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Reaction of *ortho*-Phenylenediamines with Electron Rich Alkenes and Formaldehyde

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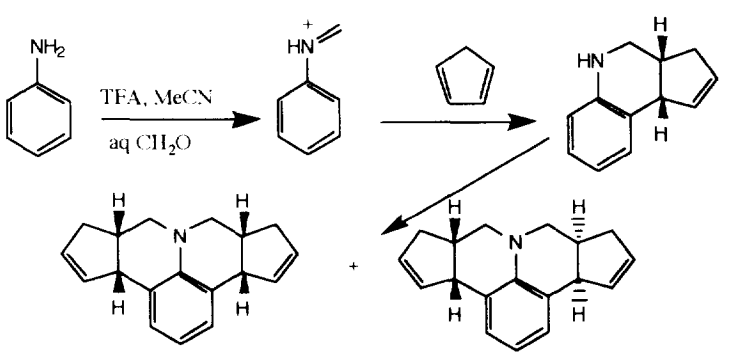
Abstract: *ortho-Phenylenediamines react with formaldehyde and cyclopentadiene in acetonitrile in the presence of trifluoroacetic acid to give two types of product. With excess formaldehyde and cyclopentadiene pentacyclic diamines are obtained. Tricyclic diamines are favoured when less formaldehyde is used. The derivatisation of the series of tricyclic benzodiazepines is described and the relationship between these benzodiazepines and the clinically important benzodiazepines is highlighted.*

The reaction of anilines[1] with formaldehyde in the presence of cyclopentadiene and trifluoroacetic acid has been shown to give adducts, which arise formally by the addition of the cyclopentadiene to a protonated imine, generated *in situ* by reaction of the amine and the aldehyde (Scheme 1). Such reactions correspond to Diels Alder processes in which the electron poor protonated azadiene, acting as the [4π] component, adds to the electron rich cyclopentadiene, acting here as the [2π] component. The reactions might be considered to be Diels Alder reactions proceeding with inverse electron demand. We have extended the initial observations of Grieco and Bahsas[1] by applying the reaction to a variety of aromatic amines, and have thus established[2,3] the synthetic utility of the procedure. Reactions of anilines, aminonaphthalenes, aminoanthraquinones, aminoquinolines and aminoisoquinolines have been studied[2,3]

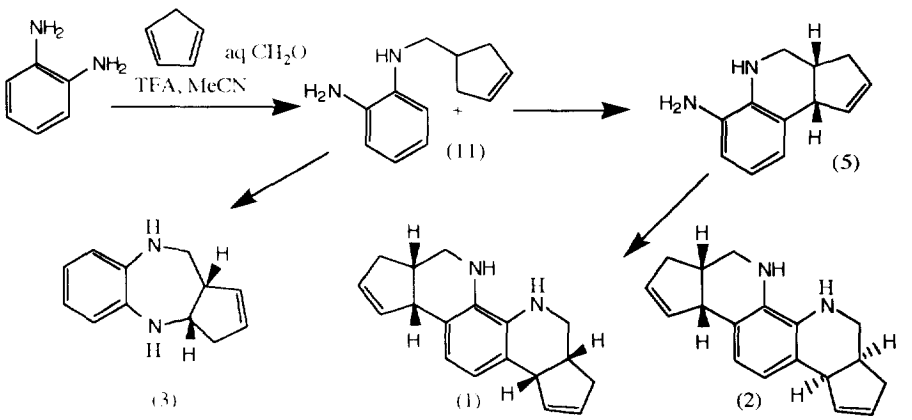
Scheme 1



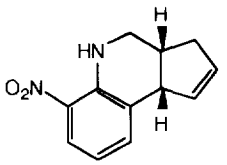
Here we wish to report the unique behaviour of *ortho*-phenylenediamines. Two series of products are obtained, one corresponding to the tetrahydroquinoline adducts observed[1-3] with other aromatic amines. A second category of products, substituted benzodiazepines, arise by the interception of reaction intermediates, The formation of these products is interesting for two reasons. It shows the non-concerted pathway of the formal Diels Alder reactions, but also it is important in giving access to a novel series of modified benzodiazepines. The earlier[4] clinical interest in the benzodiazepines has stimulated continuing[5-7] programmes in the synthesis and clinical application of benzodiazepines and related compounds. Thus recent aspects of their medicinal chemistry have been reviewed[8].

Reaction of *ortho*-phenylenediamine with formaldehyde and cyclopentadiene was carried out under the conditions used by Grieco and Bahsas[1] with aniline. Reaction with formaldehyde in acetonitrile in the presence of trifluoroacetic acid permitted initial iminium ion formation and by successive cycloadditions to cyclopentadiene evolution to afford the pentacyclic products (1) and (2). Such products could be anticipated on the basis of the prior chemistry shown in Scheme 1. However in reaction with *ortho*-phenylenediamine a further major product was observed and identified as the benzodiazepine (3) (Scheme 2). After work up and chromatography the diastereoisomers (1) and (2) were isolated as a single fraction in 35% yield, and the benzodiazepine (3) was isolated in 15-20% yield.

