Anal. Calcd. for $C_8H_{17}NO_5$: C, 46.36; H, 8.27; N, 6.76. Found; C, 46.6; H, 8.29; N, 6.78.

2-Ethylamino-2-deoxy-α-D-glucose.—A solution of 5 g. of fructosylethylamine in 250 ml. of methanol containing 0.2 ml. of acetic acid was allowed to stand for 24 hours at 24–26°. The solution, originally colorless, turned yellow in eight hours and amber in 24 hours. The solution was concentrated *in vacuo* to 15 ml., 45 ml. of acetone was added and the solution allowed to crystallize at 0° for several days. The product, 1.8 g. of yellow semi-crystalline material, was recrystallized from a mixture of 20 ml. of methanol and 50 ml. of acetone to yield 1.0 g. (20%) of colorless elongated prisms, dec. 136–137°. In the absence of acetic acid, the reaction solution requires about 72 hours to develop the same degree of color and a comparable yield of isolable crystalline product. Conducting the experiment for a longer period of time leads to a decrease in isolable crystalline product probably as a result of increased formation of dark resinous material. The pure compound is isolated in the form of white granular crystals, dec. 138–139° (preheat to 125°). *Specific Rotations:* In pyridine, $[\alpha]^{25.5}D$ +146.4° (20 min.) → +106.9° (7 hr.) (*l* 2, *c* 1.0). In 0.1 *N* hydrochloric acid, $[\alpha]^{25}D$ +108° (0) → +101.7° (2 hr.) (*l* 2, *c* 1.27) (calc. as the hydrochloride, equil. $[\alpha]D$ +86.5°). In CO_2-free water, $[\alpha]^{25}D$ +64° (0) → +49° (175 hours) (*l* 2, *c* 1.16).

Anal. Calcd. for $C_8H_{17}NO_5$: C, 46.36; H, 8.27; N, 6.76. Found: C, 46.6; H, 8.41; N, 6.70.

2-Ethylamino-2-deoxy-α-D-glucose Hydrochloride.—This salt was prepared by the same procedure as for the other hydrochlorides and was recrystallized from ethanol–acetone (1:1), sheathes of jagged needles, dec. 180–181° (preheat to 155). In water, *p*H 5.1, $[\alpha]^{25}D$ +93.6° (0) → +87.0° (2 hr.).

Anal. Calcd. for $C_8H_{18}NO_5Cl$: N, 5.75; Cl, 14.55. Found: N, 5.75; Cl, 14.5.

2-*n*-Butylamino-2-deoxy-D-gluconic Acid.—A suspension of 6 g. of red mercuric oxide[12] in a solution of 1.5 g. of 2-*n*-butylamino-2-deoxy-α-D-glucose in 250 ml. of water was heated in a hot water-bath at 97–99° for 25 minutes. When refluxing was attempted, the solution foamed severely. The solution was filtered, mercuric ion removed with hydrogen sulfide, and the solution, after removal of hydrogen sulfide by aeration, was filtered through carbon. The solution was concentrated *in vacuo* to 10 ml., 80 ml. of absolute ethanol added and the solution again concentrated to 10 ml. when crystallization took place. The suspension was diluted with 20 ml. of ethanol and stored at 0° overnight. A yield of 540 mg. of acid was obtained. The pure acid was obtained by recrystallization from 12 ml. of water plus 35 ml. of absolute ethanol as tiny fibrous crystals. Dec. 205–207° (gas), preheat 190°. *Specific Rotations;* in 0.1 *N* sodium hydroxide, $[\alpha]^{25.5}D$ +24.5° (*l* 2, *c* 1.37). Acidified with normal hydrochloric acid to *p*H 1.2, $[\alpha]^{28}D$ +6.5° (4 min.) → +19.8° (125 hours).

Anal. Calcd. for $C_{10}H_{21}NO_6$: C, 47.80; H, 8.42; N, 5.57. Found: C, 47.9; H, 8.48; N, 5,45.

(12) Procedure of F. A. Kuehl, Jr., E. H. Flynn, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **69**, 3032 (1947).

ALBANY 10, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

Neopinone[1]

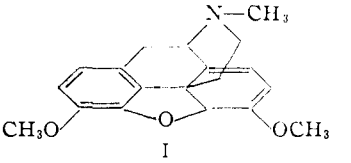
BY HAROLD CONROY

RECEIVED APRIL 29, 1955

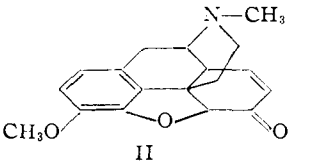
Neopinone, the ketone corresponding to the opium alkaloid neopine, has been prepared by catalytic reduction of 14-bromocodeinone. The reduction of neopinone, its reactions with aqueous acids and alkali and the unusual course of degradation of its methiodide are described in detail.

The direct hydrolysis[2] of thebaine (I) with dilute sulfuric acid provides little more than a trace of codeinone (II); most of the product is alkali soluble and contains one or more of the known rearranged derivatives,[3] thebenine, morphothebaine and the metathebainone precursor.[4] Since it was a matter of practical interest to develop a preparative method for the conversion of thebaine to codeine (III), an alternative route for the change I → II,[5] was investigated.

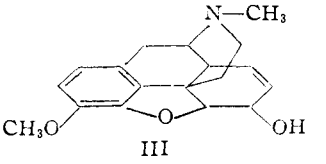
The bromination of thebaine in acetic acid as solvent gives a substance[6,7] for which two structures (IV and V) have been considered,[8] that of 14-bromocodeinone (IV) having been generally favored. The ultraviolet spectrum does not permit any distinction to be made,[9] but the infrared spectrum of this compound contains a strong peak at 1679 cm.$^{-1}$, as does that of codeinone itself, so that



I



II



III

(1) Paper presented at the Sixth Summer Seminar in the Chemistry of Natural Products, University of New Brunswick, Fredericton, N. B., Canada, August 17–21, 1954.

