derivatives of these monomers, such as the diethyl N-(vinylbenzyl)-aspartate, have been copolymerized with 0–10% divinylbenzene and the resulting beads hydrolyzed by base or acid. Details of these reactions and descriptions of the resins are subjects of forthcoming publications.

MIDLAND, MICH.

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[CONTRIBUTION FROM THE AGRICULTURAL RESEARCH DIVISION, SHELL DEVELOPMENT CO.]

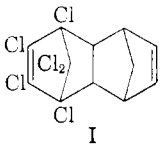
# The Preparation of Some Insecticidal Chlorinated Bridged Phthalazines[1,2]

BY J. G. KUDERNA, J. W. SIMS, J. F. WIKSTROM AND S. B. SOLOWAY

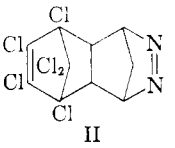
RECEIVED JULY 7, 1958

A number of bridged phthalazines, many of which are highly toxic to insects, have been prepared. Synthesis was effected *via* the Diels–Alder reaction of hexachlorocyclopentadiene, cyclopentadiene and tetrachlorocyclopentadienone dimethyl acetal with a 2,3-diazabicyclo[2.2.1]hept-5-ene obtained by known methods from cyclopentadiene and an azodiformic ester. Decarbalkoxylation of these adducts was effected under both acidic and basic conditions. In this way 5,6,7,8,9,9-hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4,5,8-dimethanophthalazine (VI) was made. A series of salts of VI was prepared. Oxidation of VI gave the azo derivative II, a nitrogen analog of the insecticide aldrin (I) in which the unchlorinated olefinic grouping is formally replaced by the isoelectronic azo group. Oxidation of II provided a stable N-oxide XIV. Thermal decomposition of II occurs with liberation of nitrogen and formation of 1,7,8,9,10,10-hexachlorotetracyclo[5.2.1.$0^{2,6}$.$0^{3,5}$]-dec-8-ene (XIII).

Aldrin (I), a commercially produced insecticide,[3–5] is the product of the Diels–Alder reaction of hexachlorocyclopentadiene with bicyclo[2.2.1]-hepta-2,5-diene and thus has a 1,4,5,8-dimethanonaphthalene structure. In considering analogs of aldrin it appeared feasible to prepare the corresponding dimethanophthalazine II wherein the unchlorinated olefinic grouping is formally replaced by the isoelectronic azo group.



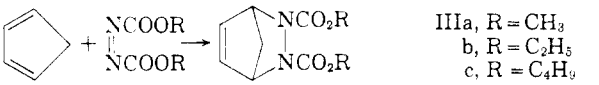
I



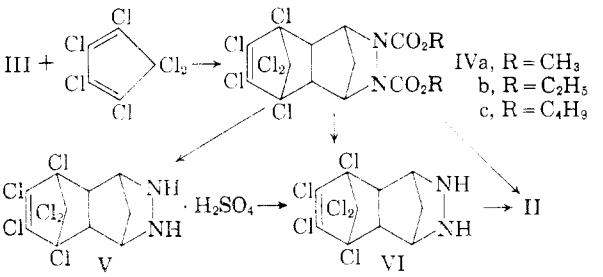
II

This view was supported by the knowledge that an intermediate which would be needed was available in the form of a bicyclo[2.2.1]hept-2-ene containing nitrogen atoms in positions 5 and 6. Accordingly, diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate[6] was prepared by the reaction of cyclopentadiene with diethyl azodiformate. This adduct, as well as others of the same type, reacted with hexachlorocyclopentadiene to give dimethanophthalazines in which the azo group readily was generated. The reaction sequences which led to the desired nitrogen analog of aldrin, II, are

The cyclopentadiene adducts IIIa and b involved in the first step were prepared following described procedures[6]; the dibutyl ester IIIc and its precursor, dibutyl azodiformate, are new. In addition to the cyclopentadiene adduct IIIb, adducts of diethyl azodiformate with furan (VII) and butadiene[6b,7] (VIII) were also made (Table I).



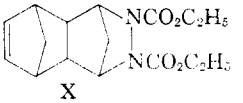
IIIa, R = $CH_3$
b, R = $C_2H_5$
c, R = $C_4H_9$



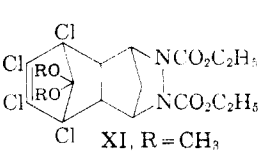
IVa, R = $CH_3$
b, R = $C_2H_5$
c, R = $C_4H_9$

V VI

The reaction of these adducts with dienic components such as cyclopentadiene, hexachlorocyclopentadiene and tetrachlorocyclopentadienone dimethyl acetal then was carried out to yield a number of phthalazinedicarboxylic esters (Table II). Diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate[6] (IIIb), for example, reacted smoothly with hexachlorocyclopentadiene at 130° to give the adduct IVb in 95% yield as a stable, colorless, crystalline solid melting at 110–111°, freely soluble in common organic solvents. Adducts IVa and IVc were obtained similarly from compounds IIIa and IIIc. Three other phthalazinedicarboxylic esters were obtained *via* this route; IX was prepared by reaction of hexachlorocyclopentadiene with VIII; X and XI from IIIb with cyclopentadiene and tetrachlorocyclopentadienone dimethyl acetal, respectively. An attempt to isolate a product from the reaction of hexachlorocyclopentadiene with VII was unsuccessful.



