Reaction of Phosphoryl Chloride in Pyridine with Halogenohydrins

By **A. Guzmán, P. Ortiz de Montellano,** and **Pierre Crabbé,*** Research Laboratories, Syntex, S. A., Apartado Postal 10–820, Mexico 10, D. F. Mexico

The reaction of iodohydrins with a solution of phosphoryl chloride in pyridine constitutes a useful modification of the Cornforth method for the stereospecific preparation of olefins.

SEVERAL methods exist for the conversion of 1,2-halogenohydrins (1) or epoxides (2) into olefins (3). These include treatment with metallic reagents such as zinc,[1,2] chromium salts,[3] sodium,[4] or magnesium [5] as well as non-metallic agents such as iodides [6] and phosphines.[7] The mixed reagent phosphoryl chloride–tin(II) chloride–pyridine has been developed by Cornforth *et al.*[3] Although several of these methods give high yields of olefin, all but the last suffer from lack of stereospecificity. The Cornforth procedure, however, is restricted to iodohydrins.[3] Furthermore, most of these procedures are incompatible with compounds containing reactive halogens such as allylic bromides, owing to reaction of these centres with the metals involved.

We report a variant of the Cornforth technique which is not only stereospecific but sometimes also applicable to bromohydrins and does not involve the use of reactive metal salts.

The reaction is illustrated by treatment of the iodohydrin (4a) with 1·5 equiv. of phosphoryl chloride in pyridine solution at 0°, which afforded the olefinic lactone (5a) in 99% yield. Similarly, the *O*-benzyl analogue (4b) provided the olefin (5b) in essentially quantitative yield.[8]

A comparative study of the reaction occurring with cyclic iodo-, bromo-, and chloro-hydrins was then undertaken with steroidal halogenohydrins.

3α-Hydroxy-2β-iodoandrostan-17β-yl acetate (7a) was prepared from 2α,3α-epoxyandrostan-17β-yl acetate (6) [9] by treatment with hydroiodic acid. The corresponding bromohydrin (7b) [10] and chlorohydrin (7c) were prepared by analogous reactions with hydrobromic and hydrochloric acids.

Treatment of the iodohydrin (7a) with 3 equiv. of phosphoryl chloride in pyridine at 5° for 1·5 h gave the olefin (8) in 94% yield. The same olefin was obtained in 10% yield when the bromohydrin (7b) was treated

[1] S. J. Cristol and L. E. Rademacher, *J. Amer. Chem. Soc.*, 1959, **81**, 1600; H. O. House and R. S. Ro, *ibid.*, 1958, **80**, 182; L. F. Fieser and R. Ettorre, *ibid.*, 1953, **75**, 1700; S. M. Kupchan and M. Maruyama, *J. Org. Chem.*, 1971, **36**, 1187.

[2] J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 112.

[3] (*a*) J. K. Kochi, D. M. Singleton, and L. J. Andrews, *Tetrahedron*, 1968, **24**, 3503; (*b*) J. K. Kochi and D. M. Singleton, *J. Amer. Chem. Soc.*, 1968, **90**, 1582.

[4] E. D. Amstutz, *J. Org. Chem.*, 1944, **9**, 310; B. Wohl, *Ber.*, 1910, **43**, 2175.

[5] F. Bertini, P. Grasselli, G. Zubiani, and G. Cainelli, *Chem. Comm.*, 1970, 144.

[6] S. J. Cristol, J. Q. Weber, and M. C. Brindell, *J. Amer. Chem. Soc.*, 1956, **78**, 598.

[7] S. Dershowitz and S. Proskauer, *J. Org. Chem.*, 1961, **26**, 3595; C. Tung and A. Speziale, *ibid.*, 1963, **28**, 1521.

[8] P. Crabbé and A. Guzmán, *Tetrahedron, Letters*, 1972, 115.

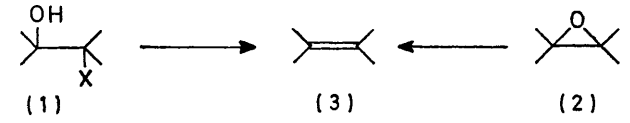
[9] J. Fajkoš and F. Šorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3115.

[10] For related mechanistic postulates, see ref. 7, and S. Winstein, D. Pressman, and W. G. Young, *J. Amer. Chem. Soc.*, 1939, **61**, 1645.

