DIFRIL. II. IMPROVED METHOD FOR THE PRODUCTION OF 1-PHENYL-2-(1,1-DIPHENYL-3-PROPYLAMINO)PROPANE

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The literature [1, 2] describes a method for the production of 1-phenyl-2-(1,1-diphenyl-3-propylamino)propane — "difril base" — consisting of the alkylation of 1-phenyl-2-aminopropane (PAP) with 1,1-diphenyl-3-bromopropane (DPBP):

$$C_6H_5CH_2CH(CH_3)NH_2 \xrightarrow{(C_6H_5)_2CHCH_2CH_2Br} (C_6H_5)_2CHCH_2CH_2NHCH(CH_3)CH_2C_6H_5.$$

Under industrial conditions the alkylation stage does not present marked difficulties as regards raw materials and technology. However difficulties do arise in the preparation of the alkylating reagent by bromination of 1,1-diphenyl-3-propanol (DPP) with 48% hydrobromic acid — the conversion of the acid is low even if it is recycled after fortifying with fresh acid. The highly corrosive properties of refluxing hydrobromic acid also cause complications.

Replacement of hydrobromic acid with phosphorus tribromide, which brominates under milder conditions [3], cannot be recommended for economic reasons.

Thus there is scope for general improvement in the alkylation technique.

Alkylating Agent. Patent sources [4, 5] mention the use of 1,1-diphenyl-3-chloropropane (DPCP) for the alkylation of several amines. An earlier reference to this compound appears in a US patent [6], which however omitted its physical properties and mentioned neither the yield nor the method of isolation. A method for the preparation of DPCP in 52.8% yield by chlorination of DPP, with thionyl chloride in dimethylformamide (DMF) has been described [7]. The same workers also described [5] the conditions for the preparation of DPCP in higher yield (78.5%) with a large excess of thionyl chloride in benzene solution. These sources make the first mention of the boiling points of DPCP under reduced pressure [bp 146 °C (4 mm) and 130°C (2 mm)]; the compound was obtained as a liquid.

We made a preliminary assessment of the efficiency of several solvents in the chlorination of DPP. Our results are summarized in Table 1, which shows that the use of thionyl chloride as solvent gives the maximum yield. However, these conditions are associated with strong foaming when the reagents are mixed, considerable waste of thionyl chloride, which cannot subsequently be regenerated, and complications because DPP has to be charged incrementally into the reactor with the thionyl chloride. For this reason we made a more detailed study of the chlorination process in chloroform and dichloroethane.

We sought the optimum conditions with a full two-factor experiment (the factors were the molar ratios of the reagents and the heating time, and the response function was the yield of DPCP, determined after vacuum distillation of the reaction mixture). From this we evaluated the dispersion and Cochrane's criterion. The calculated Cochrane's criterion (G_c = 0.725) was greater than the tabulated value [8] (G_t = 0.684), which precluded the use of a regression equation. Determination of the response function by other methods, thin-layer chromatography (TLC) and IR spectroscopy (from the intensity of the hydroxyl band in

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TABLE 1. Preliminary Assessment of Solvent Efficiency

Solvent	Reaction temperature °C	$SOCl_2$:DPP molar ratio	Yield, %
benzene [5]	80	2,5	78,5
toluene	105	2,5	75,2
methylene chlo.	45	2,5	70,0
chloroform	65	2,5	82,5
dichloroethane	80	2,5	81,5
thionyl chloride	80	5,0	86,2

*Reaction time 1 h in all cases.

