SYNTHESIS AND SPECTRAL BEHAVIOUR OF SOME NEW (SUBSTITUTED) BENZOTHIAZOLYL GUANIDINES

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A SERIES of biguanides[1,2] as antimalarials, most notably chlorguanide[2] and daraprim[3] were discovered by Rose and Coworkers. Subsequently, they felt that the activity was due to the N–H group capable of undergoing simultaneous prototropic change with the ring system. This led to the synthesis of guanidine derivatives for antimalarial[4] and antibacterial[5] activities. Recently, some (substituted) benzothiazolyl guanidines[6] have been reported by us exhibiting antiprotozoal activity against *Mycobacterium 607* and antifungal activity.

In view of the above findings and because of the antibacterial and antitubercular nature of benzothiazolyl guanidines[7,8], we have prepared some new N-*p*-bromophenyl-N'-(substituted)-benzothiazol-2-yl-N''-(*n*-propyl and *n*-butyl) guanidines by condensation[9] of 2-amino (substituted) benzothiazoles with *p*-bromophenylisothiocyanate in dry benzene and subsequently desulphurisation of the resulting thiocarbamides with alkylamines in presence of yellow lead oxide.

EXPERIMENTAL

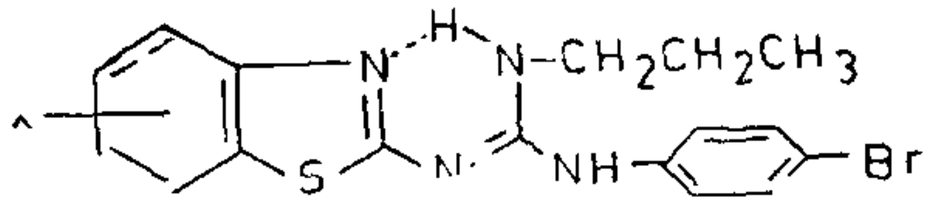
All melting points were taken by the capillary method and are uncorrected. The purity of products was tested by thin layer chromatography (TLC). Solvent systems used were: Benzene-Ether (3 : 1, R_f 1) and Benzene-Ether (6 : 1, R_f 2).

N-p-*Bromophenyl-N'-(6-methoxy) benzothiazol-2-yl-N''-*(n-*propyl*)

Guanidine 1.—A mixture of N-*p*-bromophenyl-N'-(6-methoxy) benzothiazol-2-yl-thiocarbamide (3·94 g), yellow lead oxide (4·50 g), *n*-propylamine (1·00 ml) and absolute alcohol (40 ml) was heated in a glass sealed tube on a water-bath at 80–90° for 4–6 hours. After cooling, the sealed tube was broken carefully and the hot black residue was filtered. The filtrate on concentration gave the desired product. It was crystallised from alcohol in beautiful shining crystals, yield 78%, m.p. 118°. TLC: $R_f^1 = 0{\cdot}87$. *Anal.* Calcd. for $C_{18}H_{19}N_4OSBr$: N, 13·37; S, 7·64. Found: N, 13·35; S, 7·68. IR ν_{max}^{nujol} cm^{-1}: 3438s, 3200 w, 1600s, 1470 s. NMR ($CDCl_3$)δ (J = Hz): 0·96 (3H, *t*, J = 7·0), 1·63 (2H, *m*), 3·42 (2H, *m*), 3·87 (3H, *s*) and 7·38 for the aromatic protons (7H, *m*).

Similarly, other (substituted) benzothiazolyl guanidines were obtained by condensation of different (substituted) benzothiazolyl thiocarbamides with *n*-propylamine. The structures and the purity of the compounds are recorded in Tables I and III.

