A Novel Electrochemical Synthesis of Ureides from Esters

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A novel electrochemical method of preparing ureides from esters was developed. Commercially available barbiturates such as barbital (2), allobarbital (3), phenobarbital (5) and pentobarbital (6), along with some other barbiturates and non-cyclic ureides were successfully prepared in *N,N*-dimethylformamide at room temperature.

Keywords allobarbital; barbiturate; cathodic reduction; ester; pentobarbial; phenobarbital; urea; ureide

Recently in a short communication,[1] we reported for the first time an electrochemical method of amidation of esters in the cathodic compartment of a Pt electrode. As a continuation of that work, we tried to prepare various non-cyclic ureides and barbiturates, including some important hypnotic drugs, simply by passing electricity into a mixed solution of ester and urea at room temperature. The successful results are reported in this paper.

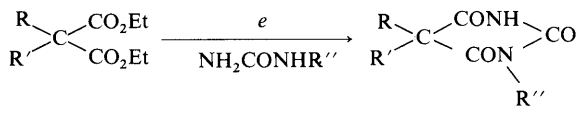
For preparing barbiturates, electrolyses were conducted with Pt electrodes in *N,N*-dimethylformamide (DMF) using tetraethylammonium perchlorate (TEAP) as the supporting electrolyte, at a controlled electrode current of 20 mA/4 cm^2. The results are summarized in Table I. The yield of 5,5-diethyl-1-phenylbarbituric acid (**1**) was better when 5 F/mol rather than 3 F/mol (on the basis of ester) of electricity was passed. In this same reaction, the use of acetonitrile in place of DMF as a solvent was tried, but resulted in a much poorer yield (5%).

Furthermore, three non-cyclic ureides were prepared in a similar way; the results obtained are given in Table II.

All the reactions, preparing barbiturates and cyclic ureides, were compared with non-electrochemical experiments: upon heating the content of the catholyte solution at 130 °C for 3 h, no trace of ureide products was found.

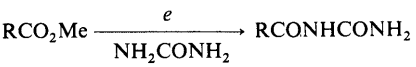
The relatively low yields seem to be due to the formation of by-products, though these were not determined, such as monoureide (in case of barbiturates), amides, *etc.* The mechanism of these reactions, possibly involving an electrogenerated base, is now under investigation.

TABLE I. Electrochemical Syntheses of Barbiturates



No.	Product R	R′	R″	Current passed (F/mol)	Isolated yield (%)
1	Ethyl	Ethyl	Phenyl	3	18
1	Ethyl	Ethyl	Phenyl	5	28
2	Ethyl	Ethyl	H	5	71
3	Allyl	Allyl	H	5	40
4	Ethyl	Benzyl	H	5	28
5	Ethyl	Phenyl	H	5	14
6	Ethyl	1-Methylbutyl	H	5	27

TABLE II. Electrochemical Syntheses of Non-cyclic Ureides



No.	R	Isolated yield (%)
7	Phenyl	67
8	4-Methoxyphenyl	50
9	4-Methylphenyl	60

Experimental

Apparatus Infrared (IR) spectra were taken with a Hitachi model 215 grating spectrophotometer. Low-pressure liquid chromatography (LPLC) was performed with a Chemco Low-Prep pump (81-M-2) and a glass column (20 × 1.5 cm) packed with silica gel SI-25-120 (25-44, Nihon Seimitsu Kagaku Co., Ltd.). Electrolyses were performed at 20 mA constant current by use of a Hokuto Denko HA-105 potentio-galvanostat connected with a Hokuto Denko HF-201 coulombmeter. An ordinary H-type cell divided into two compartments with a glass-frit plate (No. 3G), equipped with two Pt plate (4 cm^2) electrodes and a saturated calomel electrode as a reference, was used. The catholyte solution was kept at 23 ± 2 °C by external cooling with water, and stirred by use of a magnetic stirrer.

Materials Solvent acetonitrile of guaranteed reagent grade was distilled after being dried by refluxing with calcium hydride. Solvent DMF was dried on molecular sieves 4A, and distilled *in vacuo*. The starting diethyl esters of diallylmalonic, ethylphenylmalonic, ethyl-1-methylbutylmalonic and benzylethylmalonic acids were prepared from the respective esters of allylmalonic, phenylmalonic and 1-methylbutylmalonic acids by reaction with the corresponding alkyl halide.[2] All other chemicals were of guaranteed reagent grade and were used without further purification, but were dried on P_2O_5.

Electrochemical Reactions for Preparing Barbiturates All the reactions in Table I were conducted as follows. A DMF (10 ml) solution of substituted diethyl malonate (0.5 mmol), urea or phenylurea (0.5 mmol), and TEAP (1 mmol) as a supporting electrolyte was placed in the cathodic compartment. After passing 5 F/mol (on the basis of ester) of electricity, the catholyte and the anolyte were combined, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using $CHCl_3$–MeOH (80 : 1) as solvent, to obtain the barbiturate. In the case of compound **1**, further purification by use of LPLC was necessary. All barbiturates were identified by mixed fusion and the comparison of the IR spectra with those of authentic samples prepared by heating the corresponding esters with urea and sodium ethoxide in absolute ethanol.[3,4]

Electrochemical Reactions for Preparing Non-cyclic Ureides A DMF solution (40 ml) of each ester (3 mmol), urea (6 mmol) and TEAP (4 mmol) was electrolyzed in the same way as above. After passing 2.5 F/mol (on the basis of ester) of electricity, the catholyte and the anolyte were combined, the solvent was removed *in vacuo*, the residue was mixed with acetone (50 ml) and filtered to remove most of the TEAP, and the filtrate was evaporated. The residue was then purified by open-column chromatography followed by LPLC with CH_2Cl_2–hexane (10 : 1). Each of the ureides produced was identified by the mixed fusion and the comparison of the IR spectra with a standard sample, which was prepared by heating each benzoyl chloride and urea at 150 °C for 3 h.[5] *N*-Benzoylurea (**7**): mp 210 °C (lit.[6] 214—216 °C). *N*-(4-Methoxybenzoyl)urea (**8**): mp 215 °C (lit.[5] mp 214—215 °C). *N*-(4-Methylbenzoyl)urea (**9**): mp 225 °C (lit.[7] mp 224—225 °C).

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