mun., 973 (1967); (b) T. Yamaguchi and M. Kojima, Abstracts, Symposium on the Chemistry of Natural Products, Tokyo, 1973, p 205; (c) D. Horton and W. Weckerle, *Carbohydr. Res.*, **44**, 227 (1975).
(5) E. M. Acton, A. N. Fujiwara, and D. W. Henry, *J. Med. Chem.*, **17**, 659 (1974).
(6) (a) F. Arcamone, W. Barbieri, and G. Franceschi, *Chim. Ind. (Milan)*, **51**, 834 (1969); (b) T. H. Smith, A. N. Fujiwara, D. W. Henry, and W. W. Lee, *J. Am. Chem. Soc.*, **98**, 1969 (1976).
(7) (a) A. S. Kende, Y. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976); (b) A. S. Kende, D. P. Curran, Y. Tsay, and J. E. Mills, *Tetrahedron Lett.*, 3537 (1977).
(8) For a discussion of the Diels–Alder approach to anthracyclinone analogues, see (a) W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, *J. Org. Chem.*, **41**, 2296 (1976); (b) T. R. Kelly, R. N. Goerner, J. W. Gilliard, and B. K. Prazak, *Tetrahedron Lett.*, 3869 (1976); (c) T. R. Kelly, J. W. Gilliard, and R. N. Goerner, *ibid.*, 3973 (1976); (d) T. R. Kelly, J. W. Gilliard, R. N. Goerner, and J. M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977); (e) M. E. Jung and J. A. Lowe, *J. Org. Chem.*, **42**, 2371 (1977); (f) A. S. Kende, D. P. Curran, Y. Tsay, and J. E. Mills, *Tetrahedron Lett.*, 3537 (1977).
(9) (a) R. J. Boatman, B. J. Whitlock, and H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **99**, 4823 (1977); (b) T. Suzuki, R. D. Gleim, S. Trenbeath, and C. J. Sih, *Tetrahedron Lett.*, 2303 (1977); (c) R. K. Boeckman, M. H. Delton, T. Nagasaka, and T. Watanabe, *J. Org. Chem.*, **42**, 2946 (1977).
(10) (a) C. M. Wong, D. Popien, R. Schwenk, and J. TeRaa, *Can. J. Chem.*, **49**, 2712 (1971); (b) C. Wong, R. Schwenk, D. Popien, and T. L. Ho, *ibid.*, **51**, 466 (1973); (c) R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, *Tetrahedron Lett.*, 3385 (1976); (d) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60**, 829 (1976).
(11) (a) A. S. Kende, J. Billatire, T. J. Bentley, E. Hume, and J. Airey, *J. Am. Chem. Soc.*, **97**, 4225 (1975); (b) F. Suzuki, S. Trenbeath, R. D. Gleim, and C. J. Sih, *ibid.*, **100**, 2272 (1978).
(12) (a) M. J. Manning, P. W. Raynolds, and J. S. Swenton, *J. Am. Chem. Soc.*, **98**, 5008 (1976); (b) J. S. Swenton, D. K. Jackson, M. J. Manning, and P. W. Raynolds, *ibid.*, preceding paper in this issue.
(13) (a) B. Belleau and N. L. Weinberg, *J. Am. Chem. Soc.*, **85**, 2525 (1963); (b) N. L. Weinberg and B. Belleau, *Tetrahedron*, **29**, 279 (1973).
(14) We were initially concerned about side chain oxidation at the benzylic position in tetralin systems; see V. D. Parker and B. E. Burgert, *Tetrahedron Lett.* 2415 (1968); T. Inoue, K. Koyama, and S. Tsutsumi, *Bull. Chem. Soc. Jpn.*, **37**, 1597 (1964).
(15) J. M. Fortunato and B. Ganem, *J. Org. Chem.*, **41**, 2194 (1976).
(16) C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, *J. Org. Chem.*, **38**, 2675 (1973).
(17) While excess sodium methylsulfenyl carbanion was reported to react exothermically with chlorobenzene[18] the reaction of the lithium salt with the bromo ester from **12** did not appear to be complicated by attack at the bromine.
(18) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).
(19) M. J. Manning, unpublished observations.
(20) (a) M. Bender, Y. L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958); (b) M. L. Bender, F. Chloupek, and M. C. Neveu, *ibid.*, **80**, 5384 (1958); (c) M. S. Newman and S. Hishida, *ibid.*, **84**, 3582 (1962).
(21) A major difficulty is the low solubility of the 7-deoxy compound in carbon tetrachloride.
(22) T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, *J. Org. Chem.*, **42**, 3653 (1977).
(23) F. Arcamone, G. Franceschi, P. Orezzi, and S. Penco, *Tetrahedron Lett.*, 3349 (1968).
(24) All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Measurements of standard samples indicated that the observed melting points were probably 1–2 °C lower than the corrected value. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrometer. ^{1}H NMR spectra were taken at 60 MHz with Varian EM-360 or A-60A instruments, with the latter observed for all critical work. ^{13}C NMR spectra were recorded on a Bruker HX-90 instrument by Dr. Charles Cottrell. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronic MS-9 double focusing mass spectrometer. Analytical samples were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Aluminum oxide and silica gel were from E. Merck Co. Tetrahydrofuran was distilled from benzophenone ketyl directly into the reaction flask. Reactions run in an inert atmosphere made use of a three-way stopcock with $^{14}/_{20}$ ⅋ joint which allowed the flask to be flame dried under vacuum and filled with purified nitrogen. Butyllithium in hexane (Ventron) was titrated in tetrahydrofuran with a 1,10-phenantholine as the indicator. Workup as usual refers to extraction with ether, washing of the ether layers with saturated brine solution, drying over calcium sulfate, and concentration in vacuo. The earlier anodic oxidations were performed on a cooled, magnetically stirred solution using the apparatus previously described[12a] (apparatus I). More recent work was performed at constant potential relative to a platinum reference electrode using a Kepco power suppply with currents between 0.5 and 2.0 A using the platinum gauze anode previously described (apparatus II). This potentiostat was designed by R. McCreery and built by D. Henton, and information concerning this apparatus is available upon request.
(25) L. Rubenstein, *J. Chem. Soc.*, **127**, 1998 (1925).

Color Dimorphism of 14-Hydroxymorphinone. X-Ray Analysis of Two Different Crystalline Modifications

Chian C. Chiang,[1a] Wilson H. DeCamp,[1a] David Y. Curtin,*[1a] Iain C. Paul,*[1a] Sidney Shifrin,[1b] and Ulrich Weiss*[1c]

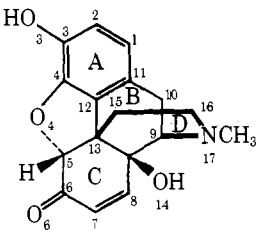
Contribution from the Department of Chemistry, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801, Macromolecular Biology Section, National Cancer Institute, Bethesda, Maryland 20014, and Laboratory of Chemical Physics, National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Maryland 20014.
Received December 19, 1977

