SEARCH FOR NEW DRUGS

PREPARATION AND PHARMACOLOGICAL EXAMINATION OF DERIVATIVES OF (ACRIDINYL)(HETERYL)METHANE

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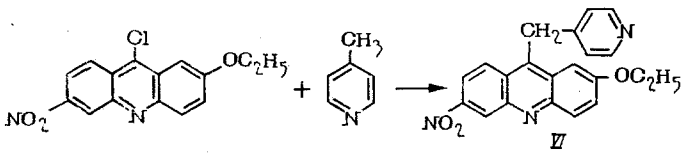
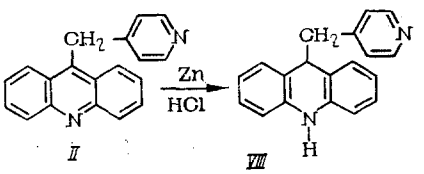
Acridine derivatives are well known to present a broad spectrum of physiological activity. We may mention, in particular, the psychotropic effects exercised by some compounds of this type [1, 2] and the analgesic properties found in other such cases [3, 4]. It therefore seemed of interest to make a study of the pharmacological properties of other compounds belonging to this species, and we chose the (acridinyl)-(heteryl)methanes and their derivatives, obtained by a method previously described [5].

In the present paper we report on the properties of the dihydrochlorides of (pyridyl-2)- (I) and (pyridyl-4)(acridinyl-9)methane (II), of the bases (quinolyl-2)- (III) and (quinolyl-4) (acridinyl-9)methane (IV), as well as of certain analogously constituted 2-ethoxy-6-nitroacridine derivatives obtained by condensing 9-chloro-2-ethoxy-6-nitroacridine with a methylheterocycle, e.g.,



Also examined was the methiodide (VII) of (VI) (obtained from the latter by treatment with methyl iodide) and (pyridyl-4)(9,10-dihydroacridinyl-9)methane (VIII) prepared by reducing (II) with zinc and hydrochloric acid:



Experiments with the compounds so obtained were carried out using white mice and rats, the preparations being administered intraperitoneally (ip).

Tranquilizing effects of the compounds were assessed in four ways: (a) by their influence on body temperature; (b) by their influence on movement coordination [6]; (c) by the degree of their inhibition of the animals' intended movements (as judged in, e.g., network-grid climbing experiments); and (d) by their ability to counteract the effects either of Corazol (pentamethylenetetrazole), on the one hand, or of hypnotic agents, on the other.

Analgesic properties of the test compounds were adjudged by the extent to which they could raise the pain-sensitivity threshold against three types of pain stimulus: (a) electrical, (b) thermal [7], and (c) mechanical [8]. [The electrical shocks in (a) were administered by alternating 0.1 msec pulses of constantly increasing amplitude].

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TABLE 1. Pharmacological Activity in a Series of (Acridinyl)-(Heteryl)Methane Derivatives†

Compound	LD_{50} (mg/kg)	Dose (mg/kg)	Change in body temperature: deviation from normal (°C)	Dislocation of animals' reactions in intended movement experiments (%)	Duration of chloral hydrate hypnosis (min)		Alternation in (electrical) pain-sensitivity threshold: deviation from normal (mA)
					control (untreated animal)	effect of test compound	
Control (untreated animal)			—0,8±0,49	0			—0,01±0,1
I	1000	200	—2,3±0,31*	0	75±9,2	121±13,3*	0
II	175	35	+0,1±0,42	0	82±13,7	125±7,9*	+0,32±0,08*
III	1000	200	—3,3±0,19*	0	82±13,7	104±16,0	+0,46±0,17*
IV	1000	200	—2,0±0,12*	0	63±2,36	89±6,2*	+0,44±0,1*
V	1000	200	—3,3±0,34*	83	107±10,7	145±7,3*	+0,16±0,11
VII	100	140	—2,7±0,25*	83	107±10,7	152±7,2*	+0,52±0,13

*Difference from control within limits of probable error as calculated at $P < 0.05$.

†The experimental procedure was to use six animals per experiment.

