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IMPROVED SYNTHESES OF SHIHUNINE, THE SPIRO PHTHALIDE PYRROLIDINE ALKALOID

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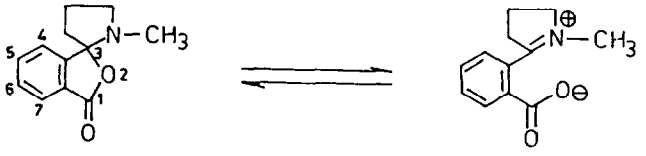
Abstract : This paper describes the syntheses of the spiro-alkaloid shihunine (1) by three different approaches. In the first, phthalic anhydride was condensed with N-methyl-2-pyrrolidone and the resulting phthalide 8 was hydrolysed to shihunine. In the second, phthalic anhydride was converted to the alkylidine phthalide 10 using Wittig reaction and then to 5 and finally to shihunine. In the third, methyl-2-formylbenzoate (16) was condensed with a zinc homoenolate to get the phthalide 20, which was then oxidised to 21, followed by cyclisation to the dilactone 14. 14 was converted to 5 through 15 and finally to shihunine.

Introduction

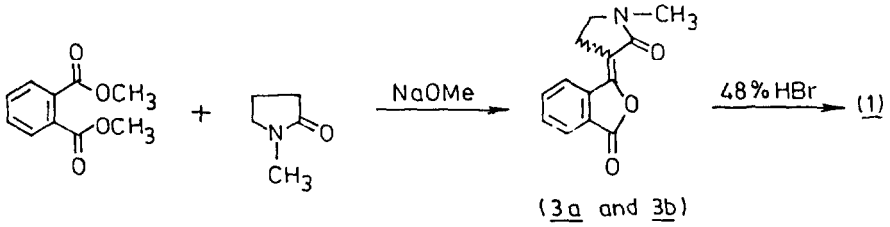
The alkaloid shihunine, optically inactive, was isolated[1] from the archidaceous plant, Dendrobium lohohense Tang et Wang. In crystalline state or dissolved in non-polar solvents (chloroform, carbon tetra chloride, hexane), the alkaloid has structure 1. However, in water or methanol solution, spectral data indicated[2] that it was rapidly and virtually completely converted into its betain 2. The cyclic compound 1 was obtained by evaporating the solvent and drying thoroughly.



(1) (2)

Three syntheses of shihunine are known. In the first, Onaka[3] condensed dimethyl-phthalate with N-methyl-2-pyrrolidone using sodium methoxide as the base. The isomeric mixture of E and Z -3-(1-methyl-2-oxo-3-pyrrolidonylidene)phthalides (3a and 3b), obtained in a poor yield of 6%, was hydrolysed with 48% HBr to get shihunine (Scheme I).

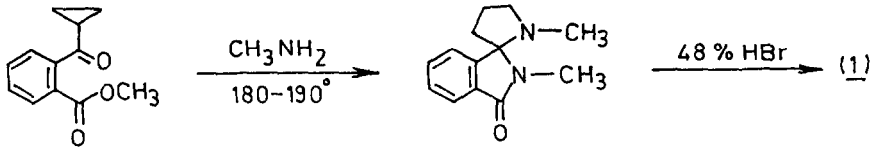
Scheme I



(3a and 3b)

In the second, Breuer and Zbaida[4] utilised the orthocarbomethoxy phenyl-cyclopropyl ketone 4, which was prepared from dicyclopropyl cadmium and phthalic acid monomethylester monoacidchloride, both of which are not conveniently obtained. The cyclopropyl ketone 4, on reaction with methyl amine at 180-190°C, gave the spiropyrrolidino-isoindolinone 5 in 26% yield. The latter on refluxing with 48% HBr yielded shihunine in quantitative yield (Scheme II).

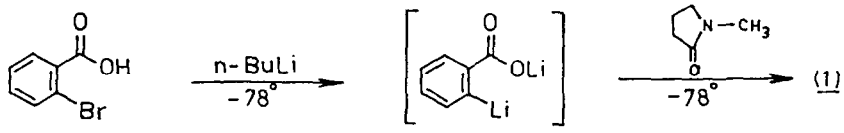
Scheme II



(4) (5)

In the third , Bodem and Leete[5] generated the dilithio compound 6 from o-bromobenzoic acid by metal halogen exchange reaction and reacted it with N-methyl-2-pyrrolidone at -78°C. Shihunine was obtained in 23% yield (Scheme III).