(2) L. Knorr and H. Hörlein, *Ber.*, **39**, 1409 (1906).

(3) For excellent summaries of the chemistry of thebenine and morphothebaine, *cf.* L. F. Small, "Chemistry of the Opium Alkaloids," U. S. Government Printing Office, Washington, D. C., 1932, pp. 321, 327; K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford University Press, London, 1954, pp. 314, 326.

(4) G. Stork, in "The Alkaloids," Vol. II, edited by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., 1953, pp. 193–197; K. W. Bentley, ref. 3, p. 319.

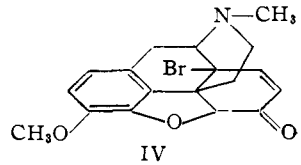
(5) The sodium borohydride reduction of codeinone to codeine proceeds stereospecifically in high yield (M. Gates, THIS JOURNAL, **75**, 4340 (1953)).

(6) M. Freund, *Ber.*, **39**, 844 (1906).

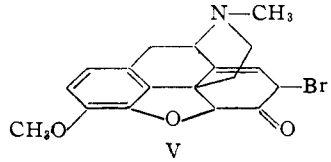
(7) E. Speyer and K. Sarre, *ibid.*, **57**, 1404 (1924).

(8) L. F. Small, ref. 3, pp. 248, 255; E. A. Kollontay, Austrian Patent 162,928 (1949); K. W. Bentley, ref. 3, p. 251.

(9) The product shows high intensity absorption, but no well-defined maximum in the 230 mμ region [λ_{max} (for the guaicol nucleus) 280 mμ, log ε 3.35 (CH_3OH)], while codeinone gives an indistinct shoulder at 227 mμ, log ε 4.16 [λ_{max} 280 mμ, log ε 3.14 (C_2H_5OH)].



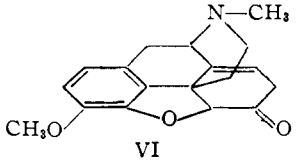
IV



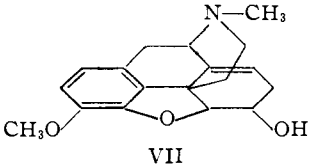
V

V, which would be expected to absorb at 1725 cm.$^{-1}$ or higher, may be excluded. The bromination of thebaine with N-bromosuccinimide in aqueous acetone also provides the bromoketone IV; the yield (85%) with this new procedure is approximately double that obtained[7] previously.

It is claimed[6] that 14-bromocodeinone can be debrominated to codeinone with iron and sulfuric acid, but in unspecified yield. Catalytic hydrogenation[7] with palladium–charcoal in acetic acid converts IV to dihydrocodeinone in poor yield, after the absorption of two equivalents of hydrogen. With a neutral solvent the results are entirely different. The palladium-catalyzed hydrogenation, done with chloroform containing 5–10% of methanol, practically ceases after the smooth addition of one equivalent of hydrogen to give the hydrobromide of a new keto base, $C_{18}H_{19}O_3N$. The base, released from its salt with aqueous carbonate or bicarbonate, and obtained, either in the free form, m.p. 130° dec., or as the 1:1 chloroform solvate, m.p. 92° dec., gave $[\alpha]^{23}D$ −9.8° (chloroform, *c* 0.713), and showed carbonyl absorption at 1735 cm.$^{-1}$ indicative of an unconjugated ketone. The structure VI has been assigned to the substance, designated "neopinone" from its relation to the rare



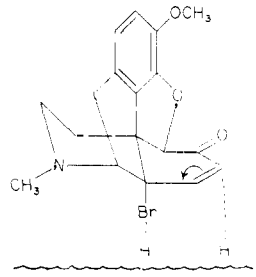
VI



VII

opium alkaloid, neopine (VII).[10] The expression VI was confirmed by the observation that sodium borohydride reduction gives neopine; the product was compared with authentic material both as the free base and as the hydrobromide. This reduction[11] constitutes the first synthesis of neopine, whose structure has been deduced only as a result of degradation experiments.

The hydrogenolytic debromination (IV → VI) gives the odd result that the double bond conjugated with the carbonyl group in IV reverts to a position removed from the carbonyl, whence the molecule loses the stabilization of resonance. On considering the probable transition state VIII we may derive the following argument: If cleavage of the C–Br bond occurs by attack of a hydrogen atom, adsorbed on the catalytic surface, on the



VIII

bromine atom, also attracted to the surface, then simultaneous substitution at C_{14} may be difficult. Several cases may be entertained, (i) top (rear) attack on C_{14} cannot occur, since as can be seen from VIII, hydrogen is not available from this direction, (ii) Attack on C_{14} from below is likely to be blocked by the bulky halogen atom. (iii) The molecule could leave the surface as a free radical, which might react later with hydrogen, although not necessarily at C_7. However this process would seem to require a higher energy input than a concerted one. (iv) The second hydrogen could approach C_7 (a position perfectly accessible to the catalyst) concomitant with the cleavage of the C–Br bond, a mechanism which must result in the shift of the π-bond to 8–14; it is this latter path which seems to be most consistent with the peculiar energetic and steric requirements of the situation.[12,13]

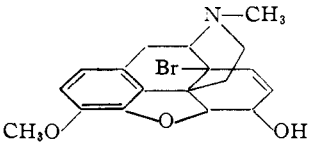
A second synthesis of neopine from 14-bromocodeinone was achieved with sodium borohydride. In this transformation, an insoluble intermediate, dec. *ca.* 150°, was found still to contain bromine, but the infrared spectrum indicated that the carbonyl grouping in IV had given way to a hydroxyl. The compound is 14-bromocodeine (IX), and the course of its further reduction to neopine may be formulated either as a direct S_N2' attack of the

(10) J. J. Dobbie and A. Lauder, *J. Chem. Soc.*, **99**, 34 (1911); C. F. van Duin, R. Robinson and J. C. Smith, *ibid.*, 903 (1926).