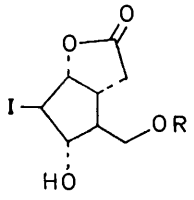
under similar conditions.* The major product of this reaction was a mixture of the bromo-chloro-derivative (7d) and the dibromo-compound (7e), as shown by the analytical and physical properties (see Experimental section).

The chlorohydrin (7c), however, did not give the olefin (8) when treated with phosphoryl chloride in pyridine. Instead the phosphate (7f) was obtained in 85% yield.

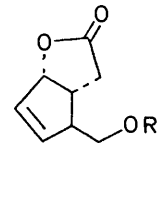
Having established the utility of the phosphoryl chloride–pyridine reagent for reductive eliminations of iodohydrins in rigid systems, we turned our attention to



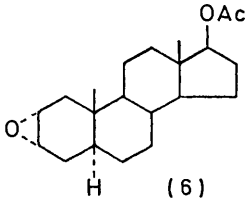
(1) (3) (2)



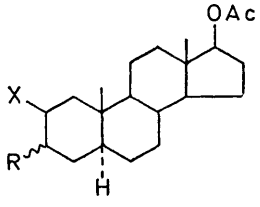
(4) a; R = Me
b; R = CH_2Ph



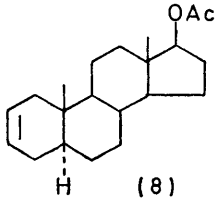
(5) a; R = Me
b; R = CH_2Ph



(6)



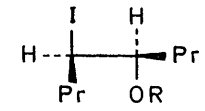
(7) a; X = I, R = α-OH
b; X = Br, R = α-OH
c; X = Cl, R = α-OH
d; X = Br, R = β-Cl
e; X = Br, R = β-Br
f; X = Cl, R = α-OP(OH)$_2$



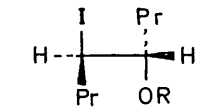
(8)

non-cyclic compounds and to the question of stereospecificity. For this purpose, the *threo*- (9a) and *erythro*-iodohydrin (10a) were prepared from the corresponding *cis*- and *trans*-olefins (11) and (12).

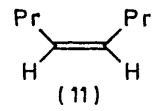
Reaction of the *threo*-iodohydrin (9a) with phosphoryl chloride in pyridine for 2 h at 0° afforded exclusively the *cis*-olefin (11) in 10% yield,* along with 50% of the phosphate (9b). When the same reaction was performed at the b.p., the yield of olefin (11) was increased to 35%. No trace of the *trans*-olefin (12) was detected by chromatographic or spectroscopic methods. In addition, the sole olefin obtained on reaction of the *erythro*-isomer (10a) at 0° was the *trans*-olefin (12) (13%),* with only the phosphate ester (10b) (50%) as a side product. The yield of (12) was 40% from a reaction at reflux temperature.



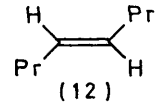
(9) a; R = H
b; R = P(OH)$_2$



(10) a; R = H
b; R = P(OH)$_2$



(11)

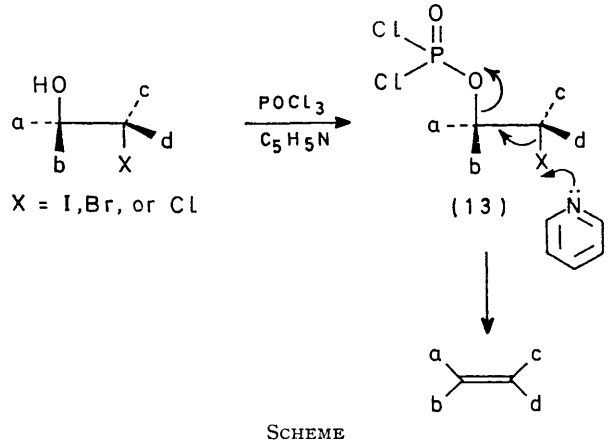


(12)

When this reaction was performed in collidine instead of pyridine, the yields were not improved, and in piperidine at room temperature the sole product was the corresponding epoxide. When hexamethylphosphoric triamide was used (reflux temperature), the yield of olefin could be increased to 50%.*

The difference in reactivity of phosphoryl chloride–pyridine in the presence or absence of tin(II) chloride is striking and unexpected. Cornforth *et al.* report that no olefin was obtained by treating one bromohydrin and one chlorohydrin in the presence of tin(II) chloride.[3] The reason for the difference in reactivity is not clear, but could be either reactions of the tin(II) reagent † with phosphoryl chloride over the longer reaction periods required for bromohydrins, or side reactions occurring with the substrate itself.

