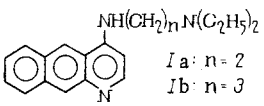
SYNTHESIS OF DERIVATIVES OF BENZO[G]QUINOLINE

XIV. 4-DIALKYLAMINO(HETERO)ALKYLAMINOBENZO[G]QUINOLINES AND THEIR N-OXIDES

N. P. Kozyreva, A. F. Bekhli,
Sh. D. Moshkovskii, S. A. Rabinovich,
and E. V. Maksakovskaya

UDC 615.281:547.831.1].012.1

In an earlier investigation we synthesized 4-diethylaminoalkylaminobenzo[G]quinolines of general formula I and these compounds were found to surpass the principal antimalarial drug chloroquine in their chemotherapeutic coefficient and low toxicity [1, 2].



I

In an attempt to increase the chemotherapeutic properties of these compounds we have synthesized a number of N-oxide derivatives with either a chlorine atom in the 10-position, or a heterocyclic group or diethanolamine group in the side chain (see Table 1).

The 10-chloro-substituted 4-diethylaminoalkylaminobenzo[G]quinolines (XII and XIII) and 4-hetero- and 4-diethanolaminoalkylamino-substituted benzo[G]quinolines (II-XI) were prepared by the condensation of the 2,3-dihydrobenzo[G]quinoline-4-(1H) with the amine in the presence of an oxidizing agent with azeotropic distillation of the water formed [3].

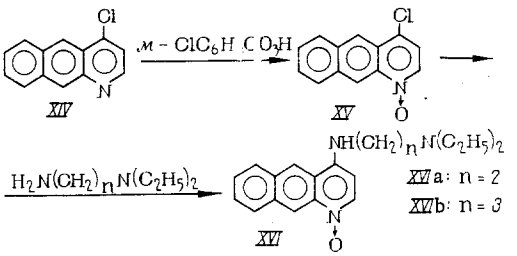
The N-oxides of Ia and b (XIVa and b) were obtained by the oxidation of 4-chlorobenzo[G] quinoline (XIV) with m-chloroperbenzoic acid followed by reaction of the N-oxide of the 4-chlorobenzo[G]quinoline obtained (XV) with the amine in ethanol in the presence of hydrochloric acid.

EXPERIMENTAL

Pharmacological

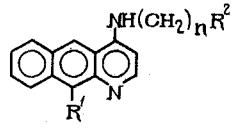
The activity and toxicity of compounds II-XIII and XVI were studied using non-pedigree white mice. Their anitimalarial action on the asexual erythrocyte stages of the malaria inducer Plasmodium berghei was studied.

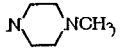
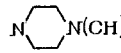
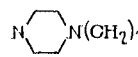
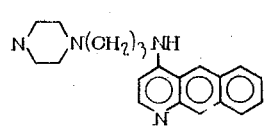
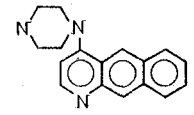
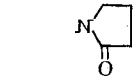
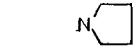
The antimalarial activity was obtained from the chemotherapeutic coefficient – the relationship between the activity and toxicity of the tested compounds compared with a standard compound; the standard chosen was delagil [chloroquine].



E. I. Martsinovskii Institute of Medical Parasitology and Tropical Medicine, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 3, pp. 73-77, March, 1978. Original article submitted August 8, 1977.

0091-150X/78/1203-0345 $07.50

TABLE 1. 4-Dialkylamino(hetero)alkylaminobenzo[G]quinolines 

Compound	R^1	R^2	n	Yield, %	Melting point, °C	Found, %		Molecular formula	Calculated, %		Chemotherapeutic coefficient
						Cl	N		Cl	N	
II	H		3	62	160–1	—	16,9	$C_{21}H_{26}N_4$	—	16,8	Inactive
III	H		3	71	154–5	—	15,5	$C_{22}H_{28}N_4O$	—	15,4	*
IV	H		3	77	145–6	—	17,7	$C_{24}H_{33}N_5$	—	17,9	*
V	H		3	49	274–5	—	15,1	$C_{36}H_{40}N_6$	—	15,1	*
VI	H		3	56	227–8	—	14,2	$C_{33}H_{31}N_5$	—	14,1	*
VII	H		3	67	191–2	—	12,7	$C_{20}H_{33}N_3O$	—	13,1	0,5
VIII	H		3	61	87–8	—	12,2	$C_{22}H_{27}N_3$	—	12,6	0,75
IX	H		3	62	176–7	—	13,0	$C_{20}H_{21}N_3O$	—	13,2	Inactive
X	H	$N(CH_2CH_2OH)_2$	3	63	245–6	—	12,2	$C_{20}H_{25}N_3O_2$	—	12,4	*
XI	H		2	38	169–170	—	14,6	$C_{19}H_{21}N_3$	—	14,4	0,25
XII	Cl	$N(C_2H_5)_2$	2	39	137–8	10,3	13,2	$C_{19}H_{22}ClN_3$	10,8	12,8	Inactive
XIII	Cl	$N(C_2H_5)_2$	3	83	151–2	10,0	12,5	$C_{20}H_{27}ClN_3$	10,4	12,3	*
		N-oxides of Compounds Ia and b									
XVIa				31	170–1 †	—	13,5	$C_{19}H_{23}N_3O$	—	13,6	0,25
XVIb				40	98–100 †	—	12,6	$C_{20}H_{25}N_3O$	—	13,0	Inactive

*Compounds II-IV, VII-XI, and XVIb were recrystallized from ethyl acetate, V from dimethylformamide (melts with decomposition), VI and XVIa from benzene, and XII and XIII from heptane.

