Anal. Calcd. for $C_{11}H_{10}O_4N_2$: N, 12.0. Found: N, 12.1.

Ultraviolet Absorption Measurements.—All determinations were made in aqueous solution. A Beckman quartz spectrophotometer was used. The spectrum was examined at 2 mμ intervals except near maxima and minima and there at 1 mμ intervals.

Summary

1. The benzenoid structure of indazole and 3-substituted indazole is confirmed on the basis of a comparison of their ultraviolet absorption spectra with those of their corresponding 1-methyl and 2-methyl derivatives.

2. Indazole and 3-cyanoindazole has been found to add to acrylonitrile to form 1-cyanoethyl derivatives exclusively.

3. The reduction of 3-cyanoindazole by means of sodium and ethanol has resulted in the cleavage of a carbon–carbon bond and the production of indazole.

4. The methylation of 3-cyanoindazole has been found to yield 1-methyl- or 2-methyl-3-cyanoindazole or a mixture of the two, depending on the procedure employed.

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[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY OF TULANE UNIVERSITY]

The Nitration of Some 1,1,1-Trihalogeno-2,2-bisarylethanes

BY DAVID A. SHIRLEY AND THEODORE N. GOREAU

The high insecticidal activity of 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)-ethane (DDT) and certain related types has stimulated interest in the biological properties of compounds containing the 1,1,1-trichloro-2,2-bisarylethane structure. 1,1,1-Trichloro-2,2-bis-(*p*-aminophenyl)-ethane has been reported[1,2] to have *in vitro* activity against *M. tuberculosis*. *In vivo* activity was also reported for this compound,[2] although more recent findings by Smith, Junge and McClosky[3] have indicated that the compound is of no value. 1,1,1-Trichloro-2,2-bis-(*p*-nitrophenyl)-ethane has been reported to have chemotherapeutic activity against murine typhus[4] and *Rickettsia mooseri* in the mouse.[5]

We have been interested in the preparation and examination for biological activity of a number of 1,1,1-trihalogeno-2,2-bisarylethanes, particularly those containing nitro and amino groups.

In an earlier paper[6] were reported the nitration of 1,1,1-trichloro-2,2-bis-(*p*-methoxyphenyl)-ethane (methoxychlor) and other transformations leading to several derivatives including an amino type. Nitration of methoxychlor gave a dinitro derivative. The positions of the nitro groups were shown by two independent methods of proof to be *ortho* to the methoxyl groups.

In the present work three additional types related to DDT and methoxychlor have been examined. These materials are 1,1,1-trichloro-2,2-bis-(*p*-bromophenyl)-ethane, 1,1,1-trichloro-2,2-bis-(*p*-tolyl)-ethane (II) and 1,1,1-tribromo-2,2-bis-(*p*-methoxyphenyl)-ethane. The reactions carried out on these compounds are summarized in Fig. 1 using 1,1,1-trichloro-2,2-bis-(*p*-tolyl)-ethane (II) as an example. The structures of the nitration products were proved by dehydrohalogenation to the corresponding ethylene compound (III) and oxidation to the known dinitrobenzophenone (V).

