pleiocorine, which is postulated by analogy with related[6,7] bisindole alkaloids.

Acknowledgments. We are grateful to Dr. T. Sevenet, Laboratoire des Plante Médicinales du CNRS, Nouméa, New Caledonia, for his help in procuring the plant material. We thank Dr. P. Potier for his interest in this work.

Registry No.—**1**, 55732-60-0; **2**, 62509-84-6; **3**, 50906-83-7.

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(9) J. Le Men and G. Lukacs, unpublished results.

The So-Called Hydroxymethylation Reaction. Synthesis of 3-Methoxy-2-methylpropiophenone

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Reaction conditions for the carbonate-catalyzed simple hydroxymethylation of phenones by means of paraformaldehyde were first reported by Fuson, Ross, and McKeever in 1938.[1] Since that time, some laboratories have questioned the work;[2a-c] one of them has offered a "better" procedure,[2b] while others have found it, nevertheless, convenient for their purposes.[2d]

We have examined this reaction using NMR spectroscopy preparatory to synthesis of a specific ^{13}C-labeled compound,[3] and wish to report that, in fact, the reaction is a better procedure for methoxymethylation than for hydroxymethylation, at least for propiophenone and *p*-fluoropropiophenone.

The original authors reported a modest yield of 2-benzoylpropyl alcohol, bp 143–145 °C (5 mm), which gave a satisfactory elemental analysis and a crystalline phenylurethane (yield unspecified) along with 80% recovery of starting material after 4 days of reaction at room temperature! Following their procedure exactly, we observed the progression of events shown in eq 1, 2, and 3 (see also Figure 1).

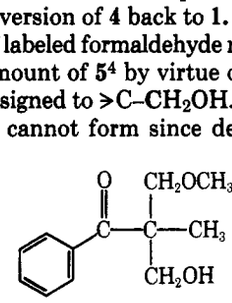
$$n\underset{\mathbf{1}}{\mathrm{ArCOCH_2CH_3}} + +\mathrm{CH_2O}+_n \rightleftarrows n\underset{\mathbf{2}}{\mathrm{ArCOCH(CH_3)CH_2OH}} \quad (1)$$

$$2 \rightleftarrows \underset{\mathbf{3}}{\mathrm{ArCOC(CH_3)=CH_2}} + \mathrm{H_2O} \quad (2)$$

$$3 + \mathrm{CH_3OH} \rightleftarrows \underset{\mathbf{4}}{\mathrm{ArCOCH(CH_3)CH_2OCH_3}} \quad (3)$$

The reaction mixture after 6 days contained **4**, **3**, and **2** in the approximate molar ratio of 80:15:5.

The reversibility of all three reactions was proved by means of one experiment in which pure **4** was treated with a very small amount of $H^{13}CHO$ in the same methanol–potassium carbonate medium. Monitoring by ^{13}C NMR spectroscopy showed that ^{13}C label was slowly introduced into the methylene group of both **4** and methacrylophenone (**3**) which was generated in the equilibration. This incorporation requires reversion of **4** back to **1**. In addition to those results, the use of labeled formaldehyde made evident the formation of a small amount of **5**[4] by virtue of its ^{13}C resonance at δ_c = 66 ppm, assigned to >C–CH_2OH. The bismethoxymethylated ketone, **6**, cannot form since dehydration of **5** is impossible. This



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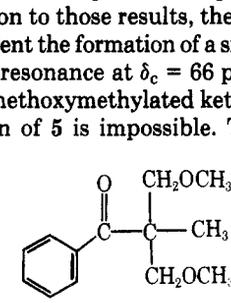

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long-term label-incorporation experiment also showed evidence of the concomitant Cannizzaro reaction with enhancement in the signal for $^{13}CH_3OH$, and the appearance and growth of a signal at δ_c = 170.4 ppm, assigned to $H^{13}CO_2^-$.

