enthone 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.

Acknowledgment. One of us (J.C.B.) wishes to thank the Department of Scientific and Industrial Research for a maintenance grant.

ABERDEEN, SCOTLAND

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

Base-Catalyzed Rearrangements in the Nepenthone Series

K. W. BENTLEY AND J. C. BALL

Received January 20, 1958

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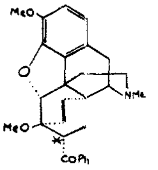
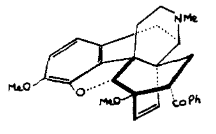
[1] K. W. Bentley and J. C. Ball, *Chem. & Ind.* (*London*), 1428 (1956).

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

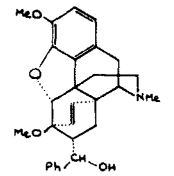
with alkali in an attempt to bring about epimerization at the asterisked carbon atom to the *exo*-compound. In the initial experiments poor yields of two substances were obtained after four hours heating under reflux with 5% methanolic sodium hydroxide. In a later experiment however, crystallization occurred in the boiling solution after ten minutes, and a 75% yield of a third base, isonepenthone, was obtained. Subsequently this base could always be obtained in good yield by seeding the reaction mixture after five or ten minutes' treatment with alkali.



(I)



(IA)

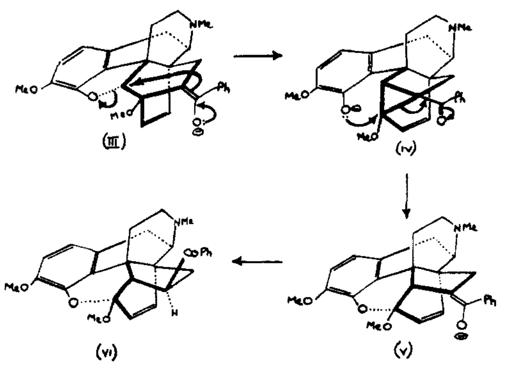


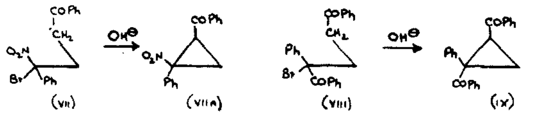
(II)

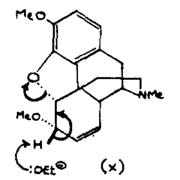
Isonepenthone is isomeric with nepenthone, is non-phenolic, and still contains the benzoyl group (infrared band at 1677 cm.$^{-1}$, 5.96μ). The benzoyl group is essential for this change, since the secondary alcohol, nepenthol (II), derived from nepenthone does not undergo a similar change on heating with alkalis. Isonepenthone may, however, be converted into a secondary alcohol, isonepenthol, isomeric with nepenthol, by reduction with sodium borohydride.

Isonepenthone differs from nepenthone in being extremely sensitive to acid hydrolysis. Whereas the latter is recovered unchanged after boiling for four hours with 5% hydrochloric acid, the former is very rapidly hydrolyzed by this reagent, and even by cold acetic acid or picric acid, to ψ-nepenthone, $C_{27}H_{27}O_4N$, and this difference in the behavior of the two isomers makes it very unlikely that isonepenthone is the expected epimer of nepenthone. This possibility will, however, be considered in detail later.

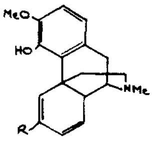
As nepenthol is stable to base undoubtedly the first stage in the conversion of nepenthone into isonepenthone is the removal of a proton from the PhCOCH group, with the formation of the enolate ion (III). A reasonable second step is then the displacement of the phenate ion with the formation of the cyclopropane ring, as in III → IV. Analogies for this may be cited in the formation of a cyclopropane ring with the displacement of a bromide ion from the compounds VII and VIII, which give the compounds VIIA and IX, respectively on treatment with alkali[3,4] and the formation of thebainone $\Delta^{5,7}$-enol methyl ether (XI, R = OMe) from codeine methyl ether (X) on treatment with sodium



