of the β-O-glycoside which is anomerized to the α-O-gylcoside under the influence of mercuric bromide. This could then rearrange to the N-substituted compound **9**. For an example, see G. Wagner and H. Frenzel, *Arch. Pharm.* (*Weinheim*), **299**, 536 (1966).

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(17) Melting points were determined on a Kofler micro hot stage and are corrected values. Nmr spectra were determined on a Varian T-60A spectrometer using TMS as the internal reference. Ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and uv spectra were obtained on a Beckman DK-2 spectrophotometer. Elemental analyses were performed by the Baron Consulting Co., Orange, Conn., or the Spang Microanalytical Laboratory, Ann Arbor, Mich. Moist organic solutions were dried over anhydrous magnesium sulfate. Evaporations were carried out on a rotary evaporator under reduced pressure and a bath temperature of about 40°, except where noted otherwise. Tlc was performed on precoated silica gel F-254 plates (E. Merck, Darmstadt) of 0.25 mm thickness. Spots were first located with an ultraviolet lamp and the plates were then sprayed with a solution of 20% ethanolic sulfuric acid and heated in an oven at 140°.
(18) Reagent grade methanol was percolated through a column of molecular sieve 3A and stored over calcium hydride. Distillation under nitrogen through a column of Raschig rings gave anhydrous methanol which was stored over molecular sieve 3A.
(19) (a) It was expected that the olefinic protons would produce a typical AB quartet. When this region was swept over a 50 Hz width, some separation into two very broad peaks was accomplished. (b) Molecular models showed that the acetyl groups at C-2′ or C-5′ can interact with the double bond and, therefore, be influenced by an anisotropic effect, which probably accounts for the shift in one of the methyl peaks.
(20) Triethylamine was purified by distillation from phenylisocyanate just prior to use.
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Crystal and Molecular Structure of β-Peltatin A Methyl Ether

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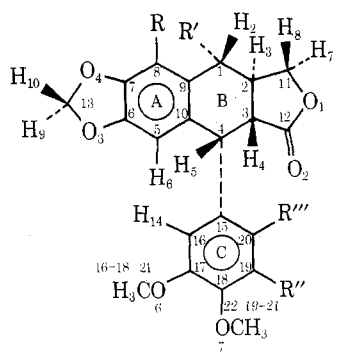
Received June 18, 1974

The crystal structure of β-peltatin A methyl ether ($C_{23}H_{24}O_8$), a natural antitumor agent, has been solved by direct methods with the aid of the combined figure of merit. The space group is $C222_1$. Cell dimensions are a = 23.670, b = 10.024, c = 17.611 Å, and Z = 8. The structure was refined to R = 0.046. The conformation is similar to that of the 5′-demethoxy compound except for the methoxyl groups, which are all rotated differently in the two compounds. Presumably the favored conformation of other antitumor lignans is similar except for methoxyl rotation.

β-Peltatin A methyl ether (I) and 5′-demethoxy-β-peltatin A methyl ether (II), both isolated from the Mexican plant *Bursera fagaroides* (Burseraceae),[1] are antitumor agents of the podophyllotoxin (III) class. An X-ray study on II[2] revealed its conformation in the crystalline state. We have now completed an X-ray study of the former, which shows some aspects of the conformations of the two substances to be similar and some different. This is the second X-ray study of an antitumor lignan; in addition, a derivative, 2′-bromopodophyllotoxin (IV), was recently studied[3] to check the absolute configuration of the compounds of this series.



	R	R′	R″	R‴
I	$O^5C^{14}H_3^{11-13}$	H^1	$O^6C^{23}H_3^{22-24}$	H^{15}
II	OCH_3	H	H	H
III	H	OH	OCH_3	H
IV	H	OH	OCH_3	Br

Experimental Section

Collection and Reduction of the Data. Oscillation and Weissenberg photographs of a needle 0.2 × 0.2 × 0.4 mm indicated space group $C222_1$. The cell parameters were found by least-squares fitting of the settings for the four angles of eight reflections on a Picker-FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 23.670 (9), b = 10.024 (4), c = 17.611 (8) Å, ρ_{calcd} = 1.37, ρ_{obsd} = 1.40 g/ml, and Z = 8. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, 2°/min scan rate, 10-sec background counts, attenuators when the count rate exceeded 10^4 counts/sec, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1889 independent reflections measured, $1630 > 3\sigma(I)$ were considered observed. Three standard reflections were monitored every 50 measurements; no decrease in the intensity of the standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Solution and Refinement. The structure was solved by direct methods using the MULTAN[4] program with 308 E's > 1.4. The correct solution had the highest *combined* figure of merit (C), defined as

