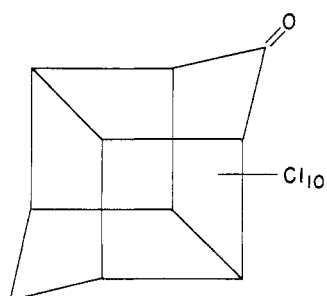




prepared fall into four general classes: compound IIa and its derivatives prepared via the hydroxyl group (Table I), Grignard derivatives (Table II), compounds made by heating Kepone with various ketones and keto esters (Table III), and compounds made by heating Kepone with malonate esters (Table IV). The third and fourth categories are of interest, in that no catalyst is required to induce reaction, although one is usually required when one ketone reacts with another or with malonic esters. Another noteworthy point is that secondary ketones (such as 3-pentanone or cyclohexanone) react, as well as methyl ketones. The secondary ketones might have been expected to be unreactive, since the carbonyl group of Kepone is sterically hindered.

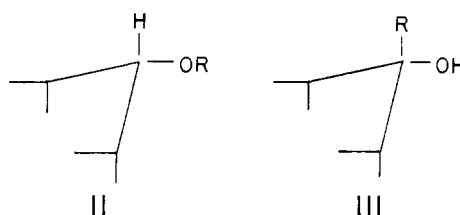


- IIa. R = H  
 b. R = CH<sub>3</sub>NHCO—  
 c. R = C<sub>2</sub>H<sub>5</sub>OCOCH<sub>2</sub>NHCO—

oppositely in both solvents. IIa could be oxidized to Kepone with chromic acid.

**Esters of IIa.** The organic esters were prepared by refluxing a toluene solution of IIa with the corresponding acid chloride for 24 hours. The solvent was then removed, and the crude ester recrystallized from acetone-hexane. The sulfate of IIa was prepared by adding chlorosulfonic acid dissolved in 100 ml. of tetrachloroethylene (9.5 grams, 0.081 mole) to IIa (40 grams, 0.081 mole) dissolved in 250 ml. of tetrachloroethylene at room temperature with stirring. Stirring was continued for about 30 minutes, after which dilute aqueous potassium hydroxide was added to neutrality. The resulting slurry was filtered and dried.

Quaternary titration showed a molecular weight of 616 (theoretical for the



- IIIa. R = CH<sub>3</sub>—  
 b. R = C<sub>6</sub>H<sub>5</sub>—  
 c. R = C<sub>2</sub>H<sub>5</sub>OCOCH<sub>2</sub>CH<sub>2</sub>COCH<sub>2</sub>—  
 d. R = (CH<sub>3</sub>OCO)<sub>2</sub>CH—

**Carbamate Derivatives of IIa.** The *N*-methylcarbamate was prepared by heating IIa (25 grams, 0.051 mole), methyl isocyanate (3 grams, 0.053 mole), acetone (50 ml.), and triethylamine (3 drops) for 4.5 hours at 90° to 100° C. Evaporation of the acetone gave the desired product in high purity. Phenyl isocyanate and the other higher boiling isocyanates were made to react with IIa by refluxing in toluene for 11 hours with pyridine as catalyst.

The infrared spectra in all cases were consistent with the carbamate structure. Compound IIc analyzed as follows: Calculated: 29.0% C, 1.5% H, 2.3% N; found: 29.8% C, 1.7% H, 2.8% N.

**Reaction of IIa with Phosphorus Halides.** IIa (30 grams, 0.061 mole) and phosphorus pentachloride (40 grams, 0.19 mole) were heated at 150° C. for 3 hours with stirring. The cooled reaction mixture was poured into 125 ml. of methanol, and the precipitated solid was filtered and washed with methanol, yielding 14 grams of white solid product. Calculated for C<sub>10</sub>Cl<sub>11</sub>H: 76.3% Cl, found 75.5% Cl. The compound contained no phosphorus. The infrared spectrum showed the absence of hydroxyl group. IIa (30 grams, 0.061 mole), phosphorus tribromide (54 grams, 0.2 mole), and bromine (32 grams, 0.2 mole) were mixed and heated in a sealed Carius tube for 9 hours at 140° to 60° C. The cooled reaction mixture was mixed with water, filtered, dried, and recrystallized from methanol-methylene chloride. Calculated for C<sub>10</sub>Cl<sub>10</sub>BrH: 72.0% total halogen as

### Preparation of Test Compounds

**Compound IIa.** Previous attempts by others (3) to prepare this material were unsuccessful; repetition during the present study of the attempted preparation under the conditions used previously confirmed the conclusion that no IIa is thus formed. The following conditions were found to be satisfactory, however.