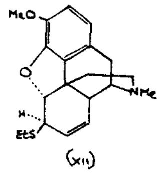




(X)



(XI)

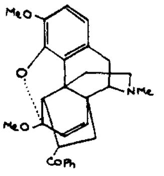


(XII)

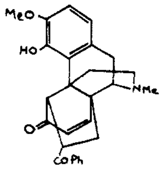
ethoxide[5] and of β-ethylthiocodide (XI, R = SEt) on treatment of α-ethylthiocodide (XII) with alkali.[6,7]

If this process is involved, however, some subsequent changes must take place, as isonepenthone in non-phenolic. A plausible further step is the opening of the cyclopropane ring by attack by the phenate ion, as in IV → V, giving the enolate ion V, which would be discharged under reversible conditions to give the most stable epimer of the ketone. Examination of models shows that the non-bonded interactions are least in the epimer VI; a model of this substance can be constructed without strain, and this is assumed to be the structure of isonepenthone. All the reactions may be regarded as reversible, but presumably isonepenthone is less strained than nepenthone; in any case it is removed from the reaction mixture by crystallization, and thus the reactions would proceed in one way only.

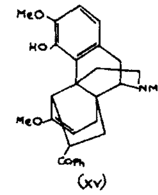
The structure VI ≡ XIII represents isonepenthone as the mixed acetal of an α,β-unsaturated



(XIII)



(XIV)



(XV)

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[3] C. F. H. Allen and H. P. Bridges, *J. Am. Chem. Soc.*, **51**, 2151 (1929).

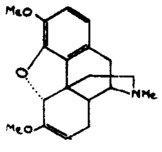
[4] C. F. H. Allen and W. E. Barker, *J. Am. Chem. Soc.*, **54**, 736 (1932).

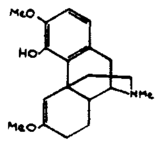
[5] L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).

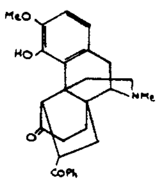
[6] R. Pschorr, *Ann.*, **373**, 1 (1910).

[7] D. E. Morris and L. F. Small, *J. Am. Chem. Soc.*, **56**, 2159 (1934).

ketone, and acid hydrolysis would be expected to proceed readily, as is actually observed, to give the phenolic α,β-unsaturated ketone, ψ-nepenthone (XIV). A model of the structure VI shows that the double bond of isonepenthone is less hindered than that of nepenthone, and whereas the latter is resistant to hydrogenation, isonepenthone can be reduced in ethanolic solution at 50° to dihydroisonepenthone, which is phenolic. In VI ≡ XII the double bond is part of an allylic ether system, which could suffer 1:4-reduction to give the phenol XV, which structure is proposed for dihydroisonepenthone; the double bond of XV, being part of an enol ether system, would be expected to resist further reduction. Bases in the morphine series in which the oxide ring is part of such an allylic ether system are readily reduced with the opening of the oxide ring and the production of phenols, *e.g.* dihydrothebaine (XVI) can be reduced to dihydrothebainone Δ⁵-enol methyl ether (XVII).[8]


(XVI)

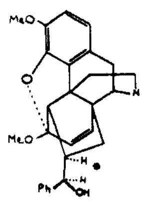

(XVII)


(XVIII)

As formulated in XV dihydroisonepenthone is an enol ether and, like dihydrothebainone Δ⁵-enol methyl ether (XVII), would be expected to be very readily hydrolyzed to the corresponding ketone, and in fact on treatment with dilute acid this base affords dihydro-ψ-nepenthone (XVIII), also obtainable by the catalytic reduction of ψ-nepenthone (XIV). This ketone, as expected on the basis of the structure XVIII, shows bands at 1703 cm.$^{-1}$ (5.86μ) and 1668 cm.$^{-1}$ (6.0μ) in the infrared spectrum, attributable to the saturated and aromatic carbonyl groups, respectively.