Abstract: 14-Hydroxymorphinone can be obtained in two crystalline modifications, one yellow (**1**-Y) and the other white (**1**-W), depending on the solvent used for crystallization. Infrared spectral differences suggested that there was a difference in the hydrogen bonding in the two forms. Single-crystal X-ray analyses have been carried out on both forms. The crystals of both **1**-Y and **1**-W are orthorhombic and the space group is $P2_12_12_1$; the cell dimensions of **1**-Y are a = 13.150 (3), b = 13.508 (3), and c = 7.837 (1) Å, and those of **1**-W are a = 12.918 (3), b = 14.074 (3), and c = 8.035 (2) Å. The conformations of the molecules in **1**-Y and **1**-W are very similar with possible O(14)—H- - -N intramolecular hydrogen bonding. The aromatic ring A is slightly nonplanar in these and in most other morphine derivatives. A significant difference between **1**-Y and **1**-W is in the orientation of the O–H group with respect to the C(aromatic)–O bond. In **1**-Y, the phenolic hydroxyl group forms an intermolecular hydrogen bond to a carbonyl oxygen, while in **1**-W, the phenolic hydroxyl group forms an intermolecular hydrogen bond to the aliphatic alcohol. There may be a very weak charge-transfer effect in the crystal of **1**-Y between the aromatic ring A and the ketone group in a symmetry-related molecule. This possibility, which may in part explain the color difference between the two forms, has also been examined by spectroscopic methods.

Introduction

It was observed a number of years ago that the phenolic α,β-unsaturated ketone, 14-hydroxymorphinone (**1**), can exist in two modifications, which show striking differences in color and solid-state IR spectra. They are readily interconvertible in solution: recrystallization from polar solvents, such as ethanol or acetone, yields bright yellow, transparent, square platelets (**1**-Y), while crystallization from a large volume of benzene (in which **1** is only slightly soluble) produces perfectly

0002-7863/78/1500-6195$01.00/0



1

colorless needles (**1**-W). Recrystallization from the appropriate solvent converts either form into the other one. Neither modification contains solvent of crystallization. Both yellow and colorless forms seem stable indefinitely in the solid state; no visible change is noticeable in samples surviving from the initial work. Upon heating, the yellow form blackens at about 250 °C but shows no volume increase up to ~300 °C; the white crystals darken above 200 °C and decompose at 255 °C to a voluminous black mass.[2] Color differences persist in solutions of **1**; methanol solutions are yellow, while those in benzene or methylene dichloride are colorless.

In the IR spectra in KBr pellets, the carbonyl stretching band of the colorless modification occurs at 1685 cm^{-1}; that of the yellow form occurs at 1660 cm^{-1}. The occurrence of carbonyl bands in *both* modifications precludes any interpretation of these two forms as the keto and enol tautomers, respectively. In addition, enolization of **1** is inherently improbable, since the enol would have to contain a double bond in position 5–6. To the best of our knowledge, no known compound of the morphine series with intact bridge and normal stereochemistry of the ring system contains a double bond in this position; undoubtedly, such a structure would be impossibly strained.[3]

However, the location of the C=O stretching bands suggests an explanation. In the colorless form, this location is the normal one for a free cyclohexenone, while the lower frequency found for the yellow form is consistent with a hydrogen-bonded enone. It seemed probable, therefore, that the two forms differ in the nature of hydrogen bonding in the crystal lattice, only that of the yellow form involving the oxygen of the carbonyl.

In order to obtain unequivocal information on the nature of this dimorphism, an X-ray crystallographic investigation of the two modifications was undertaken. This work is part of a series of studies that have been carried out in one of our laboratories of color changes in compounds that exhibit dimorphism.[4] In addition, more evidence was obtained for the existence of a systematic nonplanarity of ring A in morphine derivatives with the ether bridge intact that may be responsible for the chiroptical effects in the 240–250-nm region in these compounds.[5]

Experimental Section

X-ray Analysis of the Yellow Form (1-Y). Samples of **1**-Y and **1**-W remaining from the initial work[2] were used. Cell dimensions for **1**-Y were determined by a least-squares fit to the angular settings for 12 reflections hand-centered on a Picker FACS-1 diffractometer (Cu Kα, λ = 1.54178 Å).

Crystal data: $C_{17}H_{17}O_4N$; M = 299.3; orthorhombic; a = 13.150 (3), b = 13.508 (3), and c = 7.837 (1) Å; V = 1392 (1) × 10^{-24} cm^3; Z = 4; ρ_{calcd} = 1.428 g cm^{-3}; μ(Cu Kα) = 8.5 cm^{-1}; systematic absences $h00$ when $h = 2n + 1$, $0k0$ when $k = 2n + 1$, and $00l$ when $l = 2n + 1$; space group $P2_12_12_1$.

Intensity data were collected to 2θ = 130° on a Picker FACS-1 diffractometer using Cu Kα radiation and a 2θ scan technique. Data collection procedures have been described previously.[6] A total of 1379 intensities was measured; of these, 1255 were considered nonzero at the 3σ significance level. The structure was solved without difficulty by direct methods with the use of the MULTAN program.[7] Full-matrix least-squares refinement of positional and anisotropic thermal parameters for the nonhydrogen atoms reduced R and R_2 to 0.082 and 0.104.[8] The quantity minimized was $\Sigma w\|F_o| - |F_c\|^2$. Initially unit weights were used, but later the weighting scheme was that suggested by Corfield et al.[9] All hydrogen atoms were located from a difference map and included in the refinement with isotropic thermal parameters. The refinement converged to values of R and R_2 of 0.052 and 0.064. However, some of the dimensions involving hydrogen atoms were chemically unreasonable and some of the resulting B_{iso} values were rather high. Four low-order reflections (200, 120, 301, and 121) showed evidence of being affected by secondary extinction and were removed from the data set. Subsequent refinement gave much more reasonable dimensions and temperature factors for the hydrogen atoms. The final values of R and R_2 were 0.036 and 0.038. The final value of $\Sigma w\Delta^2/(m - n)$ was 1.91. The scattering curves for C, N, and O used were those of Cromer and Mann,[10] while that for H was calculated by Stewart et al.[11] The final atomic coordinates are listed in Table I.

Table I. Final Atomic Coordinates for the Yellow Form (**1**-Y) of 14-Hydroxymorphinone[a]

