Tetrahedron. Vol. 31, pp 305 to 309. Pergamon Press 1975. Printed in Great Britain

CONSTITUENTS OF COPER-SPURGE SEED (LATHYRIDIS SEED)—II[1]

NOVEL ACID-CATALYZED REACTIONS OF EPOXYLATHYROL

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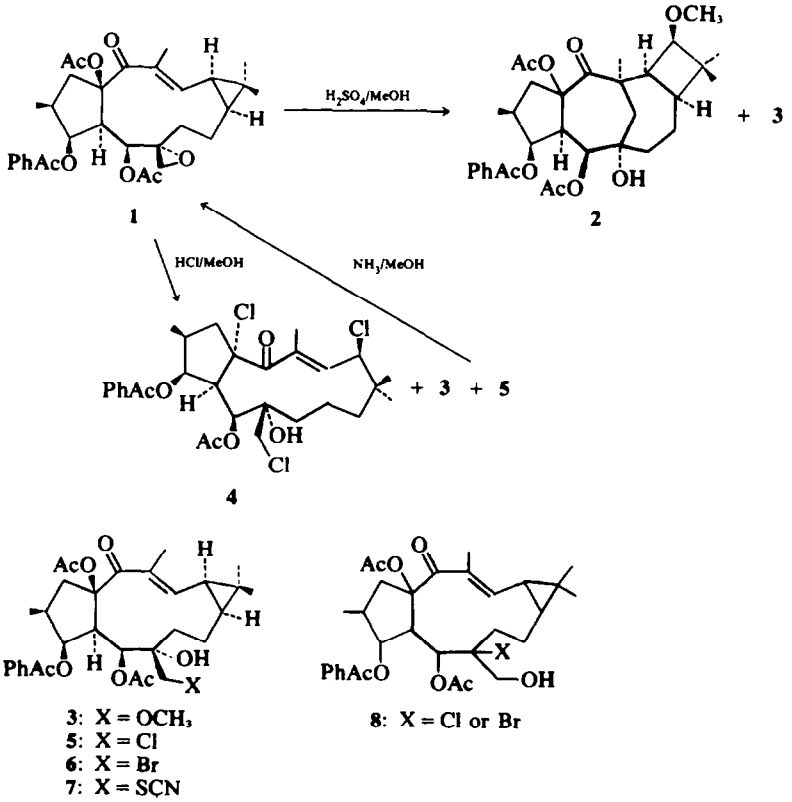
(*Received in Japan* 23 *July* 1974; *Received in UK for publication* 31 *October* 1974)

Abstract—Reaction of epoxylathyrol (1) with hydrochloric acid and other acids in THF led to simple fission of the epoxy ring and yielded the corresponding hydrin derivatives. When anhydrous methanol was used as the solvent, reaction of 1 with hydrochloric acid gave, as the major product, the novel macrocyclic trichloride (4) which has the jatrophane skeleton. Reaction with sulfuric acid afforded the transannular cyclization product (2) and methoxyhydrin (3). The structures of these compounds were deduced from spectral evidence.

The results were rationalized by different participation of solvents on the intermediary carbonium ions.

Epoxylathyrol[2] (1) is a diterpenoid having a unique macrocyclic structure and is sensitive to acid.[1] We have studied the acid-catalysed reactions of 1 and found novel nucleophilic additions which are associated with transannular cyclisation or migration.

Treatment of 1 with fifty molar equivalents of concentrated sulfuric acid in methanol afforded colorless needles of 2, m.p. 152–155°, $C_{33}H_{44}O_9$ (*m/e* 548, M^-), $[\alpha]_D + 48{\cdot}6°$ ($CHCl_3$) and colorless plates (3), m.p. 142–145°, $C_{33}H_{44}O_9$ (*m/e* 548, M^+), in 26% and 17% yields respectively. The IR spectrum of 2 shows the presence of a tertiary OH group which is characterised by the failure to acetylate under mild conditions and a 7-membered CO function at 3500 and 1708 cm^{-1}, and the disappearance of the conjugated CO group. The UV chromophore of the α,β-unsaturated ketone also had disappeared. The NMR