Isonepenthone on reduction with sodium borohydride affords isonepenthol (XIX), and this, like the parent ketone, is very readily hydrolyzed by acids, giving ψ-nepenthol (XX), also obtainable by the sodium borohydride reduction of ψ-nepenthone (XIV). The reduction of only one of the two carbonyl groups of ψ-nepenthone under these conditions may be attributed to the fact that, as shown in XXI, only the aromatic carbonyl group of this compound is easily accessible to attack by a hydride ion; the αβ-unsaturated carbonyl group is effectively screened by the other parts of the molecule.

The structures assigned to ψ-nepenthone (XIV) and ψ-nepenthol (XX) show a skeletal resemblance to that proposed for flavonepenthone (XXIII),[2] and in fact ψ-nepenthol should give flavonepenthone simply on dehydration. This dehydration was effected with formic acid, but it was also found that the hydrolysis of isonepenthol (XIX) to ψ-nepenthol (XX) with hot 5% hydrochloric acid was always accompanied by some dehydration of the product and flavonepenthone was recovered from the products of this reaction in about 50% yield. The production of flavonepenthone under such mild conditions strongly supports the view that the 1:2-shift of the bridge occurs in the original base-catalyzed conversion of nepenthone into isonepenthone, and hence the formulas assigned above to the compounds of the isonepenthone–ψ-nepenthone series. Flavonepenthone is easily obtained in very good yield from isonepenthol and ψ-nepenthol by heating with concentrated hydrochloric acid and acetic acid, but as this treatment also brings about the rearrangement of nepenthol to flavonepenthone,[2] only the production of the last-named base under the milder conditions reported above has significance to the present discussion.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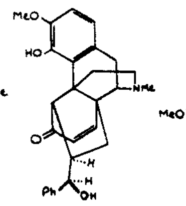
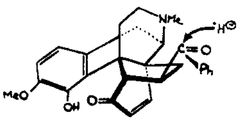
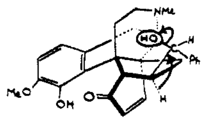

(XX)


(XXI)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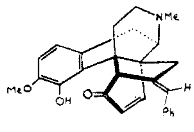
(XXIII)

As previously mentioned, in the early experiments two bases different from isonepenthone were obtained after heating nepenthone for five hours with 5% methanolic sodium hydroxide. These two bases, compound-X and compound-Y, were obtained in yields of about 10%.

Compound-X has the composition $C_{29}H_{33}O_5N$ (*i.e.* isonepenthone + CH_3OH) and contains three methoxyl groups. It is phenolic and ketonic (infrared band at 1680 cm.$^{-1}$, 5.96μ), and on hydrolysis with dilute acid it affords ψ-nepenthone in good yield. Compound-Y, which also contains three methoxyl groups, is isomeric with compound-X, is phenolic but non-ketonic, and also affords ψ-nepenthone in good yield on hydrolysis with dilute acid.

As both these substances are produced after prolonged treatment of nepenthone with alkali it is reasonable to suppose that they are further transformation products of isonepenthone, which is known to be present in the mixture after ten minutes. The hydrolysis of each of them to ψ-nepenthone with the loss of CH_3 and CH_3O indicates that no skeletal rearrangement is involved

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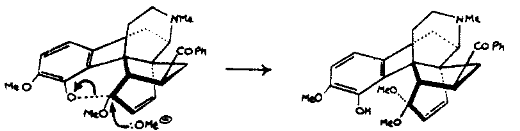
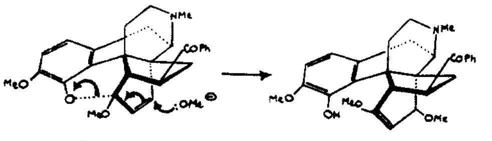
(8) K. W. Bentley, Sir Robert Robinson, and A. E. Wain, *J. Chem. Soc.*, 958 (1952).

in their production from isonepenthone, and suggests that they are both acetals of ψ-nepenthone, and the non-ketonic nature of compound-Y indicates that if this is so the aromatic carbonyl group must also be involved in some way in the acetal system in this base.

