methylene chloride (750 ml) was added slowly while the temperature was maintained at −25 to −30°. Triethylamine (228 g, 2.26 mol) was then added dropwise in 2.5 hr. During this addition the temperature was maintained at −20 to −30° for the first 90 min. The temperature was allowed to rise to −10° over the last hour. Further methylene chloride (about 250 ml) was added to aid stirring. When the addition was complete, water (1 l.) was added. The mixture was then filtered to collect the solids, and the organic and the aqueous layers of the filtrate were separated. The aqueous layer was extracted with methylene chloride. The filter cake was washed with hot methylene chloride six times. The combined organic layers were washed with hydrochloric acid (6 *M*, 300 ml) twice followed by brine (300 ml) twice. The organic phase was dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded crude II (42 g). Recrystallization from ethyl acetate provided colorless needles of the product, mp 155–155.5°. The mother liquor (which contained a skin irritant) was refrigerated and a second batch of solid was obtained. This material was worked up to yield additional II (21 g). The overall yield was 33%. The spectroscopic properties of the product were identical with those reported by Eaton and Cole.[2]

6,10-Dibromopentacyclo[5.3.0.0^{2,6}.0^{3,10}.0^{4,8}]deca-5,9-dione (III).—Dimer II (5 g, 15.7 mol) was dissolved in hot methanol (60 ml) and then cooled to room temperature. Methanolic hydrogen chloride (2 ml) was added. The mixture was transferred to a Pyrex irradiation cell with additional methanol (20 ml). The solution was irradiated with an Hanovia 450-W mercury lamp for 90 min. The solvent was removed *in vacuo*. The orange waxy solid was dissolved in benzene (300 ml) and the mixture was boiled to remove methanol. The hot benzene solution was passed through basic alumina (10 g) and the column was flushed with hot benzene. The solution was evaporated to dryness. The solid was dissolved in benzene (10 ml). *n*-Hexane was added dropwise to precipitate the product. Recrystallization from benzene yielded III (4.2 g, 84%, mp 228–230°). The product exhibited the spectroscopic properties reported by Eaton and Cole.[2]

1,4-Dicarboxycubane (IV).—In a typical experiment, compound III (5.0 g, 15.7 mmol) was added to sodium hydroxide solution (25%, 50 ml). The mixture was refluxed (110°) for 2 hr, then cooled to 0°. The solution was neutralized by the dropwise addition of cold concentrated hydrochloric acid. The temperature of the solution was kept near 0°. As the pH was reduced the solution changed from dark brown to light tan. The precipitation of the product appeared to be complete between pH and 1 and 3. Filtration yielded the desired product as a very light tan powder (2.3 g, 75%). Pure 1,4-dicarboxycubane, mp 226° dec, was obtained by recrystallization from acetic acid. The crude diacid (2.3 g, 11.9 mmol) was dissolved in methanol (50 ml) containing the hydrogen form of methanol washed Bio-Rad cation exchange resin AG 50w.-X8 (300 mg). The mixture was refluxed for 12 hr. The warm solution was filtered to collect the resin and 1,4-dicarbomethoxycubane (2.35 g, 90%, mp 161–162° after recrystallization from methanol) precipitated as the solution cooled.

Registry No.—II, 32846-64-3; III, 25867-85-0; IV, 32846-66-5.

Formation of an Unusual Dihydropyrazine Di-*N*-oxide during Hydrolysis of an α-Oximino Acetal

