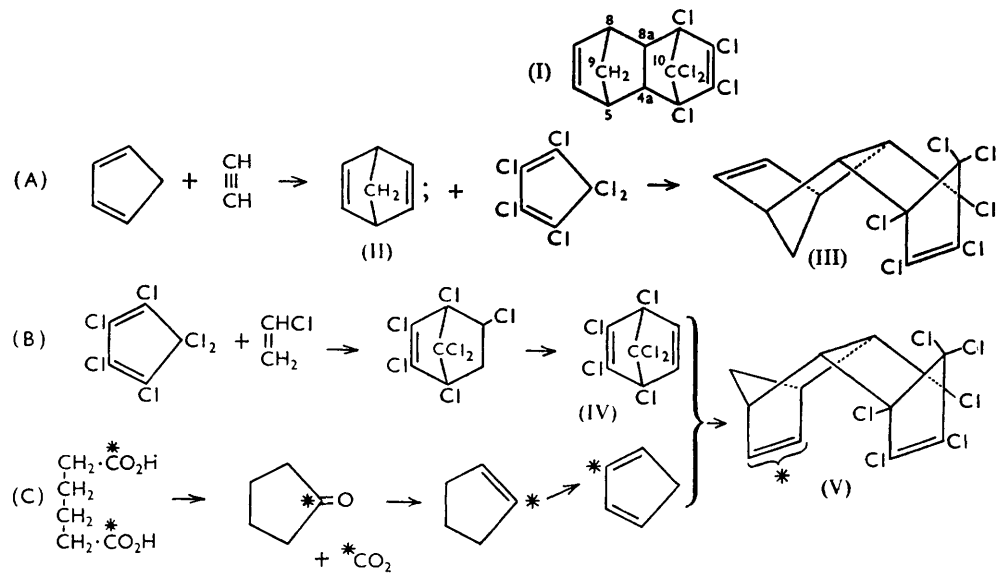
739. *The Synthesis of* ^{14}C-*Labelled* 1 : 2 : 3 : 4 : 10 : 10-*hexachloro*-6 : 7-*epoxy*-1 : 4 : 4*a* : 5 : 6 : 7 : 8 : 8*a*-*octahydro*-exo-1 : 4-exo-5 : 8-*dimethanonaphthalene* (*Endrin*).*

By G. T. Brooks.

A study of the absorption, metabolism, and excretion of insecticides derived from decahydro-1 : 4 : 5 : 8-dimethanonaphthalene required a method for the preparation on a millimolar scale of such compounds labelled with ^{14}C. ^{14}C-Labelled endrin has now been synthesised by peracetic acid oxidation of ^{14}C-labelled isodrin prepared by Diels–Alder addition [1] of [2-^{14}C]*cyclo*pentadiene to 1 : 2 : 3 : 4 : 7 : 7-hexachloro*bicyclo*[2 : 2 : 1]hepta-2 : 5-diene.[2]

Aldrin (1 : 2 : 3 : 4 : 10 : 10-hexachloro-1 : 4 : 4a : 5 : 8 : 8a-hexahydro-*exo*-1 : 4-*endo*-5 : 8-dimethanonaphthalene *) and its *exo,exo*-isomer isodrin, having the basic structure of 1 : 2 : 3 : 4 : 10 : 10 - hexachloro - 1 : 4 : 4a : 5 : 8 : 8a - hexahydro - 1 : 4 - 5 : 8 - dimethano - naphthalene (I), are represented stereochemically by formulæ (III) and (V), respectively, and the corresponding 6 : 7-epoxides are known as dieldrin and endrin.



As part of a research into the mechanism of insect resistance to insecticides, a method was required for synthesis, on a millimolar scale, of aldrin, or related compounds derived from decahydro-1 : 4-5 : 8-dimethanonaphthalene, labelled with ^{14}C.

* For name, see British Standard 1831: 1957. The numbering used is based on that of the Ring Index, No. 2229. The trivial names aldrin, isodrin, etc., are used here for convenience, though they normally refer to not quite pure materials.

[1] Bluestone, U.S.P. 2,676,132/1954.
[2] Kleiman, U.S.P. 2,655,513/1953.