X



XI, R = $CH_3$

(1) Paper presented in part before the Division of Agricultural and Food Chemistry at the 133rd Meeting of the American Chemical Society in San Francisco, Calif., April, 1958.

(2) J. G. Kuderna, U. S. Patent 2,802,012 (to Shell Development Co.), August 6, 1957.

(3) For the purpose of this paper aldrin is considered to be the pure compound 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo*, *exo*-5,8-dimethanonaphthalene.

(4) R. E. Lidov, H. Bluestone, S. B. Soloway and C. W. Kearns, *Adv. in Chem. Ser.*, **1**, 175 (1950); R. E. Lidov, U. S. Patent 2,635,977 (to Shell Development Co.), April 21, 1953.

(5) S. B. Soloway, Ph.D. Thesis, Univ. of Colorado, 1955.

(6) (a) O. Diels, J. H. Blum and W. Koll, *Ann.*, **443**, 242 (1925); (b) J. C. J. MacKenzie, A. Rodgman and G. F. Wright, *J. Org. Chem.*, **17**, 1666 (1952); (c) A. Rodgman and G. F. Wright, *ibid.*, **18**, 465 (1953).

(7) K. Alder, H. Niklas, R. Ammüller and B. Olson, *Ann.*, **585**, 81 (1954).

TABLE I

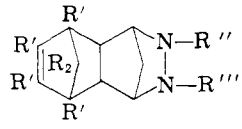
ADDITION PRODUCTS FROM AZODIFORMIC ESTERS ROOCN=NCOOR AND DIENES

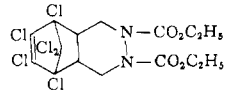
| Adduct | R | Diene | Yield, % | M.p., °C. | B.p. °C. | Mm. | $n^t$D | t, °C. | Empirical formula | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IIIa | $CH_3$ | Cyclopentadiene | 90 | 82 | ..... | .. | .... | .. | $C_9H_{12}N_2O_4$[b] | | | 13.2 | | | 13.2 |
| IIIb | $C_2H_5$ | Cyclopentadiene | 97 | .. | 105–113 | 0.1 | 1.4834 | 25 | $C_{11}H_{16}N_2O_4$ | 55.0 | 6.6 | 11.6 | 54.8 | 6.9 | 11.5 |
| IIIc | $C_4H_9$ | Cyclopentadiene | 34 | .. | 150–152 | .6 | 1.4734 | 20 | $C_{15}H_{24}N_2O_4$ | 60.8 | 8.1 | .. | 60.6 | 8.0 | .. |
| VII | $C_2H_5$ | Furan | 97 | .. | [a] | .. | 1.4756 | 25 | $C_{10}H_{14}N_2O_5$[c] | | | 11.6 | | | 11.2 |
| VIII | $C_2H_5$ | Butadiene | 70 | .. | 106–110 | .6 | 1.4714 | 25 | $C_{10}H_{16}N_2O_4$ | 52.6 | 7.2 | 12.3 | 52.3 | 7.0 | 12.0 |

[a] Product could not be distilled without decomposition. [b] $H_2$ equivalent calcd. 212, found 218. [c] Molecular weight calcd. 242, found 214.

