ON THE FORMATION OF SYMMETRICAL DIBENZO-CYCLO-DOCOSANE-DIONE.

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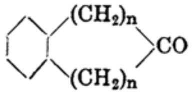
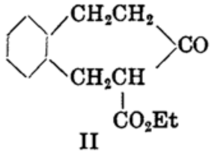
Received September 30th, 1935. Published January 28th, 1936.

Researches designed to synthesize isocyclic ketones with a benzene ring condensed at the ortho-position have engaged our attention since the researches of Ruzicka and his collaborators(1) in the preparation of many-membered alicyclic ketones. In a previous paper(2) one of the authors described a method of synthesizing a seven-membered cyclic ketone, *o*-benzo$^{4:5}$-cycloheptanone-(1) [benzene-(pentanone-3-ylene)$_{1,2}$] (I, n = 2), which is the parent ketone of ethyl 3-ketophen-heptamethylene-2-carboxylate (II) identified by Titley(3) only as its phenylhydrazone.



I



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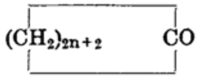
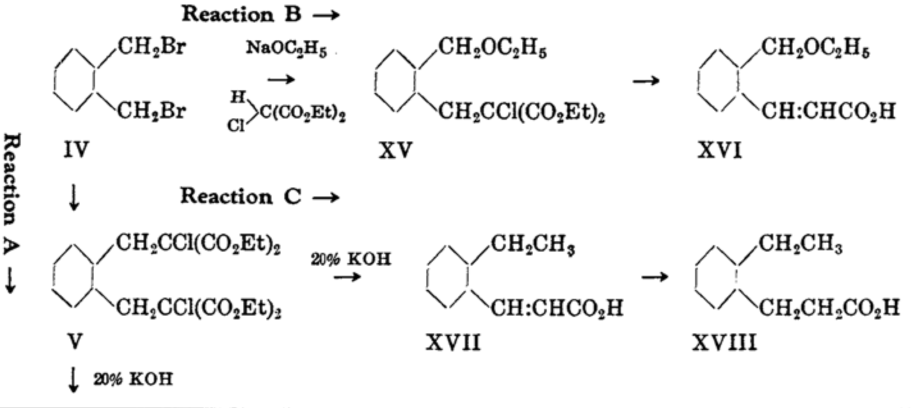


III

Following the compound with n = 2 in I we have further proceeded to the preparation of a series of ketones of this type intending to compare their properties with those of the alicyclic ketone III already known, and we have attempted to synthesize a compound with n = 4 in I. The course of reactions, however, resulted in the formation of a diketone XIV, symmetrical dibenzo-cyclo-docosane-dione, as shown below:



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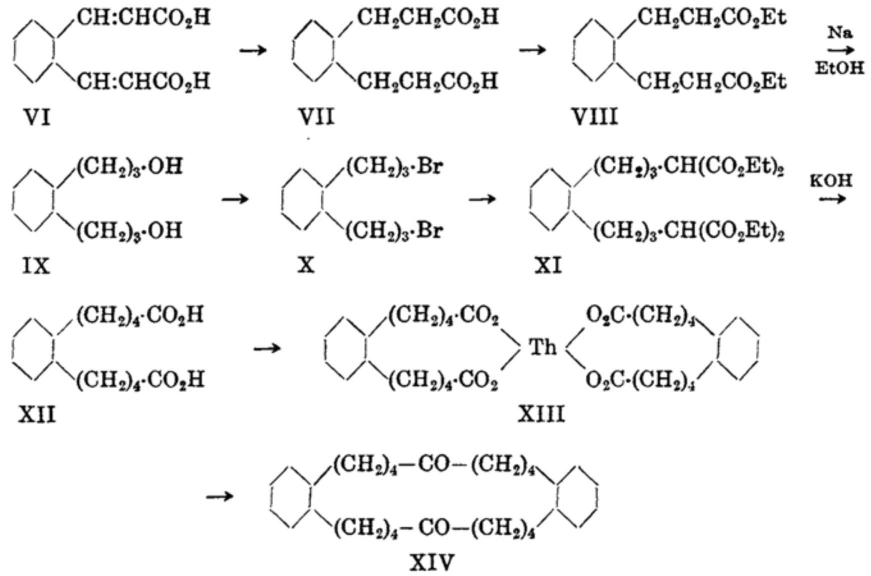
(1) Ruzicka, *Helv. Chim. Acta*, **9** (1926), 230.
(2) This Bulletin, **6** (1931), 103.
(3) Titley, *J. Chem. Soc.*, **1928**, 2571.



