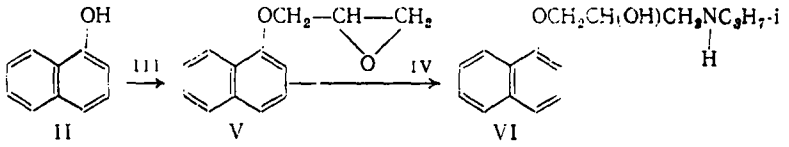
EPOXYALKYLATION OF α-NAPHTHOL UNDER INTERPHASE CATALYSIS CONDITIONS

I. M. Gella

UDC 615.217.012.1.002.62

The known β-adrenoblocking agent anapriline, 1-isopropylamino-3-(1-naphthoxy)-2-propanol hydrochloride (I) is usually obtained by successive condensation of α-naphthol (II) with epichlorohydrin (III) and isopropylamine (IV) [1-4].



The yield of the intermediate 1-(1-naphthoxy)-2,3-epoxypropane (V) is 50-60%, and the isolation of (V) by vacuum distillation is accompanied by the formation of a considerable amount of difficultly removable residue in the still. It was proposed [1] to prepare anapriline base (VI) without isolation of (V) from the reaction mixture, but the data given for the almost quantitative yield of (VI) are not reproducible. The presence of considerable amounts of resinous impurities in crude (V) prevents the isolation of base (VI) in fairly pure state. Nevertheless, by using unpurified (V), the technological preparation of (I) could be substantially simplified. It is clear that combination of the preparation of (V) and its reaction with (IV) is possible only if the yield of (V) is substantially increased and the content of the resinous products in the reaction mixture is decreased.

The epoxyalkylation of several phenols proceeds in high yield under interphase catalysis conditions [6], but during the epoxylation of (II) in a CH_2Cl_2—aqueous alkali system, in the presence of triethylbenzylammonium chloride (TEBAC), the yield of (V) was not more than 40%. The reaction was accompanied by the formation of a considerable amount of dinaphthoxymethane, due to the reaction of (II) with the solvent. It could be assumed that if the reactions were carried out in an inert solvent the yield of (V) would be increased. However, replacement of methylene chloride by toluene did not lead sufficiently to an increase in the yield of (V) (see Table 1).

In recent years it was found that, in addition to the quaternary onium salts and crown ethers, poly(ethylene glycols) (PEG) with molecular weight of 600 and higher can serve as effective phase transition catalysts (PCT) [5]. An important, distinctive feature of PEG and poly(ethylene oxides) (PEO) is their availability and low cost. We therefore studied the condensation of (II) with (III) in the presence of PEG with molecular weights from 400 to 2000.

TABLE 1. Reaction Conditions in Preparation of 1-(1-Naphthoxy)-2,3-epoxypropane (V) and Yield of Product

PTC	Amount of PTC, g per mole of (II)	Reaction temperature, °C	Yield of (V), %
TEBAC	5	40	32
TEBAC	5	60	55
—	—	70—75	70
PEG-600	6	70—75	75
PEG-2000	5	60—70	74
PEG-1500	10	65—70	85
PEG-400	10	70—75	77
PEG-400	15	70—75	86
PEG-600	25	82—88	75
PEG-600	25	65—70	87

Note. In experiments with TEBAC, toluene was used as the solvent [500 ml per mole of (II)].

Kharkov Scientific-Research Institute of Endocrinology and Hormone Chemistry. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 6, pp. 730-732, June, 1986. Original article submitted February 19, 1985.

 0091-150X/86/2006- 0430$12.50

In experiments without a catalyst it was found that carrying out the epoxyalkylation reaction in an excess of (III) promotes increase in the yield of (V), and therefore the influence of PEG on the yield of (V) was studied only in an excess of epichlorohydrin. At the end of the reaction, the excess of (III) is easily removed by steam distillation, and the distillate of (III), after the separation of water, is suitable for repeated use.

Carrying out the epoxyalkylation reaction in the presence of PEG in an amount of 3.5-4% of (II) used leads to an increase in the yield of (V) to 75%. Increase in the amount of the PTC to 7-10% increases the yield of (V) to 85-87%, while further increase in the amount of PCT practically does not affect the yield of the desired end product. It should be noted that to attain an equal catalytic effect, a somewhat greater amount of PEO-400 is required than of, for example, PEO-1500.

The course of the reaction of (II) with (III) is noticeably influenced by the temperature. It has been noted in [2] that under basic catalysis conditions (triethylamine in butanol), the reaction proceeds at a fair rate at 60-80°C. It is possible that this temperature range is optimal, since decrease of the temperature to 50-60°C noticeably increases the reaction time, while increase of the temperature to 80°C and higher leads to a decrease in the yield of (V) (see Table 1).

Thus, by carrying out the epoxyalkylation of (II) in an excess of (III) using PEG as the PTC, the yield of (V) can be increased from 50-60 to 85-86%. This raises the possibility of developing a one-step method for the preparation of base (VI) without the isolation or purification of the intermediate epoxide (V).

EXPERIMENTAL

The PTC used in the investigation were PEG-600 (from Loba Chemie), PEG-2000 (from Merck, GFR), PEO-400 (FS 42-1242-79) and PEO-1500 (FS 42-1885-82).

1-(1-Naphthoxy-2,3-epoxypropane (V). A 41 g portion of sodium hydroxide in the form of a 45% aqueous solution is added in the course of 25-30 min, with stirring, to a solution of 144 g of (II), and 10-15 g of poly(ethylene glycol) in 200 ml of epichlorohydrin; the temperature of the reaction mixture thus rises to 70-75°C. A more rapid addition of the alkali solution may lead to boiling up and overflowing of the reaction mixture. Stirring is continued for 1.5-2 h to a complete clarification of the reaction mixture, and the excess of (III) is steam-distilled. The contents are transferred from the flask into a separatory funnel, the lower organic layer is separated, washed twice with distilled water, and distilled in vacuo. The main fraction is collected at 192-196°C (6 mm). The yield of (V) is 154-172 g.

LITERATURE CITED

1. Inventor's Certificate No. 318561 (USSR); Otkrytiya, No. 32 (1971).
2. B. A. Mamedov, A. V. Ragimov, and Ch. O. Ismailova, Azerb. Khim. Zh., No. 6, 47-52 (1983).
3. USSR Patent No. 322880; Otkrytiya, No. 36 (1971).
4. I. B. Simon, V. P. Vvedenskii, and V. Ya. Gorodinskaya, Khim. farm. Zh., No. 7, 13-16 (1968).
5. J. M. Harris, N. H. Handley, T. G. Shannon, and E. C. Struck, J. Org. Chem., 47, 4789-4791 (1982).
6. A. McKillor, J.-C. Fiaud, and R. P. Hug, Tetrahedron, 30, 1379-1382 (1974).