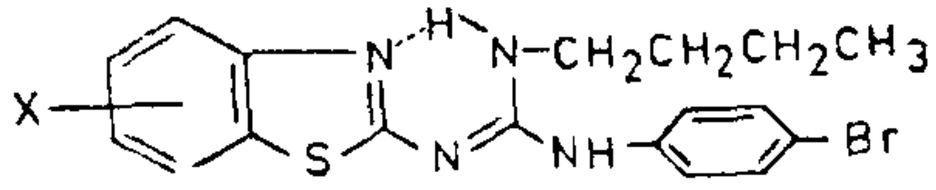
TABLE I



Sl. No.	Substituent X	Molecular formula	Yield (%)	(m.p.) (°C)	Nitrogen (%) Found	Nitrogen (%) Calcd.	Sulphur (%) Found	Sulphur (%) Calcd.	R_f* Values
1.	H	$C_{17}H_{17}N_4SBr$	82	98	14·37	14·39	8·12	8·23	·88
2.	4–CH_3	$C_{18}H_{19}N_4SBr$	63	119	13·86	13·89	7·84	7·94	·89
3.	5–CH_3	$C_{18}H_{19}N_4SBr$	68	131	13·82	13·89	7·92	7·94	·82
4.	6–CH_3	$C_{18}H_{19}N_4SBr$	71	141	13·79	13·89	7·84	7·94	·81
5.	4–Cl	$C_{17}H_{16}N_4SClBr$	62	126	13·12	13·22	7·52	7·55	·85
6.	5–Cl	$C_{17}H_{16}N_4SClBr$	58	128	13·20	13·22	7·57	7·55	·87
7.	6–Cl	$C_{17}H_{16}N_4SClBr$	74	120	13·21	13·22	7·49	7·55	·88
8.	6–Br	$C_{17}H_{16}N_4SBr_2$	68	203	11·92	11·96	6·63	7·84	·87
9.	4–OCH_3	$C_{18}H_{19}N_4OSBr$	59	110	13·27	13·37	7·53	7·64	·81
10.	6–OCH_3	$C_{18}H_{19}N_4OSBr$	78	118	13·35	13·37	7·68	7·64	·87
11.	4–OC_2H_5	$C_{19}H_{21}N_4OSBr$	66	161	12·92	12·93	7·38	7·39	·86

* R_f values were measured on developing the TLC plates (adsorbent, silica gel BDH) in Benzene and Ether (3:1) mixture.

TABLE II



Sl. No.	Substituent X	Molecular formula	Yield (%)	(m.p.) (°C)	Nitrogen (%) Found	Nitrogen (%) Calcd.	Sulphur (%) Found	Sulphur (%) Calcd.	R_f* Values
1.	H	$C_{18}H_{19}N_4SBr$	83	85	13·82	13·89	7·82	7·94	·54
2.	4-CH_3	$C_{19}H_{21}N_4SBr$	71	103	13·42	13·43	7 65	7·67	·69
3.	5-CH_3	$C_{19}H_{21}N_4SBr$	65	101	13·40	13·43	7·68	7·67	·64
4.	6-CH_3	$C_{19}H_{21}N_4SBr$	84	108	13·41	13·43	7·58	7·67	·74
5.	4-Cl	$C_{18}H_{18}N_4SClBr$	38	103	12·70	12·80	7·41	7·31	·26
6.	5-Cl	$C_{18}H_{18}N_4SClBr$	49	94	12·65	12·80	7·32	7·31	·83
7.	6-Cl	$C_{18}H_{18}N_4SClBr$	65	114	12·78	12·80	7·30	7·31	·79
8.	6-Br	$C_{18}H_{18}N_4SBr_2$	70	128	11·65	11·62	6·68	6·64	·80
9.	4-OCH_3	$C_{19}H_{21}N_4OSBr$	68	123	12·81	12·93	7·37	7·39	·36
10.	6-OCH_3	$C_{19}H_{21}N_4OSBr$	74	87	12·91	12·93	7·35	7·39	·40
11.	4-OC_2H_5	$C_{20}H_{23}N_4OSBr$	72	173	12·44	12·54	7·30	7·16	·81

*R_f values were measured on developing the TLC plates (adsorbent, silica gel BDH) in Benzene and Ether (6:1) mixture.

