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The Diels–Alder Reaction with Thebaine. Thermal Rearrangement of Some Adducts from Acetylenic Dienophiles

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The facile thermal rearrangement of the adducts of thebaine with dimethyl acetylenedicarboxylate (DMA) and ethyl propiolate (EP) has been investigated. On the basis of spectroscopic and degradative evidence, benzazocine structures have been deduced for the thermal isomers of these adducts. Some anomalous properties of these thermal isomers are discussed in terms of their possible bearing on the stereochemistry of this phenylfurobenzazocine system.

As part of a study of thebaine transformations, some Diels–Alder adducts of thebaine with acetylenic dienophiles were prepared. These adducts were found to be subject to thermal rearrangement under exceedingly mild conditions. The bulk of the present report will be concerned with the elucidation of the structures and some properties of the rearrangement products.

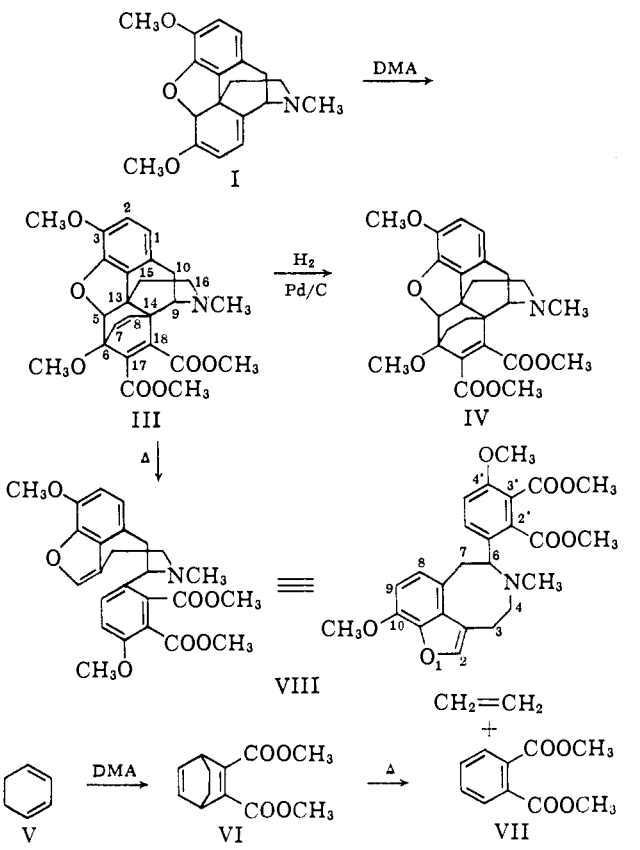
Thebaine (I), long known to participate in Diels–Alder reactions,[2-7] and dimethyl acetylenedicarboxylate (DMA) (II) in equimolar proportions reacted smoothly in benzene at 50°, providing the crystalline adduct III in high yield. Purification of adduct III was accomplished by utilizing its weak basicity ($pK_a \sim 3.3$) as compared to that of thebaine ($pK_a \sim 8.2$) to remove any unreacted thebaine, and by conducting all crystallizations at or below room temperature by an evaporative procedure.

A number of independent observations on adduct III attested to its thermal instability. It was found, for example, that its melting behavior was largely dependent upon the rate of heating; the highest and sharpest melting range was observed with a rapid heating rate. Furthermore, sublimation of adduct III at 135° (0.01 mm.) provided a glassy sublimate which could not be crystallized under conditions used to crystallize III. The ultraviolet and infrared spectra of the sublimate differed considerably from those of III, while analytical data indicated that the sublimate was isomeric with III.

Hydrogenation of adduct III proceeded rapidly, giving the dihydroadduct[8] IV which was demonstrated to be saturated at C_7–C_8 by carbonyl absorption in the infrared at 1720 cm.$^{-1}$, the same frequency as shown by the ester moieties of adduct III. In contrast to III, the dihydroadduct IV was endowed with complete thermal stability to at least 208°, as determined spectrophotometrically.

Preparation of the thermal isomer in quantity was achieved by heating a solution of adduct III under reflux in di-*n*-butyl ether for 10–15 min. The thermal isomer was thus obtained in almost quantitative yield as a colorless glass which could not be obtained crystalline. Preparation of a crystalline picrate from which the thermal isomer was regenerated by chromatography on alumina still left a glass, although identical infrared spectra for all the fractions indicated homogeneity. The thermal isomer also proved to be very weakly basic ($pK_a \sim 3.3$) and quaternization presented difficulties. With methyl iodide, only amorphous material resulted; however, the use of dimethyl sulfate with subsequent precipitation by potassium iodide provided a crystalline methiodide in poor yield.

A suggestion as to the structure of the thermal isomer first came from the various reports[9-16] on the pyrolysis of some Diels–Alder adducts of DMA. The simplest example is provided by the reaction of 1,3-cyclohexadiene (V) and DMA (II) to give the bicyclooctadiene adduct VI. At elevated temperatures, VI undergoes decomposition[16] to dimethyl phthalate (VII) and ethylene. On the basis of these analogies, the thermal isomerization of III was tentatively formulated as proceeding through disruption of the doubly allylic C_{5-6} and C_{13-14} bonds to give the thermal isomer VIII. In order to establish conclusively the structure



of the thermal isomer, evidence of two major types was gathered: (1) spectroscopic, utilizing both ultra-

(1) National Institutes of Health Predoctoral Fellow.

(2) C. Schöpf, K. von Gottberg and W. Petri, *Ann.*, **536**, 216 (1938).

(3) W. Sandermann, *Ber.*, **71**, 648 (1938).

(4) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford Univ. Press, London, 1954, p. 289.

(5) K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1863 (1956).

(6) J. Meinwald and G. A. Wiley, *J. Am. Chem. Soc.*, **79**, 2569 (1957).

(7) K. W. Bentley and J. C. Ball, *J. Org. Chem.*, **23**, 1720 (1958).

(8) Throughout the discussion, a pragmatic nomenclature has been used, based on the chemical transformations. In the Experimental section, an attempt has been made also to provide systematic names.

(9) H. Pines and C. T. Chen, *J. Am. Chem. Soc.*, **81**, 928 (1959).

(10) M. Avram, C. D. Nenitzescu and E. Marcia, *Ber.*, **90**, 1857 (1957).

(11) E. D. Parker and L. A. Goldblatt, *J. Am. Chem. Soc.*, **72**, 2151 (1950).

(12) W. Reppe, O. Schlichting, K. Klager and T. Toepel, *Ann.*, **560**, 1 (1948).

(13) W. Sandermann and R. Hohn, *Ber.*, **76**, 1257 (1943).

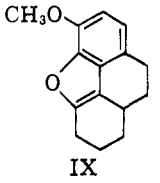
(14) G. Dupont and R. Dulou, *Atti congr. intern. chim.* (10th Congr.), **3**, 123 (1939); *Chem. Abstr.*, **33**, 9312 (1939).

(15) K. Alder and H. F. Rickert, *Ber.*, **70**, 1364 (1937).

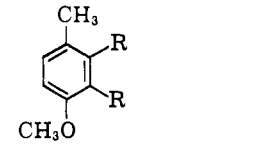
(16) K. Alder and H. F. Rickert, *Ann.*, **524**, 180 (1936).

violet and nuclear magnetic resonance absorption; and (2) degradative.