$$C = \frac{\Sigma\alpha - \Sigma\alpha_{min}}{\Sigma\alpha_{max} - \Sigma\alpha_{min}} + \frac{(\psi_0)_{max} - \psi_0}{(\psi_0)_{max} - (\psi_0)_{min}} + \frac{R_{max} - R}{R_{max} - R_{min}}$$

where $\Sigma\alpha$ (absolute figure of merit), ψ_0, and R are the usual three indicators employed in the program. The correct solution was 11th in $\Sigma\alpha$, 27th in ψ_0, and 5th in Resid. All the nonhydrogen atoms were located from the E map. Two cycles of full matrix isotropic least-squares refinement of nonhydrogen atoms reduced R to 0.145, and then two anisotropic cycles to 0.094. A difference Fourier map showed all the hydrogens except H-16–H-18, whose positions were calculated. One more cycle of least-squares refinement in which nonhydrogen atoms were refined anisotropically and hydrogen atoms isotropically reduced R to 0.046. Refinement was terminated at this stage since the average ratio of shifts in parameters to standard deviations was less than 0.3. Unit weights were used and refinement was based on F_o with $\Sigma(F_o - F_c)^2$ minimized. The scattering factors used were those of Hanson, *et al.*[5] No correction was applied for extinction.

Table I
Fractional Coordinates and Estimated Standard Deviations

Atom	x/a	y/b	z/c
O-1	−0.2411 (2)	0.6094 (5)	0.2454 (3)
O-2	−0.1525 (2)	0.6941 (4)	0.2508 (3)
O-3	−0.0638 (2)	0.1530 (5)	0.5647 (3)
O-4	−0.1521 (2)	0.0825 (5)	0.6005 (2)
O-5	−0.2591 (2)	0.1926 (5)	0.5215 (2)
O-6	−0.0938 (2)	0.0379 (3)	0.2111 (2)
O-7	−0.0385 (2)	0.1902 (4)	0.0946 (2)
O-8	−0.0292 (2)	0.4520 (4)	0.1104 (2)
C-1	−0.2483 (3)	0.3599 (7)	0.4025 (4)
C-2	−0.2321 (2)	0.4267 (6)	0.3283 (3)
C-3	−0.1840 (2)	0.5207 (6)	0.3407 (3)
C-4	−0.1290 (2)	0.4449 (5)	0.3563 (3)
C-5	−0.0935 (3)	0.3028 (6)	0.4619 (3)
C-6	−0.1037 (3)	0.2139 (6)	0.5201 (3)
C-7	−0.1567 (3)	0.1731 (7)	0.5409 (3)
C-8	−0.2034 (3)	0.2211 (7)	0.5056 (4)
C-9	−0.1952 (2)	0.3111 (6)	0.4428 (3)
C-10	−0.1412 (3)	0.3494 (5)	0.4232 (3)
C-11	−0.2764 (3)	0.5152 (7)	0.2910 (4)
C-12	−0.1880 (3)	0.6190 (7)	0.2745 (4)
C-13	−0.0951 (4)	0.0774 (8)	0.6178 (4)
C-14	−0.2710 (4)	0.1129 (8)	0.5872 (4)
C-15	−0.1056 (2)	0.3749 (4)	0.2870 (3)
C-16	−0.1105 (2)	0.2360 (4)	0.2774 (3)
C-17	−0.0873 (2)	0.1774 (5)	0.2138 (3)
C-18	−0.0617 (2)	0.2482 (5)	0.1581 (3)
C-19	−0.0561 (2)	0.3885 (5)	0.1690 (3)
C-20	−0.0774 (2)	0.4459 (5)	0.2311 (3)
C-21	−0.0671 (9)	−0.0417 (10)	0.1680 (7)
C-22	−0.0747 (6)	0.1881 (12)	0.0338 (6)
C-23	−0.0259 (3)	0.5927 (7)	0.1143 (5)
H-1	−0.279 (2)	0.417 (4)	0.443 (2)
H-2	−0.276 (2)	0.292 (5)	0.386 (3)
H-3	−0.219 (2)	0.371 (4)	0.289 (2)
H-4	−0.194 (2)	0.575 (4)	0.389 (2)
H-5	−0.096 (2)	0.497 (5)	0.376 (2)
H-6	−0.050 (2)	0.315 (5)	0.449 (2)
H-7	−0.307 (2)	0.587 (5)	0.339 (3)
H-8	−0.314 (2)	0.496 (5)	0.252 (3)
H-9	−0.091 (2)	0.125 (6)	0.670 (3)
H-10	−0.068 (2)	0.021 (6)	0.645 (3)
H-11	−0.322 (2)	0.127 (5)	0.598 (3)
H-12	−0.272 (2)	0.166 (6)	0.637 (3)
H-13	−0.244 (2)	0.022 (6)	0.587 (3)
H-14	−0.137 (2)	0.192 (4)	0.314 (2)
H-15	−0.075 (2)	0.518 (5)	0.254 (3)
H-16	−0.038 (2)	−0.042 (5)	0.128 (3)
H-17	−0.045 (3)	−0.089 (6)	0.204 (4)
H-18	−0.021 (3)	−0.025 (8)	0.190 (4)
H-19	−0.111 (2)	0.128 (6)	0.052 (3)
H-20	−0.048 (2)	0.147 (6)	−0.002 (3)
H-21	−0.108 (2)	0.242 (7)	0.029 (4)
H-22	−0.068 (2)	0.637 (6)	0.102 (3)
H-23	−0.007 (2)	0.633 (5)	0.060 (3)
H-24	0.009 (2)	0.622 (6)	0.165 (3)