	x	y	z
C(1)	0.3319 (3)	0.5559 (3)	0.1647 (5)
C(2)	0.3027 (3)	0.6307 (3)	0.2785 (5)
C(3)	0.3568 (3)	0.7186 (2)	0.2942 (5)
C(4)	0.4398 (2)	0.7298 (2)	0.1888 (4)
C(5)	0.6009 (3)	0.7668 (2)	0.1060 (4)
C(6)	0.6676 (3)	0.7242 (3)	0.2469 (4)
C(7)	0.6784 (3)	0.6167 (3)	0.2640 (5)
C(8)	0.6560 (3)	0.5566 (3)	0.1353 (5)
C(9)	0.5621 (3)	0.5210 (2)	−0.1436 (5)
C(10)	0.4611 (3)	0.4899 (3)	−0.0558 (5)
C(11)	0.4150 (3)	0.5694 (2)	0.0575 (4)
C(12)	0.4643 (3)	0.6590 (2)	0.0704 (4)
C(13)	0.5604 (2)	0.6886 (2)	−0.0194 (4)
C(14)	0.6252 (3)	0.5950 (2)	−0.0383 (4)
C(15)	0.5381 (3)	0.7324 (3)	−0.1976 (5)
C(16)	0.4915 (3)	0.6556 (3)	−0.3154 (5)
C(17)	0.5184 (4)	0.4947 (3)	−0.4437 (6)
N	0.5535 (2)	0.5652 (2)	−0.3153 (4)
O(3)	0.3341 (2)	0.7914 (2)	0.4112 (4)
O(4)	0.5113 (2)	0.8061 (1)	0.1950 (3)
O(6)	0.7082 (2)	0.7813 (2)	0.3467 (4)
O(14)	0.7200 (2)	0.6146 (2)	−0.1227 (4)
H(1)[b]	0.292 (3)	0.491 (3)	0.156 (5)
H(2)	0.243 (3)	0.621 (3)	0.358 (5)
H(3)	0.293 (3)	0.774 (3)	0.462 (6)
H(5)	0.635 (2)	0.826 (2)	0.045 (4)
H(7)	0.702 (3)	0.590 (2)	0.380 (5)
H(8)	0.666 (2)	0.481 (2)	0.157 (5)
H(9)	0.605 (2)	0.459 (2)	−0.154 (4)
H(10a)	0.473 (3)	0.242 (3)	0.018 (4)
H(10b)	0.412 (3)	0.472 (3)	−0.159 (5)
H(14)	0.708 (4)	0.610 (3)	−0.241 (6)
H(15a)	0.599 (3)	0.757 (2)	−0.255 (4)
H(15b)	0.486 (3)	0.787 (3)	−0.186 (4)
H(16a)	0.421 (2)	0.638 (2)	−0.293 (4)
H(16b)	0.490 (3)	0.677 (2)	−0.433 (4)
H(17a)	0.512 (3)	0.534 (3)	−0.554 (5)
H(17a)	0.569 (3)	0.434 (3)	−0.448 (5)
H(17c)	0.445 (3)	0.468 (3)	−0.413 (6)

[a] Coordinates are in fractions of the cell edge; standard deviations are in parentheses. [b] Hydrogen atoms were given the number of the atom to which they are attached.

X-ray Analysis of the White Form (1-W). White, transparent, plate-like crystals of **1**-W were obtained from benzene. An untwinned crystal with dimensions ca. 0.2 × 0.4 × 0.4 mm was used for data collection.

Crystal data: $C_{17}H_{17}O_4N$; M = 299.3; orthorhombic; a = 12.918 (3), b = 14.074 (3), and c = 8.035 (2) Å; V = 1461 (1) × 10^{-24} cm^3; Z = 4; ρ_{calcd} = 1.36 g/cm^3; μ(Cu Kα) = 8.1 cm^{-1}; systematic absences, $h00$ when $h = 2n + 1$, $0k0$ when $k = 2n + 1$, and $00l$ when $l = 2n + 1$, establish the space group as $P2_12_12_1$, λ(Cu Kα) = 1.54178 Å.

Intensity data were collected as described previously. A total of 1453

Table II. Final Atomic Coordinates with Estimated Standard Deviations for **1**-W

	x	*y*	*z*
C(1)	0.3637 (3)	0.6065 (2)	0.5228 (4)
C(2)	0.4461 (2)	0.5893 (2)	0.6269 (4)
C(3)	0.4493 (2)	0.6221 (2)	0.7923 (4)
C(4)	0.3610 (2)	0.6677 (2)	0.8467 (4)
C(5)	0.2536 (2)	0.7695 (2)	0.9824 (4)
C(6)	0.2934 (2)	0.8692 (2)	0.9381 (4)
C(7)	0.2636 (2)	0.9129 (2)	0.7812 (4)
C(8)	0.1916 (2)	0.8770 (2)	0.6831 (4)
C(9)	0.0954 (2)	0.7296 (2)	0.5767 (4)
C(10)	0.1844 (3)	0.6845 (3)	0.4768 (4)
C(11)	0.2755 (2)	0.6529 (2)	0.5802 (4)
C(12)	0.2769 (2)	0.6786 (2)	0.7457 (3)
C(13)	0.1901 (2)	0.7232 (2)	0.8428 (3)
C(14)	0.1304 (2)	0.7903 (2)	0.7274 (3)
C(15)	0.1164 (2)	0.6451 (2)	0.9058 (4)
C(16)	0.0643 (2)	0.5944 (2)	0.7622 (5)
C(17)	−0.0497 (4)	0.6218 (3)	0.5231 (8)
O(3)	0.5376 (2)	0.6100 (2)	0.8809 (4)
O(4)	0.3458 (1)	0.7087 (1)	1.0025 (3)
O(6)	0.3507 (2)	0.9099 (2)	1.0351 (4)
O(14)	0.0377 (1)	0.8267 (1)	0.8034 (3)
N	0.0183 (2)	0.6643 (2)	0.6477 (4)
H(1)	0.367 (2)	0.586 (2)	0.404 (5)
H(2)	0.507 (2)	0.553 (2)	0.588 (4)
H(5)	0.211 (2)	0.767 (2)	1.090 (4)
H(7)	0.301 (2)	0.978 (3)	0.754 (4)
H(8)	0.169 (2)	0.915 (2)	0.579 (4)
H(9)	0.057 (2)	0.771 (2)	0.498 (4)
H(10a)	0.214 (3)	0.732 (3)	0.398 (5)
H(10b)	0.160 (2)	0.627 (3)	0.401 (4)
H(15a)	0.155 (2)	0.595 (2)	0.972 (4)
H(15b)	0.060 (2)	0.673 (2)	0.979 (4)
H(16a)	0.116 (2)	0.553 (2)	0.692 (4)
H(16b)	0.009 (3)	0.552 (3)	0.798 (4)
H(17a)	−0.083 (4)	0.667 (4)	0.444 (7)
H(17b)	−0.103 (4)	0.589 (4)	0.576 (8)
H(17c)	−0.009 (3)	0.579 (3)	0.455 (6)
H(3)	0.526 (3)	0.625 (3)	0.991 (6)
H(14)	−0.009 (3)	0.780 (3)	0.791 (5)

independent reflections with $2\theta \leq 130°$ was measured; of these, 1349 were considered nonzero at the 3σ significance level. The structure was solved by direct methods with the use of the MULTAN program.[7] Full-matrix least-squares refinement on the positional and anisotropic thermal parameters for the nonhydrogen atoms gave an R value of 0.081. A difference map revealed the positions of all the hydrogen atoms in the molecule. Refinement of the positional and anisotropic thermal parameters for the nonhydrogen atoms and the positional and the isotropic thermal parameters for the hydrogen atoms gave final values for R and R_2 of 0.041 and 0.045. The final value of $\Sigma w\Delta^2/(m - n)$ was 3.09. The details of the weighting schemes, form factors, etc., were as described for **1**-Y. The final coordinates for **1**-W are given in Table II. The thermal parameters and a list of structure factors for both **1**-Y and **1**-W have been deposited (see paragraph at end of paper regarding supplementary material).

Results and Discussion

(a) Molecular Geometry. Stereoscopic views of single molecules of the two forms of 14-hydroxymorphinone are shown in Figure 1. Bond lengths and angles for both forms are given in Table **III**.