TABLE II

PHTHALAZINECARBOXYLIC ESTERS

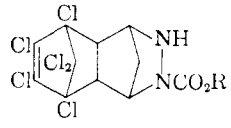


| Compound | R | R′ | R″ | R‴ | Yield, % | M.p., °C. | Empirical formula | Analyses, % Calcd. C | Calcd. H | Calcd. Cl | Calcd. N | Found C | Found H | Found Cl | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IVa | Cl | Cl | $COOCH_3$ | $COOCH_3$ | 59 | 145 | $C_{14}H_{12}Cl_6N_2O_4$[a] | 34.6 | 2.5 | 43.9 | .. | 35.3 | 2.6 | 43.6 | .. |
| XIIa | Cl | Cl | $COOCH_3$ | H | 20 | 171–172 | $C_{12}H_{10}Cl_6N_2O_2$ | 33.6 | 2.3 | 49.9 | .. | 33.9 | 2.6 | 49.8 | .. |
| IVb | Cl | Cl | $COOC_2H_5$ | $COOC_2H_5$ | 95 | 110–111 | $C_{16}H_{16}Cl_6N_2O_4$ | 37.4 | 3.12 | 41.5 | .. | 37.5 | 3.12 | 41.7 | .. |
| XIIb | Cl | Cl | $COOC_2H_5$ | H | 10 | 215–216 | $C_{13}H_{12}Cl_6N_2O_2$ | 35.4 | 2.7 | 48.3 | 6.3 | 35.2 | 2.6 | 48.2 | 6.5 |
| IVc | Cl | Cl | $COOC_4H_9$ | $COOC_4H_9$ | 33 | [a] | $C_{20}H_{24}Cl_6N_2O_4$ | 42.2 | 4.2 | 37.4 | .. | 42.6 | 4.6 | 37.4 | .. |
| X | H | H | $COOC_2H_5$ | $COOC_2H_5$ | 61 | [c] | $C_{16}H_{22}N_2O_4$ | 62.7 | 7.2 | .. | 9.1 | 62.8 | 7.0 | .. | 9.1 |
| XI | $OCH_3$ | Cl | $COOC_2H_5$ | $COOC_2H_5$ | 44 | 125–126 | $C_{18}H_{25}Cl_4N_2O_6$ | 42.8 | 4.4 | 28.2 | .. | 42.4 | 4.3 | 28.1 | .. |
| IX |  | | | | Low | [b] | $C_{16}H_{16}Cl_6N_2O_4$ | .. | .. | .. | 5.6 | .. | .. | .. | 5.5 |

[a] Alkoxy equiv. calcd. 242.5, found 242. [b] Viscous oil which could not be distilled nor crystallized. [c] B.p. 160° (0.1 mm.).

Decarbethoxylation of IVb to provide the phthalazine VI was effected easily in either acidic or basic media. When the ester was treated with 95% sulfuric acid at 85° for two hours the salt V was obtained as a high-melting solid (m.p. 235° dec.) in 95% yield. It readily was converted to VI in benzene solution by neutralization with aqueous sodium hydroxide. The crystalline phthalazine VI, m.p. 202–205°, is highly susceptible to oxidation, giving the azo compound II irreversibly and quantitatively when exposed to air or to peroxidized solvents. Unless care was exercised to exclude air or other mild oxidizing agents during the neutralization, II was the sole product obtained.

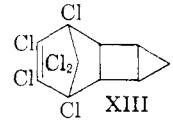
The base-catalyzed decarbethoxylation of IVb was effected at room temperature in methanolic potassium hydroxide, providing II directly in yields of 80–90%, together with small amounts (*ca.* 10%) of phthalazine monoesters (XII). The ethyl



XIIa, R = $CH_3$
b, R = $C_2H_5$

ester XIIb was usually isolated; in one instance transesterification took place and XIIa was obtained. The conversion of IV to II in basic media proved to be of less preparative value than the acidic decarbethoxylation procedure because of the frequent presence of these by-products and the necessity of carrying out the basic degradation at room temperature, where the reaction required several days for completion. At higher temperatures, considerable loss of II occurred due to thermal degradation (see below).

The nitrogen analog of aldrin II is a colorless, crystalline solid having limited solubility in most common organic solvents. Its ultraviolet absorption spectrum shows a strong peak at 345 m$\mu$ characteristic of the azo group,[8] while the dominant peak in the infrared is that at 6.24 $\mu$ which is characteristic of the vinyl chloride grouping.[9] Perhaps the most striking property of II is its thermal degradation to nitrogen and a chlorohydrocarbon, $C_{10}H_6Cl_6$, melting at 163–164°. Its infrared spectrum indicates it to be 1,7,8,9,10,10-hexachlorotetracyclo[5.2.1.$0^{2,6}$.$0^{3,5}$]dec-8-ene(XIII). This conclusion is supported by the work of Criegee[10] who has recently described the preparation of bicyclo[2.1.0]-

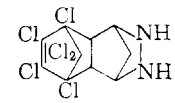


XIII

pentane by the thermal decomposition of 2,3-diazabicyclo[2.2.1]heptane. The spectra of the two degradation products are quite similar, particularly in the region from 9.5 to 11.0 $\mu$. The spectrum of XIII shows a strong absorption band at 3.26 $\mu$ characteristic of the cyclopropane ring,[11,12] and also exhibits strong bands at 1.64 and 2.22 $\mu$ in the near-infrared region. The latter bands have recently been correlated with the cyclopropane ring.[13]

(8) J. H. Harley and S. E. Wiberley, "Instrumental Analysis," J. Wiley and Sons, Inc., New York, N. Y., 1954, p. 58.
(9) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y., 1945, p. 330.
(10) R. Criegee and A. Rimmelin, *Ber.*, **90**, 414 (1957).
(11) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).
(12) F. J. Piehl and W. G. Brown, THIS JOURNAL, **75**, 5023 (1953).
(13) W. H. Washburn and M. J. Mahoney, *ibid.*, **80**, 504 (1958).