(11) The converse, *i.e.*, the oxidation of neopine to neopinone has been attempted by various workers [L. F. Small, private communication, *cf.* S. P. Findlay and L. F. Small, THIS JOURNAL, **72**, 3247 (1950); K. W. Bentley, ref. 3, p. 124 refers to a similar unpublished observation of Robinson and Salter] but has as yet not allowed the isolation of any ketone. The sensitivity of neopinone, in particular its ready enolization under basic or acidic conditions as reported here, would seem to provide ample basis for rationalization of these failures at oxidation of neopine, at least with many of the usual reagents.

(12) It is conceivable instead that a *hydride ion* attacks the halogen, yielding the neopinone–codeinone anion, which is known (*vide infra*) to yield neopinone, not codeinone, on protonation in solution. But it might seem preferable, in the absence of substantial evidence to the contrary, to regard the active species on the surface as hydrogen atoms rather than ions, since a smaller energy input ought to be required for homopolar cleavage of the hydrogen molecule than for the alternative.

(13) The apparent catalytic effect of methanol upon the hydrogenation may not be mechanistically significant, that is, it may be associated merely with the adsorptive or desorptive processes, and not with the hydrogenation step proper. However, it was noted in several experiments run in chloroform and/or benzene when no methanol was added, that the hydrogenation started very slowly and came to a complete halt after only a few per cent. of the anticipated absorption. The addition of about 7% of methanol caused the reaction to start again at a rapid rate, but the subsequent addition of another 7% of methanol caused no further change in rate.



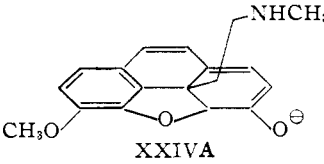
IX

complex hydride ion upon C_7, or more probably, as a base-catalyzed 1,4-elimination of the elements of hydrogen bromide yielding neopinone enol, which after ketonization, is reduced.

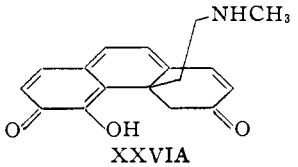
Neopinone represents the β,γ-isomer of the α,β-unsaturated ketone, codeinone, and in conformity with the general experience with such pairs we might expect that the β,γ-form could be easily isomerized to the more stable, conjugated derivative by the catalytic action either of acids or bases. This was found to be true, but the situation in each instance is somewhat complicated. In fact, the only practical conversion to codeinone devised involves treatment of the keto base with activated charcoal (Darco G-60) in refluxing ethyl acetate. With this method, codeinone may be isolated in nearly 60% yield; the charcoal actually exerts a catalytic effect, for neopinone was unchanged with conditions the same except for omission of the charcoal.

Reaction of Neopinone with Aqueous Base.—Although it is essentially insoluble in water, neopinone is remarkably acidic, and dissolves rapidly in 1.25 *M* potassium hydroxide at 25° to give a clear solution evidently containing the anion X.[14] If this solution is immediately quenched in excess aqueous potassium bisulfate, the neopinone can be recovered without change (after neutralization). The result of irreversible acidification of the resonating anion is here, in common with many other cases,[15] that the proton adds more rapidly to the central atom, with the interruption of conjugation in the product.

(14) We may reject the suggestion that this solution contains not X, but XXIVA, which is the (admittedly stable) dienone enolate which might arise by the elimination of the nitrogen bridge in X. (i) It is doubtful that regenerated neopinone would be so readily obtained on acidification of XXIVA. (ii) The anion XXIVA, related as it is to



XXIVA

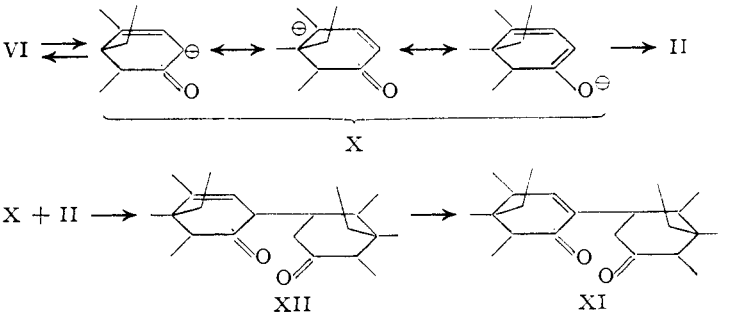


XXVIA

XXIV (*vide infra*), would be expected ultimately to give the demethylated dyestuff (XXVIA), analogous to XXVI. (But no violet color was observed in alkaline solutions of neopinone.) (iii) This alternative expression (XXIVA) does not allow a ready explanation for the formation of the dimer XI, for it would have to be postulated that the highly conjugated XXIVA reverts to the less stable X in order to undergo Michael addition.

(15) *Cf.* A. J. Birch, *Quart. Rev.*, **4**, 85 (1950); *J. Chem. Soc.*, 1551 (1950); W. E. Hugh and G. A. R. Kon, *ibid.*, 775 (1930).

Alternatively, if the aqueous solution of X is merely allowed to stand for a short time, a precipitate appears, and eventually a new crystalline substance, m.p. *ca.* 245° dec., can be obtained in good yield. The compound XI has the same composition as neopinone, but it gives two carbonyl bands in the infrared, at 1733 and 1681 cm.$^{-1}$, which are both somewhat weaker than normal in comparison to the CH and aromatic ring bands. The ultraviolet spectrum contains two maxima, at 230 mμ ($E^{1\%}_{1\,cm}$ 305) and 281 mμ ($E^{1\%}_{1\,cm}$ 48.2). These data can be accommodated only by one of the following two hypotheses: Either the substance is a mixture[16] (or molecular complex) of two different ketones (only one of which is conjugated), or it is dimeric, containing two complete, but joined, morphine-like units, with each bearing a differently situated carbonyl grouping. The value of 639 obtained in a molecular weight determination obviously favors the second. We may consider the formulation shown, wherein the dimer is represented as derived from the product XII of Michael addition of the neopinone–codeinone anion (X) to codeinone (II) (or β-codeinone[17]) itself



formed by neutralization of a portion of the dissolved anion. The structure XI embodies the required structural features, *viz.*, one conjugated and one unconjugated ketone grouping, and is otherwise generally consistent with the properties described.