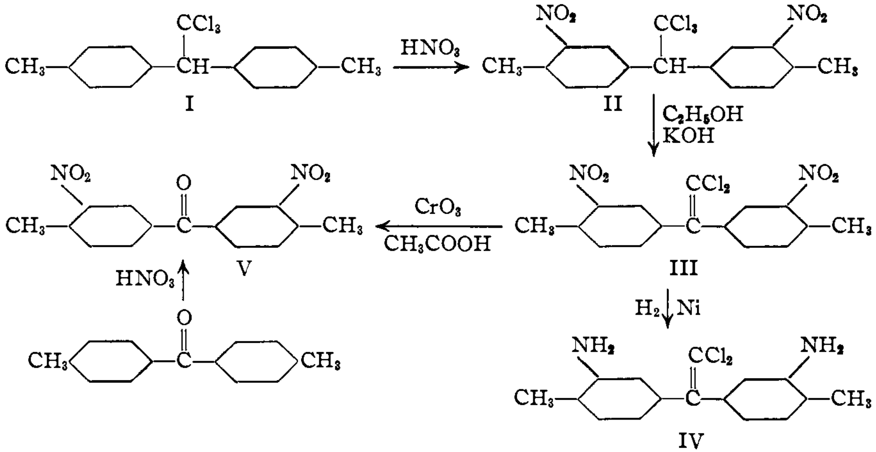

Fig. 1.

Experimental

1,1,1-Trichloro-2,2-bis-(3-nitro-4-methylphenyl)-ethane (II).—1,1,1-Trichloro-2,2-bis-(*p*-tolyl)-ethane (I),

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[1] Burger, Graef and Bailey, THIS JOURNAL, **68**, 1725 (1946).

[2] Kirkwood and Phillips, *ibid.*, **69**, 934 (1947).

[3] Smith, Junge and McClosky, *J. Am. Pharm. Assoc. Sci. Ed.*, **37**, 461 (1948).

[4] Kikuth, Office of the Publication Board, Department of Commerce Report No. 248, p. 63.

[5] Lorenz, *Chem. Ber.*, **81**, 422 (1948) [*C. A.*, **43**, 4658 (1949)].

[6] Shirley, Goreau and Eiseman, THIS JOURNAL, **71**, 3173 (1949).

TABLE I

DERIVATIVES OF 1,1,1-TRIBROMO-2,2-BIS-(*p*-METHOXYPHENYL)-ETHANE AND 1,1,1-TRICHLORO-2,2-BIS-(*p*-BROMOPHENYL)-ETHANE

Compound	Melting point, °C.	Yield, %	Molecular formula	Nitrogen, % Calcd.	Nitrogen, % Found
1,1,1-Tribromo-2,2-bis-(3-nitro-4-methoxyphenyl)-ethane[a]	178–179	54	$C_{16}H_{13}Br_3N_2O_6$	5.22	5.24
1,1-Dibromo-2,2-bis-(3-nitro-4-methoxyphenyl)-ethylene	124–125	35[b]	$C_{16}H_{12}Br_2N_2O_6$	5.72	5.71
1,1-Dibromo-2,2-bis-(3-amino-4-methoxyphenyl)-ethylene	137–138	68	$C_{16}H_{16}Br_2N_2O_2$	6.55	6.50
1,1,1-Trichloro-2,2-bis-(3-nitro-4-bromophenyl)-ethane[8]	168–169	59	$C_{14}H_7Br_2Cl_3N_2O_4$	..	..
1,1-Dichloro-2,2-bis-(3-nitro-4-bromophenyl)-ethylene	145–146	85	$C_{14}H_6Br_2Cl_2N_2O_4$	5.64	5.67
1,1-Dichloro-2,2-bis-(3-amino-4-bromophenyl)-ethylene[c]	133–133.5	21	$C_{14}H_{10}Br_2Cl_2N_2$	6.43	6.63 6.50

[a] Nitration was carried out by treating 5 g. of 1,1,1-tribromo-2,2-bis-(*p*-methoxyphenyl)-ethane in 50 ml. of acetic acid with a solution of 25 ml. of concentrated nitric acid and 25 ml. of acetic acid and refluxing the mixture for two hours. The product was recrystallized from a mixture of alcohol and benzene. [b] By-product oily material was also formed in this reaction. [c] The compound was recrystallized three times from a mixture of two parts of ethanol and one part of water.

m. p. 86°,[7] was prepared by the condensation of toluene and chloral hydrate in the presence of concentrated sulfuric acid.[8]

A solution of 5 g. (0.016 mole) of 1,1,1-trichloro-2,2-bis-(*p*-tolyl)-ethane in 100 ml. of glacial acetic acid was stirred and refluxed while 100 ml. of concentrated nitric acid was added slowly. This was followed by the addition of 20 ml. of fuming nitric acid (sp. gr. 1.50) and a four-hour reflux period. The reaction mixture was poured into an ice–water slurry and the precipitated solid filtered off, washed first with several portions of water then with cold, dilute sodium bicarbonate solution for removal of acid. The solid was recrystallized once from methanol, once from ethanol and once again from methanol to give 2.6 g. (40%) of dinitro derivative, m. p. 108–108.5°.