Starting from *o*-xylyene dibromide, *o*-phenylene-diacrylic acid was prepared by the method described by Perkin; but the reaction of *o*-xylyene dibromide with chloro-sodio-malonic ester was not so simple as we expected. When monochloro-malonic ester having a boiling point of 221–225° (corr.) was used (undoubtedly containing some dichloro-ester), the reaction, instead of taking course A, went through B and D (see experimental part), and thus resulted in the formation of *o*-(ethoxymethyl)-cinnamic acid (XVI) and phthalic alcohol diethyl-ether (XIX). This difficulty was partially overcome by preparing a monochloro-malonic ester having a boiling point 221–222°, by slightly modifying the usual method⁽⁴⁾.

o-Phenylene-diacrylic acid (VI) was reduced to *o*-phenylene-dipropionic acid (VII) with 2% sodium amalgam. A small amount of β-(*o*-ethylphenyl)-propionic acid (XVIII) was formed along with acid VII, when a crude acid of VI was reduced. The presence of XVIII indicates that reaction C partly took place during the hydrolysis of *o*-xylylene-dichloro-malonic ester (V) with concentrated alcoholic potash (although we have not isolated acid XVII). The scission of three molecules of carbon dioxide from *o*-xylylene-dimalonic ester (H substituted for Cl in V) by the action of concentrated alcoholic potash has already been reported by H.T. Lo⁽⁵⁾, and the present case shows that a similar reaction also occurs to some extent in the decomposition of the dichloro-derivative of *o*-xylylene-dimalonic ester mentioned above.

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(4) Conrad, Bischoff and Guthzeit, *Ann.*, **209** (1881), 218.

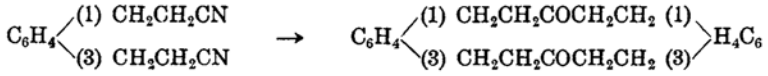
(5) H. T. Lo, this Bulletin, **5** (1930), 326.

o-Phenylene-dipropionic acid diethyl ester (VIII) was reduced with sodium and alcohol to *o*-phenylene-dipropyl alcohol (IX) having a melting point 56–57°. This gave a liquid bromide (X) when treated with dry hydrogen bromide.

The condensation of malonic ester and *o*-phenylene-dipropyl bromide (X) took place readily (formation of XI), and a syrupy tetracarboxylic acid was obtained by the saponification of the ester XI; this on being heated up to 160° evolved carbon dioxide and yielded *o*-phenylene-divaleric acid (XII). The thorium salt of this acid was submitted to high vacuum dry distillation. When the distillation pressure was lower than 0.01 mm. the oily distillate partly crystallized into flat needles, which on recrystallisation gave a sharp melting point of 133.5° (corr.). The analytical results of this compound agreed with $n = 4$ in I, but the molecular weight determination by Rast's method (in camphor) gave a double molecular weight which corresponds to XIV: a dibenzo-cyclo-docosane-dione. The remaining part of the the distillate was redistilled and fractionated. Although the lower fraction (110–195° / 0.004 mm.) was found to yield a minute quantity of XIV after a few months, no other definite compound could be obtained by treating the liquid fractions with semicarbazide, *p*-nitrophenylhydrazine, etc.

According to the results of Ruzicka⁽⁶⁾, and Ziegler⁽⁷⁾ in preparing alicyclic ketones, an eleven-membered ring proved to be one of the most difficultly formed ketones, while a twenty-two-membered cyclic diketone was obtained with better result. In our case we could obtain only a twenty-two-membered cyclic diketone in a yield of about 0.2%, but could not isolate the monoketone (I, $n = 4$). This shows that the difficulty of the formation of an eleven-membered ring is emphasized in the case of alicyclic compounds, with a condensed aromatic ring.

