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SYNTHESIS OF 8-ARYLMORPHONES AND 8-ARYLCODONES AND STUDY OF THEIR ANALGESIC ACTIVITY

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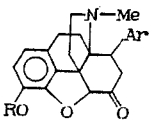
Introduction of substituents into the C ring of morphine alkaloids leads to a substantial change in their analgetic effects [2]. We synthesized several 8-arylmorphones and 8-arylcodones (I-VII) and studied the effect of the introduction of a phenyl and o-, m- and p-methoxyphenyl groups on the analgetic activity of the corresponding morphones and codones. The preparation of 8-arylcodone by the reaction of codeinone with Ph_2CuLi has already been reported in [3], but the physical characteristics of the compound obtained were not given.

The 3-hydroxy- and 3-methoxy-4,5-epoxy-6-oxo-8-aryl-17-methylmorphinanes (I-VII) were synthesized by arylation of morphine and codeine by aryl iodides under conditions for palladium catalysis, similarly to the corresponding reactions of allyl halides with allyl alcohols [5].



I-VII

R = Me (I, III, V, VI), H (II, IV, VII);
Ar = Ph (I, II), C_6H_4OMe-p (III, IV)
C_6H_4OMe-o (V, VII), C_6H_4OMe-m (VI).

EXPERIMENTAL (CHEMISTRY)

The reaction was carried out in MeCN at 80°C at a molar ratio of the reagents: morphine (codeine), ArI, $Pd(OAc)_2$ and Et_3N 125:130:2.2:125. The course of the reaction was monitored by TLC. The physical constants of the compounds obtained are given in Table 1. The data from the elemental analyses correspond to the calculated values.

General Method of Arylation of Codeine or Morphine. A 0.01 mole portion of Et_3N, 40 mg of $Pd(OAc)_2$, and 30 ml of MeCN is added with stirring to 0.01 mole of morphine (codeine); then 0.0104 mole of ArI is added dropwise. At the end of the addition of ArI, the reaction mixture is heated with stirring for 3 h at 80°C in an argon atmosphere. At the end of the

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TABLE 1. Physical Constants of 8-Arylmorphones and 8-Arylmorphones and 8-Aryl-codones I-VII

Compound	Yield, %	mp, °C	Empirical formula	IR spectrum, cm^{-1}		PMR spectrum, δ, ppm
				$\nu_{C=O}$	ν_{OH}	
I	75	160—2	$C_{24}H_{25}NO_3$	1720		2,30 (3H, s, NCH_3); 3,90 (3H, s, OCH_3); 4,85 (1H, C^5-H); 6,67 and 6,73, $^3J_{HH}$ 8,2 Hz (2H, q, C^1-H and C^2-H); 7,25 (5H, m C_6H_5)
II	60	261—3 (dec.)	$C_{23}H_{23}NO_3$	1720	3450	2,30 (3H, s, NCH_3); 4,85 (1H, s, C^5-H); 6,63 and 6,71, $^3J_{HH}$ 8,2 Hz (2H, q, C^1-H and C^2-H), 7,20 (5H, m, C_6H_5)
III	70	186—8	$C_{25}H_{27}NO_4$	1720		2,35 (3H, s NCH_3); 3,80 (3H, s, OCH_3); 3,90 (3H, s, OCH_3); 4,80 (1H, s, C^5-H); 6,67 and 6,73, $^3J_{HH}$ 8,2 Hz (2H, q, C^1-H and C^2-H); 6,81 (4H, q, C_6H_4)
IV	60	284—6	$C_{24}H_{25}NO_4$	1725	3470	2,30 (3H, s, NCH_3); 3,90 (3H, s, OCH_3); 4,85 (1H, s, C^5-H); 6,63 and 6,71, $^3J_{HH}$ 8,2 Hz (2H, q, C^1-H and C^2-H); 6,77 (4H, q, C_6H_4)
V	65	173—5	$C_{25}H_{27}NO_4 \times 0,5\ H_2O$*	1720		2,35 (3H, s, NCH_3; 3,80 (3H, s, OCH_3); 3,90 (3H, s, OCH_3); 4,80 (1H, s, C^5-H); 6,68 and 6,74 $^3J_{HH}$ 8,2 Hz (2H, q, C^1-H and C^2-H) 6,76 (4H, q, C_6H_4)
VI	75	191—3	$C_{25}H_{27}NO_4$	1720		2,35 (3H, s, NCH_3); 3,80 (3H, s, OCH_3), 3,90 (3H, s, OCH_3); 4,80 (1H, s, C^5-H); 6,67 and 6,73, $^3J_{HH}$ 8,2 Hz (2H, q, C^1-H and C^2-H); 6,79 (4H, q, C_6H_4)
VII	60	247—9 (dec.)	$C_{24}H_{25}NO_4 \times 0,5\ H_2O$*	1720	3450	2,30 (3H, s, NCH_3); 3,90 (3H, s, OCH_3); 4,85 (1H, s, C^5-H); 6,71 and 6,77, $^3J_{HH}$ 8,2 Hz (2H, q, C^1-H and C^2-H); 6,81 (4H, q, C_6H_4)