Fischer[7a] has reported the nitration of I with fuming nitric acid to yield a dinitro derivative of unknown structure which melted at 121–122°.

Anal. Calcd. for $C_{16}H_{13}Cl_3N_2O_4$: N, 6.93. Found: N, 6.84.

1,1-Dichloro-2,2-bis-(3-nitro-4-methylphenyl)-ethylene (III).—A solution of 2.4 g. (0.006 mole) of 1,1,1-trichloro-2,2-bis-(3-nitro-4-methylphenyl)-ethane (II) in 225 ml. of ethanol was heated to boiling and a hot solution of 0.67 g. (0.012 mole) of potassium hydroxide in ethanol was added. The mixture was heated until an orange-brown color appeared after which it was allowed to stand for ten minutes and concentrated hydrochloric acid added dropwise until the mixture turned yellow. The mixture was held around 50–60° for five minutes, the precipitated salt filtered off, and the filtrate cooled to precipitate the dehydrohalogenated compound. There was obtained 1.7 g. (78%) of 1,1-dichloro-2,2-bis-(3-nitro-4-methylphenyl)-ethylene, m. p. 132.5°.

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2O_4$: N, 7.64. Found: N, 7.66.

Oxidation of 1,1-Dichloro-2,2-bis-(3-nitro-4-methylphenyl)-ethylene.—1,1-Dichloro-2,2-bis-(3-nitro-4-methylphenyl)-ethylene (1.7 g. or 0.0046 mole) was added to a hot solution of 3.0 g. of chromic oxide in 75 ml. of glacial acetic acid, and the mixture heated on a water-bath for one hour. The resulting solution was poured on to an ice–water slurry. The precipitated solid was recrystallized from water–acetic acid and water–methanol solutions to yield 0.18 g. (13%) of solid melting at 143–144°. Lange and Zufall[9] report 144° as the melting point of 3,3′-dinitro-4,4′-dimethylbenzophenone (V) and offer structure proof for this compound. The above sequence of reactions leading to V indicates the position of dinitration of 1,1,1-trichloro-2,2-bis-(*p*-tolyl)-ethane. The oxidation of the dichloroethylene III to the corresponding benzophenone V with chromic oxide is a well known type of conversion used by numerous investigators.[1,6,7b,10,11] The low yield in the oxidation appeared to be due to extensive degradation of the molecule to simpler, water-soluble types. The crude water-insoluble portion isolated from the oxidation mixture was largely 3,3′-dinitro-4,4′-dimethylbenzophenone (V) with no evidence of other isomers being present.

3,3′-Dinitro-4,4′-dimethylbenzophenone was also prepared in another manner. A mixture of 1 g. of 4,4′-dimethylbenzophenone and 8 ml. of fuming nitric acid (sp. gr. 1.50) was heated on a boiling water-bath for thirty minutes. The mixture was poured into cold water and the precipitated yellow solid separated and recrystallized from a mixture of ethanol and benzene. The product weighed 1.2 g. (84% yield) and melted at 144°. A mixed melting point with the 143–144° melting material isolated above showed no depression. Errera[12] has reported the nitration of 4,4′-dimethylbenzophenone to 3,3′-dinitro-4,4′-dimethylbenzophenone.