Crude Kepone hydrate (150 grams) was refluxed with xylene (1500 ml.) to effect azeotropic dehydration, yielding a solution of 130 grams (0.27 mole) of anhydrous Kepone in xylene. This solution was added to a suspension of lithium aluminum hydride (8 grams, 0.21 mole) in ethyl ether (300 ml.) over 2 hours with stirring. The mixture was then refluxed 3 hours at 90° C. The reaction mixture was cooled, and successively treated with 8 ml. of water, 8 ml. of 15% aqueous sodium hydroxide, and 24 ml. of water. The insoluble material was filtered, and the solvent was evaporated to give 90 grams (69%) of crude IIa. It was purified by recrystallization from hexane.

IIa has an infrared absorption spectrum with a single peak at 2.85 microns which is characteristic of the hydroxyl group. It is soluble in warm hexane, but insoluble in warm 5% aqueous sodium hydroxide; Kepone behaves

Table I. Compound IIa and Derivatives

Identity of R in Formula II	Yield, %	M.P., °C. <sup>a</sup>	Screening Data, % Kill			
			Mites <sup>b</sup>	Pea aphids	Mexican bean beetle larvae	Southern armyworm larvae
H (IIa)	70-80	360 (d.)	8	11	90	100
ClCH <sub>2</sub> O—	80	146-7	8	0	90	100
(—OR = Cl)	47	380 (d.)	12	50	100	100
KO <sub>2</sub> S—	100	d. >350	13	0	100	100
(—OR = Br)	100	380 (d.)	8	100	100	100
ClF <sub>2</sub> CCO—	57	112-8	7	0	100	100
C <sub>11</sub> H <sub>23</sub> CO—	89	Oil	3	40	0	80
C <sub>17</sub> H <sub>33</sub> CO—	85	Oil	10	100	40	80
CH <sub>3</sub> NHCO—(IIb)	100	175-85	0	100	100	100
C <sub>2</sub> H <sub>5</sub> NHCO—	91	174-6	...	100	100	100
<i>n</i> -C <sub>3</sub> H <sub>7</sub> NHCO—	61	126-9	...	100	100	100
<i>n</i> -C <sub>4</sub> H <sub>9</sub> NHCO—	89	147-9	...	90	0	100
C <sub>6</sub> H <sub>5</sub> NHCO—	30	145-7	6	0	0	100
C <sub>2</sub> H <sub>5</sub> OCOCH <sub>2</sub> NHCO—(IIc)	74	141-5	11	100	100	100
<i>n</i> -C <sub>4</sub> H <sub>9</sub> OCOCH <sub>2</sub> NHCO—	86	109-12	...	100	80	100
CH <sub>3</sub> OCO(CH <sub>2</sub> ) <sub>2</sub> CH—(COOCH <sub>3</sub> ) <sub>2</sub> NHCO—	65	122-32	...	0	20	100
Kepone	...	...	0	0	100	100

<sup>a</sup> On purified samples; (d.) indicates decomposition.

<sup>b</sup> Mites. *Tetranychus telarius* (Linnaeus); pea aphids, *Macrosiphum pisi* (Harris) Mexican bean beetle larvae, *Epilachna varivestis* (Mulsant); Southern armyworm larvae, *Prodenia eridania* (Cramer).

anhydrous potassium salt is 611). The infrared spectrum indicated the presence of a sulfate group. Analysis of the tosylate of IIa showed: Calculated: 31.5% C, 1.3% H, 5.0% S; found: 31.8% C, 1.3% H, 5.1% S.

chloride; found: 69.9%. The infrared spectrum showed the absence of the hydroxyl group.