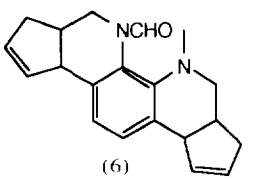
Scheme 2



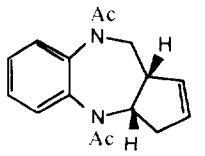
The diastereoisomers were cleanly separated by fractional crystallisation from ethyl acetate. The gross structural features of isomers (1) and (2) were recognised from their microanalysis and spectra and, in particular, their symmetry was revealed by their simplified ^{1}H- and ^{13}C- NMR spectra. The structures of the isomers (1) and (2) were confirmed by their isolation *via* an alternative synthetic pathway. 2-Nitroaniline under the reaction



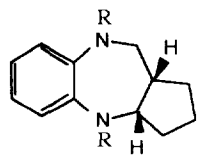
(4)



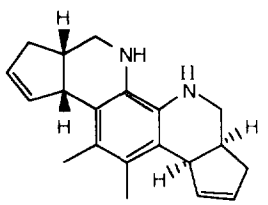
(6)



(7)



(8) R = H
(9) R = Ac
(10) R = $MeC_6H_4SO_2$



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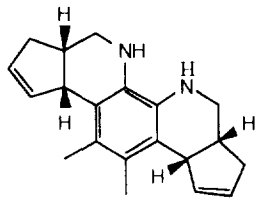

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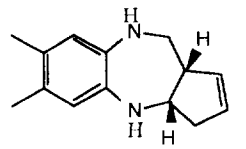

(14)

conditions of Grieco and Bahsas[1] gave the tricyclic amine (4) in 83% yield. Reduction to give the diamine (5), achieved in 95% yield with iron powder in glacial acetic acid, followed by a second cyclocondensation, achieved in 75% yield under the conditions of Grieco and Bahsas, gave the same mixture of diastereoisomers (1) and (2). Although this second route was useful in providing a structural confirmation, the simplest preparation of the isomers (1) and (2) is by the former more direct route.The stereochemical distinction between the isomers (1) and (2) was made by chiral hplc. In the case of isomer (1) having a *meso* plane of symmetry, only a single peak was observed on elution through a chiral column (4.6x250mm) derived from a triphenylmethyl methacrylate (Chiralcel-OD). In contrast the *dl*-isomers (2) were observed as two separate peaks under the same chromatographic conditions. The isolation of both the isomers (1) and (2) and the benzodiazepine (3) from the same reaction conditions led to an examination of the effect of the reaction conditions upon the product ratios. However this study led to a surprising result. In the presence of larger amounts of formaldehyde a new product was formed, which was identified as the formamide (6). Clearly the origin of the formamide is by further reaction of the pentacyclic diamines with formaldehyde followed by a hydride transfer, which might be intermolecular, but is more likely to be intramolecular, thus creating the methyl and formamide groups. Such hydride transfers[9] are well precedented.

The structure of the tricycle (3) was deduced by microanalysis, spectroscopic measurements and by the preparation of a series of derivatives. The *cis* stereochemistry was established from nOe observations. The diamine (3) was characterised as the diacetyl derivative (7) by reaction of acetyl chloride in pyridine, and

hydrogenation afforded the diamine (8), which was characterized by preparation of the diacetyl derivative (9) and the bis-sulfonamide (10). The formation of the benzodiazepine (3) is evidence of a reaction pathway (see Scheme 2) involving first formation of an iminium ion, which can react with cyclopentadiene to afford an allylic cation (11). This cation can then undergo cyclisation, either *via* an electrophilic substitution leading to a tetrahydroquinoline, or by attack by the primary amine leading to formation of the tricyclic benzodiazepine (3). The isolation of the benzodiazepine (3) is good evidence for the formation of the tetrahydroquinolines (1) and (2) by a multistep process. Although the isomers (1) and (2) are formally products of double Diels Alder reactions between first the iminium ion and then a second iminium ion with cyclopentadiene, isolation of the benzodiazepine (3) implies that their formation is *via* a non-concerted pathway. In our preliminary publication[3] evidence was obtained to indicate that the one-pot formation of tetrahydroquinolines occurred *via* non-concerted pathways from amines, formaldehyde and cyclopentadiene.

Substituted *ortho*-phenylenediamines afford products in the same manner. Reaction of 4,5-dimethyl-1,2-*ortho*-phenylenediamine gave a similar mixture of the pentacyclic diamines (12) and (13), which were not separated, and the crystalline tricyclic analogue (14). Other examples involving singly substituted *ortho*-phenylenediamines were briefly examined. However although formation of tricyclic benzodiazepines was observed, these reactions were not pursued because of the isomeric complexity of the products. Nevertheless for cases where the diamines have a plane of symmetry, the presently described elaboration permits a one-pot synthesis of cyclopenta-1,5-benzodiazepines, in which the products are readily isolated.