Although codeinone itself is substantially unchanged by treatment with aqueous base[3] under these, or somewhat more drastic conditions, no codeinone (or β-codeinone) could be isolated from the neopinone dimerization. Provided the mechanism as provisionally outlined is correct, these facts can only be taken to indicate that the α,β-unsaturated ketone is used in Michael condensation very nearly as rapidly as it is formed from the anion X. Since the rate of formation of the anion, as judged by the rate of solution of the neopinone, is quite rapid, the intermediate conjugated ketone

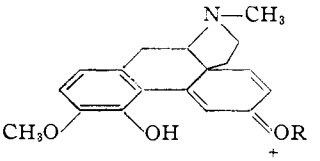
(16) The possibility of a mixture (or molecular complex) of neopinone and codeinone was further excluded by the infrared spectra; in solution each gave many peaks not shown by XI. No XI was obtained merely by mixing the two suspected components, moreover, attempted chromatographic resolution of a sample of XI failed to give any indication of separation.

(17) This designation, consistent with general usage, and especially with nomenclature in the thebainone series, is proposed for the (hypothetical) stereoisomer of codeinone with the inverted or "unnatural" configuration at C_{14}. Since the "natural" series almost certainly contains the *cis*-decalin system [G. Stork, ref. 4, p. 175] in the "β"-series the C_{14} hydrogen is *trans* to the nitrogen bridge. In principle, β-codeinone could be formed by delivery of the proton to the anion X from the direction opposite to that of the nitrogen bridge.

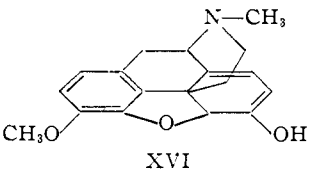
must be the rate-limiting reagent. It might then be expected *that codeinone, added to the reaction mixture with neopinone should be incorporated,* and the yield of dimer should be enhanced. So that the results with the addition of codeinone would be more significant and reproducible, it was decided best to start with the codeinone already in solution in a benzene phase to be kept mechanically in equilibrium with the aqueous base throughout. The controls, with neopinone but no codeinone, were likewise carried out with benzene, and in this situation the product XI did not precipitate but was obtained from the benzene layer. The addition of 0.6 mole codeinone/mole neopinone gave XI in a yield of 115% (crude crystalline) or 106% (recrystallized) based on neopinone. This figure is nearly twice that (58%) consistently obtained with neopinone alone under otherwise identical conditions; the result may be taken to be a powerful indication that the reaction course is appropriate as described.[18] Moreover, the suggestion of β-codeinone as an intermediate is irrelevant to the present example, and the configuration at C_{14}, in the dimer is fixed as common to the "natural" series.

This alkaline dimerization of a β,γ-unsaturated ketone is apparently without precise analogy in the literature, although certain cases[19,20] bear some resemblance. But in the present case the conjugated ketone acts only as the Michael acceptor, and (under the conditions used) not as a source of the anion, supplied only by the β,γ-unsaturated member; a subsequent aldolization is sterically not favorable. The results clearly illustrate a wide difference in rate of formation of the neopinone–codeinone anion from the two ketones, an effect which may be ascribed partly to the inaccessibility of the C_{14} proton in codeinone, and partly to the greater resonance stabilization in the transition state for proton removal from neopinone relative to that of the conjugated isomer.

Reaction of Neopinone with Acids.—One of the most striking and characteristic reactions of thebaine (I) occurs when it is dissolved in concentrated hydrochloric acid.[21] The intensely orange-red "halochromic" solution contains no thebaine, but instead the dienone conjugate acid (XV), which is the precursor[4] of metathebainone, thebenine and morphothebaine. The mechanism[4] clearly involves protonation of the oxide bridge with cleavage of the O–C_5 bond and concomitant migration of the chain to the (perhaps incipient) site of positive charge at C_{14}. Like thebaine, the enol XVI which, in principle, could be produced either from codeinone or neopinone, also contains the conjugated system required for transmission of the electronic deficiency to C_{14}. But codeinone can be recovered unchanged[22] from its (colorless) solution in hydrochloric acid. The comparatively acidic nature of neopinone would suggest that it should also enolize more readily than its isomer. In fact, upon contact with hydrochloric acid, neopinone gives at first a colorless solution which only in the course of several minutes deepens, eventually to reach the same hue as that attained almost instantly with thebaine. We may conclude, in view of the likely proviso that XVI rearranges as readily as its ether I, (1) that the gradual appearance of halochromism represents a measure of the rate of enolization of neopinone in this medium, and (2) that codeinone in contrast does not give halochromism because as a conjugated ketone it is so much more stable relative to the common enol XVI. Enolization is then not sufficiently rapid to allow accumulation of the colored material XV.



XV



XVI

The substance thebainone-B (XVII)[23] contains the neopinone structure intact, but for the oxide ring. With aqueous potassium bisulfate, thebainone-B passes into the α,β-unsaturated ketone of the "unnatural" configuration at C_{14}, namely, β-thebainone-A (XVIII). Thebainone-B is therefore very likely the intermediate[23] in the originally reported[24] conversion of dihydrothebaine-ϕ (phenolic dihydrothebaine) (XIX)[25] to β-thebainone-A. Potassium bisulfate is not a sufficiently strong acid to cause extensive rearrangement of the ethanamine chain, and it was therefore of interest to determine if the analogous change, neopinone → β-codeinone could be accomplished with this reagent. Although XVIII was obtained[24] in *ca.* 80% yield from XIX after five hours at 25°, neopinone was mostly recovered after 20 hours; the reaction proceeds so much more slowly that 19 days were required to ensure complete conversion of the neopinone. The result, aside from an amorphous fraction insoluble in chloroform, was a mixture of about equal parts of codeinone and 8-hydroxy-7,8-dihydrocodeinone (XX). The latter is known to be formed from codeinone under similar conditions[26]; no product having the properties of the stereoisomer could be isolated. We might conclude merely that closure of the 4,5-bridge influences the relative stability of the C_{14} isomers, in that β-codeinone is more highly strained, but consideration of models fails to dis-

(18) The remaining possibility might involve addition of the Michael acceptor to the anion at C_{14}; we dismiss this *a priori* on grounds of steric strain.

