Synthesis of Dieldrin Metabolites. 3. Two-Step Conversion of *syn*-12-Hydroxydieldrin into Klein's Metabolite (3,5,6,6,7-Pentachloro-11,12-*exo*-epoxypentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{5,9}]dodecan-4-one)

Colin T. Bedford* and Edward H. Smith[1]

Solvolysis of the triflate (trifluoromethanesulfonate) of *syn*-12-hydroxydieldrin led in part (40%) to a bridged ketone, which was identical in all respects (melting point; infrared, proton magnetic resonance, and mass spectra) with the hitherto unsynthesized metabolite of dieldrin known as "Klein's metabolite". This has provided the ultimate proof of its structure and has made available sufficient material for a planned study of its toxicity and metabolism. The structure of one of the by-products of the solvolysis reaction has been elucidated.

In two previous papers on the synthesis of dieldrin metabolites, we have described an improved synthesis of *trans*-4,5-dihydroaldrin-4,5-diol (Bedford and Harrod, 1972a) and the first total synthesis of *syn*-12-hydroxydieldrin (Bedford and Harrod, 1972b). In this paper we record a total synthesis of Klein's metabolite and thereby complete the synthesis of all of the known metabolites of dieldrin.

Klein's metabolite of dieldrin is formed only to a very minor extent in mammals, but the identification of this highly lipophilic compound in rat urine in 1968 (Klein et al., 1968; Richardson et al., 1968) and its characterization (Damico et al., 1968) as an intramolecularly bridged pentachlorinated ketonic derivative (I, Figure 1) made it a focus of much interest—especially, perhaps, to those who wondered how this rare example of a biological bridging reaction had been formed. Subsequent studies have shown that it is also a very minor metabolite in two strains of mouse (Hutson, 1977). It is also a metabolite of photodieldrin in the rat (Baldwin and Robinson, 1969; Klein et al., 1970), in the housefly (Khan et al., 1970), and in a rat liver microsomal preparation (Matthews and Matsumura, 1969). This provided further confirmation of its structural assignment as a 4-oxo derivative of "4-dechlorophotodieldrin", since the biosynthetic route from photodieldrin merely involved the transformation: $-CHCl \rightarrow C{=}O$ (see Figure 1). Samples of this compound that were required for toxicity studies and as reference material were available only in milligram amounts from tedious isolation procedures involving very large volumes of rat urine. To obviate this, and because it represented the stiffest synthetic challenge posed by any of the dieldrin metabolites (see Bedford and Hutson, 1976), we have undertaken its total synthesis. We report here an early approach that failed and a modification of that approach that proved successful.

EXPERIMENTAL SECTION

Methods. Melting points were determined on a Kofler hot-stage and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian HA 100 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard. Infrared (IR) spectra of solutions in dichloromethane were recorded on a Perkin-Elmer Infracord spectrophotometer and mass spectra were obtained using an AEI MS30 instrument.

Gas–liquid chromatography (GLC) was performed on a Pye Model 104 gas chromatograph fitted with a flame ionization detector. The column was 0.9 m × 6 mm glass tubing packed with 5% OV 1 on Gas-Chrom Q. Carrier gas was nitrogen, 40 mL min^{-1}. Retention times (min) using a column temperature of 195 °C were: I, 4.0; IIa, 4.15; X, 5.6; XIV, 9; IIb, 64.5.

Thin-layer chromatography (TLC) was performed on alumina (Merck 60 F_{254} type E) using the solvent system, petroleum spirit–ether (3:1), in which system compounds, I, IIa, IIb, X, and XIV had R_f values of 0.4, 0.55, 0.6, 0.6, and 0.7, respectively. Alumina for column chromatography was obtained from Hopkin and Williams (CAMAG MFC, 100–250 mesh) and was deactivated to Brockmann activity 2. Column fractions were monitored by TLC and GLC. A spray reagent for TLC detection consisted of silver nitrate (1 g), distilled water (5 mL), and 2-phenoxyethanol (10 mL) made up to 200 mL with acetone and stabilized by the addition of 1 drop of hydrogen peroxide (100 vol). Chlorinated compounds showed as black spots on exposure of the sprayed plates to ultraviolet light.