A similar reaction occurring in the meta-position of benzene, first observed by Titley⁽⁸⁾, was later confirmed by Ziegler⁽⁹⁾ in the case of *m*-phenylene-dipropionitrile.



$$C_6H_4\left\langle\begin{array}{l}(1)\ CH_2CH_2CN\\(3)\ CH_2CH_2CN\end{array}\right. \rightarrow C_6H_4\left\langle\begin{array}{l}(1)\ CH_2CH_2COCH_2CH_2\ (1)\\(3)\ CH_2CH_2COCH_2CH_2\ (3)\end{array}\right\rangle H_4C_6$$

In this reaction the dinitrile, undergoing cyclisation, merely formed a diketone and practically no monoketone. The formation of such cyclic diketones as XIV in the cyclisation of $o\text{-}C_6H_4[(CH_2)_nCOOH]_2$ series must further be investigated.

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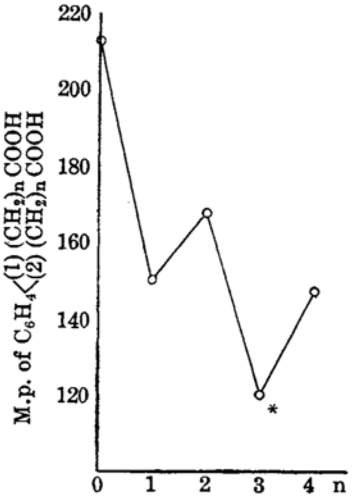
(6) L. Ruzicka, *Helv. Chim. Acta*, **11** (1928), 672.
(7) K. Ziegler, *Ann.*, **513** (1934), 43.
(8) A. F. Titley, *J. Chem. Soc.*, **1928**, 2575.
(9) K. Ziegler, *Ann.*, **511** (1934), 6.

In regard to the odour of the diketone XIV, while the odour of the oily distillate reminds us of cedar oil, owing, perphaps, to the presence of a minute trace of the monoketone (I, n = 4), the diketone is odourless, as is the case with the alicyclic twenty-two-membered diketone obtained by Ruzicka⁽⁹⁾.

Although, up to the present, we have not obtained sufficient data concerning the dicarboxylic acid series o-$C_6H_4[(CH_2)_nCOOH]_2$, there seems to exist a similar melting point rule as in the case of the aliphatic series $HOOC(CH_2)_nCOOH$, the melting point of an acid having an even number n being higher than that of the acid n−1, as can be seen in the following diagram.



Experimental.

I. Preparation of *o*-Phenylene-diacrylic Acid (VI). This acid was obtained by the procedure described by Perkin. For this reaction it was found necessary to use monochloro-malonic ester of good quality; otherwise *o*-xylylene dibromide remained unattacked, or was partly acted upon by the sodium derivative of monochloromalonic ester, and also giving rise to the following reaction:

Reaction D $o\text{-}C_6H_4(CH_2Br)_2+2NaOC_2H_5 \rightarrow$

$o\text{-}C_6H_4(CH_2OC_2H_5)_2 \leftarrow o\text{-}C_6H_4(CH_2Br)_2+2KOH+2C_2H_5OH$

XIX

The product consisted mainly of phthalic alcohol diethylether (XIX) and partly of acid XIII (described below) formed through reaction B. Therefore, in order to avoid the formation of these by-products the usual method of preparing monochloromalonic ester had to be modified.

(i) *Monochloro-malonic ester.* Dry chlorine was passed into malonic ester for a short time; the yellow solution was gently heated up to 55°, when a sudden reaction took place and hydrogen chloride was evolved. The vessel was then cooled in running water and the addition of chlorine continued until the liquid became yellow. The temperature of the ester was kept at about 30° throughout the reaction. The main part of the product boiling at 221-222° (corr.) was redistilled under reduced pressure (b.p. 116-117°/16 mm.).

(ii) *o-Xylylene dibromide* (IV). The presence of moisture during the bromination of *o*-xylene resulted in a considerably decreased yield of the dibromide. The crude dibromide was washed with chloroform and dried on a porous plate, m.p. 89°. This was used for the preparation of *o*-phenylene-diacrylic acid.

