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STEREOCHEMISTRY OF THE CONVERSION OF THE DIASTEREOISOMERIC EPOXIDES AND GLYCOLS DERIVED FROM 1-PHENYL-4-t-BUTYLCYCLOHEXENE INTO CHLOROHYDRINS

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Abstract—The rates and steric courses of the title reactions depend very much on the configuration of the substrate and type of solvent. The reactions of the two epoxides and of the diols having equatorial α-hydroxyl with HCl in dry $CHCl_3$ involve almost complete retention of configuration, while the presence of water or the use of 2-propanol as solvent considerably diminish the stereospecificity. The rate and stereospecificity of the reaction of the *trans*-diaxial diol are much lower, while the *cis*-diol with axial α-hydroxyl is completely unreactive. Mechanistic interpretations for these data are discussed.

Previous work had shown that the reactions of 1-phenyl-1,2-epoxycyclohexane and of the corresponding *cis*- and *trans*-diols with HCl gives the chlorohydrins with complete retention of configuration if conducted in dry $CHCl_3$, but is less stereospecific in the presence of water, or if EtOH is used as the solvent.[1] This investigation has now been extended to the conformationally rigid 4-t-butyl analogues[2] in order to get a better insight into the steric requirements of these reactions.[3]

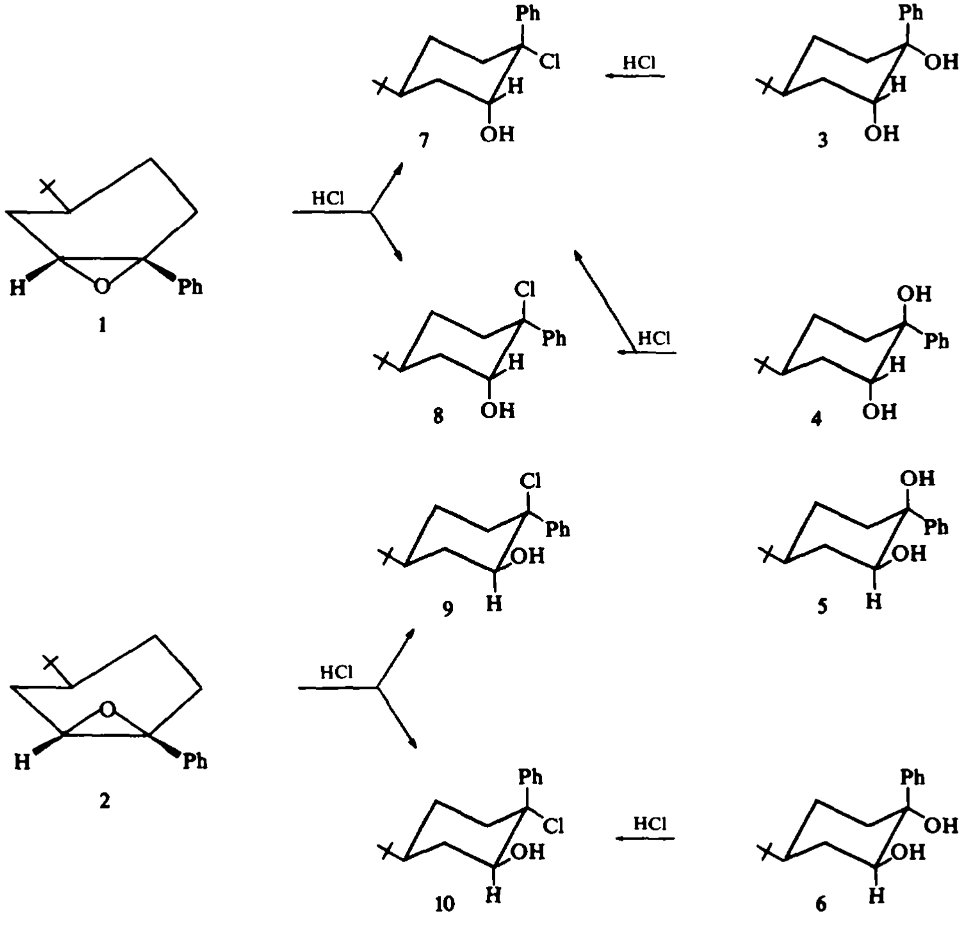
Table 1. Product compositions

Substrate	Solvent	Reaction time	%**7**	%**8**	%**9**	%**10**
1	$CHCl_3$[a]	15 min	100	0		
1	$CHCl_3$[b]	15 min	94	6		
1	2-propanol	4 hr	22	78		
3	$CHCl_3$[a]	1 hr	100	0		
3	$CHCl_3$[b]	20 min	71	29		
4	$CHCl_3$[b]	24 hr	47	53		
2	$CHCl_3$[a]	10 min			>95	<5
2	2-propanol	24 hr			60	40
6	$CHCl_3$[a]	1 hr			5	95
6	$CHCl_3$[b]	30 min			20	80

[a] Dry.
[b] Water-saturated.

Table 1 and Chart 1 summarize the results obtained in the reactions of the epoxides **1** and **2** and of the diols **3–6** with HCl. The two epoxides are opened in dry $CHCl_3$ to give almost exclusively the products of *syn* attack by chloride ion on the benzylic carbon (7 and 9). The reaction is only slightly less stereospecific in moist $CHCl_3$ (treatment of a $CHCl_3$ solution of the epoxide with conc. HCl aq), but when 2-propanol is used as the solvent considerable amounts of the *trans* chlorohydrins **8** and **10** are formed.

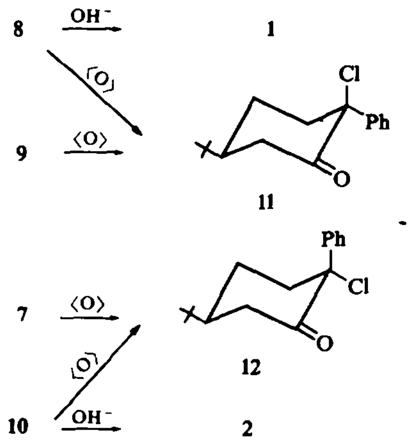
Chart 1