TABLE 2. Chlorination of DPP under Various Conditions

Series	Conditions			Yield, %	DPP in the product (by TLC)
	$SOCl_2$:DPP molar ratio	heating time, h	solvent		
I:					
a	1,5	2	chloroform	40,9	+
b	1,5	3	"	46,0	+
c	1,5	4	"	46,3	+
II:					
a	2,0	2	"	77,5	+
b	2,0	3	"	82,7	+
c	2,0	4	"	84,0	+
III:					
a	2,5	2	"	85,8	+
b	2,5	2	dichloroethane	89,2	—
c	2,5	3	chloroform	92,4	—
d	2,5	3	dichloroethane	90,8	—
e	2,5	4	chloroform	93,0	—
f	2,5	4	dichloroethane	92,1	—
IV:					
a	3,0	2	chloroform	88,0	—
b	3,0	2	dichloroethane	89,2	—
c	3,0	3	chloroform	93,2	—
d	3,0	3	dichloroethane	92,5	—
V	3,5	3	chloroform	93,3	—
VI	4,0	3	"	93,2	—

Here + denotes the presence of the impurity, - its absence.

the 3600 cm^{-1} region), gave even higher discrepancies of Cochrane's criterion. Consequently we evaluated the conditions on the basis of six series of experiments, in which the degree of conversion of the starting DPP was monitored by TLC and the product was isolated by vacuum distillation at the end of the run. Our results, summarized in Table 2, reveal that the yield of DPCP (93%) is greatest in chloroform and rather lower in dichloroethane. Although chloroform is more expensive than dichloroethane, we favored chloroform because: 1) as a result of the milder conditions of the reaction with thionyl chloride, which can be stripped off with the chloroform at the end of the reaction, the thionyl chloride can be almost completely regenerated; when dichloroethane is used the losses of thionyl chloride are greater and its quality lower; 2) other factors being equal, the yield in chloroform is on average 1% higher than in dichloroethane, and moreover since chlorination and stripping are carried out at temperatures above the boiling point of thionyl chloride when dichloroethane is used, considerable gassing can occur under industrial conditions.

The conditions of series III (c and e) seem the best. After the end of heating in these runs TLC revealed that DPP (R_f 0.29) was absent, but, apart from DPCP (R_f 0.92) another spot with R_f 0.62 was apparent on the chromatograms. This disappeared after treatment of the reaction mixture with water but in this case the starting DPP could be detected. However if the reaction mixture was not treated with water but distilled under vacuum, only DPCP could be detected in the distilled product. Thus the spot with R_f 0.62 apparently belongs to the chlorosulfinate ester, the intermediate in the chlorination of alcohols with thionyl chloride:

TABLE 3. Alkylation of PAP under Various Conditions

Solvent	PAD:DPCP molar ratio to DPCP	Additives and molar ratio to DPCP	Reaction temperature °C	Heating time, h	Yield, %
isopropyl alcohol	2,0	NaBr 0,25	85	6	29,5
dioxane	2,0	Dimethylamine	110	12	44,0
xylene	2,0	"	137	12	42,5
dimethylaniline	1,0	"	160	2	55,5*
	1,5	"	160	2	59,1*
DMF	1,5	"	156	1	56,6
DMF	1,5	" 3,0	150	1	58,5*
DMF	1,5	NaBr 0,25; K_2CO_3, 2,0	156	1	60,1
DMF	1,5	NaBr 0,25; $(C_2H_5)_3N$, 3,0	115	2	47,0*
DMF	2,0	NaBr, 0,25	156	1	80,0

*Because of resinification of the reaction mixture, product was lost during purification.

$$(C_6H_5)_2CHCH_2CH_2OH + SOCl_2 \xrightarrow[H_2O]{} (C_6H_5)_2CHCH_2CH{-}O{-}SOCl + HCl$$

$$\downarrow \text{ heat}$$

$$(C_6H_5)_2CHCH_2CH_2Cl + SO_2.$$

Attempts to isolate the sulfinate ester in the pure form and to characterize it were unsuccessful, in the presence of protic solvents it was converted to starting DPP while when distilled, even under mild conditions, in aprotic solvents it was converted to DPCP. The composition of the reaction mixture was monitored by TLC during the entire chlorination process to find the optimum reaction conditions; we found it sufficient to warm the reactants in refluxing chloroform for 1.5 h, which almost completely converted DPP to the sulfinate ester, and then to continue treatment under more forcing conditions — stripping off the chloroform with the excess thionyl chloride and heating the residue. The time required for conversion of the sulfinate ester to DPCP after stripping off the chloroform as a function of temperature is:

Temperature in mixture, °C	Reaction time, h
95	1,3—1,5
110	1,0
125	0,5
140	0,3

Resinification of the reaction mixture takes place at temperatures above 100°C.

