SYNTHESIS OF 7-AMINO-1,2,3,4-TETRAHYDROACRIDINE-9-CARBOXYLIC ACID AND ITS DERIVATIVES. REDUCTION OF NITRO COMPOUNDS UNDER ALKALINE CONDITIONS

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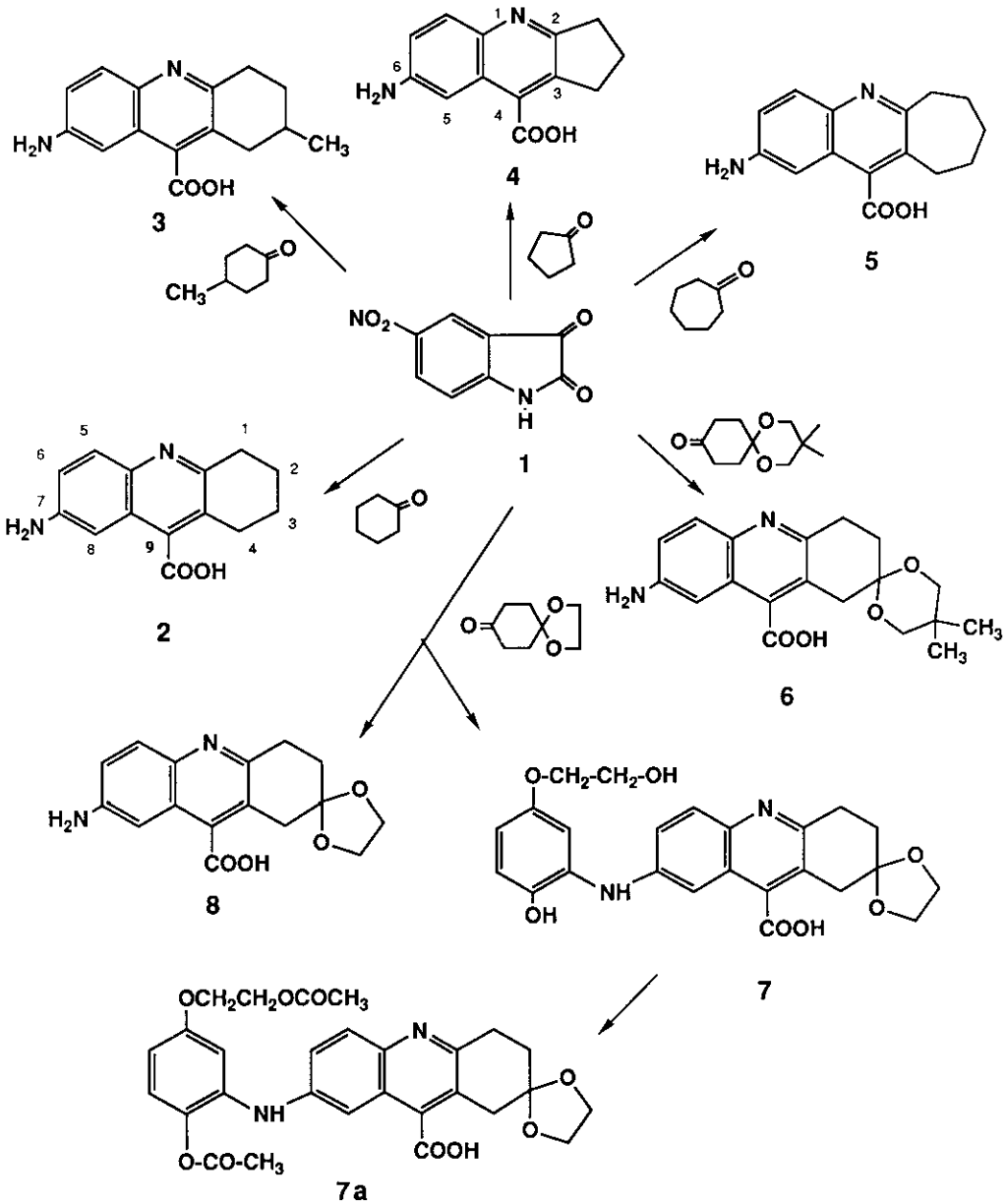
Abstract - Condensation of 5-nitroisatin (**1**) with cyclohexanone in the presence of alcoholic potassium hydroxide, unexpectedly, produced 7-amino-1,2,3,4-tetrahydroacridine-9-carboxylic acid (**2**) instead of 7-nitro derivative. The general nature of this reaction was shown by substituting several cyclic ketones in this reaction. A radical anion intermediate is proposed to explain this unusual noncatalytic reduction.

