acetate and 20 ml. of acetic anhydride was refluxed for three hours. After removal of the excess acetic anhydride under reduced pressure the residue was taken up in ether, the latter washed with 5% sodium hydroxide solution, dried over magnesium sulfate and evaporated to dryness. Aqueous methanol crystallization of the resulting crystalline mass gave 300 mg. (91%) of methyl podocarpate acetate (Ig), m.p. 124–125°. Three recrystallizations from methanol–water yielded fluffy white needles, m.p. 125–125.5°, $[\alpha]_D$ +113° (EtOH); ultraviolet spectrum (95% ethanol); λ_{max} 268.5 mμ (ϵ 680) and 275 mμ (ϵ 740).

Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 73.10; H, 8.09.

A solution of trifluoroperacetic acid, prepared by the addition of 0.085 ml. of trifluoroacetic anhydride to an ice-cold, stirred suspension of 0.014 ml. of 90% hydrogen peroxide in 10 ml. of methylene chloride, was added to a stirred mixture of 0.35 g. of anhydrous disodium hydrogen phosphate, 100 mg. of methyl 12-acetylpodocarpate and 20 ml. of methylene chloride. After a three-hour reflux the mixture was cooled and filtered. The filtrate was washed with 10% sodium carbonate solution, dried over sodium sulfate and evaporated to dryness. Crystallization of the crude crystalline product in methanol–water gave 86 mg. (74%) of methyl podocarpate acetate (Ig), m.p. 117–121°. Two recrystallizations from aqueous methanol raised the melting point to 125–125.5°, and was undepressed on admixture with an authentic sample of the ester. The infrared spectra of the two samples of ester were identical.

A mixture of 100 mg. of methyl podocarpate acetate (Ig), 150 mg. of potassium hydroxide, 15 ml. of ethanol and 10 ml. of water was refluxed for four hours. After cooling, the solution was poured into 50 ml. of 10% hydrochloric acid, extracted three times with chloroform, the combined extracts dried over magnesium sulfate and concentrated. Crystallization of the residue in methanol–water gave 86 mg. (99%) of fluffy, colorless needles, m.p. 210–213°. Recrystallization from the same medium produced methyl podocarpate, m.p. 212–213°, undepressed by admixture with an authentic sample. The infrared spectra of the two ester samples were identical.

Lithium Amide Treatment of Methyl Desoxypodocarpate (Id).—A solution of 100 mg. of methyl desoxypodocarpate (Id) in 25 ml. of anhydrous tetrahydrofuran was added to a suspension of 490 mg. of lithium amide in *ca.* 75 ml. of liquid ammonia. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The residue was partitioned between chloroform and 10% hydrochloric acid and the aqueous phase further extracted with chloroform. The combined organic extracts were washed with 10% sodium hydroxide, dried over magnesium sulfate and evaporated. The residue was chromatographed on 10 g. of alumina yielding 58 mg. of starting ester in the petroleum ether eluates and 15 mg. of desoxypodocarpamide (Ii) m.p. 191–195°, on methanol elution. The latter proved identical in m.p., mixed m.p. and infrared spectrum with an authentic sample.[6]

General Procedure for *Reductive Hydrolysis*.—A solution of the methyl ester in 25 ml. of tetrahydrofuran was added to approximately 75 ml. of liquid ammonia. Sufficient lithium metal to cause a persistent blue color was then added to the ester solution. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The residue was dissolved in chloroform and 10% hydrochloric acid. After separation of the organic layer, the aqueous phase was extracted three times with chloroform. The combined chloroform extracts were washed with four 25-ml. portions of 5% sodium hydroxide solution, dried over magnesium sulfate and evaporated, giving the crude neutral fraction. The sodium hydroxide washings were collected, acidified with concentrated hydrochloric acid and extracted thrice with chloroform. Drying over magnesium sulfate and evaporation of the combined extracts yielded the crude acidic products.

A 200-mg. run of methyl podocarpate (Ib) led to neutral material which on methanol–water crystallization gave 9 mg. of starting ester, m.p. 205–210°, and to acidic products which gave 111 mg. of podocarpic acid (Ia), m.p. 179–192°, on crystallization in aqueous methanol, m.p. 192–194° on recrystallization from same solvent. Infrared spectra of both compounds were identical with those of authentic samples.

A 100-mg. run of methyl desoxypodocarpate (Id) led to 21 mg. of desoxypodocarpinol (Ie), m.p. 90–93°, on ether elution of an alumina chromatography of the neutral products, and to 75 mg. of desoxypodocarpic acid (Ic), m.p. 195–199°, from the acid fraction.