Scheme III



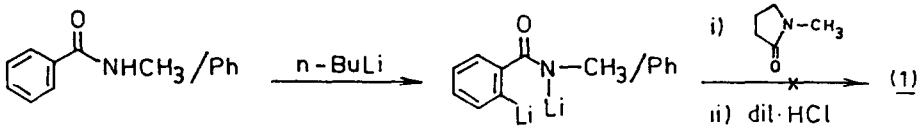
(6)

The spiro structure, present in shihunine, and the poor yields obtained in the previous syntheses attracted our attention to under take more efficient syntheses of the molecule. Our efforts are described in the present paper.

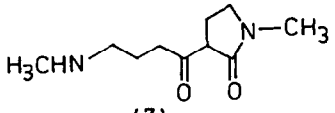
Results and Discussion :

Our first attempt was based upon the aromatic lithiation methodology (Scheme IV).

Scheme IV



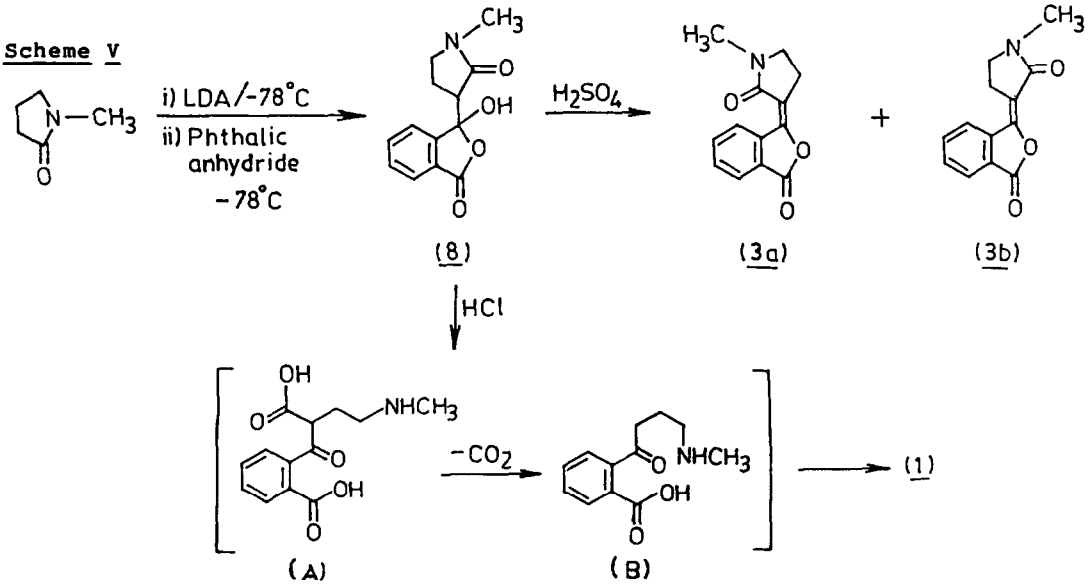
The reaction however, gave only the self condensed product of N-methyl-2-pyrrolidone, 7.



(7)

Our second attempt was similar to that of Onaka. The overall yield in Onaka's synthesis was very poor. In an attempt to increase the yield we used phthalic anhydride itself in the condensation reaction with LDA as the base. The condensation was carried out at -78°C. The desired product 8 was obtained in 87% yield. Compound 8 on treatment with conc. HCl gave shihunine in 50% yield. The formation of shihunine is presumably through the intermediates (A) and (B) (Scheme V).

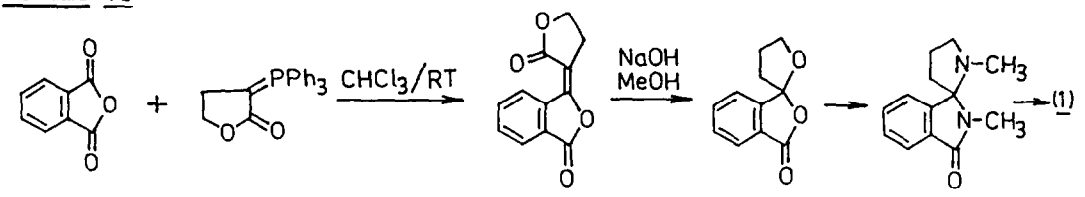
Scheme V



When compound 8 was refluxed with aqueous 50% sulphuric acid, instead of conc. HCl, an isomeric mixture of E and Z-3-(1-methyl-2-oxo-3-pyrrolidonylidene) phthalides was obtained (Scheme V) which was separated into its constituents (3a) and (3b). Onaka[3] had obtained the compound only as a mixture of (3a) and (3b).

In our third attempt, it was planned to obtain the oxygen analogue 11 of shihunine, and then convert it to the spiropyrrolidino-isoindolinone 5 in the first instance and then to shihunine (Scheme VI).

