HALOGEN DERIVATIVES OF IMPERIALINE AND THEIR MUSCARINOLYTIC ACTIVITY

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The halogenation of imperialine has given 3α-chloroimperialine, 3β-chloroimperialine, 3α,6,6-trichloroimperialine, and 3β-bromoimperialine. 3β-Chloroimperialine was identical with a known chloroimperialine. The structures of the new compounds have been established. Their muscarinolytic activities have been determined.

We have revealed a high M_2-choline-blocking activity in the alkaloid imperialine (**1**), which is the main alkaloid of the plants *Petilium eduardi* and *P. raddeana*, and also in a series of its derivatives, including esters [1, 2]. Our task was to synthesize and to determine the choline-blocking activities of a series of halogen-containing imperialine derivatives. The halogenation of imperialine [3-5] with the halogenating reagents phosphorus pentachloride and a mixture of hydrochloric and acetic acids in the solvents chloroform and benzene led to imperialine derivatives with mp 215-217°C, $C_{27}H_{42}ClNO_2$ (M^+ 447) (**2**); 203-205°C, $C_{27}H_{42}ClNO_2$ (M^+ 447) (**3**); and 187-189°C, $C_{27}H_{42}Cl_3NO$ (M^+ 501) (**4**), and bromoimperialine with mp 194-197°C, $C_{27}H_{42}BrNO_2$ (M^+ 492) (**5**). The IR spectra of (**2**), (**3**), and (**5**) showed a narrow absorption band of a hydroxy group and the presence of *trans*-quinolizidine and carbonyl groups. There was no absorption band of a carbonyl group in the IR spectrum of (**4**).

In its composition and melting point, the chloroimperialine (**3**) corresponded to the chloroimperialine obtained by T. T. Chu and J. Loh [6], but these authors did not establish the orientation of the chlorine in it. Compounds (**2**), (**4**), and (**5**) were new. The chemical shifts of the protons of the halogen derivatives of imperialine are given below (δ, ppm).

TABLE 1

Substance	$19-CH_3$, s	$21-CH_3$, s	$27-CH_3$, d(J, Hz)	20−OH, m	3−CH−Hal, m ($W_{1/2}$,Hz)
3α-Chloroimperialine (**2**)	0.66	0.98	1.01 (7)	3.35	4.50 (8)
3β-Chloroimperialine (**3**)	0.71	0.98	1.01 (7)	3.33	3.70 (20)
3α,6,6-Trichloro-imperialine (**4**)	0.92	0.99	0.98(7)	3.36	4.57(8)
3β-Bromoimperialine (**5**)	0.71	0.98	1.01 (7)	3.38	3.87(20)

In the case of compound (**4**), the absence of an absorption band of the carbonyl group in the IR spectrum, the presence of an ion with a molecular mass of 501 (M^+) in the spectrum, and a downfield shift of the signal of the protons of the $19-CH_3$ group by 25 Hz in the PMR spectrum as compared with that of imperialine [7] showed that the two chlorine atoms in (**4**) were present at C-6. A comparison of the chemical shifts of the $19-CH_3$, $21-CH_3$, and $27-CH_3$ methyl groups with the analogous values for imperialine [7] showed a displacement of the signals from the protons of the $19-CH_3$ group (Table 1), which proved the substitution of the hydroxyl at C-3 in the imperialine molecule (**1**) by the halogen. Multiplets at 4.50 and 4.57 ppm in (**2**) and (**4**), each with a half-width $W_{1/2}$ = 8 Hz, and at 3.70 and 3.87 ppm in (**3**) and (**5**) each with a half-width $W_{1/2}$ = 20 Hz showed that the halogen atoms in (**2**) and (**4**) were oriented α-axially and those in (**3**) and (**5**) β-equatorially [8].

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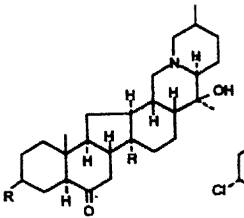
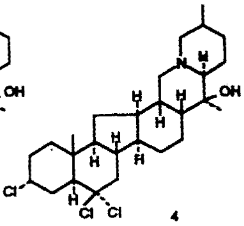
On the basis of the facts given, (2) has the structure of 3α-chloroimperialine, (3) 3β-chloroimperialine, (4) 3α,6,6-trichloroimperialine, and (5) 3β-bromoimperialine.