The neutral fraction from a 55-mg. run of methyl oleanolate (IIa) was crystallized in methanol–water giving 15 mg. of erythrodiol (IIc), m.p. 215–230°. Recrystallization from the same solvent pair raised the melting point to 233–237°. The crude acid yielded 37 mg. of oleanolic acid (IIb), m.p. 308–310°, on crystallization from aqueous methanol. The infrared spectra of both compounds were identical with those of authentic material.

A 200-mg. run of methyl dehydroabietate (IIIa) led to 177 mg. of crude neutral material whose chromatography on alumina gave 118 mg. of dehydroabietinol (IIIc). Its 3,5-dinitrobenzoate melted at 123–124° (reported[9] m.p. 123–124°). Crystallization of the 17 mg. of acidic products in aqueous methanol led to 6 mg. of dehydroabietic acid (IIIb), m.p. 165–168°.

A 450-mg. run of methyl mesitoate (IVa) yielded 422 mg. of semi-crystalline neutral product which on trituration with petroleum ether and filtration afforded 182 mg. of 2,4,6-trimethylbenzyl alcohol (IVb), m.p. 85–88°. The remaining neutral fraction showed an infrared spectrum practically identical with pure benzyl alcohol (IVb). The crude acid products amounted to only 12 mg. and were not investigated.

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(9) L. F. Fieser and W. P. Campbell, THIS JOURNAL, **61**, 2528 (1939)

AMES, IOWA

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE TEST STATION]

The Synthesis of 2,3,4,5,6-Pentachloro-4-pentachlorophenoxy-2,5-cyclohexadieneone and Some of its Reactions[1]

BY RUSSELL REED, JR.

RECEIVED JULY 29, 1957

Treatment of pentachlorophenol with a mixture of nitric acid, trifluoroacetic acid and trifluoroacetic anhydride resulted in the formation of 2,3,4,5,6-pentachloro-4-pentachlorophenoxy-2,5-cyclohexadieneone (I); some of the chemistry of I, which in several reactions appears to envolve pentachlorophenoxy radicals, is described.

Since a mixture of nitric acid and trifluoroacetic anhydride has been found to be an excellent reagent for the conversion of alcohols to nitrate esters,[2] the synthesis of pentachlorophenyl nitrate was attempted by the treatment of pentachlorophenol

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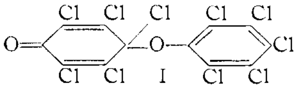
(1) Presented in part before the Division of Organic Chemistry at the 131st Meeting of the American Chemical Society, Miami, Fla., April 12, 1957.

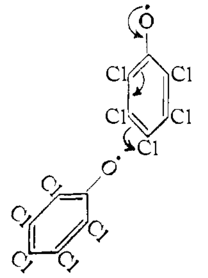
(2) E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 1695 (1952).

(PCP) with nitric acid,[3] trifluoroacetic acid and trifluoroacetic anhydride at −20°. A yellow solid I, m.p. 177–178°, was produced in 64% yield which, however, contained no nitrogen and possessed a combustion analysis in agreement with the empirical formula C_6Cl_5O; compound I reacted with a considerable variety of substances probably *via* a free radical mechanism.

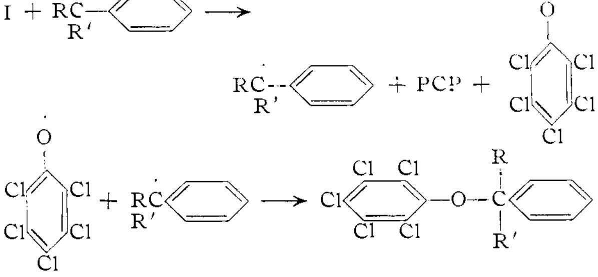
Many compounds containing C–H bonds were found to react with I; hexane, cyclohexane, cyclohexene, 1-octene, dioxane, methanol and ether reacted readily with I to yield PCP and yellow oils from which no pure compounds have yet been isolated. The compound I was soluble in hot carbon tetrachloride, benzene or chlorobenzene and could be recovered unchanged. Zinc dust in alcohol or acetic acid rapidly reduced I to PCP (the sole product). Sodium iodide in acetone converted I to the sodium salt of PCP with the formation of sodium triiodide. The presence of an active halogen in I was demonstrated by the precipitation of silver chloride in 87% yield (based on the formula $(C_6Cl_5O)_2$) when compound I was treated with silver nitrate in boiling acetonitrile; two crystalline organic compounds were isolated from the reaction, but are as yet unidentified. Boiling water did not react with I. The infrared spectrum of I exhibited absorption maxima which were very similar to those of chloranil, and thus indicative of a *p*-quinoid structure for I. However, it is believed that the spectrum of I may not be sufficiently different from that of *o*-tetrachlorobenzoquinone to permit a definite assignment of a *p*-quinoid structure. Unfortunately the ultraviolet spectrum of I could not be obtained because of its reactivity with suitable solvents. Nitric acid (99.8%) at 0° rapidly converted I to chloranil; cyclohexene and I reacted exothermically to yield chloranil as the only isolable product; bromotrichloromethane solutions of I on long refluxing gave low yields of the same product. The formation of chloranil under conditions in which the *o*-tetrachlorobenzoquinone was found to yield no chloranil strongly indicates that I contains a *p*-quinoid moiety. Magnetic susceptibility measurements of I in the solid state or in carbon tetrachloride or carbon disulfide solutions showed no paramagnetism. The foregoing data, together with elemental analysis, and a molecular weight determination indicate that I is 2,3,4,5,6-pentachloro-4-pentachlorophenoxy-2,5-cyclohexadieneone.