Mono- and diaminoacridines exhibit interesting chemical and physical properties.[1,2] These compounds and their N-alkyl derivatives are useful as dye stuffs, antibacterials, antimalarials and as enzyme inhibitors.[3] 9-Amino-1,2,3,4-tetrahydroacridine is under clinical investigation for the treatment of Alzheimer's disease.[4] Synthesis of monoaminoacridines, in general, require more than one step.[5] For example, 7-amino-1,2,3,4-tetrahydroacridine was synthesized *via* condensation of *cis* -2-hydroxymethylenecyclohexanone and *p*-diaminobenzene followed by cyclodehydration.[6] In this paper, we report a novel one-step synthesis of 7-amino-1,2,3,4-tetrahydroacridine-9-carboxylic acid (**2**) and several of its derivatives from commercially available 5-nitroisatin (**1**) and common laboratory reagents requiring no separate reduction or hydrogenation step of the nitro to amino group. Our procedure is the same as the one reported in 1908, leading to 1,2,3,4-tetrahydroacridine-9-carboxylic acid from condensation of isatin with cyclohexanone.[7,8] However, the reagents used in the reaction, *i.e.*, aqueous ethanol, potassium hydroxide, and an excess of a cyclic ketone bring about a smooth reduction of the nitro group.

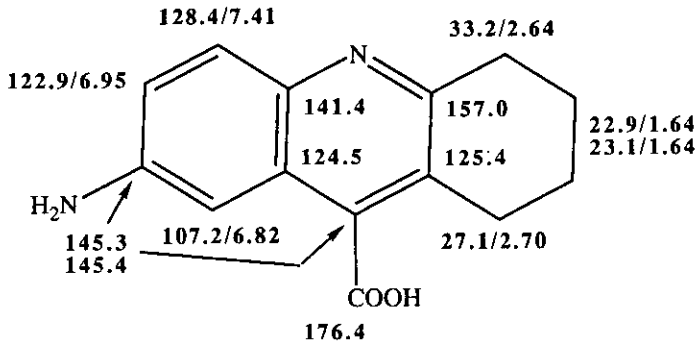
Condensation of **1** with an excess of cyclohexanone produced **2** as a greenish yellow fluorescent (tlc) compound in 32% yield (**Scheme 1**). In the ^{1}H-nmr spectrum, the upfield shift of the aromatic protons was indicative of the conversion of the nitro group into an amino group. The structure was confirmed by ^{13}C-nmr spectroscopy with 2-D experiments (see **Scheme 2**) and mass spectroscopy. The general nature of this reaction was shown by condensation of **1** with 4-methylcyclohexanone, cyclopentanone, cycloheptanone and 1,4-cyclohexadione *mono*-2,2-dimethyltrimethylene ketal, to produce corresponding amino compounds **3**, **4**, **5**, and **6**, respectively.