**Grignard Derivatives (IIIa, IIIb, and Related Compounds).** All of the compounds in Table II were prepared

**Table II. Compound IIIa and Analogs**  
(From reaction of Kepone with Grignard reagents)

Identity of R in Formula III	Yield, %	M.P., °C. <sup>a</sup>	Screening Data, % Kill			
			Mites	Pea aphids	Mexican bean beetle larvae	Southern armyworm larvae
CH <sub>3</sub> —(IIIa)	80	d. >300	10	100	100	100
n-C <sub>4</sub> H <sub>9</sub> —	60	d. >300	6	0	100	100
n-C <sub>6</sub> H <sub>13</sub> —	26	338–42	0	0	0	100
n-C <sub>10</sub> H <sub>21</sub> —	50	342–6	3	0	100	100
n-C <sub>12</sub> H <sub>25</sub> —	42	d. >300	7	0	60	100
n-C <sub>15</sub> H <sub>31</sub> —	47	d. >300	0	10	80	100
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> —	58	350 (d.)	7	0	100	100
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> —	45	306–16 (d.)	0	0	80	100
Cyclohexyl	20	d. >300	0	0	100	100
C <sub>6</sub> H <sub>5</sub> (IIIb)	63	189–93	4	100	100	100
4-ClC <sub>6</sub> H <sub>4</sub> —	57	224–34	0	0	100	100
2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> —	65	247–50	0	0	0	100
4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> —	58	198–200	5	0	100	100
2-HOC <sub>6</sub> H <sub>4</sub> —	40	247–9	5	80	100	100
4-HOC <sub>6</sub> H <sub>4</sub> —	81	251–7	0	10	80	100
Kepone	...	...	0	0	100	100

<sup>a</sup> On purified samples.

**Table III. Compound IIIc and Analogs**  
(From reaction of Kepone with ketones and ketoesters)

Ketone Used	Yield, %	M.P., °C.	Screening Data, % Kill			
			Mites	Pea aphids	Mexican bean beetle larvae	Southern armyworm larvae
Acetone	97	342–8 (d.)	0	0	100	100
Chloroacetone	64	145–62	0	22	0	100
2-Butanone	80	346–50 (d.)	8	20	100	100
2-Pentanone	80	84–160	0	0	100	100
3-Pentanone	88	344–8 (d.)	12	0	100	100
3-Methyl-2-butanone	62	139–43	24	0	0	100
4-Methyl-2-pentanone	84	160–5	25	11	100	100
2-Heptanone	63	85–6 <sup>a</sup>	0	0	0	100
2-Octanone	66	76–8	0	30	0	100
2-Nonanone	70	70–6	26	10	0	80
Acetophenone	84	152–3 <sup>a</sup>	0	0	0	100
Phenylacetone	67	140–3	0	0	0	80
Cyclopentanone	64	195–7 <sup>a</sup>	23	0	100	100
Cyclohexanone	33	166–71	4	0	0	100
Diacetyl	73	(d.)	0	0	0	100
Methyl pyruvate	71	248–51 <sup>a</sup>	...	90	80	100
Ethyl pyruvate	62	240–7 <sup>a</sup>	...	100	40	100
Ethyl acetoacetate	95	Oil	17	0	100	100
tert-Butyl acetoacetate	95	Oil	9	100	100	100
Methyl levulinate	73	112–5 <sup>a</sup>	8	90	100	100
Ethyl levulinate (IIIc)	60	91 <sup>a</sup>	15	67	100	100
n-Butyl levulinate	68	94–6 <sup>a</sup>	...	100	40	100
Dodecyl levulinate	95	Oil	4	80	100	100
Benzyl levulinate	90	Oil	5	50	100	100
2-Chloroethyl levulinate	70	114–6 <sup>a</sup>	7	0	100	100
Kepone	...	...	0	0	100	100

<sup>a</sup> On purified sample; otherwise run on crude product. Compounds decomposing rather than melting indicated by (d.).

**Table IV. Compound IIIe and Analogs**  
(From reaction of Kepone with malonic esters)

Malonate Used	Yield, %	M.P., °C.	Screening Data, % Kill			
			Mites	Pea aphids	Mexican bean beetle larvae	Southern armyworm larvae
Dimethyl (IIIe)	78	153–4 <sup>a</sup>	10	0	100	100
Diethyl	50	106–10	0	30	100	100
Di(n-butyl)	63	84–7	26	10	100	100
Di(n-hexyl)	99	Oil	5	90	100	100
Di(n-dodecyl)	90	Oil	4	0	80	100
Diphenyl	76	164.5–5.5 <sup>a</sup>	0	0	60	100
Kepone	...	...	0	0	100	100

<sup>a</sup> On purified samples; otherwise run on crude products.

by the method used by Earle (3) for making IIIb (R = C<sub>6</sub>H<sub>5</sub>—), except the two hydroxyphenyl derivatives, which resulted from demethylation of the methoxyl analogs.