†Sealed capillary

It was found that oxidation of Ia and b to the N-oxides XVIa and b was accompanied by an increase in toxicity [4] and a lowering or loss of antimalarial activity. In this the 4-aminobenzo[G]quinolines differ from the 4-aminoquinolines and the 9-aminoacridines, the N-oxides of which are characterized by higher antimalarial activity and lower toxicity than the starting compounds [5-8].

The introduction of a halogen into position 10 of compounds Ia and b to give compounds XII and XIII caused an increase in toxicity [4] and loss of antimalarial activity. Similar results are observed for the analogous 4-aminoquinolines and 9-aminoacridines. The presence of a halogen atom in position 8 or 5, i.e., in the peri position to the ring nitrogen atom causes complete loss of antimalarial action [9, 10].

When the diethylamino group in the side chain of Ia and b is replaced by a heterocyclic radical or diethanolamino group there is an increase in toxicity [4] and the antimalarial activity is lowered (compounds VII, VIII, and XI) or completely lost (compounds II-VI, IX, and X). It should be noted that quinoline compounds of similar structure with a piperazine group in the side chain exhibit high antimalarial activity [11-14].

The results of this investigation show that benzo[G]quinolines differ in a number of ways from the corresponding quinoline and acridine derivatives.

Chemical

N-oxide of 4-Chlorobenzo[G]quinoline (XV). A solution of 10.7 g (0.05 mole) of 4-chlorobenzo[G]quinoline (XIV) in 160 ml of chloroform is added to a solution of 8 g of m-chloroperbenzoic acid in 240 ml of chloroform, the mixture refluxed for 15 min, cooled, and the chloroform solution washed with a 5% sodium bicarbonate solution and then with water. After distilling off the chloroform, 9.8 g (85%) of XV is obtained, as yellow crystals mp 160-161° (from aqueous methanol). Found, %: Cl 15.8, N 6.2. $C_{13}H_8ClNO$. Calculated, %: Cl 15.4; N 6.4.

N-oxide of 4-(β-Diethylaminoethyl)aminobenzo[G]quinoline (XVIa). A mixture of 8 g (0.035 mole) of the N-oxide of 4-chlorobenzo[G] quinoline (XV), 8.1 g (0.07 mole) of β-diethylaminoethylamine, 140 ml of absolute alcohol, 21 ml water, and 3 drops of concentrated hydrochloric acid are refluxed for 24 h, the alcohol is distilled off in vacuum, and the residue treated with dilute alkali and extracted with chloroform. After evaporation of the chloroform, the residue is recrystallized three times from benzene to give red crystals (3.3 g) of XVIa which are dried at 120°C for 6 h.

N-oxide of 4-(γ-Diethylaminopropyl)aminobenzo[G]quinoline (XVIb). This is prepared by the same method and the red crystals are dried over phosphorus pentoxide for 48 h.

LITERATURE CITED

1. A. F. Bekhli, N. P. Kozyreva, Sh. D. Moshkovskii, et al., USSR Inventor's Certificate No. 476000, 1974. Otkrytiya, No. 25, 11 (1975).
2. A. F. Bekhli, N. P. Kozyreva, Sh. D. Moshkovskii, et al., Med. Parazitol., No. 1, 71 (1977).
3. A. F. Bekhli and N. P. Kozyreva, Khim. Geterotsikl. Soedin., No. 2, 294 (1969).
4. E. F. Elslager, E. H. Gold, F. H. Tendick, et al., J. Heterocyclic Chem., 1, 6 (1964).
5. E. F. Elslager and F. H. Tendick, J. Med. Pharm. Chem., 5, 1149 (1964).
6. E. F. Elslager, R. E. Bowman, and F. H. Tendick, J. Med. Pharm. Chem., 5, 1159 (1964).
7. P. E. Thompson, Am. J. Trop. Med. Hyg., 10, 335 (1961).
8. K. S. Topchiev and A. G. Bekhli, Dokl. Akad. Nauk SSSR, 55, 635 (1947).
9. F. Y. Wiselogle (editor), A Survey of Antimalarial Drugs, Vol. 2, Ann Arbor (1946), p. 1146.
10. Belgian Patent No. 612207, 1962. Chem. Abstr., 58, 9099d (1963).
11. Belgian Patent No. 645602, 1964. Chem. Abstr., 63, 11587g (1965).
12. French Patent No. M 1695, 1963. Chem. Abstr., 61, 5667n (1964).
13. French Patent No. M 2905, 1963. Chem. Abstr., 63, 16267c (1965).