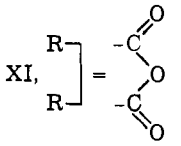
The two chromophores of structure VIII are insulated from each other and thus may act independently; therefore, if VIII represented the thermal isomer, a closely similar model ultraviolet spectrum might be composed from 6,7,8,9,10,14-hexahydromorphenol methyl ether[17] (IX) and X, the half-ethyl ester of 3-methoxy-6-methylphthalic anhydride[18] (XI).



IX

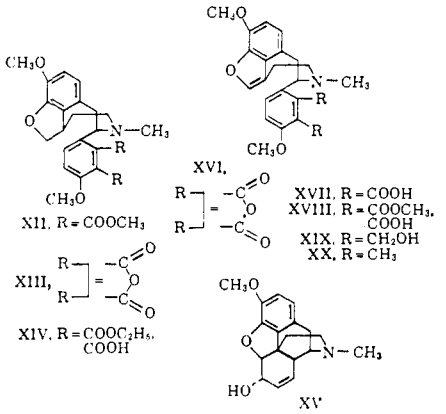


X, R = COOH, $COOC_2H_5$



In Fig. 1 is shown a comparison of the spectrum of the thermal isomer with the model spectrum, constructed[19] from IX and X. While the two spectra are comparable in their more general features, there are distinct differences, particularly at shorter wave lengths.

Of particular interest were the spectral changes produced on hydrogenation of the thermal isomer. It had been demonstrated that under certain conditions hydrogenation of the benzofuran system proceeds to saturate selectively the furanoid ring.[17,20] Accordingly, hydrogenation of the thermal isomer was carried out in glacial acetic acid with palladized carbon, and, after the uptake of 120 mole % of hydrogen, a glassy product (λ_{max}^{EtOH} 287 mμ) was isolated. Since the product (XII) was of questionable purity and could not be crystallized, it was hydrolyzed with alcoholic potassium hydroxide. The crystalline anhydride XIII obtained by continuous extraction of the acidified reaction mixture was converted to the half-ethyl ester XIV for comparison with a model spectrum. The model spectrum was constructed from codeine (XV, veratrole chromophore) and X; the comparison is shown in Fig. 1.



XII, R = $COOCH_3$

XIII,

XIV, R = $COOC_2H_5$, COOH

XVI,

XVII, R = COOH
XVIII, R = $COOCH_3$, COOH
XIX, R = CH_2OH
XX, R = CH_3

XV

Anhydride XIII exhibits strong coloration both in the crystalline form (bright orange) and as a solution

(17) H. Rapoport, A. D. Batcho and J. E. Gordon, *J. Am. Chem. Soc.*, **80**, 5767 (1958).

(18) E. Sherman and A. P. Dunlop, *J. Org. Chem.*, **25**, 1309 (1960). We are indebted to Dr. Dunlop for a sample of XI.

(19) The model spectra in Fig. 1 and 2 were composed by determining the spectrum of each compound separately and summing the extinction coefficients of both every 5 mμ.

(20) J. Entel, C. H. Ruof and H. C. Howard, *J. Am. Chem. Soc.*, **73**, 4152 (1951).

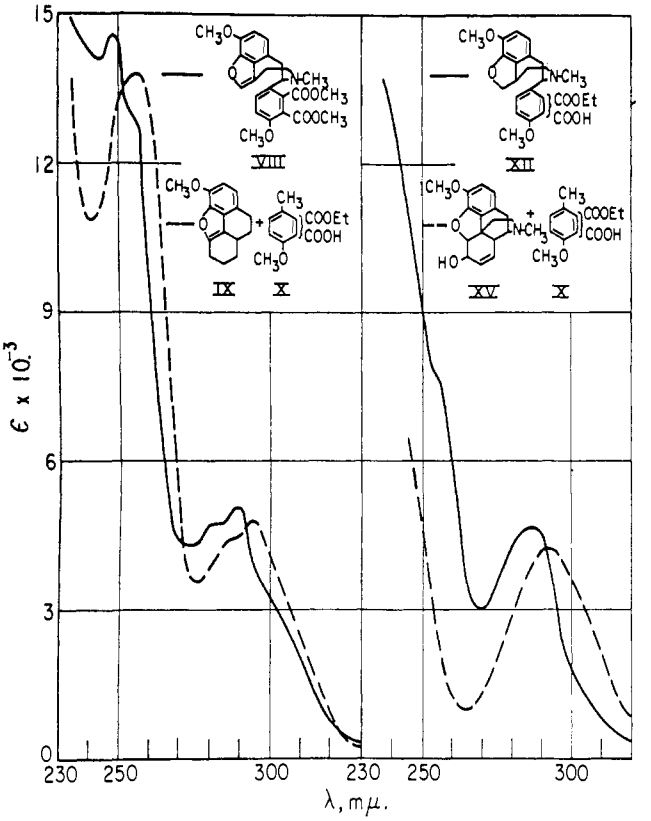


Fig. 1.—Ultraviolet absorption spectra of thebaine–DMA-thermal isomer (VIII) and thebaine–DMA-dihydrothermal isomer (XII, dimethyl ester or XIV, half-ethyl ester; spectra identical) compared with composite spectra.

(yellow-green) in aprotic solvents. Hydrolysis of the thermal isomer afforded the unsaturated anhydride XVI, of the same color as XIII both in the crystal and in solution. The absence of color in the thermal isomers XII, XIV, XVII, XVIII, XIX and XI demonstrates that the color must arise as the result of a complex between the cyclic anhydride and an electron-donating portion of the molecule.[21] That the complex is of intramolecular origin was established by showing that the absorption responsible for the color, *viz.*, weak ($\epsilon \sim 500$) absorption from 375 to 450 mμ, obeys Beer's law.

The ultraviolet spectrum of the thermal isomer anhydride XVI is shown in Fig. 2 with a model spectrum composed from IX and XI. As in the previously cited cases (Fig. 1), the model spectrum shows gross features markedly similar to those of the compound in question, yet there are persistent and significant variations which will be discussed later in relation to the stereochemistry of the thermal isomer.

Further evidence for the assignment of structure VIII to the thermal isomer was provided by its nuclear magnetic resonance spectrum (Fig. 3). The singlet at τ 2.59 is characteristic of a furan α-proton[22] and is atrributed to the benzofuran α-proton (C_6). A singlet at τ 3.38 accounts, in position and relative intensity, for the remaining two hydrogens of the benzofuran. The AB quartet centered at $\tau \sim 3.02$ ($J_{AB} \sim 8$ c.p.s.) is assigned to the protons of the methoxyphthalate ring, which carries the electron-withdrawing (deshielding) methoxycarbonyl groups. The signals from τ 6.02 to τ 6.17 are due to the molecule's four methoxyl

(21) (a) L. J. Andrews, *Chem. Rev.*, **54**, 713 (1954); (b) S. P. McGlynn, *ibid.*, **58**, 1113 (1958).

(22) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 64.