Phenylmagnesium bromide was prepared by the standard method from bromobenzene (16 grams, 0.1 mole) and magnesium metal (2.4 grams, 0.1 mole) in 100 ml. of anhydrous ether. To this solution was added, with stirring, anhydrous Kepone (49 grams, 0.1 mole) in xylene. The ether was distilled to a pot temperature of 100°, and the mixture was then refluxed for 18 hours. The reaction mixture was cooled, washed with 150 ml. of aqueous HCl and with water, and then distilled to yield a solid. It was recrystallized from methylene chloride–hexane to a melting point (uncorrected) of 189–93° C. [lit. 194.5–96.5° (3)]. The two methoxyphenyl compounds were easily demethylated with HI or HBr to the hydroxyphenyl analogs.

All of the compounds in Table II gave infrared absorption spectra in agreement with the assigned structures. The keto function of Kepone was absent, but characteristic tertiary alcohol absorption was present. Compound IIIa, the most active material in this series, analyzed as follows: Calculated: 26.1% C, 0.8% H, 70.0% Cl; found: 26.2% C, 0.8% H, 70.1% Cl.

**Ketone Derivatives (IIIc and Related Compounds).** The compounds listed in Table III were prepared by refluxing a solution of anhydrous Kepone in xylene, prepared as above, with a 50% excess of the corresponding ketone for 18 hours. The solution was cooled and filtered, and the solvent and excess ketone were removed by distillation in vacuo. Low-boiling ketones, such as acetone, were heated for longer times to compensate for their lower boiling points.

The compounds showed infrared hydroxyl group absorption at 2.95 microns. Absorption resulting from introduction of the new carbonyl group was observed at 5.87 microns, but that characteristic of Kepone at 5.55 microns is no longer present. IIIc, one of the most active compounds in this group, analyzed as follows: Calculated: 32.3% C, 1.9% H; found: 32.2% C, 1.9% H.

**Malonic Ester Derivatives (IIIe and Related Compounds).** A xylene (250 ml.) solution of anhydrous Kepone (49 grams, 0.1 mole) was refluxed for 17 hours with dimethyl malonate (13 grams, 0.1 mole). The solution was cooled, filtered, and distilled in vacuo to remove the solvent, yielding a solid residue. It was purified by recrystallization from methylene chloride–hexane. Chlorine calculated: 56.9%; found: 56.6%.

**Biological Evaluation.** The insecticidal test data recorded in Tables I to IV were obtained as follows.

**Table V. Relative Toxicity to Insects of Kepone IIc, IIIa, and IIIc**

(Kepone = 1)

Cpd.	Pea Aphids	Mex. Bean Beetle Larvae	Armyworm Larvae	Houseflies		German Roaches		Plum Curculio	Colorado Potato Beetle Larvae
				Dry bait	Liq. bait	5 days	10 days		
IIc	12	<0.5	1	<0.5	<0.5	3	1.6	1.5	3
IIIa	20	2	10	5	3	>0.5	1	1.5	3
IIIc	10	1.3	1.5	<0.5	<0.5	2	1.6	2	15

Cranberry bean plants in 2<sup>1</sup>/<sub>2</sub>-inch pots, with all foliage removed except one primary leaf, are sprayed for 2 seconds on the upper surface and 5 seconds on the under surface. Spray is delivered from a De Vilbiss atomizer nozzle at 20 p.s.i. The approximate volume of spray on the upper surface is 0.19 ml., and on the under surface is 0.48 ml. The deposits are allowed to dry on the plants and five 3rd instar armyworm larvae are then confined on each plant with 6-inch screen wire spheres. Mortality records are made 3 days after treatment. The spray is an aqueous suspension containing 0.25% by weight of toxicant, made by diluting an acetone solution of the compound. This test was used on Mexican beetle and southern armyworm larvae. The above procedure was also used on mites, except that the plants were not defoliated and were infested with mites one day before spraying.

Aphids were tested as follows: English broad bean plants are sprayed for 2 seconds on the upper surface and 5 seconds on the under surface. Adult female aphids (10 per test) are brushed from infested broad bean plants into 5-inch screen wire hemispheres and sprayed for 5 seconds. The aphids are caged over the previously sprayed plants and mortality records are made 3 days later.

The data in Tables I to IV indicate that, like Kepone, the analogous alcohols are primarily stomach insecticides active on chewing insects (bean beetles and southern armyworms) rather than contact materials active on sucking insects (mites and aphids). On the other hand, 16 of the compounds give 80% or better kill of aphids whereas Kepone is ineffective. This may reflect greater lipid solubility of the active compounds.