It is believed that the formation of I occurred through the abstraction of the phenolic hydrogen from PCP to produce a pentachlorophenoxy radical[4] which then reacted with itself as shown below, the curved arrows indicating one-electron shifts.





The reactions of I with C–H bonds probably occurred *via* the dissociation of I to produce two pentachlorophenoxy radicals which then attacked the C–H bond, as in RH for example, to give pentachlorophenol and R. The latter radical then combined with the second pentachlorophenoxy radical to form the corresponding ether of pentachlorophenol (II). Toluene, diphenylmethane and triphenylmethane reacted rapidly with I to yield the corresponding ethers IIa, IIb or IIc, respectively.



IIa, R = R' = H
IIb, R = H, R' = C_6H_5
IIc, R = R' = C_6H_5

Cyclohexene when treated with I produced a dark red solution as heat was evolved; on cooling, the solution deposited plates of chloranil in 40% yield (based on 1 mole of I giving 1 mole of chloranil); a 60% yield of PCP was the only other product isolated. Prolonged refluxing of a solution of I in bromotrichloromethane also produced chloranil; unreacted I was the only other substance isolated. In view of the formation of chloranil, it was anticipated that hexachlorobenzene would also be produced; however, since none was isolated from either reaction no explanation as to the probable mechanism of the transformation will be offered.

Chlorobenzene solutions of phenol, aniline, diphenylamine or benzylamine were rapidly oxidized by I with the formation of highly colored solutions (red, brown, blue and black, respectively); PCP was the only substance isolated except in the case of benzylamine where the addition of 2,4-dinitrophenylhydrazine in acetic acid precipitated the 2,4-dinitrophenylhydrazone of benzaldehyde in 51% yield.

Bromination of I yielded the 2,3,4,5,6-pentachloro-4-bromo-2,5-cyclohexadieneone (III, m.p. 182°); Shidlovskaya[5] prepared this bromo com-

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(3) Nitric acid has been found to oxidize PCP to chloranil, V. Merz and W. Weith, *Ber.*, **5**, 460 (1872).

(4) It has been proposed that certain substituted phenols containing alkyl substituents in the 2- and 6-positions yield phenoxy radicals on oxidation. R. Pummerer, G. Schmidutz and H. Seifert, *Ber.*, **85**, 535 (1952). A. F. Bickel, E. C. Kooyman and C. La Lau, *J. Chem. Soc.*, 3211 (1953); C. D. Cook and R. C. Woodworth, THIS JOURNAL, **75**, 6242 (1953); C. D. Cook, N. G. Nash and H. R. Flanagan, *ibid.*, **77**, 1783 (1955); C. D. Cook, D. A. Kuhn and P. Fianu, *ibid.*, **78**, 2002 (1956); C. D. Cook and B. E. Norcross, *ibid.*, **78**, 3797 (1956); E. Muller and K. Ley, *Ber.*, **87**, 922 (1954); **88**, 601 (1955); E. Müller, K. Ley and W. Kiedaisch, *ibid.*, **87**, 1605 (1954); **88**, 1819 (1955); B. S. Joshi, *Chemistry & Industry* (*London*), **17**, 525 (1957).

(5) A. H. Shidlovskaya, M. I. Gostev and I. K. Syrkine, *Doklady Akad. Nauk, S.S.S.R.*, **87**, 101 (1952).

pound by the bromination of the sodium salt of PCP.