TABLE III

SALTS OF  VI

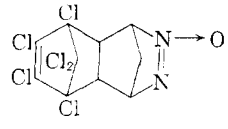
| Compound | Formula for acid (R = VI) | Yield, % | M.p., °C. | Empirical formula | Analyses, % Calcd. C | H | Cl | S | Neut. equiv.[a] | Found C | H | Cl | S | Neut. equiv.[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| V | R·$H_2SO_4$ | 85 | 235 d. | $C_{10}H_{10}Cl_6N_2SO_4$[b] | 25.6 | 2.1 | 45.6 | 6.8 | 233 | 25.2 | 2.0 | 44.8 | 7.1 | 228 |
| XV | R·HCl | 83 | >300 | $C_{10}H_9Cl_7N_2$[c] | 29.6 | 2.2 | .. | .. | 405 | 30.0 | 2.9 | .. | .. | 395 |
| XVI | R·HBr | 74 | >300 | $C_{10}H_9BrCl_6N_2$ | [d] | | | | 450 | | | | | 460 |
| XVII | R·$H_3PO_4$ | 68 | >300 d. | $C_{10}H_{11}Cl_6N_2PO_4$[e] | .. | .. | 45.6 | .. | .. | .. | .. | 45.0 | .. | .. |
| XVIII | R·$ClCH_2CO_2H$ | 58 | 138 d. | $C_{12}H_{11}Cl_7N_2O_2$ | 31.1 | 2.3 | 53.6 | .. | 463 | 31.7 | 2.1 | 53.1 | .. | 406 |
| XIX | R·$HCO_2H$ | 54 | 162 d. | $C_{11}H_{10}Cl_6N_2O_2$ | 31.8 | 2.4 | .. | .. | 415 | 32.5 | 2.5 | .. | .. | 414 |
| XX | $R_2$·$(CO_2H)_2$·$2H_2O$ | 69 | 210 d. | $C_{22}H_{22}Cl_{12}N_4O_8$ | 30.5 | 2.6 | .. | .. | 432 | 31.5 | 2.7 | .. | .. | 436 |
| XXI | R·p-$CH_3C_6H_4SO_3H$ | 60 | 195 d. | $C_{17}H_{16}Cl_6N_2SO_3$ | 37.7 | 3.0 | .. | 5.9 | .. | 37.0 | 3.2 | .. | 6.2 | .. |
| XXII | R·$CH_3CO_2H$ | 59 | 127–130 d. | $C_{12}H_{12}Cl_6N_2O_2$ | .. | .. | 49.7 | .. | 429 | .. | .. | 47.0 | .. | 416 |
| XXIII | $R_2$·HOC(COOH)$(CH_2COOH)_2$ | 65 | 203–205 d. | $C_{26}H_{24}Cl_{12}N_4O_7$ | 33.6 | 2.6 | 45.8 | .. | 465 | 34.3 | 2.8 | 45.5 | .. | 472 |

[a] Neutral equivalent. [b] $SO_4$ calcd. 20.5, found 21.0. [c] N calcd. 6.9, found 7.0. [d] Decomposes on standing at room temperature. [e] $H_3PO_4$ calcd. 21.0, found 20.0; P calcd. 6.6, found 6.1.

Compound XIII did not add hydrogen catalytically; thus the absence of an unsubstituted double bond is demonstrated.

No melting point depression is observed upon admixture of II and XIII; in fact, when II is heated the transition to XIII occurs in a capillary without visible change, and the observed melting point of the phthalazine is actually that of its degradation product. Decomposition is fairly slow at temperatures up to 50°, but much more rapid at higher temperatures, being essentially complete in one hour at 100°. The estimated half-lives of II are 34 minutes at 100°, 16 hours at 75°, 34 days at 50°, and 9 years at 25°. Although the thermal dissociation of an azo compound may or may not proceed by way of free radical intermediates,[14,15] we have not established the mechanism operative in the present case. However, the thermal conversion of II to XIII does not provide free radicals capable of initiating the polymerization of styrene, as is the case when $(C_6H_5)_3CN{=}NC_6H_5$ is decomposed at 50–60°.[14]

With the realization of the nitrogen analog II of aldrin, preparation of the corresponding N-oxide XIV was carried out. This compound is the counterpart of dieldrin, the epoxide of aldrin. Oxidation of II at 30–40° by peroxyacetic or peroxybenzoic acid gave the thermally-stable oxide XIV melting at 256° in 91% yield. The infrared spectrum of

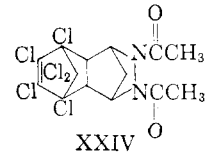


XIV

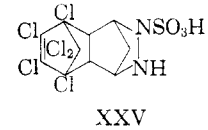
XIV shows a strong absorption band at 6.60 $\mu$ which is characteristic of the azoxy group.[16] The product is inert to the action of strong acids and bases, and only sparingly soluble in organic solvents.