Mechanistically, the reductive elimination of halogenohydrins in the presence of phosphoryl chloride–pyridine can be represented as shown in the Scheme.[10] Initial



X = I, Br, or Cl

(13)

SCHEME

reaction of the alcohol system with phosphoryl chloride leads to an intermediate of type (13), which could give the olefin. In this case, one would expect the reaction to be stereospecific, in agreement with our results.

* Conditions for obtaining the optimum yield have not been sought.

† Cornforth *et al.*[3] observed the formation of yellow phosphorus when longer reaction times are used. We did not observe formation of this material in the absence of tin(II) chloride.

The postulated mechanism can also be used to rationalise the results obtained with the chlorohydrin (7c). The elimination from the intermediate (13), when X is Cl, can be expected to be substantially more difficult energetically than for the corresponding bromide or iodide.

The very mild reaction conditions, absence of reactive metals, potential applicability to bromohydrins as well as iodohydrins, stereospecificity, frequent high yields, and technical simplicity make phosphoryl chloride–pyridine an attr ctive and useful reagent.

EXPERIMENTAL

Microanalyses are due to Dr. A. Bernhardt, Mühlheim, Germany. M.p.s were determined with a Mel-temp apparatus; they are corrected. Rotations were taken between 16 and 22° with a 1 dm tube at the sodium D-line. I.r. spectra were taken with a Perkin-Elmer model 21 instrument (NaCl prism). U.v. spectra were obtained with a Beckman spectrophotometer, model DU. Unless otherwise stated, the n.m.r. spectra were recorded with a T-60 Varian instrument for 5—8% w/v solutions in [^{2}H]chloroform containing tetramethylsilane as internal reference. Coupling constants (J in Hz) are accurate to ± 1 Hz. The mass spectra were obtained with an Atlas CH-4 spectrometer.

4-Benzyloxy(or methoxy)methyl-3,3a,4,6a-tetrahydrocyclopenta[b]furan-2-one (5).—(*a*) Treatment of the iodohydrin (4a) with phosphoryl chloride in pyridine solution in the presence of tin(II) chloride [2] afforded the corresponding olefin (5a) (70%).

(*b*) Reaction of the iodohydrin (4b) with 1·5 equiv. of freshly distilled phosphoryl chloride in anhydrous pyridine solution at room temperature for 2 h provided 99% of the olefin (5b) as a liquid; $\nu_{max.}$ 1770, 1615, and 1120 cm^{-1}; δ 3·4br (–CH_2–O–), 4·5 (CH_2Ph), 5·82, 5·88, 6·02, and 6·05 (dd, J 2 and 6, 2 vinylic H), and 7·31 p.p.m. (Ph).[8]

(*c*) Similarly, when this reaction was performed with the corresponding methyl ether (4a), the olefinic methyl ether (5a) was obtained in essentially quantitative yields. Recrystallisation from hexane afforded a sample of m.p. 31—33°; $\nu_{max.}$ 1775 cm^{-1}; δ 3·25 (d, J 10, –CH_2–O–), 3·25 (OMe), 5·53 (m, –CH–O–CO–), and 5·82, 5·87, 5·93, and 5·97 p.p.m. (dd, J 2 and 6, 2 vinylic H); *m/e* 168 (M^+).

3α-Hydroxy-2β-iodo-5α-androstan-17β-yl Acetate (7a).—To the epoxide (6) (800 mg), m.p. 105—107°; $[\alpha]_D$ +16°; $\nu_{max.}$ 1720 and 1245 cm^{-1}; δ 0·79 (18-H_3, 19-H_3), 2·0 (17-OAc), 3·1 (2-H, 3-H), and 4·60 p.p.m. (17α-H) [9] in tetrahydrofuran (10 ml) cooled to 5°, sodium iodide (720 mg) and 50% iodohydric acid (0·8 ml) were added. After being stirred for 1·5 h the mixture was poured into water and extracted with ether. The organic layer was washed with aqueous potassium hydrogen carbonate, decolourised with sodium hydrogen sulphite, washed with water until neutral, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to leave the *iodohydrin* (7a) (983 mg). Recrystallisation from acetone–ether afforded a sample of m.p. 112—114°; $[\alpha]_D$ +40°; $\nu_{max.}$ 3450, 1710, and 1260 cm^{-1}; δ 0·77 (18-H_3), 1·13 (19-H_3), 2·1 (17-OAc), and 4·2—4·8 p.p.m. (m, 17α-H, 2α-H, 3β-H) (Found: C, 54·9; H, 7·3; I, 27·55. $C_{21}H_{33}IO_3$ requires C, 54·85; H, 7·25; I, 27·6%).

