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STEREOCHEMISTRY OF NUCLEOPHILIC DISPLACEMENT REACTIONS AT THE THIOPHOSPHORYL CENTRE—II*

HYDROLYSIS OF OPTICALLY ACTIVE O-ETHYL ETHYLPHOSPHONOCHLORIDOTHIONATE

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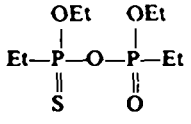
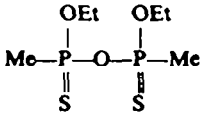
Abstract—Investigations concerning hydrolysis of optically active O-ethyl ethylphosphonochloridothionate (II) are described. Alkaline hydrolysis of the (−)chloride (II) proceeds with inversion of configuration at the asymmetric P atom. The mechanism of hydrolysis of the chloride (II) in water-DMF mixture and in the presence of imidazole or pyridine is discussed.

HYDROLYSIS of phosphoryl and thiophosphoryl compounds of four-bonded phosphorus is an important biological process and, represents one of the fundamental nucleophilic substitutions at the phosphorus atom.[1] The mechanism of the hydrolysis has been studied by using kinetic and tracer methods.[2]

Until recently, the inaccessibility of suitable optically active phosphorus compounds precluded sterochemical investigations on the mechanism of the hydrolysis. Optically active phosphoryl compounds of the general formula RR'P(O)X (where X = Cl, OR, SR or NR_2) are hydrolysed to acids RR'POOH which are optically inactive. Also, thiopyrophosphonate (A), the first optically active compound containing a thiophosphoryl P(S) grouping, is unsuitable for such investigations, because the OH ion or any other nucleophilic reagent attacks the phosphoryl group P(O).[3]



(A)



(B)

Dithiopyrophosphonate (B) containing one optically active phosphorus atom was hydrolysed in an alkaline medium.[4] Formation of racemic phosphonothioic

* Paper XXXVII in the series "Organophosphorus Compounds of Sulphur and Selenium". Stereochemistry of Nucleophilic Displacement Reactions at the Thiophosphoryl Centre—I, J. Michalski and M. Mikołajczyk, *Tetrahedron*, **22**, 3055 (1966).

[1] R. D. O'Brien, *Toxic Phosphorus Esters*. Academic Press, New York (1960).
[2] J. R. Cox and O. B. Ramsay, *Chem. Revs.* **64**, 317 (1964).
[3] J. Michalski, M. Mikołajczyk and A. Ratajczak, *Chem. & Ind.* 819 (1962); *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **13**, 277 (1965).
[4] M. Green and R. F. Hidson, *J. Chem. Soc.* 3883 (1963).

acid, Me(EtO)P(S)OH, proves that the alkaline hydrolysis proceeds with inversion of configuration at the phosphorus atom.

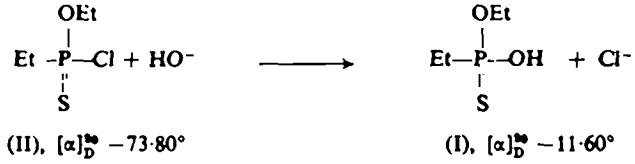
Synthesis of optically active O-ethyl ethylphosphonochloridothionate (II)[5] has enabled the stereochemistry of the hydrolysis to be investigated more extensively.

The present paper describes the results of investigations on the hydrolysis of optically active chloride (II) in an alkaline medium, in water-DMF mixture, and in the presence of imidazole or pyridine.

RESULTS AND DISCUSSION

Alkaline hydrolysis

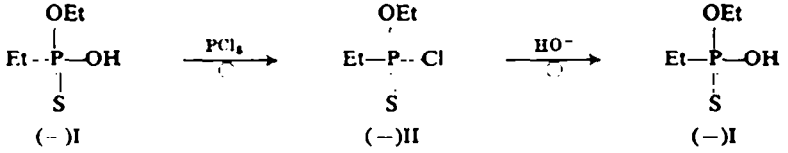
(−)Chloride II, $[\alpha]_D^{20}$ −73·80°, was hydrolysed in 2N KOH-dioxan for 5 hr at room temperature to yield (86%) (−)acid I, $[\alpha]_D^{20}$ −11·60°.