The diols **3** and **6**, in which the α-hydroxyl is equatorial, react with HCl in dry $CHCl_3$ rather rapidly and with complete retention to give **7** and **10**, while the stereospecificity is lower in the presence of water. The reaction of the diaxial diol **4** with HCl is extremely slow in dry $CHCl_3$, a little faster in moist $CHCl_3$ where it gives an almost equimolar mixture of the chlorohydrins **7** and **8**. Finally the *cis* diol **5**, with an axial α-hydroxyl, is practically unaffected by HCl both in dry and moist $CHCl_3$, even after very long times.

The configurations of the halohydrins **7**–**10** were deduced from those of the starting epoxides and diols, and from the correlations shown in Chart 2. The *trans* nature of **8** and **10** resulted from their conversion by alkali into the epoxides **1** and **2**. The

CHART 2

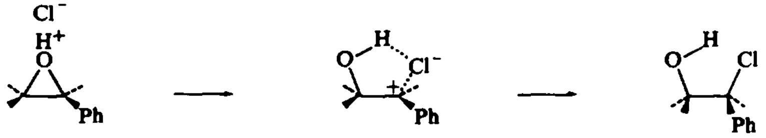


structures and epimeric nature of **8** and **9**, and of **7** and **10** were proved by their conversion with Jones reagent respectively into the chloroketones **11** and **12**. A further confirmation came from the NMR and IR spectra (Table 2). The half-band widths of the protons α to OH group are consistent with the expectations for equatorial hydrogens in **7** and **8**, and axial ones in **9** and **10**.[4] The OH stretching frequencies of the chlorohydrins in dilute CCl$_4$ solutions are in accordance with the formation of strong OH···Cl bonds in **7** and **9** (*cis*-chlorohydrins), a slightly weaker one in **10** (*trans*-diequatorial chlorohydrin), and an OH···π bond in **8** (*trans*-diaxial chlorohydrin).[5,6]

TABLE 2. NMR AND IR DATA

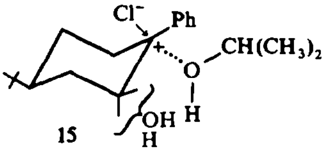
Compound	NMR δ (ppm)	NMR Half-band width (cps)	IR OH-stretching (cm^{-1})
7	4·70	6·75	3579
8	4·36	6·75	3599
9	4·05	16·50	3580
10	4·17	18·00	3586

The results of the reactions of the epoxides **1** and **2** with HCl are in accordance with those obtained with trichloroacetic acid[2] and with the well established fact that aryloxiranes undergo preferential or even exclusive *syn* cleavage under acidic conditions, particularly in solvents of low dielectric strength.[2,7] This can well be accounted for by a mechanism involving the formation of a solvent protected ion pair (**13**) in which the attack by the anion on the electron-deficient benzylic carbon takes place internally as shown in **14**.