To our surprise, when 1,4-cyclohexanedione monoethylene ketal, closely related to 1,4-cyclohexanedione *mono*-2,2-dimethyltrimethylene ketal, was used, the corresponding amino compound **8** was produced only as a minor product. The major product, however, was 7-[5-(2-hydroxyethyloxy)-2-hydroxy]phenylamino-1,2,3,4-tetrahydro-3-oxoacridine-9-carboxylic acid ethylene ketal (**7**). It is believed to have resulted from condensation of corresponding nitroso compound and 1,4-cyclohexanedione monoethylene ketal as proposed in **Scheme 3**. ^{1}H- And ^{13}C-nmr with 2-D experiments (**Scheme 5**) and mass spectroscopy was used for structural characterization of compound **7** . Acetylation gave diacetate **7a**. It is not clear why two closely related ketone acetals lead to two different products. A close inspection of the ^{1}H-nmr spectrum of crude **6** did show the presence of a product analogous to **7** as a minor component. No attempt was made to isolate it, however.

Diazomethane treatment of **2** led to a mixture of methyl 7-amino-1,2,3,4-tetrahydroacridine-9-carboxylate (**2a**) and methyl 7-methylamino-1,2,3,4-tetrahydroacridine-9-carboxylate (**2b**) (**Scheme 5**). Compound **2** gave *t* -butoxycarbonyl derivative **2c** which led to methyl 7 -*t* - butoxycarbonylamino-1,2,3,4-tetrahydroacridine-9-carboxylate (**2d**) upon diazomethane esterification.



Scheme 1.



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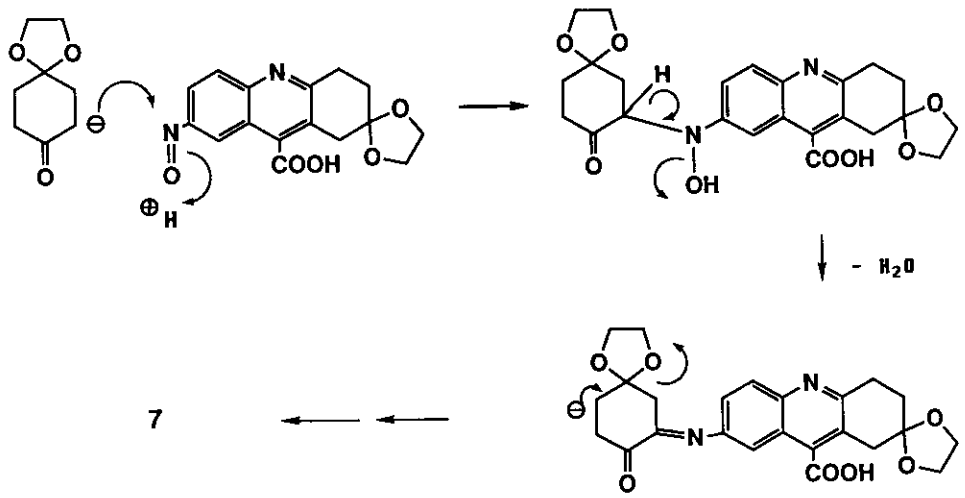
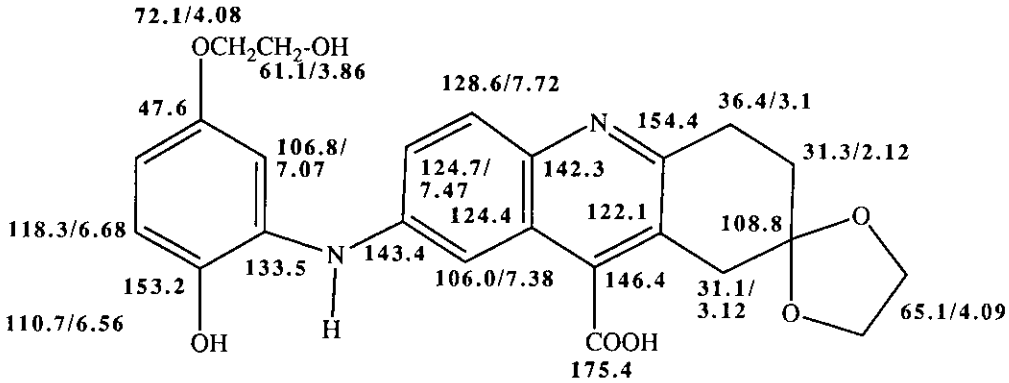
Scheme 2.