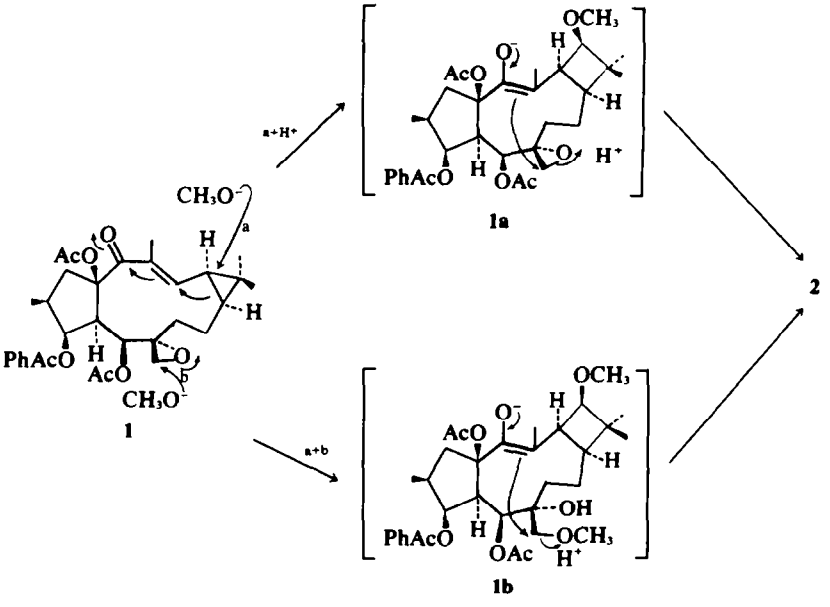
SCHEME 1

spectrum shows a secondary Me (δ 0·75, J = 6 Hz) and three tertiary Me's (δ 1·02, 1·09 and 1·11) as well as an OMe group (δ 3·17). The methine bound OMe group, and a doublet at δ 3·45 (J = 7 Hz), indicate the partial structure CH_3O–CH–CH–. Thus, the NMR spectrum agrees with the structure anticipated for the tetracyclic compound **2** (Experimental).

Compound **3** exhibits an OH group at 3490 cm^{-1} which could not be acetylated. The NMR spectrum shows signals in regions similar to **1**, except for the presence of a methoxymethyl signal, which clearly requires the compound to have structure **3**. The UV maximum at 272 nm (ϵ 15,200) agrees with the expected value.[3] Acid-catalysed reactions of the epoxy compounds have been discussed.[4]

Regarding the mechanism, the former transannular cyclisation is initiated by the nucleophilic attack to yield an intermediate (**1a** or **1b**), in which the protonated epoxide (or ether) is broken by the concerted approach of the carbanion to yield compound **2** (Scheme 2).

cm^{-1} and an absorption maximum in the UV spectrum at 230 nm (ϵ 8200), characteristic of an α,β-unsaturated ketone. The NMR spectrum of **4** shows signals at δ 2·18 (3H, d, J ≃ 1·5 Hz), δ 4·56 (1H, d, J = 10 Hz) and δ 6·10 (1H, q, J_1 = 10 Hz, J_2 ≃ 1·5 Hz) which support the presence of the partial structure –C–CO–C=CH–CH–C–, and a pair of doublets at δ 3·43 (J = 9 Hz) and δ 3·60 (J = 9 Hz) which are assigned to a chloromethyl group. The chemical shift of the C_2 Me (δ 0·73) is almost the same as that of **1**, indicating that the substituted chlorine inverts to the α-configuration.[5] These spectral results strongly support the jatrophane[6] structure **4**. The reaction of **1** with hydrogen chloride–methanol to give the trichloride **4** can be accommodated by Scheme 3. (i) The acetyl group in a postulated dichloride intermediate (**4a**) was replaced by concerted approach of the chloride ion from the rear side (the less hindered side), driven by neighboring-group participation,[7] to produce a trichloride intermediate (**4b**) which underwent 1,2-migration of chlorine in the conjuga-