From the reagents described above, a maximum yield of 80% of *o*-phenylene-diacrylic acid was obtained. The crude acid was washed with alcohol, and then with benzene.

(iii) *o-(Ethoxymethyl)-cinnamic acid* (XVI). This acid was found to be formed by reaction B when monochloro-malonic ester having a higher boiling point (221-225°) was

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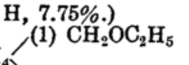
* Observed by E. Takai. M.p. 119-120° (corr.)

used. This indicates that the presence of dichloro-malonic ester (b.p. 234°) favours reaction B. The crude product of XVI was separated from *o*-phenylene-diacrylic acid by treating the mixture with benzene (*o*-phenylene-diacrylic acid is practically insoluble in benzene). The acid XVI was then recrystallized from a mixture of acetone and water, m.p. 130–130.5° (corr.). (Found: C, 69.79; H, 7.15; mol. wt., 203 (camphor), 205 (titration). Calc. for $C_{12}H_{14}O_3$: C, 69.87; H. 6.85%; mol. wt., 206.) The presence of the ethoxyl group in the acid was proved qualitatively by the usual Zeisel method. The presence of a double bond in the side chain was confirmed by the addition of bromine (see v) and hydrogen (see vi).

(iv) *Ethyl o-(ethoxymethyl)-cinnamate.* B.p. 140–141°/2 mm. (uncorr.); n_D^{22} 1.5460. (Found: C, 71.54; H, 7.93. Calc. for $C_{14}H_{18}O_3$: C, 71.75; H, 7.75%.)

(v) *β-(o-Ethoxymethyl)-α,β-dibromopropionic acid*,



$C_6H_4\left\langle\begin{matrix}(1)\ CH_2OC_2H_5\\(2)\ CHBrCHBrCOOH\end{matrix}\right.$

. Acid XVI (0.2 g.) was dissolved in 10 c.c. carbon tetrachloride and 0.17 g. bromine in 5 c.c. carbon tetrachloride was added; the solution was gently heated on the water bath for a minute, when absorption of bromine took place. The solution was then left at room temperature for an hour, then washed with sodium bisulphite solution and water, and dried over sodium sulphate. After evaporating the solvent, the residue was dissolved in benzene and recrystallized by adding some petroleum ether. Colourless crystals resembling dandelion leaves separated; when heated in a capillary tube it darkened at 155° and melted into a black liquid at 168–169° (corr.). (Found: Br, 42.4. Calc. for $C_{12}H_{14}O_3Br_2$: 43.7%.)

(vi) *o-(Ethoxymethyl)-hydrocinnamic acid.* This acid was prepared by reducing acid XVI with 2% sodium amalgam. It was recrystallized from petroleum ether in colourless needles melting at 85°, and found to be soluble in water and in benzene. (Found: C, 69.38; H, 7.85. Calc. for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75%.)

II. **o-Phenylene-dipropionic Acid** (VII). *o*-Phenylene-diacrylic acid (1 mol) was readily reduced by 2% sodium amalgam (6 atoms Na), and *o*-phenylene-dipropionic acid was obtained in a yield of 80–90%. When dried at 100°, a leafy sublimate was found to separate from the crude product. The sublimate, recrystallized from water, melted at 102.5°. No depression of the melting point was observed on mixing it with β-(*o*-ethylphenyl)-propionic acid prepared from *o*-xylylene-dimalonic ester(10). This indicates that reaction C also occurs when the ester V is saponified with a 20–25% alcoholic potash.

Ethyl *o*-phenylene-dipropionate (VIII) was prepared by refluxing one part of acid with three to five parts of a 5% alcoholic solution of hydrogen chloride for three hours. The product was washed with dilute soda solution and water successively, and dried over calcium chloride; b.p. 192–193°/8 mm. (corr.) (b.p. given by Titley(11) 200–202°/12 mm.); n_D^{22} 1.4962; d_4^{22} 1.0763; MR_D obs. 75.52 (calc. 75.56).

III. **o-Phenylene-dipropyl Alcohol** (IX). Ethyl *o*-phenylene-dipropionate was reduced to this alcohol by Bouveault Blanc's method: one part of ester VIII was dissolved in seven parts of absolute alcohol and the solution was added to a flask containing one part of metallic sodium in the course of about fifteen minutes. The flask was then

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(10) *Loc. cit.*, (5).

