which 500 mg. of a clear mobile oil was obtained; the rest of the material did not distil and appeared polymeric. The infrared spectrum of the distillate showed bands at 3250, 3050 and 1660 cm.$^{-1}$. The ultraviolet spectrum showed a maximum at 225–226 mμ, ϵ 6.1 × 10^3.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.62; H, 7.99. Found: C, 66.45; H, 8.17.

A *p*-nitrobenzoate derivative, after recrystallization from chloroform–hexane, gave crystals, m.p. 99–100°. The n.m.r. spectrum of the *p*-nitrobenzoate showed four hydrogens at 1.78 τ (aromatic), one hydrogen at 3.0 τ (multiplet), one hydrogen at 5.9 τ (doublet), two hydrogens at 5.63 τ (doublet), and five hydrogens in the region 7.0–8.0 τ.

Anal. Calcd. for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.35; H, 4.82; N, 5.10.

A 2,4-dinitrophenylhydrazone, m.p. 134–140°, was prepared.[10] After crystallization from methanol, a red solid, m.p. 146–148°, was obtained; its melting point corresponds to that reported for the 2,4-dinitrophenylhydrazone of 5-hydroxymethylcyclohex-2-enone, m.p. 147–148.5°.[10]

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER, ROCHESTER, N. Y.]

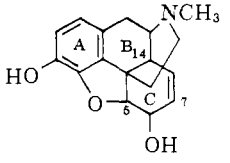
The Closure of the Oxide Bridge in the Morphine Series[1]

BY MARSHALL GATES AND MARVIN S. SHEPARD[2]

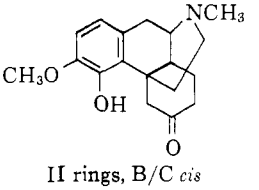
RECEIVED JUNE 13, 1962

The dibromination of *cis* and *trans*-dihydrothebainone and of *cis*-dihydrocodeinone has been shown in all probability to yield the corresponding 1,7-dibromo derivatives. The tribromination of *cis*-dihydrothebainone leads not to *cis* 1,5,7 or 1,7,7-tribromodihydrothebainone but directly to *cis*-1,7-dibromodihydrocodeinone. The role of these substances in closure of the oxide bridge from C_4 to C_5 and in other reactions is discussed.

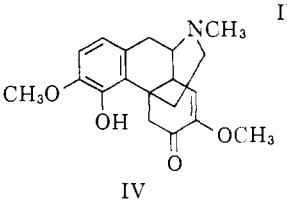
The oxide bridge which characterizes morphine (I) and related alkaloids of opium is open in a number of degradation products of these alkaloids, *e.g.*, *cis*- and *trans*[3]-dihydrothebainone (II and III), and is missing in the structurally related alkaloids sinomenine[4] (IV) and hasubanonine.



I



II rings, B/C *cis*
III rings, B/C *trans*

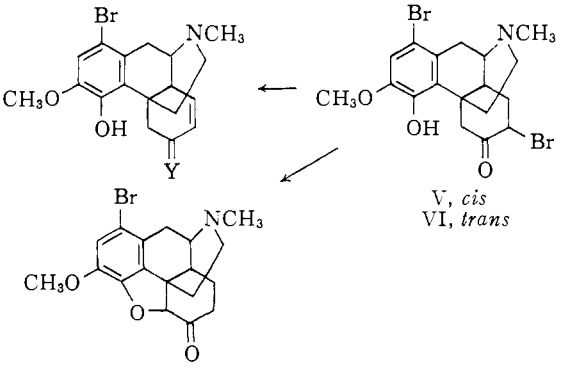


IV

The reclosure of this oxide bridge has assumed importance in several synthetic efforts.[5,6] It was first accomplished by Schöpf[7,8] by dibromination of II followed by treatment with alkali, and proceeds smoothly in high yield with *cis*-dihydrothebainone and with other substances with the natural configuration at C-14 (rings B/C *cis*). With *trans*-dihydrothebainone (III), however, the closure is difficult and only moderate yields are obtained.[9]

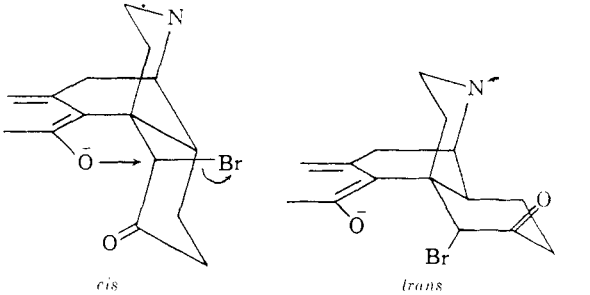
We had originally attributed the much smoother cyclization of *cis*-dibromodihydrothebainone with alkali to the more favorable spatial relationship of the displacing phenoxide ion and the bromine, assumed to be at position 5 in both C_{14}-epimers. Axial bromine at C_5 in the *cis* compound is ideally situated for displacement by phenoxide, whereas neither configuration of bromine at C_5 in the *trans* isomer is susceptible to easy displacement.

IX, *cis*, Y = NNH $C_6H_3(NO_2)_2$
X, *cis*, Y = O



V, *cis*
VI, *trans*

VII, *cis*
VIII, *trans*



(1) Taken in part from the Ph.D. dissertation of Marvin S. Shepard, University of Rochester, 1958.

(2) American Cyanamid Fellow, 1957–1958; Charles Pfizer Fellow, Summer, 1958.

