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.

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

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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[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.

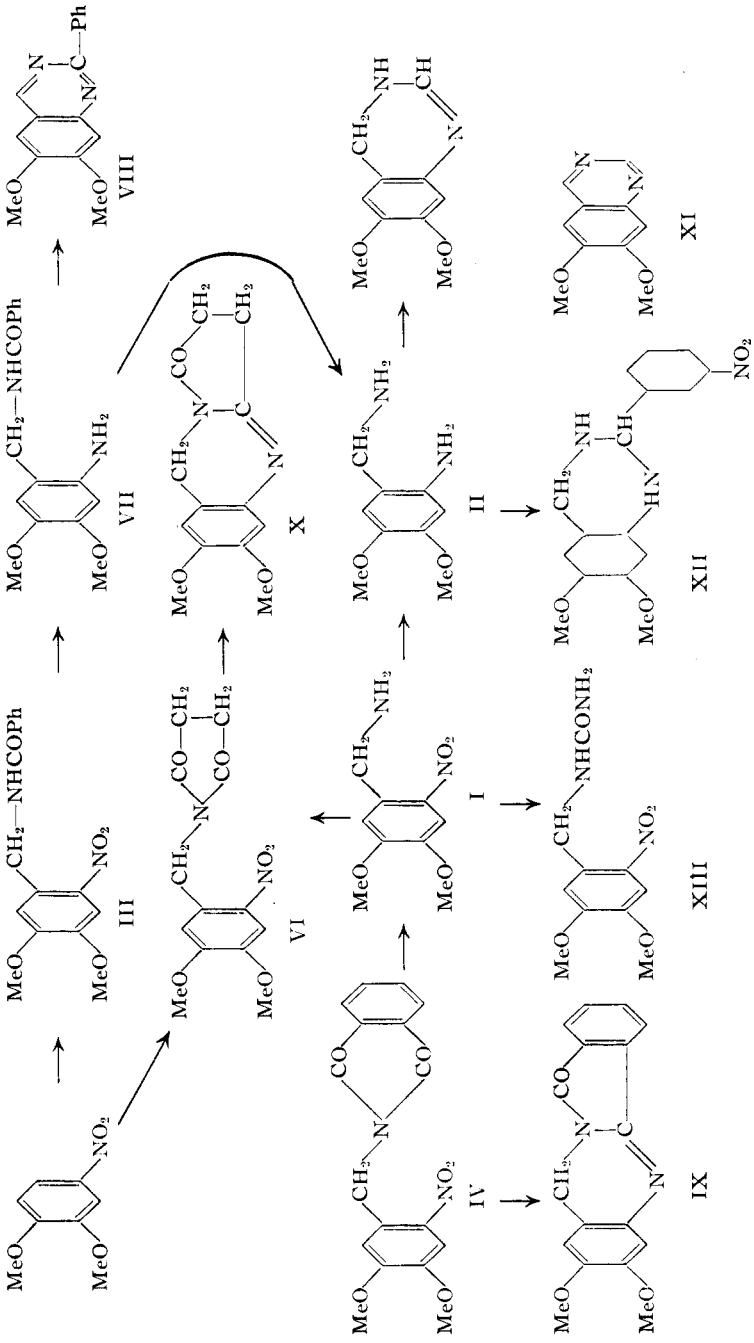
(1) Commonwealth Research Student, University of Sydney.

(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).



Hydrolysis of IV with hydrazine hydrate and the hydrochloric acid according to the method of Ing and Manske[6] provided a smooth method for the preparation of I. From this, by direct heating with succinic anhydride VI was obtained identical with that from the interaction of 4-nitroveratrole and methylolsuccinimide. Acetic anhydride converted I into V. Catalytic reduction (Raney nickel) of VI led to formation of 6,7-dimethoxy - 1 - keto - 1,2,3,9 - tetrahydropyrrolo-(2.1-b)-quinazoline (X), a substance possessing the same type ring system as is present in the alkaloids of the vasicine group.