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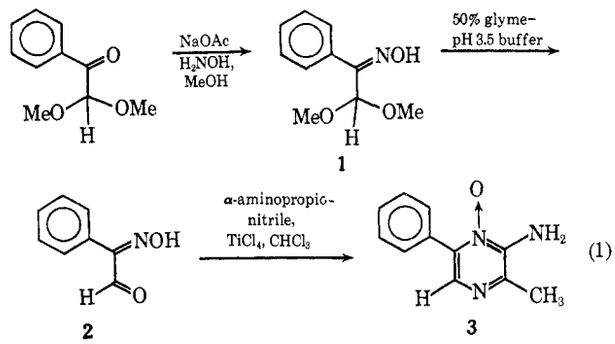
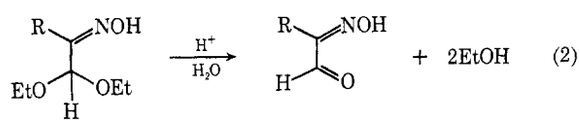
In connection with the synthesis and structural elucidation of *Cypridina* etioluciferamine,[1] certain model compounds were needed for the spectrographic information they would yield. The most important of these was 2-amino-3-methyl-6-phenylpyrazine 1-oxide (**3**) which was to be synthesized *via* the pathway shown in eq 1. It was therefore necessary to prepare the unknown phenylglyoxal 2-oxime **2**. The conversion of the known[2,3] phenylglyoxal acetal to a mixture of the *Z* and *E* isomers of **1** was accomplished in 93% yield by the conditions shown in eq 1.[4] The next step, the acid hydrolysis of an α-oximino acetal to the corresponding α-oximinoaldehyde (eq 2), is at face value a simple



(1)



(2)

reaction. The yields in this type of conversion are reported to be good, and the desired product is easily isolable (R, yield: isobutyl, 63%;[5] *sec*-butyl, 64%;[6] methyl, 82%[6]). We therefore anticipated no difficulties in the conversion of **1** to **2**. Reaction conditions similar to those stated in the literature[5,6] were used for the hydrolysis of **1**. After the isolation and recrystallization procedure described in the Experimental Section, physical data on the colorless crystals obtained (71% yield) clearly indicated that this material was not the expected phenylglyoxal 2-oxime. The 100-MHz nmr spectrum (DMSO-d_6) of the compound isolated (Figure 1) shed considerable light on its structure. The singlet at τ 2.73 corresponds to the protons of a phenyl ring which is not directly attached to an electron-withdrawing center. The two multiplets at τ 1.60–1.85 and 2.42–2.64 represent phenyl ring protons which are separated due to a powerful electron-withdrawing element attached directly to that aromatic ring.[7] Furthermore, the two doublets at τ 2.21 and 3.84 and the doublet of doublets at τ 3.68 indicate an ABX spin

(1) T. P. Karpetsky and E. H. White, *J. Amer. Chem. Soc.*, **93**, 2333 (1971).

(2) W. Madelung and M. E. Oberwegner, *Justus Liebigs Ann. Chem.*, **490**, 232 (1931); *Chem. Abstr.*, **26**, 474 (1932).

(3) W. Madelung and M. E. Oberwegner, *Chem. Ber.*, **65B**, 936 (1932); *Chem. Abstr.*, **26**, 4584 (1932).

(4) The preparation of **1** was modeled after a method originally applied to isobutyrophenone: H. M. Kissman and J. Williams, *J. Amer. Chem. Soc.*, **72**, 5323 (1950).

(5) J. J. Gallagher, G. T. Newbold, W. Sharp, and F. S. Spring, *J. Chem. Soc.*, 4870 (1952).

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(7) For example, we have found that the phenyl ring protons in 2-amino-3-methyl-6-phenylpyrazine 1-oxide (**3**) are separated into two multiplets at τ 2.10–2.28 and 2.45–2.63.

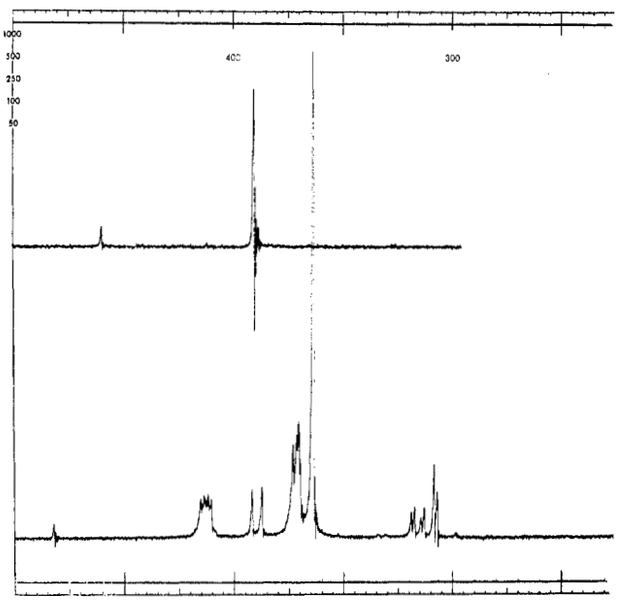
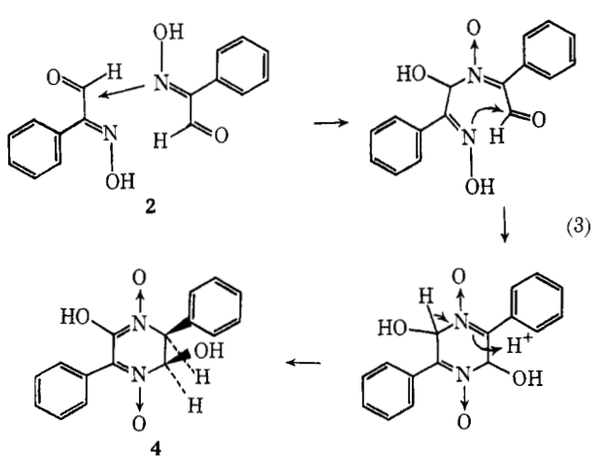