(3) Now that the stereochemistry of these substances is known with certainty, we prefer to use the descriptive term "*trans*-dihydrothebainone" for this substance and analogous names for related substances rather than any of the less rational trivial names heretofore proposed (C. Schöpf and F. Borkowsky, *Ann.*, **458**, 148 (1927); L. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939); K. W. Bentley and A. E. Wain, *J. Chem. Soc.*, 967 (1952); H. Rapoport and J. B. Lavigne, *J. Am. Chem. Soc.*, **75**, 5329 (1953)).

(4) Configurations shown in this paper have no significance in the absolute sense. Sinomenine and morphine belong to enantiomorphic series.

(5) L. Small, H. M. Fitch and W. E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936). Methyldihydromorphinone (Metopon), first described by these authors, was for a time produced commercially by a process which involved a ring closure of this type as one of its steps.

(6) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956).

(7) C. Schöpf and T. Pfeifer, *Ann.*, **483**, 157 (1930).

(8) C. Schöpf, T. Pfeifer and H. Hirsch, *ibid.*, **492**, 213 (1932).

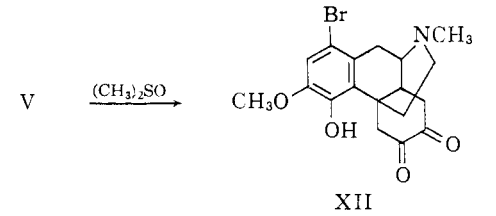
(9) M. Gates and G. M. K. Hughes, *Chemistry & Industry*, 1506 (1956).

The tacit assumption that in these dibrominated dihydrothebainones the second bromine atom is at C_5 now appears to be incorrect. We have obtained evidence along several lines which suggests most strongly that the bromine atom involved in these ring closures is at C_7. Bentley has also made a similar suggestion without offering experimental support.[10]

No small part of the difficulty in correctly interpreting these cyclizations may be attributed to the fact that in only very few[11] previously reported examples has the intermediate brominated substance been isolated or characterized. We have now been able to isolate the dibromo derivatives of both *cis*- and *trans*-dihydrothebainone, (V) and (VI), and of dihydrocodeinone (XI) as pure crystalline hydrobromides, and this has allowed a more definitive examination of their reactions, including these cyclizations.

Both V and VI exhibit carbonyl absorption at 5.80 μ (1725 cm.$^{-1}$) in the infrared and thus in both, the alicyclic bromine must be equatorial.[12,13] This observation alone strongly suggests that the bromine must in each case be at C_7, since in models it is difficult to accommodate groups much larger than hydrogen or fluorine in the equatorial position at C_5.

The pure hydrobromide of the dibrominated *cis*-ketone V smoothly yields *cis*-1-bromodihydrocodeinone (VII) (80–85%) on treatment with aqueous alkali. In contrast to cyclizations carried out on crude dibromoketone, no (−)-1-bromosinomeninone (XII) is produced. Two further reactions which are readily understandable only if bromine is at C_7 are shown by V. With 2,4-dinitrophenylhydrazine, the known *cis*-1-bromothebainone dinitrophenylhydrazone (IX) is obtained in 48% yield. In saturated α-bromoketones, the position of the double bond introduced by the use of 2,4-dinitrophenylhydrazine accurately indicates the position of the original bromine.[14] Likewise, with dimethyl sulfoxide, V as its pure hydrobromide is transformed in moderate yield to (−)-1-bromosinomeninone[7] (XII) the position of whose oxygens is known with certainty. The mechanism of this reaction[15] is not known although several plausible schemes can be imagined, but the production of XII is more simply explained if bromine is at C_7.



XII

In contrast to the ease with which V cyclizes with alkali, the pure hydrobromide of the *trans*-dibromo ketone VI gives under comparable conditions only small amounts (13%) of *trans*-1-bromodihydrocodeinone (VIII) as well as moderate amounts (20–35%) of *cis*-1-bromothebainone (X).[6,16]

The best yields (29%) of VIII are produced by the action of sodium methoxide on the hydrobromide of VI in methanol. Comparable yields are obtained by boiling VI in collidine.[9]

trans-1-Bromodihydrocodeinone (VIII) is the first *trans*-pentacyclic substance of the morphine series to be prepared. Although the capability of existence of substances of this type has been questioned,[17] it appears to be of normal stability. It is saturated and non-phenolic and can be reduced by zinc and ammonium chloride to the known[6] *trans*-1-bromodihydrothebainone. Compelling evidence that it contains an oxide bridge from C_6 to C_5 is provided by deuterium exchange. Both it and its C_{14}-epimer *cis*-1-bromodihydrocodeinone (VII) exchange only two hydrogen atoms for deuterium in the presence of deuterium oxide and potassium carbonate.[18] With a route to pentacyclic substances in the *trans* series available, it should be possible to prepare a number of interesting but heretofore unavailable substances, including *trans*-morphine itself.

trans-1,7-Dibromodihydrothebainone (VI) with 2,4-dinitrophenylhydrazine gives *cis*-1-bromothebainone 2,4-dinitrophenylhydrazone (IX) in 47% yield.[19]

(−)-1-Bromosinomeninone (XII) is formed as a by-product of the ring closure of crude *cis*-dibromodihydrothebainone[7] and can be produced in high yield by tribrominating *cis*-dihydrothebainone and treating the crude product with alkali.[8] Schöpf assumed that the intermediate in its formation was 1,5,7-tribromodihydrothebainone and Bentley[10] has suggested that the intermediate may be the 1,7,7-isomer. We find, however, that the tribromination of *cis*-dihydrothebainone leads not to a tribromo derivative, but directly to 1,7-dibromodihydrocodeinone (XI), isolated as its crystalline hydrobromide, in high yield. The substance is identical with that prepared directly from *cis*-dihydrocodeinone (XIII) by dibromination.[20] The intermediate tri-

(10) K. W. Bentley, *Experientia*, **12**, 251 (1956).