These results have two important features. The synthesis of tetrahydroquinolines by addition of cyclopentadiene to iminium ions has been described under two principal sets of conditions. The more studied[10-14] concerns the catalysed addition of preformed imines to the alkene. Thus in a recent study rare earth triflates are reported[14] to catalyse additions of imines leading to tetrahydropyridines and tetrahydroquinolines by Diels Alder addition. The less studied[1-3,15-17] concerns the reaction of imines or iminium ions generated *in situ* with the alkene. Apart from the conclusions of the existence of a non-concerted pathway, described in our preliminary publication[3], there has been little evidence against a concerted mechanism of addition. Indeed in the catalysed addition to preformed imines[11-13] the concerted pathway is suggested, although one report[18] provides evidence of a stepwise pathway in a Lewis acid catalysed addition. However the results in this paper point conclusively to a stepwise mechanism via cation intermediates, and suggest that such stepwise mechanisms may feature in other additions to imines and iminium ions.

The synthesis and study of the biological properties of both 1,4- and 1,5-benzodiazepines has been a focus[4-7] for extensive research. The main significance of our results, from a synthetic viewpoint, is the access by a one-pot reaction to the little known benzocyclopentadiazepines. Earlier more complex routes[19] to benzocyclopentadiazepines have not been developed. Our studies establish the first approach to this skeleton, permitting simple access to derivatives, which is desirable because of the biological importance[4] of related tricyclic systems.

Experimental

General methods are described elsewhere [20]

The synthesis of 3,3a,4,5,6,7,7a,8,10a,12b-decahydrodicyclopenta [c,i] [1,10] phenanthroline (3aα,7aα.10aα,12bα)-*Cis* (1) and (3aα,7aβ.10aβ,12bα)-*Trans* (2) and (3aα,10aα)-1,3a,4,5,10,10a hexahydrocyclopenta[*b*] [1,5] benzodiazepine (3).

1,2-*ortho*-Phenylenediamine (5.04g, 47 mmol) was dissolved in acetonitrile (35ml) with trifluoroacetic acid (10.61g, 93mmol), cooled in ice and stirred under nitrogen for 15 min. A solution of cyclopentadiene (15.23g, 230 mmol) and formaldehyde (7.65g, 94 mmol) in acetonitrile (20ml) cooled in ice was added slowly and the mixture stirred at room temperature for 1h. The mixture was poured into a saturated solution of sodium bicarbonate, which adjusted the pH to 8. The organic layer was extracted with dichloromethane, dried and the solvent removed under reduced pressure to yield a brown oil. Purification by column chromatography on silica gel [eluant light petroleum and ether (1:1)] afforded first the benzodiazepine (3) as a brown oil (1.5g., 19%) and then the title compounds the diastereoisomers (1) and (2) as a brown solid (4.09g, 33%). Fractional recrystallisation of the diastereoisomers afforded separate crystalline fractions of the title diamine (1) and the diamine (2).*Cis* isomer (1).m.p = 132-133°C (from ethyl acetate). υ_{max} (KBr)/ cm^{-1}: 3296, 3209, 2941, 2941, 2941, 2923, 2896, 2843, 2813. 1572, 1479, 1442, 1408, 1355, 1334, 1283. δH (400MHz) 6.78(2H,s,2xArH), 5.88-5.82 (2H,m,2xCH=C), 5.68-5.63 (2H,m,2xCH=C), 3.84 (2H,s,NCH_2), 3.11(2H,s,NCH_2), 2.75(2H,s,2xNH), 2.69-2.55(6H,m,2xCH_2,2xCH), 2.12(1H,s,CH), 2.08(1H,s,CH). δC (100MHz) 135.89(CH=), 134.36(ArC), 128.14(=CH), 123.24(ArC), 120.18(ArCH), 46.04(CH), 44.85(CH_2), 37.03(CH_2), 37.03 (CH_2), 35.96(CH). m/z =[Found: 264.1628 (M^+ 100%), 221(10), 197(27), $C_{18}H_{20}N_2$ requires 264.1626] [Found C=81.6; H=7.4; N= 10.6. $C_{18}H_{20}N_2$ requires C=81.7; H=7.6; N=10.6]. *Trans* isomer (2). m.p = 154-155°C (from ethyl acetate). υ_{max} (KBr)/cm^{-1}. 3285, 2939, 2913, 2891, 2840, 1578, 1515, 1442, 1355, 1293, 1221, 1200, 1076. δH (400MHz) 6.72 (2H,s,2xArH), 5.88-5.83(2H,m,2xCH=C), 5.68-5.63(2H,m,2xCH=C), 3.85 (2H,s,CH_2), 3.33(2H,br,2xNH), 3.13-3.07(2H,dd, J=8.0, J=8.1 NCH_2), 2.87-2.81(2H,m,2xCH), 2.68-2.61(4H,m,2xCH_2), 2.16(1H, s, CH), 2.12(2H,s,CH). δC (100MHz) 135.92(CH=CH), 134.11(ArC), 128.37(CH=CH), 123.02(ArC), 119.87(ArCH), 45.94(CH), 44.70(CH_2), 30.90(CH_2), 35.95 (CH).m/z=[Found: 264.1611 (M^+100%), 221(10), 197(25) $C_{18}H_{20}N_2$ requires 264.1626]. [Found : C=81.4; H=7.5. N= 10.6. $C_{18}H_{20}N_2$ requires C=81.7; H=7.6; N=10.6%].Crystallisation of the brown oil afforded benzodiazepine (3). mp= 120-121°C (from ether / ethyl acetate (1:1)) υ_{max} (film)/cm^{-1}. 3410, 2591, 1600, 1520, 1460. δH (270Mhz) 6.65-6.39 (4H,m,4xArH), 5.81-5.78(1H,m,CH=) 5.52-5.49(1H m,=CH). 4.21-4.16(1H,m,NCH), 3.55-3.37(2H,m,NCH_2), 3.02(2H,brs,2xNH), 2.68-2.59(2H,dd,J=8.0, 7.0 NCH_2), 2.27-2.21(1H,d,J=6.8 CH-CH=). δC (68MHz) 139.09(ArC), 136.41(ArC), 131.27(CH=), 130.27(=CH). 121.33(ArCH), 120.08 (ArCH), 119.17 (ArCH),

