Preparation of Trimethylsilyl Enol Ether 4. Triethylamine (377 mL, 2.7 mol) was added to a solution of isobutyraldehyde (180 mL, 2 mol) and chlorotrimethylsilane (372 mL, 2.6 mol) in dimethylformamide (650 mL). The mixture was refluxed at 95 °C for 20 h. After filtration, the solid was washed with pentane. The combined organic solution (2.5 L) was washed with saturated sodium bicarbonate solution (4 × 2 L). The organic layer was dried and fractionally distilled to give 178 g (61.5%) trimethylsilyl enol ether **4**; bp 108–120 °C.

Preparation of 3-(Phenylthio)-2,2-dimethylpropanal (12). To a solution of trimethylsilyl enol ether **4** (30 g, 20.8 mmol) and chloromethyl phenyl sulfide (**11**; 30 g, 18.9 mmol) in dry dichloromethane (200 mL) was added anhydrous zinc bromide (500 mg). After being stirred for 30 min, the solution was poured into an ice cold sodium chloride solution (500 mL) and extracted once more with dichloromethane (200 mL). The organic layer was dried over magnesium sulfate. Evaporation to dryness and distillation gave **12**: 33 g (82%); bp 115 °C (1.7 mm).

Registry No. **2a**, 67213-30-3; **4**, 6651-34-9; **11**, 7205-91-6; **12**, 20967-51-5; **13**, 86767-55-7; **14**, 80689-69-6; **15**, 86767-56-8; **16**, 86767-57-9; **17**, 86767-58-0; **18**, 86767-59-1; **19**, 16184-79-5; **20**, 86767-60-4; **21**, 86767-61-5; **23**, 831-91-4; **24**, 100-52-7; **25**, 86767-62-6; **26**, 86767-63-7; isobutyraldehyde, 78-84-2.

Practical Procedure for the Isolation of Emodin and Chrysophanol

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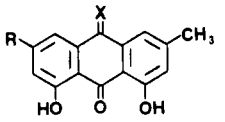
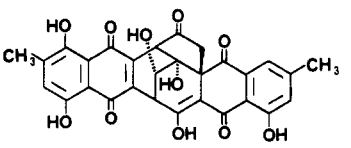
The presence of the functionalized tricyclic skeleton of emodin (**1**)[2a] and its derived anthrone (**2**)[3] in a diverse array of complex natural products (e.g., **4–6**, Chart I) suggests that **1** might serve as a useful synthetic starting material if adequate supplies could be procured. Emodin is available commerically, but the price it commands (>$50/g) would daunt all but the most intrepid investigator. Emodin occurs widely in nature,[2a] and various procedures have been reported for its isolation, but all require prior collection of plant materials.[7] We now describe a simple procedure for the isolation of emodin from readily available[8] Indian rhubarb root extract. The process also provides abundant quantities of chrysophanol (**3**).[2b]

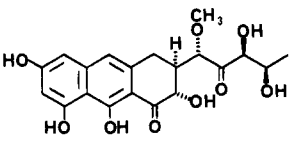
Chart I



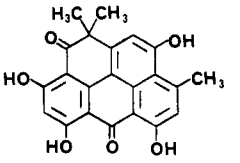
1, R=OH, X=O
2, R=OH, X=H_2
3, R=H, X=O



4, Purpurogenone[4]



5, Olivin[5]



6, Resistomycin[6]

Experimental Section

To a 5-L round-bottomed flask containing 1.5 L each of concentrated HCl and water and equipped with a mechanical stirrer and condenser is added 1 kg of "1-2 Indian Rhubarb Root Solid Extract".[8,9] The stirred mixture is refluxed overnight, cooled, and vacuum filtered. The solid is washed with water and air-dried to constant weight, giving ca. 350 g of fine black powder. The black powder is continuously extracted with ether until <1 g of additional crude extract is obtained in a 24-h period (usually 3–4 days). The crude extract is stripped of volatiles at aspirator pressure (rotary evaporator) to give 40–45 g of gummy solid which is boiled for 0.5 h with 250 mL of ether and vacuum filtered to give 27–28 g of yellow solid A. An additional 1 g of A is obtained by partially concentrating the filtrate.

