SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF CERTAIN SUBSTANCES WITH β-ADRENO-BLOCKING ACTIVITY

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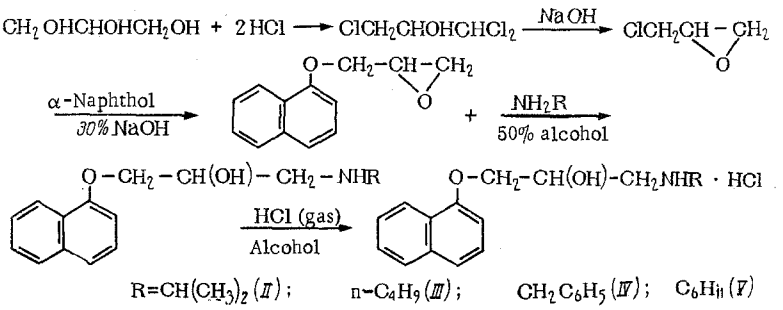
UDC 615.717

In our previous works [1, 2], we cited some experimental data on a study of inetol—one of the specific preparations with β-adreno-blocking action, corresponding to netalide (I)—2-isopropylamino-1-(2-naphthyl)-ethanol hydrochloride. In 1963 Paget [3] reported the appearance of thymus lymphosarcoma after chronic administration of I to mice. In 1965 A. G. Martinenko, who studied the toxicity and carcinogenicity of I synthesized in our Institute (by G. I. Kiprianov) by administering it to mice at a dose of 200 mg/kg for nine months, did not detect any carcinogenic manifestations. Recently data have appeared on the effectiveness and low toxicity of another blocker of the β-adrenoreceptors—inderal [II; propranolol; 1-isopropylamino-3-(1-naphthoxy)-2-propanol]; the preparation is used in the treatment of arrhythmia, cardiac insufficiency, etc. [1, 5, 6]. In a search for new active substances with this kind of activity, we synthesized and studied the pharmacological properties both of II and of its butyl, benzyl, and cyclohexyl derivatives. We have encountered very few data in the literature on methods of producing II and its derivatives. Thus, there is information [7] on the condensation of α-naphthol with N-(3-chloro-2-propanol)isopropylamine or with the epoxide of the corresponding amine, but we did not obtain satisfactory results in multiple repetitions. Therefore, we developed the following accessible scheme of synthesis:



The esterification of α-naphthol with epichlorohydrin was conducted at 30-35° with periodic cooling of the mass with water, and then to complete the reaction the mixture was kept overnight. The epoxide obtained was condensed with the corresponding amine in 50% alcohol, in a 1:3.5 molar ratio at 35-38°. The bases III and IV were not isolated in the crystalline form on account of their oily properties, and were directly converted to the hydrochlorides.

The specific activity was evaluated according to antagonism to stimulation of the β-adrenoreceptors of the blood vessels with isadrin (hypotensive reaction) in experiments on cats. The blocking action of II in a dose of 0.05 mg/kg was manifested with respect to a dose of isadrin of 0.3 μg/kg; correspondingly, II in a dose of 0.15 mg/kg blocked 3 μg/kg isadrin; I in a dose of 1.5 mg/kg blocked 3 μg/kg isadrin; III in a dose of 1 mg/kg blocked 0.75 μg/kg and in a dose of 3-5 mg/kg blocked the action of isadrin in a dose of 3 μg/kg; IV in a dose of 15 mg/kg only partially blocked the action of isadrin in a dose of 3 μg/kg. Doses eliminating the hypotensive response to isadrin when 5 μg/kg of it was administered also eliminated the tachycardia induced by the latter. However, in the case of simultaneous injection of isadrin and injection after the blocker, an increase in the rhythm in comparison with the background, where catecholamine was administered, was always noted, although the final rhythm (after the blocker and catecholamine), as a rule, remain slower than the initial rhythm, before the administration of the two preparations.

Khar'kov Institute of Endrocrinology and Hormone Therapy. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 7, pp. 13-16, July, 1968. Original article submitted January 29, 1968.

In experiments on dogs narcotized with morphine with chloralose at the same dose, the compounds studied prevented a positive inotropic response to a 0.5 μg/kg dose of isadrin, evaluated according to the increase in the amplitude of the complexes of the ballistocardiogram. In doses eliminating the hypotensive effect of isadrin when 3 μg/kg of it was administered, the preparations potentiated the hypertensive response to adrenalin. A quantitative evaluation of I and II indicated that with larger doses of these preparations, the doses of isadrin inducing a hypotensive response and a positive inotropic response increase. The maximum tolerable doses of III, IV, and V did not provide blockage of the response when the isadrin dose was increased. Thus, these substances can be arranged in the following series with respect to decreasing specific activity: II > I > III > V > IV. The action of the first two representatives of this series is prolonged (1.5 h); the action of the following three ends within 20-30 min. The preparations can be arranged in the following series with respect to decreasing activity according to the strength of the antiarrhythmic action in the case of arrhythmias induced with trilene in conjunction with catecholamines (adrenalin or isadrin): II > I > III > V > IV. When the superthreshold arrhythmic doses of catecholamines are increased, the last three preparations in the maximum tolerable doses did not show any antiarrhythmic activity. At the same time, V and III were close to II in antiarrhythmic action in the case of strophanthin arrhythmia in cats and arrhythmia induced by tying off the coronary artery in dogs.