N - p - Bromophenyl-N'-(6-methyl) benzothiazol-2-yl-N''-(n-butyl) guanidine 2.—A mixture of N-*p*-bromophenyl-N'-(6-methyl) benzothiazol-2-yl-thiocarbamide (3·78 g), yellow lead oxide (4·50 g), *n*-butylamine (1·2 ml) and absolute alcohol (40 ml) was treated as above to afford the required product. It was crystallised from 80% ethanol into shining needles, yield 84%, m.p. 108°. TLC : $R_f^2 = 0·74$. *Anal.* Calcd. for $C_{19}H_{21}N_4SBr$: N, 13·43 ; S, 7·67. Found : N, 13·42 ; S, 7·58. IR ν_{max}^{nujol} cm^{-1} : 3235s, 3105m, 1610s, 1522s. NMR ($CDCl_3$) δ : 0·97 (3H, *m*), 1·25 (2H, *m*), 3·46 (2H, *m*), 2·46 (3H, *s*) and 7·49 for aromatic protons (7H, *m*).

Similarly, other (substituted) benzothiazolyl guanidines were synthesized. Their structures and the purity of the compound are recorded in Tables II and III.

DISCUSSION

Varian-A 60D model was used for recording of NMR spectra, *Perkin Elmer-257* for IR and a *Coleman-Analyzer* for analyses.

The NMR spectrum (Fig. 1) of the compound *1* in $CDCl_3$ shows a singlet at δ 3·87 for the ring methoxy protons, a multiplet at δ 3·42 for –NH–CH_2–CH_2 protons, a triplet at δ 0·96 (J = 7·0 Hz)