A comparison of the pharmacological activities of the halogen derivatives of imperialine with the standard M-blocker atropine (6) showed that they, just like imperialine, retained a high tropicity for the M_2-subtype of choline blocker. In the degree of expression of antagonism to carbocholine bradycardia, the compounds mentioned can be arranged in the following sequence: (2), (3), (4), (6), (5).



1.R=OH; 2.R=αCl
3.R=βCl; 5.R=βBr



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EXPERIMENTAL

The IR spectra of the compounds under investigation were recorded on a UR-20 spectroscope in the 3700-700 cm^{-1} region in tablets with potassium bromide, and the mass spectra on an MKh-1310 mass spectrometer with double-focussing and a system for direct injection of the sample into the ion source, at an ionizing energy of 40-70 eV and a temperature of 100-170°C.

PMR spectra were taken on a Tesla B5 567 A/100 MHz instrument ($CDCl_3$, δ, ppm). HMDS was used as internal standard.

3α-Chloroimperialine (2) and 3α,6,6-Trichloroimperialine (4). In small portions, 9 g of phosphorus pentachloride was added to a cooled solution of 4 g of imperialine in 200 ml of chloroform. Then the mixture was poured into cooled water, and the solution was made weakly alkaline with ammonia and extracted with chloroform. The chloroform layer was separated off and distilled in vacuum. The resulting mixture of products was separated on a column of silica gel (125-250 μm) and was eluted with hexane—chloroform—methanol (10:1:1), the eluate being collected in 15- to 20-ml fractions. 3α,6,6-Trichloroimperialine (4) (0.12 g) with mp 187-189°C (hexane—acetone) was isolated from the initial eluates, and from the later ones α-chloroimperialine (2) (1.52 g) with mp 215-217°C (acetone). IR spectrum of compound (2) (KBr, ν, cm^{-1}): 3485 (OH), 2990-2810 (—CH_2—CH3), 2785 (*trans*-quinolizidine), 1710 (C=O). Mass spectrum, *m/z*: 447 (M^+), 429, 428, 431, 411, 410, 389, 375, 150, 151, 155, 139, 112 (100%), 111, 98. IR spectrum of (4) (KBr, γ, cm^{-1}): 3460 (OH), 2985-2805 (—CH_2—CH_3), 2780 (*trans*-quinolizidine). Mass spectrum, *m/z*: 501 (M^+), 486, 483, 324, 155, 149, 112 (100%), 111, 98.

3β-Chloroimperialine (3). A solution of 12 g of imperialine in 30 ml of acetic acid was treated with 30 ml of hydrochloric acid, and the mixture was heated for 3 h. After cooling, it was made alkaline with ammonia and extracted with chloroform. The chloroform solution was concentrated and acetone was added. This led to the crystallization of a mixture of crystals of imperialine and (3). After the separation of the mixture of crystals, the mother solution was chromatographed on a columnn of silica gel (125-250 μm). Elution with chloroform—methanol (100:1) yielded, first, 3β-chloroimperialine (3) (5 g), mp 203-205°C (acetone), and then imperialine (0.5 g).

IR spectrum of compound (3) (KBr, ν, cm^{-1}): 3490 (OH), 2990-2810 (—CH_2—CH_3), 2790 (*trans*-quinolizidine), 1710 (C=O). Mass spectrum, *m/z*: 447 (M^+), 429, 428, 411, 410, 404, 366, 150, 151, 112 (100%), 111, 98.

3β-Bromoimperialine (5). With heating, 1 g of imperialine was dissolved in 200 ml of benzene, and, after part of the benzene had been distilled off, 1 ml of acetic acid and, dropwise, 20 ml of hydrobromic acid were added to the reaction mixture. This was cooled, made alkaline with ammonia, and extracted with chloroform. After the chloroform had been distilled off, the residue was separated on a column of silica gel (125-250 μm) in the chloroform—methanol (100:1) system. The initial fraction yielded 3β-bromoimperialine (5) (0.1 g) with mp 194-197°C. IR spectrum (KBr), ν, cm^{-1}): 3500 (OH), 2990-2820

($-CH_2-CH_3$), 2790 (*trans*-quinolizidine), 1715 (C=O). Mass spectrum, *m/z*: 491 (M^+), 476, 472, 411, 354, 150, 112 (100%), 111, 98.

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