Figure 1.—100-MHz nmr spectrum (τ 0-5.5, DMSO-d_6) of 2,5-dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-dioxide (**4**). Upper curve offset, 400 Hz.

system under the influence of some powerful electron-withdrawing substituent. The infrared spectrum of this material shows a medium-intensity band at 1595 cm^{-1} interpretable as the imine *N*-oxide stretch (C=N^+—O^-).[8-10] Finally, the elemental analysis indicates that this unknown compound has a molecular formula that is consistent with that of phenylglyoxal 2-oxime ($C_8H_7NO_2$) or some multiple thereof.

Our interpretation of these facts is that the unknown material is 2,5-dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-dioxide (**4**). This material probably arises from the dimerization of two molecules of **2** with concomitant bond shifts as shown in eq 3. Reactions of



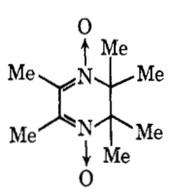
(3)

this sort, involving nucleophilic attack of the nitrogen of an oxime on an aldehydic carbonyl, are known. For example, this type of condensation has been used to prepare benzimidazole 3-oxides[11,12] and is the basis for a synthetic route to purine 1-oxides.[12,13]

The stereochemistry of the substituents about the 5 and 6 carbons of the dihydropyrazine 1,4-dioxide ring is believed to be as shown in structure **4**. These assignments are supported by the coupling constant (3 Hz) between the protons on the 5 and 6 carbons indicating that they are cis axial equatorial. This structure is also consistent with the proposed reaction mechanism.[14]

The formation of **4** from **1** appeared to be a major stumbling block in our synthesis of **2**. However, upon examining the change in the 100-MHz nmr spectrum (DMSO-d_6) of **4** with time, it was seen that the complex pattern characteristic of the protons of **4** slowly disappeared, to be replaced by the three-line spectra one would expect for **2**. The half-life of this conversion, as measured by nmr integration, was found to be 110 min at 40°. After removal of the DMSO at reduced pressure, the infrared spectrum (KBr) of the remaining oil had a strong band at 1698 cm^{-1} indicative of an unsaturated aldehyde, and the absorption at 1595 cm^{-1} characteristic of **4** had completely disappeared. Thus, although **4** is the thermodynamically stable form in certain solvents, **2** is the thermodynamically stable form in DMSO. We were thus able to use **4** as a direct source of **2**, which was not characterized but which was directly converted to the desired model compound **3** in moderate yield.[15] In addition, we found that the conversion of **4** to **2** is reversible, **4** being produced when **2** is subjected to the conditions given in the Experimental Section for the synthesis of **4** from **1**.[16] This fact indicates that the acetal **1** probably goes through the aldehyde **2** during the production of the heterocycle **4**.

