$$ROH + SOCl_2 \longrightarrow ROSOCl + HCl \qquad (4)$$

$$ROSOCl \longrightarrow RCl + SO_2 \qquad (5)$$

carried out in thionyl chloride, without the use of pyridine, and the chlorosulfite esters have shown very low stability, in contrast to the cyclic sulfite esters formed from glycols and the sulfur groupings encountered in the present work. The isolation of products D and E, with a higher degree of sulfur substitution than of chlorine substitution, seems to be evidence against the presence of chlorosulfite esters in the chlorocelluloses.

Since only three isomeric monochloroglucoses (2-, 3-, and 6-) are possible, the isolation of four isomers from a chlorocellulose hydrolyzate raises the possibility of Walden inversion on either carbon 2 or 3 to give a monochloromannose or aldose. This type of alkyl-oxygen fission can occur either by reaction 3 or reaction 5. There is also a possibility of 2,3- and 3,6-anhydro derivatives being formed, either with or without chlorine. The latter possibility is shown by the isolation of three crude fractions (5–1, 5–2, and 6–2) with low chlorine contents. Ohle and co-workers[19] have reported the isolation of a 3,6-anhydro-1,2-isopropylidene-5-*O*-tosyl-D-glucose by the action of tosyl chloride and pyridine on 1,2-*O*-isopropylidene-D-glucofuranose.

Assuming that each sulfur atom in a chlorocellulose is linked to three oxygen atoms as a sulfite ester, it can be calculated that the empirical formulas of chlorocelluloses A, B, and C contain 0.6, 0.86, and 0.77 oxygen atoms in excess of the number necessary to combine with hydrogen as hydroxyl groups. This is a further indication of the possible presence of anhydro-ring formation.

Acknowledgments. Gratitude is expressed to B. L. Browning and members of the analytical group of The Institute of Paper Chemistry for the carbon and hydrogen determinations reported herein. This paper represents a portion of a thesis submitted in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence College, Appleton, Wis., June, 1953. This work was done under the direction of John W. Green.

APPLETON, WIS.

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[19] H. Ohle and E. Dickhauser, *Ber.*, **58**, 2593 (1925); H. Ohle, L. von Vargha, and H. Erlbach, *Ber.*, **61**, 1211 (1928).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

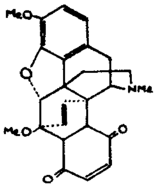
Acid-Catalyzed Rearrangements in the Nepenthone Series

K. W. BENTLEY AND J. C. BALL

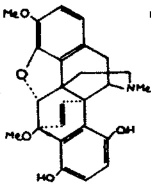
Received January 20, 1958

Thebaine on condensation with phenyl vinyl ketone affords a Diels-Alder adduct, nepenthone,[1] which has been rearranged in acid solution. Reduction affords nepenthol, which has been dehydrated to an olefin, nepenthene, and both nepenthol and nepenthene have been rearranged to flavonepenthone, an analog of flavothebaone. Mechanisms are advanced for the changes reported.

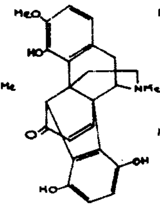
Thebaine, on condensation with *p*-benzoquinone affords the adduct (I)[2,3] which can be isomerized by acids to the quinol (II), and this on heating with hydrochloric acid undergoes a concerted opening of the cyclic ether and 1:2-shift of the quinol nucleus, giving flavothebaone[3–5] which has the structure (III).[4,5] During work on the structure of the last named base attempts were made to effect a similar rearrangement in somewhat simpler compounds.



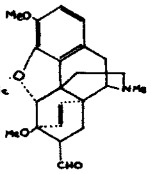
(I)



(II)



(III)



(IV)

The simplest thebaine adduct reported in the literature is thebaine-acrolein (IV),[6] but attempts to rearrange this in acid solution led to the immediate production of black intractable materials. The adduct of thebaine and phenyl vinyl ketone (V) was obtained from the two components in excellent yield, and was subjected to a variety of transformations. On account of the extremely

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[1] K. W. Bentley and J. C. Ball, *Chem. & Ind.* (*London*), 1428 (1956).

[2] W. Sandermann, *Ber.*, **71**, 648 (1938).

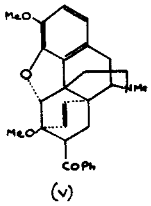
[3] C. Schöpf, K. von Gottberg, and W. Petri, *Ann.*, **536**, 216 (1938).

[4] K. W. Bentley, J. Dominguez, and J. P. Ringe, *Chem. & Ind.* (*London*), 1353 (1956); *J. Org. Chem.*, **21**, 1348 (1956); **22**, 409, 418, 422, 424, 599 (1957).