(II), $[\alpha]_D^{20}$ −73·80° (I), $[\alpha]_D^{20}$ −11·60°

As the (−)chloride II, $[\alpha]_D^{20}$ −81·85°, obtained from (−)acid I, $[\alpha]_D^{20}$ −14·00°, was at least 97·5% optically pure,[5] the stereospecificity of the alkaline hydrolysis may be estimated at 97%. The slight decrease in the stereospecificity of the hydrolysis is doubtlessly caused by racemization of the (−)chloride II in the presence of chloride ions formed in the reaction.[6]

The synthesis of optically active chloride II and its alkaline hydrolysis form a cycle of two reactions, each of which proceeds with inversion of configuration at the thiophosphoryl centre and which together lead to the acid I of the original configuration.



This stereochemical interpretation is confirmed by studies on the stereochemistry of alkaline hydrolysis of optically active thio- and dithiopyrophosphonates.[7,8] In a similar cycle also composed of two reactions, the first reaction proceeds with the asymmetric centre left unaffected, whereas the second, i.e. the alkaline hydrolysis, involves inversion of configuration at the thiophosphoryl centre. As a result, the cycle afforded acid I of the configuration opposite to the original.

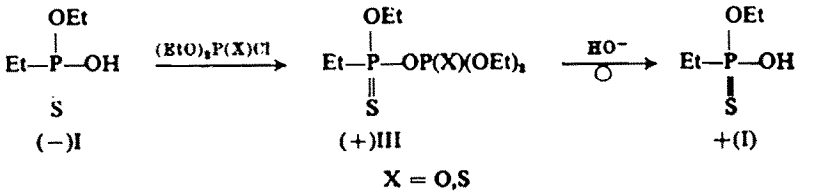
In the alkaline hydrolysis of chloride II and of other thiophosphoryl compounds, the transition state most likely to occur appears to be a trigonal bipyramid with pd-sp^2 hybrids, in which the entering nucleophile and the leaving group occupy axial

[5] J. Michalski and M. Mikołajczyk, *Chem. & Ind.* 661 (1964); *Chem. Comm.* 35 (1965); *Tetrahedron* **22**, 3055, (1966).

[6] J. Michalski, M. Mikołajczyk, A. Halpern and K. Prószyńska, *Tetrahedron Letters* No. **18**, 1919 (1966).

[7] J. Michalski, M. Mikolajczyk and J. Omelańczuk, *Tetrahedron Letters* No. 23, 1779 (1965).

[8] J. Michalski, M. Mikołajczyk, B. Młotkowska and J. Omelańczuk, paper in preparation.



positions. An alternative bipyramid transition state also resulting in inversion, but with the nucleophile and the leaving group occupying radial positions, appears to be less likely for the nucleophilic substitution of phosphorus acyclic esters.[9] The demonstration of a highly stereospecific inversion of configuration during the alkaline hydrolysis of optically active chlorides, anhydrides[4,7,8] and esters[7] containing the thiophosphoryl grouping proves also that in the same conditions the same nucleophile will react with related systems to produce the same stereochemical results. This assumption has often been made previously without experimental support.

Hydrolysis in water-dimethyl formamide mixture

Catalytic action of dimethylformamide (DMF) in reactions of phosphorus acid chlorides with nucleophilic reagents (water, alcohols, amines and acids) is usually interpreted in terms of formation of reactive DMF-chloride adducts as intermediates.[10-13] Phosphorus oxychloride yields a stable adduct[14] with DMF, for which the following alternative structures have been suggested:

$$(Me_2N{=}CH{-}O{-}P(O)Cl_2)^{+}Cl^{-} \qquad (Me_2N{=}CH{-}Cl)^{+}Cl_2P(O)O^{-}$$
a b

The results obtained[11] during the isolation of the dimethylchloromethyleneammonium cation as the hexachloroantimonate, support structure (b). The existence of this cation in the adduct of DMF to *p*-chlorophenyl phosphorodichloridate has therefore, been proved. The formation of transitory adducts of structure (c) in the reactions of dialkyl phosphorochloridates with nucleophilic reagents in the presence of DMF have been postulated.[10]

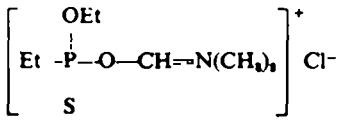
$$[(CH_3)_2N{=}CH{-}O{-}P(O)(OR)_2]^{+}Cl^{-}$$
c

Attempts to isolate the adduct of type (c) as the hexachloroantimonate failed. This fact may speak against the existence of a stable adduct, but it does not preclude its participation in phosphorylation reactions.

