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The synthesis of a series of N_6 -alkyl derivatives of the 2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline as potential narcotic antagonists is reported.

J. Heterocyclic Chem., 17, 155 (1980).

In connection with a research program on the synthesis and pharmacological activities of derivatives of imidazo[1,2-c]quinazoline (1-3) it was found that 2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline (**Ia**) (3) and 2-methyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline (**Ib**) display narcotic antagonist activity at a dose of 25 mg./kg. and 50 mg./kg. respectively s.c. in the mouse (4).

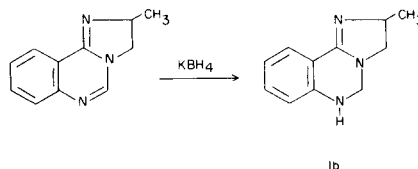
In order to obtain compounds more powerful than **Ia** and to investigate, through structural modifications, the structure-activity relationships of this new type of narcotic antagonist, a series of 6-alkyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazolines was synthesized. The N_6 -alkyl groups of the compounds **Ic-f** were selected among those which induce narcotic antagonist activity in analgesic molecules (5).

For comparison also the N_6 -methyl derivative (**Ic**) and 5-methyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline (**Ig**) were synthesized.

The 2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline (**Ia**) was synthesized by a previously reported method (3). Many attempts to obtain the compounds **Ic-f** by alkylation of **Ia** being unsuccessful, it was necessary to resort to a different

synthesis. The goal was reached by condensation of the corresponding 2-(*o*-alkylaminophenyl)-4,5-dihydroimidazole (**III**) with formaldehyde (Scheme I). The imidazoles **III** were in turn prepared by reaction of the ethylenediamine with suitable *o*-alkylaminobenzonitriles (**II**) which were synthesized by alkylation of the *o*-aminobenzonitrile. The 5-methyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline (**Ig**) was prepared by condensation of 2-(*o*-aminophenyl)-4,5-dihydroimidazole with acetaldehyde.

Finally 2-methyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline (**Ib**) was synthesized by reduction with potassium borohydride of 2-methyl-2,3-dihydroimidazo[1,2-c]quinazoline (2):



The pharmacological evaluation of the compounds **Ic-g** is now in progress and will be published elsewhere.

EXPERIMENTAL

Melting points were taken in capillary tubes on an electrothermal apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Jeol JNH-MH-60 spectrometer. Infrared spectra were recorded on a Perkin Elmer 257 grating spectrophotometer. Analyses were performed with a Perkin Elmer 240 CHN analyzer.

General Procedure for the Preparation of *o*-Alkylaminobenzonitriles (II).

A mixture of 0.2 mole of *o*-aminobenzonitrile, 0.2 mole of alkyl bromide (methyl iodide in the case of **IIc**) and 26.5 g. of sodium carbonate was refluxed at 90-160° for 12 hours. The reaction mixture was diluted with water and extracted several times with chloroform. Evaporation of the solvent gave an oily residue which, in the case of **IIc**, was chromatographed on silica gel column eluting with benzene; evaporation of the first eluate gave a colorless oil which darkens with time. In the other cases the oily residue was distilled under vacuum. In these instances the narrow boiling fraction which was obtained was shown to be a mixture of compounds by tlc. The mixture was therefore chromatographed on a silica gel column eluting with a mixture of cyclohexane-benzene 70:30. Evaporation of the second eluate gave an oily residue which, in the case of **IIc**, solidifies (see Table I).

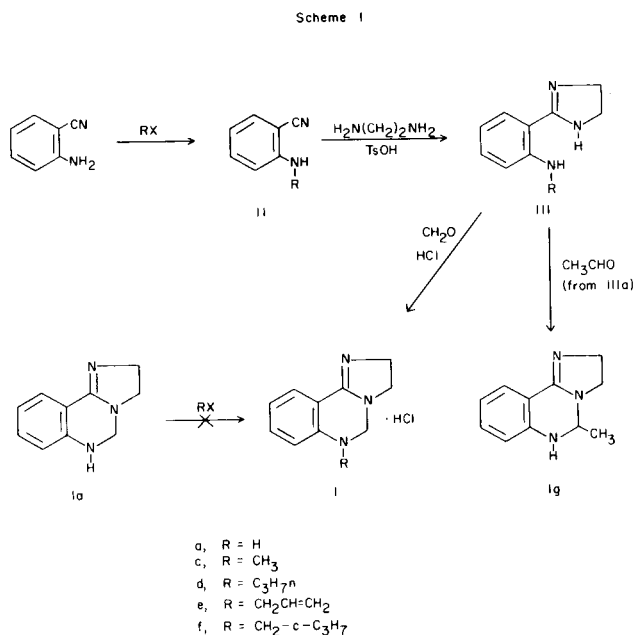


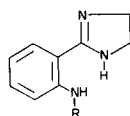
Table I



Compound No.	R	B.p. °C (mm)	Yield %	M.p., °C	Recrystallization Solvent	Formula	Analysis					
							Calcd.		Found		Found	
						C	H	N	C	H	N	
IIc	CH ₃	95-97 (0.9)	53	69-70 (a)	cyclohexane	C ₉ H ₈ N ₂	72.70	6.10	21.20	72.91	6.28	21.03
IIId	CH ₂ CH ₂ CH ₃	88-89 (0.6)	24			C ₁₀ H ₁₂ N ₂	74.96	7.55	17.49	75.12	7.41	17.65
IIe	CH ₂ CH=CH ₂	88-89 (0.4)	32			C ₁₀ H ₁₀ N ₂	75.92	6.37	17.71	75.81	6.51	17.59
IIIf			58			C ₁₁ H ₁₂ N ₂	76.71	7.02	16.27	76.57	7.15	16.08

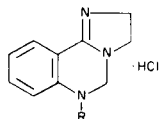
(a) Lit m.p. 73-74° (reference 5).