(19) L. H. Briggs, C. W. Harland, C. Ralph and H. A. Simmonds, *J. Chem. Soc.*, 3788 (1953); L. H. Briggs and L. D. Colebrook, *Chem. and Ind.*, 200 (1955).

(20) *Cf.* G. Büchi, J. H. Hansen and E. Koller, Abstracts of Papers, 126th Meeting, American Chemical Society, New York, September 12–17, 1954, p. 89-O, and earlier references cited.

(21) C. Schöpf and F. Borkowsky, *Ann.* **458**, 148 (1927).

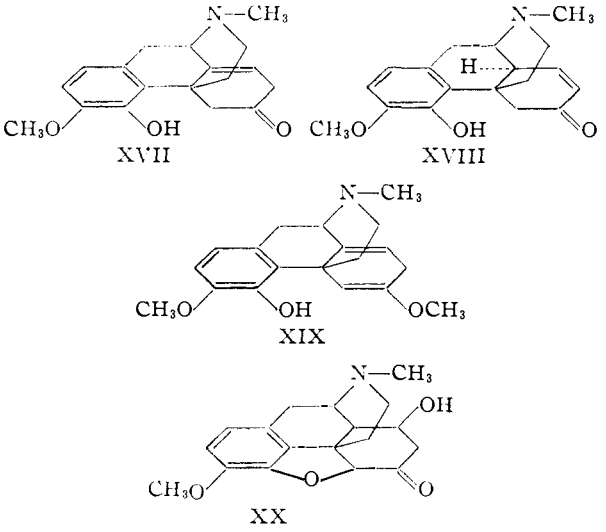
(22) C. Schöpf and H. Hirsch, *ibid.*, **489**, 224 (1931), *cf.* p. 249.

(23) K. W. Bentley and A. E. Wain, *J. Chem. Soc.*, 967 (1952).

(24) L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).

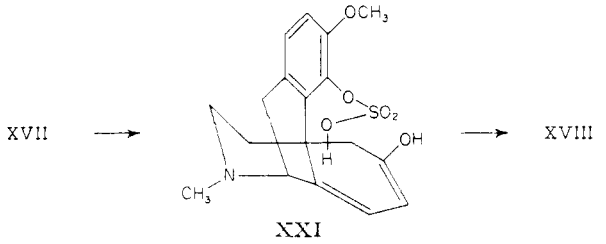
(25) G. Stork, THIS JOURNAL, **73**, 504 (1951); **74**, 768 (1952); K. W. Bentley, R. Robinson and A. E. Wain, *J. Chem. Soc.*, 958 (1952).

(26) S. P. Findlay and L. F. Small, THIS JOURNAL, **72**, 3247 (1950); **73**, 4001 (1951).



close any obvious indication of such effect. The special feature of the phenolic hydroxyl group in thebainone-B may well be responsible for the intervention of the stereochemically abnormal reaction.

It is certainly true that the preferential formation of β-thebainone-A from thebainone-B must be rate- rather than equilibrium-controlled, for the equilibrium mixture of thebainone-A and β-thebainone-A contains a lower percentage (*ca.* 16%)[27] of β-thebainone-A than that (*ca.* 80%) isolated[24] in the potassium bisulfate hydrolysis–isomerization experiment. A tentative but specific hypothesis may deserve consideration, as follows. The enolic form XXI of the bisulfate ester which may be presumed to arise from thebainone-B could suffer internal proton transfer to C_{14} in only one steric sense—to give the β-configuration:



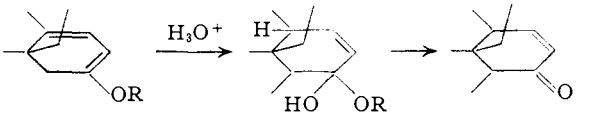
it is possible that this intramolecular process would be faster than one in which the solvated proton approaches from without, though the latter would give the normal epimer. But in the neopinone–codeinone change, where no such bisulfate ester is involved, it is reasonable to assume that the proton is delivered from the less hindered side of the enol XVI, that is *cis* to the nitrogen bridge, as is common in the morphine series with other reagents as well.[28] It is then not surprising that this external attack proceeds much more slowly than the internal one.

(27) M. Gates and R. Helg, THIS JOURNAL, **75**, 379 (1953).

(28) Thus catalytic hydrogenation of an 8,14-double bond quite generally results in the production of the normal configuration at C_{14} [*cf.* G. Stork, ref. 4, p. 175] and the peracid hydroxylation of thebaine results in a 14-hydroxycodeinone [M. Freund and E. Speyer, *J. prakt. Chem.*, **94**, 135 (1916)] in which it has been shown that the hydroxyl group is *cis* to the ethanamine bridge [C. Schöpf and F. Borkowsky, *Ann.*, **452**, 249 (1927)].

Thebaine in aqueous potassium bisulfate solution after standing for 19 days at 25°, gave a mixture of codeinone and 8-hydroxy-7,8-dihydrocodeinone, along with some amorphous material, just as had been obtained with neopinone. The possibility that neopinone is the intermediate in this hydrolysis was ruled out by the observation that after only 20 hours the thebaine was mostly unchanged, but that (*ca.* 10%) which had undergone reaction was converted to codeinone. No neopinone was found by infrared spectroscopic examination of the total reaction product or of the mother liquor after the bulk of the thebaine had been removed. If any neopinone had been formed, most of it would have survived under these conditions (*vide supra*).