The compound I was found to be quite stable on storage at room temperature but when heated for 20 hours at 160° in a sublimation apparatus it decomposed producing golden crystals of sublimate (m.p. 106°) which was found to be identical with the 2,3,4,4,5,6-hexachloro-2,5-cyclohexadieneone (IV) described by Zincke,[6] Barral,[7] Biltz,[8] Shorygin[9] and Denivelle[10]; the residue which yielded colorless needles, V, on recrystallization, was found to be only very slightly soluble in organic solvents and to possess a combustion analysis in excellent agreement with the empirical formula C_6Cl_4O. The needles V proved to be identical with a sample of the "perchlorophenylene oxide" described by Merz,[3] Hugouniq[11] and Zincke[12] and obtained by thermal decomposition of either PCP or its potassium salt.

Denivelle and Fort[13] reported the formation of a yellow solid with the formula given as $(C_6Cl_5O)_2$, m.p. 177°, which was obtained from the action of a compound described as 2,2,3,4,5,6-hexachloro-3,5-cyclohexadieneone (VI, m.p. 51°) on the sodium salt of PCP; to this compound they assigned the structure of 2-pentachlorophenoxy-2,3,4,5,6-pentachloro-3,5-cyclohexadieneone. These authors[14] also prepared the yellow solid by treatment of a substance described as 2,3,4,5,6-pentachloro-4-bromo-2,5-cyclohexadieneone (VII, m.p. 87°) with the sodium salt of PCP; in addition VII was reported to lose bromine on standing to yield the yellow solid. Because of the possible identity of I and the compound obtained by Denivelle and Fort, several attempts were made to repeat this work but all were unsuccessful. The first two reactions may have failed because they involved the displacement of a halogen which possessed positive character. The demonstrated reactivity of I with bromine to yield the relatively stable 4-bromo-derivative III would seem to preclude the possibility of obtaining I from VII. The *o*-quinoid structure which Denivelle suggested for the yellow solid would be indicated by its formation from VI while the *p*-quinoid configuration (herein proposed for I) would be considered likely by its formation from the 4,4-dihalo-compound VII. However, structure assignments based on the halides VI or VII are questionable in view of the controversy existing as to their configuration. Denivelle[13–15] stated that the hexachloro derivative VI had the *o*-quinoid structure (*i.e.*, 2,2,3,4,5,6-hexachloro-3,5-cyclohexadieneone) and that its higher melting (m.p. 106°) isomer IV, as well as the bromo compound, m.p. 87°, were *p*-quinoid derivatives (*i.e.*, 4,4-dihalo derivatives of the 2,3,4,5,6-pentachloro-2,5-cyclohexadieneones) based on studies of the infrared and ultraviolet spectra. While Shorygin,[16] also on the basis of spectral investigations, considered VI and VII to be aromatic hypochlorites, IV and the higher melting (m.p. 182°) isomer of VII (*i.e.*, III) were said to be 4,4-dihalo-2,5-cyclohexadieneones. But since VII has an infrared spectrum very similar to chloranil, a hypohalite structure is believed unlikely (see Experimental). Shidlovskaya[5] and Shorygin[9] also reported a compound described as $C_6Cl_5OOC_6Cl_5$, m.p. 178°, which Denivelle and Fort[10] considered to be identical with their compound, m.p. 177°. From dielectric constant measurements of this substance, Shidlovskaya[5] postulated a peroxide structure with two rings lying in planes perpendicular to each other. But again the infrared spectrum of I indicates quinoid character which would rule out the peroxide structure.

On the basis of the ready formation of chloranil from I it is believed that I possesses a *p*-quinoid configuration and, because of the doubt as to the structures of the halides III, IV, VI and VII, their use in the synthesis of I would not establish configuration. The bromination of I to yield the 4-bromo derivative III (m.p. 182°) would indicate the *p*-configuration for I if the structure proposed by Shidlovskaya[5] for III is accepted; similarly the isolation of the 4,4-dichloro compound IV from the thermal decomposition of I would also support the proposed structure for I.

Experimental[17]

Preparation of 2,3,4,5,6-Pentachloro-4-pentachlorophenoxy-2,5-cyclohexadieneone (I).—To a stirred suspension of 106.4 g. (0.400 mole) of pentachlorophenol (PCP, m.p. 190–191°) in a mixture containing 300 ml. of trifluoroacetic acid and 450 ml. of trifluoroacetic anhydride was added 42.0 ml. (1.00 mole) of 99.8% colorless nitric acid. The temperature of the reaction mixture was maintained at −20° for 4 hours. The orange-yellow powder which had formed was removed by filtration and washed with three 100-ml. portions of ether to yield 67.5 g. (64%) of crude I, m.p. 175–176.5°; recrystallization from boiling carbon tetrachloride gave 57.3 g., m.p. 177–178°. The infrared spectrum of I exhibited absorption bands at 5.90, 6.35, 7.95, 9.00, 11.56, 11.74, 12.65, 12.95, 13.74 and 14.44 μ. Chloranil exhibited bands at 5.90, 6.35, 7.95, 9.00, 11.05, 13.27 and 14.44 μ; *o*-tetrachlorobenzoquinone absorbed at 5.88–5.91, 6.41, 6.59, 7.25, 7.95–8.00, 8.14, 8.44 and 8.66 μ. Attempts to obtain the ultraviolet absorption spectrum of I failed because of its reactivity with suitable solvents such as ether, alcohol or alkanes. The solutions were initially yellow but soon became nearly colorless. Magnetic susceptibility measurements of the solid I or its carbon tetrachloride or carbon disulfide solutions indicated that the compound was diamagnetic. Cryoscopic molecular weight determinations of I in nitrobenzene gave values of 521, 527 and 536 (calcd. 530).