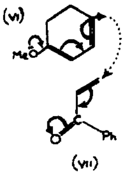
[5] J. Meinwald and G. A. Wiley, *Chem. & Ind.* (*London*), 957 (1956); *J. Am. Chem. Soc.*, **79**, 2569 (1957).

[6] S. I. Kaneveskaya and S. F. Mitryagina, *J. Gen. Chem. U.S.S.R.*, **17**, 1023 (1947).

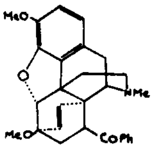
cumbersome nature of the systematic names for the Diels-Alder adducts of thebaine in general and of the phenyl vinyl ketone adduct in particular this substance was assigned the trivial name "nepenthone" in order to simplify subsequent discussion of the results.



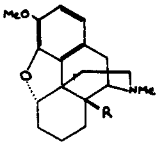
(V)



(VII)



(VIII)



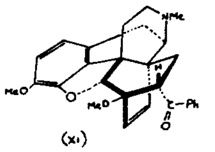
(IX)

TABLE I

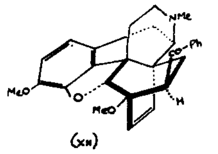
Base	pK	Mol. Wt., Found	Mol. Wt., Calcd.
Morphine	6.85	285	285
Thebaine	6.80	313	311
14-Hydroxycodeinone	6.65	310	313
Codeine	6.60	300	299
Nepenthone	5.80	443	443
Nepenthol	5.80	443	445
Flavonepenthone	5.80	417	413
Thebaine-acrolein	5.80		
Thebaine–methyl vinyl ketone	5.80	381	381
Dihydrothebaine-quinone	5.25	419	421
14-Acetoxycodeinone	5.25	358	355
Thebainequinone	4.90	—	—
Dimethylthebaine-maleate	4.80	—	—

The adduct was formulated as V rather than as VIII on consideration of the potential electronic shifts shown in VI and VII, in which electrons are most available at $C_{(14)}$ of thebaine and the terminal carbon atom of the vinyl group in the unsaturated ketone is electron-deficient. The adduct appeared to consist exclusively of one isomer, and a careful examination of the mother liquors failed to reveal any of the isomeric VIII. However, in order to place any interpretation of the complex reactions of nepenthone on a sure foundation it soon became essential to have definite evidence on this structural point. The assignment of structure V to nepenthone was strongly supported by the basic strengths of the adduct, its derivatives, and several other bases of the morphine-thebaine group. The basic strengths of the compounds examined were found to be quite sharply divided into three groups (see table) as follows: (a) Bases of the type IX, where R = H or OH, with pK about 6.70; (b) Bases of the nepenthone series, where on the basis of structure V R = $CH—CH_2$, with pK about 5.80; (c) Bases such as the adduct I where R = $CH—C=O$ or $O—C=O$, with pK about 5.0.

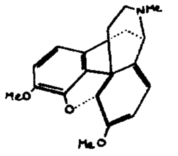
The marked difference in the basic strengths of the bases of groups (a) and (c) is due partly to steric hindrance at the nitrogen atom by the substituent at $C_{(14)}$ and partly to interaction between the nitrogen atom and the unsaturated carbonyl group suitably placed, in space. Adducts such as nepenthone, thebaine-acrolein and, thebaine–methyl vinyl ketone show a much smaller reduction in basic strength, indicating that the carbonyl group is further removed from the nitrogen atom than it is in, say, thebainequinone (I), and the possibility that nepenthone has the structure (VIII) may thus be discounted. The potentiometric titrations by which the basic strengths were determined provided a very accurate method of determination of the molecular weights of the bases, and this proved of great value in the investigation. The stereochemistry of nepenthone is of importance in a consideration of the transformations of this base. Addition of the dienophile to thebaine would be expected to occur on the least hindered side of the molecule (X) and to give the *endo* product XI, rather than the epimeric *exo* compound (XII), as the production of the former would involve the greatest overlap of the two unsaturated groups during the addition process. In support of this view it was found impossible to hydrogenate the double bond of nepenthone, as would be expected on the basis of the structure (XI), in which the ethylenic bridge is shielded by the other parts of the molecule, whereas in the epimeric structure (XII) such screening is not present. It may be noted that the ethylenic bridge in thebaine quinone, assigned the structure (XIII) by Schöpf,[3] is unreducible. Two oximes, presumably geometrical isomers, can be prepared from nepenthone.



