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Drugs Acting on CNS: Syntheses of 2-Substituted & 2,3-Disubstituted Benzo(6,7)quinazoline-4-ones*

C. M. GUPTA, A. P. BHADURI & N. M. KHANNA
Central Drug Research Institute, Lucknow

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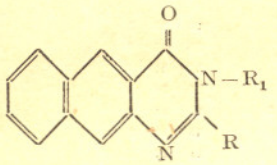
A series of 2-substituted and 2,3-disubstituted benzo(6,7)quinazoline-4-ones have been synthesized as possible CNS depressants. 2-Substituted products, viz. hydrazino, phenylhydrazino and amino, have been obtained by the reaction of 2-ethylthio-benzo(6,7) quinazolin-4-one with hydrazine, phenylhydrazine, and primary and secondary amines. The 2,3-disubstituted derivatives have been obtained by the reaction of 2-mercapto-3-phenyl-benzo(6,7)quinazoline-4-one with appropriate alkyl, arylalkyl, dialkylamino-alkyl halides in the presence of alcoholic sodium hydroxide. Some of the compounds exhibit CNS-depressant activity at high dosage.

IN view of the significant tranquillo-sedative activity exhibited by 3-aminobenzo (6,7) quinazoline-4-one[1], it was considered of interest to synthesize a series of 2-substituted and 2,3-disubstituted benzo(6,7)quinazoline-4-ones (I) and study their action on the central nervous system. The syntheses of such compounds are reported in this communication.



(I)

Attempt to prepare 2-mercaptobenzo(6,7)quinazoline-4-one according to Narang *et al.*[2] gave a very poor yield of the required product. It was, therefore, synthesized by an alternate procedure. 3-Amino-2-naphthoic acid was cyclized with benzoylisothiocyanate to yield 2-mercapto-3-benzoyl-benzo-(6,7)quinazoline-4-one, which on hydrolysis with aqueous sodium hydroxide gave 2-mercaptobenzo-(6,7)quinazoline-4-one in good yields. The latter on treatment with ethyl iodide in the presence of sodium ethoxide furnished the 2-ethylthio derivative.

Reaction of 2-ethylthio-benzo(6,7)quinazoline-4-one with hydrazine, phenylhydrazine, primary and secondary amines yielded 2-hydrazino, 2-phenylhydrazino and 2-substituted aminobenzo(6,7)quinazoline-4-ones.

Refluxing 3-amino-2-naphthoic acid with excess acetic anhydride gave benzo(6,7)acetanthranil. The latter on treatment with various primary amines and substituted hydrazines yielded the corresponding 2-methyl-3-substituted-benzo(6,7)quinazoline-4-ones.

2-Mercapto-3-phenyl-benzo(6,7)quinazoline-4-one was prepared either by fusing 3-amino-2-naphthoic acid with phenylthiourea or by refluxing with phenylisothiocyanate in alcohol. The latter procedure gave a better yield. 2-Mercapto-3-phenyl-benzo(6,7)quinazoline-4-one yielded the corresponding 2-alkyl, arylalkyl or dialkylamino-alkylthio derivatives on treatment with appropriate alkyl, arylalkyl, dialkylamino-alkyl halides in the presence of alcoholic sodium hydroxide.

2-Alkylthio-3-phenyl-benzo(6,7)quinazoline-4-one was dethionated with Raney nickel in boiling isopropanol to give 3-phenyl-benzo(6,7)quinazoline-4-one. Hydrolysis of the same alkylthio compound with 6*N* HCl furnished 3-phenyl-benzo(6,7)quinazoline-2,4-dione.