Anal. Calcd. for $C_{12}Cl_{10}O_2$: C, 27.16; Cl, 66.81. Found: C, 27.34; Cl, 66.77.

Suspensions of sodium pentachlorophenoxide in carbon tetrachloride or chlorobenzene containing dissolved 2,2,3,4,-5,6-hexachloro-3,5-cyclohexadieneone (VI) or 2,3,4,5,6-pentachloro-4-bromo-2,5-cyclohexadieneone (VII) (VI and VII prepared by the method of Merz[3]) were allowed to stand at room temperature for 30 days, or they were heated at 70° for 10 days; however, compound I was never isolated. When VII was allowed to stand at room temperature or at

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(6) Th. Zincke and C. Schaum, *Ber.*, **27**, 539, 543 (1894).

(7) E. Barral, *Bull. soc. chim. France*, [3] **11**, 559 (1895); [3] **13**, 423 (1895).

(8) H. Biltz, *Ber.*, **37**, 4005 (1904).

(9) P. P. Shorygin and M. I. Gostev, *Zhur. Fiz. Khim.*, **28**, 762 (1954).

(10) L. Denivelle and R. Fort, *Bull. soc. chim. France*, 1834 (1956).

(11) M. Hugouniq, *Ann. chim. et phys.*, [6] **20**, 546 (1890).

(12) Th. Zincke and C. Schaum, *Ber.*, **27**, 550 (1894).

(13) L. Denivelle and R. Fort, *Compt. rend.*, **238**, 124 (1954).

(14) L. Denivelle and R. Fort, *ibid.*, **240**, 2542 (1955).

(15) H. Stammreich, R. Forneris, R. Fort and L. Denivelle, *ibid.*, **239**, 1516 (1954); L. Denivelle and R. Fort, *ibid.*, **240**, 1550 (1955).

(16) P. P. Shorygin and M. I. Gostive, *Zhur. Fiz. Khim.*, **24**, 938 (1950).

(17) All melting points are corrected. The author is grateful to Dr. Allen L. Olsen for the determination of the infrared spectra and to Mr. Everett M. Bens for the microcombustion analyses.

50°, bromine was evolved slowly but again compound I was not isolated.

Compound I and Zn dust in alcohol or acetic acid solutions rapidly produced PCP in 90% yield. When compound I was treated with sodium iodide in acetone, sodium triiodide and the sodium salt of PCP were formed. Silver nitrate in boiling acetonitrile gave a precipitate of silver chloride (87% yield); no pure organic products were isolated. When compound I was added to nitric acid (99.8%) at 0° and the yellow solution immediately poured onto ice there was obtained an 80% yield of chloranil, m.p. 290° after recrystallization from cyclohexane. The mother liquors yielded only additional chloranil.

Bromination of I.—To a solution of 2.65 g. (0.00500 mole) of I in 50 ml. of carbon tetrachloride was added 1.60 g. (0.0100 mole) of bromine. After refluxing 30 minutes, the solution was boiled to remove excess bromine. A volume of 25 ml. remained. The solution was cooled and scratched to yield small yellow nodules of 2,3,4,5,6-pentachloro-4-bromo-2,5-cyclohexedieneone (III), m.p. 182–183° (lit. reports[5] 182°), yield 1.50 g. (87%); III was identified by a comparison of its infrared spectrum with that of an authentic sample prepared by the bromination of the sodium salt of PCP[5]; a mixed melting point with authentic material showed no depression. The infrared spectrum of III possessed absorption bands at 5.92, 6.34, 7.40, 7.90 and 9.03 μ.