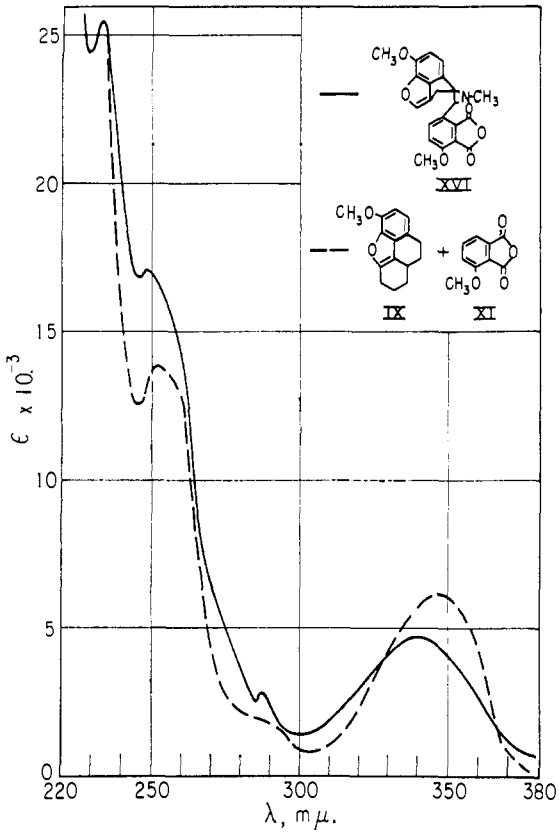


Fig. 2.—Ultraviolet absorption spectrum of thebaine–DMA-thermal isomer anhydride (XVI) compared with composite spectrum.

groups, and the singlet at τ 8.04 arises from the N-methyl protons.

While all the spectral evidence appeared to be consistent with VIII as the structure of the thermal isomer, degradative evidence was needed on which to rest the final proof. In seeking a route by which the thermal isomer might be degraded to recognizable fragments, the major obstacle was the apparent inertness of the tertiary nitrogen toward quaternization. Since it was considered that the C_2'-methoxycarbonyl group might possibly be implicated in this inertness, modification of the methoxycarbonyl groups was undertaken.

Lithium aluminum hydride reduction of the thermal isomer afforded the crystalline diol XIX, and quaternization of this diol proceeded rapidly at room temperature with nearly quantitative conversion to the methiodide. The diol was also found to be considerably more basic ($pK_a \sim 6.7$) than the thermal isomer ($pK_a \sim 3.3$). Since the envisaged degradation scheme involved the use of an oxidation step, attempts were made to convert the benzylic alcohol groups of the diol XIX to methyl groups (XX). Hydrogenolysis, acetylation, tosylation and conversion to chloride all failed to provide isolable derivatives; therefore, we proceeded directly with diol XIX.

Treatment of the methiodide of XIX with refluxing aqueous alkali gave the methine XXI in 49% yield. Ozonolysis of XXI at $-78°$ and subsequent treatment with peroxide afforded a neutral product, m.p. 153–155°, identified as 4-hydroxymethyl-5-methoxy-phthalide (XXII) in the manner described below.

Elemental analysis and molecular weight determination were in agreement with a molecular formula of $C_{10}H_{10}O_4$, containing one methoxyl group. The infrared spectrum displayed absorption at 3390 and at 1735 cm.$^{-1}$, indicating the presence of both hydroxyl

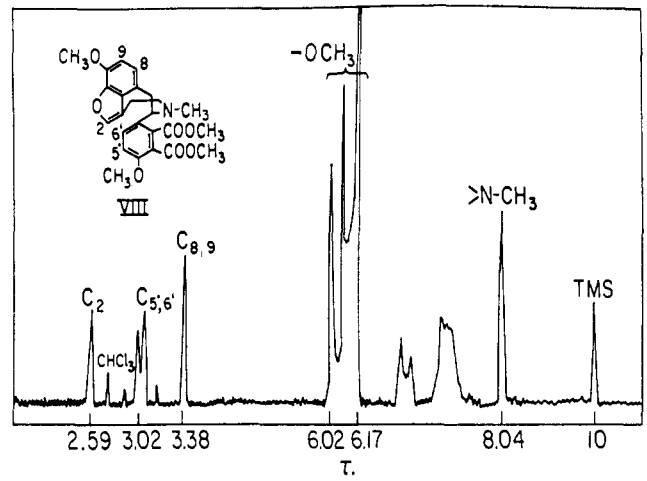
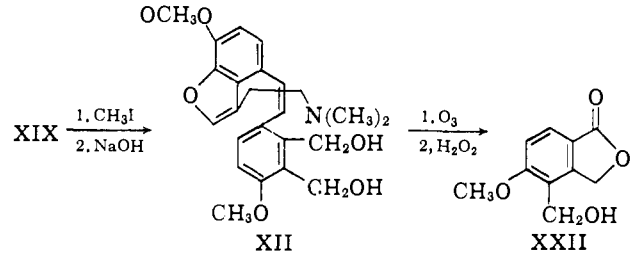


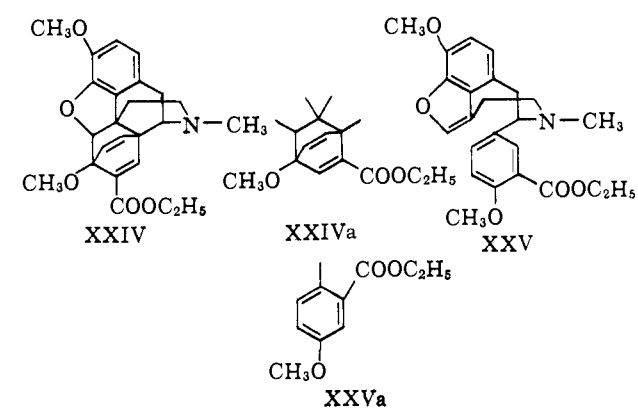
Fig. 3.—Nuclear magnetic resonance spectrum of the thebaine–DMA-thermal isomer (VIII) in deuteriochloroform.

and carbonyl moieties. A comparison of the ultraviolet spectrum of the ozonolysis–peroxide product with the spectra of the three anisic acids[23] demonstrated the *para* relationship of the methoxyl group with respect to the carbonyl-bearing carbon.



Conclusive evidence for XXII as the structure of the ozonolysis–peroxide product came from its nuclear magnetic resonance spectrum. A sharp singlet at τ 6.04 arises from the aromatic methoxyl (C_5), and two signals at τ 5.28 and τ 4.60 are assigned to the protons of the hydroxymethyl group at C_4 and the protons of the lactone ring (C_3), respectively. The AB quartet centered at $\tau \sim 2.53$ is attributable to the two aromatic protons (C_6, C_7); their coupling constant ($J_{AB} \sim 8$ c.p.s.) indicates that they must have an *ortho* relationship.[24] Thus, with the identification of the ozonolysis product as 4-hydroxymethyl-5-methoxyphthalide (XXII), the structure of the thermal isomer was definitively established as VIII.

During the course of our investigation of the thermal isomer VIII, we prepared the adduct of thebaine (I) and ethyl propiolate (EP) (XXIII). In contrast to the case of the DMA-adduct III, the EP-adduct XXIV

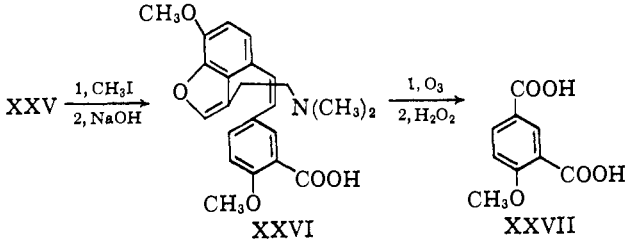


(23) C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951).
(24) Reference 22, p. 85.

proved quite difficult to obtain, and it was isolated only in poor yield. Large amounts of unreacted thebaine could be recovered from the reaction mixture, suggesting that the ethyl propiolate (XXIII) was unstable under the reaction conditions and underwent rapid polymerization. As with the DMA-adduct III, the weak basicity ($pK_a \sim 3.5$) of XXIV was used in separating it from unreacted thebaine.