The direct transformation of the phthalazinedicarboxylic esters IV into salts of the phthalazine VI was effected with sulfuric acid, as described above, and also with hydrochloric acid. Similar conversions with phosphoric and acetic acids were attempted but without success. Salts of these acids as well as a number of others were made by neutralization in benzene solution of the phthalazine VI, which in every case behaved as a monoacidic base (Table III). The salts of the stronger acids (sulfuric, V, hydrochloric, XV, chloroacetic, XVIII, etc.) were stable and formed readily; weak acids such as acetic acid gave less stable salts. For example, the acetate XXII readily was hydrolyzed by water to give the phthalazine VI quantitatively. These products possessed an inappreciable solubility in organic solvents and could not be purified by recrystallization.

In addition to the salts obtained from VI, this intermediate was utilized in the synthesis of three other chlorinated dimethanophthalazines. Although VI acts only as a monoacidic base, as does phthalazine itself,[17] both nitrogen atoms are available for attack by reagents such as acetic anhydride and methyl chloroformate. Thus, IVa, initially prepared by the Diels–Alder reaction, also was obtained from VI by reaction with methyl chloroformate in benzene in the presence of sodium carbonate. Further, treatment with acetic anhydride afforded the 2,3-diacetyl derivative XXIV. With chlorosulfonic acid, however, VI reacted to give only the monosulfonic acid XXV.



XXIV



XXV

Two other products of some interest in this study were prepared from the adduct XI of tetrachlorocyclopentadienone dimethyl acetal with the diazabicycloheptene IIIb. Base-catalyzed decarbethoxylation gave the dimethanophthalazin-9-one acetal XXVI in yield of 60%. However, when XI was treated with concentrated sulfuric acid in an effort to carry out simultaneous decarbethoxylation and hydrolysis of the acetal function, the reaction proceeded beyond the desired stage. Both the acetal function and the methano carbon atom were eliminated, and a product which is presumably the tetrachloromethanophthalazine sulfate XXVII was

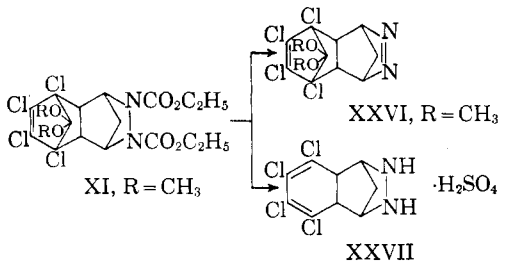
(14) G. V. Schulz, *Naturwissenschaften*, **27**, 659 (1939).

(15) H. Wieland, T. Ploetz and H. Indest, *Ann.*, **532**, 166 (1937).

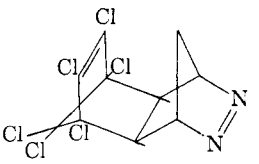
(16) B. W. Langley, B. Lythgoe and L. S. Rayner, *J. Chem. Soc.*, 4191 (1952).

(17) J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publishers, Inc., New York, N. Y., 1953, p. 70.

obtained in low yield. These reactions are similar to those reported by McBee.[18]




The stereochemistry of the dimethanophthalazines was not studied. Because these compounds are made by the reaction of hexachlorocyclopentadiene with a bicycloheptene double bond, as is aldrin, they are assumed to have the same configuration.[5] Thus, II can be represented as shown below and identified as 5,6,7,8,9,9-hexachloro-1,4,4a,5,8,-8a-hexahydro-1,4-*exo,endo*-5,8-dimethanophthalazine.



The insecticidal activity of most of the compounds described has been determined by our Entomology Department. Of particular interest are the nitrogen analog of aldrin II and its N-oxide XIV, which are 40 and 50 times, respectively, more toxic than DDT toward the common house fly. These compounds have high toxicity to mammals both orally and percutaneously.

**Acknowledgment.**—The authors wish to thank several members of our Physical and Analytical Department for assistance: P. M. Saliman and Mrs. B. Haynes for the analyses, and G. E. Pollard for the infrared data and interpretations.

## Experimental[19]

**Diels–Alder Adducts of Azodiformic Esters (Table I).**—The cyclopentadiene adducts of dimethyl,[6c] diethyl[20] and dibutyl azodiformate were prepared as described in the literature.[6] Dibutyl azodiformate (b.p. 88–96° at 0.3 mm., $n^{27}D$ 1.4311. *Anal.* Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.2; H, 7.8. Found: C, 51.9; H, 7.6) was prepared in 90% yield by oxidation of dibutyl bicarbamate[21] with hypochlorous acid.[20] Diethyl azodiformate reacted with furan to give an adduct which could not be distilled without decomposition.