Mechanistically the formation of compound-X could be represented as the displacement of the phenate ion in isonepenthone by the direct attack of a methoxide ion, as in XXIV, giving XXV as the structure of compound-X, which would then be ψ-nepenthone dimethyl acetal. Such a process is stereochemically acceptable, as the site of the attack by OMe is relatively unhindered. ψ-Nepenthone would then arise from compound-X by the simple hydrolysis of the acetal system of XXV. Alternatively the phenate ion could be displaced as shown in XXVI, in which case compound-X would have the structure XXVII, and would be methoxydihydroisonepenthone. The hydrolysis of this enol ether would give the β-methoxyketone, from which methanol would be easily eliminated, giving ψ-nepenthone.

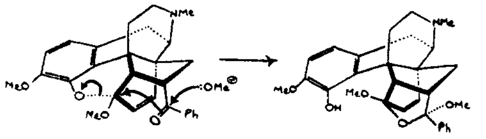


(XXIV) (XXV)

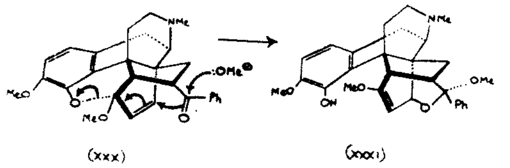


(XXVI) (XXVII)

If the aromatic carbonyl group is to participate in the acetal formation, as it apparently does in the formation of compound-Y, epimerization of the —CHCOPh group of isonepenthone must occur as a first step. Presumably in alkaline solution isonepenthone (VI) will be in equilibrium with the presumably less stable epimer XXVIII, and in this attack by OMe$^-$ could occur with displacement of the phenate ion as shown in XXVIII, giving XXIX as the structure of compound-Y. The alternative process shown in XXX can be envisaged, giving XXXI as the structure of compound-Y, but seems less likely on steric grounds. Both XXIX and XXXI on treatment with dilute acid would be expected to give ψ-nepenthone XXI → XIV with the regeneration of the two carbonyl groups, and the epimerization of the —CHCOPh group to the more stable form.

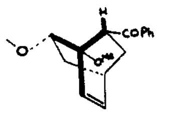


(XXVIII) (XXIX)

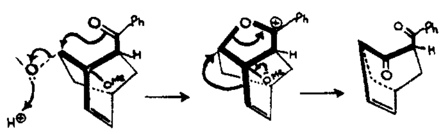


(XXX) (XXXI)

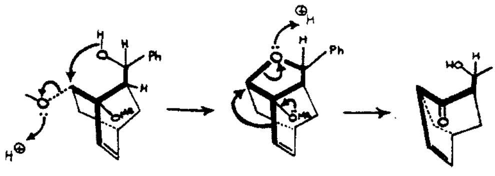
Attempts to probe the structures of the compounds of the isonepenthone–ψ-nepenthone series further by degradation proved unsuccessful; none of the compounds could be induced to form quaternary salts or *N*-oxides, and the various oxidation processes that were tried gave intractable materials. Accordingly the validity of the structures proposed above rests on their success in explaining a complex of data. That being so the possibility that isonepenthone is the originally expected epimer of nepenthone cannot be rejected without serious consideration. It was discounted earlier in this discussion on the basis of the marked difference in stability of nepenthone and isonepenthone towards dilute acids. Nepenthone is assigned the part-structure XXXII, and it is conceivable that the epimeric structure XXXIII might undergo oxide ring fission in acids under conditions in which XXXII does not, as a result of the participation of the carbonyl group as shown in XXXIII → XXXIV. However, the resulting carbonium ion XXXIV could reasonably be expected to have only two alternative fates, *viz.* reaction with water with the addition of a hydroxyl group and the formation of a non-ketonic hemi-acetal, or the stereochemically favorable further rearrangement with a 1:2-shift of the ethylenic bridge, to give the β-diketone represented by the part-structure XXXV. If this occurred then ψ-nepenthone would have the structure XXXVI, which it cannot have if the structure XXIII assigned to flavonepenthone[2] is correct.