The hydrolysis of optically active chloride II was studied in the presence of DMF in order to gain an insight into the mechanism. If chloride II is hydrolysed via formation of the adduct (IV) and its subsequent hydrolysis, the resulting acid I may be expected to have the same configuration as the parent chloride II. Retention of configuration in this case would be the result of two inversions at the thiophosphoryl centre caused by

[9] N. K. Hamer, *J. Chem. Soc.* 404 (1966).
[10] F. Cramer and M. Winter, *Chem. Ber.* **94**, 989 (1961).
[11] Z. Arnold and A. Holy, *Collection* **27**, 2886 (1962).
[12] R. Rätz and O. J. Sweeting, *J. Org. Chem.* **28**, 1608 (1962).
[13] A. Zwierzak, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **11**, 333 (1963).
[14] H. Bredereck, R. Gomper, K. Klemm and H. Rempfer, *Chem. Ber.* **92**, 837 (1959).

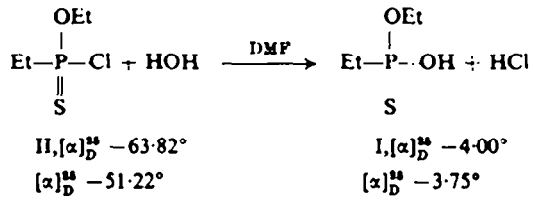
(i) the nucleophilic attack by the DMF carbonyl oxygen atom on the P atom of the chloride II and (ii) the nucleophilic attack by a water molecule on the P atom of the adduct IV.



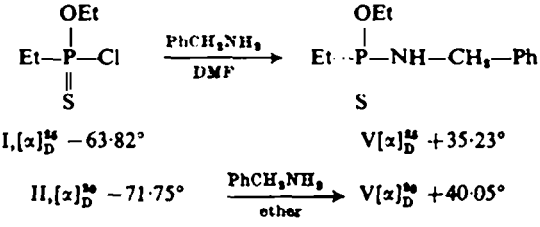
IV

These stereochemical considerations are valid if the two reactions proceed through the bipyramid transition state with the leaving and the entering group in axial positions. This transition state is responsible for inversion of configuration at the P atom and has been generally accepted for typical nucleophilic substitutions of phosphorus esters.[15] Moreover, no example has so far been reported of a simple substitution proceeding with retention of configuration at the P atom.

Preliminary experiments showed that racemic chloride II is rapidly hydrolysed in water-DMF mixture. It was however somewhat difficult to obtain the acid I free from residual DMF. Analytically pure acid I was prepared via the cyclohexylammonium salt in 60% yield. Hydrolysis of (−)chloride II, $[\alpha]_D^{20}$ −63·82°, gave (−)acid I, $[\alpha]_D^{25}$ −4·00°. In another experiment carried out in the same conditions, (−)chloride II, $[\alpha]_D^{25}$ −51·22°, yielded (−)acid I, $[\alpha]_D^{25}$ −3·75°.



The formation of the laevorotatory acid I indicates that, as in the alkaline medium, the hydrolysis in dimethylformamide–water mixture proceeds with inversion of configuration at the thiophosphoryl centre, though with a much reduced stereospecificity. Two factors may account for the diminished stereospecificity, viz., participation of the above-mentioned retention mechanism in the hydrolysis and/or racemization of (−)chloride II by the hydrogen chloride which is produced. The latter factor appears to be the more likely, especially in the light of the data concerning aminolysis of (−)chloride II with benzylamine in DMF or ether as solvent. Comparison of the signs and specific rotations of the amidates V, with due account of the



[15] R. F. Hudson and M. Green, *Angew. Chem.* 75, 47 (1963).

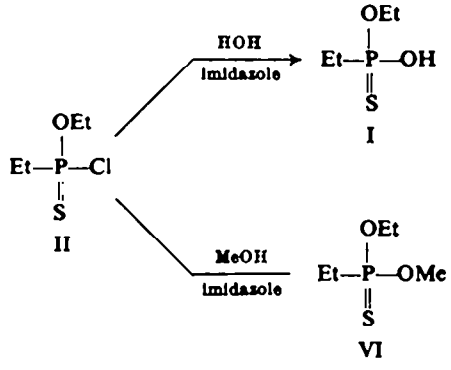
differences in the optical purity of the starting chlorides II, indicates that in each solvent the stereospecificity and configurational changes are the same.