Scheme 3.



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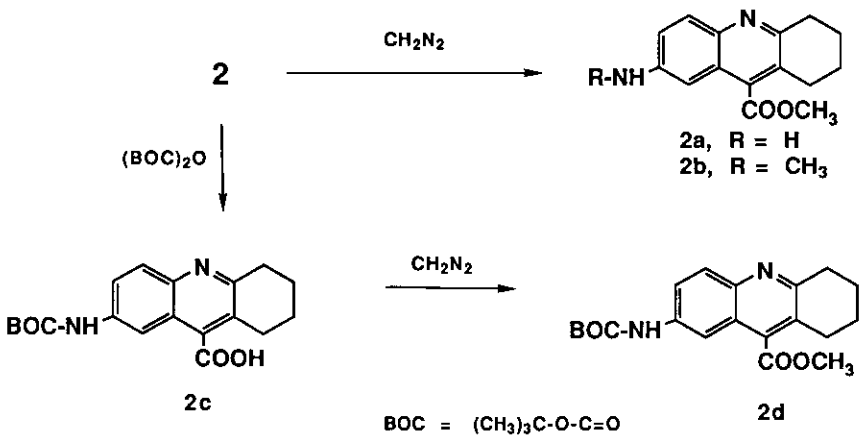
Scheme 4.



Scheme 5.

Aromatic nitro compounds are reduced to various products by sodium or potassium hydroxide in alcohol [9], sodium alkoxides, sodium hydroxide in glycols in the presence of a quinone [10], and by lithium in tetrahydrofuran.[11] The intermediacy of a radical anion has been suggested in these cases. The results of the present communication can be rationalized in the terms of a radical anion intermediate resulting in noncatalytic reduction of the nitro to the amino group at any stage in the reaction.

EXPERIMENTAL

Chemicals were purchased from Aldrich Chemical Company, Milwaukee, WI. Nmr spectra were run on a General Electric QE300 and GN300 instruments. Accurate mass measurements were done by Fast Atom Bombardment (FAB) using a Kratos MS-50 and VG 705EQ mass spectrometers. The matrix was a 1:1 mixture of glycerol and thioglycerol. Analytical tlc was done on Whatman MKC18F reversed phase plates. Reversed phase preparative tlc was done on PLKC18F, 20 x 20 cm, 1,000 m thick plates. Preparative lc on reversed phase was done with Waters Associates, Prep LC System 500A equipped with two prep PAK^R-500/C-18 columns.

7-Amino-1,2,3,4-tetrahydroacridine-9-carboxylic Acid (**2**): 5-Nitroisatin (**1**) (10.0 g, 52 mmol) and cyclohexanone (20.0 g, 204 mmol) were refluxed in absolute ethanol (80 ml) and 30% aqueous KOH (40 ml) for 4 h with stirring. Tlc examination (methanol : water : acetic acid 60 : 40 : 0.5) showed a complete disappearance of **1** and showed a single yellow fluorescent spot (R_f = 0.9). The solvent was removed under reduced pressure and the residue was dissolved in methanol and acidified with acetic acid. A yellow precipitate resulted upon addition of ether (300-400 ml). The precipitate was removed *via* filtration and triturated with water. Filtration followed by air drying produced 6.4 g (32%) of **2** as a yellow powder, ^{1}H-nmr: (DMSO-d_6) δ 7.58 (d, J = 9.2, 1H), 7.08 (dd, J = 9.2, 2.6, 1H), 6.62 (d, J = 2.6, 1H), 2.92 (pseudo t, 2H), 2.78 (pseudo t, 2H), 1.80 (br m, 4H) ppm. ^{13}C-Nmr: (D_2O/NaOD), see **Scheme 2**. Ms: $(M)^+$ *m/z* 242.1045 (Electron Impact); calcd for $C_{14}H_{14}N_2O_2$, 242.1055.