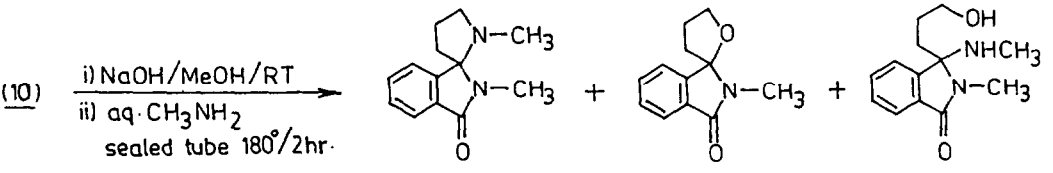
Scheme VI



(9) (10) (11) (5)

The alkylidine phthalide[6] 10 was obtained in 78% yield by Wittig reaction of phthalic anhydride and the phosphorane[7] 9. The phthalide 10 was hydrolysed with methanolic sodium hydroxide at room temperature and the resulting disodium salt heated in a sealed tube with aqueous methylamine. The required spiropyrrolidino-isoindolinone 5 was obtained in only 15% yield, along with two other compounds, 12 in 35% and 13 in 22% (Scheme VII).

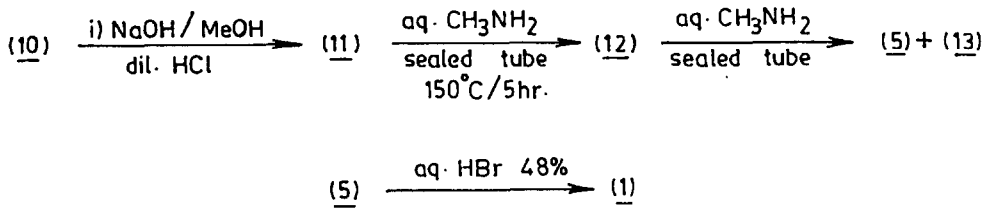
Scheme VII



(5) (12) (13)

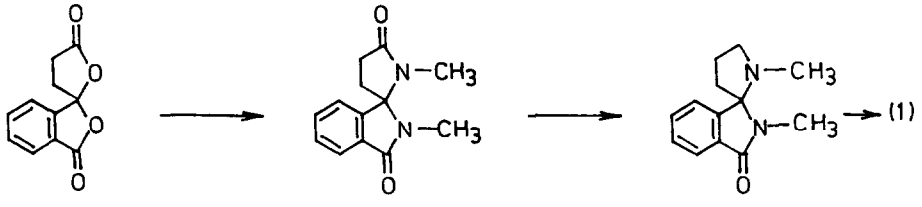
In another experiment, the disodium salt, obtained by the hydrolysis of the alkylidene phthalide 10 was acidified when 11 was obtained in 67% yield. Compound 11 on heating in a sealed tube, gave the spiroamide 12 in 68% yield. The latter on further heating at 150°C in a sealed tube for 5h with aqueous methylamine gave the spiropyrrolidino-isoindolinone 5, now in 50% yield. Compound 5 was then converted to shihunine by treatment with HBr. The open chain compound 13 was also obtained in the above reaction in 22% yield (Scheme VIII).

Scheme VIII



The conversion of the oxygen analogue 11 of shihunine to the spiropyrrolidino-isoindolinone 5 was not satisfactory. In the next attempt it was then decided to synthesise the spirodilactone 14 in the first instance, convert it to the spirodiamide 15 and reduce the non conjugated t-amide to get 5 (Scheme IX).

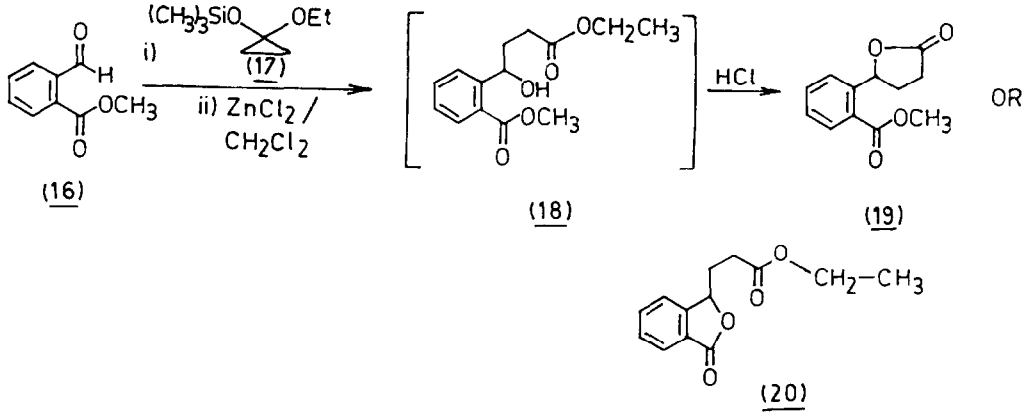
Scheme IX



(14) (15) (5)

Selective reduction of a non-conjugated t-amide is indeed readily possible. The spirodilactone was proposed to be synthesised, making use of the zinc homoenolate, generated in situ from cyclopropanone hemiketal 17[8] with Lewis acids such as $ZnCl_2$ or ZnI_2. Methyl-o-formyl benzoate (16) was chosen as the substrate. Advantage was taken of the fact that zinc homoenolates react only with aldehydes and ketones but not with esters[9].