Our first attempt to synthesize labeled **4** from paraformaldehyde containing ~90% ^{13}C[5] was a preparative failure which was ultimately attributed to the resistance of the reagent to depolymerize in the medium as readily as did the unlabeled paraformaldehyde.[6] Thin-layer chromatography showed many unknown products along with only a little **4**. In order to circumvent this problem, which seemed related to improper stoichiometry, we adopted the use of aqueous formaldehyde which worked as well or better than paraformaldehyde. Equilibrium concentrations were reached in ca. 5–6 days at ambient (22–25 °C) temperature. It is possible that the addition of a drying agent to the reaction would change the equilibrium concentrations vis-à-vis **2** and **4**, but since our ultimate goal was a β-chlorophenone, *p*-$FC_6H_4COCH(CH_3)$-$^{13}CH_2Cl$, labeled **2**, **3**, and **4** were all satisfactory for our purposes.

Experimental Section[7]

Preferred Procedure for 3-Methoxy-2-methylpropiophenone. A mixture of 5.1 g (62.9 mmol) of 37% formaldehyde, 8.43 g (62.8

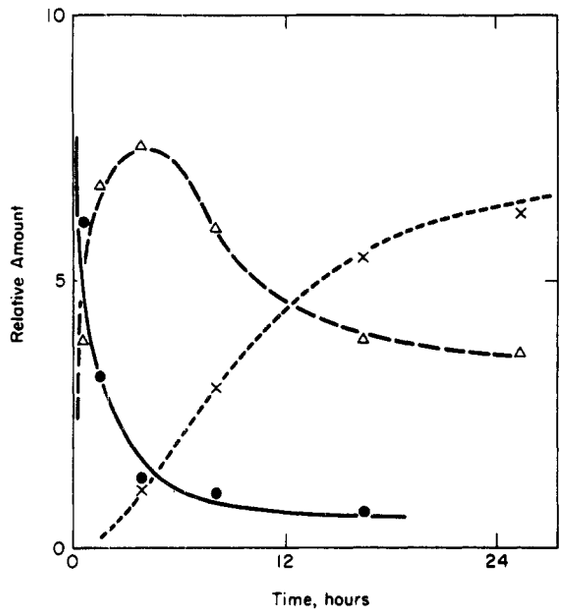

Figure 1. Composition during initial stages of a 30 °C reaction of HCHO with 1 in methanol, K_2CO_3 catalysis (as in Experimental Section). Data taken from ^{13}C NMR methyl signal intensities. (● - ●) 1; (△ - - - △) 2; (x - - - x) 4. Methacrylophenone (3), present at a low (ca. 10–15%) equilibrium concentration, is not shown.

mmol) of propiophenone, and 750 mg (5.4 mmol) of potassium carbonate was stirred in 39 mL of methanol for 6 days at room temperature. Proton NMR (60 MHZ) showed a mixture which could be integrated for 10–15 mol % of **3**. Carbon NMR spectroscopy showed **2** and **4** to be present in the ratio of 1:15 compared to 1:4 after only 3 days. The solvent was removed in vacuo without applied heat, and the residual oil was taken up in benzene, washed with water, and dried over sodium sulfate. Fractional distillation gave 6.1 g (55%) of pure **4**: bp 75 °C (0.1 mm); 60-MHz ^1H NMR ($CDCl_3$) δ 1.2 (d, 3, CH_3–C), 3.25 (s, 3, CH_3O), 3.35–3.95 (m, 3, CH, CH_2), 7.2–8.15 (m, 5, ar); mass spectrum *m/e* (rel intensity) 178 (M^+, 5), 163 (3), 146 (25), 136 (16), 105 (100), 77 (74). GC assay showed ca. 16% more of **4** distributed between the forerun (60% pure) and the pot residue.

Anal. Calcd for $C_{11}H_{14}O_2$ (178.2): C, 74.13; H, 7.92. Found: C, 74.19; H, 8.24.

^{13}C Incorporation Experiment. To a solution of 107 mg of **4** diluted to 0.3 mL with 9:1 MeOH:H_2O saturated with K_2CO_3 was added 11 μL of 20% aqueous formaldehyde, 90% ^{13}C. The resulting solution was stored at ambient temperature and observed by ^{13}C NMR spectroscopy periodically. After 3 weeks, the CH_2 signal had doubled, indicating ca. 1% ^{13}C incorporation. Cannizzaro reaction products were evident, as was **5** (see text).