The conformations of the 14-hydroxymorphinone molecule in the two forms seem quite similar. Since the early paper by Mackay and Hodgkin on morphine hydriodide dihydrate,[12] there have been a number of X-ray investigations on morphine derivatives. In previous X-ray structural papers on morphine derivatives, the morphine molecule has often been described as a T-shape[12,13] with the best plane through rings A, B, and the ether ring defining the stem of the T and that through rings C and D describing the top. In **1**-Y and **1**-W, the angle between these planes is 90.3 and 84.7°, respectively. In rough qualitative terms in both molecules, ring A and the ether ring approach planarity, ring B is a half-chair, ring C is a distorted half-chair, while ring D is a fairly regular chair. These are the first examples of a morphine derivative with a cyclohexenone ring as ring C for which X-ray data are available. Ring C is somewhat flatter in **1**-W than in **1**-Y, with a large difference in the torsion angle around the C(6)-C(7) ring bond; the values of the torsion angle in the bonds in ring C in the two compounds are as follows (**1**-W values in parentheses): C(14)-C(13) 46.4° (40.8°), C(13)-C(5) −26.4° (−29.4°), C(5)-C(6) −6.7° (4.3°), C(6)-C(7) 19.1° (9.9°), C(7)-C(8) 4.2° (2.8°), and C(8)-C(14) −36.4° (−27.9°). In contrast, the C(9), C(10), C(11), C(12), and C(13) portion of ring B is more planar in **1**-Y than in **1**-W. Another difference is the position of the phenolic [O(3)] hydrogen atom, which in **1**-Y is in the plane of the phenyl ring and pointing on the side of C(2), while in **1**-W, it is in the plane of the ring but lies on the side of O(4). It is of interest that the greatest differences in bond lengths between the two molecules are in the C(1)-C(2)-C(3)-O(3) region, with C(1)-C(2) and C(3)-O(3) appearing longer in **1**-Y than in **1**-W, and the reverse being true of C(2)-C(3). The general pattern of bond lengths in this region as found in **1**-Y is also encountered in the molecules of oxymorphone hydrate,[14] naloxone hydrochloride dihydrate,[15] and morphine hydrochloride trihydrate,[16] whereas a pattern somewhat similar to that found in **1**-W is also found in 6-deoxy-6-azidodihydroisomorphine.[17] The orientation of the phenolic hydroxyl group appears to have an effect also on the exocyclic C-C-O bond angles. In **1**-Y, C(2)-C(3)-O(3) is 123.9 (3)°, while C(4)-C(3)-O(3) is 119.5 (3)°; in **1**-W, these two angles are 118.6 (3) and 126.0 (3)°, respectively. These variations in bond angles are presumably due to the steric interaction between the hydroxyl hydrogen atoms and the ortho substituent, whether it be hydrogen or ether oxygen.

In both forms of **1**, there is an intramolecular O(14)—H- - -N hydrogen bond. In **1**-Y and **1**-W, respectively, the O(14)- - -N distances are 2.742 (4) and 2.618 (3) Å, the H(14)- - -N distances are 2.20 (5) and 2.03 (4) Å, the C(14)—O(14)- - -N angles are 61.0 (2) and 60.0 (1)°, and the O(14)—H(14)- - -N angles are 116 (4) and 122 (3)°. While the O—H- - -N angles may appear unfavorable for hydrogen bonding, it should be pointed out that the O—H- - -N (lone pair) angle would be much more favorable. In **1**-W, O(14) is the acceptor of an intermolecular hydrogen bond (from the phenolic hydroxyl); there may also be a weak intermolecular O(14)—H- - -O(4) interaction making the O(14)-H hydrogen bond bifurcated [to nitrogen and to O(4)] in **1**-W.

(b) Nonplanarity of Ring A. In both molecules, there is a distortion of the phenolic ring from planarity which is probably induced by the strained O(4) ether bridge. Torsion angles around this ring in a number of morphine derivatives are given in Table IV. In **1**-Y and **1**-W, the torsion angles around the bonds C(4)-C(12) and C(12-)-C(11) are quite large (5-6°), with the C(4)-C(12) torsion angle being negative and the C(12)-C(11) angle being positive. A best plane calculation through the six atoms of ring A shows, in both forms, C(2) and C(12) lying to the side of the plane toward the nitrogen-containing ring D (maximum deviation 0.031 Å) while the other four atoms lie on the opposite side (maximum deviation 0.022 Å); the atoms O(3) and O(4) each lie significantly on the side of ring D from this plane [0.042 and 0.098 Å for O(3) and 0.187 and 0.095 Å for O(4) in **1**-Y and **1**-W, respectively]. In view of the interest in the chiroptical properties of morphine derivatives,[5] the extent of planarity of ring A was examined in a series of morphine derivatives (Table IV). A pattern similar to that in **1**-Y and **1**-W is noted in the naloxone hydrochloride dihydrate,[15] oxymorphone hydrate,[14] nalbuphine

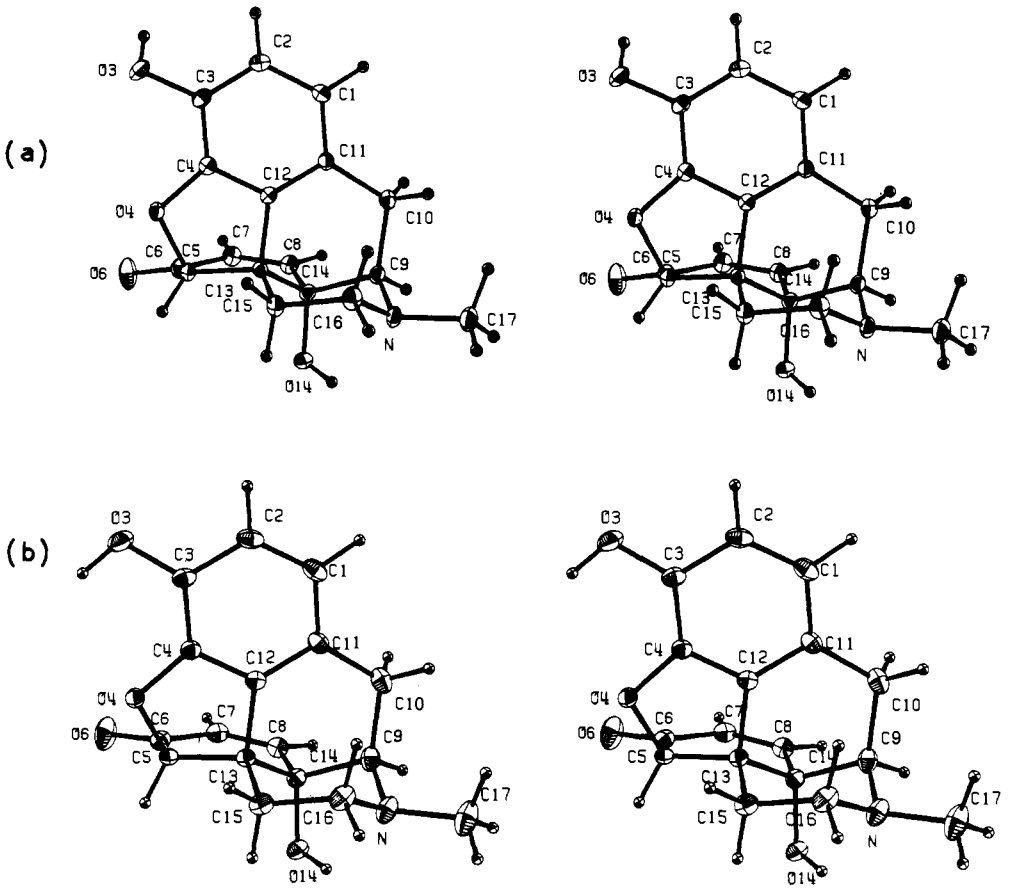


Figure 1. Single molecules of 14-hydroxymorphinone: (a) yellow form; (b) white form.