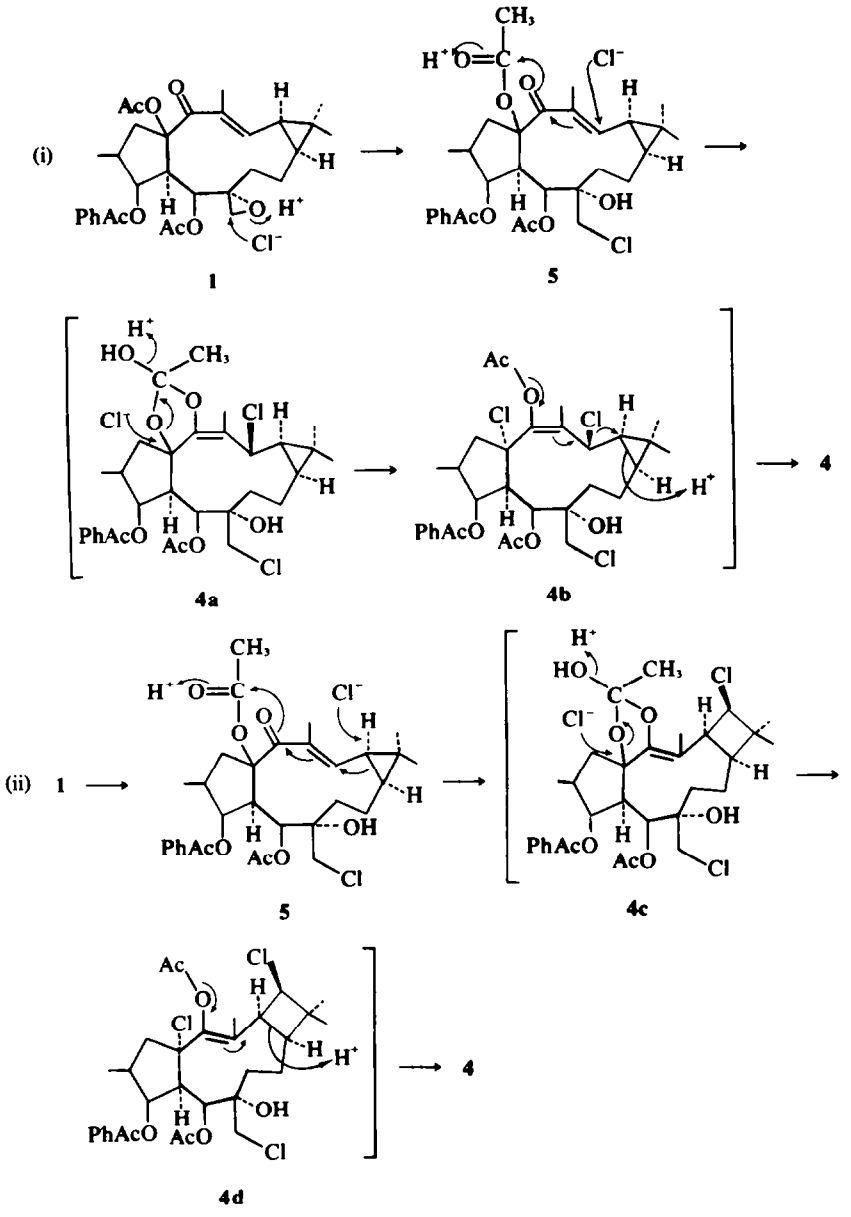


SCHEME 2

Treatment of **1** with excess hydrogen halides, on the other hand, proceeds in a different manner depending upon the solvent used. In tetrahydrofuran **1** reacted with hydrogen halides to give predominantly the anti-Markovnikov products (**5** and **6**). Similarly, treatment of **1** with thiocyanic acid in ether gave the corresponding thiocyanate **7**, m.p. 168–170°, $[\alpha]_D$ −64·1°. In contrast, **1** reacted with hydrogen chloride more rapidly in methanol and gave a mixture from which **4** (45%), **5** (21%) and **3** (17%) were isolated. The main product **4**, m.p. 212–213°, shows the composition $C_{30}H_{39}O_6Cl_3$. The trichloro-derivative (**4**) reveals IR bands 1688 and 1624 tion with cyclopropane ring fission to form **4**, or (ii) the chloride ion attacked as described the Scheme 2, and concerted replacement of the acetyl group gave an intermediate trichloride (**4c**), in which the cyclobutane ring led to expansion[8] with formation of **4**.