Scheme X

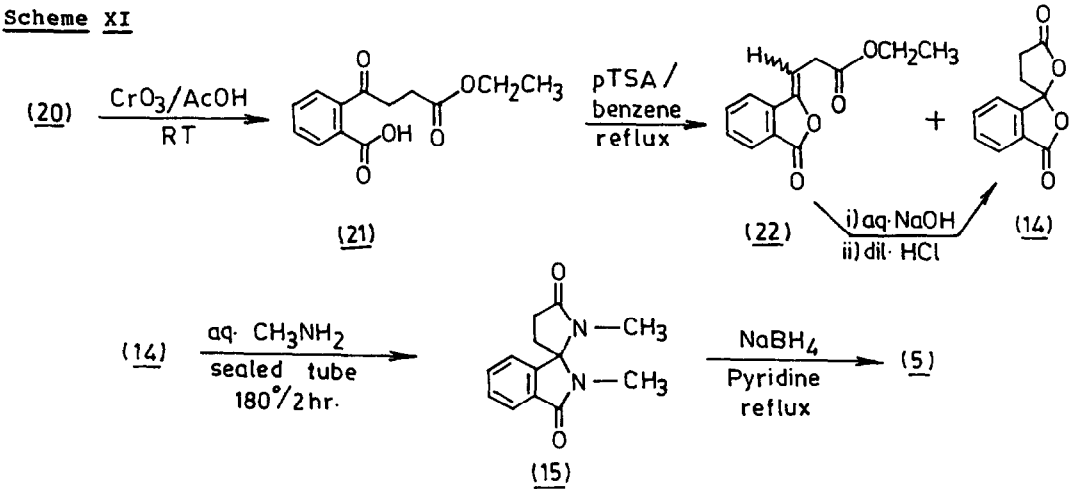


(16) (18) (19)

(20)

The ester 16, on reaction with cyclopropanone hemiketal 17, in presence of $ZnCl_2$, could give either 19 or 20 through the intermediate 18. In our reaction, the compound, obtained in 70% yield, was identified as the 3-substituted phthalide 20. Compound 20 was then converted to the spiropyrrolidino-isoindolinone 5 and finally to shihunine (Scheme XI).

Scheme XI



Compound 20 was oxidised with chromium trioxide in acetic acid to get ethyl-4-(o-carboxyphenyl)-4-oxo-butanoate (21) in 72% yield. The latter, on refluxing with pTSA in benzene, gave the spirodilactone 14 in 42% yield, and further heating with aqueous methylamine in a sealed tube at 180°C, the spirodiamide 15 in 70% yield.

In the reaction with pTSA/benzene, the alkylidene phthalide 22 was also obtained in 27% yield. The phthalide 22 could be converted to the spirodilactone 14 in 70% yield by treating first with aqueous sodium hydroxide and then with dil. HCl, thus increasing the overall yield of the spirodilactone 14 to 62% (from 42%).

The spirodiamide 15 has two tertiary amide carbonyl groups, one conjugated to the benzene ring, and the other non-conjugated. The non-conjugated amide was reduced to the corresponding amine by sodium borohydride in refluxing pyridine[10] to obtain compound 5, which was converted to shihunine by refluxing with 48% HBr.

Experimental

All solvents and reagents used, were purified and dried according to standard procedure. Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Perkin

Elmer 337 instrument. ^{1}H and ^{13}C spectra were obtained on Jeol FX 90Q spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shifts are given in δ units downfield from the internal standard.Coupling constants are expressed in Hz. Elemental analyses were performed on Hosli C, H analyser. Mass spectra were recorded on Finnigan MAT 1020 GC/MS instrument. Flash chromatography was performed on Eyela EF-10 flash chromatograph using silica gel or basic alumina, finer than 200 mesh. All organic extracts were washed with brine and water successively and dried over Na_2SO_4 (anhydrous).