The adduct IIIb gave a **dihydrophenyltriazole**, m.p. 129°, recrystallized from hexane–chloroform (1:1). *Anal.* Calcd. for $C_{17}H_{21}N_5O_4$: N, 19.5. Found: N, 19.2.

**The dibromide** of IIIb melted at 65–67° after recrystallization from hexane. *Anal.* Calcd. for $C_{11}H_{16}Br_2N_2O_4$: Br, 40.0. Found: Br, 40.5.

**Diethyl 5, 6, 7, 8, 9, 9-Hexachloro-1, 2, 3, 4, 4a, 5, 8, 8a-octahydro-1,4,5,8-dimethano-2,3-phthalazinedicarboxylate (IVb).**—Reaction of IIIb (120 g., 0.50 mole) with 546 g. (2.0 moles) of hexachlorocyclopentadiene was carried out under nitrogen at 130° for a period of 20 hours. A trace amount of di-*t*-butylhydroquinone was added to the reaction mixture prior to heating. At the conclusion of the heating period, the excess diene was removed by steam distillation; the crude product solidified upon cooling in the still-pot. It was extracted with ether and upon removal of the solvent, 254 g. of IVb, m.p. 75–103°, was obtained. Recrystallization from aqueous methanol gave a colorless, crystalline product, m.p. 110–111°, in 95% yield. The infrared spectrum of IVb shows a strong absorption peak at 6.24 μ due to C=C—Cl[9] and other principal bands at 5.68, 5.82, and 7.64 μ.

Preparation of other phthalazinedicarboxylic esters was carried out in analogous fashion from the appropriate dienes and dienophiles to give the adducts shown in Table II.

**5,6,7,8,9,9-Hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4,-5,8-dimethanophthalazine Sulfate (V).**—Forty five grams (0.088 mole) of IVb was mixed with 90 ml. of 95% sulfuric acid and the mixture was heated at 85° until gas evolution had ceased and a homogeneous solution had been obtained (1–2 hours). The mixture was poured onto crushed ice and the resulting solid was filtered. The product was washed with hot benzene and was obtained as a brown, amorphous powder melting at 235° dec. It was only sparingly soluble in common solvents. Infrared absorption bands were prominent at 3.14 μ (–NH), 6.16 μ (sulfate salt) and at 6.27 μ (C=C–Cl).

**The hydrochloride XV** was prepared in 80% yield by suspending IVb in concentrated aqueous hydrochloric acid and heating the mixture at 100° for 140 hours. Other salts shown in Table III were prepared by neutralizing V suspended in benzene with aqueous sodium hydroxide and treating the resulting solution of VI with the appropriate acid.

**5,6,7,8,9,9-Hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4,5,8-dimethanophthalazine (VI).**—The phthalazine VI was obtained by neutralizing V with 10% sodium hydroxide (350 ml.). The product was extracted with benzene under an atmosphere of nitrogen and recrystallized from benzene–cyclohexane, m.p. 202–205°; the yield was 90%; VI was also prepared more conveniently by hydrolysis of the acetate salt XXII. The latter (3 g.) was triturated with 25 ml. of water for about four hours, and the solid was recovered, yielding 2.4 g. (92%) of VI, m.p. 202–205°.

*Anal.* Calcd. for $C_{10}H_8Cl_6N_2$: C, 32.5 H, 2.2; Cl, 57.7; neut. equiv., 369. Found: C, 32.3; H, 2.3; Cl, 57.7; neut. equiv., 368.

**5,6,7,8,9,9-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanophthalazine (II). Method A.**—Two hundred grams of V (0.39 mole, based upon analysis showing 92% available sulfate salt) was suspended in 500 ml. of benzene and a 10% aqueous solution of sodium hydroxide (37.5 g., 0.93 mole, in 337 ml. of water) was added gradually. The slurry was stirred at room temperature for 8 hours and then filtered. The benzene solution was evaporated and 128 g. (90% yield) of II was obtained. The product was a colorless, crystalline solid showing a capillary melting point of 163–164°.

*Anal.* Calcd. for $C_{10}H_6Cl_6N_2$: C, 32.7; H, 1.63; Cl, 58.0; N, 7.6. Found: C, 32.6; H, 1.53; Cl, 57.7; N, 7.7.