These conditions give higher yield and superior purity of DPCP, the product prepared by this procedure crystallizes and has mp 32-33°C.

Alkylation. Although the patent specification [1] includes the use of any halopropane, it does not mention the process conditions, except to require that alkylation be carried out in a medium containing a hydrogen halide acceptor. The patent disclosure includes an example of the alkylation of PAP using DPBP. However alkylation with DPCP cannot be carried out under conditions like those described. We have found that the necessary conditions for this are either the use of solvents that accelerate nucleophilic reactions or the use of bromide or iodide salts. The simultaneous observance of these two requirements seems reasonable.

We set out to identify the conditions of alkylation with DPCP by varying solvents, reactant ratio, reaction time and temperature, and the extra reagents — several bases and bromide salts (it was apparent even in the first stage of the work that iodides have no advantages over bromides). The degree of conversion of the reagents and the yield of difril base were measured by gas—liquid chromatography (GLC).

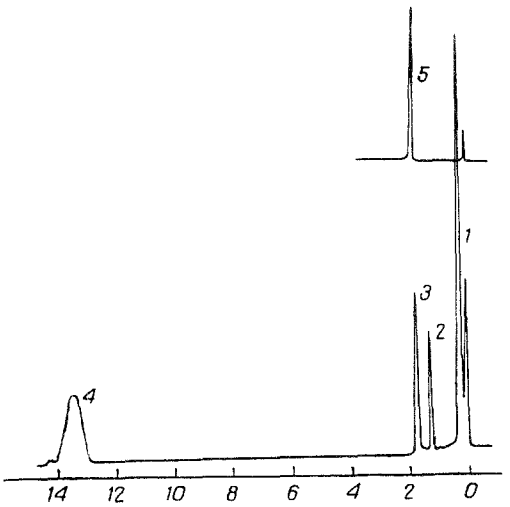

Fig. 1. Chromatogram of the reaction mixture after 30 min reaction; 1) PAP; 2) DPCP; 3) DPBP; 4) difril base; 5) pure DPBP added as standard.

Table 3 shows the results of alkylation at the most favorable temperature and with the optimum reaction time. The maximum yields were derived only by using DMF.

Although other factors being equal the use of bases also increased the yield, we got the highest yield by using excess PAP as the base.

In the runs we used sodium and potassium bromides. The higher solubility of the potassium salt in organic solvents suggests that it would be more efficient. However this was not the case in practice and so subsequently we used only sodium bromide.

We detected the product of the Finkelstein reaction by GLC of the reaction mixture at the end of the alkylation reaction (conditions DMF, sodium bromide, 100% excess of PAP, 156°C). While the reaction proceeded rapidly (first 20 min) we detected by GLC three peaks, of DPCP, PAP, and difril base. As the rate of alkylation diminished a fourth component accumulated in the reaction mixture, giving a peak that coincided exactly in emergence time with DPBP (Fig. 1). This suggests that the exchange reaction of sodium bromide with DPCP does not limit the alkylation.

Our work on the alkylation reaction has revealed the conditions for the efficient use of the more accessible alkylating agent DPCP, increased the yield of difril base, and considerably reduced the reaction time.

