PREPARATION AND ANTIBACTERIAL ACTIVITY OF CERTAIN 9-METHYLAMINO-7-NITROACRIDINE DERIVATIVES

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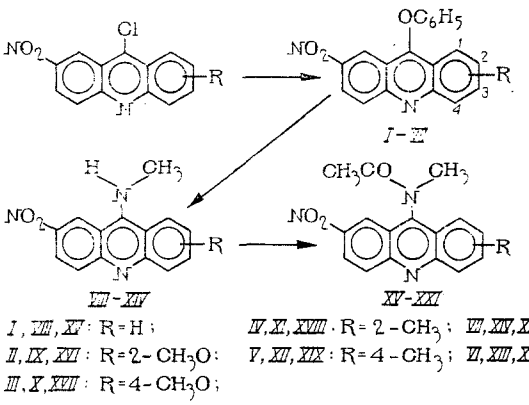
We have previously found [1, 2] that substituted acridines showing a broad spectrum of antimicrobial action could inhibit the growth of Bacillus pyocyaneus, which is resistant to a number of medicinal preparations commonly employed in dermatological practice. We established further that the antibacterial activity of such acridine derivatives depended not only on their structure but also on the nature of the vehicle carrying them: The composition of the ointment base to a marked degree could intensify or minimize their effect [1]. Bearing in mind the possibility of the use of substituted acridines in dermatological practice, we have now further developed our work on the antimicrobial activity of nitroacridines [2, 3] by preparing 9-methylamino-7-nitroacridine (VIII), its 2- and 4-methoxy-, methyl-, and chloro-derivatives (IX-XIV), and the seven N-acetyl derivatives (XV-XXI) of these compounds, in accordance with the following scheme:



I, VIII, XV: R=H;
II, IX, XVI: R=2-CH_3O;
III, X, XVII: R=4-CH_3O;
IV, XI, XVIII: R=2-CH_3;
V, XII, XIX: R=4-CH_3;
VI, XIII, XX: R=4-Cl
VII, XIV, XXI: R=2-Cl

Our starting materials were 9-chloro-7-nitroacridine and its 2- and 4-methoxy-, methyl-, and chloro-derivatives [4, 5, 6]. These, on heating with an excess of phenol, gave the corresponding 9-phenoxy derivatives (I-VII) which, on treatment with methylamine hydrochloride in a phenol medium, furnished the methylamino-derivatives (VIII-XIV). Acylation with an excess of acetic anhydride in pyridine then afforded 9-acetylmethylamino-7-nitroacridine (XV) and its methoxy-, methyl-, and chloro-derivatives (XVI-XXI) (Table 1).

The IR spectra of (VIII-XIV) exhibited an intense, constant-frequency band at 1590 cm^{-1}. This band, absent from the spectra of (XV-XXI), can evidently be regarded as being the result of deformation vibrations of the N-H grouping. In the region of N-H stretching vibrations of compounds VIII-XIV there is a single band at 3440-3450 cm^{-1}. Intense bands at 1680-1690 cm^{-1}, attributable to the carbonyl group, could be distinguished in the spectra of (XV-XXI). The spectra of compounds (VIII-XXI) showed intense,

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TABLE 1. Derivatives of 7-Nitroacridine

Compound	Yield, %	mp (in deg)	Found N, %	Empirical formula	Calc. N, %
I	80	190—1	8,90	$C_{19}H_{12}N_2O_3$	8,86
II [4]	80	172—3	8,12	$C_{20}H_{14}N_2O_4$	8,08
III	72	280 (sinters)	8,10	$C_{20}H_{14}N_2O_4$	8,08
IV	79	187—8	8,47	$C_{20}H_{14}N_2O_3$	8,45
V	70	229—30	8,49	$C_{20}H_{14}N_2O_3$	8,45
VI	73	191—3	8,02	$C_{19}H_{11}ClN_2O_3$	7,98
VII	74	229—30	8,00	$C_{19}H_{11}ClN_2O_3$	7,98
VIII	78	210—2	16,67	$C_{14}H_{11}N_3O_2$	16,60
IX	80	222—4	14,87	$C_{15}H_{13}N_3O_3$	14,84
X	76	248—50	14,89	$C_{15}H_{13}N_3O_3$	14,84
XI	80	220—2	15,78	$C_{15}H_{13}N_3O_2$	15,72
XII	68	258—60	15,74	$C_{15}H_{13}N_3O_2$	15,72
XIII	82	222—4	14,65	$C_{14}H_{10}ClN_3O_2$	14,60
XIV	78	248 (sinters)	14,62	$C_{14}H_{10}ClN_3O_2$	14,60
XV	72	280	14,30	$C_{16}H_{13}N_3O_3$	14,24
XVI	70	208—10	12,96	$C_{17}H_{15}N_3O_4$	12,93
XVII	69	266—7	12,95	$C_{17}H_{15}N_3O_4$	12,93
XVIII	73	255—6	13,62	$C_{17}H_{15}N_3O_3$	13,59
XIX	67	254—5	13,64	$C_{17}H_{15}N_3O_3$	13,59
XX	70	257—8	12,80	$C_{16}H_{12}ClN_3O_3$	12,74
XXI	68	236—8	12,78	$C_{16}H_{12}ClN_3O_3$	12,74

Note: Compounds (I-VII) were crystallized from benzene; (VIII-XIV) from aqueous DMF; (XV-XXI) from ethanol.