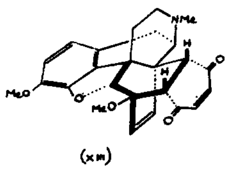
(XI)



(XII)



(X)

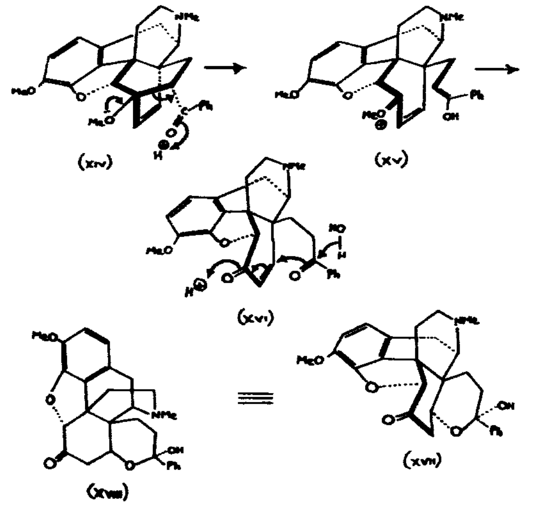


(XIII)

Nepenthone was found to be stable in dilute acids, being recovered unchanged after boiling for four hours with 5% hydrochloric acid, but on heating with concentrated hydrochloric acid and glacial acetic acid at 100° (the conditions of the thebainequinol→flavothebaone transformation) it afforded two bases, neonepenthone-A and neonepenthone-B, in yields of approximately 25% and 10%, respectively.

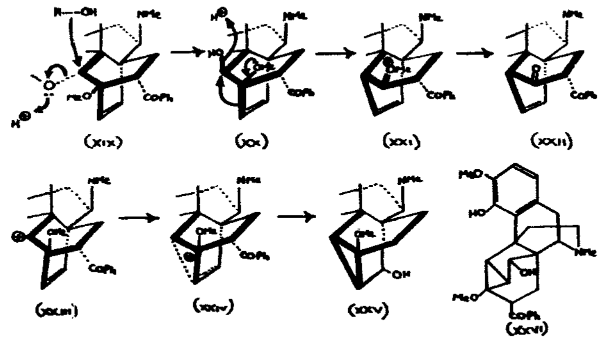
Neonepenthone-A, m.p. 135°, is nonphenolic and has the composition $C_{27}H_{29}O_5N$, *i.e.* nepenthone $C_{28}H_{29}O_4N$ $-$ CH_2 $+$ H_2O. The infrared spectrum shows a hydroxyl band at 3430 cm.$^{-1}$ (2.94μ), and one carbonyl band at 1717 cm.$^{-1}$

(5.83μ), indicating that the compound contains only a saturated ketone system.



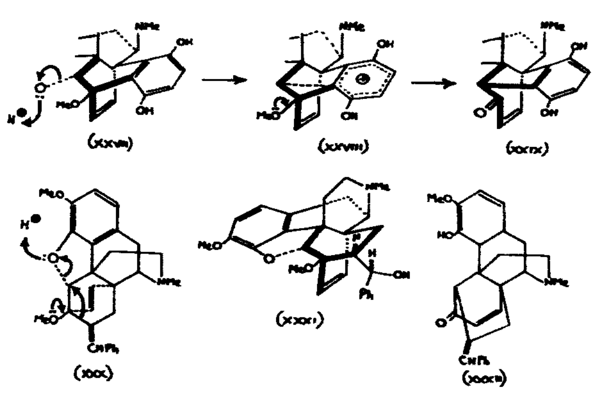
Clearly the transformation involved in the production of neonepenthone-A from nepenthone is different from the flavothebaone rearrangement, and the processes XIV → XVI might be initiated by attack of the aromatic carbonyl group of nepenthone by a proton. This is in essence an acid-catalyzed dealdolization, and the product may well exist in the acid mixture as XIV, which, during isolation and purification, could suffer addition of the aromatic carbonyl group to the $\alpha\beta$-unsaturated ketone system, XVI → XVII. This would lead to the formulation of neonepenthone-A as the saturated ketone (XVIII). Only in this way can the single carbonyl infrared absorption at 1717 cm.$^{-1}$ (5.83μ) be rationally accounted for. Nothing further is known about neonepenthone-A.

Neonepenthone-B, m.p. 275°, obtained in about 10% yield, is phenolic and has the composition $C_{28}H_{31}O_5N$ (mol. wt. calcd. 461, found 464) *i.e.* nepenthone $C_{28}H_{29}O_4N + H_2O$; the infrared spectrum contains a hydroxyl band at 3470 cm.$^{-1}$ (2.85μ) and a carbonyl band at 1670 cm.$^{-1}$ (5.98μ). One simple explanation of these properties would be that a hydrolytic fission of the oxide bridge of nepenthone had taken place as depicted in the partial structures XIX → XX, but it seems highly unlikely that this explanation is correct, as XX, under the strongly acid conditions, would be expected to undergo the geometrically favorable 1:2-shift of the ethylenic bridge, giving finally the ketone XXII.