Table II



Compound No.	R	M.p. °C	Recrystallization Solvent	Yield %	Formula	Analysis					
						Calcd.		Found		Found	
					C	H	N	C	H	N	
IIIc	CH ₃	76-78	Ethyl acetate	35	C ₁₀ H ₁₃ N ₃	68.54	7.48	23.98	68.31	7.62	24.08
IIId	CH ₂ CH ₂ CH ₃	85-87	Methanol	24	C ₁₂ H ₁₅ N ₃	71.61	7.51	20.88	71.43	7.68	21.06
IIIe	CH ₂ CH=CH ₂	92-94	Methanol	18	C ₁₂ H ₁₃ N ₃	72.33	6.57	21.09	72.51	6.72	20.92
IIIIf		70-72	Methanol	32	C ₁₃ H ₁₇ N ₃	70.90	8.43	20.67	71.10	8.63	20.51

Table III



Compound No.	R	M.p. °C	Recrystallization Solvent	Yield %	Formula	Analysis					
						Calcd.		Found		Found	
					C	H	N	C	H	N	
Ia	H	208-210	Ethanol-Acetate	25	C ₁₀ H ₁₁ N ₃ ·HCl	53.14	5.31	20.11	53.01	5.18	19.98
Ic	CH ₃	185-187	Ethanol-Acetone	83	C ₁₁ H ₁₃ N ₃ ·HCl	59.05	6.30	18.78	58.92	6.28	18.62
Id	CH ₂ CH ₂ CH ₃	218-220	Ethanol-Acetone	55	C ₁₃ H ₁₇ N ₃ ·HCl	62.01	7.20	16.69	61.93	7.03	16.81
Ie	CH ₂ CH=CH ₂	239-241	Ethanol-Acetone	82	C ₁₃ H ₁₅ N ₃ ·HCl·½H ₂ O	60.34	6.62	16.24	60.12	6.55	16.14
If		242-245	Ethanol-Acetone	51	C ₁₂ H ₁₇ N ₃ ·HCl	63.74	6.87	15.93	63.50	6.77	15.74

General Procedure for the Preparation of 2-(*o*-Alkylaminophenyl)-4,5-dihydroimidazoles (**III**).

A mixture of 0.02 mole of **II**, 0.022 mole of ethylenediamine and 0.022 mole of *p*-toluenesulfonic acid was heated at 200° for 8 hours. The reaction mixture was made alkaline with a saturated aqueous solution of sodium carbonate and extracted several times with chloroform. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column eluting with methanol. Evaporation of the second eluate gave an oily residue which solidifies upon scratching (See Table II).

General Procedure for the Preparation of 6-Alkyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline Hydrochlorides (**Ic-f**).

To 4.64 mmole of **III** in 20 ml. of ethanol was added 1 ml. of 10 *N* hydrochloric acid and 0.7 ml. of 40% aqueous solution of formaldehyde. The reaction mixture was stirred at room temperature for 2 hours. Evaporation of the solvent gave in the cases **Id,e,f** a residue which was triturated with acetone to afford a solid which was filtered and recrystallized. In the case of **Id**, evaporation of the ethanol gave a residue which was made alkaline with a saturated aqueous solution of sodium carbonate and extracted several times with chloroform. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column eluting with methanol. Evaporation of the eluates containing the second fraction gave a solid which was dissolved in acetone; dry hydrochloric acid was bubbled through the solution and the solid obtained was filtered and recrystallized (see Table III).

5-Methyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline Hydrochloride (**Ig**).

To 1 g. (6.2 mmoles) of 2-(*o*-aminophenyl)-4,5-dihydroimidazole (**3**) dissolved in 20 ml. of ethanol was added 1.18 g. (26.7 mmoles) of acetaldehyde and 1.8 ml. of 10 *N* hydrochloric acid. After 3 hours the yellow solid which separated out was filtered and recrystallized from ethanol to give 0.7 g. (51%) of product, m.p. 190-192°.

Anal. Calcd. for C₁₁H₁₃N₃·HCl: C, 59.05; H, 6.30; N, 18.78. Found: C, 58.86; H, 6.13; N, 18.51.

2-Methyl-2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline (**Ib**).

To 4.32 mmoles of 2-methyl-2,3-dihydroimidazo[1,2-c]quinazoline (**2**) in 50 ml. of methanol were added dropwise with stirring 18 mmoles of potassium borohydride dissolved in 7 ml. of water. The reaction mixture was stirred at room temperature for 24 hours. Evaporation of the solvent gave a residue which was extracted several times with ethyl acetate. The solvent was removed in vacuum to leave a small volume, which in time crystallized to a solid which was filtered. The product was recrystallized from ethyl acetate to give 0.30 g. (37%) of crystals, m.p. 141-143°; ¹H nmr (deuteriochloroform): δ 1.37 (3H, d, J = 6.5 Hz, H₂CH₃), 2.63-3.65 (2H, m, H₃); 3.80-4.40 (3H, m, H_{2,3}); 5.17 (1H, broad s, NH); 6.60-7.37 (3H, m, H_{7,8,9}); 7.87 (1H, dd, J = 1.7 Hz, H₁₀).

Anal. Calcd. for C₉H₁₃N₃: C, 66.22; H, 8.03; N, 25.75. Found: C, 65.98; H, 8.14; N, 25.91.

Acknowledgment.

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