If codeinone is not formed from thebaine by way of neopinone, then it must arise by direct proton attack at C_{14} in thebaine, as shown. We are therefore presented with an interesting con-



I, R = CH_3
XVI, R = H

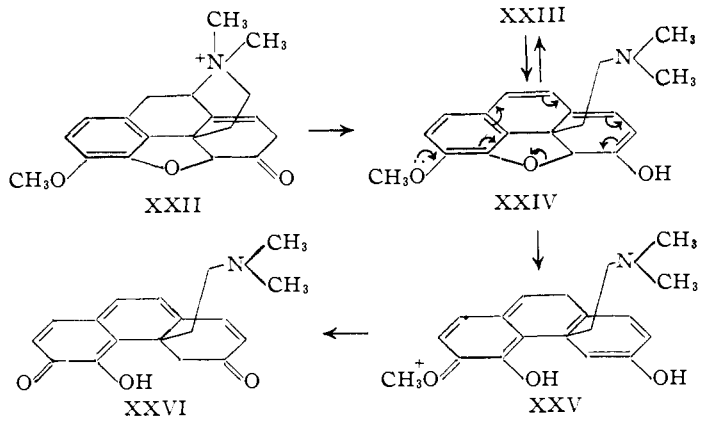
II

trast: Cationoid attack on the *neutral dienol ether* I, and probably on the dienol XVI itself, occurs more rapidly at the end of the conjugated system, but as indicated, irreversible proton attack on the corresponding *dienolate anion* X occurs on a central atom.

Degradation of Neopinone Methiodide.—Neopinone readily gives a crystalline methiodide $C_{19}H_{22}NO_3I \cdot H_2O$ (XXII), but it was not found possible to isolate a normal des-base XXIII on Hofmann elimination. Even under the mildest conditions, as with aqueous methanolic sodium bicarbonate at 40°, or on boiling with aqueous ethanol but no added base, the methiodide was degraded instead to an intensely colored violet substance. This compound, m.p. 183° after chromatography on Florisil, showed three maxima at 258, 385 and 528 mμ (CH_3OH); although not very satisfactory, the analytical figures were consistent with $C_{18}H_{19}NO_3$, indicating the loss of the elements of methyl iodide during the degradation. The spectrum was virtually unchanged in a dilute acidic medium, but was altered in base, facts strongly suggesting the presence of an acidic grouping contiguous to the chromophore, but also that the nitrogen atom is not a part of the absorbing system. These features are best accommodated in the quinone XXVI formed as shown.

The first step is analogous to the conversion of thebainone-B methiodide to its methine,[29] which likewise proceeds under very mild conditions, and is believed to involve thebainone-B enol as an intermediate. The parallel to the thebainone series ends with the change (XXIV → XXV), unusual in that it represents a case of cleavage of the oxide bridge under basic conditions, but rendered facile by the extended conjugated system allowing an exceptional degree of resonance stabilization. The

(29) K. W. Bentley and R. Robinson, *Experientia*, **6**, 353 (1950); K. W. Bentley, R. Robinson and A. E. Wain, *J. Chem. Soc.*, 958 (1952).



hydrolysis of the methyl group, which otherwise would be unexpected under the conditions, is clearly aided by the positive charge on the adjacent oxygen in XXV. The possibility of aromatization of XXVI with expulsion of the angular chain as is the case, for example, in the degradation of thebaine to the thebaol[30] and derivatives, or of codeinone methiodide to 3-methoxy-4,6-dihydroxyphenanthrene,[30] was illustrated by the fact that on warming with concentrated hydrochloric acid the violet compound soon gave a nearly colorless solution, probably containing 3,4,6-trihydroxyphenanthrene.

Experimental

14-Bromocodeinone (IV).—Thebaine (62.2 g., 0.2 mole) was suspended in 200 ml. of 2:1 (by volume) acetone–water mixture. A solution of 37.0 g. (0.208 mole) of N-bromosuccinimide in 400 ml. of 2:1 acetone–water was run in with mechanical stirring over a period of 15 minutes. The temperature was maintained at 15–18° by external cooling during the addition, and thereafter for 10 minutes. One liter of water was added over a period of 30 minutes with stirring, when the bromocodeinone began to crystallize. Stirring was continued for one hour at 20°, and then for another two hours at 0–5°. The product was sucked dry and washed with 500 ml. of water. The yield, after drying at 60°, was 64 g. (85%). Although the literature[7] gives m.p. 156–157° for 14-bromocodeinone, we have had difficulty in obtaining this value either with crude or purified material. When the sample is inserted in the Hershberg apparatus heated to 157°, it melts to a deep red liquid immediately, but if inserted at 154° or below, it does not melt, even if the temperature is raised above 157°. Instead decomposition takes place in the solid state leading to brown amorphous and apparently infusible material. The crude 14-bromocodeinone prepared as given above is suitable directly for use in the reduction to neopinone, but it may be purified by recrystallization from benzene–ligroin with good recovery.