Catalytic reduction of I yielded 2 - amino - 4,5 - dimethoxybenzylamine (II), identical with that obtained by acid hydrolysis of VII. This base is readily characterized by its bis-salicylidene and bis-5-bromosalicylidene derivatives. Treatment of the hydrochloride with anhydrous formic acid and sodium formate followed by oxidation with potassium ferricyanide solution readily yielded the 6,7-dimethoxyquinazoline (XI) previously described by Fetscher and Bogert.[7]

The base II also readily reacts with *m*-nitrobenzaldehyde to give a product which, by analogy, is almost certainly 2-(*m*-nitrophenyl)6,7-dimethoxy-1,2,3,4-tetrahydroquinazoline (XII).

Finally, it should be recorded that treatment of I with nitrourea converted it to 2-nitro-4,5-dimethoxybenzylurea (XIII) which was reduced to 2-amino-4,5-dimethoxybenzylurea (XIV). Attempts to effect ring closure of XIV to 2-amino - 6,7 - dimethoxyquinazoline, using such agencies as heat, phosphorus trichloride and phosphorus pentoxide all failed.

Experimental

N-(2-Nitro-4,5-dimethoxybenzyl)-benzamide (III).—4 - Nitroveratrole (54.9 g.) was dissolved in cold concentrated sulfuric acid (360 ml.) and methylolbenzamide[2] (45.6 g.) slowly added with stirring, avoiding any temperature rise. The red solution was then set aside at room temperature for five days after which it was poured onto crushed ice (about 1 kg.). The crude solid product which separated was filtered, washed with water and dried. It was then dissolved in benzene and the solution thoroughly washed with acid and alkali. The yellow benzene solution was then dried and the solvent removed, leaving a yellow gum which was induced to crystallize and then recrystallized several times from ethyl acetate; yield 29.3 g. (31%); m. p. 129.5–132°.

Anal. Calcd. for $C_{16}H_{16}N_2O_5$: C, 60.8; H, 5.1; N, 8.9. Found: C, 60.8; H, 5.1; N, 8.9.

N-(2-Nitro-4,5-dimethoxybenzyl)-phthalimide (IV).—4-Nitroveratrole (18.3 g.) was dissolved in cold sulfuric acid (120 ml. concentrated acid + 20 ml. water; 90% by weight) and methylolphthalimide[8] (17.7 g.) slowly added

(6) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

(7) Fetscher and Bogert, *J. Org. Chem.*, **4**, 71 (1939).

(8) Sachs, *Ber.*, **31**, 1231, 3230 (1898). The methylolphthalimide was not rigidly purified by the method of Sakellarios (THIS JOURNAL, **70**, 2822 (1948)) as the work described had been completed before publication of this method.

with stirring. After standing five days the solution was poured onto ice and the product allowed to stand until the initial pink color was dispelled. The pale yellow solid (30.1 g. 88%) was then collected, washed with water and a little alcohol and recrystallized from ethyl acetate, and then several times from alcohol; pale yellow needles, m. p. 175–176°.

Anal. Calcd. for $C_{17}H_{14}N_2O_6$: C, 59.7; H, 4.1; N, 8.2. Found: C, 59.2; H, 4.1; N, 8.2.

7,8-Dimethoxy-12-keto-10,12-dihydro-isoindolo(1.2-b)quinazoline (IX).—(a) A solution of stannous chloride (5 g.) in concentrated hydrochloric acid (8 ml.) was added to a suspension of IV (2 g.) in alcohol (100 ml.) and the mixture warmed almost to boiling for three hours, a red substance gradually separating. After cooling excess sodium hydroxide was added and the free base recovered and recrystallized from alcohol; yield 1.25 g. (69%); fluffy yellow needles, m. p. 245–246°.

(b) IV (2 g.) was suspended in hot alcohol (300 ml.) and reduced with hydrogen at a few hundred mm. pressure using Raney nickel. After filtration, concentration and cooling, the base crystallized from the hot solution; yield 1.36 g. (75%); m. p. 245–246°.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.4; H, 4.8; N, 9.5. Found: C, 68.8; H, 4.9; N, 9.6.

The red **hydrochloride** of IX melted at 235–236° dec.

Anal. Calcd. for $C_{17}H_{15}N_2O_3Cl$: N, 8.5. Found: N, 8.5.