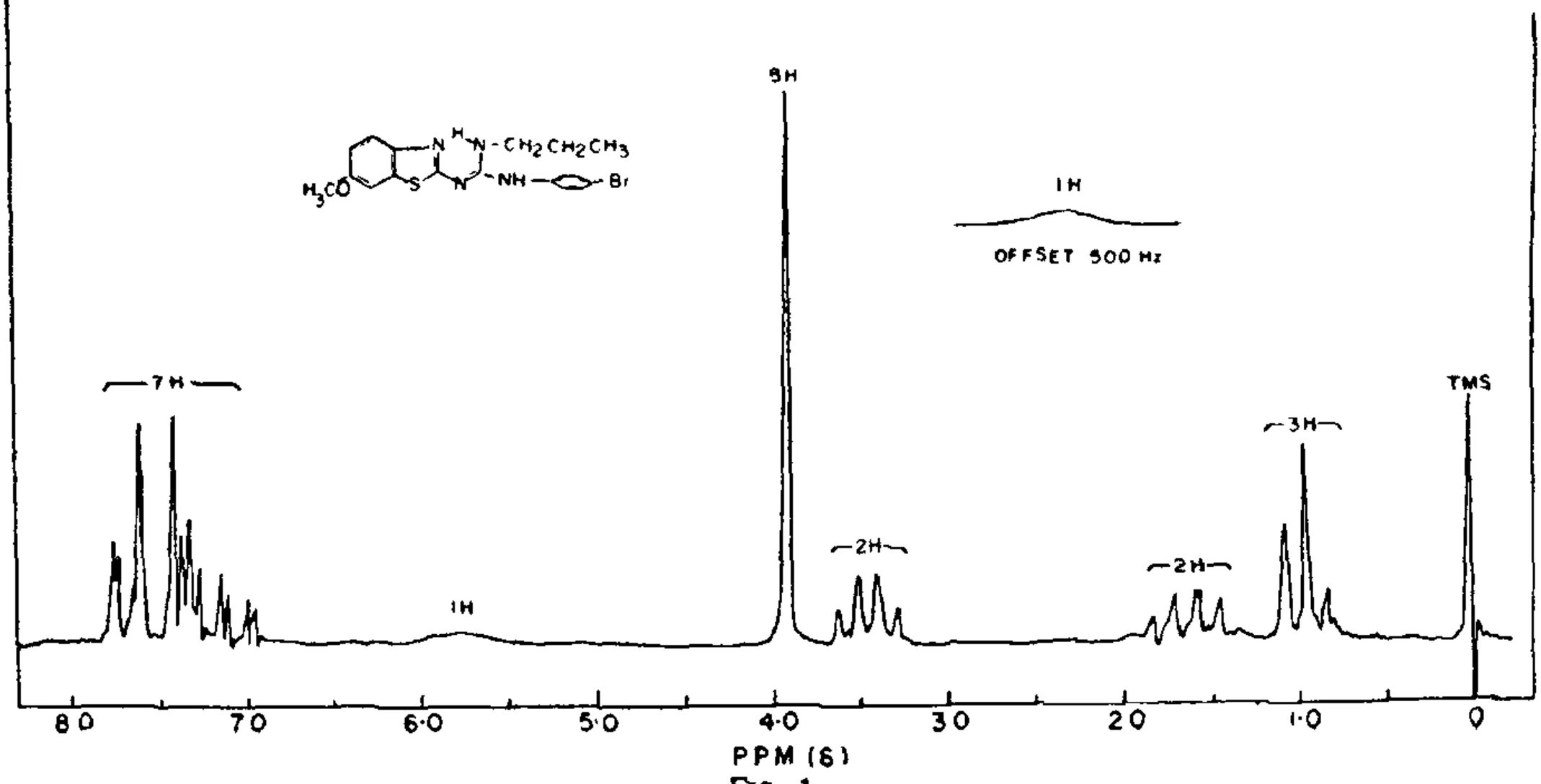
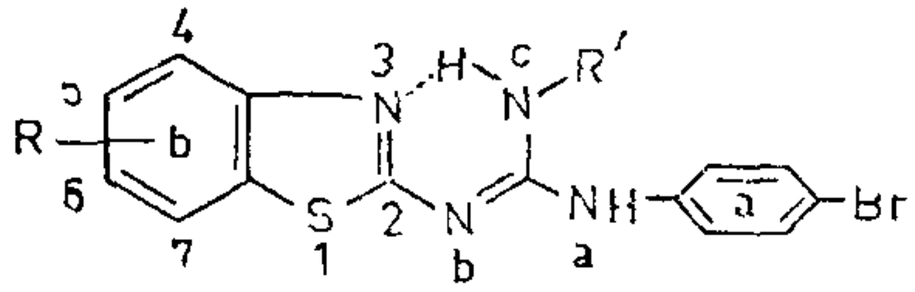