Since the thermal instability of XXIV was found to be nearly identical to that of III, the EP-thermal isomer XXV was prepared by the same method used for the DMA-thermal isomer VIII. The EP-thermal isomer is (as is VIII) a colorless glass, forming a crystalline picrate. Its ultraviolet spectrum, as expected, is very similar to that of VIII, indicating the intrinsic similarity of the two chromophoric systems. The basicity of XXV, like that of VIII, is very weak ($pK_a \sim 3.3$), but quaternization with methyl iodide proceeded smoothly at room temperature to give an amorphous methiodide in quantitative yield.

Although the ultraviolet spectrum of EP-thermal isomer XXV satisfactorily demonstrated its relationship to DMA-thermal isomer VIII, the question as to the placement of the ethoxycarbonyl function remained. Electronic considerations of the Diels–Alder reaction[25] led us to favor XXIV, rather than XXIVa, for the structure of the EP-adduct, and thus XXV, instead of XXVa, as the structure of the EP-thermal isomer. In order to decide this point, the following degradative scheme, based on previous work with VIII, was undertaken.



On refluxing the methiodide of XXV with aqueous alkali, the methine XXVI was obtained in 62% yield. Ozonolysis of this provided an acidic product, $C_9H_8O_5$, identified as 4-methoxyisophthalic acid (XXVII) by virtue of its melting point and ultraviolet[26] and n.m.r. spectra. Hence, the ethoxycarbonyl moiety is located at C_{17} as in XXIV and C_3' as in XXV.

The unexpected ease with which both the DMA-adduct III and the EP-adduct XXIV underwent thermal isomerization led us to make a comparison of their thermal instability with that of dimethyl bicyclo-[2,2,2]octa-2,5-diene-2,3-dicarboxylate (VI). This was conveniently done using ultraviolet absorption to follow the extent of isomerization. At 100°, adduct III (and XXIV) had a half-life of about 150 minutes while the half-life of the bicycloöctadiene was over four times greater (620 minutes). Undoubtedly, this increased lability of adducts III and XXIV is the result of a number of factors, particularly the allylic and benzylic nature of the bonds which are broken and the stability of the new aromatic systems which are formed.[27]

As evidence was being gathered for the assignment of structures VIII and XXV to the DMA- and EP-thermal isomers, respectively, it became increasingly apparent that, in order to account for some anomalous properties of the thermal isomer system, a consideration of its stereochemistry would be warranted. In particular, an explanation was sought for three observations: (1) the rather large differences between the ultraviolet spectra of these compounds and their respective model spectra (Fig. 1, 2); (2) the strong coloration of anhydrides XIII and XVI, both in the crystal and in solution, originating (see above) from an intramolecular complex; (3) the relationships among VIII, XIX and XXV with regard to both their basicity and their quaternization with methyl iodide.

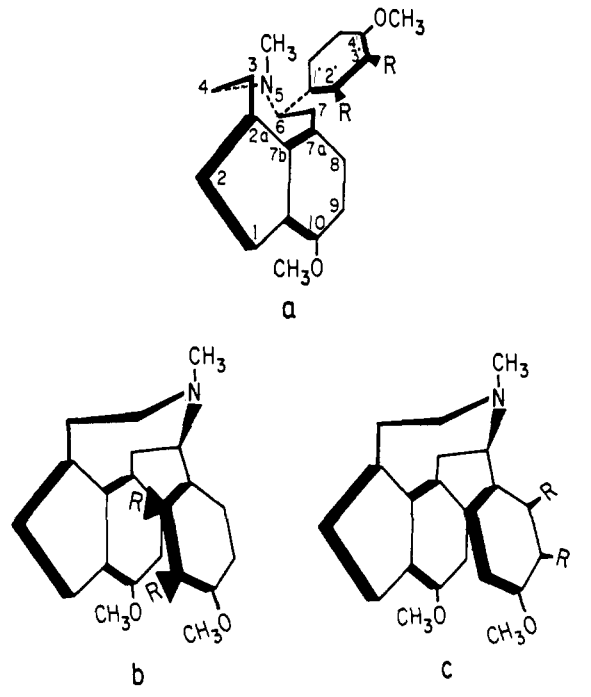


Fig. 4.—Conformations of the thebaine–DMA-thermal isomer system.

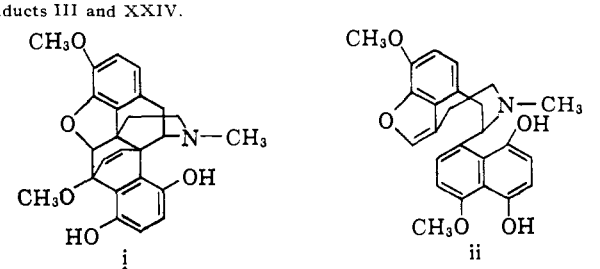
Examination of models suggests that there are only two stable conformations available to the eight-membered ring of the thermal isomer system (Fig. 4)[28]; these we shall designate as "open" (a) and "closed" (b, c). This holds true as a result of the planar configuration imposed on five (C_7, C_{7a}, C_{7b}, C_{2a} and C_3) of the eight members of the methoxybenzofuran portion of the molecule. Moreover, models indicate that any interchange between the two conformations would be attended by severe bond distortion and steric crowding in the transition state, thus relegating such an interchange highly improbable at ordinary temperatures.

In comparing the open and closed conformations, it may be seen that while the two chromophores are widely

(25) M. C. Kloetzel in "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 9.

(26) S. E. Hunt, J. I. Jones and A. S. Lindsey, *J. Chem. Soc.*, 3099 (1956).

(27) Since thebaine-hydroquinone (i), which appeared to have the necessary prerequisites for a similar thermal isomerization, had been prepared[2] at 140°, the possibility arose that it might be the thermally isomerized product ii. We have found that thebaine-hydroquinone is unchanged in refluxing di-*n*-butyl ether (b.p. 141°) for 48 hours. That i is its structure beyond question is demonstrated by its n.m.r. spectrum in $CDCl_3$ in which the split absorption at τ 5.32 is assigned to the C_8–H, coupled ($J \sim 2$ c.p.s.) with the vinyl proton at C_7. Such an absorption is typical of the thebaine adducts III and XXIV.



Thus, an electron-withdrawing group at $C_{17,18}$ may be necessary to facilitate the thermal isomerization.

(28) It is to be noted that the configuration at C_9 in the original adduct (III or XXIV) is retained at C_6 in the thermal isomer since C_9 plays no part in the isomerization.

separated in the open (a) form, they are forced into rather close proximity in the closed (b, c) form. Accordingly, free rotation of the benzene ring is possible in the open conformation, while it is severely restricted in the closed conformation, allowing the existence of two rotamers, b and c.

Accepting, then, the improbability of interconversion between the open and closed conformations, the problem becomes one of distinguishing the conformation represented in the thermal isomer system. An approach to this problem is through a consideration of the stereochemical aspects of the isomerization itself. It can be seen that the first direct stereochemical consequence of the isomerization is the assumption of the closed conformation (b, c). Moreover, since in the adducts III or XXIV, the C_{17}–C_{18} bridge is in a *cis* relationship to the ethanamine bridge,[29] the rotamer resulting from the isomerization must be represented as b.

