SYNTHESIS OF SOME INDOLO[3,2-*c*]QUINOLINES AND [3,2-*d*]BENZAZEPINES.

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Abstract:

The title compound were prepared by reaction between 5-hydrazino-2-methoxy-*N*,*N*-diethyl or dimethylbenzylamines and either, 7-substituted 1,2,3,4-tetrahydro-4-quinolone or 8-substituted-2,3,4,5-tetrahydrobenzazepine-5-one.

Introduction:

Indoloquinolines were first synthesized as large flat molecules analogous to amodiaquine which showed superior antimalarial activity, through the more effective inter- celative binding to DNA and RNA, and antitumor activity (1-6). As an extension of this work, we have synthesized some indoquinolines and indolobenzazepines from which we found that 3-chloro-9-dimethylaminomethyl-8-methoxy[11*H*]-indolo(3,2-*c*)quinoline showed useful antitumor activity (7).These promising results drove me to synthesize some other derivatives for lower toxicity and higher activity.

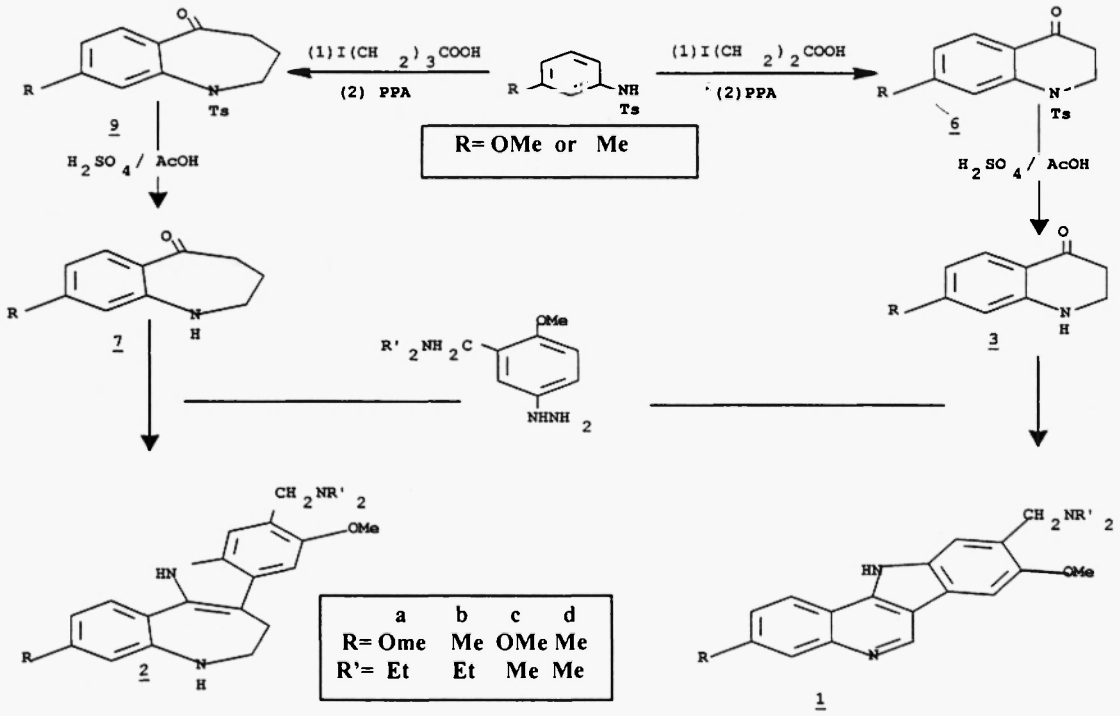
Results and Discussion:

In this work I would like to introduce four new indolo-quinolines namely; 3-methoxy or methyl-8-methoxy-9-diethyl or dimethylaminomethyl-[11 *H*]-indolo(3,2-*c*)quinolines **1a-d** and four indolobenzazepines namely 3-methoxy or methyl-6,7-dihydro-9-methoxy-10-diethyl or dimethyl-aminomethylindolo(3,2-*d*)-1-benzazepines **2a-d**.