Reaction of N-methylbenzamide and N-methyl-2-pyrrolidone

To the refluxing solution of N-methylbenzamide (0.675g, 5mmol) in dry THF (25ml) n-BuLi (in hexane, 1M, 15ml, 15mmol) was added. The deep red coloured solution of metallated amide was cooled to -78°C and treated with N-methyl-2-pyrrolidone (1.48g, 15mmol). The reaction mixture was stirred at -78°C for 1h and then allowed to come to room temperature. The THF was removed under reduced pressure and the residue decomposed with dil. HCl (total volume about 30ml). Extraction with chloroform (10mlx3) afforded the starting N-methylbenzamide (0.403g, 60%). The aqueous layer was made basic with 10% KOH solution and extracted with chloroform (10mlx3). The residue obtained after evaporation of solvent was purified by flash chromatography (basic alumina) with chloroform : methanol (97:3) as eluent to get N-methyl-4-oxo-4-[(N-methyl-(2-oxo-3-pyrrolidinyl)]-butylamine (7)(0.150g, 15%), reddish oil ; ν_{max} (Neat) : 3300 and 1650 cm^{-1} ; ^{1}H NMR : 1.00-1.40 (4H, m, 2xCH_2-CH_2-CH_2), 1.70-2.20 (2H, m, CO-CH_2-CH_2), 2.60-3.80 (11H,includes doublet J=5 at 2.75 for -NH-CH_3 and singlet at 2.90 for N-CH_3 2xN-CH_2-CH_2 and CO-CH-CO).

3-Hydroxy-3,3'(N-methyl-2-oxo-pyrrolidinyl)-phthalide (8)

To an LDA solution (20mmol, prepared from n-BuLi and diisopropyl amine) cooled to -78°C, was added N-methyl-2-pyrrolidone (1.0g, 10mmol). The mixture was stirred at -78°C for 30 min. to this was added phthalic anhydride (1.48g, 10mmol) in dry THF (10ml).After stirring at -78°C for 1h, the reaction mixture was allowed to attain the room temperature. Solvent was removed under vaccum. To the residue dil.HCl was added and reaction mixture was extracted with dichloromethane (25mlx3). Evaporation of the solvent and flash chromatography of residue over silica gel using chloroform : methanol (95 : 5) as eluent gave compound (8) (2.14g,87%), colourless solid ; 121-122°C (chloroform : methanol) ; ν_{max} (Nujol) : 3200, 1780, 1654 cm^{-1} ; ^{1}H NMR : 1.10-1.90 (2H,m,-CH_2-CH_2-CH),2.90 (3H, s, N-CH_3), 3.00-3.50 (3H, m, -N-CH_2-CH_2 and CO-CH-CH_2), 7.48-7.82 (3H, m, ArH), 7.91 (1H, dd, J=8, 1.5, C_7-H), 8.15 (1H, broad

hump, -OH, exchangeable).Found : C, 63.04; H, 5.40; $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30, Mass : M^+ 247.

Shihunine (1) :

To compound (8) (0.494g, 2mmol) was added 10ml of conc.HCl. The mixture was refluxed in oil bath for 15h, diluted with water (about 30ml) and basified with aqueous sodium carbonate. The basic aqueous layer was extracted with ether (25mlx5). Evaporation of ether and chromatography over basic alumina using chloroform : methanol (95 : 5) as an eluent gave shihunine (1) (0.20g, 50%), ν_{max} (Neat) : 1750 cm^{-1} ; ^1H NMR : 2.10 (3H, s, -N-CH$_3$), 1.95-2.40 (4H, m, -C-CH$_2$-CH$_2$-CH$_2$-), 2.95-3.40 (2H, m, -N-CH$_2$-CH$_2$), 7.30-7.70 (3H, m, ArH), 7.85 (1H, dd, J=8,2,C_7-H), ^{13}C-NMR : 20.66, 32.03, 39.27, 53.49, 111.37, 122.25,123.86, 124.86, 129.12, 133.67, 146.58, 168.69. Picrate, m.p.156-157°C (lit.[4] m.p. 159-160°C); ν_{max} (Nujol): 1740, 1690, 1625 cm^{-1} ; Mass : m/e : 203 and 229.

3-(1-Methyl-2-oxo-3-pyrrolidonylidene)phthalide (3a and 3b)

