Rearrangement of Isoindolo[1,2-*b*][3]benzazepinium to Dibenzo[*a*,*g*]quinolizinium Ions: Application to the Total Synthesis of (±)-Tetrahydropalmatine

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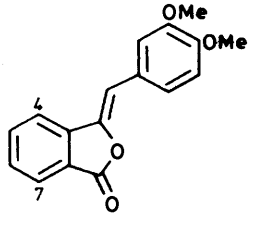
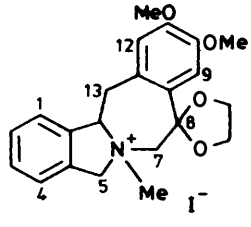
(±)-Tetrahydropalmatine (**17**) has been synthesized in 16% yield from 6,7-dimethoxy-3-(3,4-dimethoxybenzylidene)phthalide (**4**) as follows. Reaction of compound (**4**) with glycine afforded 6,7-dimethoxy-3-(3,4-dimethoxybenzylidene)phthalimidin-2-ylacetic acid (**6**) which, on hydrogenation to compound (**8**) followed by cyclization, gave 13,13a-dihydro-3,4,10,11-tetramethoxyisoindolo[1,2-*b*]-[3]benzazepine-5,8(7*H*)-dione (**10**). Reduction of the ethylene acetal of (**10**) [(**11**)], and quaternization with methyl iodide gave 7,8,13,13a-tetrahydro-3,4,10,11-tetramethoxy-6-methyl-8-oxo-5*H*-isoindolo[1,2-*b*][3]benzazepinium iodide ethylene acetal (**12**) which, on treatment with base, rearranged to 5,6,13,13a-tetrahydro-2,3,9,10-tetramethoxy-7-methyl-5-oxo-8*H*-dibenzo[*a*,*g*]-quinolizinium iodide ethylene acetal (**13**). Conversion of this latter compound to the corresponding acetate followed by pyrolysis and treatment with borane led to compound (**17**). Attempts to cyclize a methylenedioxy derivative of 3-benzylidenephthalimidin-2-ylacetic acid under various conditions have so far given unsatisfactory results.

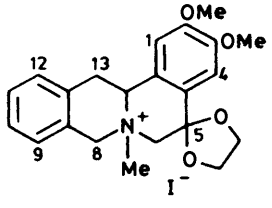
In a previous paper[1] we reported the base-catalysed isomerization of the isoindolo[1,2-*b*][3]benzazepinium salt (**2**) [easily obtainable from compound (**1**)] to the dibenzo[*a*,*g*]quinolizinium salt (**3**), and we also anticipated that such a reaction could be used as the key step of a new route to berbines, enabling both the functionalization of C-5, and the regiospecific location of appropriate substituents at C-9, C-10, C-11, and C-12.†



(**1**)



(**2**)



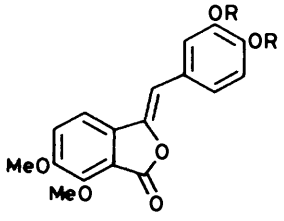
(**3**)

The first step in the planned approach has been recently accomplished with the elaboration of an efficient and regiospecific method of preparation of alkoxy substituted 3-benzylidenephthalides, which constitute the starting materials of the new synthesis.[3] Here we report a further development leading to (±)-tetrahydropalmatine.

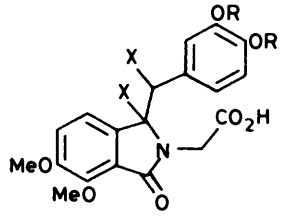
† The most typical substitution pattern of natural berbines is the presence of two contiguous oxygenated functions either at C-9 and C-10, or at C-10 and C-11. The former derivatives are not easily obtainable by the classical methods of isoquinoline synthesis.[2]

Results and Discussion

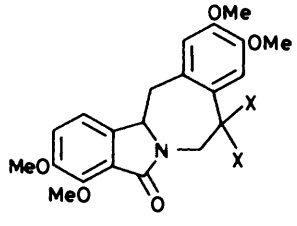
3-Benzylidenephthalide derivatives (**4**) and (**5**) were chosen in order to check the general applicability of the approach. Thus, both compounds reacted with potassium glycinate in aqueous dioxane to give, after treatement with acid, a mixture of the (*E*)- and (*Z*)-3-benzylidenephthalimidin-2-ylacetic acid derivatives (**6**) and (**7**) respectively. The components of each mixture were not separated, but catalytically hydrogenated to the 3-benzyl-