Diels–Alder addition of acetylene to *cyclo*pentadiene [3,4] affords *bicyclo*[2 : 2 : 1]hepta-2 : 5-diene (II) which reacts (scheme A) with hexachloro*cyclo*pentadiene to give aldrin (III), while inclusion of the chlorine atoms in the dienophilic reactant (scheme B) leads to isodrin (V). Each synthesis requires two Diels–Alder additions in which diene, dienophile, or both might be labelled with ^{14}C. In either case ^{14}C-labelling of the intermediate dienophile (II or IV) involves Diels–Alder addition under conditions unfavourable to small-scale working and between components susceptible to decomposition. Thus, vinyl bromide (from acetylene) has been condensed with *cyclo*pentadiene to give dehydronorbornyl bromides, which with hexachloro*cyclo*pentadiene gave aldrin hydrobromides, subsequently dehydrobrominated to aldrin. A repetition of this synthesis on a millimolar scale with [^{14}C]acetylene gave no radio-active aldrin.[5]

An alternative approach, involving ^{14}C-labelling of the diene component only, requires the synthesis of hexachloro[^{14}C]*cyclo*pentadiene for scheme A or [^{14}C]*cyclo*pentadiene for scheme B. Krall [5] reports the use of trichloro[^{14}C]ethylene in the Prins synthesis [6] of hexachloro*cyclo*pentadiene, but the product, used in scheme A, gave no radioactive aldrin on a millimolar scale. The synthesis of [^{14}C]*cyclo*pentadiene would lead directly to isodrin (scheme B) and might lead, with suitable extension, to aldrin.

Synthesis of ^{14}C-labelled isodrin and endrin on a millimolar scale *via* [2-^{14}C]*cyclo*pentadiene (scheme C) is now reported.[7] [1-^{14}C]*cyclo*Pentanone, from [1 : 6-$^{14}C_2$]adipic acid by pyrolysis with barium hydroxide,[8] was reduced to [1-^{14}C]*cyclo*pentanol which afforded [1-^{14}C]*cyclo*pentene on dehydration. Bromination of the *cyclo*pentene gave 1 : 2-dibromo[1-^{14}C]*cyclo*pentane, which was then dehydrobrominated to [2-^{14}C]*cyclo*pentadiene. Diels–Alder condensation of [2-^{14}C]*cyclo*pentadiene with 1 : 2 : 3 : 4 : 7 : 7-hexachloro*bicyclo*[2 : 2 : 1]hepta-2 : 5-diene (IV) gave [^{14}C]isodrin. Oxidation of this product with peracetic acid in benzene [1] gave the corresponding 6 : 7-epoxide, endrin.

The pyrolysis of [1 : 6-$^{14}C_2$]adipic acid gave an 80% yield of *cyclo*pentanone containing half the initial ^{14}C (one ^{14}C atom was lost during pyrolysis) so that recovery of isotope was 40% on this stage. A 90% yield of *cyclo*pentanol was obtained from the crude ketone by reduction with aqueous sodium borohydride; [9] this avoided drying the ketone and facilitated isolation of the *cyclo*pentanol.

Liquid reagents were preferred for the dehydration of *cyclo*pentanol and, of these, 88% orthophosphoric acid regularly afforded 80—90% yields of *cyclo*pentene.[10] Quantitative bromination of the latter was accomplished *in vacuo* at a low temperature without a solvent. Dehydrobromination procedures presented difficulty on account of the small scale of working and the tendency of *cyclo*pentadiene to polymerise during the reaction. Thus, the sodium acetate–acetic acid method of Zelinsky and Lewina [11] gave negligible yields of *cyclo*pentadiene from 0·1-molar quantities of 1 : 2-dibromo*cyclo*pentane, while the sodium hydroxide–ethylene glycol method [12] gave 20—30% yields of *cyclo*pentadiene on this scale but proved unsuitable for small-scale operations. 8-Hydroxyquinoline gave a 36% yield of *cyclo*pentadiene which readily afforded pure isodrin in the subsequent Diels–Alder reaction, and this method gave equally good results on the centimolar scale.