(11) K. Goto, H. Shishido and K. Takubo, *Ann.*, **495**, 122 (1932); **497**, 289 (1932), have isolated and characterized 1,5-dibromosinomenine hydrobromide and 1,5,8-tribromosinomeninone hydrobromide. The former substance cyclizes to 1-bromosinomeneine merely on standing in alcohol.

(12) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952); E. J. Corey, *ibid.*, **75**, 2301, 3297 (1953). Both parent ketones II and III absorb at about 5.87 μ (1703 cm.$^{-1}$).

(13) These hydrobromides were obtained after equilibration of the bromination mixtures in the presence of hydrogen bromide. *Cf.* A. Hantzsch, *Ber.*, **27**, 355, 3168 (1894); F. Kröhnke and H. Timmler, *ibid.*, **69**, 614 (1936); F. Krohnke, *ibid.*, **69**, 921 (1936); C. W. P. Crowne, R. M. Evans, G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 4351 (1956).

(14) Unpublished work by E. R. Glazier. Particularly cogent is the case of 2-bromo-3,3-dimethylcyclohexanone which forms a bromo-2,4-dinitrophenylhydrazone completely stable toward boiling acetic acid, but which with boiling collidine gives a mixture of 3,3-dimethylcyclohexanone and 5,5-dimethylcyclohexen-2-one.

(15) N. Kornblum, *et al.*, *J. Am. Chem. Soc.*, **79**, 6562 (1957).

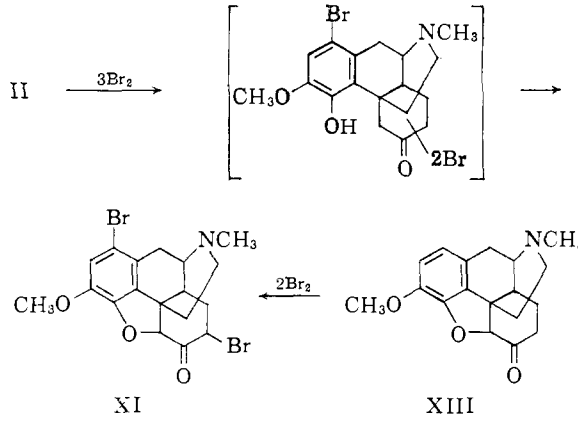
(16) Undoubtedly produced by base-catalyzed epimerization of the initially formed *trans*-1-bromothebainone (*cf.* M. Gates and R. Helg, *ibid.*, **75**, 379 (1953)).

(17) K. W. Bentley and H. M. E. Cardwell, *J. Chem. Soc.*, 3252 (1955).

(18) The exchange reaction with the *trans* compound VIII was carried out by Dr. Clifford O. Eddy, Jr. Enolization and enolate anion formation in the direction of C_5 are of course sterically impossible when the oxide ring is closed.

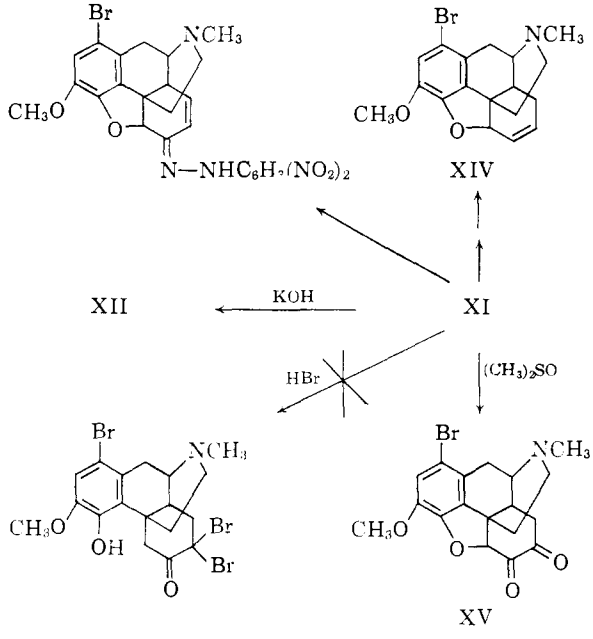
(19) *trans*-1-Bromothebainone 2,4-dinitrophenylhydrazone is known to epimerize at C_{14} under the usual conditions of 2,4-dinitrophenylhydrazone formation; see ref. 6 and 16.

(20) The second bromine atom, equatorial on the basis of the car-



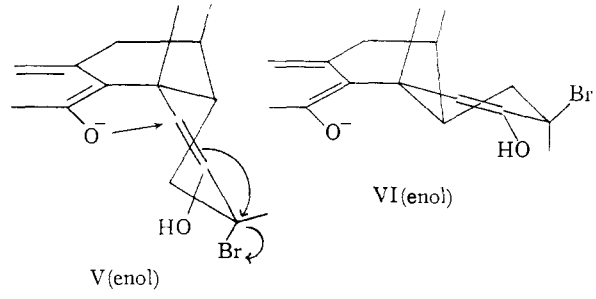
bromo compound (1,5,7 or 1,7,7?) apparently cyclizes readily even in acid.[21]

cis-1,7-Dibromodihydrocodeinone hydrobromide on treatment with 2,4-dinitrophenylhydrazine gives *cis*-1-bromocodeinone 2,4-dinitrophenylhydrazone in 35% yield,[22] and with dimethyl sulfoxide gives (−)-1-bromosinomeneine ketone (XV).



The conversion of XI to the diketone XII by the action of alkali is well-known[8] and very facile, and in our hands proceeds in 80% yield. The suggestion of Bentley[10] that 1,7,7-tribromodihydrothebainone, produced by 1,4-addition of hydrogen bromide to the allylic ether system of 1,7-dibromodihydrocodeinone enol, is the intermediate giving rise to XII, is untenable. Not only does XI yield XII under alkaline conditions precluding the presence of hydrogen bromide, but it is also completely stable to hydrogen bromide under the conditions of the bromination.