After 8 weeks, incorporation was measured at ca. 1.7%. The solution was worked up and analyzed by gas chromatography–mass spectroscopy, giving values of 1.4–2% ^{13}C incorporation, based on ratios of M^+ to $M^+ + 1$ ions of both **3** and **4**. GC–MS analysis of a trimethylsilylated sample also showed a substance: *m/e* (rel intensity) 280 (M^+, 5), 265 (11), 215 (83), 179 (78), 173 (51), 135 (58), 105 (100), 77 (82), which we consider as further evidence for **5** [$C_{12}H_{15}O_3$–$Si(CH_3)_3$, mol wt 280].

Acknowledgment. Thanks are due to Patricia Cala for the mass spectral experiments, and to Robert Reamer for some of the NMR measurements.

Registry No.—1 (Ar = Ph), 93-55-0; **3** (Ar = Ph), 769-60-8; **4** (Ar = Ph), 62509-81-3; **5**, 62509-82-4; **5** Me_3Si ether, 62509-83-5; formaldehyde, 50-00-0.

References and Notes

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(3) To be published elsewhere.
(4) Cf. T. I. Temnikova and N. A. Oshueva, *J. Gen. Chem. USSR* (*Engl. Transl.*), **33**, 1368 (1962); and R. C. Fuson, W. E. Ross, and C. H. McKeever, *J. Am. Chem. Soc.*, **61**, 414 (1939).
(5) From M. S. D., Canada. Prior thermal depolymerization of the reagent would, of course, have been possible, but less convenient.
(6) From Aldrich Chemical Co.
(7) Boiling points are uncorrected. Elemental analyses were performed by Mr. J. P. Gilbert and associates of these laboratories. ^1H NMR spectra were obtained on a Perkin-Elmer R-24A spectrometer in $CDCl_3$, unless otherwise noted. ^{13}C NMR data were obtained with a Varian CFT-20 FT spectrometer, referenced to external Me_4Si in acetone-d_6. Mass spectral analyses were obtained on a Finnigan 3200, GC inlet, operated at 70 eV.

A Convenient Synthesis of [3.3]Paracyclophane

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[3.3]Paracyclophane (**1**) is a pivotal structure among the [*m.m*]paracyclophanes. It is intermediate in ring size between [2.2]paracyclophane, where ring strain and transannular effects are pronounced, and [4.4]paracyclophane, where these effects are absent.[1] While some chemical and physical studies of **1** have been reported,[1,2] it has been much less studied than, for example, the more readily available[3] [2.2]paracyclophane. Chemical transformations for which the ring size in **1** is particularly suited have been neglected because this ring system is not easily accessible. Of the three reported syntheses of **1**, the first[4] utilizes 1,3-diphenylpropane as starting material, involves an acyloin ring closure, and gives the final product in an overall yield of about 0.1%. Two more recent and improved syntheses utilize diazomethane[5] or solvolytic[6] ring expansion routes from [2.2]paracyclophane, itself prepared in low yield (10%) by the most convenient method,[3] and provide **1** in overall yields of 7–19%, the latter involving preparative GLC isolation.

Our interest[7] in novel structures derivable from **1** necessitated a synthetically less expensive route to this compound. We now report for **1** a new synthesis which is particularly convenient and which does not require at any stage the use of special separation procedures.

Treatment of *p*-bis(2-hydroxyethyl)benzene[8] with 48% hydrobromic acid gives the corresponding dibromide **2** in 72% yield. Addition of a dilute solution of **2** and *p*-xylene-α,α'-dithiol (**3**) in benzene to hot alcoholic potassium hydroxide affords 2,13-dithia[4.4]paracyclophane (**4**) and 2,13,22,33-tetrathia[4.4.4.4]paracyclophane (**5**) in yields of 39 and 6%, respectively. The yields in this reaction have not been optimized; higher dilution conditions than we employed would likely increase the ratio of **4** to **5**. Oxidation of **4** with 30% hydrogen peroxide provides the disulfone **6** quantitatively. The disulfone on pyrolysis at 470 °C under diminished pressure gives essentially pure **1** (94%) as a cold trap condensate. The pyrolysis requires rather simple apparatus, proceeds to completion in a matter of seconds on a 100-mg scale, and can be done repetitively to yield appreciable quantities of **1** in a short time.

Ring contraction by sulfone pyrolysis has been used to advantage by others[9–11] for the preparation of bridged aromatic compounds. In virtually all cases, however, the sulfones have