3-Methyl-7-amino-1,2,3,4-tetrahydroacridine-9-carboxylic Acid (**3**): Compound **1** (2.0 g, 10.4 mmol) and 4-methyl-cyclohexanone (4.0 g, 39.2 mmol) similarly produced 1.5 g (56 %) of **3** . ^{1}H-Nmr: (DMSO-d_6) δ 7.42 (d, J = 8.8, 1H), 6.92 (dd, J = 2.6, 8.8, 1H), 6.77 (d, J = 2.6, 1H), 2.75-3.00 (br m, 3H), 2.27 (m, 1H), 1.90 (br s, 1H) 1.78 (br, 1H) 1.42 (m, 1H), 1.04 (d, J = 6.6, 3H) ppm. ^{13}C Nmr: (D_2O/NaOD) 176.40, 156.75, 145.44, 145.30, 141.40, 128.40, 125.01, 124.40, 122.96, 107.28, 35.49, 32.60, 31.14, 29.05, 21.74 ppm. Ms: $(M + H)^+$ *m/z* 257.1278; calcd for $C_{15}H_{17}N_2O_2$, 257.1290.

6-Amino-[2,3]-cyclopentanoquinoline-4-carboxylic Acid (**4**): Compound **1** (2.0 g, 10.4 mmol) and cyclopentanone (4.0 g, 47.6 mmol) upon condensation, in a similar fashion, produced low yields of impure **4**, which was purified two times over reverse phase (methanol:water:acetic acid 60:40:0.5) preparative plates to yield 0.08 g (3 %) of **4** . ^{1}H-Nmr: (DMSO-d_6) δ 7.46 (d, J = 8.8, 1H), 7.05 (d, J = 2.6, 1H), 6.91 (dd, J = 8.8, 2.6, 1H), 2.85 (pseudo t, 4H), 1.98 (m, 2H) ppm. ^{13}C-Nmr: (D_2O/NaOD) 175.92, 165.81, 142.30, 140.93, 131.60, 128.79, 125.01, 122.23, 122.96, 108.10, 34.22, 29.95, 23.74 ppm. Ms: $(M - H)^-$ *m/z* 227.0820; calcd for $C_{13}H_{11}N_2O_2$, 227.0826.

6-Amino[2,3]cycloheptanoquinoline-4-carboxylic Acid (**5**): Compound **1** (2.0 g, 10.4 mmol) and cycloheptanone (4.0 g, 35.7 mmol) were refluxed in 30 % aqueous KOH (8 ml) and absolute ethanol (16 ml) for 3 h. The reaction mixture was evaporated and purified over two columns eluting with methanol:water:acetic acid (45:65:0.5). Combination and evaporation of appropriate fractions yielded 0.76 g (28%) of **4** as a yellow powder. ^{1}H-Nmr: (DMSO-d_6) δ 7.60 (d, J = 9.2, 1H), 7.06 (dd, J = 9.2, 2.2, 1H), 6.61 (d, J = 2.2, 1H), 3.05 (br d, J = 6.25, 2H), 2.80 (br d, J = 6.25, 2H) 1.90-1.55 (br m, 6H) ppm. Ms: $(M + H)^+$ *m/z* 257.1296, calcd for $C_{15}H_{17}N_2O_5$, 257.1290.

