The Radiation-induced Synthesis of the Insecticide "Gammexane"—II Synthesis by High-energy Radiation

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A study of the preparation of 1:2:3:4:5:6-hexachloro*cyclo*hexane by radiation from cobalt-60 has shown that the Gammexane content of the crude material is independent of dose rate, benzene concentration and duration of the chlorination process. Small increases in the Gammexane content can be effected by low temperature chlorination.

When compared with the conventional photo-initiated reaction the radiation method exhibits a marginal improvement in Gammexane content but the efficiency of energy utilization is similar.

LA SYNTHÈSE INDUITE PAR LE RAYONNEMENT DE L'INSECTICIDE "GAMMEXANE"—II. SYNTHÈSE AU RAYONNEMENT DE HAUTE ÉNERGIE

La recherche sur la préparation de l'1:2:3:4:5:6-hexachlorocyclohexane au moyen du rayonnement du cobalt 60 a montré que le titre de Gammexane dans la matière crue est indépendant du taux de dose, de la concentration de benzène et de la durée du procédé de chlorination. La chlorination à température basse peut achever de petites augmentations du titre de Gammexane.

Comparée avec la réaction photo-initiée conventionnelle, la méthode à rayonnement montre une amélioration marginale du titre de Gammexane mais l'efficacité d'emploi de l'énergie est pareille.

РАДИАЦИОННЫЙ СИНТЕЗ ИНСЕКТИЦИДА "ГАММЕКСАН"—II. СИНТЕЗ С ПОМОЩЬЮ ИЗЛУЧЕНИЯ ВЫСОКОЙ ЭНЕРГИИ

Исследование получения 1:2:3:4:5:6-гексахлорциклогексана при помощи излучения Со⁶⁰ показало, что содержание гаммексана в неочищенном веществе не зависит от мощности дозы, концентрации бензола и продолжительности процесса хлорирования. Небольшое увеличение содержание гаммексана достигается низко-температурным хлорированием.

По сравнению с обычным фото-инициированием радиационный метод несколько увеличивает содержание гаммексана, но эффективность используемой энергии не меняется.

STRAHLUNGINDUZIERTE SYNTHESE DES INSEKTENVERTILGUNGSMITTELS "GAMMEXAN"—II. SYNTHESE DURCH HOCHENERGETISCHE STRAHLUNG

Eine Untersuchung der Herstellung von 1:2:3:4:5:6-Hexachlorocyklohexan durch Strahlung von Co⁶⁰ zeigt, dass der Gammexan-Gehalt im Rohmaterial von Dosisrate, Benzol-Konzentration und der Dauer des Chlorierungsprozesses unabhängig ist.

Im Vergleich mit der üblichen photosynthetischen Reaktion zeigt die Strahlungsmethode eine leichte Verbesserung des Gammexan-Gehaltes, aber die Wirksamkeit der Energieverwertung ist gleich.

4

1. INTRODUCTION

PART I of this paper⁽¹⁾ has described the initiation of the reaction by ultra-violet light when it was found impossible to increase the γ -isomer yield by the addition of various inorganic and organic materials. The yield of "Gammexane" obtained ranged from 12–16 per cent and under optimum conditions where the rate of halogenation was a

Radiation source

Radiation was obtained from a 700 c cobalt-60 source housed in a concrete shield, the design and operation of which has been described elsewhere.⁽²⁾ The irradiation chamber was illuminated by a low-power ruby bulb in order to obviate any risk of photochemical initiation of the reaction.

Dosimetry

The ferrous sulphate system was used to measure the dose received by the contents of the reaction vessel. Experiments were carried out with the reaction vessel containing an amount of dosimeter solution equivalent to the charge used in the chlorination runs and with the cooling jacket filled with water.

The reaction vessel

This consisted of an inner cylinder of 100

maximum about 12-14 per cent of the product consisted of the ν -isomer.

The aim of the present work was to investigate the effect of dose rate, benzene concentration, temperature and degree of conversion on both the γ -isomer content and the overall yield of product for the highenergy radiation-initiated reaction.

2. EXPERIMENTAL

ml capacity surrounded by an annular jacket through which cooling water could be passed. The inlet for chlorine and nitrogen extended to the bottom of the vessel and a thermo-couple well, terminating at the centre of the reaction volume, was included. The exit gases were discharged through a bulb surrounded by an ice-salt mixture. The bulb acted as a combined splash head and condenser from which spray and condensate drained back into the reaction vessel.