EXPERIMENTAL

1,1-Diphenyl-3-chloropropane. To 1,1-diphenyl-3-propanol (106 g) in dry chloroform (150 ml) was added dropwise with stirring thionyl chloride (90 ml) at a rate that ensured the smooth evolution of HCl (about 30 min). After the addition of thionyl chloride the reaction mixture was refluxed for 1.5 h. The reflux condenser was then switched to direct distillation and the chloroform was stripped off with the thionyl chloride, raising the temperature in the mixture to 95-100°C. Heating was continued at the same temperature and with vigorous stirring for another 1.5 h. The end of the reaction was identified by TLC, which gave a single spot of DPCP (R_f 0.92). Benzene (0.5 liter) was added to the cooled mixture, which was stirred until complete dissolution, transferred to a 1 liter separating funnel, and shaken with 0.5% aqueous sodium hydroxide (200 ml). The benzene layer was separated, washed twice with water, dried over calcium chloride with stirring for 2 h, and filtered. The benzene was stripped off. The residue (a brown syrupy mass) was technical DPCP. The yield was 112 g (98%) of purity not less than 96%. Technical DPCP crystallized on standing, mp 29-30°C. Pure DPCP was derived by vacuum distillation of the technical product. The fraction with bp 152-155°C (5 mm) was collected; pure DPCP crystallized in the receiver. The yield was 93%.

Silufol UV-254 plates were used for TLC in the system ethyl acetate–n-heptane (1:4).

1-Phenyl-2-(1,1-diphenyl-3-propylamino)propane. A mixture of DPCP (115.25 g), sodium bromide (13 g), PAP (153 ml), and DMF (250 ml) was heated in a 0.75 liter flask at 150°C for 1 h and then cooled to 50°C and transferred in small portions to a 1.5 liter flask containing benzene (0.5 liter) and 10% hydrochloric acid (0.5 liter). It was stirred vigorously for 2 h. The precipitated fine granules were filtered off and washed with water until the washings were neutral. The residue was carefully pressed and washed twice with ethyl acetate cooled to 5-6°C. Drying gave difril hydrochloride (146.2 g, 80%), mp 189-190°C. Technical DPCP gave a yield of about 70% by the same method.

Gas–liquid chromatography was carried out on an LKhM-8 MD 1 chromatograph [10% PEGA on Chromaton 0.20-0.25 mm, column length 1 m, column temperature 250°C, injector temperature 325°C, katharometer detector, current 100 mA, carrier gas flow rate (helium) 60 ml/min]. A sample of the reaction mixture (5 ml — exact volume) was treated with 20% aqueous alkali (5 ml) and extracted with benzene (3 × 5 ml). The extracts were shaken for 15 min with anhydrous potassium carbonate, filtered, and evaporated to one quarter of the original volume; the volume of the residue was then adjusted to 5 ml exactly with dry benzene.

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REACTION OF CARBOXY-, ETHOXYCARBONYL- AND HYDROXYMETHYLPYRIDINES WITH AMIDES OF PHOSPHOROUS ACID

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Amides and ester amides of phosphorous acid can act as aminating agents toward several compounds with hydroxy [1], carboxy [2-5], and alkoxycarbonyl groups [5, 6]. 1-Substituted uracils react with hexamethylphosphorous triamide to give 1,N-disubstituted cytosine derivatives [7].

Interaction of o-hydroxybenzyl alcohol with diethyl N,N-diethylphosphoramidite forms, in addition to 2-(diethylaminomethyl)phenol and diethyl phosphite, diethyl o-hydroxybenzylphosphonate and diethylamine [1].

Acetic anhydride also gives acetyl phosphites and acetylamides with N,N-dialkylphosphoramidites [2].

The reaction of hexaethylphosphorous triamide (HETP) with the free primary hydroxyl group of 1,2,3,4-di-O-isopropylidenegalactopyranose or the sterically hindered secondary hydroxyl group of 1,2,5,6-di-O-isopropylideneglucofuranose gives only the corresponding phosphites [8]. However only diethylacetamide could be derived from acetic anhydride [3].

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