Results and Discussion

Table I shows the observed atomic coordinates. Figure 1 shows the bond lengths in I and, in parentheses, the corresponding bond lengths in II.[2] There appears to be some disordering of the C-21 methoxyl carbon. As can be seen in the ORTEP[6] drawing in Figure 2, this study confirms the constitution and relative configurations proposed for I.[1]

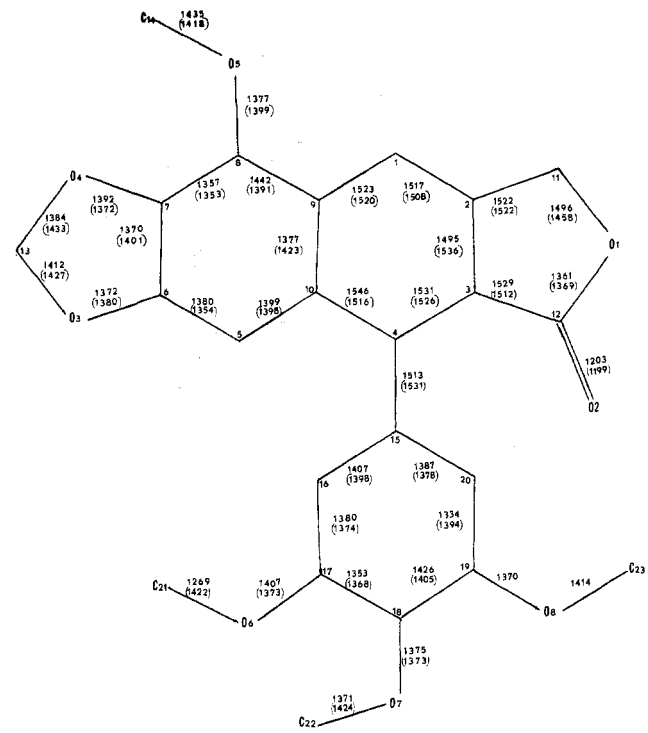


Figure 1. Bond lengths (picometers) in the molecule compared with bond lengths (picometers) in 5′-demethoxy-β-peltatin A methyl ether (in parentheses). The average σ values are 8 and 5 pm, respectively.