(XXXII)



(XXXIII) (XXXIV) (XXXV)



(XXXVI) (XXXVII) (XXXVIII)

A rearrangement of the type shown in XXXIII → XXXV would be expected to require much more vigorous conditions than those found to be required for the conversion of isonepenthone into ψ-nepenthone. Moreover the transformation of isonepenthol into ψ-nepenthol by a similar process would involve the participation of the alcoholic hydroxyl group as shown in XXXVII, and would lead to the cyclic ether XXXVIII, from which a ketone can be obtained only by the further rearrangement XXXVIII→XXXIX, which would result in the representation of ψ-nepenthol by the part-structure XXXIX, *i.e.* as a saturated ketone, which is contrary to observation. Finally, if isonepenthone were the epimer of nepenthone there is no reason why the reduction of the former should afford a phenolic dihydro-compound (dihydroisonepenthone) that gives a ketone (dihydro-ψ-nepenthone) on hydrolysis. Attempts to prepare enol acetates of nepenthone and isonepenthone, which would be identical if the two compounds were epimers, were unsuccessful; nepenthone was always recovered unchanged, and isonepenthone gave acetyl-ψ-nepenthone enolacetate.

These arguments must lead to the rejection of the possibility that isonepenthone is the epimer of nepenthone, and indirectly support the structures assigned above to the compounds of the isonepenthone–ψ-nepenthone series.

EXPERIMENTAL

Isonepenthone. Nepenthone (15 g.) was heated under reflux in methanol (300 ml.) and sodium hydroxide (15 g.) was added to the boiling solution. After the sodium hydroxide had completely dissolved (in about 5–10 min.) the solution was seeded with isonepenthone, when extensive crystallization occurred in the reaction mixture. In the absence of seeds crystallization either occurred spontaneously after some time or could be induced by vigorous scratching of the walls of the reaction flask. If crystallization did not occur and the heating was continued for 4 hr. no isonepenthone could be recovered from the mixture, only compounds X and Y (see below) being obtained. The *isonepenthone* was collected, washed with cold methanol, and recrystallized from ethanol, when it was obtained as colorless needles, m.p. 174°, followed by resolidification and remelting at 188°, $[\alpha]_D^{20}$ −37° ($CHCl_3$, *c* 0.39); λ_{max} 244, 289 mμ, ϵ_{max} 21,880, 2,180.

Anal. Calcd. for $C_{28}H_{29}O_4N$: C, 75.8; H, 6.6; (2)OMe, 14.0. Found: C, 75.7; H, 6.6; OMe, 14.5%.

Attempts to prepare salts of this base afforded only derivatives of ψ-nepenthone.

Compounds X and Y. Nepenthone (15 g.) was heated under reflux with methanol (300 ml.) and sodium hydroxide (15 g.) for 4 hr. In the initial experiments crystallization of isonepenthone did not occur. The methanol was removed under reduced pressure and water (200 ml.) was added. The organic material was extracted with ether, and the washed and dried ether extract was evaporated, leaving a mass of yellow crystals (3.0 g.), m.p. about 195°, $[\alpha]_D^{18}$ −69° ($CHCl_3$, *c* 0.62). This material consisted of a mixture of two bases which were separated as follows. The mixture was dissolved in chloroform (50 ml.) and the solution evaporated to a sirup, and diluted with ethanol (30 ml.). After several days a mat of colorless needles had separated, and in this was embedded clumps of yellow needles. The two types of crystal were separated by hand picking, and the bases recrystallized from ethanol.

Compound-X was obtained as regular colorless rods, m.p. 216°, $[\alpha]_D^{20}$ −10° ($CHCl_3$, *c* 0.50), λ_{max} 2400, 2810 Å, ϵ_{max} 27,540, 10,470.

Anal. Calcd. for $C_{29}H_{33}O_5N$: C, 73.2; H, 7.0; (3)OMe, 19.6. Found: C, 73.6; H, 7.2; OMe, 20.0%.