Table III. Bond Lengths[a] and Angles in **1**-Y and **1**-W

bond length, Å	**1**-Y	**1**-W	angle, deg	**1**-Y	**1**-W	angle, deg	**1**-Y	**1**-W
C(1)-C(2)	1.401 (6)	1.375 (5)	C(2)-C(1)-C(11)	120.4 (4)	121.0 (3)	C(12)-C(13)-C(14)	107.1 (2)	108.5 (2)
C(2)-C(3)	1.390 (5)	1.408 (5)	C(1)-C(2)-C(3)	122.2 (4)	122.6 (3)	C(15)-C(13)-C(14)	109.5 (3)	109.1 (2)
C(3)-C(4)	1.377 (5)	1.379 (4)	C(2)-C(3)-C(4)	116.5 (3)	115.3 (3)	C(5)-C(6)-C(7)	119.8 (3)	119.9 (3)
C(3)-O(3)	1.377 (4)	1.356 (4)	C(2)-C(3)-O(3)	123.9 (3)	118.6 (3)	C(5)-C(6)-O(6)	118.5 (3)	119.0 (3)
C(4)-C(12)	1.371 (4)	1.365 (4)	C(4)-C(3)-O(3)	119.5 (3)	126.0 (3)	C(7)-C(6)-O(6)	121.7 (3)	121.1 (3)
C(11)-C(12)	1.377 (4)	1.378 (4)	C(3)-C(4)-C(12)	121.0 (3)	121.5 (2)	C(6)-C(7)-C(8)	121.0 (4)	122.9 (3)
C(1)-C(11)	1.390 (4)	1.393 (4)	C(3)-C(4)-O(4)	126.4 (3)	126.5 (2)	C(7)-C(8)-C(14)	122.2 (4)	122.8 (3)
C(4)-O(4)	1.396 (3)	1.393 (3)	C(12)-C(4)-O(4)	112.4 (3)	112.0 (2)	C(8)-C(14)-C(13)	110.2 (3)	112.4 (2)
O(4)-C(5)	1.469 (4)	1.476 (3)	C(4)-C(12)-C(11)	123.5 (3)	123.7 (2)	C(8)-C(14)-C(9)	113.8 (3)	114.7 (2)
C(5)-C(13)	1.538 (4)	1.534 (4)	C(4)-C(12)-C(13)	109.2 (3)	109.4 (2)	C(8)-C(14)-O(14)	104.2 (3)	104.5 (2)
C(12)-C(13)	1.501 (5)	1.503 (4)	C(11)-C(12)-C(13)	126.6 (3)	126.9 (2)	C(13)-C(14)-C(9)	106.7 (3)	106.2 (2)
C(5)-C(6)	1.523 (5)	1.455 (5)	C(1)-C(11)-C(10)	125.0 (3)	126.5 (3)	C(13)-C(14)-O(14)	112.0 (2)	112.4 (2)
C(6)-C(7)	1.465 (6)	1.455 (5)	C(1)-C(11)-C(12)	116.2 (2)	115.6 (3)	C(9)-C(14)-O(14)	109.9 (3)	106.6 (2)
C(6)-O(6)	1.221 (5)	1.218 (4)	C(10)-C(11)-C(12)	118.4 (3)	117.7 (3)	C(14)-C(9)-C(10)	113.5 (3)	114.7 (2)
C(7)-C(8)	1.328 (6)	1.319 (4)	C(4)-O(4)-C(5)	104.9 (2)	104.8 (2)	C(14)-C(9)-N	105.5 (2)	103.9 (2)
C(8)-C(14)	1.511 (5)	1.497 (4)	O(4)-C(5)-C(13)	105.9 (3)	105.3 (2)	C(10)-C(9)-N	116.6 (3)	116.8 (3)
C(13)-C(14)	1.532 (4)	1.533 (4)	O(4)-C(5)-C(6)	104.7 (3)	106.5 (2)	C(9)-C(10)-C(11)	114.1 (3)	114.7 (3)
C(14)-O(14)	1.436 (5)	1.439 (3)	C(6)-C(5)-C(13)	113.8 (3)	113.4 (2)	C(9)-N-C(16)	112.3 (3)	112.7 (2)
C(9)-C(14)	1.539 (5)	1.549 (4)	C(5)-C(13)-C(12)	100.1 (2)	99.1 (2)	C(9)-N-C(17)	112.9 (3)	113.4 (3)
C(9)-C(10)	1.554 (6)	1.539 (5)	C(5)-C(13)-C(15)	112.4 (3)	113.2 (2)	C(16)-N-C(17)	111.5 (3)	113.4 (3)
C(10)-C(11)	1.520 (5)	1.507 (5)	C(5)-C(13)-C(14)	115.9 (3)	116.7 (2)	N-C(16)-C(15)	110.1 (3)	110.0 (3)
C(13)-C(15)	1.545 (5)	1.541 (4)	C(12)-C(13)-C(15)	111.5 (3)	109.5 (2)	C(13)-C(15)-C(16)	111.4 (3)	111.1 (2)
C(15)-C(16)	1.518 (6)	1.514 (5)						
C(16)-N	1.468 (5)	1.472 (4)						
C(9)-N	1.477 (5)	1.471 (4)						
N-C(17)	1.460 (5)	1.459 (6)						

[a] In **1**-Y, the C-H distances range from 0.97 (3) to 1.07 (4) Å, and the O-H distances are 0.71 (4) from O(3)-H(3) and 0.94 (5) from O(14)-H(14). In **1**-W, the C-H distances range from 0.93 (6) to 1.06 (4) Å, while O(3)-H(3) is 0.92 (4) and O(14)-H(14) is 0.90 (4) Å.

dihydrochloride dihydrate,[18] morphine hydrate,[19] morphine hydrochloride trihydrate,[16] and codeine hydrobromide dihydrate[13] structures and, to a lesser extent, in the structure of 6-deoxy-6-azidodihydroisomorphine.[17] It is of interest that torsion angles differing significantly from zero around these same bonds are also found in the structure of dihydrometa-

Table IV. Torsion Angles (Degrees)[a,b] in the Phenolic Ring (Ring A) in a Number of Compounds Related to Morphine