13 **14**

The decrease in stereospecificity in the presence of water and more in 2-propanol solution can be explained by a solvation of the carbonium ion which interferes with the process depicted in **14**. Both from **1** and **2** there is formed an excess of the chlorohydrin with axial chlorine; while this could be justified in part in terms of thermodynamic control, it may well be that the excess of axial attack by the chloride ion is due to preferential solvation of the carbonium ion from the equatorial side, which shields more from equatorial than from axial attack, as schematically shown in **15**.



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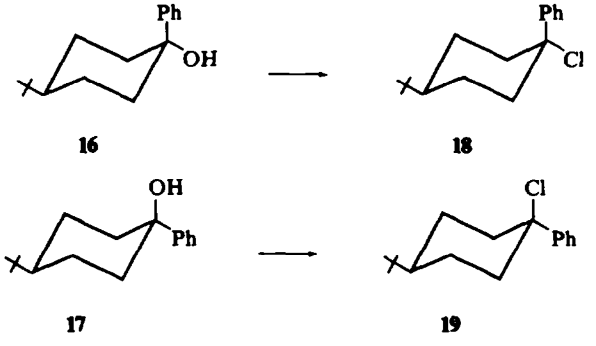
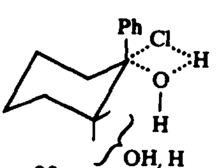
The rates and steric courses of the reactions of the diols **3**–**6** with HCl exhibit an interesting dependence on the conformation at the α and β carbons. It must be stressed that the inductive effect of the β-hydroxy group has a very pronounced rate depressing effect. Recent results by Erickson *et al.*[8] show that the *cis*- and *trans*-isomers of 1-phenyl-4-t-butylcyclohexanol (**16** and **17**) are converted into the chlorides **18** and **19** under very mild conditions (HCl in hexane at −70°); although only **18** was obtained from **16**, and **19** from **17**, the low recoveries of the chlorides (33% for **19**, unstated for **18**) do not allow us to deduce the degree of stereospecificity of these reactions. In the case of **3**–**6** only the analogues of **16** with equatorial OH (**3** and **6**) but not those of **17** with axial OH (**4** and **5**) undergo a facile and stereospecific displacement of OH by Cl: since the steric effect of the additional β-OH group alone could not justify the difference, the complete lack of reactivity of **5**, as compared with the easy reaction of **17**, must also be due to the inductive effect, which prevents the reaction in the absence of a favourable conformational situation.



16 **18**

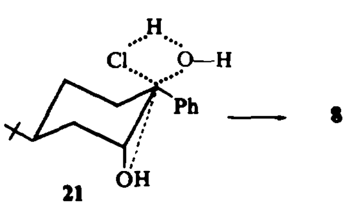
17 **19**

The observed steric course is fully consistent with the hypotheses previously expressed[1] to explain the behaviour of the conformationally mobile 1-phenylcyclohexane-1,2-diols, i.e., that the $S_{N}i$-type reaction with HCl (**20**) takes place preferentially in the conformations with equatorial benzylic OH, even if these are thermodynamically unfavoured (axial Ph), the ease of attack by the acid on the OH group and the



20

possibility to attain a transition state similar to **20** being essential. When the α-OH group is constrained in the axial position, the approach of the acid to it is hindered and reaction is only possible when also the β-OH group is axial, as in **4**, and can thus provide anchimeric assistance to the breaking of the benzylic C—O bond. The non-stereospecificity of the reaction of **4** must be due to the unfavourable character of a transition state of type **21**, which allows for other types of mechanisms to complete with the S_Ni-type displacement: for instance the reaction could proceed at least in