Thionation of 2,4-dihydroxy-benzo(6,7)quinazoline[3] with P_2S_5 in pyridine gave 2-oxo-benzo(6,7)quinazoline-4-thione. Thionation at 4 position was proved by mixed m.p. of this compound with an authentic sample of 2-mercapto-benzo(6,7)quinazoline-4-one. IR spectrum of the thionated product revealed peaks at 1530, 1320, 1240 cm.$^{-1}$ $\left(\begin{matrix}\text{C-NH}\\ \|\\ \text{S}\end{matrix}\right)$ and at 1700 cm.$^{-1}$ $\left(\begin{matrix}\text{—C-NH}\\ \|\\ \text{O}\end{matrix}\right)$ indicating that the compound exists predominantly as 2-oxo-benzo(6,7)quinazoline-4-thione.

Attempt to prepare 2-hydroxy-4-ethylthio-benzo-(6,7)quinazoline by treating 2-oxo-benzo(6,7)quinazoline-4-thione with ethyliodide in the presence of sodium ethoxide gave 2,4-dihydroxy-benzo(6,7)quinazoline; identified through superimposable IR with an authentic sample.

Pharmacological screening of the compounds synthesized revealed CNS-depressant action at high dosage.

Experimental Procedure

All melting points are uncorrected. The physical and analytical data of the compounds synthesized are given in Table 1, unless otherwise mentioned. All the compounds synthesized were, as a routine, checked by their IR spectra. Satisfactory analysis for C, H were obtained for all the compounds.

2-Mercapto-3-benzoyl-benzo(6,7)quinazoline-4-one—A mixture of 3-amino-2-naphthoic acid (14 g.) and benzoylisothiocyanate (11·9 g.) in dry acetone (300 ml.) was refluxed for 5 hr, cooled, filtered and crystallized; yield 21·7 g.

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TABLE 1 — 2-SUBSTITUTED AND 2,3-DISUBSTITUTED BENZO(6,7)QUINAZOLINE-4-ONES (I)