This base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, and gave a blue-green color with quinone chloroimine.

Compound-Y. This was obtained as bunches of pale yellow needles m.p. 225°, $[\alpha]_D^{25}$ −101° ($CHCl_3$, *c* 0.39), λ_{max} 240, 281 mμ, ϵ_{max} 19,950, 3,390.

Anal. Calcd. for $C_{29}H_{33}O_5N$: C, 73.2; H, 7.0; (3)OMe, 19.6. Found: C, 73.2; H, 7.1; OMe, 20.0%.

This base gave an immediate red color with diazotized sulfanilic acid, in alkaline solution, and a blue-violet color with quinone chloroimine.

Dihydroisonepenthone. Isonepenthone (5.0 g.) was shaken with hydrogen in alcohol (200 ml.) in the presence of platinum oxide (0.1 g.) at 50°. After 2.5 hr. about three quarters of a molar equivalent of hydrogen had been absorbed and hydrogenation had become very slow. The catalyst was removed and the solution concentrated to 75 ml. and cooled, when 3.77 g. of *dihydroisonepenthone* was obtained. Recrystallization of this material from ethanol gave the base as colorless needles, m.p. 195°, $[\alpha]_D^{22}$ −118° ($CHCl_3$, *c* 0.57), λ_{max} 240, 279 mμ, ϵ_{max} 20,890, 2,630.

Anal. Calcd. for $C_{28}H_{31}O_4N$: C, 75.4; H, 7.0. Found: C, 75.3; H, 6.9%.

The base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, a deep blue color with quinone chloroimine and an olive-green color with alcoholic ferric chloride.

Isonepenthol. Isonepenthone (5.0 g.) was suspended in methanol (100 ml.) and heated under reflux with sodium borohydride (0.40 g.) until a clear solution was obtained. The mixture was then evaporated to small bulk and diluted with water, when *isonepenthol* (4.4 g.) was obtained. Recrystallization of this material from 60% ethanol afforded the base as colorless prisms m.p. 238°, $[\alpha]_D^{18}$ +69° ($CHCl_3$, *c* 1.13).

Anal. Calcd. for $C_{28}H_{31}O_4N$: C, 75.4; H, 7.0. Found: C, 75.5; H, 7.1%.

The base gave no color with diazotized sulfanilic acid or with quinone chloroimine.

The Meerwein-Ponndorf reduction of isonepenthone was complicated by the difficulty of isolating the product in the presence of aluminum hydroxide without acidification of the mixture. However isonepenthol was clearly formed since acidification of the mixture resulted in the isolation of ψ-nepenthol (see below).

ψ-Nepenthone. (a) *From isonepenthone.* Isonepenthone (2.0 g.) was dissolved in boiling ethanol (50 ml.) and a boiling solution of picric acid (2 g.) in ethanol (25 ml.) was added to the solution. Yellow crystals of *ψ-nepenthone picrate* (2.90) separated almost at once. The salt was collected and washed with ethanol, when it was obtained as yellow needles, m.p. 245°.

Anal. Calcd. for $C_{27}H_{27}O_4N.C_6H_3O_7N_3$: C, 60.1; H, 4.6; N, 8.5. Found: C, 60.0; H, 4.6; H, 8.1%.

ψ-Nepenthone was recovered from the picrate by shaking the salt (2.0 g.) with dilute ammonia solution and benzene. The benzene layer was separated, washed once with dilute ammonia solution, and evaporated, when 1.32 g. of the base was obtained. This was recrystallized from ethanol, when it was recovered as colorless rods, m.p. 202°, $[\alpha]_D^{23}$ −68° ($CHCl_3$, *c* 0.73), λ_{max} 238, 284 mμ, ϵ_{max} 20,890, 3,160.

Anal. Calcd. for $C_{27}H_{27}O_4N$: C, 75.5; H, 6.3; (1)OMe, 7.2. Found: C, 75.4; H, 6.4; OMe, 7.8%.

The base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, and a blue-green color with quinone chloroimine.