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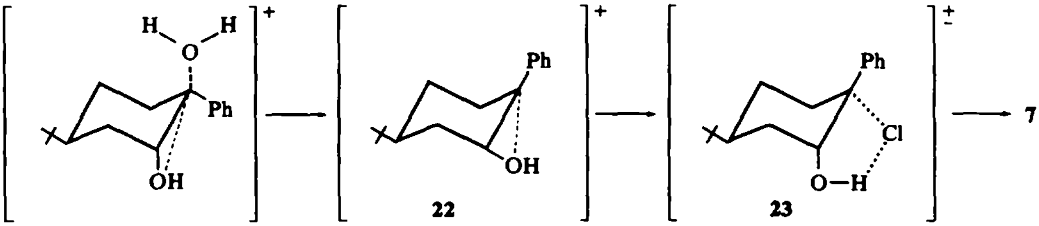

22 **23**

part through the stabilized carbonium ion **22** which could give the inverted chlorohydrin **7** through a transition state involving an ion pair **23**, similar to that leading from the epoxide **1** to **7**.

The decrease in stereospecificity and the increase in rate when the reactions are conducted in the presence of water can be attributed to a facilitation in the formation of the positive charge α to the Ph group and to its solvation.

EXPERIMENTAL

M.ps were determined on a Kofler apparatus and are uncorrected. IR spectra for comparisons between compounds were taken on paraffin oil mulls on a Perkin-Elmer Infracord Model 137 and those for the determination of OH stretching bands with a Perkin-Elmer Model 257 double beam grating spectrophotometer in dried (P_2O_5) CCl_4, using the indene band at 3110 cm^{-1} as a calibration standard; a quartz cell of 2 cm optical length was employed, and the concentration of the solns was $5{\cdot}10^{-3}$M or lower to prevent intermolecular association. NMR spectra were determined on *ca.* 10% $CDCl_3$ solns with a JEOL C 60 HL spectrometer using TMS as an internal standard. The relative amounts of **7** and **8** were estimated from the NMR spectra on the basis of the area of the signals at 4·70 and 4·36 δ corresponding to the protons α to the OH group; the method has an accuracy of about ±5%. This method could not be used for analysis of mixtures of **9** and **10** because of the partial overlap of the signals. The mixtures were therefore analyzed by TLC on silica gel plates (Merck F_{254}) containing a fluorescent indicator, dried for 3 hr at 120° and 2 hr at 150°, a 7/3 mixture of pet ether–ethyl ether being used as the eluant. Spots were detected under UV light (245 nm) and the relative amounts of the products were estimated by visual comparison of the intensities of the spots with those relative to a series of artificial mixtures; although the precision of this method is not high, the results are certainly valid within a limit of error of $\pm 10\%$. All comparisons between compounds were made on the basis of their IR and NMR spectra. "Usual treatment" stands for washing with water, sat $NaHCO_3$ aq, water, drying and evaporation. $MgSO_4$ was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Pet ether refers to the fraction boiling at 30–50°. $CHCl_3$ was refluxed over P_2O_5 and rectified.

The preparation of compounds **1**, **2**, **3**, **4**, **5** and **6** has already been described.[2]

Reactions of t-4-t-*butyl*-r-1,2-*epoxy*-1-*phenylcyclohexane* (**1**)*

(a) *With* HCl *in dry* $CHCl_3$. Dry gaseous HCl was bubbled through a soln of **1** (0·100 g) in dry $CHCl_3$ (10 ml) to saturation. After 15 min at room temp the usual treatment gave a residue (0·098 g) (Table 1) which was crystallized from 2-propanol-H_2O to yield *t*-5-t-butyl-*c*-2-chloro-2-phenyl-*r*-cyclohexanol (**7**) (0·060 g), needles, m.p. 79–81°. (Found: C, 71·97; H, 8·77; $C_{16}H_{23}ClO$ requires: C, 72·01; H, 8·69%). The IR spectrum of crude mixture was practically identical to that of pure **7**, carbonyl compounds being completely absent.

(b) *With* 36% *aqueous hydrochloric acid in* $CHCl_3$. A soln of **1** (0·100 g) in $CHCl_3$ (10 ml) was shaken 50 min with 36% HCl aq (2·1 ml); usual treatment gave a residue (0·096 g) which consisted mostly of **7** and **8** (Table 1). The IR spectrum of the crude reaction product showed a weak CO band at 1700 cm^{-1}.

