growth on two test species, tobacco and beans. The emulsified compound (10^{-3} M) when applied to the axils of decapitated tobacco plants effected a complete inhibition of bud growth for at least 14 days.[13] Necrosis of the meristematic tissue usually occurred and was also observed in the application of the tropone lactone to the second internode of 7-day-old bean plants. Concentrations of 1, 5, or 10 μg of the compound suspended in lanolin were sufficient to cause necrosis above the point of application within 4 days. Inhibition of growth (46%) with no indication of necrosis was observed with an application of 0.1 μg of harringtonolide to the second internode. No translocation of the harringtonolide below the point of application was seen.

Very few tropones have been found in higher plants, although the number of tropolones (2-hydroxytropones) identified in the Cupressaceae and Liliaceae is somewhat greater.[14] The latter compounds, derived from terpenes, are thought to function as fungicidal compounds in the heartwood of a number of species of trees.[15] Many terpenic lactones have been isolated from higher plants and exhibit growth regulatory activity.[16] Harringtonolide appears to be the first complex tropone containing a lactone function to be characterized. No effort has been made thus far to determine the portion(s) of the molecule responsible for the observed biological activity. We do not know whether similar compounds remain to be discovered in other *Cephalotaxus* species.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and were uncorrected. UV spectra were obtained with a Beckman 25 spectrophotometer. IR spectra were taken as KBr pellets on a Perkin-Elmer 621 spectrophotometer. ^{1}H NMR spectra were obtained at 100.1 MHz and the ^{13}C spectra at 25.2 MHz with a Varian XL-100 spectrometer. $CDCl_3$ was the solvent with Me_4Si as the internal standard. HPLC was performed on a Spectra-Physics 3500B instrument equipped with a Schoeffel 700 spectrophotometric detector. Low-resolution mass spectra were obtained with a Du Pont 21-491B spectrometer using the direct-probe method with a 70-eV ionizing voltage. High-resolution mass spectral analyses were made on an AEI MS-9 mass spectrometer by the direct-probe method using an electron-impact ionization at 70 eV. The ion source temperature was 180 °C and perfluorkerosene was the internal standard.

Isolation of Harringtonolide. Seeds of *Cephalotaxus harringtonia*[17] (2.5 kg) were ground and extracted exhaustively with *i*-PrOH at 80 °C. The resulting extract was partitioned between hexane–MeOH–H_2O (10:9:1). The MeOH-soluble portion was partioned by countercurrent distribution in four separatory funnels with the two-phase system, CCl_4–$CHCl_3$–MeOH–H_2O (280:120:320:80). The inhibitor was located in the upper phases of the four funnels by use of the bean second-internode assay. The active fraction was then applied to a gel permeation column packed with Bio-Beads S-X2 in THF. The further purified fraction was then chromatographed on a silica gel column with $CHCl_3$–CH_3CN (9:1). A R_f of 0.50 was obtained for harringtonolide on silica with $CHCl_3$–CH_3CN (4:1). The active compound was recrystallized from CH_2Cl_2 by addition of MeOH (30 mg). The final purification was done by HPLC with the detector set at 319 nm with 640 psi and a flow rate of 0.8 mL/min. The column used was 0.25 m × 4 mm with Spherisorb 5 μm silica. The solvent was $CHCl_3$–CH_3CN (9:1).

Harringtonolide. The compound was obtained as pale yellow crystals: mp 285–288 °C dec; $[\alpha]^{30}_D$ 83.0° (*c* 1.5, $CHCl_3$); UV (EtOH) λ_{max} 242 nm (ε 20 000), 310 (7000); IR (KBr) 3400, 2960, 2925, 1758, 1730 (sh), 1624, 1560, 1430, 1370, 1235, 1075, 960, 870, 750 cm^{-1}; MS *m/e* 310.1241, 310 (M^+, 21), 283 (18), 282 (M^+ − CO, 100), 225 (13), 209 (15), 207 (11), 199 (61), 197 (11), 195 (18), 181 (30), 179 (22), 169 (30), 168 (28), 167 (40), 165 (40), 153 (35), 144 (40), 143 (67), 142 (30).

Reduction of Harringtonolide. Compound (4 mg) was dissolved in EtOAc and then reduced at 45 psi of H_2 over 5% Pd/C: low-resolution MS 316 (M^+, 89), 314 (71), 312 (32), 298 (36), 282 (17), 258 (74), 55 (100).

Plant Bioassays. Harringtonolide was applied to plants in a lanolin carrier or as an emulsified suspension prepared by dissolving the compound in THF and adding Tween 20 surfactant to give a final concentration of 1% solvent and surfactant on addition of H_2O. Xanthi tobacco was used in the assay. Beans (*Phaseolus vulgaris* cv. Pinto) were used for the second internode assay. Treatments were replicated at least twice.