The fact that the ultraviolet spectra of the thermal isomer systems deviate from their model spectra (Fig. 1 and 2) we feel to be in accord with the closed conformation (b, c) rather than the open (a). Direct mixing of the model chromophores, as an alternative to summation of the separate spectra, does not alter the model spectrum, indicating the intramolecular origin of the deviations. An auxochromic effect involving the nitrogen is ruled out by the virtual identity of the spectra of the free bases (VIII, XIX and XXV) and their corresponding methiodides. Similar spectral perturbations of intramolecular origin have been observed in certain paracyclophanes, some of which are attributed to a π–π interaction between the two chromophores in the macrocycle.[30] In the case of the paracyclophanes, the macrocyclic ring holds the aromatic systems close enough for π–π interaction to occur; in the present case, the "locked" nature of the closed conformation would accomplish this result. In the open conformation, of course, intramolecular π–π interaction would be impossible.

Since the coloration of anhydrides XIII and XVI had been shown to arise from an intramolecular complex, the closed conformation (b, c) seems to provide a particularly attractive explanation of this phenomenon; the aromatic anhydride being the electron acceptor and the methoxybenzofuran (XVI) or the veratrole (XIII) being the electron donors.[21a] Caution must be used in applying this interpretation, however, for when anhydride XVI in tetrahydrofuran is treated with *p*-toluenesulfonic acid, the solution is decolorized and a colorless salt precipitates. This could mean either that protonation of the nitrogen perturbs the complex enough to cause the disappearance of color, or that the nitrogen itself is interacting with the anhydride as would be possible in rotamer b.

The apparent influence of the C_2'-methoxycarbonyl group on the difficult quaternization of the DMA-thermal isomer VIII is best explained in terms of rotamer b in which the C_2'-substituent is held near the tertiary nitrogen. Rotamer c, on the other hand, would be expected to behave very much as EP-thermal isomer XXV (C_2'-H), the quaternization of which presents no difficulties. Both thermal isomers VIII and XXV are weak bases ($pK_a \sim 3.3$), demonstrating that protonation is independent of the size of the C_2'-substituent. Since the nitrogen is probably not involved in an electronic interaction in these compounds (see above), the cause of their weak basicity is perhaps best explained by a more general hindrance within the molecule to the formation of a solvent shell needed to stabilize the protonated nitrogen. The increased basicity of diol XIX ($pK_a \sim 6.7$) presents an interesting example of what is probably hydrogen-bond stabilization of the protonated nitrogen[31] by the C_2'-hydroxymethyl function.

(29) The stereochemistry of these thebaine-adducts will be discussed in detail in a forthcoming publication.

(30) D. J. Cram, N. L. Allinger and H. Steinberg, *J. Am. Chem. Soc.*, **76**, 6132 (1954), and references therein.

Experimental[32]

Thebaine–Dimethyl Acetylenedicarboxylate (DMA) Adduct; 17,18-Bis-(methoxycarbonyl)-6,14-ethenocodeine Methyl Ether (III).—A solution of 8.8 g. (28 mmoles) of thebaine (I) and 4.0 g. (28 mmoles) of dimethyl acetylenedicarboxylate (II) in 75 ml. of dry benzene was stirred at 50° for 1 hour. The tan solution was cooled to room temperature and allowed to stand for 24 hours, during which time the adduct separated as stout prisms. Concentration of the reaction mixture *in vacuo* to 25 ml. provided 11.5 g. (90%) of crystals, m.p. 138–140°. Further purification was accomplished by dissolving this material in benzene (room temp.), washing the solution with 0.3 *M* phosphate, *p*H 3.0, and evaporating the dried benzene solution *in vacuo* at 25° until crystallization began. Cooling afforded pure adduct III as colorless prisms, m.p. 141–142° (heating rate, ~ 5° per min.), λ_{max} 255–270 mμ (ε 3700); $\nu_{max}^{CHCl_3}$ 1720(s), 1730(m) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{27}NO_7$: C, 66.2; H, 6.0; OCH_3, 27.4. Found: C, 66.4; H, 5.9; OCH_3, 27.3.

Thebaine–DMA Dihydroadduct; 17,18-Bis-(methoxycarbonyl)-6,14-ethenodihydrocodeine Methyl Ether (IV).—Hydrogenation of 455 mg. (1.0 mmole) of adduct III in 10 ml. of glacial acetic acid with 230 mg. of 10% palladized carbon as catalyst proceeded at 25° with the absorption of 100 mole % of hydrogen in 30 minutes and then slowed considerably. After 60 minutes (124 mole % absorption), the catalyst was removed by filtration, the filtrate was added to 100 ml. of distilled water, and the solution was alkalized (*p*H 8) with satd. aqueous sodium carbonate. The resulting suspension was extracted with methylene chloride (3 × 50 ml.), and the combined, dried, organic phase was evaporated *in vacuo*, leaving 455 mg. of residue, m.p. 160–175°. Recrystallization from absolute methanol gave 235 mg. (49%) of dihydroadduct IV as colorless needles, m.p. 196–197°, λ_{max} 278 mμ (ε 2620); ν_{max}^{KBr} 1720(s) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.9; H, 6.4; OCH_3, 27.2. Found: C, 65.8; H, 6.4; OCH_3, 27.1.

Thebaine–DMA Thermal Isomer; 6-[2′,3′-Bis-(methoxycarbonyl)-4′-methoxyphenyl]-10-methoxy-5-methyl-3,4,6,7-tetrahydrofuro-5H-[4,3,2-fg] [3]benzazocine (VIII).—To 50 ml. of anhydrous di-*n*-butyl ether (b.p. 141°) was added 5.2 g. (11.4 mmoles) of adduct III (m.p. 138–140°). The mixture was heated to reflux, whereupon the adduct went into solution. After a reflux period of 10 minutes, the solvent was removed under reduced pressure and the tan residue was dissolved in benzene (100 ml.) and extracted with 0.5 *M* phosphoric acid (4 × 25 ml.). After a benzene wash (2 × 25 ml.), the combined acidic extracts were neutralized (*p*H 7) with saturated aqueous sodium carbonate. The suspension was extracted with methylene chloride (4 × 25 ml.) and the combined organic extracts were washed with 25 ml. of 0.3 *M* (*p*H 3.0) phosphate buffer, dried and evaporated to provide 4.5 g. (87%) of thermal isomer VIII as a colorless glass. An analytical sample was prepared by sublimation at 135° (10 μ); λ_{max} 248 mμ (ε 14,500), 255sh. (12,900), 282sh. (4750), 289 (5050); $\nu_{max}^{CHCl_3}$ 1728(s), 1733(sh, m) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{27}NO_7$: C, 66.2; H, 6.0; OCH_3, 27.4. Found: C, 66.1; H, 6.0; OCH_3, 27.0.

The picrate of VIII crystallized when 450 mg. (0.99 mmole) of the base in 10 ml. of hot abs. ethanol was added to 25 ml. of a saturated solution of picric acid in abs. ethanol. Recrystallization from abs. ethanol–acetone yielded 625 mg. (92%) of thermal isomer picrate as yellow needles, m.p. 206–208° dec.