Figure 3 compares the conformations of I and II, after least-squares overlapping of the A rings *via* the BMFIT program of Nyburg.[7] The conformations are quite similar to one another—and presumably to the other antitumor lignans—except for the orientations of the methoxyl groups, which are rotated very differently. The angle between the aromatic rings is 81.7° in I and 88.8° in II; similar angles were observed in the two crystallographically independent molecules of the bromide IV,[3] as expected with the 2′-bromo group. The B ring is in the usual cyclohexene half-chair conformation, as evidenced by torsion angles, starting from the C-9–C-10 bond and proceeding clockwise around the ring, of −1.3, 13.7, −46.4, 71.1, −54.1 and 20.5° in I. The γ-lactone ring approximates an envelope conformation with C-2 at the point, opposite the ring from the C-12–O-1 partial double bond; the torsion angles in this ring, clockwise starting from the C-12–O-1 bond, are −3.6, −18.4, 32.1, −33.7, and 23.8°. The other five-membered ring is a nearly flat envelope with C-13 at the point; torsion angles clockwise from the C-6–C-7 bond are 0.3, 3.3, −5.8, 6.0, and 3.9°.

In the absence of ortho substituents on both sides, the methoxyl carbon in a methoxybenzene generally prefers to lie nearly in the plane of the benzene ring, permitting (with sp^2 hybridization of the ether oxygen) resonance interaction between the oxygen and the ring.[8] This is the situation in I for C-23 (torsion angle of 3.5° between the C-23–O-8–C-19 plane and plane of the adjacent aromatic ring), and in II for C-21 (torsion angle 4.3°) and C-22 (torsion angle 5.8°). Surprisingly, C-21 in I is not similarly found pointing away from its ortho substituent, but *toward* it, with a torsion angle of 15.2°. This is very likely the result of packing forces, since the 3- and 5-methoxyls in the 3,4,5-trimethoxyphenyl group of reserpine[9] adopt the usual conformation, and it can be seen from Figure 4 that the usual conformation is precluded since it would put the C-21 methyl group too close to C-13 and O-4 in an adjacent molecule: The C-22 methoxyl, flanked by two ortho methoxyls, expectedly

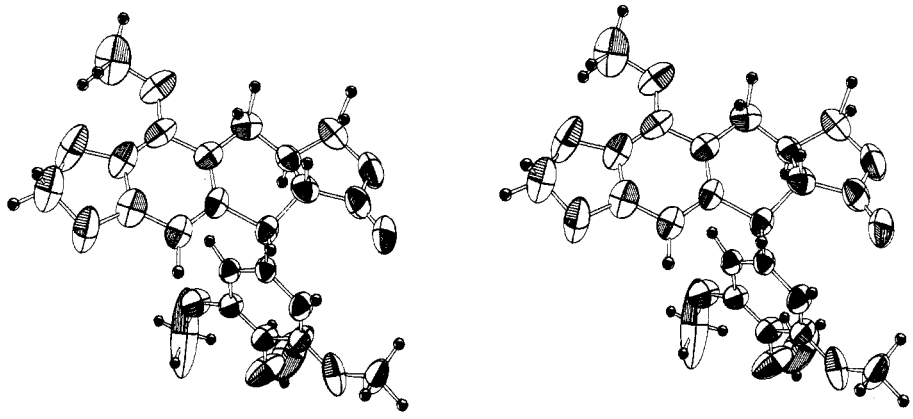


Figure 2. Stereoscopic view of β-peltatin A methyl ether. Hydrogen atoms are shown as spheres, and other atoms as 50% probability ellipsoids.