With the demonstration that in both *cis*- and *trans*-dibromodihydrothebainones (V and VI) closure of the 4,5-oxide ring involves bromine at C_7, the course of these cyclizations may profitably be discussed. Bentley[10] has suggested that ring closure of the *cis* compound V may proceed by allylic substitution of bromine at C_7 by phenoxide at C_5 on the enol of V, and the known[23] *cis* stereochemical requirements of the SN2′ reaction are met by equatorial bromine at C_7. This favorable geometry does not, however, obtain in the *trans* enol, and the



observed difficulty in carrying out the cyclization of VI may be the result of the necessity for epimerization of bromine to the less favorable axial conformation before ring closure.

Another possibility that deserves serious consideration is that the reaction proceeds through a cyclopropanone intermediate (V, VI→VIII).[9,24] Here again, an explanation of the difference in ease of cyclization of V and VI is readily offered. The formation of the cyclopropanone intermediate requires in effect a *cis*-6,5-ring fusion with V, but the much less favorable *trans*-6,5-fusion with VI. In the *cis* case, intramolecular attack by phenoxide ion on C_5 presumably almost completely supersedes external hydroxide ion attack on the carbonyl leading to normal Favorskii rearrangement. In the *trans* case, approximately 35–50% of material remains unaccounted for either as the cyclized VIII or as *cis*-1-bromothebainone (X), and may well be Favorskii rearrangement product.

bonyl frequency of the substance in the infrared (5.73 μ, 1745 cm.$^{-1}$; XIII, 5.80 μ, 1725 cm.$^{-1}$) can be assigned to C_7 with confidence, inasmuch as enolization of the parent ketone cannot occur toward C_8 as shown by the deuterium exchange experiments cited above. Furthermore, reduction with sodium borohydride followed by treatment with zinc dust yields what appears to be 1-bromodesoxycodeine-C (XIV) (L. Small and S. G. Turnbull, *J. Am. Chem. Soc.*, **59**, 1541 (1937)) although a direct comparison was not made. See Experimental part.

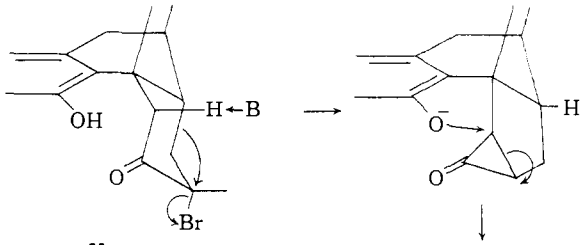
(21) In contrast, *trans*-dihydrothebainone on tribromination gives a stable crystalline tribromo derivative in high yield (ref. 6). This substance, however, neither cyclizes nor gives α,β-unsaturated derivatives readily.

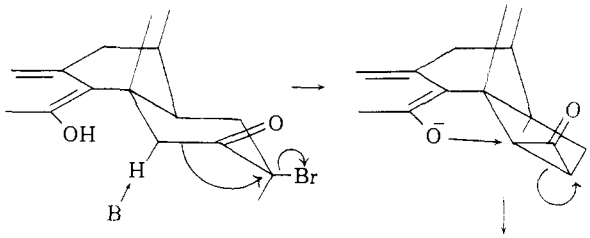
(22) This and the preceding observation clarify the reaction described in ref. 6 whereby *cis*-dihydrothebainone (II) was converted into 1-bromocodeinone dinitrophenylhydrazone by tribromination followed by treatment with 2,4-dinitrophenylhydrazine.

(23) G. Stork and W. N. White, *J. Am. Chem. Soc.*, **78**, 4609 (1956); G. Stork and F. H. Clarke, *ibid.*, **78**, 4619 (1956); W. G. Young, I. D. Webb and H. L. Goering, *ibid.*, **73**, 1076 (1951).

(24) R. B. Loftfield, *ibid.*, **73**, 4707 (1951); M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955); R. Futaki, *ibid.*, **23**, 451 (1958). See also J. G. Aston and J. D. Newkirk, *J. Am. Chem. Soc.*, **73**, 3900 (1951); J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954); G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960); and H. O. House and W. F. Gilmore, *ibid.*, **83**, 3980 (1961). Dipolar forms such as

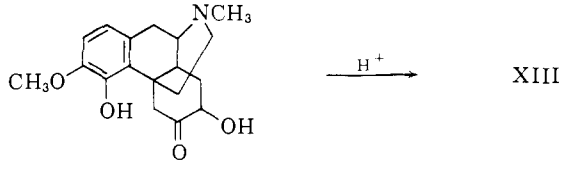
which have been considered to be intermediates in the formation of cyclopropanones, might, in the special environment under study here, cyclize directly with phenoxide ion at C_4 rather than collapsing to cyclopropanones. Their geometry (carbon atoms 5, 6 and 7 coplanar) would lead to more facile cyclization in V than in VI.