Compounds **1** were prepared through the Fischer indolisation of 7-methoxy or methyl-1,2,3,4-tetrahydro-4-quinolones **3a,b** with 3-diethyl or dimethylaminomethyl-4-methoxyphenyl-hydrazines (7) **4a,b** to give: 3,8-dimethoxy-9-diethylaminomethyl-[11*H*]-indoIo(3,2-*c*)quinoline 1a, 3-methyl-8-methoxy-9-diethylaminomethyl-[11*H*]-indolo(3,2-*c*)quinoline **1b**, 3,8-dimethoxy-9-dimethylaminomethyl-[11*H*]-indolo(3,2-*c*)quinoline **1c** and 3-methyl-8-methoxy-9-dimethyl-aminomethyl-[11 *H*]-indolo(3,2-*c*)quinoline **1d**. The aminoketones **3a,b** were prepared by adaptation of the literature methods (7-9). Cyclisation of N-tosyl-β-(3-methoxy or methyl-anilino)propionic acid **5** by heating with poly phosphoric acid afforded the corresponding N-tosyl-7-methoxy or methyl-1,2,3,4-tetrahydro-4-quinolones **5a**,b Detosylation of compounds **5** using sodium in liquid ammonia gave a very poor yield of **3**, but when it was heated with sulphuric/acetic acid mixture at 80°C, the yield was almost quantitative.

Compounds **2** were prepared through condensation of 8-methoxy or methyl-2,3,4,5-tetrahydro-1-benzazepine-5-one **7** and the required hydrazines **4a,b** similar to the above reaction to afford: 3-diethylaminomethyl-4,10-dimethoxy-6,7-dihydroindolo(3,2-*d*)-1-benzazepine **2a**, 3-diethylaminomethyl-4-methoxy-6,7-dihydro-10-methylindolo(3,2-*d*)-1-benzazepine **2b**, 3-dimethylaminomethyl-4,10-dimethoxy-6,7-dihydroindolo(3,2-*d*)-1-benzazepine **2c** and 3-dimethylaminomethyl-4-methoxy-6,7-dihydro-10-methylindolo(3,2-*d*)-1-benzazepine **2d**.

Tetrahydro-1-benzazepine-5-ones **7a,b** were prepared by cyclization of N-tosyl-γ-(3-methoxy or methylanilino)butyric acid **8** by the action of polyphosphoric acid to give the N-tosyl-8-methoxy or methyl-2,3,4,5-tetrahydro-1-benzazepine-5-one **9** which was then detosylated to **7**. The new compounds were identified through the study of their analytical and spectroscopic data.



Experimental

Melting points were obtained on a Mel-Temp II melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1430 ratio recording spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemmini (200 Mhz) instrument. All spectra were determined using duteriodimethyl-sulphoxide as solvent, unless otherwise stated, using tetra-methylsilane as internal standard. Thin-layer chromatography was carried out on 5 X 20 cm coated with silica gel GF 254 type 60, mesh size 50-250.

N-Tosyl-β-(3-methoxy or methylanilino)propionic acid 5 and N-tosyl-γ-(3-methoxy or methylanilino)butyric acid 8:

A mixture of N-tosyl-3-substituted anilines (0.013 mole), β-iodopropionic acid or 8-iodobutyric acid (0.013 mole) and sodium carbonate (1.4 g, 0.0132 mole) was heated for three hours at 120°C. The mixture was then extracted with chloroform, the extract was washed with water, dried and evaporated to give the title compounds; mp, tlc ...

N-Tosyl-7-methoxy-1,2,3,4-tetrahydro-4-quinoione6andN-tosyl-8-substituted-2,3, 4,5-tetrahydro-1-benzazepine-5-ones 9:

N-Tosyl-β-(3-methoxy or methylanilino)propionic acid or N-Tosyl-γ – (3-metthoxy or methyl)butyric acid (0.325 mole) was stirred at 135°C, for one and a half hours in polyphosphoric acid [250 g (phosphoric acid 100 g and phosphorous pentoxide 150 g)]. After cooling, the mixture was poured onto an ice water mixture, neutralized with sodium hydroxide and extracted with chloroform. The extract was dried over sodium sulphate and evaporated leaving the title compounds 6 and 9 which were crystallised from ethanol.

Compd.No	Formula	M.P. °C	Yield %	Calcd.			Found		
				C	H	N	C	H	N
6 a	$C_{17}H_{17}NO_4S$	132	30	61.63	5.13	4.22	61.55	5.43	4.38
b	$C_{17}H_{17}NO_3S$	135	39	64.76	5.39	4.44	64.53	4.92	4.29
9 a	$C_{18}H_{19}NO_4S$	99	45	62.60	5.50	4.05	62.42	5.38	4.22
b	$C_{18}H_{19}NO_3S$	79	45	65.65	5.77	4.25	65.78	5.89	4.42