The results of hydrolysis and aminolysis of optically active chloride II do not support formation of adduct IV in the experimental conditions employed. The higher rate of hydrolysis of chloride II in DMF-water as compared with that in water is attributed to the higher polarity and better solvating properties of the reaction medium.

Hydrolysis in the presence of heterocyclic amines

Heterocylic amines can catalyse solvolysis of phosphorus halides and anhydrides, by acting either as basic or as nucleophilic catalysts.[2] Sterically unhindered bases particularly imidazole and pyridine are believed to act as nucleophilic catalysts. In propanol containing 2,6-lutidine, tetrabenzyl pyrophosphate is solvolysed by a general base catalysis,[16] whereas in the presence of N-methylimidazole the catalysis involves the nucleophilic attack on phosphorus.[17] In the presence of imidazole, the same process goes via N (dibenzylphosphoryl) imidazole as an intermediate.[17] Similarly, the catalytic effect of pyridine is attributed to its being highly nucleophilic towards phosphorus. This view is consistent with the effect of pyridine and 2,6-lutidine on the stereochemistry of the reaction of optically active acid I with dicyclohexylcarbodiimide.[18]

Hydrolysis of the optically active chloride II in the presence of imidazole was studied. Hydrolysis and methanolysis of racemic chloride II occur within ca. 20 hr at room temperature to afford acid I and ester VI, respectively. Physical constants and IR spectrum of the ester VI were identical with those of the authentic specimen.



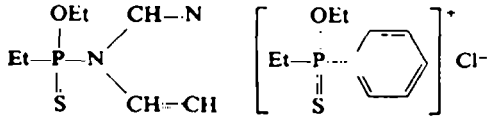
When hydrolysed under these conditions, optically active (−)chloride II, $[\alpha]_D^{25}$ −43·10°, yielded a dextrorotatory acid I with a very low specific rotation. The optical rotation of pure acid I was as follows $[\alpha]_{589}^{25}$ +0·054°, $[\alpha]_{578}^{25}$ +0·063°, $[\alpha]_{546}^{25}$ +0·070°, $[\alpha]_{436}^{25}$ +0·103°.

Although this result may be evidence for formation of N-(O-ethyl ethylphosphonothioyl)imidazole (VII)* as an intermediate, and thus for two inversions accompanying the hydrolysis, it is considerably weakened by the almost complete deficiency

* The synthesis and properties of VII will be descibed elsewhere.

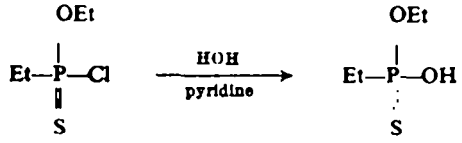
[16] G. O. Dudek and F. H. Westheimer, *J. Amer. Chem. Soc.* **81**, 2641 (1959).
[17] R. Blakeley, F. Kerst and F. H. Westheimer, *J. Amer. Chem. Soc.* **88**, 112 (1966).
[18] M. Mikolajczyk, *Chem. Ber.* in press.

of optical activity in the resulting acid I. The reason is presumably a rapid racemization of (−)chloride II in the presence of imidazole hydrochloride.



VII VIII

With pyridine as catalyst, hydrolysis of the (+)-chloride II, $[\alpha]_D^{25}$ +51·90° yielded the racemic acid I. In this case, racemization may have been effected not only



II, $[\alpha]_D^{25}$ +51·90° I, $[\alpha]_D^{25}$ 0·00°

by a rapid chloride–chloride exchange in the chloride II but also by formation of an unstable pyridinium cation VIII which on decomposition produces a planar phosphonium cation, phosphorylating water rapidly. This hypothesis requires further experiments with optically active objects in which the first type of the racemization is excluded.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Extracts were dried over $MgSO_4$. Optical activity measurements were made with a Hilger and Watts polarimeter (sensitivity ±0·01°). In one case a Perkin–Elmer 141 photopolarimeter (sensitivity ±0·002°) was used. Neat compounds were used for all specific rotation determinations mentioned in the paper.