Anal. Calcd. for $C_{25}H_{27}NO_7 \cdot C_6H_3N_3O_7$: C, 54.5; H, 4.4; N, 7.2. Found: C, 54.2; H, 4.4; N, 7.9.

The methiodide of VIII was prepared by heating a solution of 200 mg. (0.44 mmole) of the base and 126 mg. (1.0 mmole) of freshly distilled dimethyl sulfate in 12 ml. of methanol under reflux for 4 hours. Evaporation of the solvent left a yellow oil which was partially dissolved in distilled water. After the aqueous solution was washed with benzene to remove a water-insoluble gum, satd. aqueous potassium iodide was added to precipitate the methiodide. The precipitate was redissolved in hot water and the process repeated; then the thermal isomer methi-

(31) H. Rapoport and S. Masamune, *ibid.*, **77**, 4330 (1955).

(32) All melting points are corrected, and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Unless otherwise specified, all reactions were carried out in a nitrogen atmosphere. Ultraviolet spectra were taken in ethanol unless otherwise specified, and nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer, with tetramethylsilane (TMS) as internal standard.

odide slowly crystallized from a cooled aqueous solution as prisms, m.p. 166–168°; λ_{max} 248 mμ (ε 16,500), 255 (sh.) (14,600), 281(sh.) (4,600), 289 (5,250); ν_{max}^{KBr} 1722(s), 1738(s) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{30}NO_7I \cdot {}^1/_2H_2O$: C, 51.7; H, 5.2; I, 21.0. Found: C, 51.5; H, 5.1; I, 21.0.

Thebaine–DMA Dihydrothermal Isomer; 6-[2′,3′-Bis-(methoxycarbonyl)-4′-methoxyphenyl]-10-methoxy-5-methyl-2-2a,3,4,6,7-hexahydrofuro-5H-[4,3,2-fg][3]benzazocine (XII).—A solution of 450 mg. (0.99 mmole) of thermal isomer VIII in 10 ml. of glacial acetic acid was hydrogenated (25°) in the presence of 230 mg. of 10% palladized carbon. After the absorption of 88 mole % of hydrogen in 4.5 hours, the reaction slowed and was allowed to proceed until 120 mole % had been absorbed (10 hr.). Using the previously described isolation procedure, 350 mg. of crude dihydrothermal isomer XII was obtained as a colorless glass, λ_{max} 287 mμ.

Thebaine–DMA Dihydrothermal Isomer Anhydride; 6-(4′-Methoxyphenyl)-10-methoxy-5-methyl-2,2a,3,4,6,7-hexahydrofuro-3H-[4,3,2-fg] [3]benzazocine-2′,3′-dicarboxylic Anhydride (XIII).—A solution of 330 mg. of crude dihydrothermal isomer XII in 30 ml. of 5% ethanolic potassium hydroxide was heated under reflux for 12 hours. The ethanol was removed under reduced pressure and the residue dissolved in 200 ml. of distilled water. After acidification (*p*H 2.5) with phosphoric acid, the aqueous phase was continuously extracted with methylene chloride for 48 hours. Removal of the solvent *in vacuo* left a yellow glass, which was dissolved in hot benzene (25 ml.) and the benzene was evaporated to dryness on a steam-bath to remove all traces of water. In this manner, an orange, semicrystalline residue (195 mg.) was obtained which, when recrystallized from benzene–hexane to constant melting point, yielded 110 mg. of anhydride XIII as deep orange needles, m.p. 222–223°; λ_{max} 287 mμ (ε 4700); ν_{max}^{KBr} 1772(s), 1832 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{23}NO_6$: C, 67.5; H, 5.7; OCH_3, 15.2. Found: C, 68.2; H, 5.8; OCH_3, 15.3.

Thebaine-DMA thermal isomer anhydride; 6(4′-methoxyphenyl)-10-methoxy-5-methyl-3,4,6,7-tetrahydrofuro-5H-[4,3,2-fg][3]benzazocine-2′,3′-dicarboxylic anhydride (XVI) was prepared using the same procedure employed for XIII above. From 6 g. (13.2 mmoles) of thermal isomer VIII there was obtained 3.5 g. (65%) of thermal isomer anhydride XVI as orange needles after recrystallization from benzene; m.p. 236–238°; λ_{max} 248 mμ (ε 14,500), 255(sh) (12,900), 282(sh) (4800), 289 (5000); $\lambda_{max}^{CH_3CN}$ 233 mμ (ε 25,400), 248 (17,200), 287 (2,750), 337 (4,700); ν_{max}^{KBr} 1765(s), 1840(w) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{21}NO_6$: C, 67.8; H, 5.2; OCH_3, 15.2. Found: C, 68.2; H, 5.1; OCH_3, 14.8.

The half-methyl ester XVIII, a colorless glass, was obtained by warming anhydride XVI with methanol and removing the solvent *in vacuo*. The glass fused to a yellow melt at *ca.* 120°, which then crystallized as orange needles of anhydride XVI, m.p. 236–238°.

The diacid XVII was prepared by dissolving anhydride XVI in hot water; upon cooling, the diacid crystallized as colorless needles, m.p. 127–128°; $\lambda_{max}^{H_2O}$ 248 mμ (ε 16,500), 256 (14,400), 280 (3,460), 287 (3,140). As in the case of half-methyl ester XVIII, the diacid formed a yellow melt which spontaneously crystallized to orange needles of anhydride XVI, m.p. 236–238°.

Anal. Calcd. for $C_{23}H_{23}NO_7 \cdot 2H_2O$: C, 59.9; H, 5.9; OCH_3, 13.4. Found: C, 60.2; H, 5.9; OCH_3, 13.4.

Thebaine–DMA Thermal Isomer Diol; 6-[2′,3′-Bis-(hydroxymethyl)-4′-methoxyphenyl]-10-methoxy-5-methyl-3,4,6,7-tetrahydrofuro-5H-[4,3,2-fg][3]benzazocine (XIX).—To a solution of 2.7 g. (5.95 mmoles) of thermal isomer VIII in 300 ml. of anhydrous ether was added 9.0 ml. (18.9 mmoles) of 2.1 *M* ethereal lithium aluminum hydride, and the resulting white suspension was stirred under reflux for 6 hours. After excess hydride was decomposed with ethyl acetate, the mixture was shaken with 100 ml. of 30% aqueous sodium hydroxide. The aqueous phase was extracted with methylene chloride (3 × 50 ml.), the combined organic phase was dried over magnesium sulfate, and solvent was removed *in vacuo* to give 2.37 g. of colorless glass. Crystallization was initiated by trituration with a small amount of benzene, and the white solid was recrystallized from benzene–hexane as colorless prisms (2.05 g., 86%), m.p. 160–162°; λ_{max} 248 mμ (ε 13,300), 256 (12,400), 281 (4,150), 288 (3,850); $\nu_{max}^{CHCl_3}$ 3380 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}NO_5$: C, 69.5; H, 6.8; OCH_3, 15.6. Found: C, 69.8; H, 7.0; OCH_3, 16.5.

The methiodide of XIX precipitated slowly when 1 g. (2.52 mmoles) of the base in 20 ml. of benzene was treated with 10 ml. of methyl iodide and allowed to stand at 25° for 4 days. Recrystallization from methanol–acetone afforded 1.27 g. (93%) of the methiodide as colorless rods, m.p. 153–154° dec.