Neopinone (VI).—The crude 14-bromocodeinone (58.0 g., 0.154 mole) was dissolved in 300 ml. of chloroform and the solution was filtered to remove a trace of insoluble matter. Methanol (20 ml.) and 5.0 g. of 10% palladium-on-charcoal were added and the mixture hydrogenated in a low pressure shaker at 25°. After several hours the absorption practically ceased at a pressure drop corresponding to 97% of theory for one molar equivalent of hydrogen. The catalyst was removed by filtration, and the clear brownish solution of neopinone hydrobromide was shaken with a cold (0°) solution of 20.0 g. (0.145 mole) of potassium carbonate (anhydrous) in 200 ml. of water. The organic phase was washed three times with 300 ml. of ice-water, dried over 30 g. of anhydrous sodium sulfate and evaporated under reduced pressure below 40°. The solid crystalline residue was pumped dry in a good vacuum, and then recrystallized from 100 ml. of warm (40°) ethyl acetate. Thorough cooling to −20° was employed to obtain the maximum separation of product. The combined yield over several crops was 37.0 g. (81%) of colorless to pinkish needles, m.p. *ca.* 125° dec., depending on the rate of heating. For analysis a sample was recrystallized twice (again) from ethyl acetate. It gave $[\alpha]^{23}D$ −9.8° (chloroform, *c* 0.713); λ_{max} 1735 cm.$^{-1}$ (chloroform); λ_{max} 283 mμ, log ε 3.18 (ethanol); m.p. 132–133° (rapid heating).

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.87; H, 6.32; N, 5.13.

In later runs it was found desirable to make use of the somewhat better crystallizing properties of the neopinone–chloroform solvate, with which it was possible to obtain slightly higher yields of a colorless product. Thus in a preparation of the same scale as that above, the crude neopinone, after evaporation of most of the chloroform, was dissolved in 80 ml. of chloroform, when the addition of an equal amount of ethyl acetate caused crystallization of the solvate. The yield of colorless material, m.p. *ca.* 92° dec. (rapid heating), was 55 g. (86%); in chloroform solution the compound had an infrared spectrum identical with that of neopinone. The solvate is fairly stable in the air at 25°, but rapidly loses chloroform when heated to 100°. An air-dried sample lost 27.8% of its weight when heated to constant weight at 90–100°; the calculated percentage of chloroform for a 1:1 adduct is 28.5. Codeinone does not appear to form a stable chloroform solvate.

Codeinone (II).—A solution of 2.0 g. of neopinone in 20 ml. of ethyl acetate containing 2.0 g. of Darco G-60 activated charcoal was refluxed under nitrogen for two hours. The mixture was cooled and filtered, and the charcoal cake was washed with 20 ml. of hot ethyl acetate. The filtrates were combined and evaporated under reduced pressure until the codeinone began to crystallize; the product was left overnight in the refrigerator. The first crop, m.p. 182–182.5° dec., weighed 1.08 g. (54%). The infrared spectrum of the material was identical with that of an authentic sample.

Repetition of the experiment with the omission of the charcoal, but with other factors the same, gave neopinone (1.3 g.); no codeinone was obtained.

Neopine (VII). (A).—A solution of 2.0 g. of neopinone in 20 ml. of methanol was added to a suspension of 0.6 g. of sodium borohydride in 12 ml. of methanol. The mixture was allowed to stand at 25° for 90 minutes, then concentrated under reduced pressure, and diluted with 10 ml. of 10% sodium hydroxide. The solution was heated momentarily to boiling, diluted with 50 ml. of water and extracted with three 100-ml. portions of chloroform. The extract was washed with water, and the chloroform was removed by distillation. The neopine was left as a colorless glass, which slowly crystallized on seeding with a sample of authentic neopine base, and whose infrared spectrum in chloroform was identical with that of authentic neopine. A portion of the material was treated with excess aqueous alcoholic hydrobromic acid, whence the crystalline hydrobromide was obtained. After recrystallization from aqueous ethanol the salt had m.p. 284–286° dec., undepressed upon admixture with authentic neopine hydrobromide. The infrared spectra of the two samples of hydrobromide in Nujol suspension were identical.

14-Bromocodeine (IX).—A solution of 1.5 g. of sodium borohydride in 10 ml. of water was added to a stirred suspension of 5.0 g. of finely powdered recrystallized 14-bromocodeinone in 50 ml. of methanol. The temperature was maintained at 0–5° during the 10-minute period of addition. After another five minutes at 0° the solid was removed by filtration, washed with methanol, and with acetone. The solid, consisting of fine needles, weighed 3.8 g. (76%); its infrared spectrum showed the virtual absence of the 1679 cm.$^{-1}$ band of 14-bromocodeinone, but contained a peak at *ca.* 3400 cm.$^{-1}$ associated with the hydroxyl group. The sensitivity of the compound caused several failures in the attempt to recrystallize it, for there was obvious evidence of decomposition when it was warmed in solution. A satisfactory method, although attendant with some loss, consisted in dissolving the substance in the minimum quantity of chloroform at 25°, filtering, and adding acetone to cause crystalli-

(30) M. Freund and E. Gobel, *Ber.*, **28**, 941 (1895); L. Knorr, *ibid.*, **37**, 3499 (1904).

zation. Nearly colorless, twice recrystallized material, dec. *ca.* 150° (but melting when inserted in a bath > 150°), was analyzed.

Anal. Calcd. for $C_{18}H_{20}NO_3Br$: C, 57.15; H, 5.33; N, 3.70; Br, 21.13. Found: C, 57.75; H, 5.12; N, 4.05; Br, 20.68.

Neopine (VII). (B).—One gram of 14-bromocodeine (IX) was suspended in a solution of 1.0 g. of sodium borohydride in 15 ml. of 1:2 aqueous methanol. The mixture was kept at 40° for 90 minutes; hydrogen was evolved, and the solid dissolved in the course of this time. The workup was the same as that described above for the sodium borohydride reduction of neopinone. The neopine hydrobromide was recrystallized twice from aqueous ethanol and identified as such by comparison of the infrared spectrum with that of authentic material.