Sl No.	R	R_1	m.p. °C.	Crystallized from	Mol. formula	N (%) Found	N (%) Reqd
1	SH	$CO.C_6H_5$	202-3	AcOH	$C_{19}H_{12}N_2O_2S$	7·90	8·00
2	SH	H	330	do	$C_{12}H_8N_2OS$*	11·88	11·81
3	SC_2H_5	H	221-2	EtOH	$C_{14}H_{12}N_2OS$	10·63	10·93
4	N-Methylpiperazino	H	277-9	Aq.DMF	$C_{17}H_{18}N_4O$	18·90	19·04
5	N-Phenylpiperazino	H	316	do	$C_{22}H_{20}N_4O$	15·20	15·73
6	Morpholino	H	302-3	do	$C_{16}H_{15}N_3O_2$	14·63	14·94
7	Piperidino	H	271-2	Aq.EtOH	$C_{17}H_{17}N_3O$*	14·43	14·58
8	Homopiperidino	H	265	do	$C_{18}H_{19}N_3O$†	13·13	13·50
9	$NH-(CH_2)_2.N-(C_5H_5)_2$	H	98-100	do	$C_{18}H_{22}N_4O$*	18·10	17·55
10	β-(2′-Pyridyl)ethyl-amino	H	227-8	Aq.DMF	$C_{19}H_{16}N_4O$	18·06	17·72
11	$NH.NH_2$	H	>320	AcOH	$C_{12}H_{10}N_4O$	24·59	24·77
12	$NH.NH.C_6H_5$	H	278-9	Aq.DMF	$C_{18}H_{14}N_4O$	18·69	18·54
13	CH_3	C_6H_5	134-5	C_6H_6-petrol	$C_{19}H_{14}N_2O$†	9·80	9·79
14	CH_3	C_6H_4-CH_3(*o*)	159-60	do	$C_{20}H_{16}N_2O$	8·87	9·33
15	CH_3	C_6H_4-Cl(*p*)	173-4	Aq.EtOH	$C_{19}H_{13}ClN_2O$*	8·35	8·49
16	CH_3	$(CH_2)_2$-N-$(C_2H_5)_2$	97-99	Ether-petrol	$C_{19}H_{23}N_3O$†	12·54	12·84
17	CH_3	β-Pyrrolidyl ethyl	111-12	do	$C_{19}H_{21}N_3O$	13·10	13·64
18	CH_3	$(CH_2)_2$-C_6H_5	159	Aq.EtOH	$C_{21}H_{18}N_2O$	8·43	8·43
19	CH_3	C_6H_4-Br(*p*)	211-12	do	$C_{19}H_{13}BrN_2O$*	7·50	7·69
20	CH_3	N-Homopiperidyl	158-9	Aq.EtOH	$C_{19}H_{21}N_3O$	13·49	13·68
21	CH_3	CH_2-C_6H_3-Cl_2(*m,p*)	189-90	Aq.AcOH	$C_{20}H_{14}Cl_2NO$†	7·02	7·23
22	CH_3	4′-Pyridyl	220	Acetone	$C_{18}H_{13}N_3O$	14·99	14·63
23	CH_3	2′-Tetrahydrofurfuryl	154-5	C_6H_6-pet. ether	$C_{17}H_{16}N_2O$*	9·20	6·68
24	CH_2	NH_2	186-7	Aq.EtOH	$C_{13}H_{11}N_3O$	19·13	18·66
25	CH_2	*p*-Diethylamino-*o*-methyl phenyl	199-200	do	$C_{24}H_{25}N_3O$	11·52	11·32
26	CH_3	β(2′-Pyridyl)ethyl	129-30	C_6H_6-pet. ether	$C_{20}H_{17}N_3O$*	12·61	12·96
27	CH_3	2′-(6-Methyl)pyridyl	174-5	do	$C_{19}H_{15}N_3O$†	12·80	13·16
28	SH	C_6H_5	330 (d)	Aq. dioxane	$C_{18}H_{12}N_2OS$	8·96	9·21
29	$S.C_2H_5$	C_6H_5	190-91	*i*-Propanol	$C_{20}H_{16}N_2OS$	8·32	8·43
30	$S-CH_2.C_6H_5$	C_6H_5	180-82	Acetone-$CHCl_3$	$C_{25}H_{18}N_2OS$	6·85	7·10
31	H	C_6H_5	219-20	*i*-Propanol	$C_{18}H_{12}N_2O$	10·61	10·29
32	OH	C_6H_5	189-90	do	$C_{18}H_{12}D_2O_2$*	9·36	9·72
33	$S-(CH_2)_2-N-(C_2H_5)_2$	C_6H_5	145-6	EtOH	$C_{24}H_{25}N_3OS$	10·40	10·42

*Crystallized as hemihydrate.
†Crystallized as monohydrate.

2-*Mercaptobenzo*(6,7)*quinazoline*-4-*one* — 2-Mercapto-3-benzoyl-benzo(6,7)quinazoline-4-one (16·6 g.) was dissolved in aq. NaOH (10 per cent; 100 ml.). The resulting solution was heated over a steam-bath for 1 hr, cooled, filtered and acidified with conc. HCl. The precipitated solid was filtered, washed with water, aq. $NaHCO_3$ and finally with water; yield 11·1 g.

2-*Ethylthiobenzo*(6,7)*quinazoline*-4-*one* — To a solution of sodium (0·23 g.) in ethanol (20 ml.), 2-mercaptobenzo(6,7)quinazoline-4-one (2·3 g.) was added, followed by ethyl iodide (1 ml.) and the mixture refluxed for 3 hr, cooled, filtered and after dilution with water the separated solid crystallized; yield 2·9 g.

2-Alkyl- or arylalkyl-thio-3-phenyl-benzo(6,7)-quinazolin-4-ones were likewise prepared from 2-mercapto-3-phenyl-benzo(6,7)quinazoline-4-one and the appropriate alkyl or arylalkyl halides.

2-*Hydrazino, substituted hydrazino, and* 2-*substituted amino benzo*(6,7)*quinazoline*-4-*one* — 2-Ethylthiobenzo(6,7)quinazoline (1 mole) was dissolved in the required base (3 moles) and the resulting solution was heated at 120° for 5-6 hr, cooled, triturated with ether, filtered and crystallized from appropriate solvents; yield 50-70 per cent. Compound Nos. 4-12 (Table 1) were prepared as above.