It is interesting to note that structures related to **4** have never been reported as products of hydrolysis of α-oximino acetals. Whether the hydrolysis of **1** represents a special case or whether the dihydropyrazine di-*N*-oxides have been previously overlooked is a matter for speculation at this time. Only recently have papers appeared on the preparation and properties of such 2,3-dihydropyrazine 1,4-dioxides as **5**.[17,18] Fi-



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(8) R. F. C. Brown, V. M. Clark, and A. Todd, *J. Chem. Soc.*, 2105 (1959).
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(11) A. J. Boulton, A. C. G. Gray, and A. R. Katritzky, *Chem. Commun.*, 741 (1966).
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(13) E. C. Taylor and E. E. Garcia, *J. Amer. Chem. Soc.*, **86**, 4721 (1964).
(14) The possibility of **4** being a substituted 5,6-dihydropyridazine 1,2-dioxide was ruled out by the nmr and infrared spectra of **4**.
(15) The preparation of **3** and other substituted 2-aminopyrazine 1-oxides using titanium tetrachloride as a condensing agent will be the subject of a future publication (see also ref 1).
(16) The ease of reversiblility of the dimerization reaction might explain the somewhat anamolous ultraviolet spectrum of **4**. On the basis of model compounds, one would expect an absorption above 280 nm for **4**: T. Thesing and W. Sirrenberg, *Chem. Ber.*, **91**, 1978 (1958). However, if **4** dissociates in ethanol to give **2**, the spectrum of an acetophenone oxime derivative would be expected, as found.
(17) M. Lamchen and T. W. Mittag, *J. Chem. Soc. C*, 2300 (1966).
(18) M. Lamchen and T. W. Mittag, *ibid.*, 1917 (1968).

nally, substituted 2,3-dihydropyrazine 1,4-dioxides offer intriguing possibilities for biologic investigation, since it is know that different *N*-oxides such as nicotinamide *N*-oxide, various purine *N*-oxides, 4-nitroquinoline *N*-oxide, and chlordiazepoxide function variously as biological oxidants, antimetabolites, oncogenic agents, and tranquilizers.[19]

Experimental Section[20]

2,5-Dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-Dioxide (4).—To a solution of 4.57 g (23.4 mmol) of phenylglyoxal dimethyl acetal oxime[4] (**4**) in 22.5 ml of glyme was added 22.5 ml of a pH 3.5 buffer (1 *N* acetic acid, 0.1 *N* sodium acetate; the oxime was insoluble in this buffer alone or in aqueous methanol). This homogeneous solution was stirred and refluxed. Tlc (Eastman alumina sheets no. 6063, acetone as eluent) indicated a slow reaction rate and 24 hr was required for 1 (R_f 0.49) to disappear and to be replaced by a new compound (R_f 0.22). The solution was then cooled to room temperature, and the solvents were partially removed under reduced pressure (water aspirator). The resulting orange oil and pale yellow liquid was treated with 10 ml of water and extracted with ethyl acetate (three 50-ml portions). These extracts were combined and dried over sodium sulfate; the solvent was then removed to give 3.5 g of an orange oil that crystallized into colorless prisms (perhaps the dimerization occurs at this stage). Recrystallization of this material from ethyl acetate–benzene gave 1.98 g (13.3 mmol, 57%) of colorless prisms. A second crop of 0.50 g (3.4 mmol, 14%) was obtained by concentrating the mother liquor. Infrared spectra run on these two crops of crystals were identical with one another and with that of the analytical sample. This latter sample was prepared by recrystallizing the material twice from ethyl acetate–benzene to give colorless prisms: mp 114.5–117.5°; uv max (MeOH) 221.0 nm (log ϵ 4.31) and 249.0 (4.00, shoulder); ir (KBr) 3225, 3050, 2935, 2875, 2815, and 1595 cm^{-1}; 100-MHz nmr (DMSO-d_6) τ −1.82 (singlet, 0.83 H),* 1.60–1.85 (multiplet, 1.84 H), 2.21(doublet, 1.01 H, J = 9.0 Hz),* 2.42–2.64 (multiplet), 2.73 (singlet, 8.66 H together with previous multiplet), 3.68 (doublet of doublets, 0.84 H, J = 9.0 and 3.0† Hz), and 3.84 (doublet, 0.78 H, J = 3.0 Hz).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73. Found: C, 64.49; H, 4.85.