Chemicals. Sodium benzoate (Hopkin and Williams, General Purpose reagent) was dried for 12 h over phosphorus pentoxide at 0.05 mmHg/100 °C and stored in a desiccator over self-indicating silica gel prior to use. Dimethylformamide (DMF) was dried for 2 days over barium oxide, distilled under reduced pressure, and stored in a desiccator over self-indicating silica gel. Chloroform was dried over molecular sieve type 4A and distilled prior to use. Unless otherwise stated petroleum spirit refers to the hexane fraction from petroleum, bp 67 °C.

12-*syn*-Hydroxydieldrin (IIa) was available from a previous synthesis (Bedford and Harrod, 1972b). The *p*-toluenesulfonate IIb (mp 183–184 °C) and trifluoromethanesulfonate X (mp 136–138 °C) of compound IIa were prepared according to standard procedures (Su et al., 1969).

Acetolysis. Acetolysis of IIb and X was conducted in acetic acid containing sodium acetate (0.02 M) and acetic anhydride (1%), and progress of reaction was monitored by TLC and GLC. The products of reaction were isolated by the addition of equal volumes of water and chloroform and evaporation of the water-washed chloroform layer. Isolation of the individual products of reaction from X was achieved by chromatography over alumina as follows: The concentrated chloroform extract (typically 347.6 mg from 408.7 mg of X) was placed on an alumina column (2 cm × 45 cm; 120 g) and the products were eluted in fractions

Shell Research Ltd., Shell Toxicology Laboratory (Tunstall), Sittingbourne Research Centre, Sittingbourne, Kent, ME9, 8AG, United Kingdom.

[1]Present address: University Chemical Laboratory, Lensfield Road, Cambridge, United Kingdom.

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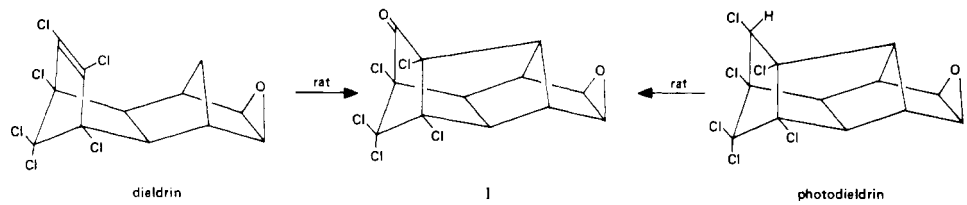


Figure 1. The structure of the bridged ketonic metabolite (I) formed in the rat from both dieldrin and photodieldrin.