TABLE 2. Composition of Ointment Bases (in grams)

Ingredients	Ointment base No.				
	1	2	3	4	5
Distilled water	—	37,0	36,0	37,0	47,0
Glycerol	—	5,0	—	5,0	5,0
Dimethyl sulfoxide	—	10,0	—	—	—
Mineral oil	—	—	25,0	—	—
Olive oil	—	10,0	—	10,0	10,0
Nipagin	—	—	0,15	—	—
Nipasol	—	—	0,25	—	—
OS-20	—	4,0	—	4,0	4,0
PEG-400	80,0	—	12,0	—	—
PEG-1500	20,0	30,0	—	30,0	30,0
Volatile fraction of sperm-whale oil alcohols	—	—	25,0	—	—
Tween-80	—	—	2,0	—	—
Emulsified waxes	—	4,0	—	4,0	4,0
Ethyl cellosolve	—	—	—	10,0	—

Note: OS-20 — Hydroxyethylated volatile fractions from sperm oil alcohols with 20 ethylene oxide molecules; PEG-400 and PEG-1500 — polyethyleneglycol with 10 and 35 ethylene oxide molecules, respectively; emulsified waxes — potassium salts of phosphoric acid esters of lower-boiling fractions from sperm oil alcohols.

constant-frequency bands corresponding to the nitro group; [1305-1310 cm^{-1} for (VIII-XIV), and 1345-1350 cm^{-1} for (XV-XXI)] and unsymmetrical (1490-1495 cm^{-1}) stretching vibrations of the NO_2 group [7, 8]. The fall in frequency of the stretching vibrations of the nitro group in the compounds studied as compared with similar frequencies in the 6-nitro analogs [3], is caused by the marked conjugation between the electron-donating 9-methylamino grouping and the 7-nitro group.

Antimicrobial activity in the compounds (VIII-XIV) was assessed, using the serial dilution method, by their action on Bacillus pyocyaneus and Staphylococcus 209P. The bacteriostatic action was determined after inoculated media had been kept in the thermostat at 37°C for 24 h (with subsequent seeding into sectors of meat-peptone agar). For each of the compounds (VIII-XIV) the minimum bacteriostatic concentration against B. pyocyaneus was 1:250; against Staphylococcus 209P however, the minimum bacterio-

TABLE 3. Antimicrobial Activity of 7-Nitroacridine Derivatives Incorporated in 1% Ointments Using Various Ointment Bases

Compound	Ointment base No.			
	1		2	
	a	b	a	b
VIII	17,7	19,3	12,0	14,3
IX	—	13,7	—	11,3
X	—	13,7	—	18,3
XI	17,3	12,7	15,0	—
XII	17,0	15,3	—	12,7
XIII	15,3	16,7	—	14,0
XIV	—	11,7	—	16,0
B	17,7	14,3	15,0	12,7
Ts	20,7	—	15,3	10,7

Note: a) Zone of growth-inhibition of Staphylococcus 209 P (mm); b) zone of growth-inhibition of B. pyocyaneus (mm); B) boric acid; Ts) tsiminal In all experiments the mean error of the arithmetic means was ±0.3 mm.

static conconcentrations were 1:250 for (XII), (XIII), and (XIV); 1:500 for (X); and 1:16,000 for (VIII), (IX), and (XI).

Since the ointment bases play an important part in the pharmacodynamics of these preparations and can profoundly influence their efficacy, the antimicrobial activity of the compounds (VIII-XXI) was also determined by measuring their diffusion from ointments into an agar gel containing Staphylococcus 209P or B. pyocyaneus, and comparing this with the activity of boric acid and of tsiminal. In a number of ointment bases 1% ointments of the test compounds were studied (Table 2). In the experimental procedure use was made of the microbiological test described in [9-12]. The size of the growth-inhibition zone of the microorganism was determined after incubation in a thermostat at 37° for 24 h. Experiments with each type of ointment were in quadruplicate, and arithmetic means of zone diameters were processed for experimental error by the mathematico-statistical method of [13].* The results are shown in Table 3.

The diffusion of the test compounds, and hence also their antimicrobial activity, is determined in large part by the nature of the ointment base, and the results show that much the most suitable in this respect were the water-soluble base No. 1 and the emulsified base No. 2 (Table 2). All the compounds studied (VIII-XXI) were practically wholly immobilized in ointment bases Nos. 3, 4, and 5. As regards antimicrobial effect, compounds (VIII), (XI), and (XII) proved to be the most highly active, but none of the acetylated compounds, (XV-XXI), showed any activity at all.

EXPERIMENTAL METHOD

The IR spectra were obtained using a spectrophotometer unit UR-20 fitted with lithium fluoride and sodium chloride prisms.

7-Nitro-9-phenoxyacridines (I-VII). A mixture of the appropriate chloracridine (6.5 g) and phenol (15 g) was stirred and heated at 100° for 30 min. The cooled mass was treated with a 10% solution of sodium hydroxide, and the resulting precipitate filtered off, washed with water, dried, and recrystallized.

9-Methylamino-7-nitroacridines (VIII-XIV). The appropriate phenoxyacridine (6.8 g) was dissolved in phenol, and the solution stirred and treated with methylamine hydrochloride (2.5 g). The temperature was then rapidly raised to 105-110°, and the stirring continued at this temperature during 1.5 h. The cooled mass was treated with a 10% solution of sodium hydroxide, and the resulting precipitate washed with water, dried, and recrystallized.

9-Acetylmethylamino-7-nitroacridines (XV-XXI). Each of the preceding products, (VIII-XIV), (5 g) was dissolved in pyridine (15 ml), and the solutions treated with freshly distilled acetic anhydride (10 ml) and heated under reflux at 120-130° during 2 h. The mixtures so obtained were poured out into warm water, and the resulting precipitates filtered off, washed first with a 5% solution of sodium bicarbonate then with water, and finally dried and recrystallized.

*References [12] and [13] are not given in the original — Consultants Bureau.

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