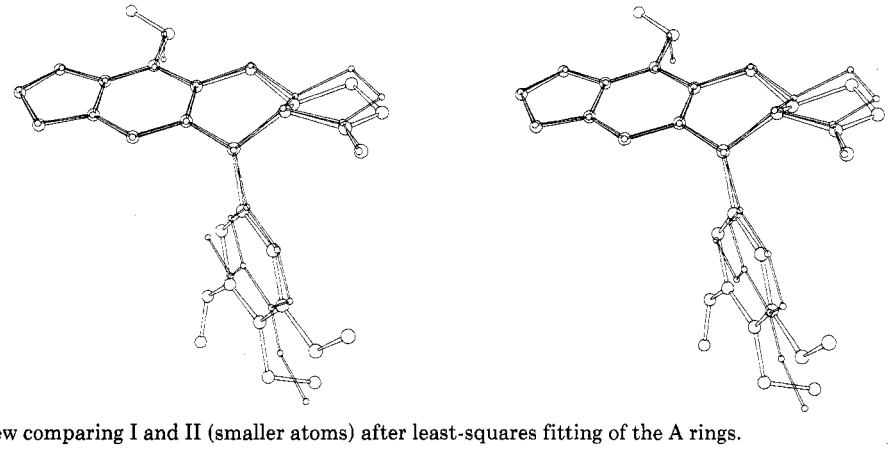


Figure 3. A stereoview comparing I and II (smaller atoms) after least-squares fitting of the A rings.

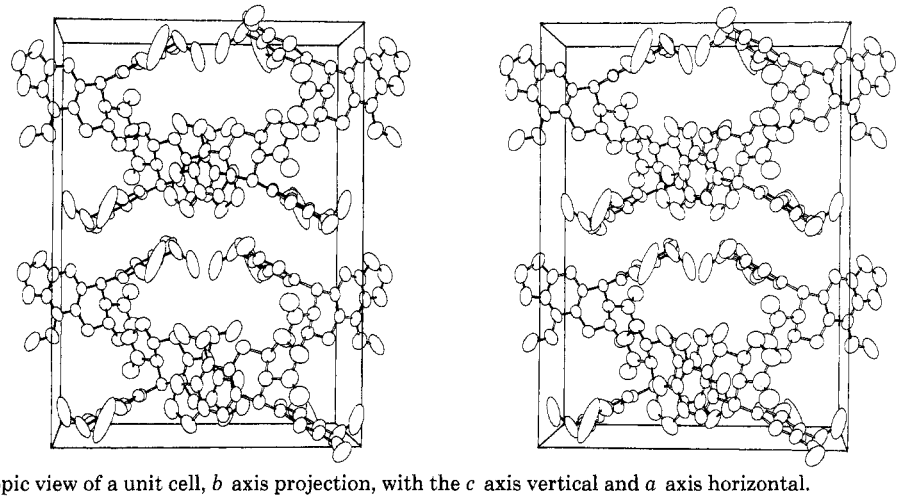


Figure 4. Stereoscopic view of a unit cell, *b* axis projection, with the *c* axis vertical and *a* axis horizontal.

has a torsion angle (87.6°) close to 90°.[9] The C-14 methoxyls in I and II provide a surprise: their torsion angles are 5.2 and 80.2°, respectively. The large difference is almost surely due to packing forces. Unfortunately, since packing in I appears to preclude the conformation adopted in II and *vice versa*, it does not seem possible at this time to say which conformation is preferred in the absence of packing forces.

The shortest intermolecular distance between hydrogens is H-19–H-10 of 2.24 Å. The shortest intermolecular distances between nonhydrogen atoms are O-6–C-11 (3.082 Å), O-6–C-13 (3.228 Å), O-3–C-23 (3.431 Å), O-4–O-2 (3.443 Å), O-5–C-7 (3.468 Å), and O-1–C-2 (3.492 Å).

Acknowledgments. We thank the Public Health Service (CA-10944) for financial aid and the University of Arizona Computer Center for computer time. Also, we thank Professor S. C. Nyburg of the University of Toronto for sending us the program BMFIT.

Registry No.—I, 23978-65-6.

Supplementary Materials Available. Tables of temperature factors, bond distances involving hydrogen, bond angles, least-squares planes, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all

of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-28.