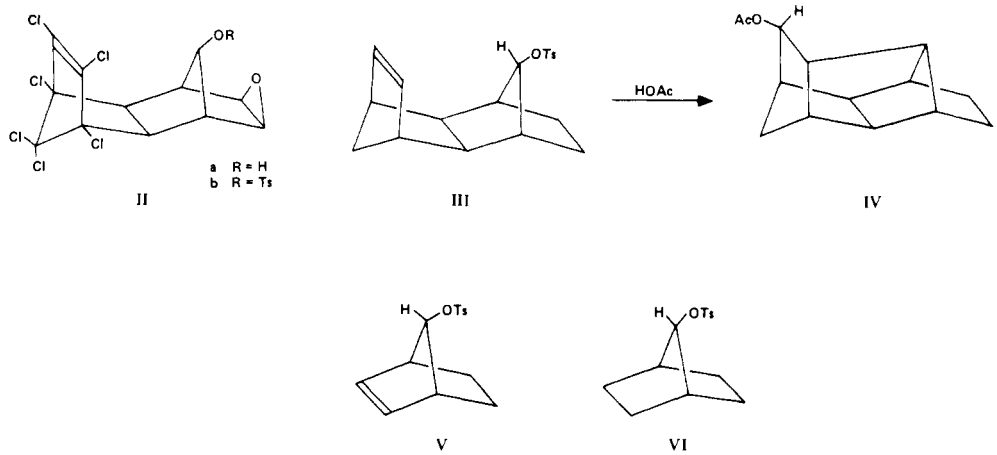


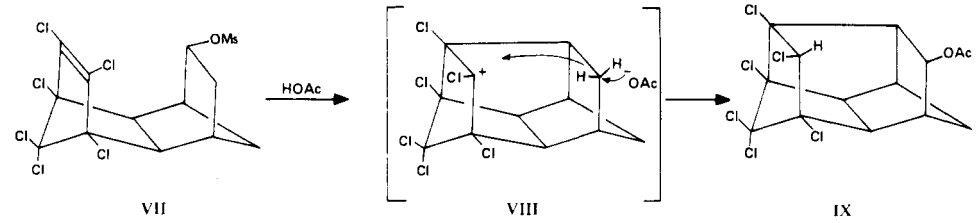
Figure 2. The structural formulae of *syn*-12-hydroxydieldrin (IIa) and its tosylate (IIb); an example of the formation of a bridged product (IV) by acetolysis of a nonchlorinated tetracyclic tosylate (III); the structures of the tosylates of *anti*-7-hydroxynorbornene (V) and of 7-hydroxynorbornane (VI).

of 10 mL with petroleum spirit–ether (2:1). Fractions 22–35 containing I, the last compound to emerge from the column under the conditions, were combined and concentrated to give a white solid, mp 182–190 °C (110 mg; 39%).

Reaction of X with $PhCO_2Na$/DMF. Derivative X (11.5 mg; 0.022 mol) was dissolved in dimethylformamide (2 mL) and treated with sodium benzoate (58 mg, 0.4 mmol). The suspension was stirred at 95 °C (bath temperature) until the by-product XIV could just be detected on thin-layer chromatograms (5–7 h). The reaction mixture was allowed to cool, treated with chloroform (10 mL), and filtered. The precipitate was washed with chloroform (2 × 5 mL) and the combined filtrate and washings were concentrated at room temperature, first at 12 mmHg and finally under high vacuum to remove dimethylformamide. The yellow, oily residue (14 mg) was treated with petroleum spirit (3 × 2 mL) and the combined extracts were evaporated to yield an almost colorless gum (11.6 mg). Elution with petroleum spirit–ether (3:1) of this gum from an alumina column (1 cm × 7.5 cm; 5 g) in fractions of 5 mL gave compound XIV as a white solid, mp 150–190 °C (slow dec), in fractions 15–20 (1.0 mg; 11%); compound X as a white solid, mp 134–137 °C, in fractions 20–30 (3.0 mg); and compound I as a white solid, mp 180–184 °C, in fractions 33–50 (4.95 mg; 63%). I was recrystallized from petroleum spirit to yield white microcrystals, mp 188–189 °C, mixed mp 186–189 °C. A small sample was recrystallized again for analysis, mp 192–194 °C. Anal. Calcd. for $C_{12}H_7O_2Cl_5$: C, 39.99; H, 1.96; Cl, 49.18. Found: C, 39.80; H, 2.10; Cl, 47.9. IR 5.5 μ (C=O); ^{1}H NMR see Figure 5 and Table I; ms *m/e* 358 (M^+, 5 Cl pattern). XIV was recrystallized from petroleum spirit to yield colorless prisms, mp 165–190 °C (slow dec). Anal. Calcd for $C_{12}H_7OCl_7$: C, 34.70; H, 1.70; Cl, 59.75. Found: C, 34.60; H, 1.80; Cl, 54.5. ^{1}H NMR, see Figure 5 and Table I; ms *m/e* 412 (M^+, 7 Cl pattern).