The gas train (Fig. 1)

The supply of nitrogen and chlorine was described in Part I of this paper. The gas train was protected by two surge bottles, one on either side of the wall of the shield through which the gases passed. As the passage of the dry gas mixture caused considerable



evaporation losses from the reaction vessel. the gases were passed through a presaturator whose contents were identical with those of the reaction vessel. It was found that the use of the pre-saturator and the partial condenser prevented any overall losses from the reaction vessel. The outgoing gases were passed to the atmosphere through a polythene tube connected to the splash head. Several three-way taps were incorporated to extend the usefulness of the system. Taps Aand B could be opened to the atmosphere to avoid the "suck-backs" which otherwise occurred on interruption of the gas flow. Tap B could also be used to isolate the first stage of the system for testing the flow meters. The removal of the contents of the reaction vessel resulted in the copious liberation of chlorine even when these had been well purged with nitrogen, hence a product removal loop was essential. By applying a back pressure of nitrogen through taps C and D while tap A was closed, the product could be displaced through the gas delivery tube and tap E into the receiver. Any residual product was removed with additional solvent introduced through the inlet of the splash head and displaced as above.

The chlorination of benzene

Benzene or a mixture of benzene and carbon tetrachloride (80 ml) was added to the reaction vessel and chlorine passed for 1 hr to de-aerate and saturate the hydrocarbon. Previous work had indicated this to be the optimum period. The vessel was then irradiated for a given time, usually 15 min, and finally most of the excess chlorine was removed by the passage of nitrogen. During the reaction the supply of cooling water was adjusted periodically to maintain an even temperature. The product was then discharged into a receiver and isolated as before.

Separation of the isomers of 1:2:3:4:5:6hexachlorocyclohexane

The products from several identical runs (80g) were combined, and separated as

described in Part I of this paper.⁽¹⁾ There were obtained γ -isomer (5·38g), m.p. 112·5°C, unchanged when mixed with authentic material, α -isomer (17·02g), m.p. 157-157·5°C, and β -isomer (17·0g), m.p. 309°C.

Analysis of 1:2:3:4:5:6-hexachlorocyclohexaney-isomer

The polarographic method for the determination of γ -isomer has been referred to in Part I. It has been stated in the literature⁽³⁾ that by-products of low chlorine content can give rise to spurious polarographic results. The presence of materials of low chlorine content was unlikely in the present work owing to the conditions used, but the validity of the polarographic technique was verified by two alternative methods.

Several analyses were conducted by a biological technique in which grain weevils— *Calandra granaria*—were incubated on filter paper impregnated with graded amounts of the samples under test. A similar control incubation was carried out with pure Gammexane. The response curve relating concentration of toxic material with percentage morality is of a sigmoid form and the necessary probit transformation and statistical evaluation of such results has been described by FINNEY.⁽⁴⁾

Biological evaluation of γ -isomer

A series of ten petri dishes each containing a closely fitting disc of filter paper was prepared for each sample and various amounts of an alcoholic solution of the sample were added to each plate so that the concentration range $20-200 \text{ mg/m}^2$ was covered in equal steps. The plates were then exposed to the atmosphere until the odour of the solvent had disappeared. A similar series was prepared with pure γ -isomer for the concentration range $2-20 \text{ mg/m}^2$. Another group of plates was treated with solvent only to act as a blank.

One hundred grain weevils were added to each of the plates which were then sealed with adhesive tape and incubated at 22°C for 24 hr. After incubation the insects were removed to a warmed enamel dish and the living insects counted and removed with a suction bottle. The remaining insects were re-warmed and those which showed no movement after an individual examination of 5 sec were counted as dead.

From the relationship between the concentration at each level and the percentage mortality after correcting for the mortality observed in the blanks, the dose sufficient to kill half of the insects could be calculated— 50% lethal dose (L.D.50). In later runs the probit transformation and the consequent statistical analysis was carried out on a Ferranti Mercury computer according to a programme which has been reported by COOPER.⁽⁶⁾ The γ -isomer content of the test series was obtained by comparison with the L.D. 50s of the control experiments.