(**4**) R = Me
(**5**) R,R = CH_2



(**6**) R = Me, X,X = bond
(**7**) R,R = CH_2, X,X = bond
(**8**) R = Me, X = H
(**9**) R,R = CH_2, X = H



(**10**) X,X = O
(**11**) X,X = OCH_2CH_2O

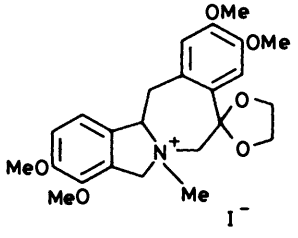
phthalimidin-2-ylacetic acid derivatives (**8**) and (**9**) respectively, in good overall yields. However, whereas compound (**8**) underwent smooth cyclization to (**10**) upon dehydration with polyphosphoric acid, compound (**9**) failed to give the corresponding cyclized product even under a variety of conditions;[4] either uncharacterizable complex mixtures or the unchanged starting

material were obtained. These unsuccessful results, which indicate the present limits of this approach, may be due both to the instability to cleavage of the methylenedioxy group in strong acid conditions (indeed, yields of acylation of methylenedioxybenzenes are generally lower as compared with the same reaction performed with other alkoxybenzenes),[5] and to the greater ease of formation of a seven-membered ring with respect to a six-membered one, for which successful intramolecular acylations are reported.[4,*]

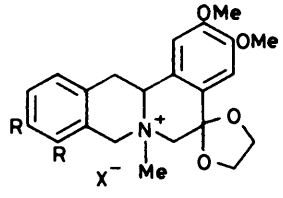
Acetalization of compound (**10**) under standard conditions afforded the tetracycle (**11**), which was reduced with lithium aluminium hydride in refluxing tetrahydrofuran. Owing to its instability, the amine was not characterized but was directly converted into the corresponding methiodide (**12**). As expected, compound (**12**) underwent smooth rearrangement to the methiodide (**13**) by the action of hot aqueous potassium hydroxide. The structures of compounds (**12**) and (**13**) were deduced both on the basis of previous work,[1] and from their analytical and spectral characteristics.

Among the methods described in the literature for the *N*-demethylation of methylammonium salts,[6] the one involving conversion of compound (**13**) into the acetate (**14**), followed by pyrolysis to compound (**16**), proved to be the most satisfactory. Treatment of the crude acetal (**16**) with borane in tetrahydrofuran afforded finally a product (**17**) which had physical and spectral characteristics identical with those reported for (±)-tetrahydropalmatine.[7]

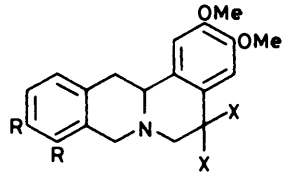
Although no comparison with an authentic sample has been made in this case, an analogous sequence of reactions performed with the iodide (**3**)[1] led to compound (**18**), which was identical with an authentic specimen.[8]



(**12**)



(**13**) R = OMe, X = I
(**14**) R = OMe, X = AcO
(**15**) R = H, X = AcO



(**16**) R = OMe, X,X = OCH_2CH_2O
(**17**) R = OMe, X = H
(**18**) R = X = H

Experimental

M.p.s were determined with a Kofler apparatus; i.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 197 spectrophotometer, and the most intense and/or representative absorption bands are given; n.m.r. spectra were recorded with a Varian EM360A for compound (**6**) and (**7**), and with a Varian CFT-20 instrument for all other compounds, and most significant signals are quoted in p.p.m. from $SiMe_4$ as an internal standard; evaporation of solvents was carried out with a rotary evaporator under diminished pressure. For some procedures reference is made to previous work: this means that more experimental details may be found for the analogous preparations described in ref. 1.