FIG. 1

TABLE-III

NMR spectra and characteristic IR** peaks of*

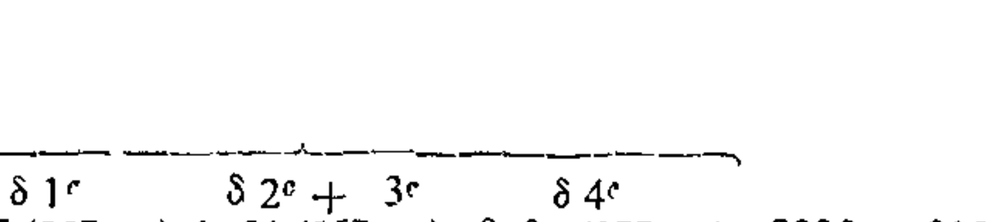


are recorded

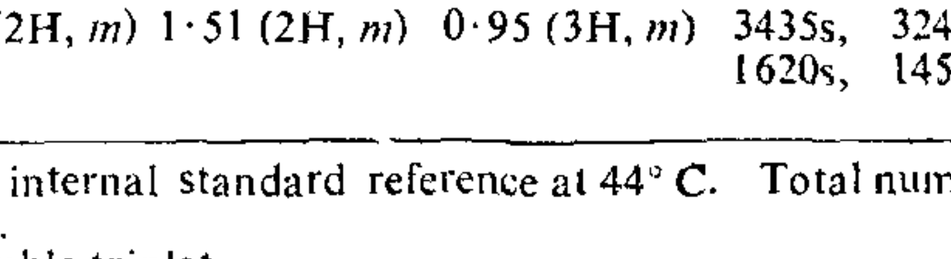
Sl. No.	Sub-stituent R	δ aromatic^{a+b}	δ R^{b}	δ R'^{c}			Characteristic IR peaks (cm^{-1})	
			$R' = -\overset{1^c}{CH_2}-\overset{2^c}{CH_2}-\overset{3^c}{CH_3}$	δ 1^{c}	δ 2^{c}	δ 3^{c}		
1.	5–CH_3	7·00–7·85 (7H, *m*)	2·46 (3H, *s*)	3·44 (2H, *m*)	1·55 (2H, *m*)	0·93 (3H, *t*) J = 7·0 Hz	3430s, 1580*m*,	3165w, 1365s,
2.	6–CH_3	7·00–7·83 (7H, *m*)	2·46 (3H, *s*)	3·45 (2H, *m*)	1·58 (2H, *m*)	0·93 (3H, *t*) J = 7·0 Hz	3438s, 1575s,	3180w, 1365s,
3.	6–OC_2H_5	6·75–7·88 (7H, *m*)	4·28 (2H, d_q) J = 8·0 Hz, 1·45 (3H, d_t) J = 8·0 Hz	3·50 (2H, *m*)	1·63 (2H, *m*)	0·99 (3H, *t*) J = 7·0 Hz	3220s, 1585s,	1615s,
			$R' = -\overset{1^c}{CH_2}-\overset{2^c}{CH_2}-\overset{3^c}{CH_2}-\overset{4^c}{CH_3}$	δ 1^{c}	δ 2^{c} + 3^{c}	δ 4^{c}		
4.	4–CH_3	7·12–7·79 (7H, *m*)	2·58 (3H, *s*)	3·47 (2H, *m*)	1·54 (2H, *m*)	0·95 (3H, *m*)	3235s, 1610s,	3105*m*, 1522s,
5.	6–Cl	7·22–7·82 (7H, *m*)		3·48 (2H, *m*)	1·51 (2H, *m*)	0·95 (3H, *m*)	3435s, 1620s,	3240w, 1450s,

* NMR spectra were recorded in $CDCl_3$ using TMS as internal standard reference at 44° C. Total number of protons and multiplicity of bands are indicated in brackets.
s = singlet, *t* = triplet, d_q = double quartet and d_t = double triplet.
In case of multiplets, the mean positions of the δ values are given.
All the compounds gave two NH resonances centred at approx. δ 5·65 and 10·75 respectively.
**IR spectra were recorded in nujol.
w = weak, m = medium and s = strong.

for the $-CH_2-\mathit{CH_3}$ protons, a multiplet at δ 1·63 for the $-CH_2-\mathit{CH_2}-CH_3$ protons and a multiplet at δ 7·38 for aromatic protons. Along with these bands, two >NH resonances have observed at approx. δ 5·65 and 10·75 respectively. On D_2O exchange, the two >N–H resonances disappear and the multiplet type band at δ 3·42 changes into a triplet (J = 7·0 Hz). Therefore, it is evident that the $-NH-\mathit{CH_2}-CH_2-$ protons are coupled with an exchangeable proton (J = 5·0 Hz) as well as with an adjacent methylene protons. The above evidences suggest the structure I but not II and IV for the compound *1*. The structure III is unlikely