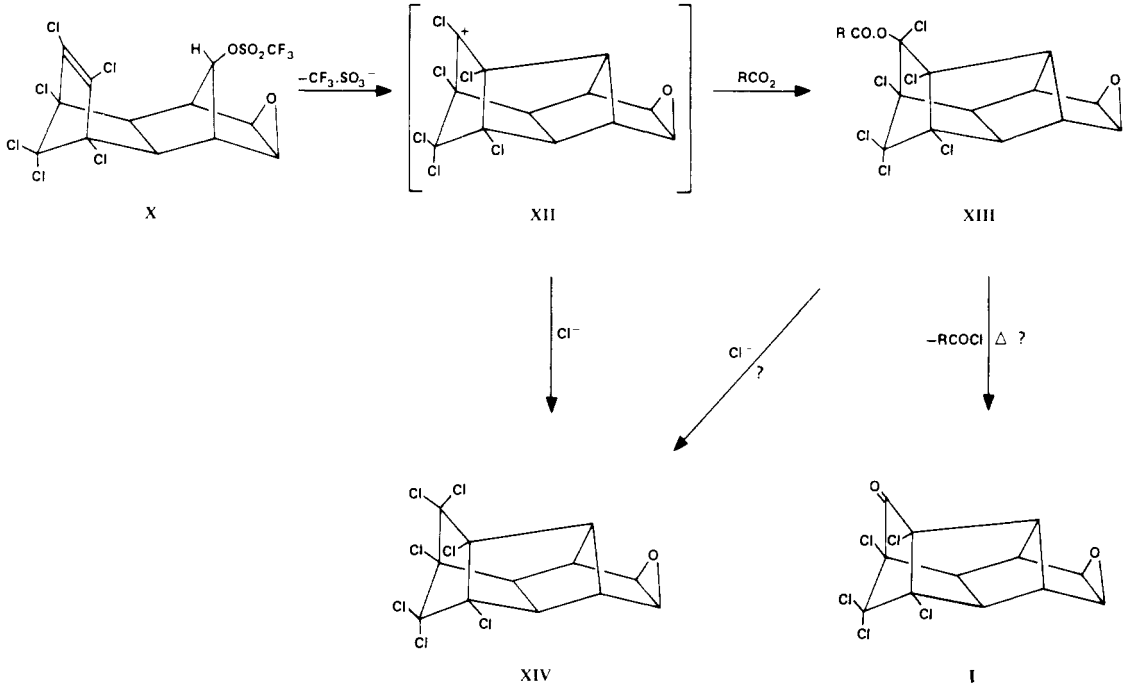
RESULTS AND DISCUSSION

Inspection of the structure of *syn*-12-hydroxydieldrin (IIa) revealed that the close juxtaposition of C-12 and the dichlorinated double bond offered the possibility of effecting a transannular bridging reaction between the two to form the caged ring system of Klein's metabolite (I). The general approach that was devised to exploit this feature of *syn*-12-hydroxydieldrin was to subject its tosylate (IIb) to solvolysis to see whether this would induce the desired bridging via interaction of the double bond with the incipient carbonium ion generated at C-12. That such a reaction was feasible rested on two observations. First, acetolysis of the closely analogous nonchlorinated tosylate (III) had yielded the bridged acetate (IV) as the major product (Winstein and Hansen, 1960) (Figure 2). Moreover, the rate of its (ready) solvolysis was approximately the same as that of the tosylate of *anti*-7-hydroxynorbornene (V), a compound that constitutes one of the classical examples exhibiting anchimeric assistance (its solvolysis rate is 10^{11} larger than that of its saturated analogue VI. Secondly, although the two electron-withdrawing chlorine atoms attached at the termini of the double bond of *syn*-12-hydroxydieldrin (IIa) would be expected to much reduce its reactivity toward electrophiles, the formation of the bridged reaction product, IX, as an acetolysis product of the isodrin-derived mesylate (VII) must necessarily have involved initial formation of the bridged carbonium ion, VIII, from which IX is derivable by an unexceptionable transannular hydride shift (Bird et al., 1961) (Figure 3). There remained one feature of the tosylate of *syn*-12-hydroxydieldrin (IIb) that could affect the outcome of its solvolysis: the epoxy grouping. Optimistically, it was considered that this grouping ought to survive the acetolysis conditions, though there was a



VII VIII IX

Figure 3. The formation of a bridged product by acetolysis of an isodrin derivative (VII).