Amino-1,2,3,4-tetrahydro-3-oxoacridine-9-carboxylic Acid 2,2-Dimethyltrimethylene Ketal (**6**): 5-Nitroisatin (**1**) (1.0 g, 5 mmol) and 1,4-cyclohexanedione mono-2,2-dimethyltrimethylene ketal (3.0 g, 15 mmol) were refluxed with stirring in 30% aqueous KOH (4 ml) and absolute ethanol (8 ml) for 2 h. The reaction mixture was evaporated and the residue was dissolved in methanol (20 ml). Addition of acetic acid (2 ml) and an excess of ether produced a precipitate The precipitate was collected *via* filtration, washed thoroughly with water and dried to yield 0.8 g of a brown powder. A portion of the product was purified on reverse phase preparative plates (methanol : water : acetic acid 60:40:0.5) to yield a yellow powder. ^{1}H-Nmr: (DMSO-d_6) δ 7.45 (d, J = 8.8, 1H), 6.93 (dd, J = 8.8, 2.6, 1H), 6.81 (d, J = 2.6, 1H), 3.60-3.40 (m, 4H), 3.04 (s, 2H), 2.86 (br t, J = 6.25, 2H), 2.13 (br t, J = 6.25, 2H), 0.96 (s, 3H), 0.93 (s, 3H) ppm. Ms: $(M+ H)^+$ *m/z* 343.1657; calcd for $C_{19}H_{23}N_2O_4$, 343.1658.

7-[5-(2-Hydroxyethyloxy)-2-hydroxylphenylamino-1,2,3,4-tetrahydro-3-oxoacridine-9-carboxylic Acid Ethylene Ketal (**7**) and 7-Amino-1,2,3,4-tetrahydro-3-oxoacridine-9-carboxylic Acid Ethylene Ketal (**8**): 5-Nitroisatin (**1**) (10 g, 52 mmol) and 1,4-cyclohexanedione monoethylene ketal (25.0 g, 160 mmol) were refluxed in 30% KOH (40 ml) and absolute ethanol (80 ml) for 4 h. The reaction mixture was evaporated and the residue was triturated with methanol (100 ml). Acidification with acetic acid and dilution with ether produced a dark oil. Upon standing the oil solidified. The solid was collected on a filter and washed well with water and air dried to yield a brown powder (8.2 g). A portion of this product (1.5 g) was dissolved in methanol:water (80:20) with the help of 29 % NH_4OH, injected on two C-18 columns, and eluted with methanol: water: acetic acid (40:60:0.5). The fractions were combined after tlc to produce **8** as a yellow compound (0.06 g) (fluorescent spot on tlc). ^{1}H-Nmr of **8**: (DMSO-d_6) δ 7.44 (d, J = 8.8, 1H), 6.95 (dd, J = 8.8, 2.2, 1H), 6.78 (d, J = 2.2, 1H), 3.93 (s, 4H), 2.97 (br t, J = 6.25, 2H), 2.93 (s, 2H), 1.95 (br t, J = 6.25, 2H) ppm. Ms of **8**: $(M + H)^+$ *m/z* 301.1191; calcd for $C_{16}H_{17}N_2O_4$, 301.1188 The fractions containing the slower moving nonfluorescent compound were combined and evaporated to yield 0.8 g of **7** as a dark yellow solid. ^{1}H-Nmr: (DMSO-d_6) δ 9.09 (s, 1H), 7.81 (s, 1H), 7.75 (d, J = 9, 1H), 7.50 (dd, J = 9, 2, 1H), 7.18 (d, J = 2, 1H), 6.86 (d, J = 2, 1H), 6.80 (d, J = 9, 1H), 6.44 (dd, J = 9, 2, 1H), 3.96 (s, 4H), 3.86 (br t, J = 6.25, 2H), 3.66 (br t, J = 6.25, 2H), 3.11 (br t, J = 6.25, 2H), 2.99 (s, 2H), (br t, J = 6.25, 2H) ppm. ^{1}H-Nmr and ^{13}C-nmr: (D_2O, NaOD), see **Scheme 4**. Ms of **7**: low resolution, $(M + H)^+$ *m/z* 453. Electron impact high resolution spectrum, $(M)^+$ *m/z* 452.1587; calcd for $C_{24}H_{24}N_2O_7$ 452.1583.