ψ-Nepenthone was also obtained from isonepenthone by dissolving the latter in hydrochloric acid and pouring the solution into hot water. The crystalline salt so obtained was shaken with ammonia and benzene, when ψ-nepenthone was recovered from the benzene layer. It was also obtained by dissolving isonepenthone in cold glacial acetic acid, diluting the solution at once with water, and neutralizing with sodium carbonate. In both cases the base was identical with that prepared as above through the picrate.

(b) *From compound-X.* Compound-X (0.50 g.) was dissolved in concentrated hydrochloric acid (4 ml.) and the solution immediately poured into hot water (20 ml.). Colorless crystals (0.50 g.) separated and were collected and converted into the base by shaking with warm aqueous sodium carbonate and benzene. The dried benzene solution was evaporated and the residue recrystallized from methanol, when ψ-nepenthone was obtained (0.32 g.) as colorless rods, m.p. 203° undepressed on mixing with material prepared from isonepenthone.

(c) *From compound-Y.* Compound-Y (0.50 g.) was hydrolyzed under the same conditions as those used from the hydrolysis of Compound-X, and afforded 0.34 g. of ψ-nepenthone, m.p. 203°, undepressed on mixing with material prepared from isonepenthone.

Acetyl-ψ-nepenthone. ψ-Nepenthone (1 g.) was allowed to stand for 17 hr. at room temperature in acetic anhydride (10 ml.) and pyridine (10 ml.). The mixture was then poured into water, treated with aqueous ammonia, and the precipitated base extracted with ether-chloroform mixture. The extracts on evaporation afforded a residue that crystallized from methanol, when *acetyl-ψ-nepenthone* (0.67 g.) was obtained as colorless needles m.p. 174°.

Anal. Calcd. for $C_{29}H_{29}O_5N$: C, 73.9; H, 6.2; OAc, 9.1. Found: C, 73.8; H, 6.4; OAc, 9.8%.

Acetyl-ψ-nepenthone enol acetate. ψ-Nepenthone (0.80 g.) was heated under reflux with acetic anhydride (50 ml.) and fused sodium acetate (0.2 g.) for 8 hr. The volatile materials were removed under reduced pressure at 100° and the residue was repeatedly extracted with acetone. Evaporation of the acetone extracts and recrystallization of the residue from methanol afforded *acetyl-ψ-nepenthone enol acetate* (0.64 g.) as colorless needles, m.p. 204°, depressed to 184° on mixing with ψ-nepenthone.

Anal. Calcd. for $C_{31}H_{31}O_6N$: C, 72.5; H, 6.0. Found: C, 72.3; H, 5.8%.

The same substance was obtained when isonepenthone was treated in the same way, but a similar experiment with nepenthone yielded only unchanged starting material.

Dihydro-ψ-nepenthone. (a) *From ψ-nepenthone.* ψ-Nepenthone (3.28 g.) was shaken under hydrogen at 50° in ethanol (200 ml.) in the presence of platinum oxide (0.1 g.). After about 2 hr. one molar equivalent of hydrogen had been absorbed. The mixture was then filtered from catalyst and evaporated, and the residue was recrystallized from ethanol, when *dihydro-ψ-nepenthone* (2.25 g.) was obtained as colorless rods, m.p. 191°, $[\alpha]^{19}_{D}$ −77° ($CHCl_3$, *c* 0.34), λ_{max} 235, 277 mμ, ϵ_{max} 19,950, 3,390.

Anal. Calcd. for $C_{27}H_{29}O_4N$: C, 75.2; H, 6.8. Found: C, 75.2; H, 6.7%.

The base gave an immediate red color with diazotized sulfanilic acid in alkaline solution, an olive-green color with alcoholic ferric chloride and a blue-green color with quinone chloroimine.