Acknowledgments. The authors thank D. W. Spaulding for conducting the bean second internode assay and M. S. Greenbaum for technical assistance. The NMR analyses were performed by M. O. Mattingly of the Department of Chemistry, University of Maryland. The high-resolution analysis was performed at the Mass Spectrometry Laboratory of the Florida State University. The samples of isoharringtonine and mixed alkaloids from *Cephalotaxus* were furnished by R. G. Powell, Horticultural and Special Crops Laboratory, Northern Regional Research Center, ARS, Peoria, Ill.

Registry No.—Harringtonolide, 64761-48-4; hexahydroharringtonolide, 64761-49-5.

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(18) Figure 1 was drawn using the computer program ORTEP: J. K. Johnson, "Report ORNL-3794", Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(19) Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the U.S. Department of Agriculture and does not imply its approval to the exclusion of other products that may also be suitable.

A Correction on the Reduction of Dihydrocodeinone with Formamidinesulfinic Acid. Stereoselective Reduction of Dihydropseudocodeinone

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We have shown in earlier papers[2,3] that formamidinesulfinic acid (FSA, aminoiminomethanesulfinic acid) reduces the carbonyl group of a number of 6-ketones of the morphine series with complete stereoselectivity to the corresponding secondary alcohols with β configuration of the hydroxyl. This stereoselectivity stands in marked contrast to the one observed on hydride reduction, where such ketones tend to

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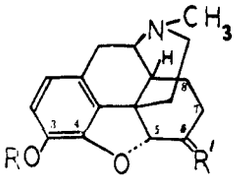
produce both epimers, with strong preponderance of the compound with α-OH.[4,5]

With one exception (see below), all compounds of the morphine series which have been reduced with FSA so far contained a free phenolic hydroxyl in position 3.

The reduction product of the one nonphenolic compound, dihydrocodeinone (1), was assumed[3] to be dihydroisocodeine, 2, by analogy with the results obtained with the phenolic ketones; this assignment seemed further supported by the mass spectrometric molecular weight and by comparison of the ^{1}H NMR spectrum with one of authentic dihydroisocodeine shown in a paper by Okuda et al.[7]

It has recently been brought to our attention by Dr. F. I. Carroll[8] that repetition of our reduction of 1 yielded not 2 but an isomer, the phenolic ketone dihydrothebainone,[9] 3. We

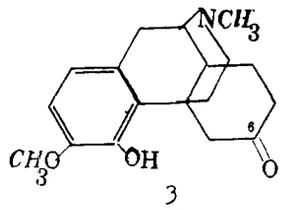


1 : R = Me, R' = O

2 : R = Me, R' = OH (H)

4 : R = H, R' = O

5 : R = H, R' = OH (H)



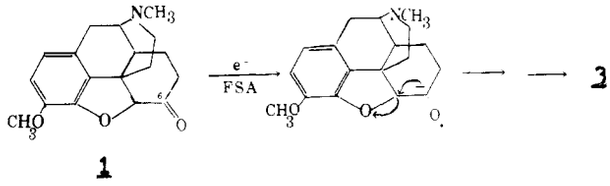
3

have now reinvestigated this reaction and wish to report that it does indeed yield 3 rather than 2; the product, obtained in 63% yield, was identified by melting point, mixture melting point, and comparison of its IR and ^{1}H NMR spectra with those of an authentic sample.[10] In marked contrast to the other reductions with FSA studied so far, the reduction of 1 proceeds thus with opening of the oxygen bridge and, surprisingly, with retention of the carbonyl. Scission of the oxygen bridge has been observed repeatedly during reduction of 1 and related ketones by various methods[11] and is not unexpected in such α-keto ethers. It is of interest, however, that it should take place in 1 and not in any of the closely related 6-ketones with free phenolic hydroxyl which had been examined earlier;[2,3] in particular, dihydromorphinone, 4 (compound 9 of ref 2), the free phenol of which 1 is the methyl ether, is smoothly reduced to dihydro-α-isomorphine, 5, with intact oxygen bridge; compound 5 was unequivocally identified by comparison (decomposition point, IR, ^{1}H NMR) with an authentic sample.[10a] This discrepancy in the behavior of 1 and 4 will be discussed below.