A more plausible process is depicted in the partial-structures (XXIII) → (XXV), in which the classical carbonium ion resulting from opening of the oxide ring becomes the non-classical bridged ion (XXIV), which then adds a hydroxyl group at the least hindered position giving XXV. On the basis of these changes neonepenthone-B may be represented as XXVI. Zeisel determination shows the presence of only one methoxyl group in neonepenthone-B, whereas, the structure XXVI contains two such groups; however the methoxyl group of XXV, which is highly hindered might not be affected under the conditions normally used in the Zeisel determination, though the low methoxyl value may be due to solubility reasons.[7]

It was inferred from the failure of the acid treatment of nepenthone to give an analog of flavothebaone that the production of the latter from thebainequinol involves the participation of the aromatic nucleus in a nonclassical ion as shown in the partial-structures XXVII → XXVIII → XXIX, and that when formation of such an ion cannot take place, the reaction can take a different course with the participation of the ethylenic bridge instead, XXIII → XXV. Accordingly we felt that it should be possible to prepare an analog of flavothebaone from the styrene (XXX).



Nepenthone on reduction with aluminium isopropoxide or with sodium borohydride affords the related alcohol, nepenthol. Models indicate that on steric grounds the reduction will afford the epimer (XXXI). Unlike nepenthone, nepenthol is rearranged in 90% yield in hot concentrated hydrochloric acid and glacial acetic acid solution, giving a new base, named flavonepenthone by analogy with flavothebaone, although the characteristic yellow color of the last named base is not observed.

Color reaction with diazotized sulfanilic acid and with quinone chloroimine, together with the

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(7) Phenyldihydrothebaine derivatives consistently give methoxyl values for one methoxyl group less than actually present under the normal conditions of the Zeisel determination, presumably for solubility reasons [L. F. Small, L. J. Sargent, and J. A. Bralley, *J. Org. Chem.*, 12, 839 (1947)].

alkali-solubility of flavonepenthone clearly demonstrate that this base is phenolic, and in confirmation of this a monoacetyl derivative and a monomethyl ether have been prepared. Analyses indicate the composition $C_{27}H_{27}O_3N$, showing that H_2O as well as CH_2 is lost during the rearrangement, and in agreement with this the ultraviolet absorption spectrum is styrenoid; the spectrum also shows the long wave length band with λ_{max} 3,400 A and ϵ_{max} 2,500, which is an outstanding feature of the ultraviolet spectrum of flavothebaone. The infrared spectrum of flavonepenthone shows an $\alpha\beta$-unsaturated carbonyl absorption band at 1675 cm.$^{-1}$ (5.96μ), which is shifted to 1710 cm.$^{-1}$ (5.85μ) when the base is reduced to a tetrahydro derivative with sodium amalgam; the styrenoid ultraviolet absorption also disappears during this reduction.

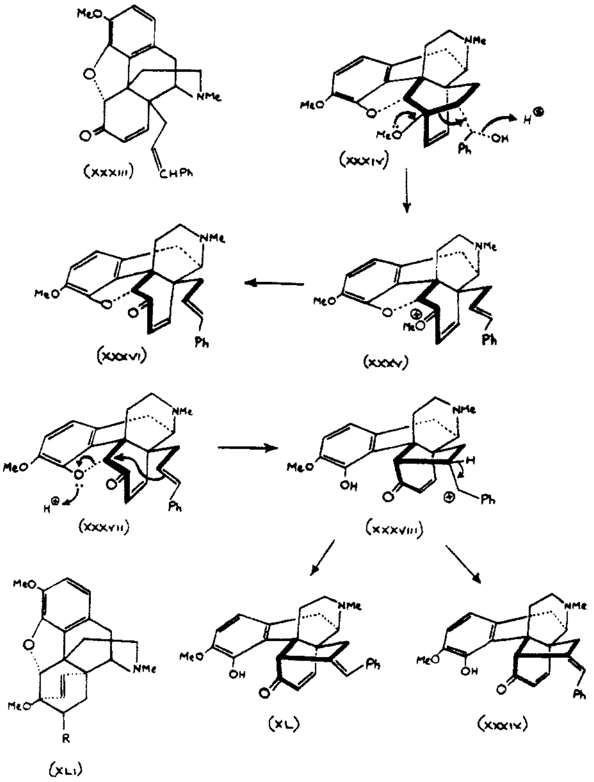
All these properties clearly point to the structure (XXXII) for flavonepenthone, which could arise as a result of the dehydration of nepenthol (XXXI) to the olefin (XXX) followed by the predicted 1:2-shift of the PhCH=C—CH$_2$-bridge. The similarity of the ultraviolet spectra of flavonepenthone and flavothebaone in the region 3,200–3,600 Å is, as already indicated,[4] strong support for the view that the long wave length band common to these spectra is due to perturbation of the orbitals of the cyclohexenone system by the other unsaturated group (styrene and quinol, respectively) present in the molecules of these bases.