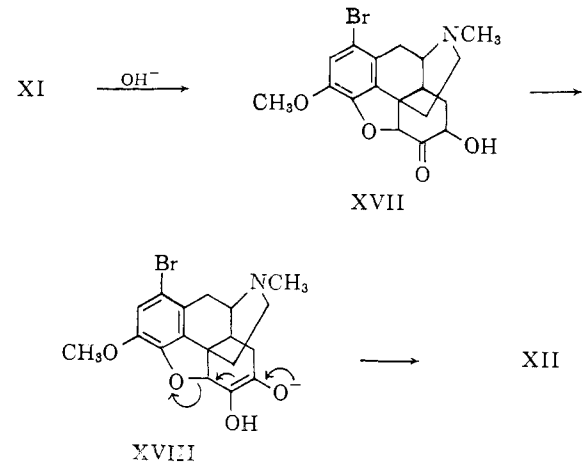


There exists little basis on which to assign a structure to the initially formed tribromination product of *cis*-dihydrothebainone (II) (1,5,7 or 1,7,7?) which cyclizes spontaneously to *cis*-1,7-dibromodihydrocodeinone (XI), although it is worth noting that the dibromination product of sinomenine (IV) cyclizes to 1-bromosinomeneine merely on standing in alcohol without treatment with alkali.[11] These facile cyclizations may exemplify the great ease with which axial or pseudo axial bromine at C_5 is displaced intramolecularly by phenoxide. Although the 1,5,7-structure has been assigned[6] to the isolable tribromo derivative of *trans*-dihydrothebainone, this can only be regarded as tentative.

The cyclization of dihydrosinomeninone (XVI) by acids[25] also involves a substituent at C_7, and can in similar fashion be regarded as proceeding through a 5,6-enol or a cyclopropanone intermediate, the hydroxyl group at C_7 in each case being activated toward elimination by protonation.



The conversion of *cis*-1,7-dibromodihydrocodeinone (XI) to (−)-1-bromosinomeninone (XII) by alkali may be regarded as an attack by hydroxide ion at C_7 of the enol of XI with SN_2' displacement of phenoxide ion at C_5, the required *cis* displacement being in this case sterically acceptable if not as easy as attack from the opposite side. A more attractive alternative, suggested to us by Professor Gilbert Stork, is that the enolate anion XVIII, produced by hydroxide ion displacement of bromine at C_7 and basic equilibration of the resulting ketol XVII, undergoes normal β-elimination to give XII.



Experimental[26]

***cis*-1,7-Dibromodihydrothebainone Hydrobromide (V).**—*cis*-Dihydrothebainone (1.625 g.) was dissolved in 15 cc. of glacial acetic acid and brominated by the dropwise addition of 5 cc. of a glacial acetic acid–bromine mixture containing 10.8 millimoles of bromine. The bromine was decolorized rapidly. The solution was allowed to stand for 24 hours, and as much as possible of the acetic acid was then removed under diminished pressure. The viscous residue was treated with 10 cc. of ether. The gummy solid which precipitated agglomerated to a filterable amorphous solid on standing for 10 hours. It was collected and washed with a large volume of ether and then crystallized from water as follows: the amorphous solid was dissolved in boiling water, cooled, and a small amount of methanol was added to redissolve a small amount of solid. Scratching induced crystallization; 2.6 g. (82%), m.p. 215–225°, frothing, dec. Its ferric chloride test is positive (green). Its infrared absorption spectrum shows a maximum at 5.79μ (1727 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{22}NO_3Br_3 \cdot 2H_2O$: C, 37.52; H, 4.55. Found: C, 37.58; H, 4.49.

Its specific rotation is approximately −45° (*c* 1.50, water, D line of sodium) but cannot be determined with precision owing to cyclization of the sample during solution and observation. Warming in water on the steam bath is sufficient to cyclize the substance to 1-bromodihydrocodeinone hydrobromide,[7] $\alpha^{23}D$ −89° (*c* 1.21, water).

Action of Alkali on *cis*-1,7-Dibromodihydrothebainone Hydrobromide.—*cis*-1,7-Dibromodihydrothebainone hydrobromide (200 mg.) was dissolved in a mixture of water 5 cc. and 2 cc. of glacial acetic acid and this solution was added to 13 cc. of 7 *N* sodium hydroxide. A colorless precipitate separated immediately. The mixture was allowed to stand at room temperature for 4 hours, then extracted with three 25-cc. portions of chloroform. The chloroform extracts were dried, filtered and concentrated to yield a colorless crystalline residue, 86 mg. (81%), m.p. 204°. Recrystallization from ethyl acetate raised this to 204.5–206.5°, undepressed by admixture of *cis*-1-bromodihydrocodeinone (VII).[7] Its infrared absorption spectrum contains a maximum at 5.79μ (1727 cm.$^{-1}$).

The Action of 2,4-Dinitrophenylhydrazine on V. *cis*-1-Bromothebainone 2,4-Dinitrophenylhydrazone (IX).—A solution of 200 mg. of *cis*-1,7-dibromodihydrothebainone (V) in 10 cc. of glacial acetic acid was treated with 84 mg. of 2,4-dinitrophenylhydrazine and heated on a steam-bath for 30 minutes, then cooled, diluted with water, just neutralized with ammonium hydroxide and extracted five times with 30-cc. portions of chloroform. The combined chloroform extracts were washed twice with dilute ammonia and once with water, dried over sodium sulfate, filtered and concentrated to yield an orange-red residue (194 mg.) which was chromatographed in alcohol-free chloroform on 10 g. of Woelm (acid-washed) alumina. Elution gave 145 mg. of crude crystalline dinitrophenylhydrazone, which after recrystallization from ethyl acetate yielded a total of 86 mg. (48%) of *cis*-1-bromothebainone 2,4-dinitrophenylhydra-

(25) K. Goto and I. Yamamoto, *Proc. Japan Acad.*, **36**, 145 (1960).