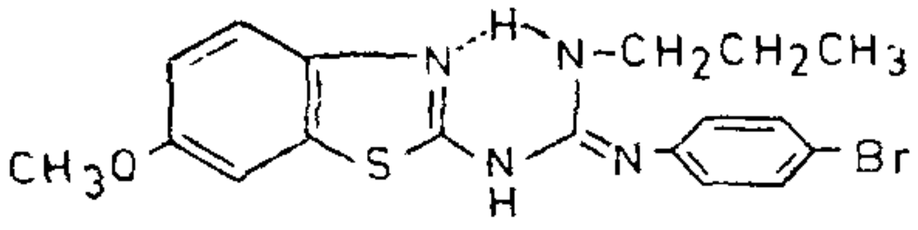


(I)



(II)

since the structure I is more stable by a more effective conjugation of the planar six-membered ring formed by the hydrogen bonding. The strong IR peak at



(III)

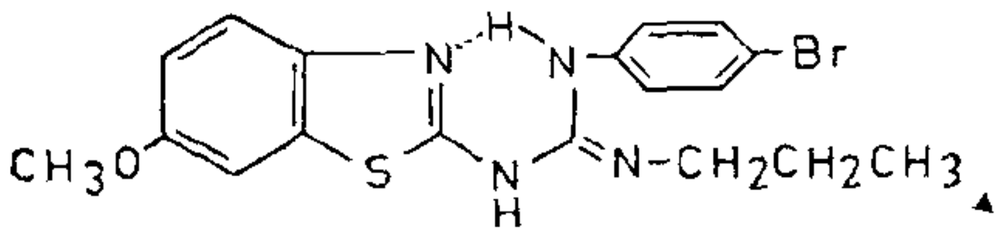
1600 cm^{-1} which is characteristic of an aromatic type –C=N–bond also support the above structure for the compound.

The PMR spectra of the compound *2* in $CDCl_3$ also shows along with other normal peaks a multiplet type band at δ 3·47 for the –NH–CH_2–CH_2– protons which on D_2O exchange changes into a triplet (J = 7·00 Hz). These facts, therefore, also support the structure for the compound 2 having a skeleton of type I. The strong IR peak at 1595 cm^{-1} is also in agreement to its structure.

Screening Results.—The microbiological and pharmacological activities of these compounds were carried out at Bristol Laboratories, Syracuse, New York, U.S.A. These compounds were found to be inactive microbiologically but showed remarkable *pharmacological activities. Most notably, N-p-*bromophenyl-N'-(6-bromo) benzothiazol-2-yl-N''-(*n*-butyl) guanidine showed CNS depressant, muscle relaxant and anticonvulsant (protection *vs.* electroshock) as given below :

S. No.*	Area	Microbiological	Pharmacological	MED/MIC	Species
8	Central Nervous System (CNS)	None	Behav. Dep. Muscle Relax. Electroshock	160 mg/kg po 160 mg/kg po 160 mg kg po	Mouse

MED = Minimum effective dose; MIC = Minimum inhibitory concentration.
*S. No. corresponds to the S. No. of the compound in Table II.



(IV)

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OBSERVATIONS ON HORNBLENDE PORPHYROBLASTS IN BASIC GRANULITES AROUND BARAMBA, ORISSA

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OCCURRENCE of hornblende porphyroblasts in basic granulites around Baramba (20° 27′ 30″ to 20° 25′ N ; 85° 20′ to 85° 23′ E), hitherto not reported, is recorded here for the first time.

Basic granulite with porphyroblastic hornblende is sporadically exposed in the close vicinity of the non-porphyroblastic varieties[1], both types of basic rock being associated with typical Eastern Ghat rocks. These two varieties are seen in outcrops separated by soil but they can be mapped as single unit based on their field occurrences and absence of lateral variation between the two types.

Porphyroblasts of hornblende (Fig. 1) occur as euhedral to anhedral crystals with sharp outline