Alkaline Dimerization. (A) **With Neopinone.**—Two grams of neopinone–chloroform solvate and 20 ml. of benzene were added to a solution of 1.0 g. of potassium hydroxide in 15 ml. of water. The mixture was stirred vigorously under nitrogen so as to maintain an emulsion. After one hour the layers were separated, the aqueous phase was extracted with benzene, and the combined benzene extracts were washed twice with water. The gum remaining after evaporation of the benzene was taken up in ethyl acetate when the dimer was obtained in crystalline condition immediately. In one run the yield was 0.81 g., in a second run 0.87 g. (58 ± 3%), of material m.p. *ca.* 245° dec. For analysis a portion was recrystallized from chloroform–ether; the sample had m.p. *ca.* 245° dec., the value depending on the rate of heating; the ultraviolet maxima (ethanol) were at 230 mμ ($E^{1\%}_{1\ cm}$ 305) and 281 mμ ($E^{1\%}_{1\ cm}$ 48.2), the infrared spectrum had bands at 1681 and 1733 cm.$^{-1}$ (chloroform) and a molecular weight determination (ebullioscopic, in benzene) gave the value 639.

Anal. Calcd. for $C_{36}H_{38}O_6N_2$: mol. wt., 594; C, 72.71; H, 6.44; N, 4.71. Found: C, 72.67; H, 6.41; N, 4.12, 4.32, 4.05.

(B) **With Neopinone and Codeinone.**—Two grams of neopinone–chloroform solvate and 20 ml. of benzene were added to a suspension of 1.0 g. of codeinone in a solution of 1.0 g. of potassium hydroxide in 15 ml. of water. The reaction was carried out and worked up exactly as described above in (A). In one run the yield was 1.64 g. (115% of theory based on neopinone alone) of crude crystalline material indistinguishable from that produced in (A); the yield after one recrystallization from chloroform–ethyl acetate was 1.52 g. (106%) of material whose infrared spectrum was the same as that of the analytical sample.

Reaction of Neopinone with Aqueous Potassium Bisulfate.—Two grams of neopinone–chloroform solvate was dissolved in a solution of 4.0 g. of potassium bisulfate in 20 ml. of water. After standing under nitrogen for 20 hours at 25° the mixture was neutralized with sodium bicarbonate and the oily precipitate taken up in chloroform. Partial evaporation of the chloroform and the addition of ethyl acetate caused the crystallization of unchanged neopinone (as chloroform solvate). The recovery amounted to 1.7 g. (85%). When a similar solution of neopinone in potassium bisulfate was allowed to stand for 19 days there was obtained after neutralization an amorphous solid (0.4 g.) quite insoluble in chloroform, as well as a chloroform soluble fraction (1.1 g.). The latter yielded some codeinone by trituration with cold ethyl acetate. A sample of the chloroform soluble fraction gave an infrared spectrum identical with that of an equimolar mixture of codeinone and 8-hydroxy-7,8-dihydrocodeinone. The infrared spectrum of the latter compound is characterized by bands at 3300 and 1727 cm.$^{-1}$

Reaction of Thebaine with Aqueous Potassium Bisulfate.—Thebaine (1.5 g.) was dissolved in a solution of 4.0 g. of potassium bisulfate in 20 ml. of water. After standing under nitrogen for 20 hours at 25° the mixture was neutralized with sodium bicarbonate and the oily precipitate was taken up in chloroform. Evaporation of the chloroform left a crystalline residue consisting largely of unchanged thebaine, but containing a small proportion (*ca.* 10%) of codeinone as estimated from the 1679 cm.$^{-1}$ band in the infrared spectrum. The intense 1735 cm.$^{-1}$ band of neopinone was not present. When a similar solution of thebaine in potassium bisulfate was allowed to stand at 25° for 19 days there was obtained after neutralization and chloroform extraction an amorphous solid (0.4 g.) and 1.1 g. of a mixture of approximately equal parts of codeinone and 8-hydroxy-7,8-dihydrocodeinone, as determined by infrared spectra.

Neopinone Methiodide (XXII).—Five milliliters of methyl iodide was added to a solution of 5.0 g. of neopinone in 20 ml. of benzene, and the mixture was allowed to stand at 25° for 30 minutes. The methiodide, which precipitated as an amorphous white solid, was obtained by filtration. Trituration of the material with 10–20 ml. of cold aqueous methanol caused it to assume the crystalline form. The yield was 6.5 g. (88%) of substance with m.p. 154–155° dec. For analysis a sample was recrystallized by dissolving it in the minimum quantity of hot water, cooling rapidly, and adding ethanol. Undue prolongation of the crystallization procedure leads to decomposition of the material and the formation of the violet compound XXVI. The methiodide was obtained as colorless needles, m.p. 154° dec.

Anal. Calcd. for $C_{19}H_{22}O_3NI\cdot H_2O$: C, 48.90; H, 5.29; N, 3.06. Found: C, 50.17; H, 5.51; N, 3.10.

Formation of the Violet Substance (XXVI).—Two grams of neopinone methiodide and 0.50 g. of sodium bicarbonate were dissolved in 20 ml. of 1:1 aqueous methanol; the mixture was stirred at 40–50° for two hours. The nearly black liquid was diluted with 100 ml. of water and allowed to stand in order to allow completion of precipitation of the crude dyestuff. After drying, the black material which weighed approximately 150 mg. was dissolved in chloroform and the deeply colored solution chromatographed on 500 g. of Florisil. The most intensely colored fraction, eluted with methanol–chloroform, gave black crystalline material upon evaporation to dryness. After one recrystallization from aqueous methanol, the yield of tiny black needles, m.p. 183°, was 25 mg.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 71.26; H, 7.09; N, 3.72.

The absorption maxima in methanol were at 528 mμ (293), 385 mμ (268), 258 mμ (270) with a shoulder at 305 mμ (137); maxima in 10% methanol 0.1 *N* in hydrochloric acid were 538 mμ (314), 382 mμ (307), 258 mμ (300); maxima in 10% methanol 0.1 *N* in sodium hydroxide were 551 mμ (156); 377 mμ (215), 245 mμ (442). (Values in brackets are $E^{1\%}_{1\ cm}$).

Acknowledgment.—We wish to express our thanks to Dr. Lyndon F. Small, Dr. Marshall Gates and Dr. Henry Rapoport, who very kindly furnished samples of various derivatives for comparison.

RAHWAY, NEW JERSEY