(26) All melting points are corrected. Analyses for the most part were carried out by Miss Annette Smith, Mr. Thomas A. Montzka and Micro-Tech Laboratories. Infrared spectra were recorded on a Perkin-Elmer model 21 spectrophotometer equipped with sodium chloride optics (chloroform solution or potassium bromide pellets).

zone, m.p. 201–204°, undepressed by admixture with an authentic sample.[5]

The Action of Dimethyl Sulfoxide on *cis*-1,7-Dibromodihydrothebainone (V).—*cis*-1,7-Dibromodihydrothebainone hydrobromide (200 mg.) was dissolved in 8 cc. of dimethyl sulfoxide, allowed to stand at room temperature for 20 hours, then diluted with 100 cc. of ice water and extracted with four 100-cc. portions of ether. The combined ether extracts were dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure to yield 31 mg. (22%) of crystalline material, m.p. 224° dec. There was no depression of melting point upon admixture with an authentic sample of (−)-1-bromosinomeninone (XII). The infrared absorption spectra of the two samples were indistinguishable. Its methiodide melted at 242–244°; reported[27] for its enantiomorph, 244–246°.

***trans*-1,7-Dibromodihydrothebainone Hydrobromide (VI).** *trans*-Dihydrothebainone perchlorate (4.07 g.) was suspended in 10 cc. of dilute ammonia and the free base extracted with three 20-cc. portions of chloroform. The chloroform extracts were washed two times with cold water, dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The glassy residue was taken into 20 cc. of glacial acetic acid and brominated with 10 cc. of a glacial acetic acid–bromine mixture (containing 0.0203 mole of bromine) added dropwise. Decoloration of the bromine was rapid; the yellow perbromide that initially separated was dissolved by the addition of 0.1 cc. of 48% hydrobromic acid. The solution was allowed to stand for 20 hours at room temperature, then most of the acetic acid was taken off under reduced pressure. The viscous residue was taken into 5 cc. of methyl alcohol and scratched vigorously. The hydrobromide separated immediately and was collected and washed with small portions of methanol. Recrystallization from water gave prisms, 4.25 g. (74%), m.p. 205–206° dec., $\alpha^{27}D$ + 11° (*c* 1.37, methanol). Its ferric chloride test is positive (green). Its infrared absorption spectrum shows a maximum at 5.80 μ (1725 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{22}NO_3Br_3 \cdot 2H_2O$: C, 37.52; H, 4.55. Found: C, 37.07; H, 4.23.

The Action of Alkali on Crude *trans*-1,7-Dibromodihydrothebainone (VI).—The crude brominated product prepared as described above from 1.00 g. of *trans*-dihydrothebainone perchlorate was treated, after removal of acetic acid but before crystallization, with 35 cc. of 7 *N* sodium hydroxide, added in small portions at 5°. The mixture was warmed to 40° for 20 minutes, cooled, and allowed to stand at room temperature for 4 hours. The basic aqueous solution was extracted with five 50-cc. portions of chloroform, and the combined extracts were dried, filtered and concentrated. The residue crystallized when covered with ethyl acetate to yield 120 mg. (13%) of crystalline material, m.p. 163–165°, undepressed on admixture with *trans*-1-bromodihydrocodeinone prepared as described below.

The basic aqueous layer was just neutralized with acetic acid and extracted six times with 40-cc. portions of chloroform. The combined chloroform extracts were washed with water, dried, filtered and concentrated. The residue was crystallized twice from ethyl acetate; 291 mg., m.p. 193–195°; reported[6] for *cis*-1-bromothebainone (X), 198.5–199.5°. Its infrared absorption spectrum shows a maximum at 6.01μ (1686 cm.$^{-1}$). Its 2,4-dinitrophenylhydrazone melted at 205°; reported[6] 205–207°.

***trans*-1-Bromodihydrocodeinone (VIII).**—*trans*-Dihydrothebainone perchlorate (1.61 g.) was converted to the free base by distribution between chloroform and dilute sodium carbonate. The chloroform layer and washings were filtered and treated with 1.60 g. of bromine dissolved in 8 cc. of glacial acetic acid. After standing 1 hour (heavy oily second layer) the solvents were removed as completely as possible at 40° under diminished pressure. The residue was taken into 25 cc. of collidine, filtered from collidine hydrobromide, and heated to reflux for 30 minutes. Collidine was removed by steam distillation, and the residue was extracted several times with chloroform. The dried and concentrated chloroform extracts were chromatographed on 50 g. of alumina. Development with alcohol-free chloroform gave 413 mg. of crude *trans*-dihydrocodeinone (VIII) which was crystallized from methanol to yield 356 mg. (23%) of colorless boat-shaped prisms, m.p. 165–166°. An analytical sample melted at the same temperature, infrared maximum 5.79μ (1725 cm.$^{-1}$), $\alpha^{25}D$ −65° (*c* 1.37, alc.). The substance is insoluble in aqueous alkali.

Anal. Calcd. for $C_{18}H_{20}NO_3Br$: C, 57.15; H, 5.33. Found: C, 57.29; H, 5.56.

The Action of Sodium Methoxide on VI.—*trans*-1,7-Dibromodihydrothebainone hydrobromide (200 mg.) was suspended in 5 cc. of methanol and added to 15 cc. of methanol and sodium methoxide (85 mg.). The pale yellow solution was allowed to stand at room temperature for 6 hours, then concentrated to dryness under diminished pressure; 15 cc. of water was added to the residue which did not dissolve completely. The insoluble residue was collected, washed carefully with water, air-dried (69 mg.) and chromatographed on 10 g. of Woelm alumina. Elution with alcohol-free chloroform gave, after recrystallization from 70% methanol, 38 mg. (29%), m.p. 162–164°, undepressed on admixture with a sample of *trans*-1-bromodihydrocodeinone (VIII) prepared as above.