Alkaline hydrolysis of the (−)*O-ethyl ethylphosphonochloridothionate* (II). A soln of the (−)chloride II (3·45 g, 0·02 mole), $[\alpha]_D^{20}$ −73·80° in dioxan (40 ml) was added with stirring to KOH (11·2 g, 0·2 mole) in water (100 ml). The soln was stirred for 5 hr then extracted with benzene (30 ml). The alkaline layer was acidified with conc HCl (30 ml) and extracted with benzene (5 × 25 ml). After removing of the solvent the residue was distilled, to give I (2·65 g, 86%), b.p. 49–51°/0·01 mm, n_D^{20} 1·4905, $[\alpha]_D^{20}$ −11·60°. (Found: C, 31·25; H, 7·4; P, 19·45. Calc. for $C_4H_{11}O_2PS$: C, 31·2; H, 7·2; P, H 20·1%.)

Hydrolysis of the (±)*O-ethyl ethylphosphonochloridothionate* (II) *in water-DMF mixture.* The racemic chloride II (3·45 g, 0·02 mole) was added to the soln of water (5 ml) and DMF (15 ml). The mixture was stirred for 2 hr at room temp, evaporated at 60° under red. press. (1·5 mm) on rotatory evaporator and the residue taken up in benzene (50 ml). The organic layer was extracted with NaOHaq. The aqueous layer was acidified with conc H_2SO_4 (5 ml) and extracted with chf (4 × 25 ml). After drying and removal of the solvent, the residue was distilled to give 2·3 g of the acidic fraction b.p. 49–53°/0·01 mm, n_D^{25} 1·4837. It was converted into cyclohexylamonium salt, m.p. 126–127°, (2·85 g, 57%). Mixture m.p. with authentic cyclohexylammonium salt of the acid I gave no depression.

The free acid I obtained from cyclohexylammonium salt had b.p. 51–52°/0·02 mm, n_D^{27} 1·4870 (1·37 g).

Hydrolysis of the (−)*O-ethyl ethylphosphonochloridothionate* (II) *in water-DMF mixture.* Following the above procedure, the (−)chloride II (2·87 g, 0·017 mole), $[\alpha]_D^{26}$ −51·22°, was hydrolysed in a mixture of water (5 ml) and DMF (10 ml), to give 2·29 g of the acidic fraction b.p. 49–54°/0·02 mm, n_D^{24} 1·4823, $[\alpha]_D^{26}$ −1·66°. The cyclohexylammonium salt (3·12 g) prepared had m.p. 120–124°. (Found: C, 47·4; H, 9·35; P, 12·3; S, 12·5; N, 5·5. Calc. for $C_{10}H_{24}O_2PSN$: C, 47·4; H, 9·55; P, 12·2; S, 12·65; N, 5·5%.)

This salt was dissolved in water (15 ml), acidified with conc H_2SO_4 (2 ml) and extracted with chf (4 × 25 ml). After drying, the chf was removed. Distillation of the residue gave I b.p. 49–50°/0·01 mm, n_D^{26} 1·4870, $[\alpha]_D^{26}$ −3·75° (1·56 g, 61%). Found: C, 31·25; H, 7·1; P, 20·1; S, 20·7. Calc. for $C_6H_{11}O_3PS$: C, 31·2; H, 7·2; P, 20·1; S, 20·5%.)

According to this procedure in another experiment with (−)chloride II (3·45 g, 0·02 mole) $[\alpha]_D^{25}$ −63·82°, the acidic fraction (3·43 g), n_D^{21} 1·4820, $[\alpha]_D^{20}$ −1·02°, was obtained. It was converted into cyclohexylammonium salt m.p. 119–124° (3·50 g), from which pure I was liberated b.p. 49–50°/0·01 mm, n_D^{26} 1·4876, $[\alpha]_D^{25}$ −4·00° (1·69 g, 55%).