Anal. Calcd. for $C_{24}H_{30}NO_5I$: C, 53.4; H, 5.6; I, 23.5. Found: C, 53.4; H, 5.7; I, 23.2.

Thebaine–DMA Thermal Isomer Diol Methine (XXI).—To a solution of 1.37 g. (2.54 mmoles) of the methiodide of diol XIX in 5 ml. of hot methanol was added 200 ml. of 20% aqueous sodium hydroxide, and the turbid solution was heated under reflux for 3 hours. On cooling to room temperature, a white precipitate (880 mg.) separated. After being washed with distilled water (50 ml.), the precipitate was recrystallized from 95% ethanol, providing 510 mg. (49%) of methine XXI as colorless, silky needles, m.p. 163–164° dec.; λ_{max} 256(sh) mμ, (ε 10,500), 308 (16,000).

Anal. Calcd. for $C_{24}H_{29}NO_5$: C, 70.0; H, 7.1; N, 3.4. Found: C, 70.2; H, 7.3; N, 3.2.

Ozonolysis of Methine XXI; 4-Hydroxymethyl-5-methoxyphthalide (XXII).—A solution of 360 mg. (0.87 mmole) of the methine XXI in 100 ml. of 0.02 *M* methanolic sulfuric acid was ozonized at −78° with a stream of oxygen containing ozone. When 97 mole % of ozone had been absorbed, 5 ml. of 30% hydrogen peroxide was added and the solution warmed gradually to reflux on a steam-bath. The course of the peroxide oxidation was followed by observing the appearance of the absorption maximum at 257 mμ. When this reached a constant value after 50 minutes, the reaction mixture was concentrated *in vacuo* to 25 ml. and diluted with 225 ml. of distilled water. Excess oxidant was destroyed with sodium thiosulfate and the solution was acidified to *p*H 1–2 with sulfuric acid and continuously extracted for 24 hours with methylene chloride. The organic phase (100 ml.) was washed with 10% aqueous sodium bicarbonate (2 × 25 ml.), dried, and evaporated to dryness. The amorphous residue was sublimed at 110° (25 μ) and recrystallized from benzene–hexane to provide 45 mg. (26%) of 4-hydroxymethyl-5-methoxyphthalide (XXII) as colorless rods, m.p. 153–155°; λ_{max} 257 mμ (ε 14,000); ν_{max}^{KBr} 3390(s), 1735(s) cm.$^{-1}$; n.m.r. absorption in liq. SO_2: OCH_3, τ 6.04; C_8–H_2, 5.28; C_3–H_2, 4.60; C_6–H, 2.85(d); C_7–H, 2.24 (d).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.8; H, 5.2; OCH_3, 16.0. Found: C, 61.8; H, 5.4; OCH_3, 16.2.

Thebaine–Ethyl Propiolate (EP) Adduct; 17-Ethoxycarbonyl-6,14-ethenocodeine Methyl Ether (XXIV).—A solution of 22 g. (70 mmoles) of thebaine (I) and 10.8 g. (110 mmoles) of ethyl propiolate (XXIII) in 275 ml. of dry benzene was stirred for 8 hours at 50°. The reaction mixture was cooled to 25° and extracted with 0.5 *M* phosphoric acid (3 × 100 ml.). The combined aqueous extracts were washed with benzene (2 × 50 ml.) and neutralized (*p*H 7) with satd. aqueous sodium carbonate, and the suspension was extracted with methylene chloride (6 × 50 ml.). The semicrystalline residue (13.6 g.) obtained on removal of solvent was triturated with ethanol and the solid (9.3 g., m.p. 140–180°) collected. This was dissolved in 200 ml. of benzene and washed with 0.6 *M* (*p*H 3.0) phosphate buffer (4 × 50 ml.). Evaporation of the benzene gave 1.7 g. of a white solid which was crystallized from ethanol to give adduct XXIV as colorless needles, m.p. 130–131° (heating rate, 5° per min.); λ_{max} 255–290 (sh) mμ, (ϵ_{280} 3300); $\nu_{max}^{CHCl_3}$ 1709(s) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{27}NO_5$: C, 70.4; H, 6.6. Found: C, 70.5; H, 6.9.

Thebaine–EP thermal isomer; 6-[2′-(ethoxycarbonyl)-4′-methoxyphenyl]-10-methoxy-5-methyl-3,4,6,7-tetrahydrofuro-5H-[4,3,2-fg][3]benzazocine (XXV) was prepared in the same manner as the thebaine–DMA thermal isomer VIII above. Thus, 115 mg. (0.28 mmole) of adduct XXIV afforded 103 mg. (90%) of thermal isomer XXV as a colorless glass, which was sublimed at 130° (20 μ); λ_{max} 238(sh) mμ (ε 17,700), 255(sh) (12,900), 280 (3,970), 289 (4,400); $\nu_{max}^{CHCl_3}$ 1710(s) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{27}NO_5$: C, 70.4; H, 6.6. Found: C, 70.5; H, 7.0.

The picrate of XXV was obtained by adding 1.0 ml. of a saturated solution of picric acid in abs. ethanol to a hot solution of 25 mg. of XXV in abs. ethanol. The precipitate was twice crystallized from abs. ethanol to give fine, yellow needles, m.p. 205–207°.

Anal. Calcd. for $C_{24}H_{27}NO_5 \cdot C_6H_3N_3O_7$: C, 56.4; H, 4.7; N, 8.8. Found: C, 56.5; H, 4.6; N, 8.9.

Thebaine-EP Thermal Isomer Methine (XXVI).—The methiodide of thermal isomer XXV was prepared from 500 mg. (1.22 mmoles) of the base and 10 ml. of methyl iodide in benzene (15 ml.) at 25° for 48 hours. The amorphous methiodide (650 mg., 96%) was reprecipitated from methanol with ether. To a solution of 500 mg. (*ca.* 0.9 mmole) of this methiodide of XXV in 2 ml. of methanol was added 30 ml. of distilled water. The turbid solution was warmed on a steam-bath and 20 ml. of 40% aqueous sodium hydroxide was added. After a reflux period of 1 hour, the clear solution was cooled slowly to 0° and the colorless needles of the sodium salt were collected. The needles were dissolved in 50 ml. of distilled water, and the solution acidified (*p*H 5) with phosphoric acid. The resulting white precipitate was collected at 0° and crystallized from water to give needles of the trihydrate of methine XXVI (250 mg., *ca.* 60%), m.p. 232–235° dec.; λ_{max} 213 mμ (ε 25,000), 253(sh) (11,500), 295 (9,700).

Anal. Calcd. for $C_{23}H_{25}NO_5 \cdot 3H_2O$: C, 61.4; H, 6.9. Found: C, 61.8; H, 7.0.