Although the structures of halogenohydrins were tentatively assigned for **8** in the proceeding paper,[1] assignment of α-configuration to the OH group was favored by the following experimental result. The treatment of chlorohydrin **5** with ammonia in methanol gave single product, epoxylathyrol (**1**), in high yield.

These differences in the mode of reaction can be



SCHEME 3

explained by participation of solvents on the transition state.[9] The solvent effect of the ethers on the ring-opening process of the epoxides is in agreement[4] with our observed results. In the protic solvents the carbonium ion promoting by protonation of the CO function is solvated to give a more stable cation which facilitates migration or transannular cyclization in the conjugate manner.

EXPERIMENTAL

All m.ps were taken on a Yamato Model MP-21 apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-S spectrophotometer, and UV spectra in 95% EtOH solns were taken on a Hitachi EPS-3 spectrophotometer. NMR spectra were taken on Varian T-60 and Hitachi R-20 spectrometers. The chemical shifts (δ) were calculated on the basis of TMS as an internal standard. Mass spectra were determined on a Hitachi RMU-6D mass spectrometer. TLC was carried on Merk TLC-plates silica gel F_{254} pre-coated.

Reactions of epoxylathyrol (1) *with hydrogen chloride in MeOH.* To a methanolic soln of 1 ($5{\cdot}43 \times 10^{-4}$ M) was added 9 ml of 14% HCl–MeOH ($3{\cdot}42 \times 10^{-2}$ M) followed by refluxing the mixture for 15 min. The solvent was removed by distillation *in vacuo*, and the mixture was extracted 3 times with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, 5% $NaHCO_3$ aq, and dried over $NaSO_4$. Removal of the solvent yielded an oily residue which was

subjected to chromatography on a silica gel column (Kiesel Gel 60, 20 g). The column was washed with benzene and eluted gradually with benzene–AcOEt (20:1). First eluate gave a white solid which after recrystallization from isopropyl ether–acetone gave colorless needles (**4**), m.p. 212–213°, 90 mg (45% yield). NMR (δ) $CDCl_3$: 0·73 (d, J = 6 Hz, 3, >CH–CH$_3$), 1·20 (s, 3, CH$_3$–C(–CH$_3$)–), 1·27 (s, 3, CH$_3$–C(–CH$_3$)–) 2·10 (s, 3, –OAc), 2·18 (d, J≃1·5 Hz, 3, =C(–CH$_3$)–), 3·43 (d, J=9 Hz, 1, –CHH–Cl) 3·60 (d, J = 9 Hz, 1, –CHH–Cl), 3·68 (s, 2, –OCOCH$_2$–C$_6$H$_5$), 4·56 (d, J = 10 Hz, 1, >CH–Cl), 5·40 (t, J≃3 Hz, 1, >CH–OCOCH$_2$C$_6$H$_5$), 5·45 (d, J = 6 Hz, 1, >CH–OAc), 6·10 (q, J_1 = 10 Hz, J_2≃1·5 Hz, 1, CH$_3$–C(=CH–)–), 7·33 (s, 5, –CH$_2$C$_6$H$_5$). IR (cm^{-1}) Nujol: 3450 (OH), 1736 (CH$_3$CO–), 1718 (C$_6$H$_5$CH$_2$CO–), 1688 and 1624 (α,β-unsaturated ketone). UV (nm) EtOH: 216 (ϵ 8800), 230 (8200), 315 (150). MS: Mol. wt 600 (100%), M + 2 (105%), M + 4 (35%) (Found: C, 59·79; H, 6·79. $C_{30}H_{39}O_6Cl_3$ requires: C, 59·85; H, 6·53%).