(b) *From dihydroisonepenthone.* Dihydroisonepenthone (0.50 g.) was dissolved in hydrochloric acid (5 ml.) and the solution was poured into hot water (20 ml.). The solution was basified with ammonia after 1 min., and the precipitated organic base was extracted with ether. Evaporation of the ether extract afforded a solid residue, which was recrystallized from methanol, when dihydro-ψ-nepenthone (0.4 g.) was obtained as colorless rods, m.p. 191° undepressed on mixing with material prepared by the reduction of ψ-nepenthone, $[\alpha]^{19}_{D}$ −79° ($CHCl_3$, *c* 0.24).

ψ-Nepenthol. (a) *From ψ-nepenthone.* ψ-Nepenthone (2.0 g.) was heated under reflux with methanol (100 ml.) and sodium borohydride (0.35 g.) for 10 min. The solution was concentrated to 50 ml., and hot water (60 ml.) was added, causing the separation of 1.35 g. of fine needles. These were collected and recrystallized from 70% ethanol, when *ψ-nepenthol* was obtained as colorless needles, m.p. 313°, $[\alpha]^{19}_{D}$ +64° ($CHCl_3$, *c* 0.84).

Anal. Calcd. for $C_{27}H_{29}O_4N$: C, 75.2; H, 6.8. Found: C, 75.5; H, 6.9%.

The base gave an intense red color immediately with diazotized sulfanilic acid in alkaline solution, and a deep green color with quinone chloroimine.

(b) *From isonepenthol.* Isonepenthol (2.0 g.) was dissolved in cold 5*N* hydrochloric acid (10 ml.) and the solution poured into boiling water (100 ml.). Colorless needles soon began to separate, and after 2 hr. cooling these were collected. The liquors were basified with ammonia and the precipitated base was collected and recrystallized from 70% ethanol, when ψ-nepenthol (0.33 g.) was obtained as colorless needles, m.p. 313°, undepressed on mixing with material prepared by the reduction of ψ-nepenthone.

The needles that separated in the acid solution (1.05 g.) were dissolved in hot water and converted into the base by treatment with sodium carbonate solution. Recrystallization of the base afforded 0.65 g. of flavonepenthone as colorless rods, m.p. 263° alone or mixed with flavonepenthone,[2] $[\alpha]^{21}_{D}$ +32° ($CHCl_3$, *c* 0.41) (flavonepenthone $[\alpha]^{18}_{D}$ +33°).

Flavonepenthone. (a) *From ψ-nepenthol.* ψ-Nepenthol (0.5 g.) was heated with anhydrous formic acid (10 ml.) for 16 hr. on the water bath. Dilution of the mixture with water (50 ml.) and addition of ammonia solution precipitated flavonepenthone (0.2 g.), which was collected and recrystallized from ethanol, when it was obtained as colorless rods, m.p. 262°, undepressed on mixing with an authentic specimen of flavonepenthone.

The base was more conveniently obtained by heating ψ-nepenthol (1.10 g.) in glacial acetic acid (6 ml.) and concentrated hydrochloric acid (6 ml.) under reflux for 5 hr. Dilution of the mixture with water (20 ml.) resulted in the precipitation of a crystalline salt (0.80 g.). This was collected and converted into the base by treatment with hot aqueous sodium carbonate. The base was recrystallized from ethanol, when flavonepenthone (0.51 g.) was obtained as colorless rods, m.p. 262°, undepressed on mixing with an authentic specimen of flavonepenthone.

(b) *From isonepenthol.* In addition to the production of flavonepenthone during the hydrolysis of isonepenthol to ψ-nepenthol, it was prepared most conveniently from this base as follows. Isonepenthol (1.3 g.) was heated with glacial acetic acid (6 ml.) and concentrated hydrochloric acid (6 ml.) under reflux for 5 hr. Dilution of the mixture with water (20 ml.) precipitated flavonepenthone hydrochloride (0.82 g.) from which flavonepenthone (0.53 g.) was recovered as colorless rods m.p. 262°, undepressed on mixing with a specimen of flavonepenthone.

Acknowledgment. One of us (J. C. B.) wishes to thank the Department of Scientific and Industrial Research for a maintenance grant.

ABERDEEN, SCOTLAND