N-(2-Amino-4,5-dimethoxybenzyl)-benzamide (VII).—(a) III (11.5 g.) dissolved in warm ethanol was hydrogenated using Raney nickel catalyst and a pressure of a few hundred mm. Uptake of hydrogen was rapid. After removal of the nickel and alcohol the residue was recrystallized from benzene; yield 9.25 g. (89%); m. p. 158–162°.

(b) Reduction of III (15 g.) with zinc filings and alcoholic hydrochloric acid exactly similarly to the method described by Gabriel and Jansen[9] yielded 10.5 g. of recrystallized base (77%), m. p. 160–162°.

(c) A solution of stannous chloride (5 g.) in hydrochloric acid (8 ml.) was added to a solution of III (2 g.) in alcohol, with cooling. The mixture was then warmed at 90° for thirty minutes. Basification followed by ether extraction yielded the base which was recrystallized from ethyl acetate; m. p. 160°. For analysis a specimen of the base was recrystallized several times from benzene. It then melted at 161–162°.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.1; H, 6.3; N, 9.8. Found: C, 67.1; H, 6.3; N, 9.7.

2-Phenyl-6,7-dimethoxyquinazoline (VIII).—VII (5 g.) was refluxed with phosphorus oxychloride (50 ml.) for two and one-half hours. After removal of the excess phosphorus oxychloride *in vacuo* the residue was poured onto ice, basified with ammonia and the solid filtered off and recrystallized from ethanol; white plates m. p. 175–176°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 71.7; H, 5.3; N, 10.5.

The **picrate** melted at 194°.

Anal. Calcd. for $C_{22}H_{17}N_5O_9$: N, 14.1; OCH_3, 12.5. Found: N, 12.9; OCH_3, 12.5. (The substance was difficult to burn.)

The m. ps. recorded for VIII and its picrate are 175 and 190°, respectively.[4]

2-Nitro-4,5-dimethoxybenzylamine (I).—IV (10 g.) was suspended in alcohol (200 ml.) and hydrazine hydrate (50% by weight soln., 3 g.) added to the hot suspension. The mixture was refluxed. After thirty-five minutes solution was complete, and within an hour a solid commenced to deposit. Refluxing was continued for a further one and one-half hours. Concentrated hydrochloric acid (10 ml.) was then added and refluxing continued for thirty minutes. The hot liquid was filtered and most of the alcohol removed by distillation. After cooling and basification with excess sodium hydroxide solution the base I was recovered, washed and dried with the help of ether as a yellow solid which absorbed carbon dioxide from the air; yield 5.53 g. (89%).

It was characterized as its **hydrochloride, picrate** and **5-bromosalicylidene derivative.** The **hydrochloride** formed pale yellow needles, m. p. 209–211° dec. from alcohol.

Anal. Calcd. for $C_9H_{12}N_2O_4 \cdot HCl \cdot {}^1/_2H_2O$: C, 42.0; H, 5.9; N, 10.9. Found: C, 41.7; H, 5.5; N, 10.9.

The **picrate** formed long yellow needles from alcohol, m. p. 218–220°.

Anal. Calcd. for $C_{15}H_{15}N_5O_{11}$: N, 15.9. Found: N, 15.8.

The **5-bromosalicylidene derivative** was prepared by heating equimolecular quantities of the base and the aldehyde together for a short time in alcoholic solution. The product formed fluffy yellow needles from alcohol, m. p. 182–184°.

Anal. Calcd. for $C_{16}H_{15}N_2O_5Br$: N, 7.1. Found: N, 7.1.

N-(2-Nitro-4,5-dimethoxybenzyl)-succinimide (VI).—(a) Methylolsuccinimide[10] (5.5 g.) was dissolved in a cool solution of nitroveratrole (7.8 g.) in concentrated sulfuric acid (55 ml.), the solution allowed to stand five days and then poured onto ice. The small yield of product (0.17 g., 1.4%) was recrystallized from ethyl acetate and obtained as tiny pale yellow plates, m. p. 178–180°.

Anal. Calcd. for $C_{13}H_{14}N_2O_6$: C, 53.1; H, 4.8; N, 9.6. Found: C, 52.7; H, 4.9; N, 9.6.

From other experiments employing slightly diluted sulfuric acid (98.7 and 93%) only unchanged nitroveratrole was isolable.