Much more surprising is the failure of the ketone 3 to be reduced further by the FSA used in its preparation. Nakagawa and Minami[12a] have shown that FSA in aqueous ethanolic alkali smoothly reduces a wide variety of ketones to the secondary alcohol in high yield; the survival of the carbonyl of 3 is thus puzzling.[12b]

The unexpected finding that FSA merely cleaves the oxygen bridge of 1 while leaving its carbonyl intact nullifies the claim made earlier[3] that 6β-OH derivatives of the *codeine* series are accessible directly by FSA reduction of the corresponding

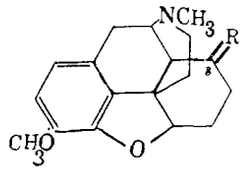
Scheme I



1

ketones. However, the preparation of these alcohols by reduction of 6-ketones with free phenolic hydroxyl (e.g., 4) with FSA and methylation of the resulting secondary alcohol (e.g., 5) should still be much superior to other methods reported in the literature.[13]

Our observations during the reduction of 1 illustrate the need for a thorough study of the scope and limitations of the FSA reduction of ketones. As a contribution to this study we have examined the behavior of dihydropseudocodeinone,[14] 6, on reduction with FSA. As expected, this 8-ketone of the codeine series gave nonphenolic dihydropseudocodeine,[15] 7,



6: R = =O

7: R = OH (H)

the corresponding secondary alcohol with β orientation of the hydroxyl; the reaction in this case conforms entirely to the FSA reduction of the phenolic 6-ketones.[2,3] Compound 7 (mp 152–155 °C), obtained in 52% yield, was identified by comparison with an authentic sample[10a] (mixture melting point, IR, ^{1}H NMR).

We further attempted the reduction of two ketones completely unrelated to the morphine series. The carbonyl of camphor did not undergo reduction under a variety of conditions; (+)-3-bromocamphor was debrominated to (+)-camphor having the same optical activity as that of an authentic sample.

The fact that the oxygen bridge is cleaved in the phenol ether 1 but not in the corresponding free phenol 4 calls for some further comment. Such cleavage reactions have been observed frequently enough in free 3-phenols of the morphine series; the long-known conversion of morphine itself into apomorphine[16] on treatment with acid, its isomerization into *O*-demethylthebainone[17] under the influence of Pd/C, and instances of hydrogenolysis[18] of morphine derivatives with a double bond in position 6 may be quoted. However, all those reactions take place in *acidic* or *neutral* medium. In contrast, the reductions with FSA are carried out in the presence of alkali, i.e., on the phenolate ion, and it is understandable that formation of another such ion in ortho position to the existing one (in the morphine series) should be suppressed. Nakagawa and Minami[12a] have formulated the reduction of fluorenone by FSA as a free-radical process on the basis of ESR studies and the formation of the pinacol, (9,9'-bifluorenyl)-9,9'-diol, under certain conditions. Assuming general validity of this interpretation, the reduction of 1 can be written as shown in Scheme I. Admittedly, this formulation fails to explain the resistance of 3 to further reduction. We are at present examing the reduction of 3 and other related compounds lacking the oxygen bridge.

Experimental Section

Experimental procedures were as reported earlier.[2] Formamidinesulfinic acid was obtained from Eastman Organic Chemicals, Rochester, N.Y. Optical rotations were measured on a high-precision polarimeter No. 80 (O.C. Rudolph and Sons). The (+)-3-bromocamphor was obtained from Aldrich Chemicals Co., Inc., Milwaukee, Wis.

Reduction of Dihydropseudocodeinone (6) to Dihydropseudocodeine (7). A solution of 114 mg (0.38 mmol) of the free base 6 was dissolved in EtOH (20 mL). This solution was stirred under a current of nitrogen. A solution of FSA (164 mg, 1.52 mmol) and NaOH (121.6 mg, 3.04 mmol) in H_2O (15 mL) was added, and the reaction mixture was heated on a water bath at 80–85 °C for 2 h. It was next cooled and EtOH was carefully removed by evaporation. The white precipitate formed on chilling was collected by suction filtration and washed with ice cold water. The product, **7**, mp 152–155 °C (lit.[15] mp 155 °C), weighed 60 mg (52%): IR (KBr disk) 3380, 3170, 2940, 1605, 1625, 1500 cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$, Me_4Si 6.7 (q, 2 H, aromatic), 4.54 (m, 1 H, 8α-H), 3.86 (s, 3 H, OCH_3), 3.49 (broad s, 1 H, 5β-H), 2.42 (s, 3 H, NCH_3); mass spectrum (70 eV) *m/e* 301 (M^+).