	1-Y	1-W	naloxone HCl·$2H_2O$[c]	codeine HBr·$2H_2O$[d,e]	oxymorphone hydrate[d,f]	morphine hydrate[d]	morphine HCl·$3H_2O$[d,g]	nalbuphine HCl·$2H_2O$[d,f]	dihydrometacodeinone HCl[d]	6-azidomorphine[d]	*N*-methyl-D-normorphinan HBr[d]	DL-cyclazocine[d]	L-cyclazocine HBr·H_2O[d]
C(11)-C(1)-C(2)-C(3)	−2.6	−4.0	−0.8	−3.1	−0.3	−2.1	−1.9	−2.5	4.5	−1.4	4.5	1.8	2.3
C(1)-C(2)-C(3)-C(4)	1.5	4.0	−0.9	3.9	−0.6	2.7	0.8	2.4	−4.8	2.3	−3.9	−3.7	−0.6
C(2)-C(3)-C(4)-C(12)	2.6	0.6	4.3	0.5	3.6	0.9	3.3	1.5	−0.1	−0.3	0.9	3.3	−0.9
C(3)-C(4)-C(12)-C(11)	−5.9	−5.5	−6.7	−6.1	−6.0	−5.1	−6.7	−5.6	6.0	−2.8	1.6	−0.9	0.7
C(4)-C(12)-C(11)-C(1)	4.6	5.4	4.8	6.6	4.9	5.5	5.4	5.4	−6.3	3.6	−1.1	−1.1	0.9
C(12)-C(11)-C(1)-C(2)	−0.4	−0.7	−1.1	−2.1	−1.8	−2.0	−1.1	−1.3	1.0	−1.5	−1.9	0.6	−2.5
ref	present work	present work	15	13	14	19	16	18	20	17	22	21	21

[a] The torsion angle A-B-C-D is considered positive if, when one looks along the B-C bond, atom A has to be rotated clockwise to eclipse atom D. [b] In addition to the three examples included in Table IV, we calculated the torsion angles for a number of morphine derivatives without the ether bridge, and in the case of 2,9β-dimethyl-6,7-benzomorphan hydrochloride,[23] apomorphine hydrochloride hydrate,[24] (−)-5-*m*-hydroxyphenyl-2-methylmorphan hydrobromide,[25] and (+)-3-methoxy-*N*-methylmorphinan hydrobromide monohydrate,[28] we found no torsion angles greater than 2.6°. We did calculate rather larger torsion angles from the available coordinates for (−)-*N*-allyl-3,6β-dihydroxymorphinan hydrobromide[26] and for 2-allyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan hydrobromide monohydrate.[27] However, in the former structure, the precision of the analysis is such that these values are not significant, while in the latter structure, we find small (~0.05 Å) differences, but without a consistent pattern, in the bond lengths we calculate from the published coordinates from those given in the paper. Two morphine derivatives which have been studied but have not been included in any comparisons are the iron tricarbonyl complex of thebaine (no coordinates available) [A. J. Birch, H. Fitton, M. McPartlin, and R. Mason, *Chem. Commun.*, 531 (1968)] and pentachloroethoxycodide [I. L. Karle and J. Karle, *Acta Crystallogr., Sect. B*, **25**, 1097 (1969)]. [c] Values for torsion angles are given in the original paper. [d] Torsion angles were calculated by us from atomic coordinates found in the original work. [e] While the drawings and discussion in ref 13 refer to the correct absolute configuration, the atomic coordinates given are for the opposite configuration (as stated in the text by the authors). The torsion angles included in the present table correspond to the correct absolute configuration. [f] While the drawings and discussion in ref 14 and 18 refer to the correct absolute configuration, the packing diagram (Figure 2) has a left-handed coordinate system and the atomic coordinates given correspond to the opposite configuration. The torsion angles included in the present table correspond to the correct absolute configuration. [g] In ref 16, the *x* coordinate of C(3) should be 0.1806 instead of 0.1068 (D. Carlstrom, personal communication).

codeinone hydrochloride,[20] but, in that structure, they are of opposite sign. However, the dihydrometacodeinone structure has the bridging nitrogen-containing ring attached at C(13) and a different stereochemistry at C(5), factors which may have an influence different from those in the morphine structures with the normal nitrogen-containing ring. When the O-bridging group is absent, as in the cyclazocine structures[21] and in a number of other morphine derivatives,[22-28] ring A is much more planar and there is less evidence for twist in the C(4)-C(12) and C(12)-C(11) region of the molecule. The nonplanarity of ring A found by X-ray methods in those morphine derivatives with an intact ether bridge is thus believed[5] to be responsible for a band at ~240-250 nm that is present in the CD spectrum of all compounds of this type studied so far and is absent from the curves of morphine derivatives lacking the oxygen bridge.

(c) Molecular Packing. The crystal structures of the two forms of **1** are quite different, with the intermolecular hydrogen bonding involving different acceptors. In **1**-Y, the phenolic hydrogen lies on the C(2) side and there is intermolecular hydrogen bonding to the carbonyl group. The O(3)-H group in the reference molecule hydrogen bonds to O(6) in the molecule at $-\frac{1}{2} + x$, $1\frac{1}{2} - y$, and $1 - z$; the O(3)- - -O(6) and H(3)- - -O(6) distances are 2.703 (4) and 2.01 (4) Å, and the O(3)—H- - -O(6) and C(3)—O(3)- - -O(6) angles are 164 (5) and 109.9 (2)°. This hydrogen bonding, which has the effect of lowering the C=O stretch to 1660 cm^{-1}, causes the formation of chains of molecules running along the *a* direction (Figure 2); these chains zigzag by as much as the *c*-axial length. In **1**-W, the phenolic hydrogen lies to the O(4) side and there is intermolecular hydrogen bonding to the aliphatic hydroxyl group. The O(3)-H group hydrogen bonds to O(14) in the molecule at $\frac{1}{2} + x$, $1\frac{1}{2} - y$, $2 - z$; the O(3)- - -O(14) and H(3)- - -O(14) distances are 2.689 (4) and 1.79 (5) Å, and the O(3)—H- - -O(14) and C(3)—O(3)- - -O(14) angles are 163 (8) and 117.0 (2)°. The carbonyl group is not involved in hydrogen bonding in the white form and the C=O stretch occurs at 1685 cm^{-1}. The phenol-alcohol hydrogen bonding in **1**-W causes the formation of chains of hydrogen-bonded molecules along the *a* direction (Figure 2, b). Among neutral morphine derivatives, O(3)—H- - -O(14) hydrogen bonding occurs in the 6-deoxy-6-azido-14-hydroxydihydroisomorphine crystal.[29]

It is of interest to compare the packing of **1**-Y and **1**-W in some more detail. This is best achieved by viewing the packing of **1**-Y down the *b* axis (Figure 2, c) and comparing this with the view of **1**-W down *c* (Figure 2, b). If one compares the shaded molecules of **1**-W in Figure 2, b, and imagines a rotation of the C-O(H) bond by 180° such that it is now on the side of C(2), then hydrogen bonding to O(6) in the adjacent shaded molecule ($1 - x$, $-\frac{1}{2} + y$, $1\frac{1}{2} - z$) could readily be accomplished. The appropriate O(3)- - -O(6) intermolecular distance in **1**-W is 4.603 (4) Å, while the O(3)- - -O(14) ($-\frac{1}{2} + x$, $1\frac{1}{2} - y$, $-z$) intermolecular distance in **1**-Y is 2.996 (4) Å. In this way, the zigzag chains found in **1**-Y (see above) could be formed. However, the relationship between adjacent chains would not be the same as in **1**-Y unless there were a major reorientation of half the molecules in the crystal.