The isodrin thus produced (9·1% yield from adipic acid) was chemically identical with an authentic specimen and was shown to be radiochemically pure by the constancy of its specific activity on recrystallisation and by reversed-phase paper chromatography in

[3] Hyman, Freireich, and Lidov, B.P. 701,211/1953.
[4] Plate and Pryanishnikova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1956, 741.
[5] Krall, *Diss. Abs.*, 1957, **17**, 2421.
[6] Prins, *Rec. Trav. chim.*, 1950, **69**, 1003.
[7] Preliminary communication: Brooks, *Chem. and Ind.*, 1958, **7**, 194.
[8] Vogel, "Practical Organic Chemistry," Longmans, Green & Co., London, 2nd edn., 1951, p. 338.
[9] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.
[10] Kogl and Ultée, *Rec. Trav. chim.*, 1950, **69**, 1576.
[11] Zelinsky and Lewina, *Ber.*, 1933, **66**, 477.
[12] Hine, Brown, Zalkow, Gardner, and Hine, *J. Amer. Chem. Soc.*, 1955, **77**, 594.

several solvent systems [13] with the authentic compound, located by the permanganate technique developed for pyrethroids.[14] The labelled compound was located on paper by radiometric scanning.[15]

From scheme C and the geometry of the diene addition the product is a mixture of [6-^{14}C]- and [7-^{14}C]-isodrin, though this designation makes no allowance for possible randomisation during the preparation of [^{14}C]*cyclo*pentadiene from [1-^{14}C]*cyclo*pentanol. Such randomisation, which might result in general labelling of the unchlorinated terminal five-membered ring in isodrin, has been observed previously during a reaction of [1-^{14}C]-*cyclo*pentanol involving an intermediate carbonium ion.[16]

Experimental

General.—Materials were of " AnalaR " grade where possible. For assay of ^{14}C, samples were mounted on 1·75 cm. diameter Whatman No. 1 filter circles impregnated with soya-bean oil (from a 3% v/v solution in ether) and counted under a thin-end-window Geiger–Müller tube under standardised conditions of geometry, taking the mean of pairs of counts made over both faces of the discs. The self-absorption correction was treated as constant since the weights of the discs did not vary appreciably and the weights of added solids were negligible.

Authentic samples of hexachloro*cyclo*pentadiene, isodrin, and endrin were kindly presented by Shell Research Ltd.

[1-^{14}C]cyclo*Pentanone.*—A mixture of adipic acid (2·24 g.) and [1 : 6-^{14}C$_2$]adipic acid (0·236 g., 5 millicuries, purchased from the Radiochemical Centre, Amersham) was dissolved in absolute ethanol (50 c.c.) by heat, the stirred solution evaporated to dryness, and the residue cooled in a desiccator. A sample (50 mg.) was dissolved in absolute ethanol (10 c.c.), and the solid from a 5 μl. portion of the solution, counted as indicated, gave 4475 counts/min.

An intimate mixture of the labelled adipic acid and barium hydroxide octahydrate (0·125 g.), contained in a small-scale pyrolysis apparatus, was heated to 290° during 90 min. and held at this temperature for 2½ hr.; a mixture of *cyclo*pentanone and water distilled into a receiver containing anhydrous potassium carbonate (0·5 g.), while labelled carbon dioxide (containing half the initial ^{14}C) was absorbed in bubblers containing aqueous 2N-sodium hydroxide. The mixture of water and *cyclo*pentanone was distilled at 0·1 mm. into a 50 c.c. flask, cooled to −196°, and weighed (1·25 g.). In experiments with inactive material the dried ketone had n_D^{20} 1·4364 (1·0—1·1 g.).