2β-Bromo-3α-hydroxy-5α-androstan-17β-yl Acetate (7b).—Prepared according to the reported procedure,[9] this had m.p. 190—192°; $[\alpha]_D$ +33°; $\nu_{max.}$ 3450, 1720, and 1260 cm^{-1}; δ 0·77 (18-H_3), 1·10 (19-H_3), 2·1 (17-OAc), 4·3 (m, 2α-H), 3β-H), and 4·64 p.p.m. (17α-H).

2β-Chloro-3α-hydroxy-5α-androstan-17β-yl Acetate (7c).—A solution of compound (6) 10·8 g in chloroform (80 ml) was cooled to 5° and 10N-hydrochloric acid (3 ml) was added. The mixture was stirred at room temperature for 1 h. Water was added and the organic layer was neutralised, washed, and dried. Evaporation left material which was recrystallised from methylene chloride, providing pure *chlorohydrin* (7c) (813 mg), m.p. 215—217°; $[\alpha]_D$ +21°; $\nu_{max.}$ 3450 and 1725 cm^{-1}; δ 0·79 (18-H_3), 1·08 (19-H_3), 2·05 (17-OAc), 4·08 (m, 2α-H, 3β-H), and 4·56 p.p.m. (17α-H) (Found: C, 67·7; H, 8·45; Cl, 9·35. $C_{21}H_{33}ClO_3$ requires C, 68·0; H, 8·4; Cl, 9·55%).

Treatment of the Iodohydrin (7a) *with Phosphoryl Chloride.*—To compound (7a) (500 mg) in anhydrous pyridine (3 ml) kept at 5° was added freshly distilled phosphoryl chloride (0·04 ml). The mixture was stirred for 1·5 h at 5°, then poured into water and extracted with ether. The extract was washed with aqueous sodium hydrogen sulphite, dilute hydrochloric acid, and water until neutral, dried (Na_2SO_4), and evaporated to yield 5α-androst-2-en-17β-yl acetate (8) (318 mg), m.p. 95—97° (from methanol); $[\alpha]_D$ +52°; $\nu_{max.}$ 1720 and 1430 cm^{-1}; δ 0·77 (18-H_3), 0·79 (19-H_3), 2·0 (17-OAc), and 5·6 p.p.m. (m, 2 vinylic H), identical with an authentic sample [9] (mixed m.p., t.l.c., and i.r.).

Treatment of the Bromohydrin (7b) *with Phosphoryl Chloride.*—To compound (7b) (500 mg) in anhydrous pyridine (3 ml) kept at 5° was added freshly distilled phosphoryl chloride (0·15 ml). The mixture was stirred for 20 min at room temperature, and then poured into ice–water. Extraction with chloroform was followed by washing with 10% hydrochloric acid and then with water until neutral. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The amorphous product was separated by preparative t.l.c. The first crystalline compound obtained (10%, 36 mg) was the androst-2-ene (8), identical with an authentic sample. The second (79%, 510 mg) was an inseparable mixture of the chloro-bromo-derivative (7d) and the dibromide (7e), m.p. 152—154° (from methanol); $[\alpha]_D$ +59°; $\nu_{max.}$ 1720 cm^{-1}; δ 0·79 (18-H_3), 1·08 (19-H_3), 2·0 (17-OAc), and 4·54—4·76 p.p.m. (m, 17α-H, 2α-H, 3β-H); *m/e* 432 [M^+ of (7d)] and 478 [M^+ of (7e)].