A number of the compounds examined showed some slight tranquilizing properties at 35-200 mg/kg dose levels. Thus, the compounds (I), (II), (IV), (V), and (VII) lowered the temperature of the rectum by 2-3.3°C. The last two of these preparations [(V) and (VII)] could, in addition, inhibit the animals' intended movements. None of the compounds studied interfered with movement coordination, and none acted as a Corazol antagonist. The compounds (II), (III), (IV), and (VII) exercised a weak analgesic action as evidenced by their ability, 30 min after introduction, to raise the pain-sensitivity threshold against electrical irritation (see Table 1); on the other hand, the same four compounds were unable to counteract the effects of thermal or mechanical irritants [except, that is, compound (IV) which raised the pain threshold in hot-plate experiments by a factor of 1.5]. Compound (II) was toxic, having an LD_{50} of 175 mg/kg (ip in mice); the other preparations under investigation were for the most part of low toxicity.

Physiological activity in this series of compounds is determined neither by the nature of the heteryl residue attached to the acridine nucleus nor by modifications in the latter moiety (such as introduction of substituent groups or reduction to the acridine condition). In this connection, the action of (II) should be compared with that of (VII), and, similarly, (IV) should be compared with (V). Finally, the pharmacological properties of the bases are not distinct from those of their water-soluble salts.

It may therefore be presumed that the observed physiological properties in this group of compounds must be attributed to the presence of the (acridinyl)(heteryl)methane structure itself.

EXPERIMENTAL

(Quinolyl-2)- (III) and (Quinolyl-4)(acridinyl-9)methane (IV). These two compounds were obtained by the method previously described [5].

(Pyridyl-2)- (I) and (Pyridyl-4)(acridinyl-9)methane (II) Dihydrochlorides. The calculated amount of concentrated hydrochloric acid was added to an alcoholic solution of the base, in each case. The resulting crystalline precipitates were filtered off and recrystallized from ethanol. Dihydrochloride (I) had mp 242-245°. Found %: N 8.21. Its isomeride (II) had mp 235-238°. Found %: N 7.78. $C_{19}H_{14}N_2 \cdot 2HCl$. Calculated %: N 8.12.

(Quinolyl-4)(2-ethoxy-6-nitroacridinyl-9)methane (V). A mixture of 9-chloro-2-ethoxy-6-nitroacridine (1.52 g) and lepidine (2.15 g) in anhydrous butanol (5 ml) was boiled for 15 min, then placed on a boiling water bath for 2 h, and finally cooled. The resulting deposit was filtered off, washed with butanol, and recrystallized from pyridine. Yield, 1.6 g (78%), mp 252-254°. Found %: C 72.9; H 4.7; N 10.4. $C_{25}H_{19}N_3O_3$. Calculated %: C 73.3; H 4.8; N 10.3.

(Pyridyl-4) (2-ethoxy-6-nitroacridinyl-9)methane (VI). A mixture of 9-chloro-2-ethoxy-6-nitroacridine (1 g) and 4-picoline (1.53 g) in anhydrous butanol (5 ml) was boiled for 1.5 h and then cooled. The resulting deposit was filtered off, washed with ethanol, and crystallized from a 2N solution of hydrochloric acid. The material so obtained was dissolved in water, treated with aqueous ammonia, and the base recovered in this manner recrystallized from butanol. Yield, 0.65 g (54%), mp 234°. Found: C 70.3; H 4.9; N 10.6. $C_{21}H_{17}N_3O_3$. Calculated %: C 70.2; H 4.8; N 10.7.

(Pyridyl-4)(2-ethoxy-6-nitroacridinyl-9)methane Methiodide (VII). A mixture of the preceding compound (VI) (1.2 g) and methyl iodide (3 ml) was boiled in butanol for 1 h. A yellow precipitate had begun to form at the commencement of the operation, and this solid, after cooling, was filtered off and recrystallized from water. Yield, 1.1 g (67%), mp 250-252°. Found %: C 53.0; H 4.1; N 8.8. $C_{22}H_{20}IN_3O_3$. Calculated %: C 52.7; H 4.0; N 8.4.

(Pyridyl-4)(1,2-dihydroacridinyl-9)methane (VIII). The compound (II) (base) (2 g) was dissolved in 20 ml of an 18% solution of hydrochloric acid, treated, in portions, with zinc dust (1.5 g) during the course of 1 h, and then allowed to stand for a further 0.5 h. The mixture was neutralized with aqueous ammonia, and the resulting precipitate filtered off and recrystallized from pyridine. Yield, 1.6 g (80%), mp 196-197°. Found %: C 83.4; H 6.0; N 10.7. $C_{19}H_{16}N_2$. Calculated %: C 83.8; H 5.9; N 10.3.

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