The results were consistent with those obtained polarographically although standard deviations of the order 3–5 per cent were obtained. These were attributed to several factors which could only be controlled in a laboratory fully equipped for biological evaluations of this type. It was observed, for instance, that the toxicity of a given material varied widely with the age of the insect and since some 7000 insects were used for the parallel estimation of each five samples, it was impractical to standardize the age of the insects used. The counting of the plated insects was a lengthy procedure both by reason of the numbers involved and the difficulty of deciding in a brief examination if an insect was dead or alive. As this decision was necessarily subjective it was essential to employ only one operator and to randomize the order in which the plates were examined. This imposed a considerable variation in the length of time the insects were in contact with the toxic material before counting and introduced a significant random variation to the results.

Some typical results were as follows: Polarographic $13\cdot3 \pm 0\cdot2\%$; $13\cdot7 \pm 0\cdot2\%$; $13\cdot7 \pm 0\cdot2\%$. Biological $15 \pm 3\%$; $11 \pm 5\%$; $12 \pm 3\%$.

Since further refinements of the biological evaluation were not possible in a general laboratory, an alternative method was used. Infra-red analysis, conducted according to the method of HUDSON⁽⁵⁾ gave the following results on three different samples obtained during the present work:

Polarographic $12.7 \pm 0.2\%$ $17.5 \pm 0.3\%$ $13.6 \pm 0.2\%$ Infra-red $11.9 \pm 1.8\%$ $16.4 \pm 1.3\%$ $14.4 \pm 1.9\%$

From these alternative procedures it was concluded that the polarographic method would be suitable for all further determinations.

3. RESULTS AND DISCUSSION

(a) The influence of reaction conditions on γ -isomer content

The effect of dose rate and benzene concentration. The γ -isomer yield was measured at several dose rates for various benzene-carbon tetrachloride mixtures as shown in Table 1. (Figures in parentheses indicate the degree of replication.) The results obtained

Benzene concen-	Dose rate (rads/hr)								
(vol. %)	2.33×10^{3}	4.05×10^3	5.56×10^{3}	7.06×10^3	8.22×10^3	2.09×10^4	5.13×10^{4}	Average	
20	16.7	16.9	16.2	11.3	$15.2 \pm 2.5(2)$	15.7	12.7	$15.0 \pm 2.2(8)$	
40	$15.8 \pm 10(2)$	17.7	13.0	13-1	14.4	12.6	15.6	$16.8 \pm 1.8(8)$	
60	17.3	17.4	13.6		14.1	15.4	15.9	$15.6 \pm 1.6(6)$	
80	15·6 ± 1·2(3)	$14.3 \pm 0.3(3)$	$16.3 \pm 0.4(2)$		-	12.7		$15.0 \pm 1.4(9)$	
100	$15.9 \pm 0.9(8)$	17.4	15.1			16.3		$16.0 \pm 1.0(11)$	
Average	$15.9 \pm 1.0(15)$	$16.1 \pm 1.6(7)$	$15.1 \pm 1.5(6)$	$12.2 \pm 1.3(2)$	$14.7 \pm 1.5(4)$	14·5 ± 1·8(5)	$14.7 \pm 1.8(3)$	15·3 ±1·6(42)	

TABLE 1. γ -Isomer content at several dose rates and benzene concentrations

Temp. (°C)	Medium	Dose rate (rads/hr)	Gamma content (%)	
-72	20% benzene-	7.03×10^3	18.1 ± 0.2	
25	20% benzene- chloroform	7.03×10^3	16.6 ± 0.1	
21	100% benzene	7.03×10^{3}	16.5 ± 0.4	
80	100% benzene	7.03×10^3	13.6 ± 0.2	

TABLE 2. γ -Isomer content at several reaction temperatures

indicated no real change either with benzene concentration or dose rate.

The effect of temperature. The variation of the yield of γ -isomer with temperature was also studied between -72° and 80° C. At the lower temperature, mixtures of benzene and carbon tetrachloride could not be used since these solidified. By the determination of the freezing points of a number of benzenechloroform mixtures, it was found that mixtures containing less than 40 per cent by volume of benzene were liquid at -72° and therefore a 20% solution of benzene in chloroform was chosen as the reaction medium. The reaction was carried out in a Dreschel bottle of dimensions similar to those of the water-jacketed flask used for runs at room temperature, using a mixture of solid carbon dioxide and alcohol as a refrigerant. Similarly a further series of experiments was conducted at the boiling point of benzene. The results are shown in Table 2. A comparison of the results at 25° and 21°C in benzene-chloroform and pure benzene indicates no change in the γ -isomer content due to the use of a different reaction medium.

