IMPROVING METHODS FOR THE PRODUCTION OF p-OXYPROPIOPHENONE

N. I. Men'shova and V. I. Maksimov

UDC 615.012.1:547.572.1]002.62.

The conditions for the regrouping of the phenol ester of propionic acid in various solvents are studied with the object of increasing the yield of the p isomer of oxypropiophenone, this being the initial product in the industrial synthesis of diethylstilbesterol. p-Oxypropiophenone is generally produced by condensation of phenol and propionic acid hydrochloride and subsequent regrouping of the Fris ester formed. The various conditions for the regrouping of the phenol ester of propionic acid are known: i.e., heating in the presence of $ZnCl_2$ at 155° to give p-oxypropiophenone, but in only 12% yield [1]; heating at 120-130° in the presence of anhydrous $AlCl_3$ without a solvent to give the p isomer in 50-55% yield [2]. The yield of the p isomer can be significantly increased (up to 85%) by using BF_3 as catalyst [3].

Regrouping and subsequent decomposition of the reaction mass is facilitated in the presence of a solvent. However, few data are available on the ratio of the isomers formed in the regroupings carried out in various solvents. It has already been shown [4] that in regrouping the phenol ester of caprylic acid in the presence of anhydrous $AlCl_3$ at 70° the relative quantity of p-oxyketone formed in nitrobenzene as medium is greater than in tetrachloroethane as medium, i.e., 71% instead of 63%. The yield of the p isomer in regrouping the phenol ester of propionic acid in nitrobenzene and chlorobenzene does not exceed 32-46%, and in petrol ether 32% [3]; in CS_2 as medium the corresponding yield is 45% [5], but additional purification of the products is required (the yields are calculated on the basis of phenyl propionate which is obtained from phenol and propionic acid hydrochloride in 80-85% yield).

The phenol ester of propionic acid was obtained by acylation of the phenol by means of propionyl chloride at room temperature. Without isolation, the phenyl propionate formed undergoes regrouping under the action of $AlCl_3$ in various solvents, i.e., nitrobenzene, dichloroethane, and so on. The best results were obtained in dichloroethane, which dissolves $AlCl_3$ and facilitates subsequent decomposition of the reaction mass with water. Comparative tests in dichloroethane medium at the boiling point of the latter and at room temperature show convincingly that the reduction in temperature has a favorable effect on the formation of the p isomer. In boiling dichloroethane the p isomer was obtained in 68-70% yield, and at room temperature at a yield of 80-81%, with due allowance for the propionyl chloride used in the reaction, i.e., a two-stage reaction. Dichloroethane is also more suitable from the point of view that at room temperature the p-isomer is practically insoluble in it. After cooling the reaction mass the p-oxypropiophenone is separated off, and washed free from the o isomer impurity and with water until the reaction is neutral. The high melting point of the substance obtained (148.5-150°) indicates that it can be used without further purification.

EXPERIMENTAL

The samples of the reaction mass and the reaction products were analyzed with a model "Pai" argon chromatograph with a β ionization detector, using a glass column (1200 × 4) packed with grade E-301 5% silicone elastomer supported on silanated Celite 545 (80-100 mesh). The column and detector temperature were 185°, and the argon flow rate 43 ml/min. The relative retention time for the phenyl propionate was 0.64, and for the o-oxypropiophenone 1.00 (retention time under given conditions 2.2 min), and for p-oxypropiophenone 3.14. The chromatograms were interpreted by the normalization method, the peak areas being

---

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 9, pp. 37-41, September, 1972. Original article submitted July 15, 1971.

determined by means of an integrator. Thin-layer chromatography was carried out on grade "Silufol UV-254" sorbent, using 2.5% methanol in benzene as the solvent system, and concentrated H_2SO_4 (with heating) for development. The R_f values for the phenyl propionate, the o isomer, and the p isomer were 0.55, 0.85, and 0.45 respectively.

Production of p-Oxypropiophenone. To 55 g of phenol was added with stirring 49.2 g of propionyl chloride, and the mixture was stirred at room temperature for 45 min, until the vigorous evolution of HCl ceased. To the phenyl propionate formed was added 100 ml of dry dichloroethane, and with continuous stirring 111 g of anhydrous $AlCl_3$ was added in portions at such a speed that the temperature of the reaction mass did not exceed 40-45° (40-50 min). After adding the $AlCl_3$ the dark red, mobile mass was heated at 75-80° and held at this temperature for 5 h. The course of the regrouping was controlled by means of thin layer and gas-liquid chromatography. During the holding time, while the phenyl propionate in the reaction mass gradually decreased and finally almost completely disappeared, the mixture was cooled to 10-15°. With continuous stirring and cooling 480 ml of water was added to the reaction mass over 20 min and the reaction mass was stirred with cooling for 1 h. The crystals of p-oxypropiophenone were filtered off, washed with cold dichloroethane and water to a neutral reaction of the aqueous filtrate, and dried to constant weight at 70-80° to give 55.35 g of p-oxypropiophenone (69.3% calculated on the basis of propionyl chloride), of melting point 148.5-150°.

When the reaction was carried out under these conditions but with the reaction mass held for 24 h at 10-20° after the addition of $AlCl_3$, the product obtained was 64.5 g (80.6%) of p-oxypropiophenone of melting point 148.5-150°.

LITERATURE CITED

1. A. K. Goldzweig and A. Kaiser, J. Prakt. Chem., 43, 86 (1891).
2. L. H. Ferinholt, M. C. Harden, and D. Twiss, J. Amer. Chem. Soc., 55, 3386 (1933).
3. S. Dongorosi, Rev. Chim. (Buc), No. 8, 357 (1957).
4. A. W. Ralston, M. R. McCorkle, and S. T. Bauer, J. Org. Chem., 5, 645 (1940).
5. Organic Reactions [in Russian], Collection No. 1 (1948), p. 473.