The separation of the rearrangement of nepenthol to flavonepenthone into two distinguishable and perhaps non-simultaneous steps led logically to an attempt to prepare the olefin (XXX) and realize the 1:2-shift of the bridge as a separate reaction. The dehydration of nepenthol was accomplished by heating with anhydrous formic acid at 100° for sixteen hours, and the new base, nepenthene, so obtained was found to give flavonepenthone when heated with concentrated hydrochloric acid. However, the dehydration is not the simple process envisaged, since nepenthene shows a prominent unsaturated carbonyl absorption band at 1663 cm.$^{-1}$ (6.01μ) in its infrared spectrum. The analytical data indicate a composition $C_{27}H_{27}O_3N$ isomeric with that of flavonepenthone. The ultraviolet spectrum is styrenoid, and this together with the absence of hydroxyl absorption bands in the infrared spectrum shows that dehydration has certainly occurred. The oxide ring is still intact since nepenthene is non-phenolic. Catalytic reduction involves saturation only of the styrenoid double bond, giving dihydronepenthene, whereas sodium amalgam reduction gives only a non-crystalline product in which the carbonyl group is saturated as shown by the infrared spectrum which contains only one carbonyl absorption band, and that at 1703 cm.$^{-1}$ (5.86μ) compared with 1663 cm.$^{-1}$ (6.01μ) in nepenthene.

Only the structure XXXIII appears satisfactorily to account for these facts. The dehydration of nepenthol to nepenthene may be depicted as in the structures XXXIV→XXXVI. The conversion of nepenthene into flavonepenthone presents no real problem, and may be represented as in XXXVII→XXXIX. On steric grounds there seems little to choose between the structures XXXIX and XL for flavonepenthone, and under acid conditions interconversion through an ion such as XXXVIII is possible. If anything XXXIX involves the least steric compression of groups.

Attempts to degrade nepenthone and flavonepenthone proved fruitless. No quaternary salts or *N*-oxides could be formed, presumably as a result of steric hindrance at the nitrogen atom; no adduct could be prepared from thebaine methiodide and phenyl vinyl ketone. Neither double bond in flavonepenthone could be attacked with peracids or with alkaline hydrogen peroxide.

Thebaine has also been condensed with methyl vinyl ketone and with acrylonitrile to give the adducts (XLI, R = CO.CH$_3$) and (XLI, R = CN), respectively; the second of these has also been prepared by the dehydration of the oxime (XLI, R = CH=N.OH) of the acrolein adduct IV.



EXPERIMENTAL

Phenyl vinyl ketone. The method described by Mannich[8] was modified as follows. Acetophenone (80 g.), powdered paraformaldehyde (20 g.), and dimethylamine hydrochloride (55 g.) were heated together under reflux in ethanol (100 ml.). After 10 min. a clear solution was obtained, and after 0.5 hr. 80 ml. of ethanol were removed by distillation

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[8] C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922).

Acetone (300 ml.) was added to the hot residue and the resulting solution transferred at once to a beaker. Colorless crystals of ω-dimethylaminopropiophenone hydrochloride, m.p. 156° (98 g.) separated rapidly. The salt was collected and dried and steam distilled until about two liters of distillate had been collected. A small amount of quinol was added to the distillate which was then extracted with ether. The ether extract was dried over sodium sulfate and evaporated, and the residue distilled, when 21 g. of phenyl vinyl ketone, b.p. 98–97°/15 mm., was obtained.

Nepenthone (V). Freshly distilled phenyl vinyl ketone (26 g.) together with a small amount of quinol, was added to a solution of thebaine (60 g.) in boiling benzene (240 ml.), and the resulting solution boiled under reflux for 2 hr. The benzene was removed by distillation *in vacuo.* Hot alcohol (450 ml.) was added and the solution allowed to cool, when *nepenthone* separated as irregular plates, m.p. 155°, after recrystallization from ethanol. Yield 60 g. $[\alpha]^{20}_{D}$ −232° ($CHCl_3$, *c* 1.09). λ_{max} 2,400 Å; ϵ_{max} 2,630.

Anal. Calcd. for $C_{28}H_{28}O_4N$: C, 75.8; H, 6.6; (2)OMe, 14.4. Found: C, 75.6; H, 6.4; OMe, 14.4%.

In an attempt to prepare a methiodide of nepenthone thebaine methiodide was recovered unchanged after heating under reflux with phenyl vinyl ketone in chloroform for 4 hr.

