SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 2-OXOFURO[2,3c]PIPERIDINES

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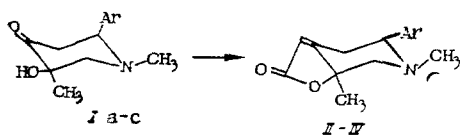
The 2-oxofuro[2,3-c]piperidines are studied very little at the present time. Compounds of this type have been reported to have been prepared by a multi-step synthesis from 4-piperidinones [13] and have been isolated in low yields from the product mixture resulting from the reaction of dichloroketene with pyridine N-oxides [10]. Nevertheless, these compounds may be of interest as intermediate products for the synthesis of other functional derivatives of piperidine as biologically active compounds [13].

The present report is concerned with a study of the pharmacological properties of the previously unknown 2-oxofuro[2,3-c]piperidines (II-IV), which we have prepared by the Wittig–Horner reaction [9] of 3e-hydroxy-4-piperidines (Ia-c) with phosphonoacetic esters.

The structures of the lactones II-IV were established by means of data from elemental analysis and by IR, PMR, and mass-spectroscopy. Thus, their IR spectra showed valence-bond oscillation bands for C=C and C=O at 1640 and 1755 cm^{-1}, respectively, which are characteristic for unsaturated γ-lactones [4]. In the PMR spectrum of compound II the protons of the lactone ring from a doublet ($J_{3,4\alpha}$ = 1.5 Hz) at 5.60 ppm, the 4S and 5S protons of the piperidine ring form an octet at 2.56 ppm and two quadruplets at 2.96 and 3.04 ppm, and the 7S protons form two doublets at 2.26 and 3.42 ppm with spin-spin constants $J_{4e,5\alpha}$ = 3 Hz, $J_{4\alpha,5\alpha}$ = 11 Hz, $J_{4e,4\alpha}$ = 13 Hz, and $J_{7e,7\alpha}$ = 10.5 Hz, which indicates the piperidine ring to be in the chair form with equatorial orientation of the methyl groups on the nitrogen atom [2].



Ia, II: Ar = C_6H_5; Ib, III: Ar = 4-$CH_3C_6H_4$; Ic, IV: Ar = 4′-$CH_3OC_6H_4$

EXPERIMENTAL — CHEMICAL

IR spectra of samples in carbon tetrachloride solution were obtained with a Specord-75 instrument (GDR), and PMR spectra were recorded as 5-10% solutions in carbon tetrachloride or deuteriochloroform with a Tesla BS-567A spectrometer (ChSSR), with hexamethyldisilane as internal standard. Mass spectra were recorded with a Varian MAT-311 instrument (USA) at 70 eV. The mass-spectra of all of the compounds showed molecular ions corresponding to the calculated molecular weight. Physicochemical properties of the synthesized compounds are presented in Table 1.

6e,8a-Dimethyl-2-oxo-5e-arylfuro[23-c]piperidines(II-IV). To a solution of sodium isopropylate, prepared from 0.11 mole of metallic sodium and 50 ml of isopropyl alcohol, was added 0.12 mole of isopropyl diethylphosphonoacetate in 250 ml of methylal, and a solution of 0.1 mole of piperidone Ia-c in 50 ml of methylal was poured in at 20-25°C. The solution was concentrated, and the residue was dissolved in toluene and washed with water. To the solution, dried with sodium sulfate, was added 0.01 mole of sodium isopropylate, and the solution was boiled for 1 h with slow distillation of toluene. The reaction mixture was cooled, washed with water, dried with sodium sulfate, and passed through a layer of L40/100 silica gel. After distillation of part of the toluene, the product was crystallized from a toluene-hexane mixture.