117.24 (ArCH), 59.63(CH), 50.35 (CH), 46.59(CH_2) 40.90 (CH_2). m/z=[Found 186.1163 (M^+ 58%), 133(20), 120(22), 119(100) $C_{12}H_{14}N_2$ requires 186.1157]. [Found : C=77.1; H=7.6; N= 14.95. $C_{12}H_{14}N_2$ requires C=77.4; H=7.6; N=15.0%].

A second synthesis of 3,3a,4,5,6,7,7a,8,10a,12b-decahydrodicyclopenta [*c,i*] [1,10] phenanthroline (3aα,7aα.10aα,12bα)-*cis* (1) and (3aα,7aβ.10aβ,12bα).*trans* (2).

2-Nitroaniline (2.0, 14mmol) was dissolved in acetonitrile (10ml) to give an amine solution (1.4M), trifluoroacetic acid (1.7g, 15mmol, 1.1eq) was added and the solution stirred under nitrogen for 10min. A solution of formaldehyde (5.22g, 5eq,70mmol) and cyclopentadiene (4.61, 5eq, 70mmol) in acetonitrile (5ml) at 0°C was then added and the solution stirred under nitrogen for 1h. The organic layer was added to a solution of saturated sodium bicarbonate (100ml) extracted with dichloromethane (3x50ml), dried, and the solvent removed under reduced pressure to yield a black oil. Purification by flash chromatography on silica gel [eluant light petroleum/ ether (8:2)] afforded as red crystals 9-nitro-1,2,3,7-tetrahydro (2aα,5aα) dihydrocyclopenta [*c*] quinoline (4) (2.53g 83%) mp= 81-82°C. (from ethyl acetate) υ_{max} (film)/cm^{-1} 3422, 3018, 1640, 1216. δH (300MHz) 8.03-8.02(2H,d,J=8.0 ArH), 7.36-7.33(1H,d,J=8.5 ArH), 6.63-6.59(1H, t, J = 8.5), 5.75(2H,s, CH=CH), 3.96(2H, brs,$NHCH_2$) 3.34-3.29(1H,dd, J=4.8, J=5.0, CH), 2.68-2.63(2H,brs,CH_2NH), 2.19-2.14(1H,d,J=8.0, CH). δC(75MHz) 144.39(ArC-NO_2), 136.19(CH=), 135.81(=CH), 129.37(ArCH), 127.46(ArC), 124.55 (ArCH), 115.34 (ArCH), 46.35 (CH), 42.47 (CH_2NH) 37.23 (CH_2-C=) 34.27(CH). m/z= [Found 216.0899 (M^+100), 197 (30), 168 (70), 154 (20), 115 (20), $C_{12}H_{12}N_2O_2$ requires 216.0899] .

9-Nitro-1,2,3,7-tetrahydro (2aα,5aα) dihydrocyclopenta [*c*] quinoline (4) (1.09g,5.05 mmol) was dissolved in glacial acetic acid (25ml) and whilst warming the dark solution to 80°C under nitrogen, water (20ml) was added slowly. The temperature was maintained between 80-90°C and iron powder (1.87g, 33 mmol) added slowly with stirring over a period of 20min. The solution was stirred under nitrogen for 2h, cooled to room temperature and a saturated solution of sodium bicarbonate added to adjust the pH to 8. The organic layer was extracted with dichloromethane (3x50ml),dried and the solvent removed under reduced pressure to yield a red oil. Purification by column chromatography on silica gel [eluant light petroleum /ether (8:2)] afforded 9-amino-1,2,3,7-tetrahydro-(2aα,5aα)-dihydrocyclopenta [*c*] quinoline (5) as a brown oil (0.90g, 95%). υ_{max} (film)/ cm^{-1}. 3320, 3000, 2930, 2845, 1630 , 1500, 1450 δH (300MHz) 6.82-6.80(1H,d, ArH,J=7.5), 6.73-6.68 (1H,t,ArH,J=7.3), 6.59-6.57(1H,d,ArH, J=7.4), 5.89(1H,s,CH=), 5.72(1H, s,=CH), 3.93(1H,s,NH), 3.33 (2H,m,CH_2NH), 3.19(1H,dd,J=4.0, J=5.0 CH), 2.71-2.69(2H,m,CH_2) 2.21-2.16(1H,d,CH,J=1.4). δC (75 MHz) 136.08(ArCNH_2), 135.34(ArC), 134.20(ArC), 128.65(ArCNCH_2) 126.13(ArC), 121.40(CH=), 119.02 (=CH), 114.20(ArC-CH),46.31(CH-CH_2), 44.98(CH_2-NH), 37.33(CH_2) 36.24(CH-CH=). m/z=[Found: 186.1158 (M^+100), 185 (51), 168 (30.87), 145 (25.50) $C_{12}H_{14}N_2$ requires 186.1157].