Thermal Decomposition of I.—When 8.00 g. (0.0151 mole) of I was heated in a sublimation apparatus for 20 hours at 165° there was produced 3.60 g. (79%) of 2,3,4,4,5,6-hexachloro-2,5-cyclohexadieneone (IV) as a golden yellow sublimate, m.p. 106–107° (lit. reports[6] 106°). An authentic sample of IV (prepared by the method of Zincke[6]) gave no depression with IV on mixture melting point; the infrared spectra were identical. The crystalline non-volatile residue from the sublimation was orange in color and weighed 3.47 g., m.p. 320°. Recrystallization from 2 liters of benzene gave 3.32 g. (93%) of V as colorless needles, m.p. 326–328°; V possessed an infrared spectrum identical with a sample prepared by thermal decomposition of PCP or its potassium salt. The literature reports[3,11,12] that this latter decomposition yields "perchlorophenylene oxide" (m.p. 320–325°[12]). A mixed melting point of the sample prepared by the thermal decomposition of I with that obtained from PCP or its potassium salt showed no depression. Compound V was not sufficiently soluble to permit a determination of molecular weight and was unaffected by prolonged boiling with 12 *N* hydrochloric acid.

Anal. Calcd. for C_6Cl_4O: C, 31.35; Cl, 61.69. Found: C, 31.30; Cl, 61.75.

Reactions of I with Hydrocarbons. Toluene: 1-Benzyloxy-2,3,4,5,6-pentachlorobenzene (IIa).—A mixture of 0.50 g. (9.4 × 10^{-4} mole) of I was refluxed in 10 ml. of toluene for 10 minutes. The orange-colored solution was cooled to yield 0.20 g. (60%) of colorless needles of IIa, m.p. 164–165° (lit. reports[18] 167–168°), m.p. 165–166° after recrystallization from toluene.

The mother liquor from IIa was evaporated to a small volume and treated with hexane. Upon standing PCP slowly crystallized; yield 0.078 g. (31%).

Diphenylmethane: 1-(Diphenylmethoxy)-2,3,4,5,6-pentachlorobenzene (IIb).—A mixture of 2.65 g. (0.00500 mole) of I and 15 g. of diphenylmethane was heated at 150° for 5 minutes. The clear solution was cooled to room temperature and treated with 15 ml. of methanol which caused the crystallization of IIb as large colorless plates, yield 1.80 g. (83%), m.p. 138.5–140°; recrystallization from boiling hexane raised the m.p. to 140–141°.

Anal. Calcd. for $C_{19}H_{11}Cl_5O$: C, 52.75; H, 2.56; Cl, 40.98. Found: C, 52.93; H, 2.39; Cl, 40.94.

PCP was isolated from the mother liquor (as above); yield 0.60 g. (45%).

Triphenylmethane: 1-(Triphenylmethoxy)-2,3,4,5,6-pentachlorobenzene (IIc).—A mixture of 1.40 g. (0.0027 mole) of I, 0.85 g. (0.0035 mole) of triphenylmethane and 3 ml. of chlorobenzene was heated to 100° and the clear yellow solution then cooled to 25°. The solution soon crystallized to a nearly solid mass which was filtered; the crystals were washed with methanol and then with hexane to yield 1.21 g. (88%) of IIc, m.p. 238–240°; recrystallization from benzene raised the melting point to 240–241° (darkening).

Anal. Calcd. for $C_{25}H_{15}Cl_5O$: C, 59.03; H, 2.97; Cl, 34.85. Found: C, 58.89; H, 3.11; Cl, 34.78.

From the mother liquor there was isolated 0.29 g. (40%) of PCP.

Cyclohexene: Formation of 2,3,5,6-Tetrachlorobenzoquinone (Chloranil).—To 15 ml. of boiling cyclohexene was added 2.0 g. (0.0038 mole) of I. The solution boiled vigorously and became red-colored. Upon cooling chloranil was obtained as orange plates, m.p. 290° (lit. reports[3] 290°), yield 0.36 g. (40% based on 1 mole of I giving 1 mole of chloranil). Chloranil was identified by a comparison of its infrared spectrum with that of an authentic sample; a mixture melting point with the authentic material showed no depression. The mother liquor from the chloranil crystallization was evaporated to a small volume, hexane added, and the solution repeatedly frozen and thawed to finally yield 0.61 g. (60%) of PCP.

Cyclohexane.—When 2.65 g. (0.005 mole) of I was heated in 50 ml. of boiling cyclohexane the solution became orange-colored as compound I dissolved. A pungent sulfur-like odor was noted although neither of the reagents contained sulfur compounds. The solution was evaporated to a volume of 5 ml., cooled to 5° and allowed to stand 3 days. Crystalline PCP was removed by filtration; yield 1.20 g. (90%). The mother liquor from the PCP was evaporated to 2 ml. and a second crop of PCP, 0.01 g., was obtained; the mother liquor from the last crop yielded only yellow oils on repeated attempts at crystallization. The use of chromatography with Celite and silica gave oils which resisted attempts at crystallization.