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TABLE 1. Properties of the Synthesized Compounds

Compound	Yield, %	mp., °C	Found, %		Empirical Formula	Calculated, %	
			N	S		N	S
II	70	134—135	5,72	—	$C_{15}H_{17}NO_2$	5,76	—
II·CH_3SO_3H	83	202—203	4,03	9,58	$C_{16}H_{21}NO_5S$	4,13	9,44
III	95	113—114	5,58	—	$C_{16}H_{19}NO_2$	5,45	—
III·CH_3SO_3H	88	193—194	3,70	9,15	$C_{17}H_{23}NO_5S$	3,98	9,07
IV	73	148—149	5,17	—	$C_{16}H_{19}NO_3$	5,13	—
IV·CH_3SO_3H	84	217—218	3,61	8,82	$C_{17}H_{23}NO_6S$	3,79	8,67

6e,8a-Dimethyl-2-oxo-5e-arylfuro[3,3-c]piperidine Methanesulfonates (II·CH_3SO_3H — IV·CH_3SO_3H). The lactones II-IV were dissolved in a minimum quantity of acetone and treated with methanesulfonic acid to a slightly acidic reaction. The resulting methanesulfonates were filtered off and washed with cold acetone.

EXPERIMENTAL—PHARMACOLOGICAL

The pharmacological properties of the methane sulfonates of II-IV were studied in 184 mice and 214 rats.

Acute toxicity determinations were carried out with randomly-bred white mice by intraperitoneal introduction. The toxicity (LD_{50}) was determined by the Miller—Tainter probit analysis method [1]. The influence of the materials on systematic arterial blood pressure was studied in acute experiments on rats narcotized with urethane [3]. An electrocardiogram was recorded simultaneously with the registration of arterial pressure of II [5] to indicate the influence of this material on the bioelectric activity of the heart [6]. The influence of salts of II-IV on the coronary vessels of the heart was studied on isolated white mice hearts. Perfusion of the coronary vessels was carried out by the method of Langendorff [11].

The anti-arrhythmic activity of the synthesized materials was estimated by their influence on the course and result of heart arrhythm activity initiated in rats by the intravenous injection of 10% calcium chloride solution at the rate of 2 ml/kg of animal weight [12]. The anti-inflammatory activity of the methanesulfonates of II-IV was evaluated by their capacity to suppress the development of foot edema in rats induced by the subplantar injection of inflammatory agents as histamine, serotonin and formalin [7]. The latter were introduced in the form of 0.25, 0.5 and 1% solutions, and the test substances were injected intraperitoneally 30 min after injection of the inflammatory agents.

Anti-tumor activity was investigated by means of the effect of the materials on Pliss'-lymphosarcoma [8]. Experimental animal tumors were grafted under the skin. The methanesulfonates of II-IV in the form of 3% suspensions in water, for which Tween-80 was used as a dispersing agent, were introduced every 24 h for 9 days beginning on the second day after the tumor graft. Control animals were injected at the same times with isotopic sodium choride solution.

Study of the pharmacological properties of these compounds as their methanesulfonates II-IV showed that they possessed low toxicity. Their LD_{50} in white mice by intraperitoneal injection was 678, 731, and 812 mg/kg, respectively. Intravenous injection of a 0.1 LD_{50} dose of compounds II-IV lowered the arterial pressure by 47, 63, and 35% with hypotensive durations of 16, 5, and 6 min, respectively. All compounds decreased the frequency of heart contractions by 20-40% of the initial values, while the intensity of the hypotensive reaction indicated bradycardia.

The methanesulfonates II-IV did not show a significant influence on the tonus of the coronary vessel. The liquid volume pumped by the heart was not changed by instantaneous injection of these materials in liquid perfusions at doses of 0.1 and 0.2 μg, nor by perfusion of the heart with concentrations of 10^{-4} and 10^{-5} g/l.

Methanesulfonate II possessed weak anti-arrhthymic activity. After its introduction at a dose of 0.1 LD_{50}, the heart activity (extrasystolia, fibrillation) produced by the injection of calcium chloride was disrupted. This occurred later (by an average of 16 seconds) in the experimental animals than in the controls. Compounds III and IV did not possess antiarrhythmic activity.

The methanesulfonates II-IV moderately (by 23-26%) suppressed the edamatous inflammation produced by subplantar injection of histidine. Compound III furthermore showed antiexudative activity in the serotonin and formalin inflammations, suppressing their effects by 11 and 21%, respectively.

The methanesulfonates II and IV in a dose of one-eighth of the LD_{50} inhibited the growth of a malignant tumor, Pliss' lymphosarcoma by 25% ($P < 0.001$), and at a dosage of 0.25 LD_{50}, by 40% ($P < 0.001$). Compound III did not show this effect.

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