Registry No.—1, 5470-84-8; 2, 62509-45-9; 3, 62509-46-0; 4, 62509-47-1; 5, 62509-48-2; 6, 62509-49-3; (12Z)-6, 62509-50-6; 7, 62509-51-7; 8, 62509-52-8; 9, 62509-53-9; 9 bistrimethylsilyl derivative, 62509-54-0; 8-bromooctanoic acid, 17696-11-6; triphenylphosphine, 603-35-0; 7-carboxyheptyltriphenylphosphonium bromide, 52956-93-1; 4-benzyloxy-1-butanol, 4541-14-4; dimethyl (2-oxoheptyl) phosphonate, 62509-55-1.

References and Notes

(1) The syntheses of other eicosatrienoic acid analogues have been reported; for example, R. van der Linde, L. van der Wolf, H. J. J. Pabon, and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **94**, 257 (1975); U. H. Do and H. Sprecher, *Arch. Biochem. Biophys.*, **171**, 597 (1975).
(2) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(3) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964); H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973).
(4) Dr. S. Stolzenberg, SRI Biomedical Research Department, conducted the prostaglandin synthetase inhibition studies.
(5) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).
(6) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(7) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim., Fr.*, 197 (1948).
(8) P. A. Grieco and J. J. Reap, *J. Org. Chem.*, **38**, 3413 (1973).

Structure Analysis by Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Pleiocraline, a New Bisindole Alkaloid from *Alstonia deplanchei* van Heurck et Muell. Arg.[1,2]

Bhupesh C. Das,* Jean-Pierre Cosson, and Gabor Lukacs

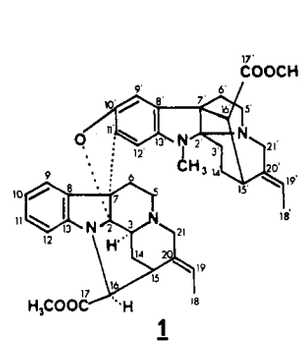
Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif-sur-Yvette, France

Received February 23, 1977

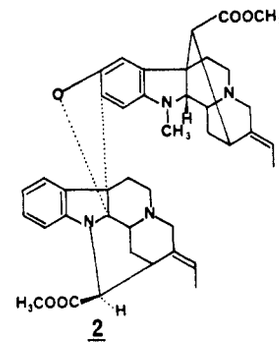
Previously, we reported[3] the ^{13}C NMR structural analysis of pleiocorine (1), a bisindole alkaloid isolated from the stems and leaves of the New Caledonian plant *Alstonia deplanchei* van Heurck et Muell. Arg. (Apocynaceae). We now wish to describe a new isomeric congener bisindole alkaloid, namely, pleiocraline (2), whose structure has also been elucidated principally from an analysis of its ^{13}C NMR spectrum.

Pleiocraline, $C_{41}H_{46}N_4O_5$ (by high-resolution mass spectrometry), $[\alpha]^{20}_D$ +124° (*c* 1.0, chloroform), colorless plates from methanol, decomposes above 300 °C. The mass spectrum of pleiocraline is similar to that of pleiocorine, showing an intense molecular-ion peak at *m/e* 674 but lacking any characteristic fragmentation peak except the M − 59 peak at *m/e* 615 due to the loss of a carbomethoxy group. The UV spectrum of pleiocraline showed λ_{max}^{EtOH} at 244, 295, and 344 nm (ε 29 000, 7250, and 14 150), while its infrared spectrum showed ester (1725 cm^{-1}) and dihydroindole (1605 cm^{-1}) bands but lacked NH or OH absorption. Its structural resemblance with pleiocorine was also revealed from the 240-MHz ^1H NMR spectrum[4] which showed the presence of one *N*-methyl (singlet, δ 2.65, 3 H), two carbomethoxyls (singlet, 3.70, 6 H), two ethylidene side chains (two doublets centered at 1.54 and 1.58, *J* = 7 Hz, 3 H each; two quartets centered at 5.33 and 5.42, *J* = 7 Hz, 1 H each) and six aromatic protons (between δ 6.1 and 7.2) of which two appeared as singlets (δ 6.35 and 6.6) suggesting the presence of an aromatic C(10),C(11) disubstituted indole alkaloid moiety. A one-proton doublet at δ 4.68 (*J* = 4 Hz) as well as the splitting pattern[5] of the aromatic protons suggested that pleiocraline comprises a 2,7-dihydropleiocarpamine moiety which is also known to be a constituent part of pleiocorine (1)[3] and several bisindole alkaloids such as villalstonine,[6] pycnanthine,[6] dihydropycnanthine,[7] etc.

Earlier, unambiguous carbon signal assignments of 2,7-dihydropleiocarpamine moiety of villalstonine and pleiocorine have been achieved through analysis of their ^{13}C NMR spectra.[3] Comparison of the ^{13}C NMR spectra[8] of pleiocraline (2) and pleiocorine (1) clearly indicated (see Table I) the presence



1



2

of a 2,7-dihydropleiocarpamine unit in the new alkaloid, substituted (as in pleiocorine) at C(2) and C(7) through an oxygen and a carbon, respectively.

