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PHASE-TRANSFER CATALYSIS BY POLY (ETHYLENEGLYCOL) 600 IN THE BILTZ SYNTHESIS OF PHENYTOIN

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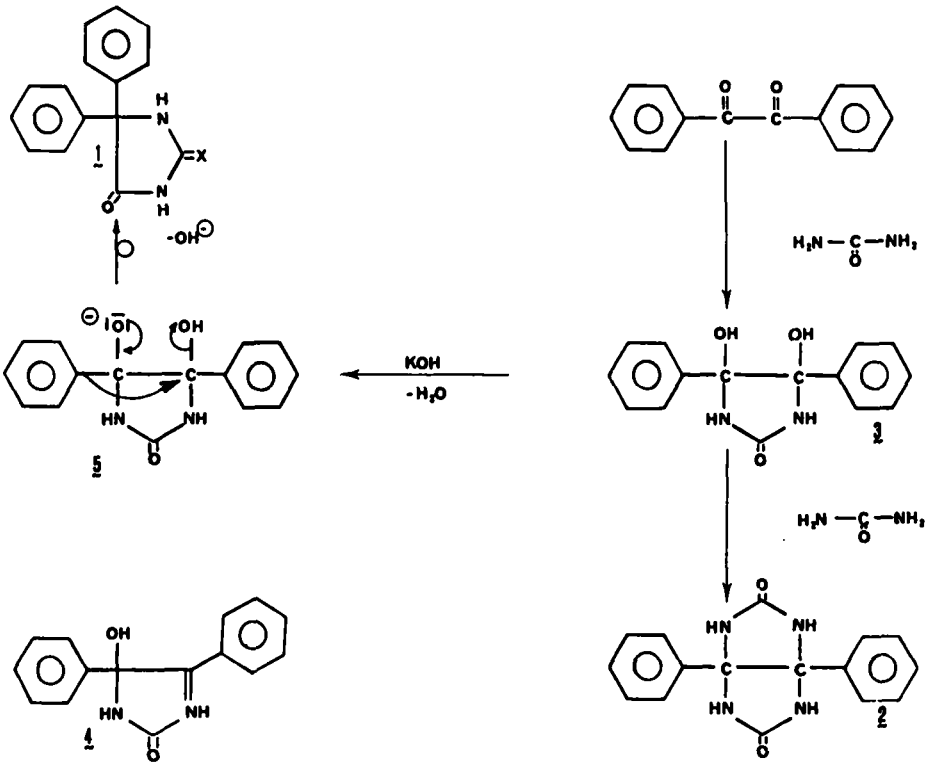
SUMMARY

A reinvestigation of the Biltz synthesis of phenytoin was undertaken to selectively produce the hydantoin derivative instead of a mixture of the hydantoin and the glycoluryl derivative. A solution of this problem was found in carrying out the reaction in a two-phase system (n-butanol:water) and in the presence of a phase-transfer catalyst (poly(ethyleneglycol)600). In these conditions, a 87-93% yield of phenytoin can be obtained. Extension of this approach to the synthesis of other hydantoin derivatives was also found superior to one-phase conditions.

Phenytoin (5,5-diphenyl-2,4-imidazolidinedione, 1) is a very potent antiepileptic agent regarded as the drug of choice for the treatment of generalized tonic-clonic seizures and elementary partial seizures[1]. It was introduced in clinical practice in 1938[2], thirty years after the first synthesis of this compound by the German chemist H. Biltz[3], who found that the treatment of benzil and urea with potassium hydroxide resulted in the formation of 1. This reaction was subsequently reinvestigated in detail by Dunnavant and James[4], who showed that the formation of 1 involved a benzilic rearrangement; a mechanism explaining the concomitant formation of a 3a, 6a-diphenylglycoloril compound (2) via a 4,5-diphenyl-4,5-dihydroxy-2-imidazolidinone (3) was also proposed by these authors[4]. The scope and the limitations of the Biltz reaction were studied by Dietz and Mayer[5] in 1968. The mechanism of Dunnavant and James has been revised recently by Butler and Leicht[6], and by Hayward[7] who postulated the existence of 4 as an intermediate in the formation of 1. In homogeneous reaction conditions, when ethanol or ethanol:water mixtures are employed as solvent, the yield in analytically pure material never exceeds 50-55%[5,7,8]. It should be noted also that a wide variety of bases can be employed to promote the reaction (sodium ethoxide, tetrabutylammonium hydroxide, lithium hydroxide, ...). These variations, however, did not significantly affect the ratio 1:2. As the production of 2 could not be reduced in single-phase systems, we have focused our attention on two-phase systems. We anticipated that, if the ionized forms of 3 (5) or 4 could be removed from the aqueous phase (where urea is present) and transported into the organic phase by means of a phase-transfer catalyst (PTC), the yield of 1 could be considerably improved and the production of 2 substantially lowered. Using a toluene:water system and classical PTC's (Dibenzo-18-crown-6,benzyltriethylammonium chloride)[9], 2 was virtually absent from the reaction product; however, the yield of 1 was very low (17-23%). When an n-butanol:water system and polyethyleneglycol[10] (average molecular



weight 600) as PTC were employed, the yield of 1 was 87-93.
In view of the success met with this approach, the same reaction was attempted with thiourea, N-methyl and N-phenylthiourea, in all cases the yield was nearly quantitative. No significant difference was observed in the yield when dibenzo-18-cr-6 or benzyltriethylammonium chloride were employed instead of PEG 600. To finally test the limitation of our reaction system, we have reacted together para-methoxybenzil with urea for 48 h and obtained a 47% yield of 5-(4-methoxyphenyl)-5-phenylhydantoin. Dietz and Mayer reported that no reaction occur under one-phase homogeneous conditions.

We believe that our two-phase reaction condition using PEG 600 as PTC may be worth considering specially in the elaboration or the production of radiolabelled or stable-isotope analogues of phenytoin employed in the drug monitoring of this major antiepileptic drug.

EXPERIMENTAL

Homogeneous conditions

19.97g of benzil (0,095 mol), 9.97 g of urea (0.166 mol) and 10.14g of potassium hydroxide (0.178 mol) were covered by 325 ml of 95% ethanol. Stirring was started and after 10 min, when a yellowish paste had formed, the mixture was gradually heated in an oil bath to ensure a steady reflux for 2 h. The reaction mixture was poured into distilled water to obtain a final volume

of 1 liter. The precipitate was filtered and washed twice with 100 ml of 0.5N sodium hydroxide and then with 100 ml of distilled water. This material was recrystallized from DMF:ethanol to give 6.3g of 2[11].
The combined filtrates were acidified with acetic acid to pH 6 and the resulting precipitate was filtered and washed with 100 ml of distilled water. It was dried to constant weight at 95°C/20 mmHg to give 17.6g of crude material which was recrystallized from 300 ml of 95% ethanol to yield 12.8g of pure (HPLC) 1.
m.p. 297-298°C. The ^{13}C-NMR spectrum (0.25 M in DMSO-d_6) was identical to that reported previously.

Two-phase conditions

Benzil, urea and potassium hydroxide (in the same quantities as in the preceeding section) and 2.5g of PEG 600 were stirred and heated at 100°C for 2 h (oil bath) in a two-phase system consisting of 200 ml of n-butanol and 200 ml of distilled water. After cooling, the mixture was filtered and acidified to give a precipitate, which was washed with water and cold ether, dried in vacuo and recrystallized from ethanol to give 87-93% of pure (HPLC) 1.

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