9-Amino-1,2,3,7-tetrahydro-(2aα,5aα)-dihydrocyclopenta [*c*] quinoline (5) (0.25g, 1.35 mmol) was dissolved in acetonitrile (10ml) to give an amine solution (0.14M). Trifluoroacetic acid (0.15g, 1.35 mmol) was added and

the solution stirred under nitrogen for 10 min. A mixture of formaldehyde (0.11g, 1.36 mmol) and cyclopentadiene (0.44g, 6.67 mmol) in acetonitrile (5ml) at 0°C was added and the mixture stirred at room temperature for 1h under nitrogen. A saturated solution of sodium bicarbonate was added to afford an alkaline solution pH8. The organic layer was extracted with dichloromethane, dried and the solvent removed under reduced pressure to yield a black oil. Purification by column chromatography on silica gel [eluant light petroleum/ether (1:1)] afforded the title compound as a brown solid consisting of a mixture of the isomers(1) and (2) (0.27g, 75%).mp= 124-125°C (from ethyl acetate).

The synthesis of *N*-methyl,*N'*-formyl-3,3a,4,5,6,7,7a,8,10a,12b-decahydrodicyclopenta [*c,i*][1,10] phenanthroline (6)

1,2-*ortho*-Phenylenediamine (2.16g,20mmol) was dissolved in acetonitrile (14ml) with trifluoroacetic acid (4.56g, 40mmol) and the solution cooled in ice. A solution of cyclopentadiene (3.95g, 60mmol) and formaldehyde (11.5g, 120mmol) in acetonitrile (92ml) cooled in ice was added slowly, and the mixture stirred for 11h at room temperature. The mixture was poured into a solution of saturated sodium bicarbonate (20ml), the organic layer was extracted with dichloromethane and the solvent removed under reduced pressure. Purification by column chromatography on silica gel [eluant light petroleum/ether (1:1)] afforded the title compound (6) as a brown solid.(1.19g, 19%). mp=140-141°C (From ether). υ_{max} (film)/cm^{-1} 3020, 2800, 1654. δH (270MHz) 8.92 (H,s,CH0), 7.06-7.00(2H,tr,J=7.9, 2xArH) 6.96-6.93(1H,d,J=8.7 ArH), 6.83-6.80(1H,d,J=8.3 ,ArH), 5.84-5.61(4H,m,2xCH=CH), 4.58 (2H,m, 2xArCH), 3.81(4H,s,2xCH_2-N) 2.65-2.68(5H, s,CH_2,CH,CH_2) 2.61 (3H,s,CH_3) 2.39 (2H,t, CH_2,J=7.9), 2.09(1H,s,CH), 1.88(1H,d,J=8.0, CH-Ar). δC (68MHz) 163.58(CO), 134.56(CHO), 133.83(CH), 129.09(C-Ar), 126..95(C-Ar), 123.52 (CH=), 123.12 (=CH), 47.36(CH), 46.94 (CH_3) 46.93(CH), 46.78(CH), 43.19(CH_2), 41.43(CH_2), 37.40(CH_2), 37.13(CH_2), 28.71(CH), 28.58 (CH).m/z=[Found: 306.1714 (M^+67%), 278 (100), 263 (20), 197 (15) $C_{20}H_{22}N_2O$ requires 306.1732]

The synthesis of *N,N'*-diacetyl (3aα,10aα)-1,3a,4,5,10,10a-hexahydrocyclopenta [*b*] [1,5] benzodiazepine (7).