Subsequent eluate gave starting material (34 mg) and chlorohydrin **5** (61 mg, 21%), m.p. 219–221°, (lit.[1] m.p. 219–221°). $[\alpha]_D^{20}$ – 135·1° ($CHCl_3$, c = 0·5). NMR (δ) $CDCl_3$: 0·70 (d, J = 6·0 Hz, 3, >CH–CH$_3$), 1·18 (s, 3, CH$_3$–C(–CH$_3$)–), 1·32 (s, 3, CH$_3$–C(–CH$_3$)–), 1·87 (s, 3, =C(–CH$_3$)–), 2·02 (s, 3, –OAc), 2·09 (s, 3, –OAc), 3·10 (broad q, 1, –CO–O–CH–CH–CH–OAc), 3·48 (d, J = 11·9 Hz, 1, >CHH–Cl), 3·62 (s, 2, –CH$_2$–C$_6$H$_5$), 3·78 (d, J = 11·9 Hz, 1, >CHH–Cl), 5·47 (t, J = 4 Hz, 1, >CH–O–COCH$_2$C$_6$H$_5$), 6·42 (broad d, 1, >CH–OAc), 6·55 (d, J = 10 Hz, 1, >C=CH–CH<), 7·28 (s, 5, –CH$_2$–C$_6$H$_5$). IR (cm^{-1}) Nujol: 3450 (OH), 1742 (sh) (C$_6$H$_5$CH$_2$CO–), 1735, 1239 (CH$_3$CO–), 1655, 1620 (α,β-unsaturated ketone). UV (nm) EtOH: 215 (ϵ 6240), 271 (16,600) (Found: C, 65·31; H, 7·19; Cl, 6·50. $C_{32}H_{41}O_6Cl$ requires: C, 65·24; H, 7·01; Cl, 6·02%).

The last fractions using benzene–AcOEt (20:1) as eluent gave a white solid. Recrystallization from aq. MeOH afforded colorless plates of **3**, m.p. 142–145°. 48 mg (17% yield). NMR (δ) $CDCl_3$: 0·71 (d, J = 6 Hz, 3, >CH–CH$_3$), 1·16 (s, 3, CH$_3$–C(–CH$_3$)–), 1·33 (s, 3, CH$_3$–C(–CH$_3$)–), 1·85 (s, 3, =C(–CH$_3$)–), 2·01 (s, 3, –OAc), 2·13 (s, 3, –OAc), 3·20 (overlapped, 2, –CH$_2$–O–CH$_3$), 3·23 (s, 3, –OCH$_3$), 3·63 (s, 2, –CH$_2$–C$_6$H$_5$), 5·43 (t, J=4 Hz, 1, >CH–OCOCH$_2$C$_6$H$_5$), 6·13 (d, J = 10 Hz, 1, >CH–OAc), 6·53 (broad d, J = 12 Hz, 1, CH$_3$–C=CH–), 7·23 (s, 5, –CH$_2$–C$_6$H$_5$). IR (cm^{-1}) Nujol: 3490 (OH), 1738, 1230 (CH$_3$CO–), 1655, 1621 (α,β-unsaturated ketone). UV (nm) EtOH: 272 (ϵ 15,200). MS: Mol. wt. 584 (Found: C, 67·53; H, 7·79. $C_{33}H_{44}O_9$ requires: C, 67·79; H, 7·59%).

Reaction of **1** with approximately two molar equivalents of hydrogen chloride under the same conditions resulted in a recovery of 40% of starting material and isolations of 5% of **4**, 39% of **5**, and 11% of **3**.

Conversion of chlorohydrin (**5**) *to epoxylathyrol* (**1**). A soln of **5** (28 mg) in 8 ml of ammonia-saturated MeOH was stirred for 2 hr at ambient temp. At that time the TLC monitoring showed that no starting material remained. Solvent removal *in vacuo* gave a white solid which after recrystallization from EtOH gave 20 mg (80%) of **1** as colorless needles, m.p. 201–203°, identical with an authentic sample (Found: C, 69·79; H, 7·33. $C_{32}H_{40}O_8$ requires: C, 69·54; H, 7·30%).