Reduction of (+)-3-Bromocamphor. To a solution of (+)-3-bromocamphor (11.55 g, 0.05 mol) in 95% EtOH (50 mL) was added NaOH (16 g, 0.4 mol) in H_2O (16 mL) and FSA (21.6 g, 0.2 mol). The reaction mixture was stirred under a current of nitrogen at 80–85 °C, as in the previous experiment, for 2 h; it was cooled and then concentrated to half its volume and extracted with $CHCl_3$ (50 mL), the organic layer was washed with water, dried (Na_2SO_4), and evaporated in vacuo to give 5 g of (+)-camphor (66%): mp 179.5 °C; $[\alpha]^{20}_D$ +44.2° (*c* 10, $CHCl_3$).

Acknowledgment. We thank Mr. Charles H. Strom for obtaining NMR and mass spectra. One of us (N.C.) is thankful to Dr. Ralph A. Stephani for his helpful discussions and encouragement. Supported in part by Grants No. DA-00297. We are thankful to Mr. Henry Reha for his assistance in preparing illustrations.

Registry No.—**6**, 5056-91-7; **7**, 3883-12-3; (+)-3-bromocamphor, 55057-87-9; (+)-camphor, 46449-3; FSA, 1758-73-2; dihydrocodeinone, 125-29-1; dihydrothebainone, 847-86-9.

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N,N-Dialkyl-2-oxocycloalkanonecarboxamide Photochemistry. Possible δ-Hydrogen Abstraction in 2-Substituted Cycloalkanones

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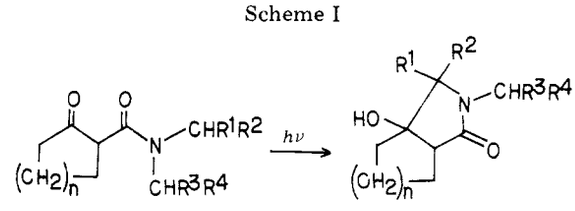
The Norrish types I and II reactions of ketones are the most widely studied of photochemical processes.[1] Cyclic ketones bearing γ hydrogens can undergo both reactions.[2] The rate of the type I reaction (α cleavage) is enhanced by a substituent on the α carbon, and reducing the size of the ring increases the rate of α cleavage.[2a,b] Consequently, little hydrogen abstraction is observed from 2-substituted cyclopentanones because the rate constant for γ-hydrogen abstraction is not fast enough to compete with the rate of α cleavage.[2a,b] It is well-known that the rate of δ-hydrogen abstraction is much slower than that of γ-hydrogen abstraction.[3] Therefore, there is no example of δ-hydrogen abstraction of 2-substituted cyclopentanones or cyclohexanones. We previously reported the photocyclization of acyclic β-oxo amides to pyrrolidin-2-ones[4] and now wish to report that of *N,N*-dialkyl-2-oxocycloalkanonecarboxamides to bicyclic lactams via an unprecedented δ-hydrogen abstraction in simple 2-substituted cycloalkanones.

Irradiation of a benzene solution of *N,N*-dibenzyl-2-oxocyclopentanecarboxamide (**1a**) in a Pyrex vessel under nitrogen with a high-pressure mercury lamp gave the bicyclic lactam **2a**, mp 116–117 °C, in 64% yield (see Scheme I). The structure of the lactam **2a** was elucidated by spectral data and elemental analysis. The IR spectrum of **2a** showed characteristic hydroxy (3400 cm^{-1}) and five-membered lactam carbonyl (1670 cm^{-1}) absorptions. The NMR spectrum showed a singlet at δ 4.17, attributable to the C-4 methine proton. These results indicate that only one stereoisomer was produced exclusively from the oxo amide **1a**. The C-4 phenyl group seems to be trans to the C-6 methylene group by analogy to pyrrolidin-2-ones.[4b] This configuration would be expected to be the more thermally stable. Similarly, irradiation of *N,N*-diisopropyl-2-oxocyclopentanecarboxamide (**1b**) and 2-oxocyclohexanecarboxamide (**1c**) under the same conditions also afforded the corresponding bicyclic lactams **2b** and **2c**, respectively. The structures of the lactams were determined by IR and NMR spectra and by elemental analyses. The ring-fusion stereochemistry of **2a**, **2b**, and **2c** was presumed

Scheme I



	1					2					
	n	R^1	R^2	R^3	R^4	*n*	R^1	R^2	R^3	R^4	yield, %
a,	1	H	Ph	H	Ph	1	H	Ph	H	Ph	64
b,	1	Me	Me	Me	Me	1	Me	Me	Me	Me	41
c,	2	Me	Me	Me	Me	2	Me	Me	Me	Me	46
d,	1	H	H	H	H	1	H	H	H	H	0
e,	2	H	H	H	H	2	H	H	H	H	0
f,	1	H	Ph	H	H	1	H	Ph	H	H	18

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