Ozonolysis of Methine XXVI; 4-Methoxyisophthalic Acid (XXVII).—A solution of 200 mg. (0.45 mmole) of methine XXVI in 150 ml. of 0.02 *M* methanolic sulfuric acid was ozonized at −78° as described for methine XXI. Absorption of ozone ceased after 110 mole % was consumed (60 min.). The reaction mixture was boiled with 5 ml. of 30% hydrogen peroxide for 6 hours and evaporated to dryness *in vacuo*, and the oily residue was dissolved in 200 ml. of distilled water. After acidifying (*p*H 1) the solution with sulfuric acid, it was continuously extracted (36 hr.) with methylene chloride. The residue obtained from the methylene chloride was hydrolyzed with 5% methanolic potassium hydroxide (30 min., reflux) and the residue remaining on removal of solvent was dissolved in 25 ml. of distilled water. Acidification (congo red) with phosphoric acid and extraction with methylene chloride (4 × 25 ml.) provided 110 mg. of material which was fractionally sublimed. At 100° (50 μ), 20 mg. of a yellow gum was obtained and was discarded. Further sublimation at 140° (50 μ) gave 60 mg. of a powdery sublimate which was crystallized from water, affording 30 mg. (34%) of 4-methoxyisophthalic acid (XXVII) as colorless prisms, m.p. 274–275°; λ_{max} 217 mμ (ε 25,500), 253 (13,600), 293 (2,380) [reported[26] m.p. 276°; λ_{max} 217.6 mμ, (ε 39,000), 253 (17,000), 293 (3,240)]; ν_{max}^{KBr} 1685(s), 1722(sh) (m) cm.$^{-1}$; n.m.r. absorption in CF_3COOH: OCH_3, τ 5.75; C_5–H, 2.65 (d); C_6–H, 1.49 (m); C_2–H, 1.02 (d).

Dimethyl Bicyclo[2,2,2]octa-2,5-diene-2,3-dicarboxylate (VI).—A mixture of equal parts by weight of 1,3-cyclohexadiene and dimethyl acetylenedicarboxylate was allowed to stand at room temperature for 48 hr. The reaction mixture then was evaporated at room temperature and 20 mm. pressure, and a 1-g. aliquot of the residue was applied to an alumina (30 g., neutral) column in hexane–benzene (1:1). Material eluted with hexane–benzene was distilled at 50° (50 μ) to give the pure adduct, λ_{max} 218 (ε 5100); $\nu_{max}^{CHCl_3}$ 1710(s), 1725(sh) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.3; OCH_3, 27.9. Found: C, 64.7; H, 6.2; OCH_3, 27.6.

Determination of pK_a's.—A suitable amount (10–20 mg.) of the base to be studied was dissolved in 25.0 ml. of benzene previously saturated with the appropriate buffer solution. This solution was then equilibrated with 25.0 ml. of benzene-saturated 0.10 *M* phosphate buffer, which had been adjusted (±0.01 *p*H unit) to the desired *p*H. After allowing 10–15 min. for phase separation, an aliquot (15.0 ml.) was taken from the buffer phase and concentrated *in vacuo* (40°) to *ca.* 5 ml. in order to remove all traces of benzene. The concentrate was diluted to 10.0 ml. with distilled water, and the concentration of the base (ammonium form) determined spectrophotometrically in the ultraviolet.[33] As a check, a second equilibration was carried out with the original benzene solution using fresh buffer.

Each compound was equilibrated at two values of *p*H and the apparent partition coefficient (P') for each *p*H was used to determine K_a by the equations

$$\frac{P}{P'} = 1 + \frac{(H^+)}{K_a'}; \quad K_a' = \frac{P_1'(H_1^+) - P_2'(H_2^+)}{P_2' - P_1'}$$

The precision was about ±0.2 pK_a' unit.

(33) Since most of the bases studied showed substantial spectral shifts in acid, it was necessary first to determine the spectrum of each base at the appropriate *p*H. This was done by diluting 1.0 ml. of an ethanolic solution of the base to 10.0 ml. with the buffer solution used for the equilibration.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

Inhibition and Quenching of the Light-induced Reductions of Benzophenone to Benzpinacol and to Benzhydrol[1]

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Light-induced reductions of benzophenone by 2-propanol to benzpinacol and, in the presence of sodium 2-propoxide, to benzhydrol have been studied and effects of 2-mercaptomesitylene, mesityl disulfide and naphthalene have been examined. Rates of formation of benzpinacol and of benzhydrol are nearly equal in the absence of retarders, rates of reduction of benzophenone differing by a factor of about 2. The mercaptan and disulfide retard formation of benzhydrol less efficiently than they retard formation of benzpinacol. It is concluded that radical I, $(C_6H_5)_2\dot{C}OH$, is formed during inhibition of formation of benzpinacol by sulfur compounds, and that benzpinacol is not an intermediate in the formation of benzhydrol, the latter resulting from disproportionations involving radical ion Ia, $(C_6H_5)_2\dot{C}{-}O^-$. Naphthalene is similarly effective in retarding formation of benzpinacol and benzhydrol, but is much less effective than the sulfur compounds in retarding formation of benzpinacol. Naphthalene must quench short-lived excited benzophenone, while the sulfur compounds react with longer-lived radicals. The reactions show linear dependence of $1/\Phi$ on concentration of quencher or retarder.

We have recently reported[2] that the aromatic mercaptans, thiophenol and 2-mercaptomesitylene, and their disulfides, when present in low concentration, 10^{-3}–10^{-2} *M*, are effective retarders and inhibitors of the photochemical reduction of benzophenone to benzpinacol by secondary alcohols. Similar effectiveness is shown by a thiol and its disulfide. They undergo chemical reaction and the same equilibrium mixture of the two results during the inhibition when either is used initially. When these reactions are studied in optically active 2-octanol, racemization of remaining octanol does not occur during formation of benzpinacol in the absence of inhibitor, nor does ultraviolet irradiation of the alcohol with disulfide lead to racemization; but racemization does occur when the photoreduction of benzophenone is inhibited by the mercaptan–disulfide, and at a rate comparable to the rate of photoöxidation of the alcohol by the ketone during the uninhibited reaction. We have concluded that in this situation the normal excitation of benzophenone and the abstraction of hydrogen occur, leading to the benzophenone and alcohol derived radicals I and II.

$$(C_6H_5)_2C{=}\overset{*}{O} + R_2CHOH \xrightarrow{k_1} \underset{\text{I}}{(C_6H_5)_2\dot{C}{-}OH} + \underset{\text{II}}{R_2\dot{C}{-}OH} \quad (1)$$

Normally radical II reacts with benzophenone, forming additional I and ketone, and radicals I dimerize.[3]

$$II + (C_6H_5)_2C{=}O \xrightarrow{k_2} R_2C{=}O + I \quad (2)$$

$$2I \xrightarrow{k_3} (C_6H_5)_2C(OH){-}C(OH)(C_6H_5)_2 \quad (3)$$

We have proposed that in the presence of mercaptan and disulfide other reactions compete with reactions 2 and 3. Radical I is reconverted to benzophenone by thiyl radical or disulfide, and radical II is converted to starting alcohol (racemic) by mercaptan.[4]

$$(C_6H_5)_2\dot{C}{-}OH + AS\cdot \xrightarrow{k_4} (C_6H_5)_2C{=}O + ASH \quad (4)$$

$$R_2\dot{C}{-}OH + ASH \xrightarrow{k_5} R_2CHOH + AS\cdot \quad (5)$$

(1) We are pleased to acknowledge generous support of this work by the U. S. Atomic Energy Commission, AT(30-1)-2499.

(2) S. G. Cohen, S. Orman and D. A. Laufer, *J. Am. Chem. Soc.*, **84**, 3905 (1962).

(3) J. N. Pitts, Jr., R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald and R. B. Martin, *ibid.*, **81**, 1068 (1959).

(4) Additional evidence for the latter, which will be reported in a later publication, is found in transfer of deuterium from oxygen to carbon when the inhibition is studied in O-D labeled 2-propanol.