**Method B.**—To a solution of 15.8 g. (0.24 mole) of 85% potassium hydroxide in 170 ml. of absolute methanol, 30.8 g. (0.06 mole) of IVb was added. The suspension was warmed to 45° for a few moments until complete solution occurred, whereupon the solution was set aside at room temperature for 3 days. The reaction mixture was filtered, and the filtrate evaporated to dryness. The product II was isolated from the residue by ether extraction; yield 19.9 g. (90%) melting at 157–160°; m.p. 163–164° after recrystallization from absolute methanol.

In a repetition of the experiment of method B, there was obtained in addition to II, a 10% yield of ethyl 5,6,7,8,9,9-hexachloro-3,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethano-2-(1H)-phthalazinecarboxylate (XIIb) (see Table II). The infrared spectrum is characterized by a strong peak at 3.00 μ due to the N–H group.

The corresponding methyl phthalazinecarboxylate XIIa, shown in Table II, was obtained when 46.2 g. (0.09 mole) of IVb was held in a solution of 23.7 g. of 85% potassium hydroxide in 255 ml. of absolute methanol. The reaction was carried out for four days at room temperature. Work-up as previously described yielded 7.6 g. (20%) of XIIa, m.p. 171–172°, recrystallized from carbon tetrachloride–ether.

The identification of II as prepared by methods A and B was established by analysis and by examination of the ultraviolet absorption spectra of the two samples. The half-life of II was estimated at 75° (16 hours) and 50° (34 days) by ultraviolet spectral analysis, and at 100° (34 minutes) by measurement of the amount of nitrogen evolved.

(18) E. T. McBee, W. R. Diveley and J. E. Burch, THIS JOURNAL, **77**, 385 (1955).

(19) All melting points are uncorrected.

(20) N. Rabjohn, *Org. Syntheses*, **28**, 58 (1948).

(21) A. W. Dox, THIS JOURNAL, **48**, 1954 (1926).

**1,7,8,9,10,10-Hexachlorotetracyclo[5.2.1.0$^{2,6}$.0$^{3,5}$]dec-8-ene (XIII).**—The thermal degradation of II was quantitatively carried out by dissolving 11 g. (0.03 mole) in 125 ml. of benzene and refluxing the solution for 2 hours. The product was recovered and recrystallized from aqueous methanol to yield 10 g. of XIII, m.p. 165°.

*Anal.* Calcd. for $C_{10}H_6Cl_6$: C, 35.4; H, 1.8; Cl, 62.8; mol. wt., 339; $H_2$ uptake, mole/mole, 0.0. Found: C, 35.4; H, 1.9; Cl, 62.5; mol. wt., 338; $H_2$ uptake, mole/mole, 0.0.

**5,6,7,8,9,9-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanophthalazine 2-oxide (XIV).**—Eleven and one-half grams (0.031 mole) of II was added to 244 g. of a chloroform solution containing 8.3 g (0.06 mole) of peroxybenzoic acid. The solution was allowed to stand at room temperature for 136 hours. Evaporation of the solvent left a solid which was recrystallized from ether–cyclohexane to yield 10.5 g. (91%) of pure N-oxide XIV, m.p. 256° dec. The infrared spectrum of XIV shows principal peaks at 6.25 $\mu$ (C=C–Cl) and at 6.60 $\mu$ (azoxy group).[16] Compound XIV heated at 110° for three hours did not produce a change in its melting point or analysis.

*Anal.* Calcd. for $C_{10}H_6Cl_6N_2O$: C, 31.3; H, 1.6; Cl, 55.6; N, 7.3. Found: C, 31.6; H, 1.7; Cl, 55.3; N, 7.4.

**2,3-Diacetyl-5,6,7,8,9,9-hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4,5,8-dimethanophthalazine (XXIV).**—Fifty grams (0.11 mole) of VI was added to a mixture of 170 g. of acetic anhydride and 25 g. of sodium acetate to produce a vigorously exothermic reaction which was controlled at 0° by cooling. The reaction mixture was poured into water, and the precipitated solid was filtered and recrystallized from benzene–hexane to yield 15 g. (33%) of the diacetyl derivative XXIV, m.p. 204°. The infrared absorption spectra showed two strong carbonyl peaks at 5.88 and 5.96 $\mu$ in addition to the usual peak at 6.27 $\mu$ (C=C–Cl).

*Anal.* Calcd. for $C_{14}H_{12}Cl_6N_2O_2$: Cl, 47.0. Found: Cl, 47.2.

**5,6,7,8,9,9-Hexachloro-3,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethano-2(1H)-phthalazinesulfonic Acid (XXV).**—Eleven and three-tenths grams (0.03 mole) of VI was dissolved in 110 ml. of benzene and 7.0 g. (0.06 mole) of chlorosulfonic acid was added dropwise with stirring at room temperature. The precipitated product was collected by filtration. It melted at 233° with decomposition, and could not be purified due to its low solubility in common organic solvents and in water. The yield was 12.8 g. (94%). The infrared spectrum showed strong peaks at 3.13 $\mu$ (N–H), 6.26 $\mu$ (C=C–Cl), and also at 8.67, 9.65 and 14.36 $\mu$, all probably due to the $SO_3H$ group.