Of the *N*-alkyl carbamates listed in Table I, the lowest three members of the homologous series (compound IIb and its ethyl and *n*-propyl analogs) are more active than the *n*-butyl analog. Similarly, IIc is more active than the two ester carbamates. In Table II, IIIa is more active than its higher homologs, and IIIb is generally more active than the other aromatic compounds. It therefore appears that the first or lower

members of the homologous series in all these cases are the most active materials, and that no benefit results from increasing the chain length or derivatizing the substituting moiety. This trend is less obvious with the compounds in Tables III and IV, where the homologs in some cases are as active as, or even more so than, the first member. Introduction of the ester group into the keto compounds of Table III appears to enhance toxicity to aphids.

Follow-up tests were run with Kepone, IIc, IIIa, and IIIb on several insects—pea aphids, Mexican bean beetle larvae, southern armyworm larvae, adult houseflies [*Musca domestica* (Linnaeus)], adult German cockroach [*Blattella germanica* (Linnaeus)], plum curculio adults [*Conotrachelus nenuphar* (Herbst)], and Colorado potato beetle larvae [*Leptinotarsa decemlineata* (Say)]. The tests with houseflies were run with dry and liquid baits, and in the case of German cockroaches with dry bait. The curculio tests were conducted by confining the beetles in contact with sprayed green apples, and the Colorado potato beetle tests by confining the insects with sprayed potato vine terminal cuttings. Dosage-mortality curves were plotted for each insect, which allowed determination of an *LC*<sub>50</sub> value. Absolute *LC*<sub>50</sub> values for Kepone itself, expressed as weight per cent toxicant in the spray, are: mites, >0.25; aphids, >0.125; Mexican bean beetle larvae, 0.05; southern armyworm larvae, 0.007; adult houseflies (dry bait), 0.06; adult houseflies (liquid bait), 0.03; German cockroach, 0.25; plum curculio, 0.022; Colorado potato beetle, 0.002. Toxicity values relative to Kepone as 1, calculated from the respective *LC*<sub>50</sub> values, are summarized in Table V for three compounds. Compound IIIb, although of comparable activity with IIIa in initial screening tests, was soon found inferior to it in follow-up tests at reduced dosages on all insects tested.

These data show that compound IIIa is equal or superior to Kepone in all cases except in the 5-day test on German

cockroaches, and that on three insects it is 5 to 20 times as effective. Compound IIc, on the other hand, is generally considerably less active than IIIa, except on German cockroaches, where IIIa is more active than either Kepone or IIc. Compound IIIc in seven of the tests is fairly close in toxicity to IIc, but is considerably more active on Mexican bean beetle larvae. The exceptional activity of IIIc on Colorado potato beetle larvae is noteworthy. It gives complete control for at least 4 weeks at a dosage of 0.125 pound of active ingredient per acre, and is therefore more active on this species than any other toxicant known to us (7).

Compound IIa resembles Kepone in being fungicidally active. A laboratory spore germination test on *Monolinia* (*Sclerotinia*) *Fructicola* gave complete inhibition at 10 p.p.m., compared to 92% for copper ion in a check test.

#### Acknowledgment

We acknowledge the assistance of Robert G. Blenk in obtaining the insecticidal test data. We are indebted to Avery E. Rich for the fungicidal test data.

#### Literature Cited

- (1) Allied Chemical Corp., General Chemical Division, Agricultural Chemical Department, "Experimental Insecticide GC-9160," 1964.
- (2) Allied Chemical Corp., General Chemical Division, Agricultural Chemical Department, "Kepone Insecticide Fungicide," 1960.
- (3) Earle, R. H., Ph.D. dissertation, Purdue University, 1957; *Dissertation Abstr.* **20**, 4275 (1960).
- (4) Farah, B. S., Gilbert, E. E., Jones, E. S., Otto, J. A., *J. Org. Chem.* **30**, 1006 (1965).
- (5) Gilbert, E. E., Giolito, S., U. S. Reissue Patent **24,749** (Dec. 15, 1959).
- (6) McBee, E. T., Wieliczko, T. B., Morton, C. J., Annual Meeting, Indiana Academy of Sciences, Oct. 30, 1964.

Received for review July 15, 1965. Accepted December 1, 1965. Ninth in a series on perhaloketones. Previous paper (4).