Compound (8) (0.247g, 1mmol) was heated at 120°C (bath temp.) with 50% aqueous H_2SO_4 (5ml) for 18 h. After cooling, the reaction mixture was diluted with water (25ml), neutralised with sodium bicarbonate and extracted with chloroform (10mlx3). Evaporation of solvent and crystallisation of solid obtained gave two distinct types of crystals which on mechanical separation gave the two geometrical isomers. E-isomer (3a) (0.10g, 43%); m.p.205-207°C (chloroform:ether); ν_{max} (Nujol) : 1780, 1690,1655 cm^{-1}; ^1H NMR : 3.05 (3H, s, N-CH$_3$), 3.20 (2H, t, J=7, -CH$_2$-CH$_2$-C), 3.60 (2H, t, J=7, -N-CH$_2$-CH$_2$), 7.55-8.10 (3H, m, Ar-H), 9.40 (1H, d, J=8, C_7H). Found : C, 67.84; H, 4.86; $C_{13}H_{11}NO_3$ requires C, 68.11; H, 4.84 and Z-isomer (3b) (0.035g, 15%); m.p. 236-237°C (chloroform:ether); ν_{max} (Nujol) : 1765, 1690, 1680 cm^{-1}; ^1H NMR : 2.95 (3H, s, -N-CH$_3$), 3.15 (2H, t, J=7, -CH$_2$-CH$_2$-C=), 3.58 (2H, t, J=7, -N-CH$_2$-CH$_2$), 7.45-7.95 (3H, m, Ar-H), 8.05 (1H, dd, J=8,2, C_7-H). Found : C, 67.94; H, 4.75; $C_{13}H_{11}NO_3$ requires C, 68.11; H, 4.84.

E-3-(2-Oxotetrahydrofuran-3-ylidine)phthalide (10)

A solution of phthalic anhydride (1.48g, 10mmol) and the phosphorane (9) (3.46g, 10mmol) in dry chloroform (20 ml) was stirred at room temperature. The reaction was slightly exothermic. The solid separated was filtered, washed with dry ether and crystallised from chloroform:ether to give compound (10) (1.68g, 78%); m.p. 212-213°C (lit.[6] m.p. 222°C); ν_{max} (Nujol) : 1785, 1745, 1660 cm^{-1}; ^1H NMR : 3.37 (2H, t, J=7, =C-CH$_2$-CH$_2$), 4.54 (2H, t, J=7, -OCH$_2$-CH$_2$-), 7.60-8.10 (3H, m, Ar-H), 9.17 (1H, d, J=8, C_7-H).

Hydrolysis of (10) and reaction with aqueous methylamine

A solution of phthalide (10) (1.08g, 5mmol) and sodium hydroxide

(0.5g, 12.5mmol) in methanol:water (20:10) was stirred at room temperature for 2 h. Methanol was removed on water bath. The mixture was heated (bath temp. 180°C) with aqueous methylamine (40% w/v, 10ml) in a stainless steel sealed tube for 8 h. The mixture was acidified with dil. HCl and extracted with ether (20 mlx3). Evaporation of solvent and flash chromatography of the residue over silica gel using chloroform as eluent gave spirotetra hyrofuran-2,3-(2'-methyl-1'-oxo-indoline),i.e.isoshihunine(12) (0.35g, 35%); m.p. 74-75°C (hexane:ether)(lit.[4] 75-77°C); ν_{max} (Nujol): 1690 cm^{-1} ; ^{1}H NMR : 2.16-2.40 (4H, m, O-CH_2-CH_2-CH_2-C), 2.95 (3H, s, -N-CH_3), 4.10-4.40 (2H, m, O-CH_2-CH_2), 7.31-7.66 (3H, m, Ar-H), 7.77 (1H, dd, J=7,2, C_7-H). ^{13}C-NMR : 23.63, 26.55, 33.43, 69.90, 97.95, 121.08, 122.66, 128.94, 130.67 131.97, 147.63, 166.59. The aqueous acidic layer was basified with sodium carbonate and extracted with chloroform. Evaporation of solvent and flash chromatography over basic alumina using chloroform:methanol (95:5) as eluent gave in the earlier fractions compound[4] spiro-[(N-methylpyrrolidine)-2,3'-(2'-methyl-1'-oxo-indoline)] (5) (0.160g, 15%), reddish syrup; ν_{max}(Neat) : 1690 cm^{-1}; ^{1}H NMR : 1.85 (3H, s, -N-CH_3), 2.00-2.40 (4H, m, $-CH_2-CH_2-CH_2$-C), 2.95 (3H, s, -N-CH_3), 3.00-3.47 (2H, m, H_3C-N-CH_2-CH_2) 7.28-7.68 (3H, m, Ar-H), 7.85 (1H, dd, J=8,2, C_7-H), Mass : M^+ : 216 ; and the later fractions compound, 3-N-methylamine-3-hydroxypropyl-N-methyl -1-oxo-indoline (13) (0.25g, 22%) thick liquid ; ν_{max} (Neat) : 3600-3000, 1675 cm^{-1}; ^{1}H NMR : 0.71-1.32 (2H, m, $-CH_2-CH_2-CH_2$), 1.74 (3H, s, -N-CH_3) 1.70-2.20 (3H, m, $-CH_2OH$ and $-CH_2-CH_2$-C), 2.82 (3H, s, -N-CH_3), 3.50 (2H, t, J=8,$-CH_2-CH_2$-OH), 7.31-7.68 (3H, m, Ar-H), 7.81 (1H, dd, J=8, 2, C$_7$-H); Mass : M^+ :234.