(11) Titley, *J. Chem. Soc.*, **1928**, 2578.

heated in an oil bath (120°) until the sodium was completely dissolved (A further addition of absolute alcohol was sometimes required for the complete dissolution of sodium). The solution was then slightly cooled and two parts of water added to saponify the ester which had not been reduced. It was then heated on the water bath for two hours. Ethyl alcohol was removed from the solution by steam distillation, and the residue was cooled, extracted four times with ether, washed with water, and dried over potassium carbonate. The solvent was removed and the syrupy residue was cooled to 0°. Crystallization of alcohol IX was induced by scratching the inner wall of the vessel with a glass rod, but as the alcohol crystallized with some difficulty, crystallization was effected in later runs by inoculating with the crystalline alcohol previously obtained. The product was drained on a porous plate. The yield of the crude product amounted to 30–40% of the theoretical. Increase in the yield of alcohol IX could not be attained by increasing the quantity of sodium. A considerable excess of sodium gives a rather poor yield as may be seen in the following table.

Na (atoms)/1 mol Ester VIII	8(theoret.)	12.1	12.4	16.9	18.0	23.9
Yield of Alcohol IX (%)	—	40	45	31	25	16

The alcohol was recrystallized from carbon tetrachloride. Lustrous scales, m.p. 56–57°. It is very soluble in alcohol, moderately soluble in carbon tetrachloride and difficultly soluble in ligroin. (Found: C, 73.97; H, 7.85; mol. wt., 184 (in camphor). Calc. for $C_{12}H_{18}O_2$: C, 74.17; H, 7.75%; mol. wt., 194.)

p-Xenyl-carbamate of o-phenylene-dipropyl alcohol(12), $C_6H_4[(CH_2)_3OCONHC_6H_4C_6H_5]_2$. M.p. 187°. (Found: N, 4.94. Calc. for $C_{38}H_{36}N_2O_4$: N, 4.79%.)

The ester VIII which had not been reduced, was recovered from the alkaline mother liquor as the free acid (VII) and was used in a subsequent run.

IV. **o-Phenylene-dipropyl Bromide** (X). Thirty grams of *o*-phenylene-dipropyl alcohol (IX) was heated to 130–140° in a glycerine bath and dry hydrogen bromide passed into it for five hours (three times the calculated quantity of hydrogen bromide was required). The heavy oil product was washed with dilute soda solution and then with water, dried over potassium carbonate, and distilled under reduced pressure. Yield, 35 g. B.p. 187–189°/7.5 mm. (corr.); n_D^{25} 1.5670; d_4^{25} 1.4824. (Found: Br, 50.1; MR_D, 70.13. Calc. for $C_{12}H_{16}Br_2$: Br, 50.0%; MR_D, 70.52)

V. **o-Phenylene-divaleric Acid** (XII). A sodium ethylate solution, prepared by dissolving 4.9 g. of metallic sodium in 60 g. of absolute alcohol, was slowly added to 68 g. of malonic ester. *o*-Phenylene-dipropyl bromide (X) (33.5 g.) dissolved in 100 c.c. dry ether was slowly added to the sodio-malonic ester solution. Precipitation of sodium bromide took place immediately after the addition of the bromide. After heating the mixture over a 50-watt carbon lamp for three hours, the excess of malonic ester was removed by distilling it under reduced pressure, and the residue was saponified by heating with 20% alcoholic potash (45 g. potassium hydroxide) on the water bath for six hours. The alcohol

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(12) The authors wish to thank Mr. T. Akita for preparing and identifying this compound.

was then driven off and the reside was dissolved in some water and the oily matter insoluble in the alkaline solution was removed by shaking with ether. *o*-Phenylene-dipropyl malonic acid separated as a syrupy mass on neutralizing the solution with dilute hydrochloric acid. The viscous acid was dissolved in ether and dried over anhydrous sodium sulphate; after removal of the ether, the syrupy residue was heated to 120-160°, when it decomposed into *o*-phenylene-divaleric acid (XII) and carbon dioxide. A part of the crude product was purified by dissolving it in a dilute sodium carbonate solution and heating on the water bath for an hour with the addition of animal charcoal. The acid thus obtained was recrystallized from a mixture of acetone and water. Colourless crystals, m.p. 148-149° (corr.). The yield was 90% of the theoretical. (Found: C, 68.98; H, 8.34; mol. wt., 285 (in camphor), 280 (titration, as dibasic acid). Calc. for $C_{16}H_{22}O_4$: C, 69.02; H, 7.97%, mol. wt., 278.) It is soluble in acetic acid, alcohol, chloroform, and acetic ester, difficultly soluble in cold water, and insoluble in petroleum ether.