*Water was determined by the Karl Fisher method.

reaction, the mixture is cooled to room temperature, transferred to a separatory funnel, 100 ml of water and 100 ml of $CHCl_3$ are added, and the organic layer is washed with three 100 ml portions of water, and then dried over Na_2SO_4, and the solvent is distilled off. The residue is chromatographed on silica gel containing 30% of water, using $CHCl_3$ as the eluent. The main fraction is recrystallized from a 5:1 mixture of heptane and ethyl acetate.

EXPERIMENTAL (PHARMACOLOGY)

The experiments were carried out on 134 male white mice weighing 18-23 g each. To determine the analgetic activity of the compounds, thermal and mechanical noniceptic irritants were used. In the thermal method, the value of the latent period was recorded from the time of submersion of the animal's tail in water (temperature 49°C) to the moment of withdrawal of the tail. In the mechanical method of irritation, the behavioral reactions of the animal were recorded in response to a pain effect, produced by imposition of a vascular clamp on the root of the tail.

The solutions of the preparations were produced as follows. A mother solution was first prepared, calculated to give 10 mg of the material in 1 ml of the solution. Since all the compounds were water-soluble, a sample of the preparation was first dissolved in 1-2 drops of Tween-60, and then the volume of the solution was brought to 5 ml by adding an isotonic NaCl solution. By successively diluting the solution obtained (1:2, 1:4, 1:10), the entire required series of concentrations was prepared for doses of 10, 25, 50, and 100 mg/kg. All the solutions were administered intraperitoneally in a volume of 0.1 ml per 10 g of the body weight. In each group of 14 animals, a solvent (the isotonic solution with Tween-60) was administered to two mice, while 4 different doses of the preparation were administered to the remaining 12 mice.

After administering the compounds studied, no significant changes in the thermal noniceptic reactions were observed. The degree of analgesia after administration of compounds I-VII varied without any evident regularity in the range from 2 to 15%, while the effect of the standard analgetic morphine is characterized by the analgetic index increasing with time to 94%.

The pain reactions arising in response to mechanical stimulation also did not change after the administration of the preparations. Practically all the animals displayed an intense response to the imposition of the clamp both before and after injection of the preparations. At the same time, the analgetic index of morphine on this model reaches 94% even 15 min after administration, and 100% after 30 min, and remains at this level for 2.5 h. On the background of the preparations studied, the degree of analgesia varied within 8-18%, without increasing either with time or with increase in dose.

In an additional series of experiments, an attempt was made to determine the capability of compounds II-VII to reduce the analgetic effect of a test dose of morphine (30 mg/kg). Morphine was administered subcutaneously, and after 15 min, 25 mg/kg of the compound studied were administered intraperitoneally. Over the period of the first 15 min after the administration of morphine the Schtraub symptom is manifested and does not disappear after the injection of compounds II-VII. The opiate analgesia also did not change under the influence of the compounds studied. On the same model, the opiate antagonist naloxone (0.05 mg/kg, subcutaneously) effectively dispelled the Schtraub symptom and analgesia induced by administration of a test dose of morphine.

The results of the investigation indicate that the compounds studied do not have analgetic activity, and also do not change the analgetic effect of a test dose of morphine.

It is known that a qualitative (acquisition of antagonistic and agonist-antagonistic properties), and a quantitative change in the analgetic effect of morphine are attained during substitution at the 3, 6, 7, 10, 14-positions and also in N-substituted derivatives of morphine [1-4]. A pain alleviating effect on models of physical pain is realized preferentially through μ-opioid receptors. The latter interact primarily with benzene and nitrogen containing moieties of the morphine molecule, and also have about 5 "satellite" fixation regions [4]. It can be assumed that aryl substituents hinder the active interaction of the compound with the receptor by screening some of the regions required for the realization of the signal function of a ligand-receptor interaction. However, the absence of both agonistic and antagonistic properties in the compounds rather indicates a loss of their ability to interact with opioic receptors. The data obtained are of interest for developing molecular principles in search for new morphine-like analgetics on the basis of their perceived interactions with specific receptors.

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