(c) *With* HCl *in 2-propanol*. A soln of **1** (0·440 g), in 2-propanol (4 ml) was treated with 6·5N soln of HCl in 2-propanol (17 ml), kept 4 hr at 5° with occasional stirring, diluted with water and extracted with ether. Usual treatment yielded a solid residue (0·420 g) composed mainly of a mixture of the chlorohydrins **7** and **8** (Table 1). Crystallization from pet ether gave pure *t*-5-t-butyl-*t*-2-chloro-2-phenyl-*r*-cyclohexanol (**8**) (0·230 g), needles, m.p. 134–135°. (Found: C, 72·00; H, 8·51; $C_{16}H_{23}ClO$ requires: C, 72·01; H, 8·69%). The IR spectrum of the crude reaction product showed a weak CO band at 1700 cm^{-1}.

Reactions of t-4-*t-butyl*-1-*phenyl*-r-1,c-2-*cyclohexanediol* (**3**)

(a) *With* HCl *in dry* $CHCl_3$. A soln of **3** (0·100 g) in dry $CHCl_3$ (10 ml) was saturated with dry gaseous HCl, left 60 min at room temp and treated as usual. The residue (0·096 g) consisted exclusively of **7**.

(b) *With* 36% *aqueous hydrochloric acid in* $CHCl_3$. A soln of **3** (0·300 g) in $CHCl_3$ (10 ml) was shaken 20 min with 36% HCl aq (2·1 ml); usual treatment gave a residue consisting of a mixture of **7** and **8** (Table 1) completely free of carbonyl compound.

Reactions of c-4-*t-butyl*-1-*phenyl*-r-1,t-2-*cyclohexanediol* (**4**).

(a) *With* HCl *in dry* $CHCl_3$. Dry gaseous HCl was bubbled through a soln of **4** (0·070 g) in dry $CHCl_3$ (10 ml) to saturation. After 40 hr at room temp the usual treatment produced a solid residue (0·068 g) which consisted mostly of unreacted **4** and of small quantity of **7**, **8** and of carbonylic products (ν_{CO} 1710 cm^{-1}).

(b) *With* 36% *aqueous hydrochloric acid in* $CHCl_3$. A soln of **4** (0·300 g) in $CHCl_3$ (10 ml) was shaken 24 hr with 36% HCl aq (2·1 ml); usual treatment gave a solid residue (0·320 g) consisting mainly of **7** and **8** (Table 1). The IR spectrum showed a weak CO band at 1700 cm^{-1}. If the reaction mixture was left only 1 hr at room temp before work-up, compound **4** was recovered almost unchanged.

When the chlorohydrins **7** and **8** were treated as described above for 24 hr they were recovered unchanged.

Reactions of c-4-*t-butyl*-r-1,2-*epoxy*-1-*phenylcyclohexane* (**2**)

(a) *With* HCl *in dry* $CHCl_3$. Dry gaseous HCl was bubbled to saturation through a soln of **2** (0·700 g) in dry $CHCl_3$ (30 ml). After 10 min the usual treatment gave a solid residue (0·784 g) (Table 1) exhibiting a small CO band at 1710 cm^{-1}. Crystallization from pet ether gave *c*-5-t-butyl-*c*-2-chloro-2-phenyl-*r*-cyclohexanol (**9**) (0·570 g), blades, m.p. 64–66°. (Found: C, 72·14; H, 8·67; $C_{16}H_{23}ClO$ requires: C, 72·01; H, 8·69%).

(b) *With* HCl *in 2-propanol*. A soln of **2** (0·200 g) in 2-propanol (3·2 ml) was treated with 8·7N soln of HCl in 2-propanol (4·8 ml), stored 24 hr at 5°, then diluted with water and extracted with ether. After the

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* The IUPAC 1968 Tentative Rules, Section E, have been adopted to designate the relative configurations; see *J. Org. Chem.* **35**, 2849 (1970).

usual treatment an oily residue (0·210 g) was obtained which consisted mainly of **9** and **10** (Table 1) and showed a CO band at 1710 cm^{-1}.