Acetylation of **7**: Treatment with acetic anhydride in pyridine gave **7a** as an orange solid. ^{1}H-Nmr: (DMSO-d_6) δ 8.14 (s, 1H), 7.82 (d, J = 9.1, 1H), 7.49 (dd, J = 9.1, 2.4, 1H), 7.24 (d, J = 2.4, 1H), 7.03 (d, J = 8.9, 1H), 6.87 (d, J = 2.8, 1H), 6.57 (dd, J = 8.9, 2.8, 1H), 4.29 (br s, 2H), 4.11 (br s, 2H), 3.97 (s, 4H), 3.13 (br t, J = 6.25, 2H), 3.02 (s, 2H), 2.15 (s, 3H), 2.06 (br t, J = 6.25, 2H), 2.02 (s, 3H) ppm. Ms: $(M + H)^+$ *m/z* 537.1867; calcd for $C_{28}H_{29}N_2O_9$, 537.1873.

Diazomethane Reaction of **2** : A partial solution of **2** in methanol was treated with an excess of diazomethane in ether. The solvents were removed under reduced pressure and the residue was purified over a silica column eluting with methylene chloride:methanol (9:1) to yield a 1:1 mixture of methyl 7-amino-1,2,3,4-tetrahydro-9-carboxylate (**2a**) and methyl 7-methylamino-1,2,3,4-tetrahydro-9-carboxylate (**2b**). ^{1}H-Nmr of **2a** and **2b** mixture: (DMSO-d_6) δ 7.61 (d, J = 9.2, 1H), 7.10 (dd, J = 9.2, 2.6, 1H), 6.53 (d, J = 2.6, 1H), 3.95 (s, 3H), 3.34 (s, 1.5 H, N-CH_3), 2.92 (br t, J = 6.50, 2H), 2.74 (br t, J = 6.50, 2H) 1.95-1.70 (m, 4H) ppm. Ms of **2a** and **2b** mixture: $(M + H)^+$ *m/z* 257.1283 and 271.1460; calcd for $C_{15}H_{17}N_2O_2$, 257.1290 and $C_{16}H_{19}N_2O_2$, 271.1446.

t -Butoxycarbonyl Derivative of **2** : Compound **2** upon treatment with di-*t* -butoxycarbonyldicarbonate in pyridine (overnight) followed by purification on a silica column (eluant 30% methanol in dichloromethane with 0.5 % acetic acid) gave 7-*t* -butoxycarbonylamino-1,2,3,4-tetrahydro-9-carboxylic acid (**2c**). ^{1}H-Nmr: (DMSO-d_6) δ 9.44 (s, 1H), 8.05 (d, J = 2.0, 1H), 7.61 (d, J = 9.2, 1H), 7.48 (dd, J = 9.2, 2.0, 1H), 2.90 (br t, J = 5.80, 2H), 2.82 (br t, J = 6.62, 2H) 1.90-1.70 (m, 4H), 1.49 (s, 9H) ppm. Ms: $(M + H)^+$ *m/z* 343.1655; cacld for $C_{19}H_{23}N_2O_4$, 343.1658.

Diazomethane Treatment of **2c** : Esterification of **2c** with diazomethane in methanol, followed by silica gel chromatography (dichloromethane:ethyl acetate 70:30) produced methyl 7-*t* -butoxycarbonylamino-1,2,3,4-tetrahydro-9-carboxylate (**2d**). ^{1}H-Nmr: (DMSO-d_6) δ 7.90-7.70 (m, 3H), 3.99 (s, 3H) 3.00 (br t, J = 6.25, 2H), 2.81 (br t, J = 6.25, 2H), 1.90 -1.75 (m, 4H), 1.50 (s, 9H) ppm. Ms: $(M + H)^+$ *m/z* 357.1810; calcd for $C_{20}H_{25}N_2O_4$, 357.1814.

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