Phenylglyoxal 2-Oxime (2).—After 745 mg (2.50 mmol) of of 2,5-dihydroxy-3,6-diphenyl-5,6-dihydropyrazine 1,4-dioxide (**4**) was dissolved in 1.5 ml of dimethyl sulfoxide (which previously sat over 5 A molecular sieves for 12 hr), dry nitrogen was blown over the clear solution before it was capped. The stirred reaction solution was then heated to 44–46° for 25 hr. The solvent was then removed by freeze-drying. The resultant oil had ir (KBr) 3125 and 1698 cm^{-1}. As ample of **4** decomposed in a similar manner in DMSO-d_6 had 100-MHz nmr τ −3.20 (singlet, 0.98 H),* 0.35 (singlet, 1.01 H), and 2.58 (singlet, 5.02 H). The material obtained was at least 95% pure by nmr and was not purified further but used immediately in the preparation of **3**.

Peaks indicated by an asterisk disappear on addition of D_2O; that indicated by dagger collapses to a doublet (J = 3.0 Hz).

Registry No.—**2**, 32538-02-6; **4**, 32538-03-7.

Acknowledgments.—This work was supported by a predoctoral fellowship from the National Institutes of Health to T. P. K. and by a grant from the Public Health Service (Research Grant No. 5 R01 7868 from the National Institute of Neurological Diseases and Blindness).

(19) The role of *N*-oxides in metabolism and the biologic properties of various types of *N*-oxides have been reviewed: M. H. Bickel, *Pharm. Rev.*, **21** (4), 325 (1969).

(20) The infrared spectra were taken on a Perkin-Elmer Model 337 spectrophotometer. Ultraviolet spectra were recorded using a Cary Model 14 spectrophotometer using matched 1-cm quartz cells. Nmr spectra were run by Mr. Joseph Ahnell using a Varian HA-100 spectrometer. Melting points were taken using a Kofler hot-stage microscope and are uncorrected.

A New Synthesis of *cis*-Jasmone

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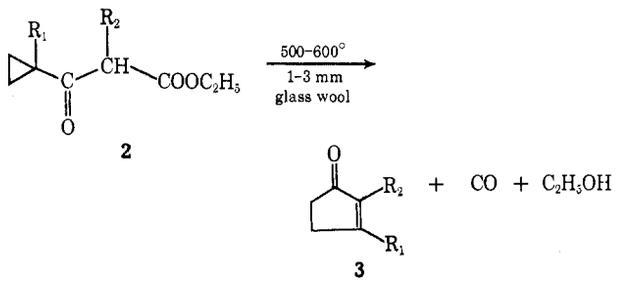
The synthesis of *cis*-jasmone (**1**) has received considerable attention in recent years.[1-10] This contribution stems from our recent discovery of the thermal rearrangement of 3-cyclopropyl-3-oxopropanoates (**2**) to 2-cyclopentenones (**3**).[11] *cis*-Jasmone (29–32% overall) and the acetylenic analog **6** (39% overall) were prepared as shown in Scheme I.[12]



Experimental Section

Melting points were determined on a Mel-Temp apparatus, and neither melting points nor boiling points were corrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Preparative gas–liquid chromatography (glpc) was done on a Varian-Aerograph Model A90-P3 thermal conductivity machine, and retention times were compared on a Varian Aerograph Model 1200 flame ionization machine; individual conditions are noted below. Infrared data were obtained with a Perkin-Elmer Model 237B grating spectrophotometer, and nmr spectra were recorded on a Varian Model A-60 A nmr spectrometer. Mass spectra were done on a Varian-Atlas Model CH-7 (modified) mass spectrometer by Professor R. R. Engel (Queens). Pyrolyses were done with a Hevi-Duty Electric Company Type 77-T (600 W, "Multi-Unit") tube oven.

Ethyl 2-(1′-Methylcyclopropanecarbonyl)-4-heptynoate (5).—Keto ester **5** was prepared by a standard alkylation sequence[11] using 5.02 g (0.105 mol) of 50% sodium hydride dispersion in mineral oil, 17.02 g (0.100 mol) of **2**,[13] and 10.25 g (0.100 mol)

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(12) The Alkyne **6** has previously been partially hydrogenated to **1** in 72.6% yield.[7]

(13) Ketone **2** was prepared by carbethoxylation of methyl methylcyclopropyl ketone in 80% yield.[11] The starting ketone was obtained either from Aldrich Chemical Co., Cedar Knolls, N. J., or by the procedure of N. L. Goldman, *Chem. Ind. (London)*, 1024 (1963), which starts with α-acetyl-α-methyl-γ-butyrolactone.