(3aα,10aα)-1,3a,4,5,10,10a-Hexahydrocyclopenta[*b*] [1,5] benzodiazepine (3) (0.13g, 0.69mmol) was dissolved in dichloromethane (3ml) and pyridine (0.19g, 2.45ml) added with stirring. Acetyl chloride (0.19g, 2.42 mmol) was added and the mixture stirred for 15h under nitrogen. The mixture was poured into water, hydrochloric acid (10ml, 86mmol) added, the organic layer extracted with dichloromethane (3x10ml), dried and the solvent removed under reduced pressure to yield a brown oil. Purification by column chromatography on silica gel [eluant light petroleum/ethylacetate (4:1)] afforded the title compound(7) as a light green solid. (0.19g, 58%). mp = 170-171°C.(from chloroform) υ_{max} (film)/cm^{-1}. 3010, 1660, 1510, 1400. δH (270Mhz) 7.39-

7.31(2H,m, 2xArH), 7.24-7.21(2H,m,2xArH), 5.66-5.63(1H,d,J=7.7,CH=), 5.52-5.47(2H, q,J=4.6, =CH), 4.56-4.49(3H, NCH_2 NCH), 2.96(1H, brs,CH), 2.24-2.21(2H,m,CH_2) 1.88(3H,s,CH_3). δC (68Mhz) 169.97(CO), 168.64(CO), 141.01(ArC), 137.28(ArC), 132.09(ArCH), 131.12(ArCH), 130.75(ArCH), 129.80 (ArCH), 128.88(CH=), 128.50(=CH), 52.68(CH), 46.86(CH_2) 42.04(CH), 31.86(CH_2) 23.10(CH_3) 22.27 (CH_3). m/z= [Found: 270.1359(M^+40%) $C_{16}H_{18}N_2O_2$ requires 270.1368]. [Found: C= 71.2; H=6.8; N=10.4. $C_{16}H_{18}N_2O_2$ requires C=71.1; H=6.7; N=10.4].

The synthesis of (3aα,10aα)-1,2,3,3a,4,5,10,10a-octahydrocyclopenta[*b*][1,5] benzodiazepine (8).

(3aα,10aα)-1,3a,4,5,10,10a-Hexahydrocyclopenta[*b*] [1,5] benzodiazepine (3) (1.09g, 5.86mmol) was dissolved in ethyl acetate (15ml) and dry methanol (5ml) and palladium on charcoal (5%, 0.32g) was added. The mixture was stirred under hydrogen until the hydrogen uptake (42ml) was completed. Filtration of the solution under gravity and removal of the solvent under reduced pressure yielded the title compound as a brown solid. Purification by column chromatography on silica gel [eluant light petroleum / ether (1:1)] afforded the title compound (8) as a light brown solid.(0.98g, 89%).mp=91-92°C. (from ethyl acetate) υ_{max} (film)/cm^{-1} 3367, 3335, 2906, 2860, 1598, 1513, 1473, 1368 1305.δH (270Mhz) 6.67-6.51(4H,m,4xArH), 4.05-4.02 (2H,m,2xNH), 3.06-3.52(1H,q, J=9.5,3.7, CH), 3.29-3.22(2H,dd,J=4.4,J=6.4,CH_2),2.31-2.21 (1H,m, CH), 2.08-2.02(2H,q, J=6.2 CH_2), 1.68-1.62(2H,m,CH_2), 1.49-1.42(2H,brm,CH_2). δC (68Mhz) 139.10 (ArC), 137.08(ArC), 121.22(ArCH), 119.79(ArCH), 119.70(ArCH), 117.93(ArCH), 61.06(CH), 48.04 (CH_2) 44.78(CH), 34.90(CH_2) 28.46(CH_2) 24.32(CH_2).m/z=[Found: 188.1333 (M^+73%), 145(22), 119 (100), $C_{12}H_{16}N_2$ requires 188.1313].

The synthesis of *N,N'*-diacetyl-(3aα,10aα)-2,3,3a,4,10,10a-octahydrocyclopenta[b][1,5] benzodiazepine (9).

(3aα,10aα)-1,2,3,3a,4,5,10,10a- Octahydrocyclopenta [*b*] [1,5] benzodiazepine (8) (0.20g, 1.06mmol) was dissolved in dichloromethane (2ml) with pyridine (0.17g) and cooled in ice. A cold solution of acetyl chloride (0.33g, 4.20mmol) in dichloromethane (2ml) was added and the solution stirred at room temperature for 11h, poured into water (20ml) containing hydrochloric acid (10ml, 0.08 mol). The organic layer was extracted with dichloromethane (3x10ml), dried and the solvent removed under reduced pressure to yield a brown oil. Purification by column chromatography on silica gel [eluant light petroleum/ether (1:1)] afforded the title product (9) as a beige solid. (0.25g 89%).mp= 101-102°C (from ethyl acetate).υ_{max} (film)/ cm^{-1}. 3017, 1654, 1499, 1397, 1215. δH (270MHz) 7.37-7.31(2H,m,2xArH), 7.29-7.17(2H,m, 2xArH), 5.20-5.12(1H,m,CH), 4.39-4.3(2h,dd,J=4.8,J=4.7,CH_2), 2.44-2.40(4H,m,2xCH_2), 1.82(3H,s,CH_3), 1.77(3H,s,CH_3), 1.52 (2H,brs, CH_2) 1.45-1.42 (1H,m,CH). δC (68MHz) 169.84(CO), 168.85(CO), 146.10(ArC), 131.12(ArCH), 129.66

(ArCH), 129.29(ArCH), 129.01(ArCH), 60.12(CH), 45.24(CH_2), 37.49(CH), 26.21(CH_2), 24.21(CH_2) 23.90(CH_3) 22.25(CH_3) 19.59(CH_2).m/z=[Found: 272.1507 (M^+36%) $C_{16}H_{20}N_2O_2$ requires 272.1525].