Spiro[(tetrahydrofuran)-2,3'-(1'-oxo-benzofuran)] (11)

Phthalide (10) (1.08g, 5mmol) was stirred in methanol:water (30ml, 1:2) solution of sodium hydroxide (1.0g, 25mmol) at room temperature for 8 h. The clear solution was acidified with 50% HCl and stirred at room temperature for 1 h. The mixture was extracted with ether (25mlx3). Evaporation of solvent and flash chromatography of the residue over silica gel using hexane:ethylacetate (85:15) as an eluent gave compound (11) (0.64g, 67%), transparent syrup; ν_{max} (Neat) : 1770 cm^{-1} ; ^{1}H NMR : 2.17-2.48(4H, m, -C-CH_2 -CH_2-CH_2), 4.12-4.40 (2H, m, $-CH_2-CH_2$-O), 7.40-7.75 (3H, m, Ar-H), 7.85 (1H, d, J=8, C_7-H); ^{13}C-NMR : 24.33, 37.33, 70.70, 114.10, 121.38, 125.15, 127.59, 130.57, 134.36, 146.55, 167.95. Found : C, 69.71; H, 5.03; $C_{11}H_{10}O_3$ requires C, 69.46; H, 5.30. Mass : M^+: 190.

Spiro[tetrahydrofuran-2,3'-(2'-methyl-1'-oxo-indoline)]i.e.isoshihunine(12)

Compound (11) (0.190g, 1mmol) in methanol (1ml) and aqueous methylamine (40% w/v, 10ml) was heated at 150°C (bath temp.) in a stainless steel sealed tube for 2 h. The mixture was extracted with ether

(5mlx3). Evaporation of solvent and flash chromatography over silica gel using chloroform as eluent gave isoshihunine (12) (0.138g, 68%) which was identical in all respects (m.p., IR, PMR) with the compound isolated in the earlier experiment.

Reaction of spiro[tetrahydrofuran-2,3'-(2'-methyl-1'-oxo-indoline)] i.e. isoshihunine (12) with aqueous methylamine

The spiroamide (12) (0.203g, 1mmol) in methanol (1ml) and aqueous methylamine (40% w/v, 10ml) was heated at 180°C (bath temp.) in a stainless steel sealed tube for 12 h. The mixture was acidified with dil. HCl and extracted with ether (10mlx3). Evaporation of ether gave, about 10-15% of isoshihunine (12) back. The acidic aqueous layer was basified with sodium carbonate and extracted with chloroform (20mlx3). Evaporation of solvent and flash chromatography over basic alumina using chloroform:methanol (95:5) as an eluent gave the basic compound (5) (0.101g, 50%) and the open amino alcohol (13) (0.050g, 22%), identical with those obtained earlier.

Shihunine (1)

The compound (5), on refluxing with 48% HBr, gave shihunine. (Identical with the sample obtained earlier).

Ethyl-3-(3'-phthalyl)propionate (20)

Methyl-2-formylbenzoate[11] (16) (0.328g, 2mmol) was stirred with freshly fused zinc chloride (1.36g, 10mmol, 5 equiv.) in dry dichloromethane (15ml) at 0°C for 30 min. To this 1-ethoxy-1-trimethylsiloxy cyclopropane (17) (0.7g, 4mmol) was added dropwise at 0°C. The reaction mixture was allowed to come to room temperature and stirred over night. The organic layer was washed with dil. HCl. Evaporation of solvent and flash chromatography of the residue over silica gel using hexane:ethylacetate (9:1) as eluent gave compound (20) (0.328g, 70%), a thick yellow oil; ν_{max} (Neat): 1780, 1745 cm^{-1}; ^1H NMR : 1.30 (3H, t, J=8, $-CH_2-CH_3$), 1.80-2.70 (4H, m, $-CH-CH_2-CH_2-COO$), 4.20 (2H, q, J=8, $-OCH_2-CH_3$), 5.70 (1H, bd, J=8, C_3-H), 7.50-8.00 (3H, m, Ar-H), 8.10 (1H, bd, J=8, C_7-H). Found : C, 66.98; H, 5.89; $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.02.