*Anal.* Calcd. for $C_{10}H_8Cl_6N_2SO_3$: N, 6.2; S, 7.1; neut. equiv., 449. Found: N, 5.8; S, 6.7; neut. equiv., 463.

**5,6,7,8-Tetrachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanophthalazin-9-one Dimethyl Acetal (XXVI).**—Thirty and two-tenths grams (0.06 mole) of XI was treated with 15.8 g. of 85% potassium hydroxide dissolved in 125 ml. of absolute methanol at room temperature over a period of four days. Work-up by ether extraction and recrystallization from ether–hexane yielded 12.8 g. (60%) of XXVI, m.p. 114°.

*Anal.* Calcd. for $C_{12}H_{12}Cl_4N_2O_2$: C, 40.0; H, 3.3. Found: C, 40.4; H, 2.8.

**5,6,7,8-Tetrachloro-1,2,3,4,4a,8a-hexahydro-1,4-methanophthalazine Sulfate (XXVII).**—Thirty and two-tenths grams (0.06 mole) of XI was added to 60 ml. of 95% sulfuric acid and the mixture was heated on the steam-bath until gas evolution ceased. The mixture was poured onto crushed ice and the precipitated solid was filtered and washed with benzene. The product XXVII amounted to 10.6 g. (46% yield), m.p. 200–203° dec.

*Anal.* Calcd. for $C_9H_{10}Cl_4N_2O_4S$: Cl, 36.9; S, 8.3; neut. equiv., 192. Found: Cl, 36.7; S, 8.0; neut. equiv., 189.

MODESTO, CALIF.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, U. S. VITAMIN CORPORATION]

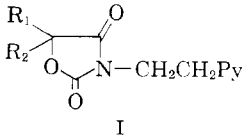
# Pyridylethylated Oxazolidinediones. II[1]

BY SEYMOUR L. SHAPIRO, IRA M. ROSE, ERIC ROSKIN AND LOUIS FREEDMAN

RECEIVED AUGUST 11, 1958

An additional series of pyridylethylated 2,4-oxazolidinediones of the type I have been synthesized and screened for pharmacological activity. Significant responses found in animals include anti-convulsant activity, depression of motor activity and prolongation of Evipal sleeping time. The products of hydrolysis of the compound IV have been examined and found to have considerably less central nervous system depressant effect than the parent structure.

In continuation[1] of our study of structural analogs of the pyridylethylated oxazolidinediones (I), we have examined additional variants[2] of $R_1$,$R_2$ for effect on pharmacological activity. The compounds are reported in Table I.



I

In general, synthetic procedures similar to those previously described were used.[1,3] The majority of the syntheses involved preparation of the cyanohydrin which was converted to the hydroxyamide through the pyrolysis of the imino ester hydrochloride. The hydroxyamide was cyclized to the 5,5-$R_1$,$R_2$-1,3-oxazolidine-2,4-dione which, in turn, upon condensation with the vinylpyridines yielded the required pyridylethylated oxazolidinediones (Table I).

In the preparation of the structures $R_1$ = cyclohexyl, $R_2$ = $CH_3$ (compounds 6–9, Table I), the synthesis was effected through cyclization of ethyl $\alpha$-cyclohexyl-$\alpha$-hydroxypropionate with urea. The requisite ester was prepared conveniently by reaction of one equivalent of cyclohexylmagnesium chloride and ethyl pyruvate.

Structures in which $R_1$ embodied a tertiary hydroxyl onto the 5-alkyl substituent was of interest, particularly with variants containing a *t*-hydroxyl function and indicated preparation of compounds 31–33 of Table I.

(1) Paper I of this series, S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, THIS JOURNAL, **80**, 1648 (1958).

(2) (a) In ref. 1 it had been established that those structures wherein $R_1$ = $C_2H_5$, $R_2$ = $CH_3$ were good potentiators of Evipal sleeping time (E.s.t.) and suggested the preparation of compounds 1–6 of Table I. The high anti-convulsant response in the absence of a potentiation of the response in the E.s.t. test with the 5,5-substituted-3-methylpentamethylene series indicated exploration of compounds 6–18 of Table I; (b) variation of groups in the 5-position using structures analogous to the active barbiturates reflected examinations of compounds 19–30 of Table I. F. J. Marshall, *J. Org. Chem.*, **23**, 503 (1958), had successfully applied this approach to the study of 3,3-disubstituted-2-pyrrolidinones; (c) introduction of hydroxyl groups

(3) J. W. Clark-Lewis, *Chem. Revs.*, **58**, 63 (1958).