From these results it could be seen that there was a marginal improvement in the percentage of γ -isomer obtained at -72° . However, this was of little practical significance since the overall yield was much reduced at this temperature.

The effect of increased reaction time. It has been reported⁽⁷⁾ that exhaustive chlorination of benzene results in a crude product from which the γ -isomer may be isolated in a 42% yield. Accordingly the normal irradiation period of 15 min used in the current work was extended to 30 and 60 min. The results obtained for the yield of γ -isomer after various times were respectively 15 min, 16·1 per cent; 30 min, 15·2 per cent; and 60 min, 15·2 per cent. It appeared that the γ -isomer content was not improved by extending the irradiation period.

(b) The influence of reaction conditions on the G-value

The above experiments were chosen in order to find any variation in the γ -isomer content under different conditions. The constancy of the γ -isomer yield under these various conditions did not justify a further kinetic study of the system but from the data available it was possible to draw some conclusions about the behaviour of the radiation-induced reaction under various conditions.

Experiments carried out at constant dose rate and composition showed that the rate of product formation was linear with time. The line did not pass through the origin but had a positive intercept on the time axis. The positive intercept corresponded to the time of travel of the source.

The efficiency of the reaction was assessed in terms of the G-value for the formation of hexachlorocyclohexane, i.e. the number of molecules of product formed for an energy absorption of 100 eV.

Data were available for the G-values at various dose rates for each concentration of benzene. When the sets of points were plotted logarithmically, linear relationships were indicated. Statistical regression lines of the log G-value y upon the log dose rate x for each concentration of benzene, are shown together with the experimental values in Table 3. The degree of correlation between the data and the calculated equations were assessed by the calculation of the correlation coefficient r and the associated probability level ascertained. The results were highly significant of a genuine linear relationship between the logarithm of the G-value and the dose rate. The standard deviations σ_b of the regression coefficients b were also calculated.

Benzene concentration (mol. fraction)	G-value	Dose rate (ergs/l/hr)	Regression equation	
0.2134	7.994×10^3	6.374×10^{10}	v = 12.37 - 0.78r	
	5.454×10^4	6.539×10^{10}	y = 12 07 0 70x	
	1.034×10^{5}	2.663×10^{9}	r = -0.998 $a = < 0.001$	
	2.080×10^{5}	9.000×10^{8}	$\sigma_{\rm s} = \pm 0.03$	
	2.202×10^{5}	1.048×10^9	0, 1000	
0.4198	$1.434 imes 10^4$	$5.842 imes 10^{10}$	v = 11.05 - 0.64x	
	$5.501 imes 10^4$	$5.994 imes 10^9$, , , , , , , , , , , , , , , , , , ,	
	1.050×10^{5}	2.441×10^9	$r = -0.985 \ a = < 0.01$	
	1.790×10^{5}	9.605×10^{8}	$\sigma_{1} = +0.04$	
	$4.714 imes 10^{5}$	2.722×10^8		
0.6202	$1.301 imes 10^5$	$5.443 imes 10^9$	v = 9.32 - 0.43x	
	1.696×10^5	2.217×10^9	, , , , , , , , , , , , , , , , , , ,	
	3.400×10^{5}	8.720×10^{8}	$r = -0.973 \ \rho = < 0.01$	
	$4\cdot 162 \times 10^{5}$	$4.279 imes 10^{8}$	> 0.001	
	$4\cdot 364~ imes~10^5$	2.472×10^8	$\sigma_b = \pm 0.06$	
0.8104	$1.914 imes10^5$	$2.008 imes 10^9$	y = 7.96 - 0.29x	
	2.715×10^{5}	5.341×10^{8}		
	2.732×10^{5}	$5.341 imes 10^8$	$r = 0.970 \ \rho = < 0.01$	
	$2.697 imes 10^{5}$	5.341×10^{8}	> 0.001	
	3.298×10^{5}	$3.981 imes10^8$	$\sigma_b = \pm 0.04$	
1.0000	$1.777 imes 10^{5}$	1.777×10^9	v = 11.64 - 0.70x	
	3.731×10^{5}	4.728×10^{8}	5	
	$5.641 imes 10^{5}$	3.464×10^{8}	$r = 0.992 \ \rho = 0.001$	
	7.882×10^{5}	1.982×10^8	$\sigma_b = \pm 0.05$	
$r = \frac{\Sigma(x - \tilde{x})}{(x - \tilde{x})}$	$\frac{(y-\bar{y})}{\sum_{a=1}^{n}\sigma_{b}^{2}} = \pm \Sigma(y - y)$	$\overline{y})^2 - \frac{\sum(x - \overline{x})(y - \overline{y})}{\sum_{x \to \infty} \frac{1}{2}} / (x - \overline{x})(y - \overline{y}) $	$\frac{\sigma_b = \pm 0.05}{(N-2)\Sigma(x-\bar{x})^2}$	