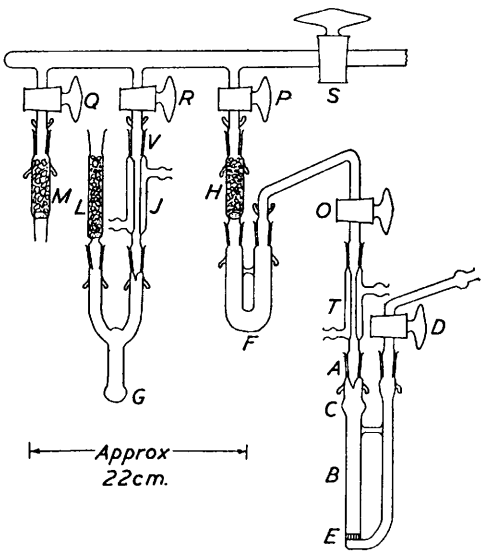
[1-^{14}C]cyclo*Pentanol.*—The wet *cyclo*pentanone was dissolved in water (10 c.c.) and reduced by gradual addition of sodium borohydride (0·45 g.) in water (5 c.c.) with cooling and swirling so that the temperature remained at 25—30°. The solution was then heated at 60—70° for 4 hr., cooled, saturated with potassium carbonate, and extracted three times with ether. The ethereal extracts were concentrated at 60° and moisture was removed from the liquid residue by successive addition and evaporation of methylene chloride (5 c.c. portions); complete removal of water was indicated by the appearance of solid inorganic salts in the vessel.

[1-^{14}C]cyclo*Pentene and* 1 : 2-*Dibromo*[1-^{14}C]cyclo*pentane.*—*cyclo*Pentanol (0·9—1·0 g.; n_D^{20} 1·4530 in inactive experiments) was distilled at 0·1 mm. into the bubbler *B* (see Figure) which was immersed in liquid nitrogen as far as bulb C. The distillate solidified at *C* and a slow stream of dry nitrogen admitted at *D* held the *cyclo*pentanol above the sintered plate *E* after removal of the coolant. 88% Orthophosphoric acid (1·5 c.c.) was added to the *cyclo*pentanol, and vessel *B* was connected to the vacuum manifold at *A*. The nitrogen admitted at *D* provided an inert atmosphere during the reaction and served both to stir the reactants and to sweep out *cyclo*pentene into the receiver *F*, cooled to −78°, during the subsequent dehydration. Receiver *F* was connected to the bromination tube *G via* the " Hidrite " tube *H* and condenser *J*. Drying tubes *L* and *M* contained calcium chloride. Before dehydration commenced, stopcocks *D*, *O*, *P*, and *Q* were open; *R* and *S* were closed. Bromine (0·7 c.c.) was placed in vessel *G* and frozen into a *neat* pool at −196°, a stopper replacing the drying tube *L*; tube *L* was replaced and vessel *G* immersed in a bath at −78°. Tap *R* was then opened and *Q* closed, so that nitrogen

[13] Mitchell, *J. Assoc. Off. Agric. Chem.*, 1953, **36**, 1183.
[14] Winteringham, Harrison, and P. M. Bridges, *Biochem. J.*, 1955, **61**, 359.
[15] Winteringham, Harrison, and R. G. Bridges, *Analyst*, 1952, **77**, 19.
[16] Lotfield, *J. Amer. Chem. Soc.*, 1951, **73**, 4709 (footnote).

entered the apparatus at *D* and left it at *L*. The oil-bath surrounding vessel *B* up to the level *C* was heated slowly to 120°, with hot water at 60—70° passing through condenser *T*; *cyclo*pentene distilled with the oil-bath at 120—125° and the temperature was allowed to rise to 140° after the reaction had apparently ceased. A stream of warm air directed on tap *O* assisted the transfer of *cyclo*pentene to trap *F*. Tap *O* was then closed and the nitrogen flow stopped. Tube *L* was replaced by a stopper, the baths round *F* and *G* were replaced by liquid nitrogen, and the apparatus was evacuated by opening tap *S*. When this tap *S* was closed and the coolant removed from trap *F*, *cyclo*pentene distilled into vessel *G*, leaving a little high-boiling residue; moisture in the product was removed in tube *H*. In experiments with inactive material the *cyclo*pentene (about 0·60 g.) had n_D^{20} 1·4213.