All five compounds induced bradycardia when injected intravenously into atropinized cats, narcotized with urotropinized cats, narcotized with urotropin; however, no relationship could be established between the slowdown of the rhythm and the specific β-blocking activity. The arterial pressure was lowered under the influence of intravenous injection of I (2.5-5 mg/kg) by an average of 31% of the initial value; after II in a dose of 0.5-1 mg/kg, it was lowered only for the period of administration, but then was immediately restored. A similar response was noted after the injection of substances III and V in a dose of 1 mg/kg; compounds IV and V produced a sharp decrease in the arterial pressure in a dose of 5-10 mg/kg.

In a determination of the local anesthetic action (surface anesthesia on the rabbit cornea according to Renier), all the preparations proved active and close in their strength of action. The greatest activity was detected for II and V, the least for IV. In the case of a single internal administration to rats, LD_{50} of II was 515 ± 43 mg/kg, while in the case of slow intravenous injection (in a period of 10 min) it was 45 ± 5.2 mg/kg. The maximum tolerable dose in the case of rapid intravenous injection was equal to 10 mg/kg for rats and rabbits. In the case of a single intraperitoneal injection in mice, LD_{50} was 149 ± 7 mg/kg; the toxicity of I, III, IV, and V in the case of this mode of administration was close to the toxicity of II.

This compound, under the name of "anaprilin," has been approved by the Pharmacological Committee of the Ministry of Health of the USSR for clinical testing in various forms of arrhythmia, stenocardia, etc. The synthesis of anaprilin is described below as an example.

EXPERIMENTAL

Epichlorophydrin was produced according to the method described in [9] from glycerin α, γ-dichlorohydrin [8], the only difference being that the pulverized sodium hydroxide was not screened through a 20-mesh sieve, but was added to the ether solution of the dichlorohydrin in portions through a normal funnel. Bp 115-118°. Yield 70-75%.

Epoxide of the Propyl Ether of Naphthol. A 600-g portion of α-naphthol was added with mixing to a solution of 183 g NaOH in 625 ml of water. After dissolving, the solution was cooled to 10° and 398 g of epichlorohydrin gradually added with mixing. In this case, the temperature of the mixture is maintained no higher than 35° for 6 h, and the mixture is left overnight. On the following day it is extracted with ether, dried with potash, and distilled under vacuum at 190-199° (14 mm [10]. Yield 441 g (50 %).

1-Isopropylamino-3-(1-naphthoxy)-2-propanol. A 400-g portion of the epoxide indicated above was dissolved in 500 ml of 50% alcohol, cooled to 10-15°, and a chilled solution of 372.5 g of isopropylamine in 50% alcohol gradually added. The temperature of the mixture should not exceed 38° in this case. After addition, the mixture is left overnight at room temperature. Then it is poured out into a mixture of water and finely crushed ice. The precipitate formed is filtered off and dried at 60-65°. Mp 92-93° [7]. Yield 483 g (93%).

Hydrochloride of 1-Isopropylamino-3-(1-naphthoxy)-2-propanol (II; Anaprilin). A 188-g portion of the base was dissolved at room temperature in 800 ml of absolute alcohol and saturated with dry HCl gas with ice water cooling. Then the solution was poured out into 3.5 liters of dry ether. On the following day

the precipitate was filtered off, washed with dry ether, and dried at 100-110°. Mp 162-163°. Yield 431 g (84-85%). Anaprilin represents an odorless white powder, with a bitter taste, readily soluble in water, moderately soluble in alcohol, poorly soluble in ether and benzene. Found, %: N 4.83, 4.85. $C_{16}H_{22}O_2NCl$. Calculated, %: N 4.73. The following were obtained in the same way: hydrochloride of III, mp 163-164°. Found, %: N 4.52, 4.74. $C_{17}H_{24}O_2NCl$. Calculated, %: N 4.52. Hydrochloride of IV, mp 168-169°. Found %: N 4.36, 4.48. $C_{20}H_{22}O_2NCl$. Calculated, %: N 4.07. V, mp 78-80°. Hydrochloride of V, mp 201-202°. Found, %: N 4.84, 4.73; Cl 10.51, 10.52, $C_{19}H_{26}O_2NCl$. Calculated %: N 4.16; Cl 10.55.

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