Synthesis of 2,3,5,6-Tetrahydroimidazo[1,2-*c*]quinazoline Derivatives as Potential Narcotic Antagonists

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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).

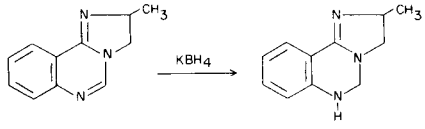
In connection with a research program on the synthesis and pharmacological activities of derivatives of imidazo-[1,2-*c*]quinazoline (1-3) it was found that 2,3,5,6-tetrahydroimidazo[1,2-*c*]quinazoline (**Ia**) (3) and 2-methyl-2,3,5,6-tetrahydroimidazo[1,2-*c*]quinazoline (**Ib**) display narcotic 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 **Id-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*]quiazoline (**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 ethylendiamine 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.

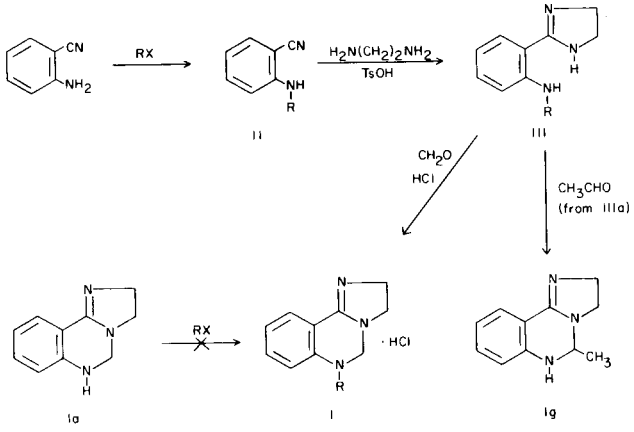
Finally 2-methyl-2,3,5,6-tetrahydroimidazo[1,2-*c*]quinazoline (**Ib**) was synthesized by reduction with potassium borohydride of 2-methyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (2):



Ib

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

Scheme I



a, R = H
c, R = CH_3
d, R = C_3H_{7n}
e, R = $CH_2CH{=}CH_2$
f, R = CH_2-c-C_3H_7

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 gratin 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 **IIf**, 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).

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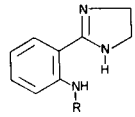
Table I

Compound No.	R	B.p. °C (mm)	Yield %	M.p., °C	Recrystallization Solvent	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIc	CH_3	95-97 (0.9)	53	69-70 (a)	cyclohexane	$C_8H_8N_2$	72.70	6.10	21.20	72.91	6.28	21.03
IId	$CH_2CH_2CH_3$	88-89 (0.6)	24			$C_{10}H_{12}N_2$	74.96	7.55	17.49	75.12	7.41	17.65
IIe	$CH_2CH=CH_2$	88-89 (0.4)	32			$C_{10}H_{10}N_2$	75.92	6.37	17.71	75.81	6.51	17.59
IIf			58			$C_{11}H_{12}N_2$	76.71	7.02	16.27	76.57	7.15	16.08

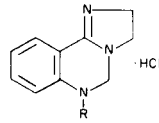
(a) Lit m.p. 73-74° (reference 5).

Table II



Compound No.	R	M.p. °C	Recrystallization Solvent	Yield %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found 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	$CH_2CH_2CH_3$	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
IIIf		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. C	Calcd. H	Calcd. N	Found C	Found H	Found 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	$CH_2CH_2CH_3$	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_2O	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 ethylendiamine 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 $C_{11}H_{13}N_3 \cdot HCl$: 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°; ^{1}H nmr (deuteriochloroform): δ 1.37 (3H, d, J = 6.5 Hz, $H_2C\underline{H}_3$), 2.63-3.65 (2H, m, H_3); 3.80-4.40 (3H, m, $H_{2,5}$); 5.17 (1H, broad s, NH); 6.60-7.37 (3H, m, $H_{7,8,9}$); 7.87 (1H, dd, J = 1.7 Hz, H_{10}).

Anal. Calcd. for $C_9H_{13}N_3$: C, 66.22; H, 8.03; N, 25.75. Found: C, 65.98; H, 8.14; N, 25.91.

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REFERENCES AND NOTES

(1) P. Franchetti and M. Grifantini, *J. Heterocyclic Chem.*, **7**, 1295 (1970).

(2) E. Claudi, P. Franchetti, M. Grifantini and S. Martelli, *J. Org. Chem.*, **39**, 3508 (1974).

(3) M. Cardellini, P. Franchetti, M. Grifantini, S. Martelli and F. Petrelli, *Farmaco, Ed. Sc.*, **30**, 636 (1975).

(4) I. Antonini, G. Cristalli, P. Franchetti, M. Grifantini and S. Martelli, unpublished results.

(5) See "Narcotic Antagonists", M. C. Brande, L. S. Harris, E. L. May, J. P. Smith, and J. E. Villareal, Eds., Raven Press, Publishers, New York, N. Y., 1973.

(6) E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2622 (1962).