Hexane.—From 0.005 mole of I, 1.13 g. (85%) of PCP was the only product isolated.

1-Octene.—From 0.005 mole of I, 1.06 g. (80%) of PCP was again the only product isolated.

Styrene and Phenylacetylene.—When 0.005 mole of I was heated in 25 ml. of styrene or phenylacetylene there was no color change after one hour. Cooling the solution gave crystals of unreacted I, 0.77 g. Evaporation of the mother liquor at reduced pressure yielded 0.37 g. (86% total recovery) of additional I as the only product.

Reactions of I with Miscellaneous Substances. Bromotrichloromethane.—A solution containing 0.005 mole of I in 100 ml. of bromotrichloromethane was refluxed for 2 days and the solvent was then removed by evaporation until a volume of 10 ml. remained. On standing 2 days this solution deposited a mixture of orange and white crystals (A) which were partially dissolved upon the addition of 10 ml. of methylene chloride. The methylene chloride solution was evaporated to a volume of 5 ml. and cooled; the solution produced golden plates of chloranil, yield 1.05 g. (85%). The crystals (A, 0.020 g.) which were insoluble in methylene chloride melted at 164–166° and were identified as unreacted I by a comparison of the infrared spectrum with that of authentic material.

Phenol, Aniline and Diphenylamine.—Equimolar quantities of phenol, aniline or diphenylamine (in chlorobenzene solutions) and compound I reacted rapidly with the evolution of heat. These reactions produced highly colored tars (soluble in benzene or carbon tetrachloride but insoluble in hexane or cyclohexane) from which no solid product other than PCP was obtained. PCP was isolated in yields of 65, 70 and 60%, respectively.

Benzylamine.—A suspension of 5.30 g. (0.0100 mole) of I in 30 ml. of carbon tetrachloride was treated with 1.07 g. (0.0100 mole) of benzylamine. The temperature of the mixture immediately rose to 50° as the solution became nearly black. After standing at 25° for 3 hours, the solution was filtered to remove a small quantity of unreacted I (identified by a mixed melting point with an authentic sample). The filtrate, which smelled strongly of benzaldehyde, was evaporated to yield a black tar, soluble in benzene but insoluble in pentane. The tar was stirred with three 50-ml. portions of pentane and the combined pentane extracts were then treated with 2,4-dinitrophenylhydrazine in acetic acid. The 2,4-dinitrophenylhydrazone of benzaldehyde immediately precipitated, m.p. 236–237° (lit. reports[19] 237°), yield 1.46 g. (51%). The tar remaining after the pentane extraction failed to yield any pure substance.

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(18) H. Biltz and W. Giese, *Ber.*, **37**, 4010 (1904).

(19) C. F. H. Allen, THIS JOURNAL, **52**, 2955 (1930).

Ether, Dioxane, Methanol and Acetic Acid.—When solutions of I in the preceding solvents were refluxed for 3 hours and the solvents evaporated, there remained orange-colored oils from which only PCP was isolated; PCP was obtained in yields of 57, 64 and 68%, respectively.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS AND CO.]

Synthetic Amebicides. III. 7-(3-Octylaminopropylamino)-benz[c]acridine (PAA-2056) and Related 7-(Alkyl- and Aralkylaminoalkylamino)-benz[c]acridines[1,2]

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A series of new 7-(alkyl- and aralkylaminoalkylamino)-benz[c]acridines have been prepared by the condensation of a 7-chlorobenz[c]acridine with the appropriate N-(alkyl or aralkyl)-diaminoalkane, by the action of an alkylamine on a 7-haloalkylaminobenz[c]acridine, or by ring-closure of an N-(alkylaminoalkyl)-2-(1-naphthylamino)-benzamide with phosphorus oxychloride. Acylation of 7-(3-hexyl- and heptylaminopropylamino)-benz[c]acridines with acetic anhydride gave the corresponding N-[3-(benz[c]acridin-7-ylamino)-propyl]-N-hexyl- and heptylacetamides. The 7-(alkyl and aralkylaminoalkylamino)-benz[c]acridines were highly active when tested against *Endamoeba histolytica in vitro*, acute intestinal amebiasis in rats, amebic colitis in dogs and amebic hepatitis in hamsters.

In a previous communication,[2] we reported the preparation of a number of 7-dialkylaminoalkylaminobenz[c]acridines which possessed good antiamebic activity against *Endamoeba histolytica in vitro*, against intestinal amebiasis in rats and against amebic hepatitis in hamsters. During the course of continuing efforts in these laboratories to develop new antiamebic drugs, we have synthesized a group of 7-(alkyl and aralkylaminoalkylamino)-benz[c]acridines (V). In structure V, X represents hydrogen or chlorine, Y a divalent alkyl group and R an alkyl or aralkyl radical.