(d) Reasons for the Color Dimorphism. In spite of the wealth of detailed information provided by the X-ray crystallographic

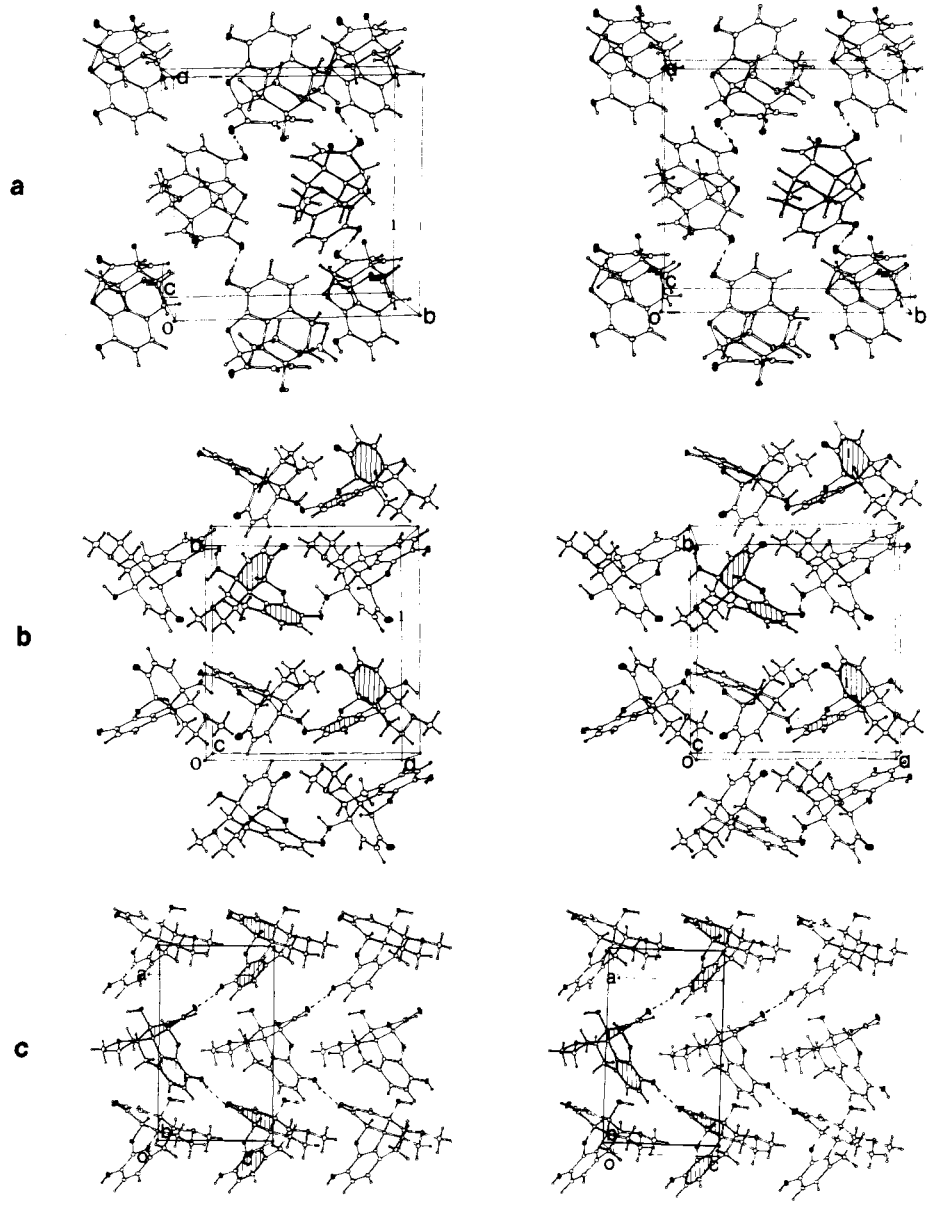


Figure 2. (a) Stereoscopic view of the molecular packing in **1**-Y looking in the c direction. The bonds in the reference molecule are darkened. Discontinuous lines indicate hydrogen bonds. (b) Stereoscopic view of the molecular packing in **1**-W looking in the *c* direction. The bonds in the reference molecule are darkened. Discontinuous lines indicate hydrogen bonds. The molecules that would make up the hydrogen bonding chains in **1**-Y are highlighted by shading of ring A and ring C. (c) Stereoscopic view of the packing of **1**-Y between the relative positions of half of the molecules in **1**-Y and **1**-W is demonstrated.

study, the yellow color of **1**-Y in the solid state, and in solution in polar solvents, remains difficult to explain. It should be pointed out that the color difference observed for solutions of **1** in polar solvents (yellow) and in nonpolar solvents (colorless) is in the direction opposite to the spectral shift usually found for ketones in solvents of differing polarity.[30] This latter shift in the UV absorption is attributed to a change in the energy of the $n \rightarrow \pi^*$ transition of the carbonyl group as a result of hydrogen bonding with solvent.[31]

There seems to be little evidence for the assumption that the difference in color between the solids **1**-Y and **1**-W could be due to differences in molecular structure. Two features, not necessarily mutually exclusive, could be used to explain the color of **1**-Y: the influence of hydrogen bonding affecting the carbonyl, and a charge-transfer effect between the aromatic ring of one molecule and the carbonyl of another.

Precedent for the first of these may be provided by the color dimorphism of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate.[4a,32] In that case the yellow form has been shown to exhibit intramolecular hydrogen bonding from the phenolic hydroxyls to the ester carbonyls, while in the white form the hydroxyls are hydrogen bonded to the chlorine atoms. This example shows that intramolecular hydrogen bonding to a carbonyl group can indeed produce a bathochromic shift sufficient to cause visible color. However, the analogy of this aromatic ester to the cyclohexenone in **1** is not as close as might be desired. No consistent pattern of small changes in bond lengths in the enone and phenolic regions of **1**-Y and **1**-W, as might be anticipated from such an interaction, is evident from the X-ray results. The alternative interpretation is based on the fact that in the crystal lattice of **1**-Y, but not in that of **1**-W, the carbonyl group of one molecule is held in the vicinity of the phenolic ring of another molecule (see Figure 2, a). Consequently, a charge-transfer interaction might furnish an explanation for the color of **1**-Y.[33] As can be seen from Figure 3, there is considerable overlap of the keto group with the phenolic ring. However, the distances between these groups are too large to allow for more than a very weak interaction;

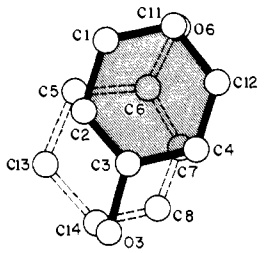
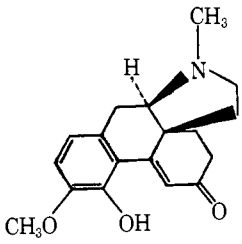


Figure 3. The projection of the atoms of the cyclohexanone ring in the molecule at $-1/2 + x$, $1\,1/2 - y$, $-z$ onto the best plane (shaded) through the six atoms of ring A.

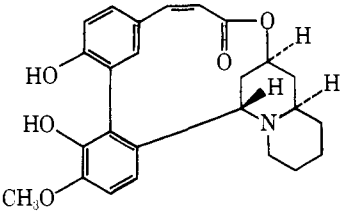
these distances from the plane of the phenolic ring are C(5) 4.249, O(6) 4.622, C(6) 4.722, and C(14) 4.241 a. The question of a charge-transfer interaction in solution has been examined spectrophotometrically.