Reaction of (−)*O-ethyl ethylphosphonochloridothionate* (II) *with benzylamine.* The (−)chloride II (1·73 g, 0·01 mole), $[\alpha]_D^{25}$ −63·82°, in ether (10 ml) was added dropwise at −10° to DMF (10 ml) and after several min this soln was treated with benzylamine (2·14 g, 0·02 mole) in ether (10 ml). After standing overnight the precipitated benzylammonium chloride was removed by fitration and the soln was evaporated under reduced press. The residue was taken up in chf (50 ml) washed with water (15 ml), dried and evaporated *in vacuo*. Crude V was purified by distillation; b.p. 98–99°/0·01 mm, $n_D^{20.5}$ 1·5492, $[\alpha]_D^{25}$ +35·23 (2·03 g, 83%). (Found: C, 54·3; H, 7·3; P, 12·55; S, 13·1; N, 5·4. Calc. for $C_{11}H_{18}ONPS$: C, 54·3; H, 7·5; P, 12·7; S, 13·6; N, 5·75%.)

Using ether as solvent (35 ml) from (−)chloride II (2·30 g, 0·013 mole) $[\alpha]_D^{25}$ −71·75° and benzylamine (2·86 g, 0·026 mole) V was obtained; b.p. 98–99°/0·01 mm, n_D^{19} 1·5556, $[\alpha]_D^{25}$ +40·05°, (2·4 g, 74%).

Hydrolysis of the (±)*O-ethyl ethylphosphonochloridothionate* (II) *in the presence of imidazole.* The mixture of water (40 ml), dioxan (30 ml) and imidazole (2·72 g, 0·04 mole) was treated dropwise with the racemic chloride II (3·45 g, 0·02 mole) in dioxan (10 ml). After 20 hr the clear soln was acidified with conc H_2SO_4 (1·5 ml), extracted with chf (5 × 25 ml), dried and evaporated *in vacuo*. The residue was taken up in pet. ether (35 ml, b.p. 30–40°) and cyclohexylamine was added. The cyclohexylammonium salt of I formed (3·36 g, 67%) had m.p. 124–127°, undepressed on admixture of the authentic specimen,

Methanolysis of the (±)*O-ethyl ethylphosphonochloridothionate* (II) *in the presence of imidazole.* The soln of the racemic chloride II (3·45 g, 0·02 mole) and imidazole (2·72 g, 0·04 mole) in MeOH (40 ml) was allowed to stand overnight (ca. 20 hr). After removed of MeOH, the residue was dissolved in chf (50 ml). The organic layer was washed with 5% HCl and water, dried and evaporated. Crude VI was distilled; b.p. 74°/15 mm, n_D^{21} 1·4670, (2·46 g, 73%). IR spectrum identical with that of VI prepared from the chloride II and sodium methoxide. (Found: C, 36·2; H, 7·4; P, 17·1; S, 18·95. Calc. for $C_6H_{13}O_3PS$: C, 35·7; H, 7·8; P, 18·4; S, 19·1%.)

Hydrolysis of the (−)*O-ethyl ethylphosphonochloridothionate* (II) *in the presence of imidazole* To the soln of imidazole (2·04 g, 0·03 mole) in water (30 ml) and dioxan (20 ml) the (−)chloride II (2·59 g, 0·015 mole), $[\alpha]_D^{25}$ −43·10°, was added at room temp. After standing for 24 hr at room temp, the reaction mixture was acidified with conc H_2SO_4 (1 ml) and extracted with chf (4 × 25 ml). After removal of chf, the residue was distilled *in vacuo* to afford I, b.p. 60–62°/0·03 mm, n_D^{20} 1·4890, (1·47 g, 64%). The optical rotation of the pure I gave the following values; $[\alpha]_{589}^{25}$ +0·054°, $[\alpha]_{578}^{25}$ +0·063°, $[\alpha]_{546}^{25}$ +0·070°. $[\alpha]_{436}^{25}$ +0·103

Hydrolysis of the (+)*O-ethyl ethylphosphonochloridothionate* (II) *in the presence of pyridine.* The soln of water (50 ml), dioxan (20 ml) and pyridine (4·75 g, 0·06 mole) was treated with the (+)chloride II (2·5 g, 0·015 mole), $[\alpha]_D^{25}$ +51·90°, at room temp and left to stand overnight. The reaction mixture was acidified with conc HCl (5 ml), extracted with chf (3 × 50 ml) and dried. After removal of the solvent the residue was distilled to give I; b.p. 62–63°/0·4 mm, n_D^{21} 1·4900, (1·5 g, 68%). The optical rotation of the pure acid was zero (±0·01°).

The author is indebted to Professor dr. J. Michalski for his interest.