DIFRIL.

METHODS OF REDUCING ETHYL 3,3-DIPHENYLPROPIONATE

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In the method currently used for synthesizing Difril, 3,3-diphenylpropan-1-ol (DPP) is prepared by reduction of ethyl 3,3-diphenylpropionate (EDPP) by the Bouveault—Blanc method with metallic sodium in isopropyl alcohol solution. The variable yield, labor-intensive nature, and fire risk of the process which arise from the use of a large excess of metallic sodium, call for a study of alternative methods of reduction.

Reduction of EDPP to the alcohol with lithium aluminum hydride in diethyl ether is known [1] to proceed easily and in good yield (87%). The same reagent also reduces 3,3-diphenylpropionic acid [2], but the fire risk and high cost of lithium aluminum hydride constitute a serious obstacle to the commercial exploitation of this efficient reducing agent. Ester functions can also be reduced to alcohols by complex borohydrides of metals of groups II and III. Alkali-metal borohydrides behave similarly in the presence of strong Lewis acids. Thus the $NaBH_4$—$AlCl_3$ system in diglyme reduces ethyl stearate to octadecanol in 91% yield [3]. We used a similar system to reduce EDPP. The chromatogram of the reaction mixture and the absence from its IR spectrum of the ester C=O stretching band at 1735 cm^{-1} implied that reduction of EDPP was complete.

Contrary to expectations [4] our attempts to use the $NaBH_4$—$MgBr_2$ and $NaBH_4$—$CaCl_2$ systems in tetrahydrofuran did not lead to the successful reduction of EDPP.

Together with this search for new reducing agents, we studied various modifications of the Bouveault—Blanc method for reduction of EDPP, namely: use of high-boiling alcohols; use of butanol and NH_4Cl; use of phenol with quinoline; and use of an inert solvent (xylene).

Reduction proceeded too slowly in isopropyl alcohol solution because of its low boiling point. Under these conditions a considerable proportion of the sodium reacted with the alcohol, which would have undesirable consequences, namely the need for a large excess of sodium and the formation of highly concentrated alcoholate solutions. This would cause serious technical difficulties, since finely divided unreacted sodium remains in the reaction mixture, which gels on cooling. By using butanol the reaction temperature could be increased to 140-150°C and the excess of sodium could be halved. Though the use of cyclohexanol allowed the reaction temperature to be raised to 180°C, on cooling the solution formed a waxy mass. Moreover, the yield did not increase.

We got the best results by using the method of [5, 6], which essentially consists of decomposing the disodium derivatives of the carbonyl compounds that are formed in the reduction process with carbon dioxide or with ammonium chloride. Reduction of EDPP in butanol in the presence of ammonium chloride proceeded rapidly; the reaction mixture on cooling remained transparent and mobile; extraction of the product was not accompanied by emulsification; and the aqueous layer gave a weakly alkaline reaction.

We also decided to study the reduction of EDPP with metallic sodium and phenol in the presence of quinoline. Thus we were able to reduce esters of hydrocinnamic acid and of phenylacetic acid to the alcohols in yields of about 90% [7]. This system reduced EDPP in 78% yield, but the use of extra components and the rather inconvenient method of treating the reaction mixture reduce the value of the method.

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TABLE 1. Results of the Reduction of Ethyl 3,3-Diphenylpropionate by Various Methods

Method of reduction			Solvent	Yield of 3,3-diphenylpropan-1-ol, %
$NaBH_4$—$AlCl_3$			Diglyme	90
Modification of the Bouvealt—Blanc method:				
excess Na, %	alcohol	other components		
100	butanol	—	Butanol	75
30	"	NH_4Cl	"	82
100	phenol	quinoline	"	78
60	butanol	—	Xylene	81
200	isopropanol	—	Isopropanol	68*

*Data from the Olaine Pharmaceutical Plant.

Reduction of EDPP with sodium suspension in xylene (Hansley's modification [8]) gave high yields (up to 86% in individual runs), though on cooling a reaction mixture that had contained finely divided metallic sodium gelled, and a considerable excess of alcohol was needed for dilution and also for complete dissolution of the sodium. Under the industrial conditions, detection of the presence of finely divided unreacted sodium is difficult, and so decomposition of the reaction products would involve a certain risk.

Table 1 summarizes the results of our study.

As Table 1 shows, reduction with sodium borohydride and ammonium chloride in diglyme gives the maximum yield of EDPP. Nonetheless reduction with metallic sodium is more economical. On the basis of our study we can recommend the modification of the Bouveault—Blanc method using butanol and ammonium chloride. Its use raises the yield of DPP, drastically cuts the sodium consumption, and simplifies the treatment of the reaction mixture. It is also not unimportant that introduction of this method would not involve restructuring the present industrial production process.