^{1}H NMR

6 a: δ (ppm) 1.2 ppm (s, 3 H, CH_3), 2.6 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2), 4.6 (s, 3 H, OCH_3) and 6.7-7.8 (m, 7 H, Ar).

b: δ (ppm) 1.2 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 2.6 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2) and 6.7-7.8 (m, 7 H, Ar)

9 a: δ (ppm) 1.2 (s, 3 H, CH_3), 2.0 (m, 2 H, CH_2), 2.4 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2), 4.5 (s, 3 H, OCH_3) and 7.2-7.8 (m, 7 H, Ar).

b: δ (ppm) 1.2 (s, 3 H, CH_3), 1.3 (s, 3 H, CH_3), 2.0 (m, 2 H, CH_2), 2.4 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2) and 7.2-7.8 (m, 7 H, Ar).

One pot reactions were tried by adding a mixture of 3-substituted anilines and either iodopropionic or iodobutyric acid to a preheated aluminium chloride to prepare 6 and 9 but all trials were unsuccessful.

7-Methoxy or methyl-1,2,3,4-tetrahydro-4-quinolones 3 and 8-methoxy or methyl-2,3,4,5-tetrahydro-1-benzazepine-5-ones 7:

The previous compounds **6a,b** or **9a,b** (0.017 mole) were added separately to a mixture of concentrated sulphuric acid (30 ml) and acetic acid (54 ml) then heated to 80 °C with stirring for one hour. The mixture was left overnight, poured onto ice-HCl mixture and extracted with chloroform, the aqueous layer was then basified with sodium hydroxide (10%) and extracted with chloroform, dried over sodium sulphate and evaporated leaving the product which was crystallized from ethanol.

Comp.No	Formula	M.P. °C	Yield %	Calcd.			Found		
				C	H	N	C	H	N
3 a	$C_{10}H_{11}NO_2$	138	98	67.79	6.21	7.90	67.98	6.00	7.73
3 b	$C_{10}H_{11}NO$	142	98	74.53	6.83	8.69	74.23	6.71	8.29
7 a	$C_{11}H_{13}NO_2$	106	98	69.10	6.80	7.42	69.31	6.92	7.65
7 b	$C_{11}H_{13}NO$	108	98	75.42	7.42	8.00	75.68	7.67	8.18

^{1}H NMR:

3 a:δ (ppm) 2.6 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2), 4.5 (s, 3 H, OCH_3), 4,65 (s, D_2O exch. NH) and 7.2-7.8 (m, 3 H, Ar).

b:δ (ppm) 1.2 (s, 3 H, CH_3), 2.6 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2), 4.65 (s, D_2O exch. NH) and 7.2-7.8 (m, 3 H, Ar).

7 a: δ (ppm) 2.0 (m, 2 H, CH_2), 2.4 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2), 4.5 (s, 3 H, OCH_3), 4.7 (s, D_2O exch. NH) and 7.2-7.8 (m, 3 H, Ar).

b: δ (ppm) 1.2 (s, 3 H, CH_3), 2.0 (m, 2 H, CH_2), 2.4 (t, 2 H, CH_2), 3.5 (t, 2 H, CH_2), 4.6 (s, D_2O exch. NH) and 7.2-7.8 (m, 3 H, Ar).

3-Methoxy or methyl-8-methoxy-9-diethylaminomethyl-11*H*-indolo-(3,2-c)quinolines 1a,b and 3-methoxy or methyl-6,7-dihydro-9-methoxy-10-diethylaminomethylindolo-(3,2-d)-1-benzazepines 2a,b

A mixture of either methoxy or methyl 1,2,3,4-tetrahydro-4-quinolone **3a,b** (0.0068 mole) or 8-methoxy or methyl-2,3,4,5-tetrahydro-1-benzazepine-5-ones **7a,b** (0.0068 mole), 3-diethyl-aminomethyl-4-methoxyphenylhydrazine (3) (1.4 g, 0.0072, mole), hydrochloric acid (20 ml) and ethanol (40 ml) was refluxed for 24 hours. The mixture was concentrated and cooled, the formed precipitate was filtered off as hydrochloride. The free base was obtained by adding ammonia solution to the hydrochloride solution and collecting the formed product of which the yield is about 50% and crystallized from ethanol.