TABLE I

N-(ALKYL- AND ARALKYL)-1,3-DIAMINOPROPANES, $H_2N(CH_2)_3NHR$

Bases^a

R	B.p., °C.	B.p., Mm.	$n^{25}\text{D}$	Yield, %	Procedure	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
$-(CH_2)_6CH_3$	110–120	7.5–8.0	1.4512	45	I	$C_{10}H_{24}N_2$	16.26	16.38
$-CHC_2H_5(CH_2)_3CH_3$	64–68	0.9	1.4487	54	II	$C_{10}H_{24}N_2$	16.26	16.47
$-(CH_2)_2C_6H_5$	110–115	1.5	1.5268	34	III	$C_{11}H_{18}N_2$	15.72	15.87
$-CH[(CH_2)_2CH_3](CH_2)_3CH_3$	72–77	0.7	1.4488	22	III	$C_{11}H_{26}N_2$	15.04	15.01
$-CH_2CHC_2H_5(CH_2)_3CH_3$	75–80	0.6	1.4518	73	III	$C_{11}H_{26}N_2$	15.04	15.19
$-CHCH_3(CH_2)_5CH_3$	90–95	2.0	1.4506	51	II	$C_{11}H_{26}N_2$	15.04	15.51^c
$-(CH_2)_3C_6H_5$	120–126	1.5	1.5213	57	III	$C_{12}N_{20}N_2{}^d$	14.57	13.96

Dihydrochlorides^b

R	M.p., °C.	Yield, %	Procedure	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
$-(CH_2)_8CH_3$	290–292 dec.^{e}	79^f	II	$C_{12}H_{28}N_2\cdot 2HCl$	10.25	9.58^g
$-(CH_2)_9CH_3$	293–295 dec.^{e}	86^f	II	$C_{13}H_{30}N_2\cdot 2HCl$	9.75	9.38^h
$-(CH_2)_{15}CH_3$	275–278^e	70^f	II	$C_{19}H_{42}N_2\cdot 2HCl$	7.54	7.35

[a] The bases were obtained as colorless liquids. [b] The dihydrochlorides were isolated as colorless solids. [c] *Anal.* Calcd.: C, 70.90; H, 14.07. Found: C, 70.86; H, 14.13. [d] Dihydrochloride crystallized from aqueous 2-propanol, m.p. 272–273°. *Anal.* Calcd.: N, 10.56. Found: N, 10.80. [e] Crystallized from ethanol. [f] Crude. [g] *Anal.* Calcd.: C, 52.73; H, 11.07. Found: C, 53.01; H, 10.81. [h] *Anal.* Calcd.: C, 54.34; H, 11.23. Found: C, 54.40; H, 11.29.

The synthesis of the 7-(alkyl- and aralkylaminoalkylamino)-benz[c]acridines (Table II) was achieved by three routes as illustrated by formulas I through VI. The method most extensively employed was the condensation of a 7-chlorobenz[c]acridine (II) with the appropriate N-(alkyl or aralkyl)-diaminoalkane in phenol. The 7-chlorobenz[c]acridines were prepared by ring-closure of an N-1-naphthylanthranilic acid (I) with phosphorus oxychloride as described previously.[2] Alternatively, the N-1-naphthylanthranilic acid was converted to the N-1-naphthanthraniloyl chloride by the action of phosphorus pentachloride in boiling benzene. Treatment of an N-alkyldiaminoalkane with the acid chloride yielded the corresponding amide IV which was not isolated but was ring-closed *in situ* with phosphorus oxychloride to the desired aminobenz[c]acridine. A third route involved the condensation of a 7-chlorobenz[c]acridine with an aminoalkanol to give a benz[c]acridin-7-ylaminoalkanol (III),[2] which upon treatment with thionyl chloride or a constant boiling hydrobromic acid–sulfuric acid mixture yielded the 7-haloalkylaminobenz[c]acridine (VI, where Hal represents Cl or Br). The condensation of a 7-haloalkylaminobenz[c]acridine with an alkyl amine in 1-pentanol at 100° gave the desired 7-alkylaminoalkylaminobenz[c]acridine (V). However, in one

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(1) Presented before the Division of Medicinal Chemistry at the 131st National A. C. S. Meeting, April, 1957, in Miami, Fla.

(2) For previous paper in this series see E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan and F. H. Tendick, THIS JOURNAL, **79**, 4699 (1957).