1,1-Dichloro-2,2-bis-(3-amino-4-methylphenyl)-ethylene (IV).—A hot solution of 2.3 g. (0.0062 mole) of 1,1-dichloro-2,2-bis-(3-nitro-4-methylphenyl)-ethylene in 60 ml. of ethanol was agitated with Raney nickel catalyst under a hydrogen pressure of 35–40 lb. The solution was filtered and the filtrate evaporated to a volume of 10–15 ml. Water was added until the hot solution was cloudy. Cooling precipitated some oil and the supernatant liquid was poured into water. The precipitated white solid was recrystallized from alcohol yielding 1.0 g. (52%) of light tan prisms of diamine, melting at 148°.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2$: N, 9.12. Found: N, 9.33 and 9.23.

Nitration of 1,1,1-Tribromo-2,2-bis-(*p*-methoxyphenyl)-ethane and 1,1,1-Trichloro-2,2-bis-(*p*-bromophenyl)-ethane.—1,1,1-Tribromo-2,2-bis-(*p*-methoxyphenyl)-ethane, m. p. 112–113°,[7a,13] was dinitrated and carried through the same sequence of steps to the diamino type as outlined above. Proof of the positions of nitration by oxidation to the ketone was not obtained, but it was considered highly probable that nitration occurred in the 3,3′-positions by analogy to the nitration of 1,1,1-trichloro-2,2-bis-(*p*-methoxyphenyl)-ethane (methoxychlor).[6]

1,1,1-Trichloro-2,2-bis-(*p*-bromophenyl)-ethane, m. p. 138–139.5°, was prepared by condensation of chloral and bromobenzene.[8,14] Dinitration in 67% yield gave a product melting at 168–169°. Zeidler[8] reported a dinitro derivative, m. p. 168–170°. Dehydrohalogenation of the dinitro derivative and oxidation of the product with

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[7] (a) Fischer, *Ber.*, **7**, 1191 (1874); (b) Harris and Frankforter, THIS JOURNAL, **48**, 3146 (1926); (c) Haskelberg and Lavie, *J. Org. Chem.*, **14**, 501 (1949).

[8] Zeidler, *Ber.*, **7**, 1180 (1874).

[9] Lange and Zufall, *Ann.*, **271**, 6 (1892).

[10] Haller, *et al.*, THIS JOURNAL, **67**, 1595 (1945).

[11] Forrest, Stephenson and Waters, *J. Chem. Soc.*, 338 (1946).

[12] Errera, *Gazz. chim. ital.*, **21**, I, 99 (1891).

[13] Brand, *Ber.*, **54**, 1987-2006 (1921).

[14] Stephenson and Waters, *J. Chem. Soc.*, 340 (1946).

chromic oxide gave 3,3′-dinitro-4,4′-dibromobenzophenone, m. p. 156.6–157.5°. Montagne[15] has prepared this ketone by another method and reported the melting point as 157.5°. This indicates that the nitro groups in these compounds are in the 3,3′-positions.

All of these compounds were prepared in general accordance with the procedures given in detail above. Data on these compounds are summarized in Table I.

Acknowledgment.—The authors wish to express appreciation for a Frederick G. Cottrell grant from the Research Corporation which supported a portion of this work.

Summary

1. A study has been made of the nitration of three compounds related to DDT. These compounds are 1,1,1-trichloro-2,2-bis-(*p*-tolyl)-ethane, 1,1,1-tribromo-2,2-bis-(*p*-methoxyphenyl)-ethane and 1,1,1-trichloro-2,2-bis-(*p*-bromophenyl)-ethane.

2. Certain derivatives of the nitrated products including the amino derivatives have been prepared.

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(15) Montagne, *Ber.*, **48**, 1032 (1915).