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Narcotic Antagonists. V. Stereochemistry of Reactions at C-6 in 14-Hydroxynoroxymorphone Derivatives

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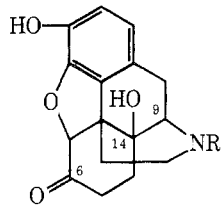
Received August 12, 1974

The epimeric products of the borohydride reduction and of the methyllithium reaction of the C-6 ketone of naloxone were isolated. The stereochemistry of the products was assigned on the basis of nmr evidence, which indicates that in each case the major product has the 6α-hydroxy orientation.

The retention of varying degrees of agonist character in virtually all of the presently known narcotic antagonists serves to limit their clinical utility. Striking exceptions are the structurally related compounds naloxone (Ia) and naltrexone (Ib) which exhibit minimal agonist activity. This

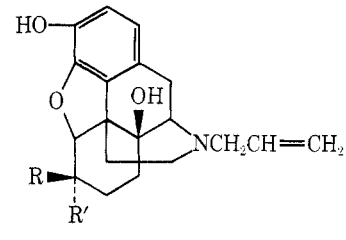


Ia, R = $CH_2CH{=}CH_2$
b, R = CH_2— 

has led to the clinical use of naloxone for the reversal of narcotic-induced effects and to the present clinical evaluation of naltrexone as a potential prophylactic agent in narcotic addiction.[1] In the course of their clinical evaluation, the metabolism of these compounds in man has been investigated and it showed that their principal transformation *in vivo* is the reduction of the 6-ketone group.[2] The report that naltrexone, unlike naloxone, gives rise to a reduced metabolite with the C-6 isomorphine configuration,[3] and that this metabolite may be responsible for its long duration of action in man,[4,5] has aroused our interest in the stereochemistry of reactions at that functional center since the epimeric relationship of their metabolites may have bearing on the difference in properties of the two drugs.

A structural feature common to both naloxone and naltrexone is the 14β-hydroxyl group which may influence the course of reaction at the C-6 position and give products with an orientation different from those obtained from the more common morphine and codeine derivatives containing a hydrogen at the C-14 position.

Sodium borohydride reduction of the C-6 carbonyl group of Ia has been previously reported on by Dayton and Blumberg,[6] and the product was identified as the 6-hydroxy compound IIa which was shown to be identical with the principal metabolite of naloxone obtained *in vivo*.[2] The orientation of the 6-hydroxy group in IIa was assigned



IIa, R = H; R′ = OH
b, R = OH; R′ = H

as α by analogy to reductions of the 6-ketone in other morphine derivatives. There have been a number of other reports on the sodium borohydride reduction of the 6-ketone in 14-hydroxy morphine and codeine derivatives in which the orientation of the products was similarly assigned by analogy to 14-hydrogen compounds. These reactions included reduction of 14-hydroxycodeinone by Sargent, *et al.*,[7] and Currie, *et al.*,[8] and the reduction of 14-hydroxydihydromorphinone by Weiss and Daum.[9] Conclusive evidence for the stereochemistry of reduction in the model 14-hydrogen series has only recently been provided by Sargent and Jacobson.[10] They compared the nmr spectra of codeine and isocodeine and noted differences in the chemical shift of the 14-proton. In isocodeine it was deshielded by the β-hydroxyl group at C-6 because of its 1,4-diaxial relationship and appeared at δ 3.08. In the spectrum of codeine, where the C-6α-hydroxyl group is equatorially oriented, the 14-hydrogen resonance was at δ 2.66. The above nmr evidence of the interaction of the C-6 and C-14 substituent suggests that the presence of a 14β-hydroxyl group makes such an analogy to the 14-hydrogen series suspect as far as the C-6 ketone reduction products are concerned, and therefore the assigned stereochemistry of IIa and the other reduced products cannot be considered secure.

Naloxone was reduced quantitatively with borohydride and gave a mixture which by tlc analysis consisted of two compounds. The less polar IIa was the major product and was estimated to be nine times greater than the yield of the lesser and more polar product IIb. Preparative tlc permitted the isolation of a small quantity of each of the two components of the mixture. Oxidation of either IIa or IIb re-