When the spectrum of **1** in methylene chloride was subtracted from that of an equimolar solution of the compound in methanol, the resulting difference spectrum showed moderately strong apparent maxima at 241 and 292.5 nm (ϵ 262 and 125, respectively) and a very weak, broad, structureless band with an indistinct maximum at ~340 nm (ϵ 13). Of these, only the band at 292.5 nm has a counterpart in the analogous difference spectrum of *o*-cresol in the same two solvents. Despite its weakness, the apparent band at 340 nm may thus be partly responsible for the difference in color and its dependence upon solvent polarity. The properties of this band (low intensity, width, and absence of fine-structure) are indeed reminiscent of those of a charge-transfer transition; the findings are thus compatible with this interpretation of the color difference, although they do not furnish conclusive proof. It should be emphasized that the spectroscopic evidence for the charge-transfer effect was obtained from solution studies. In order that a correlation between solution and solid-state structures can be made, it is necessary to postulate that an intermolecular approach, somewhat similar to that in the crystal, takes place in solution. The band at 241 nm, not found in the difference spectrum of the model compound, is believed to reflect the presence of the phenoxide ion[34] in methanolic solutions of **1**. A much better defined charge-transfer effect, and one much more clearly influential on the color, was found recently in the case of 2-(4′-methoxyphenyl)-1,4-benzoquinone.[4b] We plan to study the electronic spectra of **1** in solution as a function of solvent polarity in greater detail.

The color dimorphism of **1** is not without analogy among phenolic alkaloids. Two such cases have come to our attention. Both compounds which show this phenomenon, metathebainone (**2**)[35] and verticillatine (**3**),[36] resemble **1** in containing



2



3

α,β-unsaturated carbonyls, viz., a keto group in **2** and an ester grouping in **3**. In contrast to the situation in **1**, however, these chromophores are also conjugated with the phenolic ring in both **2** and **3**.

Metathebainone (**2**), derived from a rearranged morphinane skeleton, exists in a yellow and a colorless modification,[35] but the mode of formation of these two modifications differs from that of the two forms of **1** and does not seem to depend upon the polarity of the solvent used for recrystallization. In contrast, the behavior of **2** in solution is quite analogous to that of **1**: solutions of **2** in ethanol or water are yellow; those in benzene or chloroform are colorless.[35]

Verticillatine (**3**) resembles **1** in forming yellow crystals from methanol and white ones from chloroform,[36] its dimethyl ether is colorless. The color of the yellow modification of **3** has been ascribed[36] to the presence of some of the phenoxide ion which has a λ_{max} of 300–323 nm.

Acknowledgment. This work was supported by NIH Grant GM 19336. Dr. Eileen Duesler and Ms. Hi-Shi Chiang assisted in the preparation of the final form of the paper.

Supplementary Material Available: Tables of thermal parameters and of observed and calculated structure factors for **1**-Y and **1**-W (23 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) University of Illinois; (b) National Cancer Institute; (c) NIAMDD.
(2) U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957).
(3) This point cannot be examined with Dreiding models, since it is not possible even to build the oxygen-containing ring of morphine or any of its oxygen-bridged derivatives.
(4) (a) S. R. Byrn, D. Y. Curtin, and I. C. Paul, *J. Am. Chem. Soc.*, **94**, 890 (1972); (b) G. R. Desiraju, I. C. Paul, and D. Y. Curtin, *ibid.*, **99**, 1594 (1977).
(5) U. Weiss and T. Rüll, *Bull. Soc. Chim. Fr.*, 3707 (1965); I. H. Qureshi and U. Weiss, unpublished results.
(6) J. K. Frank and I. C. Paul, *J. Am. Chem. Soc.*, **95**, 2324 (1973); R. S. Miller, I. C. Paul, and D. Y. Curtin, *ibid.*, **96**, 6334 (1974).
(7) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(8) $R = \Sigma||F_{obsd}| - |F_{calcd}||/\Sigma|F_{obsd}|$; $R_2 = [\Sigma w||F_{obsd}| - |F_{calcd}|^2/\Sigma w|F_{obsd}|^2]^{1/2}$.
(9) P. W. R. Corfield, R. J. Doedens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).
(10) D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A*, **24**, 321 (1968).
(11) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(12) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955).
(13) G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr.*, **15**, 326 (1962).
(14) R. J. Sime, M. Dobler, and R. L. Sime, *Acta Crystallogr., Sect. B*, **32**, 2937 (1976).
(15) I. L. Karle, *Acta Crystallogr., Sect. B*, **30**, 1682 (1974).
(16) L. Gylbert, *Acta Crystallogr., Sect. B*, **29**, 1630 (1973).
(17) K. Sasvári, K. Simon, R. Bognár, and S. Makleit, *Acta Crystallogr., Sect. B*, **30**, 634 (1974).
(18) R. J. Sime, M. Dobler, and R. L. Sime, *Acta Crystallogr., Sect. B*, **32**, 809 (1976).
(19) E. Bye, *Acta Chem. Scand., Ser. B*, **30**, 549 (1976).
(20) J. V. Tillack and C. H. L. Kennard, *J. Chem. Soc., Perkin Trans. 2*, 2044 (1973).
(21) I. L. Karle, R. D. Gilardi, A. V. Fratini, and J. Karle, *Acta Crystallogr., Sect. B*, **25**, 1469 (1969).
(22) A. D. Hardy and F. R. Ahmed, *Acta Crystallogr., Sect. B*, **31**, 2919 (1975); **33**, 2351 (1977).
(23) T. G. Cochran and J. E. Abola, *Acta Crystallogr., Sect. B*, **31**, 919 (1975).
(24) J. Giesecke, *Acta Crystallogr., Sect. B*, **29**, 1785 (1973); **33**, 302 (1977).
(25) T. G. Cochran, *J. Med. Chem.*, **17**, 987 (1974).
(26) J. F. Blount, E. Mohacsi, F. M. Vane, and G. J. Mannering, *J. Med. Chem.*, **16**, 352 (1973).
(27) W. Fedeli, G. Giacomello, S. Cerrini, and A. Vaciago, *J. Chem. Soc. B*, 1190 (1970).
(28) L. Gylbert and D. Carlström, *Acta Crystallogr., Sect. B*, **33**, 2833 (1977).
(29) A. Kálmán, Z. Ignáth, K. Simon, R. Bognár, and S. Makleit, *Acta Crystallogr., Sect. B*, **32**, 2667 (1976).
(30) See, for example, H. Jaffé and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy", Wiley, New York, N.Y., 1962, pp 186–189.
(31) G. J. Brealey and M. Kasha, *J. Am. Chem. Soc.*, **77**, 4462 (1955); V. G. Krishna and L. Goodman, *ibid.*, **83**, 2042 (1961).
(32) D. Y. Curtin and S. R. Byrn, *J. Am. Chem. Soc.*, **91**, 6102 (1969).
(33) Helpful discussions on this point with Dr. Richard G. Weiss, Georgetown University, are gratefully acknowledged.
(34) D. B. Wetlaufer, *Adv. Protein Chem.*, **17**, 303 (1962); E. Mihalyi, *J. Chem. Eng. Data*, **13**, 179 (1968).
(35) L. F. Small and E. Meitzner, *J. Am. Chem. Soc.*, **55**, 4602 (1933).
(36) J. P. Ferris, C. B. Boyce, and R. C. Briner, *J. Am. Chem. Soc.*, **93**, 2942 (1971); see footnote 27 in that paper.