Oximes. Nepenthone (10 g.), hydroxylamine hydrochloride (10 g.), water (100 ml.), and ethanol (10 ml.) were heated together under reflux for 5 hr. Ammonia solution was added to the cooled mixture and the precipitated material triturated with ether. The resulting solid matter was collected, dissolved in 2-ethoxyethanol (150 ml.), and the solution was filtered, evaporated to about 70 ml., and diluted with water (20 ml.). On cooling 5.7 g. of crystalline material was obtained, and this was recrystallized from 80% 2-ethoxyethanol, when *nepenthoxime-*I was obtained as colorless prisms, m.p. 270°, $[\alpha]^{22}_{D}$ −254° ($CHCl_3$, *c* 0.83).

Anal. Calcd. for $C_{28}H_{30}O_4N_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.3; H, 6.7; N, 6.2%.

Evaporation of the mother liquors from the isolation of nepenthoxime-I afforded a viscous gum, which crystallized readily from acetone. Recrystallization from acetone afforded 3.1 g. of *nepenthoxime-II*, m.p. 188°, $[\alpha]^{21}_{D}$ −242° ($CHCl_3$, *c* 1.09). This oxime was much more soluble than nepenthoxime-I in organic solvents.

Anal. Calcd. for $C_{28}H_{30}O_4N_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.1; H, 6.6; N, 5.9%.

Acid-catalyzed rearrangement of nepenthone: neonepenthone-A and neonepenthone-B. Nepenthone (10 g.) was dissolved in glacial acetic acid (30 ml.) and concentrated hydrochloric acid (30 ml.), and the mixture was heated on the steam bath for 6 hr., during which time it became deep green. Removal of volatile material *in vacuo*, followed by treatment of the resulting sirup with methanol afforded a colorless crystalline salt (2.90 g.), which was collected and dissolved in water and the solution treated with hot aqueous sodium carbonate, when *neonepenthone-A* was obtained. This was recovered as colorless rods, m.p. 135°.

Anal. Calcd. for $C_{27}H_{29}O_5N$: C, 72.5; H, 6.6; (1)OMe, 6.9%; M.W. 447. Found: C, 72.5; H, 6.6; OMe, 7.4; mol. wt. (potentiometric titration), 442.

The base was appreciably soluble in organic solvents, and gave negative color reactions with diazotized sulfanilic acid and quinone chloroimine.

The mother liquors from the isolation of neonepenthone-A were basified with ammonia and diluted with water. The precipitated material crystallized on trituration with ether. When this material was recrystallized from 2-ethoxyethanol (50 ml.) 1.0 g. of *neonepenthone*-B, m.p. 273°, was obtained.

Anal. Calcd. for $C_{28}H_{31}O_5N$: C, 72.8; H, 6.7; (2)OMe, 13.5%; M.W., 461. Found: C, 72.9; H, 6.7; OMe, 7.8%; mol. wt. (potentiometric titration), 464.

Unlike neonepenthone-A this base is sparingly soluble in organic solvents and gives a deep red color on coupling with diazotized sulfanilic acid in alkaline solution and gives a deep green color with quinone chloroimine.

Nepenthol. (a) Nepenthone (64 g.) was heated with aluminum isopropoxide (120 g.) in boiling 2-propanol (320 ml.) with mechanical stirring. The mixture was slowly distilled through a fractionating column in such a way that a distillate was collected at the rate of about five drops per minute. Distillation was continued until the distillate no longer gave a precipitate with 2,4-dinitrophenylhydrazine hydrochloride solution (about 2.5 hr.). The reaction mixture was then poured into ice water (1500 ml.) containing concentrated hydrochloride acid (200 ml.). An excess of Rochelle salt solution was then added, and the mixture basified with aqueous sodium hydroxide, and the precipitated organic base extracted with chloroform. Evaporation of the extract and recrystallization of the residue from 2-ethoxyethanol gave 54.5 g. of nepenthol as colorless rods, m.p. 210°, $[\alpha]^{21}_{D}$ −136° ($CHCl_3$, *c* 1.25). λ_{max} 2400, 2890 Å; ϵ_{max} 6,310, 1,738.

Anal. Calcd. for $C_{29}H_{31}O_4N$: C, 75.4; H, 7.1. Found: C, 75.0, 75.8; H, 7.1, 7.1%.

(b) Sodium borohydride (0.40 g.) in methanol (10 ml.) was added to a suspension of nepenthone (5 g.) in cold methanol (100 ml.). When the mixture was heated to the boiling point and allowed to cool to room temperature nepenthol (1.5 g.), was obtained, melting point and mixed melting point with nepenthol prepared as in (a), 210°, $[\alpha]^{18}_{D}$ −136° ($CHCl_3$, *c* 0.87).

The *acetyl derivative* was obtained by the usual acetic anhydride/pyridine treatment, and on recrystallization from methanol was recovered as prisms m.p. 153°.