X XII XIII

XIV I

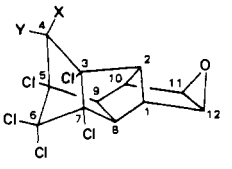
Figure 4. The probable mechanism of formation of the products of acetolysis of the triflate of *syn*-12-hydroxydieldrin (X).

possibility that the epoxy oxygen atom could interact with the incipient carbonium ion at C-12 and thereby preclude the desired bridging interaction. Precedents for such an interaction are scarce, though some are well documented (Capon and McManus, 1976). Howsoever, the availability of *syn*-12-hydroxydieldrin from our earlier synthesis (Bedford and Harrod, 1972b) and its ready tosylation led quickly to the crucial experiment.

In the event, the tosylate of *syn*-12-hydroxydieldrin (IIb) was found to be remarkably stable to acetolysis, and it was recovered entirely unchanged after 7 days at 120 °C. Even after acetolysis at 180 °C for 20 h, the tosylate was recovered in 70% yield. Disappointingly, the products of this reaction were predominantly intractable, tarry materials. Attention was therefore turned to a simple modification of the original approach.

The trifluoromethanesulfonate derivatives of alcohols (triflates) are more reactive than tosylates toward solvolysis by a factor of 10^4–10^5 (Su et al., 1969). It seemed likely therefore that the triflate of *syn*-12-hydroxydieldrin (X) might suffer solvolysis at moderate temperatures to yield tractable products. Gratifyingly, this expectation was realized, and acetolysis at 120 °C of X proceeded smoothly and produced the required bridged ketone, I, as major product (39%), together with at least four other products. The yield of I was raised to 44% by substituting the aprotic solvent, dimethylformamide, for glacial acetic acid–acetic anhydride and by reducing the temperature of reaction to 105 °C. This modified procedure led to moderate amounts (26%) of a by-product, shown by mass spectrometry, NMR, IR, and elemental analysis to be the heptachlorinated derivative, XIV (Figure 4). This compound was also formed in the acetolysis of X, but only in very minor amounts. Increased yields of the bridged ketone (I) were obtained by using the more nucleophilic salt, sodium benzoate (Reist et al., 1958, 1959) in dimethylformamide and by cessation of the reaction upon detection by TLC of the heptachlorinated by-product (XIV). In this way, isolated yields of I and XIV were 63 and 11%, respectively (85 and 15%, allowing for recovered starting material). Synthetic I gave a correct elemental analysis and proved to be identical with the bridged ketonic metabolite of dieldrin isolated from rat urine (Baldwin and Robinson, 1969) by the criteria of melting point, mixed melting point, and comparative mass spectroscopy, infrared spectroscopy and proton magnetic resonance spectroscopy. Compounds I and XIV differ from photodieldrin only in the nature of the substituents at C-4 (see Table I), and it is clear from their ^1H NMR spectra (Figure 5) that each lacked the singlet at 4.82 ppm present in the latter due to the proton at C-4, but both possess peaks, due to the remaining seven protons, of similar multiplicities to those of photodieldrin. The chemical shifts differ according to the proximity of the protons to C-4. Thus, in all three compounds, the proton at C-2 appears at ca. 2.5 ppm and is a quintuplet, the protons on the epoxide ring (C-11, C-12) appear at ca. 3.3 and 3.5 ppm as quartets and the proton at C-8 resonates between 3.07 and 3.20 ppm as an octet. The largest effects due to the change in C-4 substitution occur in the proton nearest to this position, that at C-10. Thus the signals at 4.24 and 2.63 ppm (distorted triplets) in spectra b and c (Figure 5), respectively, are assignable to the C-10 proton, which is shielded in I and deshielded in XIV by 0.45 and 1.16 ppm, respectively, compared to the corre-

Table I. Comparison of ^1H NMR Chemical Shift Data of Photodieldrin with Those of Two Products of Acetolysis (I, XIV)[a]



Position	Photodieldrin, X = H, Y = Cl		Heptachlorinated compound, XIV, X = Cl, Y = Cl		Synthetic I, X,Y = O	
	multiplicity	δppm	multiplicity	δppm	multiplicity[b]	δppm
Cl	m	3.20	m	3.15	m	3.53
C2	qn	2.54	qn	2.54	qn	2.44
C8	o	3.06	o	3.12	o	3.20
C9	q	2.68	o	2.83	q	2.59
C10	m	3.09	t	4.24	t	2.63
C11	q	3.28,3.49	q	3.23,3.47	q	3.35,3.45
C12	q		q		q	

a : t = triplet; q = quartet ; qn = quintet ; o = octet ; m = multiplet
b : assigned from the 220 MHz spectrum