Comp.No	Formula	M.P. °C	Calcd.			Found		
			C	H	N	C	H	N
a	$C_{22}H_{25}N_3O_2$	237	72.72	6.88	11.57	72.54	6.57	11.81
1								
b	$C_{22}H_{25}N_3O_2$	241	76.08	7.20	12.10	75.83	7.12	12.38
a	$C_{23}H_{29}N_3O_2$	83	72.82	7.65	11.08	72.56	7.42	11.31
2								
b	$C_{23}H_{29}N_3O_2$	79	76.03	7.98	11.57	75.87	7.69	11.42

^{1}H NMR :

1 a: δ (ppm) 1.5 (t, 6 H, 2 CH_3), 3.3 (q, 4 H, 2 CH_2) 4. (s, 2 H, CH_2), 4.3 (s, 3 H, OCH_3), 4.6 (s, 3 H, OCH_3), 6.8 (s, D_2O exch. NH) and 7.2-7.8 (m, 6 H, Ar).

b: δ (ppm) 1.2 (s, 3 H, CH_3), 1.5 (t, 6 H, 2 CH_3), 3.3 (q, 4 H, 2 CH_2), 4.0 (s, 2 H, CH_2), 4.3 (s, 3 H, OCH_3), 6.8 (s, D_2O exch. NH) and 7.2-7.8 (m, 6 H, Ar).

2 a: δ (ppm) 1.1 (t, 6 H, 2 CH_3), 2.4 (q, 4 H, 2 CH_2), 3.05 (t, 2 H, CH_2), 3.4 (t, 2 H, CH_2), 3.6 (s, 2 H, CH_2), 3.9 (s, 3 H, OCH_3), 4.3 (s, D_2O exch. NH), 4.4 (s, 3 H, OCH_3), 6.9-7.5 (m, 5 H, Ar) and 7.8 (s, D_2O exch. NH).

b: δ (ppm) 1.1 (t, 6 H, 2 CH_3), 1.2 (s, 3 H, CH_3), 2.4 (q, 4 H, 2 CH_2), 3.05 (t, 2 H, CH_2), 3.4 (t, 2 H, CH_2), 3.6 (s, 2 H, CH_2), 4.0 (s, 3 H, OCH_3), 4.3 (s, D_2O exch. NH), 6.9-7.5 (m, 5 H, Ar) and 7.8 (s, D_2O exch. NH).

3-Methoxy or methyl-8-methoxy-9-diethylaminomethyl-11*H*-indolo(3,2-*c*)quinolines 1c,d and 3-methoxy or methyl-6,7-dihydro-9-methoxy-10-dimethylaminomethyl-iodo(3,2-*d*)-1-benzazepines 2c,d :

These compounds were prepared by similar methods to **1a,b** by condensation of either **3a,b** or **7a,b** with 3-dimethylaminomethyl-4-methoxyphenylhydrazine (1.2 g, 0.00727 mole).

Comp.No	Formula	M.P. °C	Calcd.			Found		
			C	H	N	C	H	N
c	$C_{20}H_{21}N_3O_2$	235	71.64	6.26	12.53	71.46	6.18	12.60
1								
d	$C_{20}H_{21}N_3O$	239	75.23	6.58	13.16	75.34	6.41	13.27
c	$C_{21}H_{25}N_3O_2$	242	71.79	7.12	11.96	71.63	7.42	12.28
2								
d	$C_{21}H_{25}N_3O$	244	75.22	7.46	12.53	75.45	7.63	12.67

^{1}H NMR:

1 c: δ (ppm) 3.4 (s, 6 H, 2 CH_3), 4.0 (s, 2 H, CH_2), 4.6 (s, 3 H, OCH_3), 4.79 (s, 3 H, OCH_3), 7.2-7.8 (m, 6 H, Ar), and 9.0 (s, D_2O exch. NH).

d: δ (ppm) 1.2 (s, 3 H, CH_3), 3.4 (s, 6 H, 2 CH_3), 4.0 (s, 2 H, CH_2), 4.7 (s, 3 H, OCH_3) 7.2-7.8 (m, 6 H, Ar), and 9.0 (s, D_2O exch. NH).

2 c:δ (ppm)3.2 (s, 6 H, 2 CH_3), 3.9 (s, 2 H, CH_2), 4.0 (s, 3 H, OCH_2), 4.3 (s, D_2O exch. NH), 4.4 (s, 3 H, OCH_3), 6.9-7.5 (m, 5 H, Ar) and 7.8 (s, D_2O exch. NH).

d:δ (ppm) 1.2 (s, 3 H, CH_3), 3.2 (s, 6 H, 2 CH_3), 3.9 (s, 2 H, CH_2), 4.0 (s, 3 H, OCH_3), 4.3 (s, D_2O exch. NH), 6.9-7.5 (m, 5 H, Ar) and 7.8 (s, D_2O exch. NH).

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