BENZOYLATION OF PHENOBARBITAL

G. A. Frangulyan, L. Kh. Vinograd,
and S. N. D'yachkova

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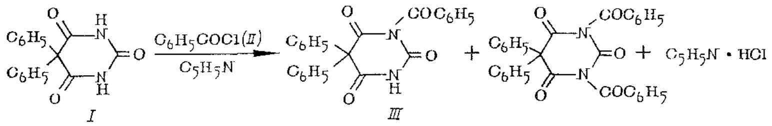
The benzoylation of 5-phenyl-5-ethylbarbituric acid (phenobarbital, I) with benzoyl chloride (II) leads to the formation of 1-benzoyl-5-phenyl-5-ethylbarbituric acid (the anticonvulsive preparation benzonal, III) [1].

In industry the process is effected by heating an equimolar mixture of (I), (II), and pyridine at 120-122°C. The main happenings in this conversion may be represented by the following scheme:



The use of pyridine is a disadvantage of this procedure. The purification of the required product from pyridine salts is brought about by washing and recrystallization. This naturally reduces the yield and leads to the formation of a large quantity of waste water containing pyridine. In addition, the benzoylation process does not go unequivocally. Together with the desired product (III) the dibenzoyl derivative (IV) is formed in significant amounts, while unreacted starting (I) remains. Purification from these contaminants causes additional losses and the overall yield of (III) does not exceed 40%.

Attempts at a more selective conduct of the reaction were undertaken. For this the sodium [2] or silver [3] salts of (I) were subjected to benzoylation. These procedures did not lead to the desired result and the yield of (III) was not increased.

We have found that regardless of the sum total of tradition, the benzoylation of (I) may be effected without first converting (I) into a salt and in the absence of pyridine. For this it was sufficient to heat an equimolecular mixture of (I) and (II) to 155-170°C in a stream of nitrogen or air. The reaction in this case proceeds according to the following equation:

$$\mathrm{I} + \mathrm{II} \rightarrow \mathrm{III} + \mathrm{HCl}$$

Thus, in addition to improving the technology, the problem of rendering a pyridine containing effluent harmless becomes superfluous. The collection and rendering harmless of gaseous HCl is not a problem in industry.

The advantages of this method are not exhausted since benzoylation proceeded more unequivocally in the absence of pyridine. The reaction mixture did not contain products of dibenzoylation but only (III), and unreacted (I) and (II). The direct yield of (III) reached 60% of the (I) loaded. Unreacted (II) may be distilled off and recycled into manufacture. The same also applied to unreacted (I) which was separated from (III) by crystallization and was practically completely recycled into manufacture.

EXPERIMENTAL

A check on the course of the reaction and on the purity of the products was effected by thin layer chromatography on plates of Silufol UV-254. Elution was carried out with a mixture of benzene–ethyl acetate–methanol (45:5:1). Substances were visualized on the chromatogram with the aid of a UV lamp. Rf: (I) 0.32, (III) 0.64, (II) 0.95.

Compounds (I) (2.32 g; 0.01 mole) and (II) (1.4 g; 0.01 mole) were heated at 155-170°C for 9 h while passing a weak current of dry nitrogen or air, then (II) (0.49 g; 0.035 mole) was distilled off at 15-20 mm Hg. Benzene (2.5-3 ml) was added to the residue, the mixture boiled for 20 min, the hot suspension was filtered,

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S. Ordzhonikidze All-Union Pharmaceutical Chemistry, Scientific-Research Institute, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 14, No. 3, pp. 102-103, March, 1980. Original article submitted July 30, 1979.

the solid was washed with benzene (0.5-1 ml), dried, and (I) (0.90 g; 0.0035 mole) was obtained. The filtrate was cooled to 20°C and left for 24 h. The solid was filtered off and recrystallized from alcohol. Compound (III) (2.02 g; 60%) was obtained of mp 135-137°C (according to literature data [1], mp 134-137°C). The mother liquors containing (III) with (I) as contaminant were evaporated, the solvent was used again, and the residue totalling 0.2 g was recycled in the benzoylation.

LITERATURE CITED

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