Treatment of the Chlorohydrin (7c) *with Phosphoryl Chloride.*—To compound (7c) (500 mg) in pyridine (4 ml) at 5° was added pure phosphoryl chloride (0·15 ml). The mixture was stirred for 2·5 h at room temperature then poured into ice–water and extracted with ethyl acetate. After usual work-up, the solvent was removed under vacuum and the amorphous product was purified by preparative t.l.c. to give *17β-acetoxy-2β-chloro-5α-androstan-3α-yl phosphate* (7f) (513 mg), m.p. 200—202° (decomp.) (from ether); $[\alpha]_D$ +38°; $\nu_{max.}$ 3450, 1750, 1240, and 1030 cm^{-1}; δ 0·79 (18-H_3), 1·08 (19-H_3), 2·1 (17-OAc), and 4·03—4·86 p.p.m. (m, 17α-H, 2α-H, 3β-H) (Found: C, 56·05; H, 7·65; Cl, 7·65; P, 6·7. $C_{21}H_{34}ClO_6P$ requires C, 56·15; H, 7·65; Cl, 7·9; P, 6·9%).

trans-4,5-*Epoxyoctane from* trans-*Oct*-4-*ene* (12).—This epoxide was prepared with *m*-chloroperbenzoic acid, according to the reported procedure; [11] b.p. 72—73° (47 mmHg); $\nu_{max.}$ 2950, 1460, and 905 cm^{-1}; 99% pure by g.l.c. (column OV-17; 120°).

cis-4,5-*Epoxyoctane.*—*cis*-Oct-4-ene (11) was treated similarly [11] with *m*-chloroperbenzoic and afforded 77% of the corresponding epoxide, b.p. 74° (45 mmHg); $\nu_{max.}$

[11] A. C. Cope and V. K. Heeren, *J. Amer. Chem. Soc.*, 1965, **87**, 3125.

2900, 1450, and 905 cm^{-1}; 99% pure by g.l.c. (column OV-17; 120°).

threo-5-Iodo-octan-4-ol (9a).—*cis*-4,5-Epoxyoctane (6 g) was added dropwise with stirring to a solution of sodium iodide (12 g) in acetic acid (24 ml) and water (2 ml). The mixture was kept for 1 h at room temperature, then poured into water and extracted with methylene chloride. The extract was washed with a saturated solution of sodium hydrogen carbonate, then with 5% sodium hydrogen sulphite, dried (Na_2SO_4), and evaporated to leave a slightly yellow unstable *oil* (9a) (95%); $\nu_{max.}$ 3350 and 1460 cm^{-1}; τ 3·0 (m, C*H*·OH) and 4·15 p.p.m. (m, CHI) (Found: I, 49·9. $C_8H_{17}IO$ requires I, 49·6%).

erythro-5-Iodo-octan-4-ol (10a).—Similar treatment of *trans*-4,5-epoxyoctene afforded the erythro-*isomer* (10a), an unstable liquid; $\nu_{max.}$ 3350 and 1480 cm^{-1}; δ 2·98 (m, C*H*·OH) and 4·15 p.p.m. (m, CHI) (Found: I, 50·0. $C_8H_{17}IO$ requires I, 49·6%).

Treatment of Compound (9a) *with Phosphoryl Chloride.*—To a solution of compound (9a) (2·56 g) in anhydrous pyridine (5 ml), cooled to 0—5°, was added freshly distilled phosphoryl chloride (2·8 ml) in pyridine (2 ml). The mixture was gently distilled and then poured into ice–water. Extraction with pentane was followed by washing with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water until neutral. After drying, removal of the solvent gave 35% of *cis*-octene (11), identical (i.r., t.l.c., and g.l.c. analysis) with an authentic sample.[12] G.l.c. did not show any of the *trans*-isomer (12).

When the same reaction was performed at 0—5° for 2 h, instead of with distillation, there was isolated 10% of the *cis*-olefin (11) and 50% of the phosphate (9b), liquid; $\nu_{max.}$ 2900, 1470, and 1240 cm^{-1}; δ 3·95 (m, C*H*·O·PO_2H_2) and 4·15 p.p.m. (m, CHI).

Treatment of Compound (10a) *with Phosphoryl Chloride.*—Similar treatment of compound (10a) with phosphoryl chloride [as for the conversion (9a) ⟶ (11)] provided 40% of the *trans*-olefin (12), devoid of *cis*-isomer (11) (g.l.c.). When the reaction was performed at 0°, the yield of (12) was 13%, and that of the phosphate ester (10b) was 50%.

We thank Mr. E. Escobar for technical assistance for part of this work and Dr. J. Fried for suggestions. We also thank Mr. E. Avila, Analytical Dept., Syntex, S. A. for most physical data, and Dr. L. Throop, Dr. L. Tökés, and their associates, Syntex Research, Palo Alto, California, for several n.m.r. and mass spectra.

[2/1746 *Received*, 25*th July*, 1972]

[12] K. N. Campbell and L. T. Eby, *J. Amer. Chem. Soc.*, 1941, **63**, 216.