Ethyl-4-(o-carboxyphenyl)-4-oxo-butanoate (21)

Compound (20) (0.117g,0.5mmol) was stirred with chromium trioxide (0.2g, 2mmol) in glacial acetic acid (3ml) at room temperature for 12 h. The reaction mixture was diluted with water (total volume about 25ml) and extracted with ethyl acetate (10mlx3). Evaporation of solvent under reduced pressure gave compound (21) (0.090g, 72%), a thick yellow liquid; ν_{max} (Neat) : 3500-3200, 1745 cm-1; ^1H NMR : 1.30 (3H, t, J=8, $-CH_2-CH_3$), 2.30-2.85 (4H, m, $OC-CH_2-CH_2-COO$), 4.15 (2H, q, J=8, $-OCH_2-CH_3$), 4.80 (1H, bh, -COOH,exchangeable), 7.50-7.80 (3H, m, Ar-H), 7.95 (1H, bd, J=8, C_7-H).

Found; C, 62.10; H, 5.47; $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.64.

Spiro[(2-oxo-tetrahydrofuran)-5,3'-(1'-oxo-benzofuran)] (14)

The compound (21) (0.250g, 1mmol) was refluxed in dry benzene with catalytic amount of p-toluenesulphonic acid for 18 h. Evaporation of solvent and flash chromatography over silica gel with hexane:ethyl acetate (9:1) of residue gave in the initial fractions the 3-carboethoxy ethylidine phthalide (22)(0.063g, 27%), yellow oil; ν_{max}(Neat): 1775, 1745 cm^{-1}; ^{1}H NMR : 1.30 (3H, t, J=8, $-CH_2\underline{CH_3}$), 3.57 (2H, d, J=8, $OC-\underline{CH_2}-CH=$), 4.25 (2H, q, J=8, $-O\underline{CH_2}-CH_3$), 5.90 (1H, t, J=8, $CH_2-\underline{CH}=C-$), 7.50-7.91 (3H, m, Ar-H), 8.00 (1H, dd, J=8,1.5, C_7-H); Found : C, 67.41; H, 5.32; $C_{13}H_{12}O_4$ requires C, 67.23; H, 5.21 and later fractions the dilactone (14) (0.084g, 42%), colourless solid; m.p. 118-119°C (chloroform:hexane) (lit.[12] m.p. 120°C), ν_{max} (Nujol) : 1780 cm^{-1} ; ^{1}H NMR : 2.80-3.30 (4H, m, $-C-\underline{CH_2}-\underline{CH_2}-CO$), 7.70-8.20 (4H, m, Ar-H). Found : C, 64.43; H, 3.87; $C_{11}H_8O_4$ requires C, 64.70; H, 3.95.

Dilactone (14) from 3-carboethoxy ethylidine phthalide (22)

The compound (22) (0.234g, 1mmol) was stirred with 2M aqueous NaOH solution (5ml) at room temperature for 12 h. The reaction mixture was made acidic with conc. HCl and stirred at room temperature for 4 h. It was diluted with water (total volume about 25ml) and extracted with ethyl acetate (10mlx2). Evaporation of solvent and crystallisation of the residue from chloroform:hexane gave compound (14) (0.143g, 70%), identical with the compound obtained earlier.

Spiro[(1-methyl-2-oxo-pyrrolidine)-5,3'-(2'-methyl-1'-oxo-indoline)] (15)

The dilactone (14) (0.140g, 0.7mmol) was heated at 190-200°C (bath temp.)in a stainless steel sealed tube with aqueous methylamine solution (5ml, 40% w/v) for 2 h. The reaction was cooled to room temperature, diluted with water (total volume 25ml) and extracted with chloroform (5mlx3). Evaporation of solvent and crystallisation of residue obtained gave the compound (15) (0.110g, 70%), colourless solid; m.p. 188-189°C (chloroform : hexane); ν_{max}(Nujol) : 1730, 1690 cm^{-1}; ^{1}H NMR : 2.30 (3H, s,$-N-\underline{CH_3}$), 2.40-2.80 (4H, m, $-C-\underline{CH_2}-\underline{CH_2}-CO$), 2.97 (3H, s, $-N-\underline{CH_3}$), 7.30-7.80 (3H, m, Ar-H), 7.95 (1H, bd, J=8, C_7-H). Found : C, 67.65; H, 6.04; $C_{13}H_{14}N_2O_2$ requires C, 67.81; H, 6.13.

Spiro-[(1-methylpyrrolidine)-2,3'-(2'-methyl-1'-oxo-indoline)] (5)

The spirodiamide (15) (0.1g, 0.43mmol) was refluxed in dry pyridine (4ml) with sodium borohydride (0.33g, 0.9mmol) for 12h. Pyridine was removed under reduced pressure, the residue decomposed with ice-cold water (about 10ml) and extracted with chloroform (5mlx3). Evaporation of chloroform, passing a solution of the residue in ethyl acetate through a bed of neutral alumina and further elution with hexane:ethyl acetate (7:3)

gave compound (5) (0.054g, 58%) identical with the sample obtained previously.

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