Anal. Calcd. for $C_{30}H_{33}O_5N$: C, 73.9; H, 6.8; OAc, 8.8. Found: C, 73.6; H, 6.9; OAc, 9.3%.

Nepenthene (XXXI). Nepenthol (1.94 g.) was dissolved in 98–100% formic acid (20 ml.) and the mixture was heated under reflux for 16 hr. The resulting solution was diluted with water, made alkaline with ammonia, and the white precipitate collected and recrystallized from a methanol/2-ethoxyethanol mixture, when *nepenthene* (1.38 g.) was obtained as needles m.p. 225°, $[\alpha]^{24}_{D}$ +87° ($CHCl_3$, *c* 0.41), λ_{max} 2400, 2860 (inflexion) Å; ϵ_{max} 24,000, 7,080.

Anal. Calcd. for $C_{27}H_{27}O_3N$: C, 78.4; H, 6.6; (1)OMe, 7.5. Found: C, 78.7; H, 6.5; OMe, 7.8%.

The base was insoluble in alkali, and gave no indication of coupling with diazotized sulfanilic acid.

Dihydronepenthene. Nepenthene (3.0 g.) in glacial acetic acid (30 ml.) was shaken under hydrogen at room temperature and pressure in the presence of platinum oxide (0.1 g.). Absorption of hydrogen was slow, and a further 0.1 g. of platinum oxide was added after 2.5 hr. After 6 hr. one mole of hydrogen had been absorbed, and the rate of hydrogenation slowed down, but the reaction did not cease entirely. The solution was freed from catalyst, evaporated *in vacuo* and the residue was dissolved in water and the solution made alkaline with ammonia. The precipitated base was collected and recrystallized from a methanol/2-ethoxyethanol mixture, when *dihydronepenthene* was obtained as plates, m.p. 179°, λ_{max} 2750 Å; ϵ_{max} 3,550.

Anal. Calcd. for $C_{27}H_{29}O_3N$: C, 78.0; H, 7.0. Found: C, 77.7; H, 7.1%.

Flavonepenthone (XXXII). (a) Nepenthol (51 g.) was dissolved in hot glacial acetic acid (150 ml.), and concentrated hydrochloric acid (150 ml.) added. The mixture was then heated on the steam bath for 4 hr.; after 1 hr. a pale yellow crystalline solid separated. The mixture was cooled and the solid matter collected (43.5 g.) and washed with concentrated hydrochloric acid. Flavonepenthone hydrochloride thus obtained had m.p. over 300°.

Anal. Calcd. for $C_{27}H_{27}O_3N.HCl.{}^1/_2H_2O$:C, 70.6; H, 6.4; Cl, 7.7. Found: C, 70.4; H, 6.4; H, 7.8%.

The free base was recovered from the hydrochloride by treating the salt with hot aqueous sodium carbonate. Recrystallization from 2-ethoxyethanol afforded flavonepenthone as colorless rods m.p. 263°, $[\alpha]_D^{18}$ +33° ($CHCl_3$-*c* 0.65) λ_{max} 2500, 3400 Å: ϵ_{max} 21,880, 2,500.

Anal. Calcd. for $C_{27}H_{27}O_3N$: C, 78.3; H, 6.6%; M.W., 413. Found: C, 78.2; H, 6.5%; mol. wt. (potentiometric titration), 417.

The base was readily soluble in alkalis, and the solution gave a deep red color on treatment with diazotized sulfanilic acid. It gave a deep green color with quinone chloroimine, a green color with ferric chloride, and an orange color with concentrated sulfuric acid.

(b) Nepenthene (0.81 g.) was dissolved in a mixture of glacial acetic acid (5 ml.) and concentrated hydrochloric acid (5 ml.) and the mixture heated on the steam bath for 6 hr. Water was added and the solution made alkaline with ammonia, which precipitated the free base. This was collected and recrystallized from 2-ethoxyethanol when flavonepenthone was obtained as colorless rods m.p. 263° alone or mixed with a specimen prepared as in (a).

Acetylflavonepenthone. Flavonepenthone (1.0 g.) was acetylated with acetic anhydride (1 ml.) in pyridine (10 ml.). The product was isolated in the usual way and recrystallized from ethanol, when *acetylflavonepenthone* was obtained as colorless rods m.p. 268°, mixed m.p. with flavonepenthone 235°.

Anal. Calcd. for $C_{29}H_{29}O_4N$: C, 76.5; H, 6.4. Found: C, 76.4; H, 6.3%.

Flavonepenthone methyl ether. Flavonepenthone hydrochloride (5 g.) was suspended in methyl sulfate (17 ml.) and a solution of sodium hydroxide (6.25 g.) in water (20 ml.) added slowly with vigorous stirring. When all the alkali had been added the mixture was heated to the boiling point to decompose excess of methyl sulfate, 10 ml. of 30% sodium hydroxide solution being added. The mixture was cooled and the insoluble material collected and crystallized and recrystallized from methanol, when *flavonepenthone* methyl ether was obtained as colorless needles m.p. 140°, $[\alpha]_D^{20}$ −4° ($CHCl_3$, *c* 0.46).