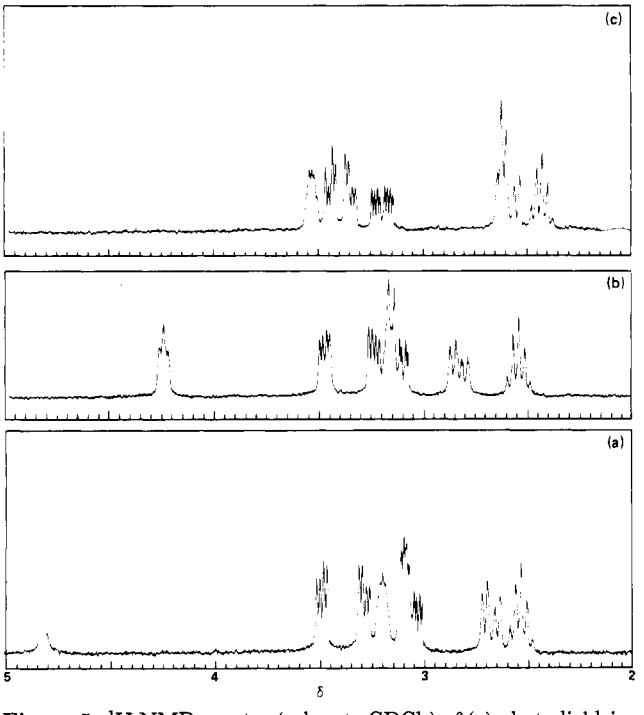


Figure 5. ^1H NMR spectra (solvent: $CDCl_3$) of (a) photodieldrin; (b) heptachlorinated compound (XIV); (c) synthetic ketone (I).

sponding proton (3.08 ppm) in photodieldrin. This provided the ultimate proof of the structure proposed for I on the basis of spectral data (Damico et al., 1968). Strictly, this total synthesis is not the first to be described, for one of the minor products of the photolysis of dieldrin in carbon tetrachloride/N_2O_4 was found to be the *trans*-chlorhydrin of Klein's metabolite, which was dehydrochlorinated with base to I (Nagl and Korte, 1972). However, the overall yield of I from dieldrin was 0.035% and full characterization was not possible with the small amounts available.

The formation of the bridged ketone I from the triflate X probably occurs via thermolytic loss of benzoyl chloride from XIII, the initially formed product of attack by benzoate anion on the bridged carbonium ion, XII. We were unable to find a direct precedent in the literature for this thermolytic reaction, though the analogous α-chloro ethers are reported to be thermally unstable at temperatures >200 °C (Kwart and Silver, 1975). The mechanism of formation of the heptachlorinated by-product XIV is at present unknown, though the results of two experiments provide some clarification. A control experiment revealed that, as expected, it was not formed from the bridged ketone I. It therefore must have derived directly from the reaction of chloride ion (released in the production of the ketone I) with the starting triflate, or the common intermediate, XIII. Proof that the former is a possibility was obtained by isolating the heptachlorinated compound XIV in good yield (59%) by reaction of the triflate X with NaCl/DMF at 95 °C. The formation of XIV from the common intermediate, XIII, would involve displacement by chloride ion of the benzoate grouping. This may be possible, but the fact that we have found the heptachlorinated compound XIV to be stable to (1) AgOAc/DMF–H_2O and (2) AgOAc/acetic acid implies that displacement of a "leaving group" at this position is not a facile reaction.

The synthetic route we have described leads to good yields of the bridged ketonic metabolite of dieldrin in a few simple steps, and the way is now clear to pursue studies of both its chemistry and its mammalian metabolism–toxicity. This, and further studies on the mechanism of the solvolytic step in the synthesis, are under way in this laboratory.

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