TABLE 3. The relationship between G-value and dose rate for several concentrations of benzene

Having established the nature of the individual lines it remained to examine the influence of the benzene concentration on the G-value. The slopes of the line appeared to vary regularly with the concentration but in view of the uncertainty indicated by the standard deviations of the slopes, these were compared by a method suggested by YATES.⁽⁸⁾ For the 20% and 40% benzene dilutions it was found that the difference between the slopes was significant at the 0.05probability level. For the 60% and 80%dilutions the probability was greater than 0.10. There was therefore insignificant evidence for the difference between the 60%and 80% slopes, and the case of the two lower concentrations was marginal. However, pooling the results for the 20% and 40% dilutions and the 60% and 80% dilutions gave two new lines for which the difference between slopes was significant at the 0.011 probability level, indicating that the results were not homogeneous.

In order to pursue this point a multiple regression was carried out. It was assumed that the data would best be represented by an equation of the form:

$$G$$
-value = $A[I]^{-b_1}[C]^{-b_2}$

where A, b_1 and b_2 are constants, [I] is the radiation intensity (ergs/litre/hour) and [C] equals the molar fraction of benzene. The empirical equation derived from all the

Source of variance	Sums of squares	Degrees of freedom	Mean squares	Variance ratio	Significance level (p)
Variation explained by [I]	4.0111	1	4.0111	294-9	0.001
Increment explained by addition of [C]	0.0290	1	0.0290	2.132	0.10
Total explained by [I] and [C] together	4.0401				
Residual	0.2311				
Total	4.2712				

TABLE 4. Multiple regression-analysis of variance

experiments conducted in diluted benzene was:

$$G = A[I]^{-0.64} [C]^{-0.18}$$

The standard errors of b_1 and b_2 were ± 0.04 and ± 0.13 respectively. Since the standard error for b_2 was large, the significance of the concentration effect was examined further by an analysis of variance after a model described by BROWNLEE⁽⁹⁾, shown in Table 4.

From this analysis it could be seen that the dose rate had a most marked effect on the G-value, significant at a probability level below 0.001, whereas the concentration effect was not significant. The result for the intensity exponent is consistent with the square root dependence often observed in radiation-induced chlorinations due to a biradical termination step in the reaction kinetics. From the differing slopes of the initial equations for each concentration of benzene there is a concentration effect but the nature of the data available does not allow this effect to be determined with the required accuracy. Further deductions from these data could only be speculative since the presence of benzene in the reaction mixture would introduce a marked protection effect on the radiation-initiated formation of radicals from the carbon tetrachloride.

(c) Comparison of radiation and ultra-violet induced reactions

In Part I of this paper⁽¹⁾ it was stated that the optimum γ -isomer content attained with ultra-violet irradiation was 13.2 + 1.3 per cent. For the radiation-induced reaction at room temperature the mean value was 15.3 +1.6 per cent. An improvement can be obtained at lower temperatures but the increased γ -isomer content is accompanied by a lower gross yield of product which is not economically attractive. G-values of the order 105-106 have been recorded at dose rates of 10³-10⁴ rads per hour. The optimum quantum yield of 8.67×10^3 for light of wavelength 3650 Å obtained in the ultraviolet experiments corresponds to a G-value of 4.25×10^4 . If the line for the 100% experiments is extrapolated to the absolute radiation intensity used in the ultra-violet runs, the calculated G-value is 427×10^4 . There is therefore little difference in the efficiency of ultra-violet or γ -radiation for producing hexachlorocyclohexane.

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