(E)- *and* (Z)-3-(3,4-*Dimethoxybenzylidene*)-6,7-*dimethoxyphthalimidin*-2-*ylacetic Acids* (**6**).—A mixture of compound (**4**) (1.0 g, 3 mmol, mixture of *E*- and *Z*-isomers),[3] glycine (1.0 g, 13.3 mmol), potassium hydroxide (0.37 g, 6.6 mmol), water (15 ml), and dioxane (5 ml) was refluxed until a homogeneous solution was obtained (8 h), and then evaporated. The residue was taken up in water, and the solution acidified with 6M-hydrochloric acid with heating on a steam-bath which caused an oil to separate. The cooled reaction mixture was extracted with ethyl acetate and the dried ($MgSO_4$) organic phase was evaporated. The residue, which slowly solidified, was recrystallized from ethyl acetate–ether to give the acid (**6**) (1.0 g, 83%) as a mixture of almost equimolar amounts of the *E*- and *Z*-isomers, m.p. 145—155 °C (Found: C, 63.3; H, 5.1; N, 3.2. $C_{21}H_{21}NO_7$ requires C, 63.15; H, 5.3; N, 3.5%). The composition of the mixture was deduced on the basis of the n.m.r. spectrum, the assignment of the signals being made by comparison with the spectra of related compounds;[1] $\delta_H[(CD_3)_2SO$–$CDCl_3]$ 4.20 (2 H, s, CH_2 of *E*-isomer), 4.55 (2 H, s, CH_2 of *Z*-isomer), 6.42 (1 H, s, vinylic H of *Z*-isomer), and 6.60 (1 H, s, vinylic H of *E*-isomer).

(E)- *and* (Z)-3-(3,4-*Methylenedioxybenzylidene*)-6,7-*dimethoxyphthalimidin*-2-*ylacetic Acids* (**7**).—From compound (**5**), by the same procedure, the *E*- and *Z*-isomers were obtained in 80% yield as a 1:1 mixture with m.p. 185—195 °C (Found: C, 62.5; H, 4.6; N, 3.4. $C_{20}H_{17}NO_7$ requires C, 62.7; H, 4.5; N, 3.65%); $\delta_H[(CD_3)_2SO$–$CDCl_3]$ 4.02 (2 H, s, CH_2 of *E*-isomer), 4.57 (2 H, s, CH_2 of *Z*-isomer), 6.23 (1 H, s, vinylic H of *Z*-isomer), and 6.63 (1 H, s, vinylic H of *E*-isomer).

3-(3,4-*Dimethoxybenzyl*)-6,7-*dimethoxyphthalimidin*-2-*ylacetic Acid* (**8**).—Compound (**6**) (6.0 g) was hydrogenated in ethanol (150 ml) at 50 °C and 1 atm in the presence of 10% Pd–C (0.5 g) to give compound (**8**) in quantitative yield, which crystallized from dichloromethane–ether as prisms, m.p. 146—148 °C (Found: C, 62.7; H, 5.7; N, 3.4. $C_{21}H_{23}NO_7$ requires C, 62.8; H, 5.8; N, 3.5%); $\nu_{max.}$ 1 650 and 1 750 cm^{-1}; $\delta_H(CDCl_3)$ 2.67, 2.76, 2.88, 2.97, 3.05, 3.12, 3.20, and 3.27 (2 H, *ABX* pattern, $CHCH_2$), 3.75, 3.84, and 3.99 (3 H, 6 H, and 3 H, s, OMe), 3.79, 4.02, 4.50, and 4.73 (2 H, ABq, NCH_2), 4.77, 4.85, and 4.93 (1 H, AB*X* pattern, $CHCH_2$), and 6.52—7.06 (5 H, m, ArH).

3-(3,4-*Methylenedioxybenzyl*)-6,7-*dimethoxyphthalimidin*-2-*ylacetic Acid* (**9**).—The *title compound* was obtained in quantitative yield by hydrogenation of compound (**7**), and crystallized from dichloromethane–ether as prisms, m.p. 170—173 °C (Found: C, 61.9; H, 4.8; N, 3.6. $C_{20}H_{19}NO_7$ requires C, 62.3; H, 5.0; N, 3.6%); $\nu_{max.}$ 1 640 and 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 2.56, 2.71, 2.80, 2.91, 2.98, 3.07, 3.20, and 3.30 (2 H, *ABX* pattern, $CHCH_2$), 3.81 and 3.95 (3 H and 3 H, s, OMe), 3.71, 4.01, 4.50, and 4.80 (2 H, ABq, NCH_2), 4.70, 4.80, and 4.90 (1 H, AB*X* pattern, $CHCH_2$), 5.85 (2 H, s, OCH_2O), and 6.35—7.05 (5 H, m, ArH).