Table I. ^{13}C NMR Chemical Shifts of Pleiocorine (1), Pleiocraline (2), and $N_{(a)}$-Methyl Deacetyldeformyl-1,2-dihydroakuammiline (2β-H) (3)

	C(2)	C(3)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(12)	C(13)
1	103.2	51.3	52.0[a]	24.6	54.0	134.4	121.6	119.2[b]	126.3	108.9	144.4
2	104.3	51.8	52.1[c]	24.7	54.1	134.7	122.8	118.5[d]	126.9	109.5	144.9

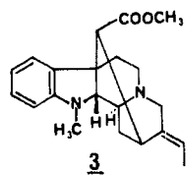
	C(14)	C(15)	C(16)	C(17)	C(18)	C(19)	C(20)	C(21)	$COOCH_3$
1	28.1	32.2	58.1	169.3	12.3	119.5[b]	136.1	48.2[a]	50.6
2	27.9	32.2	58.3	169.9	12.3	119.9[d]	135.2	48.2[c]	51.0

	C(2′)	C(3′)	C(5′)	C(6′)	C(7′)	C(8′)	C(9′)	C(10′)	C(11′)	C(12′)	C(13′)
1	97.5	40.6	55.0[e]	20.2[f]	56.9	134.8	106.1	151.1	127.4	100.1	143.6
2	80.3	53.0	55.0	31.5	43.2	140.3	104.8	153.4	127.8	104.3	148.2
3	79.1	52.8	54.7	31.1	43.0	*h*	120.5	119.0[g]	126.7	109.0	*h*

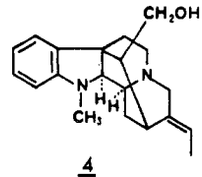
	C(14′)	C(15′)	C(16′)	C(17′)	C(18′)	C(19′)	C(20′)	C(21′)	$COOCH_3$	$N_{a'}$-CH_3
1	26.3[f]	34.7	50.9	173.1	13.4	122.5	138.8	58.1[e]	51.6	28.1
2	34.2	34.5	47.5	172.9	12.9	120.1	140.3	50.8	51.3	35.2
3	33.9	34.4	47.3	172.2	13.0	118.7[g]	*h*	50.6	51.3	33.9

[a-g] These assignments may be interchanged. [h] Because of high dilution these quaternary carbon signals were not observed.

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



3



4

^{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.

References and Notes

(1) Résonance Magnétique Nucléaire du ^{13}C de Produits Naturel et Apparentés XXXIII; for part XXXII see M. Sangaré, B. Septe, G. Berenger, G. Lukacs, K. Tori, and T. Komeno, *Tetrahedron Lett.*, 699 (1977).
(2) Part 46 in the series "Plantes de Nouvelle-Calédonie"; for part 45, see M. Hifnawy, J. Vaquette, T. Sevenet, J. L. Pousset, and A. Cave, *Phytochemistry*, **16**, 1035 (1977).
(3) B. C. Das, J.-P. Cosson, G. Lukacs, and P. Potier, *Tetrahedron Lett.*, 4299 (1974).
(4) We are grateful to Drs. S. K. Kan and G. Massiot for the 240-MHz ^1H NMR spectrum.
(5) M. Hesse, W. von Phillipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W. I. Taylor, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **47**, 878 (1964).
(6) Specialist Periodical Reports, "The Alkaloids", Vol. I, The Chemical Society, London, 1971.
(7) P. Rasoanaivo and G. Lukacs, *J. Org. Chem.*, **41**, 376 (1976).
(8) Spectra were recorded in $CDCl_3$ solution at 22.63 MHz on a Bruker HX 90E Fourier transform spectrometer using Me_4Si as internal standard. Chemical shifts in Table I are with respect to Me_4Si = 0.
(9) J. Le Men and G. Lukacs, unpublished results.

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

Seemon H. Pines* and Alan W. Douglas

Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065

Received March 3, 1977

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).

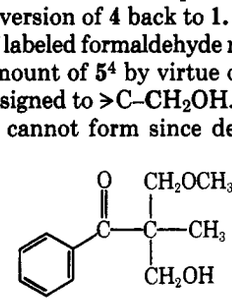
$$n\underset{\mathbf{1}}{\mathrm{ArCOCH_2CH_3}} + +\mathrm{CH_2O}+_n \rightleftarrows n\underset{\mathbf{2}}{\mathrm{ArCOCH(CH_3)CH_2OH}} \quad (1)$$

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

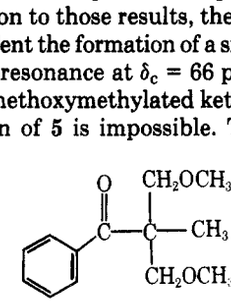
$$3 + \mathrm{CH_3OH} \rightleftarrows \underset{\mathbf{4}}{\mathrm{ArCOCH(CH_3)CH_2OCH_3}} \quad (3)$$

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



5



6

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