EXPERIMENTAL

The completeness of the reduction of EDPP and the purity of the DPP were checked by thin-layer chromatography on Silufol plates with 4:1 heptane—ethyl acetate; $R_f = 0.61$ for EDPP and $R_f = 0.32$ for DPS.

1. Reduction with the $NaBH_4$—$AlCl_3$ System. After mixing 5 g (0.132 mole) of sodium borohydride and 25.6 g (0.1 mole) of EDPP in 100 ml of dry diglyme at room temperature over a period of 30 min, the mixture was cooled to 10°C and vigorously stirred as a solution of 6 g (0.044 mole) of aluminum chloride in 50 ml of diglyme was added dropwise. When the vigorous evolution of gas had ceased, the reaction product was heated on a boiling water bath for an hour, cooled, and carefully decomposed with 5% hydrochloric acid. The product was extracted with benzene and dried over sodium sulfate; after removing the solvent by distillation, it was vacuum distilled; the fraction with bp 180-182°C (6 mm) was collected; it had n_D^{20} 1.5850, which corresponds to the literature data [2]. The yield was 19 g (90%). Pure 3,3-diphenylpropan-1-ol crystallized on standing, mp 29.5°C.

2. Modifications of the Bouveault—Blanc Method: A. Use of Butanol. Metallic sodium (18.4 g) was added in pieces to a solution of 25.6 g of EDPP in 150 ml of dry butanol, previously heated to 80°C, whereupon the temperature spontaneously rose to 120°C. When the vigorous boiling had ceased, the reaction mixture was heated for an hour on an oil bath at 140°C. The cooled reaction mixture was treated as in experiment 1. The yield was 15.9 g (75%).

B. Use of Butanol and Ammonium Chloride. A mixture of 110 ml of dry butanol, 25.6 g of EDPP, and 34 g of dry ammonium chloride was heated to 80°C, and 11.9 g of metallic sodium was added in pieces. We observed vigorous evolution of ammonia and the temperature rose to 108°C. When all the sodium had dissolved, the reaction mixture was cooled and treated according to the published method. The yield was 17.36 g (82%).

C. Use of Phenol with Quinoline Catalyst. A mixture of 60.2 g of dry phenol, 25.6 g of EDPP, and 1 ml of quinoline in 200 ml of dry butanol was stirred until completely homogenized, whereupon 18.4 g of metallic sodium was added in pieces to the reaction mixture. The temperature then rose spontaneously to 120°C. When the vigorous reaction had ceased, the reaction product was heated for a further hour at 140°C, cooled, decomposed with water, and extracted with benzene. The extract was washed successively with 20% sulfuric acid and 25% sodium hydroxide, and after removal of the solvent by distillation it was vacuum distilled. The yield was 16.5 g (78%).

D. Use of High-Temperature-Boiling Inert Solvent (xylene). The stirring speed was adjusted so that a finely divided suspension was formed when 15 g of metallic sodium in 200 ml of dry xylene was heated to boiling. Heating was discontinued and a fine stream of 25.6 g of EDPP in 50 ml of dry butanol was run in from a burette. When the vigorous reaction had ceased a further 25 ml of butanol were added and the reaction mixture was refluxed for 30 min. After cooling, the gelled mixture was treated as in Experiment 1. The yield was 17 g (81%).

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REACTION OF CHALCONES WITH PHENYLHYDRAZINE

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The reaction of chalcones with phenylhydrazine leads to the formation of phenylhydrazones, which, depending on the nature of the substituents, can be isomerized to derivatives of pyrazoline [1-3]. The connection between the nature of the substituents in ring A of the chalcone molecule and the structure of the end product of the reaction with phenylhydrazine was studied in [2, 4]. The presence of substituents such as 4'-Cl, 4'-Br, 4'-OCH_3, and 4'-CH_3 was found to result in formation of the phenylhydrazone, whereas with 3-NO_2, 4'-NO_2, 4'-OH, or 4'-$OCOCH_3$ as substituents the end product was a pyrazoline derivative. Formation of the pyrazoline heterocycle typically takes place when acid catalysts are present and also when the reaction mixture is heated (if the reaction is carried out in ethanol) [2-5]. The pyrazoline derivatives are widely used as luminescent additives to liquid and plastic scintillators [5].

Our intention in the present work was to carry out the reaction without heating or using an acid catalyst, and also to establish the connection between the nature of the substituents in the aldehydic moiety of the chalcone and the structure of the end product.

We have studied the reactions of benzalacetophenone (chalcone), 2-chlorochalcone, 3-chlorochalcone, 4-methoxychalcone, and 2'-hydroxychalcone with phenylhydrazine base and with phenylhydrazine hydrochloride. The resulting compounds were yellow in color and were highly soluble in ethanol and acetone, in which we detected bluish-violet fluorescence.

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