Solid A is boiled for 10 min with 200 mL of 20% aqueous Na_2CO_3 and the mixture filtered under vacuum while hot to give 19–20 g (after air drying) of solid chrysophanol contaminated with a small amount of emodin and tar (see below). The red Na_2CO_3 filtrate is extracted with ether (2 × 100 mL; the extract is discarded) and acidified (**Caution**: foaming) with concentrated HCl. The emodin which precipitates is filtered, washed with water, and dried to give ca. 6.2 g of nearly pure emodin. This emodin is boiled 0.5 h with 70 mL of ether, and the ether phase is removed by vacuum filtration. The solid is then stirred 0.5 h with 60 mL of benzene and the benzene phase removed by vacuum filtration to give 6.0 g of pure emodin, mp 256–257 °C (lit.[2a] mp 255 °C). If desired, recrystallization from 4:1 $CHCl_3$/MeOH (25 mL/g) at 10 °C overnight gives orange needles, mp 256–257 °C (98% recovery), identical with authentic material by direct comparison.

The impure chrysophanol obtained above can be purified as follows. Crude chrysophanol (20 g, vide supra) is washed well with 200 mL of distilled water followed by 50 mL of absolute ethanol, and without being dried it is dissolved in ca. 450 mL of hot benzene and gravity filtered while hot. The filtrate is brought to boiling, 350 mL of boiling absolute ethanol is added, and the resulting solution is allowed to stand overnight at room temperature. Filtration gives 16 g of pure chrysophanol as yellow microcrystalline leaflets, mp 194–195 °C (lit.[2b] mp 196 °C), identical with authentic material by direct comparison. Concentration (at atmospheric pressure) of the mother liquors to ca. 125 mL gives an additional 2.2 g of chrysophanol, mp 180–182

(1) Undergraduate Research Participant.

(2) For a leading reference see: Thomson, R. H. "Naturally Occurring Quinones", 2nd ed.; Academic Press: New York, 1971: (a) p 419, (b) p 388.

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(7) An unpublished procedure for the isolation of emodin provided by Professor B. Franck (Universität Münster) utilizes chrysarobin (a commerically available complex of anthraquinones) as raw material, but that procedure is more tedious and much more expensive than the one we report herein. Numerous syntheses of emodin have been described,[2a] but with one possible exception (Krohn, K. *Tetrahedron Lett.* **1980**, *21*, 3557) none appears competitive with isolation.

(8) Obtained from Chart Corp., Inc., Glen Rock, NJ. Other sources of rhubarb extract are available. See: "Chem Sources-U.S.A." and "Chem Sources-Europe"; Directories Publishing Co.: Ormond Beach, FL.

(9) The term "Solid Extract" is a misnomer as the material is a syrupy semisolid. The accurately described "Powdered Extract" can also be used, but it is more expensive, and the yield of emodin is not increased.

(10) An extractor similar to that described by Beal [Beal, G. D. In "Organic Syntheses", 2nd ed.; Wiley: New York, 1941; Collect. Vol. I, p 538] was employed.

(11) Coffey, S.; van Alphen, J. In "Chemistry of Carbon Compounds"; Rodd, E. H., Ed.; Elsevier: Amsterdam, 1956; Vol. IIIB, p 1413.

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°C [pure by TLC (silica, 1:4 EtOAc/petroleum ether)].

Acknowledgment. Support of this work by the National Institutes of Health (Grant CA 17631) is gratefully acknowledged. We thank Professors B. Franck[7] and L. A. Mitscher for exchange of information and Dr. A. Bonati for a gift of emodin.

Registry No. 1, 518-82-1; 3, 481-74-3.

Reaction of 1-Nitroso-1,2,3,4-tetrahydropyridine with Mineral Acids

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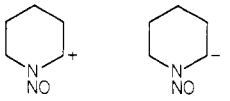
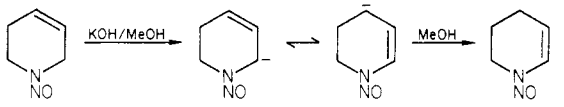
It has been postulated[2-4] that the presence of a nitroso group on an amino nitrogen allows for the stabilization of either a carbanion or a carbocation at the α-position. This



imparts to the amine the ability to accept a wide variety of substituents at the α-position that could not be introduced by conventional methods.

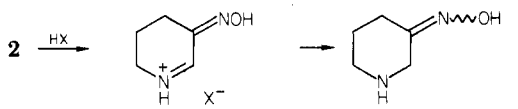
The base-catalyzed conversion of 1-nitroso-1,2,3,6-tetrahydropyridine (1) to 1-nitroso-1,2,3,4-tetrahydropyridine (2),[8] as described in detail by Michejda and co-



1 3 2

workers,[4,5] is thought to proceed in nearly quantitative yield by the initial removal of the α-allylic hydrogen to form resonance stabilized carbanion **3**. Protonation at the terminal carbon gives thermodynamically more stable **2**.