(b) I (1 g.) was intimately mixed with succinic anhydride (0.48 g.) and the mixture heated at 230–240° for ten minutes. The resulting dark solid mass was recrystallized from hot ethyl acetate with the help of decolorizing charcoal; yield 0.48 g. (36%), m. p. 178–180°, alone or admixed with the preparation from (a).

N-(2-Nitro-4,5-dimethoxybenzyl)-acetamide (V).—Attempts to prepare this substance by the amidomethylation reaction using concentrated sulfuric acid as condensing agent seemed to lead to sulfonation. When slightly diluted sulfuric acid (98 or 93%) was used the nitroveratrole appeared to remain unchanged. However, the substance could be prepared by warming I (0.9 g.) with acetic anhydride (5 ml.) at 100° for thirty minutes. Recrystallized from ethyl acetate, it melted at 157–158°.

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 52.0; H, 5.6; N, 11.0. Found: C, 51.8; H, 5.5; N, 10.9.

6,7-Dimethoxy-1-keto-1,2,3,9-tetrahydropyrrolo(2.1-b)quinazoline (X).—VI (0.33 g.) was reduced in alcoholic solution with hydrogen at a few hundred mm. pressure in presence of Raney nickel; yellow needles from alcohol, m. p. 226–227°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4. Found: C, 62.9; H, 5.8; N, 11.3.

2-Amino-4,5-dimethoxybenzylamine (II).—(a) I (10 g.) was hydrogenated in alcoholic solution at room temperature at ordinary pressure in presence of Raney nickel. Addition of concentrated hydrochloric acid to the filtrate from the nickel catalyst precipitated yellow needles (11.2 g.). These were dissolved in water and the base precipitated with sodium hydroxide; yield 8 g. (93%). (b) VII (1 g.) was refluxed with concentrated hydrochloric acid (20 ml.) for one hour. The mixture was then poured into excess sodium hydroxide solution and the base recovered with ether. This base melted indefinitely over the range 82–93°, probably because of the ease with which it carbonated when exposed to air. For the same reason the base gave bad analytical figures. However, it was readily characterized as its **bis-salicylidene** and **bis-5-bromosalicylidene**

(9) Gabriel and Jansen, *Ber.*, **23**, 2809 (1890).

(10) Cherbuliez and Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925).

derivatives. The **bis-salicylidene derivative** formed yellow needles (from alcohol), m. p. 125–126°.

Anal. Calcd. for $C_{23}H_{22}N_2O_4$: N, 7.2. Found: N, 7.2.

The **bis-5-bromosalicylidene derivative** formed orange-yellow needles from alcohol; m. p. 198–199°.

Anal. Calcd. for $C_{23}H_{20}Br_2N_2O_4$: N, 5.1. Found: N, 5.1.

6,7-Dimethoxyquinazoline (XI).—A mixture of 2-amino-4,5-dimethoxybenzylamine hydrochloride (2 g.), anhydrous sodium formate (1.5 g.) and 100% formic acid (4 ml.) was refluxed for ninety minutes. The excess formic acid was then evaporated from a water-bath. The solid residue was dissolved in water, basified with sodium hydroxide and ether extracted. After drying over solid potash, then removal of the ether, a white solid was obtained which still melted over the range 126–136° after many recrystallizations from benzene suggesting a mixture of the quinazoline and dihydroquinazoline. Hence potash solution (2 ml. of 33%) was added to a solution of some of the solid (0.16 g.) in water (5 ml.) followed by an aqueous solution of potassium ferricyanide (0.72 g.). Potash solution (20 ml. of 33%) was then added and the base collected with ether, then recrystallized from petroleum ether; fluffy white needles, m. p. 146–147° (reported,[7] 143°).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.1; H, 5.3; N, 14.7. Found: C, 62.9; H, 5.3; N, 13.7.

The **hydrochloride** melted at 225–227° (reported 227°).

2-(*m*-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroquinazoline (XII).—A solution of the diamine II (0.5 g.) and *m*-nitrobenzaldehyde (0.42 g.) in a little alcohol was refluxed for fifteen minutes. An orange-red compound was induced to crystallize on cooling. Recrystallized from absolute ethanol it formed red needles, m. p. 119–120°.

Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 61.0; H, 5.4; N, 13.3. Found: C, 60.5; H, 5.4; N, 13.5.