Reaction of **1** *with sulfuric acid in MeOH.* A soln of **1** ($5·43 \times 10^{-4}$ M) in 15 ml of 10% H_2SO_4–MeOH ($2·24 \times 10^{-2}$ M) was refluxed for 15 min. After neutralization with sat $NaHCO_3$ aq the mixture was extracted each 15 ml of $CHCl_3$ 3 times. The chloroform layer was collected and washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* and column chromatography of a liquid residue (363 mg) on silica gel (Kiesel Gel 60, 18 g) using benzene–AcOEt (20:1) as eluent gave three crystalline fractions, **1** (25 mg), **2** (78 mg) and **3** (46 mg). **2** was crystallised from MeOH to give colorless needles, m.p. 152–155°, 78 mg (26% yield), $[\alpha]_D^{28}$ + 48·6° ($CHCl_3$, c = 0·15). NMR (δ) $CDCl_3$: 0·73 (d, J = 6 Hz, 3, >CH–CH$_3$), 1·01 (s, 3, >C(–CH$_3$)–), 1·08 (s, 3, CH$_3$–C(–CH$_3$)–), 1·10 (s, 3, CH$_3$–C(–CH$_3$)–), 1·97 (s, 3, –OAc), 2·16 (s, 3, –OAc), 2·57 (q, J_1=3·5 Hz, J_2 = 9·5 Hz, 1, C$_6$H$_5$CH$_2$COO–CH–CH–CH–OAc), 3·16 (s, 3, –OCH$_3$), 3·45 (d, J = 7 Hz, 1, >CH–OCH$_3$), 3·59 (s, 2, –CH$_2$–C$_6$H$_5$), 5·55 (t, J = 3·5 Hz, 1, >CH–OCOCH$_2$C$_6$H$_5$), 6·21 (d, J = 9·5 Hz, 1, >CH–OAc), 7·30 (s, 5, –CH$_2$C$_6$H$_5$). UV (nm) EtOH: 216 (ϵ 2860), 254 (550), 258 (610), 265 (670), 279 (550). MS: Mol. wt. 584. IR (cm^{-1}) KBr: 3500 (OH), 1745 (C$_6$H$_5$CH$_2$CO–), 1730, 1230 (CH$_3$CO–), 1708 (ketone) (Found: C, 66·71; H, 7·59. $C_{33}H_{44}O_9 \cdot \frac{1}{2}H_2O$ requires: C, 66·76; H, 7·64%).

1 and **3** were identical with authentic samples by direct comparison.

Reaction of **1** *with thiocyanic acid in ether.* To a soln of **1** ($1·81 \times 10^{-4}$ M) in 10 ml of ether was added 25 mM of thiocyanic acid–ether soln. The mixture was refluxed for 5 hr and then shaken with 10 ml $NaHCO_3$ aq. The ether layer was collected and dried over $NaSO_4$, evaporated to give a solid residue. Recrystallization from EtOH afforded colorless plates (**7**), m.p. 168–170°, 42 mg. $[\alpha]_D^{25}$ – 64·1° ($CDCl_3$, c = 0·15). NMR (δ) $CDCl_3$: 0·73 (d, J = 6·0 Hz, 3, >CH–CH$_3$), 1·18 (s, 3, CH$_3$–C(–CH$_3$)–), 1·30 (s, 3, CH$_3$–C(–CH$_3$)–), 1·87 (s, 3, =C(–CH$_3$)–), 2·01 (s, 3, –OAc), 2·12 (s, 3, –OAc), 3·68 (s, 2, –CH$_2$C$_6$H$_5$), 5·43 (t, J=4·0 Hz, 1, >CH–O–COCH$_2$C$_6$H$_5$), 6·13 (broad s, 1, >CH–OAc), 6·62 (broad d, J = 11 Hz, 1, CH$_3$–C=CH–), 7·29 (s, 5, –CH$_2$C$_6$H$_5$). IR (cm^{-1}) KBr: 3440 (OH), 2140 (–SCN), 1734 (CH$_3$CO– and C$_6$H$_5$CH$_2$CO–), 1652 and 1622 (α,β-unsaturated ketone).

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