Reduction of *trans*-1-Bromodihydrocodeinone (VIII) to *trans*-1-Bromodihydrothebainone.—A mixture of 128 mg. of VIII, 0.5 g. of zinc dust, 0.5 g. of ammonium chloride, 1 cc. of water and 20 cc. of alcohol was heated to reflux for 3.25 hours, cooled, filtered and concentrated to dryness by blowing. The residue was taken into 10% sodium hydroxide solution in which it was completely soluble, and acidified to excess with perchloric acid. Small nearly colorless prisms (95 mg., m.p. 267°) separated. Two crystallizations from alcohol–water gave 74 mg., m.p. 272–274°, profound dec., undepressed by admixture with authentic *trans*-1-bromodihydrothebainone perchlorate,[6] $\alpha^{26}D$ −17.5° (*c* 2.41, 50% alc.–water). Its infrared spectrum was indistinguishable from that of the authentic sample. A sample (38 mg.) was converted to the free base by distribution between chloroform and dilute sodium carbonate. The residue left after removal of chloroform was crystallized several times from alcohol; 10 mg., m.p. 170–172°, undepressed by admixture with an authentic sample of 1-bromodihydrothebainone of m.p. 172.5–174°.[6] The infrared spectra of the two samples were indistinguishable.

Deuterium Exchange on *trans*-1-Bromodihydrocodeinone.[18]—A sample of VIII (286 mg.), dried at 78° and 0.05 mm., was heated to reflux for 6 hours with 1 cc. of deuterium oxide (99.5%) and 0.10 g. of anhydrous potassium carbonate in 10 cc. of purified dioxane. The mixture was concentrated to dryness and the equilibration repeated with an additional 1 cc. of deuterium oxide and 10 cc. of dioxane. That portion of the residue soluble in chloroform was subjected to deuterium analysis by the falling drop method; calcd. for 2 exchangeable hydrogens, 10.99; found 12.9 and 11.9 (the second value was determined on a sample which had been subjected to three successive exchanges with 99.5% deuterium oxide). A similar series of exchanges was carried out on *cis*-1-bromodihydrocodeinone (VII): calcd. for 2 exchangeable hydrogens, 10.99; found: 10.7 and 10.8 (for 2 and 3 successive exchanges, respectively).

***cis*-1-Bromothebainone 2,4-Dinitrophenylhydrazone (IX) from *trans*-1,7-Dibromodihydrothebainone (VI).**—*trans*-1,7-Dibromodihydrothebainone (VI) (200 mg.) was dissolved in 10 cc. of glacial acetic acid, treated with 85 mg. of 2,4-dinitrophenylhydrazine, and heated on a steam-bath for 30 minutes. The mixture was cooled, diluted with water, neutralized to slight excess with ammonium hydroxide, and extracted five times with 30-cc. portions of chloroform. The chloroform extracts were washed twice with dilute ammonium hydroxide, then with water, dried over sodium sulfate, filtered and concentrated to yield an orange-red residue (198 mg.) which was chromatographed in alcohol-free chloroform on 10 g. of Woelm (acid-washed) alumina. Elution with chloroform gave 153 mg. of crude crystalline dinitrophenylhydrazone which after recrystallization from ethyl acetate yielded a total of 96 mg. (47%) of *cis*-1-bromothebainone 2,4-dinitrophenylhydrazone (IX), m.p. 202–205°, undepressed on admixture with an authentic sample.

Tribromination of *cis*-Dihydrothebainone. *cis*-1,7-Dibromodihydrocodeinone Hydrobromide (XI).—*cis*-Dihydrothebainone (0.961 g.) in 15 cc. of glacial acetic acid was brominated by the dropwise addition at 10° of 5 cc. of a bromine–glacial acetic acid solution containing 0.0958 mole of bromine. The bromine was rapidly decolorized. The solution was allowed to stand for 20 hours at room temperature, and then concentrated under reduced pressure. Ether (10 cc.) was added to the oily residue, and the colorless solid

(27) K. Goto and T. Nambo, *Bull. Chem. Soc. Japan*, **5**, 73 (1930).

which precipitated was collected and washed immediately with large amounts of ether, then with smaller amounts of 1-to-1 ether–alcohol and air-dried; 1.80 g., m.p. 195° dec. Recrystallization from 95% ethanol gave 1.45 g. (82%), $\alpha^{27}D$ −184° (*c* 1.50, alcohol) m.p. 195° dec., undepressed by admixture of 1,7-dibromodihydrocodeinone hydrobromide prepared by dibromination of dihydrocodeinone. Its infrared absorption spectrum showed an absorption maximum at 5.74μ (1743 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{20}NO_3Br_3 \cdot 1.5H_2O$: C, 38.25; H, 4.10. Found: C, 38.09; H, 3.80.

***cis*-1,7-Dibromodihydrocodeinone Hydrobromide (XI) by Dibromination of *cis*-Dihydrocodeinone (XIII).**—*cis*-Dihydrocodeinone (1.43 g.) dissolved in 15 cc. of glacial acetic acid containing a five molar excess of dry hydrogen bromide was treated dropwise with 5 cc. of a bromine–glacial acetic acid solution containing 1.73 g. (0.0958 mole) of bromine. Decoloration of the bromine was rapid. The solution was allowed to stand at room temperature for 5 hours, concentrated under reduced pressure, and treated with 10 cc. of ether. The solid precipitate was collected and immediately washed with large volumes of ether. Recrystallization from water gave 2.5 g. (92%), m.p. 195° dec. The compound dissolves in potassium hydroxide solution but gives a negative ferric chloride test. It shows infrared absorption at 5.73μ (1748 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{20}NO_3Br_3 \cdot 1.5H_2O$: C, 38.25; H, 4.10. Found: C, 38.27; H, 3.79.

Repetition of the bromination without added hydrogen bromide gave essentially the same results (89%, m.p. 195–197° dec.).