Anal. Calcd. for $C_{28}H_{29}O_3N$: C, 78.6; H, 6.8; (2)OMe, 14.6. Found: C, 78.5; H, 6.8; OMe, 14.7%.

The base was insoluble in alkali and gave no color with diazotized sulfanilic acid, quinone chloroimine, or ferric chloride.

Tetrahydroflavonepenthone. Flavonepenthone hydrochloride (10 g.) was suspended in boiling ethanol (250 ml.) and treated with 510 g. of 2% sodium amalgam. The reaction mixture was kept for 4 hr. under reflux on the steam bath. Within the first few minutes the solid dissolved, and a solid subsequently separated but later dissolved again. The following day the alcoholic solution was diluted with water (1500 ml.), the mercury removed and the mixture extracted with chloroform. (300 ml.). Evaporation of the extract gave an amorphous solid (8 g.) which readily dissolved in methanol. After several days the methanol solution deposited 3.3 g. of crystalline material. This was collected and recrystallized from methanol, when *tetrahydroflavonepenthone* was obtained as colorless prisms, m.p. 100°, $[\alpha]_D^{20}$ −162° ($CHCl_3$, *c* 0.71), λ_{max} 2830 Å; ϵ_{max} 1,778.

Anal. Calcd. for $C_{27}H_{31}O_3N.CH_3OH$: C, 74.8; H, 7.8. Found: C, 74.7; H, 8.0%.

Found (dried at 160°/0.05 mm.): C, 77.4; H, 7.6%.

Thebaine–methyl vinyl ketone adduct (XLI, R = $CO.CH_3$). A solution of thebaine (15 g.) in methyl vinyl ketone (95 g.) was heated under reflux for 18 hr. and the excess of methyl vinyl ketone removed by distillation *in vacuo.* The product crystallized from methanol (60 ml.) as irregular plates (17 g.) m.p. 120°, but it contained rubbery impurities which were best removed by dissolving the product in hot concentrated hydrochloric acid, diluting with water, and filtering from black tarry matter. Recovery of the base from the acid solution followed by crystallization from ethanol afforded *thebaine–methyl vinyl ketone* as colorless plates m.p. 122°.

Anal. Calcd. for $C_{24}H_{27}O_4N$: C, 72.3; H, 7.2. Found: C, 72.5; H, 7.1%.

Dehydration of thebaine-acrolein oxime. Thebaine-acrolein oxime[6] (3 g.) in chloroform solution (20 ml.) at 0° was treated with ice cold thionyl chloride (3 ml.) in chloroform (10 ml.). The resulting yellow solution was evaporated *in vacuo* at room temperature and the residue was shaken with chloroform and aqueous ammonia. Separation of the chloroform and evaporation of the solvent gave a residue that was crystallized from methanol, when *thebaine-acrylonitrile* (2.25 g.) was obtained as colorless plates m.p. 177°, raised to 185° by recrystallization.

Anal. Calcd. for $C_{22}H_{24}O_3N_2$: C, 72.4; H, 6.7; N, 7.5. Found: C, 72.4; H, 6.9; N, 7.3%.

Condensation of thebaine and acrylonitrile. Thebaine (10 g.) was heated under reflux with freshly distilled acrylonitrile (50 ml.) containing a small quantity of quinol, for 8 hr. The excess of acrylonitrile was removed by distillation *in vacuo* and the residue crystallized from ethanol, when thebaine-acrylonitrile. ,was obtained as plates m.p. 177°. The identity of this material with that prepared by the dehydration of thebaine–acrolein oxime was demonstrated by the identity of their infrared spectra.

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ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

Base-Catalyzed Rearrangements in the Nepenthone Series

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The thebaine–phenyl vinyl ketone adduct, nepenthone, on heating with alkali is isomerized to isonepenthone. This is formulated as a molecular rearrangement of a type hitherto unobserved in the morphine series. Isonepenthone may be hydrolyzed to ψ-nepenthone, and has been related through isonepenthol and ψ-nepenthol to flavonepenthone. Two other products of base-catalyzed transformation of nepenthone, both of which yield ψ-nepenthone on hydrolysis, are reported and formulated.

Thebaine condenses readily with phenyl vinyl ketone to give the adduct (I), named nepenthone[1,2] to facilitate discussion. This adduct, which is formulated as the *endo*-compound (Ia), was heated

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[1] K. W. Bentley and J. C. Ball, *Chem. & Ind.* (*London*), 1428 (1956).

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