Reactions of c*-4-t-butyl-1-phenyl-*r*-1,*c*-2-cyclohexanediol* (**5**)

(a) *With* HCl *in dry* $CHCl_3$. A soln of **5** (0·020 g) in dry $CHCl_3$ (3 ml) was saturated with gaseous HCl and treated as usual after 7 hr at room temp. The starting product was recovered unchanged.

(b) *With* 36% *aqueous hydrochloric acid in* $CHCl_3$. A soln of **5** (0·100 g) in $CHCl_3$ (7 ml) was treated with 36% HClaq (1 ml) and shaken 65 hr. Usual treatment gave a crude residue (0·095 g) consisting mostly of unreacted **5**. The IR spectrum showed a CO band at 1700 cm^{-1} and some very weak band that are absent in the spectrum of pure **5**.

Reactions of t*-4-t-butyl-1-phenyl-*r*-1,*t*-2-cyclohexanediol* (**6**)

(a) *With* HCl *in dry* $CHCl_3$. Dry gaseous HCl was bubbled through a soln of **6** (0·180 g) in dry $CHCl_3$ (20 ml) to saturation. After 60 min at room temp the usual treatment yielded an oily residue (0·188 g) exhibiting a CO band at 1710 cm^{-1} and consisting mostly of *c*-5-t-butyl-*t*-2-chloro-2-phenyl-*r*-cyclohexanol (**10**) (Table 1). This chlorohydrin is a liquid, and it was not possible to obtain it in a completely pure form: however, the NMR and IR data (Table 2) left no doubt about its structure.

(b) *With* 36% *aqueous hydrochloric acid in* $CHCl_3$. A soln of **6** (0·100 g) in $CHCl_3$ (4 ml) was shaken 30 min with 36% HClaq (0·7 ml). Usual treatment gave a residue (0·099 g) consisting mainly of **9** and **10** (Table 1): a CO band at 1710 cm^{-1} was detected in the IR.

c*-5-t-Butyl-*r*-2-chloro-2-phenylcyclohexanone* (**11**)

(a) A soln of **8** (0·100 g) in acetone (5 ml) was treated with Jones reagent[9] (0·094 ml). After 15 min the mixture was diluted with water and extracted with ether. Usual treatment gave **11** (0·090 g) which crystallized from 2-propanol-H_2O, as needles, m.p. 62–63°, ν_{CO} 1720 cm^{-1}. (Found: C, 72·67; H, 7·97; $C_{16}H_{21}ClO$ requires: C, 72·56; H, 8·00%).

(b) **9** (0·100 g) was oxidized under the conditions used above to give **11** (0·096 g) which after crystallization from 2-propanol melted at 60–62°.

t*-5-t-Butyl-*r*-2-chloro-2-phenylcyclohexanone* (**12**)

(a) A soln of **7** (0·210 g) in acetone (5 ml) was treated with Jones reagent[9] (0·198 ml), left for 10 min at room temp, diluted with water and extracted with ether. Usual treatment gave **12** (0·206 g) which crystallized from pet ether in prisms, m.p. 122–123°, ν_{CO} 1735 cm^{-1}. (Found: C, 72·78; H, 7·93; $C_{16}H_{21}ClO$ requires: C, 72·56; H, 8·00%).

(b) Oxidation of the product obtained from the reaction of **6** with gaseous HCl in dry $CHCl_3$ (see above) (0·090 g) as described under (a) gave a solid residue (0·087 g) which was crystallized from pet ether to give **12** (0·045 g), m.p. 121–122°.

Dehydrohalogenation of **8** *and* **10**

(a) A soln of **8** (0·080 g) in 2-propanol (3 ml) was treated with 0·1N NaOHaq (5 ml), stirred for 45 min, diluted with water and extracted with ether. Usual treatment gave a solid (0·065 g) consisting of **1** (IR).

(b) A soln of product obtained from the reaction of **6** with gaseous HCl in dry $CHCl_3$ (0·090 g) (see above) in 2-propanol (5 ml) was treated with KOH (0·1 g), then heated at 100° for 1 hr, diluted with water and extracted with ether. Usual treatment yielded an oily residue (0·073 g) which gave, on crystallization from EtOH, **2** (0·040 g) (IR).

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