1-Bromodesoxycodeine-C.—*cis*-1,7-Dibromodihydrocodeinone hydrobromide (XI) (300 mg.) in 15 cc. of methyl alcohol was treated with a solution of 0.06 g. of sodium borohydride in 10 cc. of methyl alcohol. The solution was allowed to stand at room temperature for 12 hours, concentrated to dryness under reduced pressure, and the residue was taken into 3 cc. of glacial acetic acid solution. After filtration to remove undissolved solid, 22 cc. of glacial acetic acid and 0.2 g. of zinc dust was added and the mixture was refluxed for 2.5 hours, cooled, and filtered. The filtrate was made just basic with ammonium hydroxide and extracted with four 40-cc. portions of chloroform. The combined chloroform extracts were dried, filtered, concentrated and triturated under ether to yield 1-bromodesoxycodeine-C (XIV), as a crystalline solid, 90 mg. (48%), m.p. 167–175°. Recrystallization from ethanol raised the m.p. to 179–181°. It gives a negative ferric chloride test. Its infrared absorption spectrum showed no carbonyl absorption, but a weak double bond absorption maximum at 6.02μ (1663 cm.$^{-1}$).

Anal. Calcd. for $C_{18}H_{20}NO_2Br \cdot H_2O$: C, 56.85; H, 5.83. Found: C, 56.89; H, 5.90.

Sublimation (oil-pump, 185°) yields anhydrous material, m.p. 210°, reported[20] 210–212.5°.

The Action of Alkali on *cis*-1,7-Dibromodihydrocodeinone Hydrobromide (XI). (−)-1-Bromosinomeninone (XII).—*cis*-1,7-Dibromodihydrocodeinone hydrobromide (XI) (200 mg.) was added to 25 cc. of 4 *N* potassium hydroxide. A transient colorless solid precipitated but redissolved after heating for 30 minutes at 40°. The solution was cooled, filtered and extracted three times with 75-cc. portions of ether. The alkaline raffinate was then neutralized with acetic acid, made slightly basic with dilute ammonia, and extracted with five 75-cc. portions of ether. The ether extracts were washed twice with water, dried over sodium sulfate, filtered, and concentrated to dryness under diminished pressure to yield 113 mg. (79%), of a crystalline compound, m.p. 224° dec., undepressed on admixture with authentic (−)-1-bromosinomeninone.

Conversion of *cis*-1,7-Dibromodihydrocodeinone Hydrobromide (XI) to *cis*-1-Bromocodeinone 2,4-Dinitrophenylhydrazone.—Two hundred milligrams of XI was dissolved in 10 cc. of glacial acetic acid, treated with 84 mg. of 2,4-dinitrophenylhydrazine, and heated on a steam-bath for 30 minutes. The cooled mixture was diluted with water and made just basic with ammonia. The basic mixture was extracted five times with 50-cc. portions of chloroform. The combined chloroform extracts were washed twice with dilute ammonia, once with water, dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. The residue was chromatographed on 10 g. of Woelm (acid-washed) alumina. Development with alcohol-free chloroform eluted a total of 113 mg. of crystalline dinitrophenylhydrazone, m.p. 214–220°, which after recrystallization from ethyl acetate gave 68 mg. (35%) of **1-bromocodeinone 2,4-dinitrophenylhydrazone**, orange needles, m.p. 221–224°, undepressed by admixture with an authentic sample.[6]

(−)-1-Bromosinomeneine Ketone (XV).—*cis*-1,7-Dibromodihydrocodeinone hydrobromide (XI) (200 mg.) was dissolved in 15 cc. of dimethyl sulfoxide, allowed to stand at room temperature for 25 hours, then poured into 50 cc. of ice-water and extracted with five 100-cc. portions of ether. The combined ether extracts were dried over sodium sulfate, filtered, and concentrated to yield a light-yellow residue, which was recrystallized from methyl alcohol; 43 mg. (31%), m.p. 196–197°; reported[28] for its enantiomorph, 198°.

(28) K. Goto and T. Nambo, *Bull. Chem. Soc. Japan*, **5**, 165 (1930)

[CONTRIBUTION FROM THE INORGANIC CHEMISTRY LABORATORY, OXFORD UNIVERSITY, OXFORD, ENG.]

Mechanisms of Acid Hydrolysis of Carboxylic Acid Esters and Amides

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In light of the Bunnett *w* criteria, this paper suggests mechanisms of hydrolysis of carboxylic acid esters and amides. Reasons for preferring a symmetric mechanism of ester hydrolysis and formation are presented. A discussion is given of the determination of *w* from mechanism. An attempt is made to separate simultaneous nucleophilic and proton transfer functions of water contributions to *w*. Separation of these functions in ester hydrolysis and formation indicates that the "γ-butyrolactone enigma" is less serious than previously considered. A useful empirical equation (3) relating the logarithm of the activity of water to the Hammett acidity function for HCl, H_2SO_4 and $HClO_4$ up to about 10 *M* acid is derived. Two applications of this equation are made. An attempt is made to account for the non-linear Bunnett plot obtained in the acid hydrolysis of *o*-nitrophenyl oxalate by a change in rate-determining step to one with different *w* parameters. It is shown that when acid inhibition of a step of a reaction occurs in moderately concentrated acid solutions, extraordinarily high *w*-values are expected. The possibility that the acid hydrolysis of acetylimidazole presents an example of such an inhibited reaction is discussed.

Recently Bunnett[2] has proposed a new criterion for determining reaction mechanism in moderately concentrated acid solutions. In this method of analysis, the logarithm of the pseudo first-order rate constant for the protonated species is plotted against the logarithm of activity of water. Such plots yield straight lines for many reactions, and the slope, *w*, exhibits values useful in elucidating

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(2) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, (a) 4956, (b) 4968, (c) 4973, (d) 4978 (1961).