The synthesis of *N-N'*di*para*-toluenesulfonyl-(3aα,10aα)-1,2,3,3a,4,5,10,10a-octahydrocyclo-penta [*b*] [1,5] benzodiazepine (10).

3aα,10aα)-1,2,3,3a,4,5,10,10a-Octahydrocyclopenta [*b*] [1,5] benzodiazepine (8) (0.20g, 1.06mmol) was dissolved in dichloromethane with pyridine (0.25g) and *para*-toluenesulphonyl chloride added. The mixture was stirred at room temperature for 10h under nitrogen, poured into water (20ml) containing hydrochloric acid (9ml, 80mmol) and the organic layer extracted with dichloromethane, dried (3x20ml), and the solvent removed under reduced pressure to yield a black solid. Purification of the product by column chromatography on silica gel [eluant light petroleum ether (2:3)] afforded the title compound (10) as grey solid. (0.27g, 52%) mp=111-112°C. (from ether) υ_{max} (film)/cm^{-1} 3019, 2964, 1597, 1494, 1451, 1350, 1215, 1160.δH (270Mhz) 7.82-7.79 (4H,d,J=8.5, 4xArH), 7.32-7.23(6H,d,J=8.3, 6xArH), 7.22-7.19(2H,m,2xArH), 4.62-4.60(1H,m,CH), 3.74-3.71(2H,m,CH_2), 2.40 (6H,s,2xCH_3), 2.22-2.02 (1H,m,CH), 1.57-1.51(4H,m,2xCH_2), 1.17-1.10 (2H,m,CH_2). δC (68Mhz) 143.78(ArC), 143.65(ArC), 139.81(ArC), 138.38(ArC), 138.22(ArC), 131.46 (ArCH) 130.67(ArCH) 128.17(ArCH), 128.03(ArCH), 127.85(ArCH), 127.79(ArCH), 58.99(CH), 49.06 (CH_2), 40.16(CH), 27.76(CH_2), 25.69(CH_2), 21.75(CH_3), 19.08(CH_2). m/z= [Found 496.1489 (M^+10%), 340(40), 185(100) $C_{26}H_{28}N_2O_4S_2$ requires 496.1491].

The synthesis of 5,6-dimethyl-3,3a,4,5,6,7,7a,8,10a,12b-decahydrodicyclopenta[*c,i*] [1,10] phenanthrolines *trans*-(12) and-*cis*-(13) and 7,8-dimethyl (3aα,10aα)-1,3a,4,5,10,10a-octahydrocyclopenta[*b*] [1,5] benzodiazepine (14).

3,4-Dimethyl-1,2-*ortho*-phenylenediamine was dissolved in acetonitrile (13ml) with trifluoroacetic acid (3.72g, 33mmol) and allowed to stir at 0°C under nitrogen for 10min. A solution of cyclopentadiene (4.98, 75mmol) and formaldehyde (2.46g, 30mmol) in acetonitrile (5ml) at 0°C was added slowly over 15min. The reaction was stirred at room temperature for 1h, poured into water and sodium bicarbonate added to adjust the pH to 8. The organic layer was extracted with dichloromethane (3x10ml), dried and the solvent removed under reduced pressure to yield a brown oil. Purification by column chromatography on silica gel [eluant light petroleum/ ether (1:1)] afforded the diamines (12) and (13) as an oil and the diamine (14) as a brown solid. *cis*- and *trans*-5,6-dimethyl-3,3a,4,5,6,7,7a,8,10a,12b-decahydrodicyclopenta[*c,i*] [1,10] phenanthrolines (13) and (12) (0.34g, 10%) υ_{max} (film)/cm^{-1} 3330, 2925, 2830, 1670, 1590, 1450, 1360.δH (270Mhz) 5.85 (2H,s,CH=), 5.71(2H,s,=CH), 3.93(2H,brs,CH_2), 3.01(2H,brs,CH_2), 2.83-2.75(2H,brs, 2xNH), 2.61-2.48 (4H,m,2xCH_2) 2.22(3H,brs,CH_3), 2.20(3H,br,s,CH_3), 2.14-2.09(1H,m,CH), 2.05-1.98(1H,m,CH).δC (68Mhz) 135.79(ArCH), 135.54(ArCH), 132.42(ArC), 132.33(ArC), 129.25 (ArCH), 129.02(ArCH), 126.32 (ArC), 126.15(ArC), 45.09(CH), 45.05(CH), 44.03(CH_2) 36.91(CH_2) 36.51(CH), 15.56(CH_3). m/z=[Found:

292.1921 (M^+100), 289(7),225(6), $C_{20}H_{24}N_2$ requires 292.1939].7,8-dimethyl (3aα,10aα)-1,3a,4,5,10,10a-hexahydrocyclopenta[*b*] [1,5] benzodiazepine (14).(0.26g, 8%) mp= 68-69°C (from ether) υ_{max} (film)/cm^{-1} 3400, 2920, 1735, 1600, 1510, 1460. δH 6.28(1H,s,ArH), 6.23(1H,s,ArH), 5.80-5.77(1H,m,CH=), 5.52-5.49(1H,m,=CH), 4.18-4.13(1H,m, CH), 3.51-3.37(2H,m,NCH_2), 3.01 (2H,brs,2xNH), 2.80-2.60 (2H,dd, J=6.39 ,J= 7.02 CH_2), 2.26-2.20(1H,m, CH), 2.03(6H,s,2xCH_3). δC (68Mhz) 136.69(ArC), 134.16(ArC), 131.34(CH=), 130.20(=CH), 128.98(ArC), 126.86(ArC), 121.52(ArCH), 118.85(ArCH), 59.74(CH), 50.61 (CH), 46.73(CH_2) 40.83(CH_2) 18.87(CH_3), 18.73(CH_3).m/z=[Found: 214.1477 (M^+75%), 148 (30), 147 (100) $C_{14}H_{18}N_2$ requires 292.1939].

References

1. Grieco, P. A.; Bahsas, A., *Tetrahedron Lett.*, **1988**, 29, 5855.
2. Gregoire, P. J.; Mellor, J. M.; Merriman, G. D., *Tetrahedron Lett.*, **1991**, 32, 7099.
3. Mellor, J. M.; Merriman, G. D.; Riviere, P., *Tetrahedron Lett.*, **1991**, 32, 7103
4. Hamor, T. A.; Martin, I. L., *Prog. Med. Chem.*, **1983**, 20, 157.
5. Liegeois, J-F; Bruhwyler, J.; Damas, J.; Nguyen, T. P.; Chleide, E. M. G.; Mercier, M. G. A.; Rogister, F. A.; Delarge, J. E., *J. Med. Chem.*, **1993**, 36, 2107; Melchiorre, C.; Bolognesi, M. L.; Chiarini, A.; Minarini, A.; Spampinato, S., *J. Med. Chem.*, **1993**, 36, 3734.
6. Howard, H. R.; Seeger, T. F., *Ann. Rev. Med. Chem.*, **1993**, *28*, 39.
7. Jacn, J. C.; Davis, R. E., *Ann. Rev. Med. Chem.*, **1994**, *29*, 33.
8. Evans, B. E.; Bock, M. G., *Adv. Med. Chem.*, **1993**, *2*, 111.
9. Mellor, J. M.; Pathirana, R. N., *J. Chem. Soc. Perkin Trans. I*, **1983**, 2545.
10. Povarov, L. S., Russ. *Chem. Rev.*, **1967**, *36*, 656; Kametani, T.; Takeda, H.; Suzuki, Y.; Kasai, H.; Honda, T., *Heterocycles*, **1986**, *24*, 3385; Cabral, J.; Laszlo, P., *Tetrahedron Lett.*, **1989**, *30*, 7237; Trifonov, L. S.; Orahovats, A. S., *Heterocycles*, **1984**, *22*, 355; Ciufolini, M. A.; Spencer, G. O., *J. Org. Chem.*, **1989**, *54*, 4739; Borrione, E.; Prato, M.; Scorrano, G.; Stivanello, M.; Lucchini, V.; Valle, G., *J. Chem. Soc. Perkin. Trans. 1*, **1989**, 2245; Nomura, Y.; Kimura, M.; Takeuchi, Y.; Tomoda, S.,*Chem. Lett.*, **1978**, 267.
11. Cabral, J.; Laszlo, P.; Montaufier, M. T., *Tetrahedron Lett.*, **1988**, *29*, 547.
12. Lucchini, V.; Prato, M.; Scorrano, G.; Tecilla, P., *J. Org. Chem.*, **1988**, *53*, 2251.
13. Kerr, G. H., Meth-Cohn, O.; Mullock, E. B.; Suschitzky, H, *J. Chem. Soc. Perkin Trans I*, **1974**, 1614.
14. Kobayashi, S., Araki, M.; Ishitani, H, Nagayama, S, Hachiya, I, *Synlett*, **1995**, 233.
15. Hesse, K-D, *Liebigs Ann. Chem.*, **1970**, *741*, 117
16. Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S., *J. Am. Chem. Soc.*, **1982**, *104*, 5753.
17. Swan, G. A., *J. Chem. Soc. Chem. Commun.*, **1969**, 20.
18. Prato, M.; Scorrano, G., Stivanello, M., Lucchini, V., *Gazz. Chim. Ital.*, **1988**, *118*, 797.
19. Friedrichsen, W.; Oeser, H-G, *Liebigs Ann. Chem.*, **1978**, 1146 and 1161; Weissenfels, M; Schurig, H.; Huhsan, G, *Chem. Ber.*, **1967**, *100*, 584; Veibel, S.; Nielsen, J. I., *Chem. Ber.*, **1966**, *99*, 2709.
20. Mellor, J. M.; Merriman, G. D., *Tetrahedron*, **1995**, **51**, 6115.

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