13,13a-*Dihydro*-3,4,10,11-*tetramethoxyisoindolo*[1,2,-b][3]-*benzazepine*-5,8(7H)-*dione* (**10**).—Compound (**9**) (3.0 g) was cyclized with polyphosphoric acid as described,[1] to give the

* Thus, the cyclization of compound (**9**) and of other methylenedioxy substituted 3-benzylphthalimidin-2-ylacetic acids is still an open problem. However, we have found that methylenedioxy substituted 3-benzylphthalimidin-2-ylacetaldehyde acetal may be successfully cyclized to an isoindolo[1,2-*b*][3]benzazepine derivative under mild conditions, as reported in the accompanying paper.

dione (**10**) (2.2 g, 81%) which crystallized from dichloromethane–ether as prisms, m.p. 205—208 °C (Found: C, 65.5; H, 5.6; N, 3.7. $C_{21}H_{21}NO_6$ requires C, 65.8; H, 5.5; N, 3.65%); $\nu_{max.}$ 1 660 and 1 690 cm^{-1}; $\delta_H(CDCl_3)$ 3.06, 3.08, 3.24, 3.26, 3.55, and 3.64 (*ca.* 2 H, part of *ABX* pattern, part of 13-H), 3.70, 3.82, 3.85, and 3.94 (3 H, 3 H, 3 H, and 3 H, s, OMe), 3.89, 4.12, 4.91, and 5.14 (2 H, ABq, NCH_2), 4.88 (1 H, m, 13a-H), and 7.13—7.27 (4 H, m, ArH).

The Ethylene Acetal (**11**).—Compound (**10**) (2.0 g) was condensed with ethylene glycol as reported,[1] to give the acetal (**11**) (2.0 g, 90%) which crystallized from dichloromethane–ether as prisms, m.p. 220—223 °C (Found: C, 64.9; H, 5.9; N, 3.3. $C_{23}H_{25}NO_7$ requires C, 64.6; H, 5.9; N, 3.3%); $\nu_{max.}$ 1 670 cm^{-1}; $\delta_H(CDCl_3)$ 3.07, 3.25, 4.63, and 4.81 (2 H, ABq, 7-H), 2.90, 2.94, 3.07, 3.10, 3.18, 3.31, and 3.48 (2 H, 13-H), 3.90 and 4.10 (9 H and 3 H, s, OMe), 4.03—4.52 (5 H, m, 13a-H and OCH_2), and 6.77—7.31 (4 H, m, ArH).

7,8,13,13a-*Tetrahydro*-3,4,10,11-*tetramethoxy*-6-*methyl*-8-*oxo*-5H-*isoindolo*[1,2-b][3]*benzazepinium Iodide Ethylene Acetal* (**12**).—Compound (**11**) (5.0 g) was reduced with lithium aluminium hydride in tetrahydrofuran, and the crude amine was quaternized as described,[1] to give the iodide (**12**) (2.5 g, 38%) which crystallized from methanol as prisms, m.p. 193—197 °C (decomp.) (Found: C, 51.8; H, 5.6; N, 2.7. $C_{24}H_{30}INO_6$ requires C, 51.9; H, 5.4; N, 2.5%); $\nu_{max.}$ 1 050, 1 270, 1 460, and 1 600 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 3.52 (2 H, s, NMe), 3.74 and 3.80 (3 H and 9 H, s, OMe), 3.90—4.13 (2 H, m), 4.22 (4 H, m, OCH_2), 4.90—5.28 (3 H, m), and 6.96—7.19 (4 H, m, ArH).

5,6,13,13a-*Tetrahydro*-2,3-9,10-*tetramethoxy*-7-*methyl*-5-*oxo*-8H-*dibenzo*[a,g]*quinolizinium Iodide Ethylene Acetal* (**13**).—Compound (**12**) (3.0 g) was treated with 33% aqueous potassium hydroxide as described,[1] to give the quinolizinium salt (**13**) (2.8 g, 93%) which crystallized from methanol as prisms, m.p. 230—236 °C (decomp.) (Found: C, 52.0; H, 5.5; N, 2.4. $C_{24}H_{30}INO_6$ requires C, 51.9; H, 5.4; N, 2.5%); $\nu_{max.}$ 1 000, 1 080, 1 270, and 1 600 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.96 (3 H, s, NMe), 3.82, 3.85, 3.87, and 3.91 (3 H, 3 H, 3 H, and 3 H, s, OMe), 6.90, 6.97, 7.01, and 7.08 (2 H, ABq, 11-H and 12-H), and 7.13 (2 H, s, 1-H and 4-H).