With taps *P* and *R* closed the liquid nitrogen round vessel *G* was replaced by a bath at −78°; condensor *J* was water-cooled. When vessel *G* was then *carefully* allowed to warm to about −8°, reaction of *cyclo*pentene and bromine occurred. It was found that careful condensation of the bromine into a small *neat* pool at the beginning of the experiment resulted in a smooth reaction; traces of uncondensed bromine on the walls of vessel *G* initiated a violent reaction which had to be



arrested by rapid cooling. Complete bromination was ensured by condensing traces of *cyclo*pentene vapour with liquid nitrogen and repeating the bromination. Excess of bromine was transferred to trap *F*, cooled to −196° with taps *P* and *R* open and vessel *G* immersed in water at 60° for 30—60 min.; the almost colourless dibromide weighed 2·42 g. (0·011 mol., 62% yield from adipic acid). Inactive product had n_D^{20} 1·5510. Zelinsky and Lewina [11] record n_D^{19} 1·5510.

Dehydrobromination of 1 : 2-*Dibromo*[1-^{14}C]cyclo*pentane and Synthesis of* [^{14}C]*Isodrin*.—The apparatus was a modification of that illustrated. Vessel *G*, containing 1 : 2-dibromo*cyclo*pentane (2·42 g.) and 8-hydroxyquinoline (4·5 g., 0·03 mol.) now replaced *B*; the connection between condenser *T* and trap *F* had no stopcock, and the outlet *V* carried a thick-walled tube, 17 × 1·7 cm., attached by a B.10 socket and capable of being sealed while attached to the vacuum-manifold.

With stopcocks other than *D*, *P*, and *Q* closed and receiver *F* cooled to −78°, a slow stream of nitrogen was admitted at *D* and the oil-bath round vessel *G* was heated slowly to 200°. Water at 70° passed through condenser *T* and a stream of warm air directed on the connection *T*–*F* assisted transfer of hydrocarbon to trap *F*. When the effervescence in vessel *G* had ceased, the temperature was raised slowly to 230°, then heating and nitrogen flow were stopped. The connection *T*–*F* was then removed and trap *F* closed by a stopper; finally taps *P* and *Q* were closed and trap *F* cooled to −196°. The tube attached at *V* and cooled to −196° contained *freshly* redistilled 1 : 2 : 3 : 4 : 7 : 7-hexachloro*bicyclo*[2 : 2 : 1]hepta-2 : 5-diene [1,2] (2·7 g.), prepared from hexachloro*cyclo*pentadiene, and a trace of quinol. With taps *P* and *R* open, the

apparatus was evacuated, tap *S* was closed, and the hydrocarbon transferred to the reaction tube which was then sealed off from the manifold.

The mixture was shaken, heated in an oven at 90° for 5 hr., then cooled, and the tube was broken while its contents were frozen at −196°. The almost colourless mixture was diluted with methanol–acetone (4 : 1) and cooled overnight at 0°. The crystals were collected, washed with methanol–acetone (4 : 1), drained, and dried at 1 mm. for 30 min. The product (0·57 g., 1·6 millimols.; 9% yield from adipic acid) had m. p. 239—241°, undepressed on admixture with an authentic specimen of m. p. 240—242°. The solid (100 μg.) from a 5 μl. aliquot part of an acetone solution, counted as indicated, gave 3050 c.p.m. (sp. activity 0·34 mc/g.). Successive recrystallisations from acetone–methanol did not change the specific activity, and radiochemical purity was further demonstrated by reversed-phase paper chromatography with the authentic compound as carrier; soya-bean oil [13] or Vaseline (1—3% v/v in ether) was used as stationary phase and acetone–water (4 : 1) or ethanol–water (9 : 1) as mobile solvent.

[^{14}C]*Endrin*.—36% Peracetic acid (0·125 g.) was added dropwise to [^{14}C-isodrin] (0·1 g.) in benzene (0·5 c.c.). After being shaken at room temperature for 19 hr., then at 45° for 1 hr., the mixture was diluted with an equal volume of water, and the benzene expelled at 110°. The solid was filtered off from the cooled mixture, washed with water, and recrystallised from methanol, to give endrin (0·0528 g.), m. p. 243—245° (decomp.), undepressed on admixture with an authentic specimen, m. p. 244—245° (decomp.). A second crop (0·0378 g.) had the same m. p. and specific activity (0·33 mc/g.).

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