Benzo(6,7)*acetanthranil*—3-Amino-2-naphthoic acid (18·0 g.) was refluxed with acetic anhydride (125 ml.) for 3 hr. The reaction mixture was left overnight at room temperature and the crystalline solid which separated out was filtered and dried *in vacuo*; m.p. 169-70°; yield 12·0 g. (Found N, 7·08. $C_{13}H_9NO_2$ requires N, 6·63 %).

2-*Methyl*-3-*substituted amino- and hydrazinobenzo*-(6,7)*quinazoline*-4-*one* — Benzo(6,7)acetanthranil (1 mole) dissolved in dry benzene or xylene was treated with the appropriate primary amines or substituted hydrazines (1 mole) and the reaction mixture refluxed for 6 to 10 hr. The solvent was removed under reduced pressure and the residue treated with aq. NaOH (10 per cent). The solid so obtained was purified through column chromatography over alumina using benzene or chloroform as the eluents and finally crystallized from suitable solvents; yield 60-65 per cent. Compound Nos. 13-23 and 25-27 (Table 1) were likewise prepared.

2-*Mercapto*-3-*phenyl*-*benzo*(6,7)*quinazoline*-4-*one*: *Method I* — An intimate mixture of 3-amino-2-naphthoic acid (3·0 g.) and phenylthiourea (2·2 g.) was heated at 180° for 2 hr. The residue was dissolved in alcoholic NaOH, filtered, acidified with HCl (10 per cent), filtered again and crystallized; yield 1·4 g.

Method II — 3-Amino-2-naphthoic acid (5·5 g.) and phenylisothiocyanate (4 ml.) in ethanol (100 ml.) were refluxed for 18 hr. The pale yellow solid that separated out was filtered, washed with alcohol and dried; yield 5·8 g.

3-*Phenyl-benzo*(6,7)*quinazoline*-2,4-*dione*—2-Ethylthio-3-phenyl-benzo(6,7)quinazoline-4-one (1·0 g.) was dissolved in a mixture of isopropanol (25 ml.) and 6*N* HCl (15 ml.). The reaction mixture was refluxed for 8 hr. On cooling, a crystalline solid separated out, which was filtered and dried; yield 0·5 g.

3-*Phenyl-benzo*(6,7)*quinazoline*-4-*one* — To a solution of 2-ethylthio-3-phenyl-benzo(6,7)quinazoline-4-one (1·5 g.) in isopropanol (200 ml.) was added Raney nickel (10-12 g.) and the reaction mixture refluxed for 8 hr. It was filtered hot, and the solid that separated on cooling was crystallized thrice; yield 0·6 g.

2-*Methyl*-3-*aminobenzo*(6,7)*quinazoline*-4-*one* — 2-Methylbenzo(6,7)quinazoline-4-one (2·0 g.) was refluxed with hydrazine hydrate (20 ml.; 100 per cent) for 12 hr, cooled, filtered and crystallized; yield 1·2 g.

2-*Oxo-benzo*(6,7)*quinazoline*-4-*thione* — To a solution of 2,4-dihydroxy-benzo(6,7)quinazoline (5·0 g.) in pyridine (200 ml.), P_2S_5 (10·2 g.) was added and the reaction mixture refluxed for 3 hr, cooled, diluted with water (120 ml.) and acidified with HCl to *p*H 6. The yellow solid so obtained was filtered, washed with water, dissolved in aq. NaOH (10 per cent; 400 ml.) and filtered. The filtrate was acidified with HCl to *p*H 4. The yellow substance that separated was filtered, washed with water and crystallized thrice from glacial acetic acid; yield 4·5 g.; m.p. > 310° (Found: C, 60·80; H, 3·69; N, 11·66. $C_{12}H_8N_2OS.\frac{1}{2}H_2O$ requires C, 60·76; H, 3·79; N, 11·81%).

Acknowledgement

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References

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