2-Nitro-4,5-dimethoxybenzylurea (XIII).—I (7.6 g.) was heated with water (80 ml.) and nitrourea (4 g.) at 100° for an hour. After cooling the product was collected and recrystallized from much alcohol; pale yellow needles, m. p. 227–231° dec.

Anal. Calcd. for $C_{10}H_{13}N_3O_5$: C, 47.1; H, 5.1; N, 16.5. Found: C, 46.9; H, 5.1; N, 16.5.

2-Amino-4,5-dimethoxybenzylurea (XIV).—The nitro compound XIII (2 g.) was reduced in hot alcohol (400 ml.) with hydrogen and Raney nickel. The product formed fine white needles from absolute ethanol, m. p. 190–191°; yield 1.3 g. (76%).

Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.3; H, 6.7; N, 18.7. Found: C, 52.9; H, 6.7; N, 18.5.

Acknowledgments.—We are indebted to the Commonwealth Research Fund for a Studentship which enabled one of us (A. M. D.) to take part in this work; and to Miss Joyce Fildes for the microanalyses recorded in this paper.

Summary

Application has been made of Einhorn's amidomethylation procedure to nitroveratrole and several acylated 2-nitro-4,5-dimethoxybenzylamines prepared. Some of these can be directly converted to quinazoline derivatives by reduction. Hydrolysis of them yields 2-nitro-4,5-dimethoxybenzylamine, which can be reduced to 2-amino-4,5-dimethoxybenzylamine, and this, in turn, can be converted to 6,7-dimethoxyquinazoline derivatives by standard procedures.

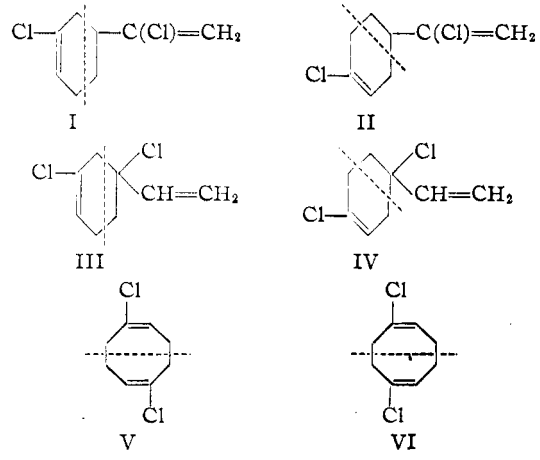
SYDNEY, AUSTRALIA RECEIVED JULY 5, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Polyolefins. VII. Structure of the Eight-membered Cyclic Dimer of Chloroprene[1]

BY ARTHUR C. COPE AND WILLIAM R. SCHMITZ

Chloroprene (2-chloro-1,3-butadiene) has been observed to dimerize on standing or heating in the presence of polymerization inhibitors, yielding a mixture from which two six-membered cyclic dimers and one eight-membered cyclic dimer have been isolated.[2–6] Dimerization by a normal Diels–Alder diene addition reaction and a related process of self-addition in which both of the monomer units are united through the 1,4-positions theoretically could yield six structurally isomeric dimers (I–VI), depending on the orientation of the monomer units. In one of the six-membered cyclic dimers actually isolated both chlorine atoms are inert (vinyl) in character, as would be the case in I and II; in the other, one



chlorine is vinyl and the other allylic as in III and IV. A monochlorotriene, presumably derived from the dimer containing reactive chlorine by elimination of hydrogen chloride, also has been isolated from the mixture of dimers. Brown,

(1) Supported in part by the Office of Naval Research under Contract N5ori-07822, Project Designation NR-055-96.

(2) Carothers, Williams, Collins and Kirby, THIS JOURNAL, **53**, 4211 (1931).

(3) Brown, Rose and Simonsen, *J. Chem. Soc.*, 101 (1944).

(4) Foster and Schreiber, THIS JOURNAL, **70**, 2303 (1948).

(5) Cope and Bailey, *ibid.*, **70**, 2305 (1948).

(6) Klebanskii and Denisova, *J. Gen. Chem.* (*U. S. S. R.*), **17**, 703 (1947); *C. A.*, **42**, 1215 (1948).