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SYDNEY]

Application of the Amidomethylation Reaction to the Synthesis of Quinazolines

BY ALAN M. DOWNES[1] AND FRANCIS LIONS

Einhorn[2] has shown that methylolamides are readily prepared, and that they can be condensed with aromatic compounds in presence of a condensing agent such as concentrated sulfuric acid, or, in some instances, alcoholic hydrochloric acid, to form acylated benzylamine derivatives. Entry of the amidomethyl group into the aromatic ring is facilitated by ortho–para directing groups and is hindered, but not entirely inhibited, by meta directing groups. In particular, Einhorn showed that diacyl derivatives of *p*-aminobenzylamine are readily prepared from an acylated aniline and a methylolamide

It seemed reasonable to the authors to anticipate that treatment of a suitable para substituted acylaniline with a methylolamide in presence of sulfuric acid would lead to formation of a diacylated *o*-aminobenzylamine derivative; and, since the *o*-aminobenzylamines can be readily converted into derivatives of quinazoline, that these might be rendered more readily accessible.

It was realized at the outset that during the hydrolysis of diacylated *o*-aminobenzylamine derivatives ring closure of an intermediate monoacylated *o*-aminobenzylamine might occur with direct formation of a dihydroquinazoline and some experimental evidence bearing on the ease of this ring closure in certain instances has been obtained.

In this preliminary study, in order to avoid this possibility, advantage was taken of the powerful orienting influence of the methoxyl groups of veratrole which direct a first substituent group into the 4-position and a second into the adjacent 5-position. It was anticipated that application of Einhorn's amidomethylation procedure to 4-nitroveratrole would lead to 2-nitro-4,5-dimethoxybenzylamine derivatives from which, by hydrolysis, 2-nitro-4,5-dimethoxybenzylamine (I) should become readily available, and from it, by reduction, 2-amino-4,5-dimethoxybenzylamine (II). Experiment has shown the correctness of these predictions.

4-Nitroveratrole could be condensed with methylolbenzamide in concentrated sulfuric acid solution to give N-(2-nitro-4,5-dimethoxybenzyl)-benzamide (III) in 31% yield. Similarly, 4-nitroveratrole could be condensed with methylolphthalimide to N-(2-nitro-4,5-dimethoxybenzyl)-phthalimide (IV), the yield being improved to 88% when concentrated sulfuric acid was replaced by 90 wt. % sulfuric acid as condensing agent. Attempts to prepare N-(2-nitro-4,5-dimethoxybenzyl)-acetamide (V) from methylolacetamide and 4-nitroveratrole in cold concentrated sulfuric acid proved abortive as did most attempts to prepare N-(2-nitro-4,5-dimethoxybenzyl)-succinimide (VI). However, in one experiment a very small yield (1.4%) of VI was obtained. V and VI were subsequently prepared by other methods.

Reduction of III, most satisfactorily with hydrogen and Raney nickel, led to ready formation of N-(2-amino-4,5-dimethoxybenzyl)-benzamide (VII), and from this, by acid hydrolysis, II was prepared. Ring closure to a quinazoline derivative under acid conditions did not, apparently, occur, in contrast to the ready formation of benzimidazoles in presence of acid recorded by Phillips.[3] Heating of VII under reflux with excess phosphorus oxychloride for two and one-half hours did, however, lead to ring closure and simultaneous loss of hydrogen and formation of the known 2-phenyl-6,7-dimethoxyquinazoline (VIII).[4]

Reduction of IV led to formation of 7,8-dimethoxy-12-keto-10,12-dihydroisoindolo-(1.2-b)-quinazoline (IX), ring closure of the intermediate N-(2-amino-4,5-dimethoxybenzyl)-phthalimide occurring spontaneously. Gabriel[5] has prepared a similar compound by reduction of 2-nitrobenzylphthalimide.

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(1) Commonwealth Research Student, University of Sydney.

(2) Einhorn, *et al.*, *Ann.*, **343**, 207 (1905); **361**, 113 (1908).

(3) Phillips, *J. Chem. Soc.*, 2393 (1928).

(4) Rilliet, *Helv. Chim. Acta*, **5**, 552 (1922).

(5) Gabriel, *Ber.*, **45**, 713 (1912).