VI. **The Symmetrical Dibenzo-cyclo-docosane-dione** (XIV). Twenty grams of *o*-phenylene-divaleric acid was dissolved in 1 l. of water by neutralizing it with sodium carbonate. Fourteen grams of thorium chloride, dissolved in 400 c.c. of water, was slowly added to the former solution with constant mechanical stirring. The yield of the thorium salt was 29.4 g. This was divided into two portions and each portion placed in a 30 c.c. distilling flask provided with a large side tube. The salt was subjected to high vacuum dry distillation by heating the flask in salt bath ($LiNO_3$-$NaNO_3$-KNO_3) of 160° and then gradually raising the temperature to about 400° in the course of eight to ten hours, the pressure meanwhile being 0.008–0.009 mm. A light yellow, viscous substance distilled over from 190° (bath temperature), a part of it solidifying into long needles after four to six hours from the beginning of distillation. The total yield of the distillate was 2.4 g. This was placed in an ice box for a few days, and the crystals were then separated. The solid product is soluble in ordinary organic solvents. It was recrystallized from ligroin with great ease. Yield, 25 m.g., m.p 133.5° (corr.). In a third run, when 6.7 g. of the salt was used, the yield of the solid product was 4.5 mg. In this case the distillation was carried out under a comparatively high pressure, i.e., 0.01–0.1 mm., and the product was found to give small oblong plates only after a few weeks' cooling in an ice box. These crystals, when recrystallized from ligroin by inoculating with the flat needles previously obtained, were changed into needle-like crystals identical with those obtained in the first distillation. (Found: C, 83.18; H, 9.43; mol. wt., 430, 439 (in camphor). Calc. for $C_{30}H_{40}O_2$: C, 83.27; H, 9.39%; mol. wt. 432.)

The semicarbazone was prepared in the usual way by adding semicarbazide acetate to the ketone (XIV) and adding alcohol until solution was complete. The reaction mixture was allowed to stand overnight at room temperature when a flocculent mass separated. The alcoholic solution was diluted with water and the flocculent precipitate was collected. As the product was difficultly soluble in absolute alcohol and practically insoluble in other solvents, it was successively washed with hot water, alcohol, ligroin, and dried in vacuum. Decomp. pt. 205–208° (corr.) (turns red). (Found: N, 14.8, 13.6. Calc. for $C_{32}H_{46}O_2N_6$: N, 15.4%). Yellow microscopic needles, probably the *p*-nitrophenylhydrazone were obtained by treating XIV with *p*-nitrophenylhydrazine; m.p. 168–172°. The substance was so scarce that analysis was impossible.

The remaining liquid part of the distillate was treated with semicarbazide, *p*-nitrophenylhydrazine, etc., but no definite product could be obtained. It was therefore redistilled and the two following fractions were collected: (1) 110–195/0.004 mm., (2) 195–250 / 0.004 mm. On standing for five months, 0.8 mg. of ketone XIV was found to have crystallized from fraction (1); no change was observed in fraction (2). Both fractions were treated with semicarbazide etc., but no derivative could be obtained. The analytical results of the fractions were: (1) C, 86.22; H, 9.51; (2) C, 87.07; H, 9.47%.

Summary.

The synthesis of an eleven-membered carbon ring attached to the ortho-position of benzene was attempted. The dry distillation of the thorium salt of *o*-phenylene-divaleric acid resulted in the formation of a twenty-two-membered diketone ring. Several new compounds incidental to the synthesis are reported.

In concluding, the authors wish to thank Mr. S. Tsutsumi and Mr. H. Yamura for the valuable assistance given us.

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