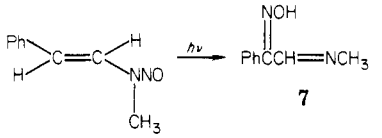
The reaction of the 1-nitroso-1,2,3,4-tetrahydropyridine (**2**) with acid was studied to determine if the double bond would protonate regiospecifically to give the α-carbocation. Reaction of **2** with trifluoroacetic acid caused the precipitation of a solid with the properties of a salt. The NMR spectrum of the solid showed an isolated vinyl proton with no α-proton coupling. This could only result from a 3,4,5,6-tetrahydro-3-pyridone derivative. The remainder of the NMR spectrum was consistent with the structure of 3-oximino-3,4,5,6-tetrahydropyridinium trifluoroacetate (**4a**). A similar reaction was observed with hydrogen



4a, X = CF_3COO^-
b, X = Cl^- **5**

chloride to give the chloride salt **4b**. These salts were reduced by sodium borohydride to 3-piperidone oxime (**5**), confirming the ring skeleton. A mixture of *Z* and *E* isomers was obtained, with the *E* isomer formed in excess.

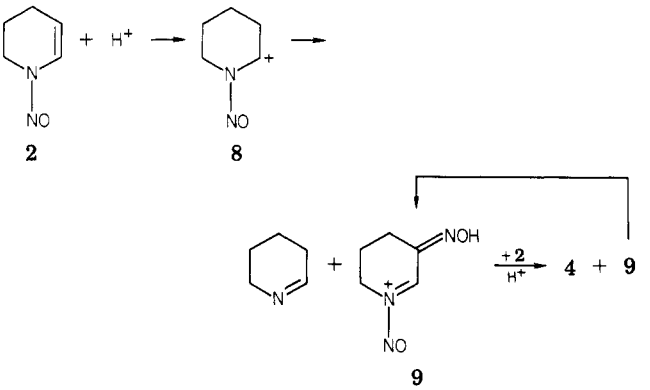
This reaction has a structural analogy in the observation by Seebach and Enders[6] that the reaction of methyl-*p*-styrylnitrosamine (**6**) under "radical producing" conditions formed an oxime (**7**) or its hydrochloride.



6 **7**

Concurrent with our studies, Michejda and co-workers[7] confirmed the finding of Seebach and Enders[6] that radical conditions caused the rearrangement of **2** to the oxime in the absence of oxygen, or 5-nitro-1,2,3,4-tetrahydropyridine if oxygen is present. These reactions appear to occur through radical intermediates.

The formation of **4** from **2** under the strongly acid conditions we used probably results from the protonation of **2** at the 3-position to give the α-carbocation **8**. This intermediate would act as a nitrosation reagent for an unprotonated molecule of **2** to form the oxime **4**.



2 **8** **9**

Experimental Section

Preparation of 1-Nitroso-1,2,3,4-tetrahydropyridine (2). The title compound was prepared by the base-catalyzed isomerization of 1-nitroso-1,2,3,6-tetrahydropyridine (1), as described by Michejda and Kupper.[4,5]

Reaction of 2 with Trifluoroacetic Acid To Form 4a. A solution of 1.0 g (9 mmol) of 1-nitroso-1,2,3,4-tetrahydropyridine (**2**) in 6 mL of chloroform was treated with 0.7 mL (9 mmol) of trifluoroacetic acid in 6 mL of $CHCl_3$ at 0 °C. The ice bath was removed after 5 min, and within 0.5–1 h a precipitate formed. The solid was removed by filtration to give 1.7 g, 7.6 mmol (85%), of 3-oximino-3,4,5,6-tetrahydropyridinium trifluoroacetate (**4a**). Two recrystallizations of the solid from acetonitrile provided an analytical sample of **4a**; mp ~100 °C dec; IR (mull) 2850 cm^{-1} (NH), 1665 cm^{-1} (COO); UV (MeOH) λ_{max} 257 nm (ϵ 1.3 × 10^4); NMR (acetone-d_6 δ [multiplicity, integration (assignment)] 2.1 [quin, 2 (C-5)], 2.9 [t, 2 (C-4)], 5.0 [d of t, 2 (C-6)], 8.6 [t (*J* =

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(5) R. Kupper and C. J. Michejda, *J. Org. Chem.*, **44**, 2326 (1979).

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(7) R. H. Smith, Jr., M. B. Kroeger-Koepke, and C. J. Michejda, *J. Org. Chem.*, **47**, 2907 (1982).

(8) The 1-nitrosotetrahydropyridines described in this paper have been shown to be potent carcinogens in animals, and extreme precautions should be observed in working with these compounds.

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