The Acetate (**14**).—This compound was obtained from compound (**13**) by ion-exchange chromatography, according to a reported procedure.[6a] Alternatively, to a hot solution of compound (**13**) (1.0 g, 1.8 mmol) silver acetate (0.3 g, 1.8 mmol) was added in portions with stirring, and the resulting suspension was filtered through Celite and the filtrate evaporated. The residue crystallized from chloroform–acetone to give the acetate (**14**) (0.65 g, 74%) as prisms, m.p. 185—189 °C (decomp.) (Found: N, 2.6. $C_{26}H_{33}NO_8$ requires N, 2.9%); $\nu_{max.}$ 1 090, 1 290, 1 560, and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 1.92 (3 H, s, $MeCO_2^-$), 3.21 (3 H, s, NMe), 3.85, 3.92, and 3.94 (3 H, 3 H, and 6 H, s, OMe), 6.71 and 7.01 (1 H and 1 H, s, 1-H and 4-H), and 6.88, 6.96, 6.99, and 7.09 (2 H, 11-H and 12-H).

5,6,13,13a-*Tetrahydro*-2,3-*dimethoxy*-7-*methyl*-5-*oxo*-8H-*dibenzo*[a,g]*quinolizinium Acetate Ethylene Acetal* (**15**).—This compound was obtained in 75% yield from compound (**3**)[1] by the procedure described for compound (**14**). Prisms, m.p. 190—193 °C (decomp.) (Found: C, 67.5; H, 7.0; N, 3.1. $C_{24}H_{29}NO_6$ requires C, 67.4; H, 6.8; N, 3.3%); $\nu_{max.}$ 1 150 and 1 560 cm^{-1}; $\delta_H(CDCl_3)$ 1.82 (3 H, s, $MeCO_2^-$), 3.15 (3 H, s, NMe), 3.90 and 3.93 (3 H and 3 H, s, OMe), 6.73 and 7.00 (1 H and 1 H, s, 1-H and 4-H), and 7.30 (4 H, m, other ArH).

5,6,13,13a-*Tetrahydro*-2,3,9,10-*tetramethoxy*-5-*oxo*-8H-*dibenzo*[a,g]*quinolizine Ethylene Acetal* (**16**).—Compound (**14**) (0.2 g), toluene (2 ml), and acetonitrile (2 ml) were sealed in a glass tube and heated in an oil-bath at 120 °C for 24 h. The cooled reaction mixture was filtered and the filtrate evaporated. The residue crystallized from dichloromethane–ether to give the acetal (**16**) (0.16 g, 95%) as prisms, m.p. 177—180 °C (Found: C, 67.0; H, 6.7; N, 3.2. $C_{23}H_{27}NO_6$ requires C, 66.8; H, 6.6; N, 3.4%); $\nu_{max.}$ 860, 1 140, 1 250, 1 270, and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 3.84 and 3.89 (6 H and 6 H, s, OMe), 3.99—4.39 (5 H, m), 6.72 and 6.99 (1 H and 1 H, s, 1-H and 4-H), and 6.81 (2 H, m, 11-H and 12-H).

(±)-*Tetrahydropalmatine* (**17**).—A mixture of compound (**16**) (0.1 g, 0.34 mmol) and a 2.2M-solution of borane in tetrahydrofuran (2.0 ml, 4.4 mmol) was refluxed for 5 h under nitrogen, and then evaporated. The residue was taken up in 2M-hydrochloric acid and the filtered solution was made basic with 2M-sodium hydroxide and extracted with dichloromethane. The organic layer was dried (K_2CO_3), filtered, and the filtrate evaporated to afford compound (**17**) in quantitative yield, which crystallized from methanol as scales, m.p. 147—149 °C (lit.,[7] 147 °C and 151 °C) (Found: C, 71.2; H, 7.3; N, 3.8. Calc. for $C_{21}H_{25}NO_4$: C, 71.0; H, 7.1; N, 3.9%); $\nu_{max.}$ 850, 1 080, 1 140, 1 220, 1 250, 1 270, and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 3.84, 3.85, and 3.88 (3 H, 6 H, and 3 H, s, OMe), 6.61 and 6.73 (1 H and 1 H, s, 1-H and 4-H), and 6.82 (2 H, m, 11-H and 12-H) [lit.,[7b] 3.84 (3 H), 3.85 (6 H), 3.87 (3 H), 6.62 (1 H), 6.76 (1 H), and 6.82 (2H)].

5,6,13,13a-*Tetrahydro*-2,3-*dimethoxy*-8H-*dibenzo*[a,g]-*quinolizine* (**18**).—Compound (**15**) was pyrolysed as described for compound (**14**), and the crude reaction product reduced with borane–tetrahydrofuran complex as described for compound (**16**). The amine (**18**) which was obtained in 80% overall yield, was purified and characterized as the hydrochloride, m.p. 238—240 °C (lit.,[8] 237—239 °C). The product was identical with an authentic sample.[8]

Acknowledgements

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