[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XXXIV.[1]
1-, 2- and 3-Methoxyphenanthrene-9,10-dicarboxylic Acid Anhydrides

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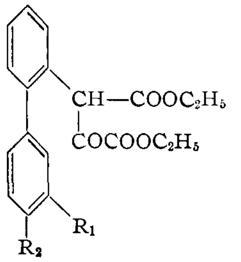
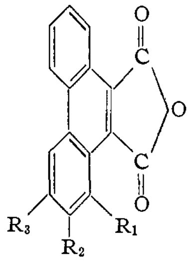
The cyclization of ethyl α-keto-α′-(3′-methoxy-2-biphenylyl)-succinate (II) in 80% sulfuric acid yields both 3-methoxy- and 1-methoxyphenanthrene-9,10-dicarboxylic acid anhydrides (V and VII). The isomeric ethyl α-keto-α′-(4′-methoxy-2-biphenylyl)-succinate (III) in a mixture of hydrobromic and acetic acids yields both 2-methoxyphenanthrene-9,10-dicarboxylic acid anhydride (VI) and 2-methoxy-10-phenanthroic acid (XIX). Cyclization of the acetylation product obtained from the anion of ethyl-α-(3-methoxy-2-biphenylyl)-propionate (XV) yielded what is believed to be 3-methoxy-9,10-dimethylphenanthrene.

The first reports[3,4] of the successful cyclodehydration of a biphenylylmethyl ketone described the cyclization of ethyl α-keto-α′-(2-biphenylyl)-succinate (I). This is an unusual example of the Bougault reaction[5] in that, instead of a hydroaromatic derivative, a fully aromatic compound IV is formed directly. The present communication describes the extension of this reaction to compounds having a methoxyl group on the ring to be attacked in the cyclization.

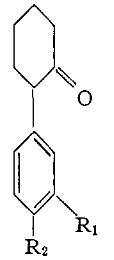


I[6]
II, $R_1 = OCH_3$
III, $R_2 = OCH_3$

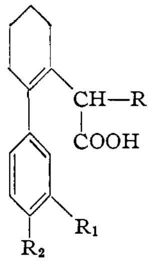


IV
V, $R_3 = OCH_3$
VI, $R_2 = OCH_3$
VII, $R_1 = OCH_3$

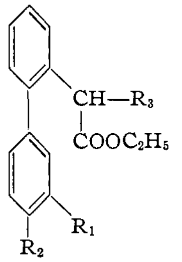
For the synthesis of ethyl α-keto-α′-(3′-methoxy-2-biphenylyl)-succinate (II), the starting material was the known 2-(*m*-methoxyphenyl)-cyclohexanone[7] (VIII). With zinc and ethyl bromoacetate, VIII yielded a product which, on dehydration and saponification, afforded X. When X was esterified and dehydrogenated with sulfur, ethyl (3′-methoxy-2-biphenylyl)-acetate (XIII) was obtained in 67% yield. Condensation of the ester XIII with ethyl oxalate was carried out in the presence of potassium ethoxide and, as usual in the Bougault reaction, the crude ketoester II was used directly in the cyclization. Cyclization was effected in only ten minutes by the use of 80% sulfuric acid, but the product consisted of a mixture of two isomers which were separated only after 37 separate recrystallizations.



VIII, $R_1 = OCH_3$
IX, $R_2 = OCH_3$



X, $R_1 = OCH_3$
XI, $R_2 = OCH_3$
XII, $R_1 = OCH_3$, $R_3 = CH_3$



XIII, $R_1 = OCH_3$
XIV, $R_2 = OCH_3$
XV, $R_1 = OCH_3$, $R_3 = CH_3$

As can be seen by inspection of formula II, cyclization can occur either *ortho* or *para* to the methoxyl group. From reports concerning other cyclizations,[8] it would be predicted that in the present instance the chief product would be the one in which condensation had occurred in the position *para* to the methoxyl. This was found to be the case, for the lower-melting isomer, which constituted 73% of the material isolated, could be decarboxylated[9] to 3-methoxyphenanthrene, and was, therefore, 3-methoxyphenanthrene-9,10-dicarboxylic anhydride (V). It appears highly probable that the higher-melting isomer is 1-methoxyphenanthrene-9,10-dicarboxylic anhydride (VII).

The synthesis of crude ethyl α-keto-α′-(4′-methoxy-2-biphenylyl)-succinate (III) from 2-(*p*-anisyl)-cyclohexanone[7] (IX) was carried out in a manner analogous to that used in the preparation of the isomer II. The yields were roughly equivalent in the two series. Cyclization of III was effected by boiling with a mixture of hydrobromic and acetic

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(1) For the preceding communication of this series see C. K. Bradsher, L. E. Beavers and N. Tokura, THIS JOURNAL, **78**, 3196 (1956).

(2) Allied Chemical and Dye Corporation Fellow 1953–1954. Taken in part from a thesis submitted by P. H. Leake in partial fulfillment of the requirements for the Ph.D. degree at Duke University, 1954. This work was supported in part by the Chemical Corps, Fort Detrick, Md., under contract with Duke University.

(3) A. Schönberg and F. Warren, *J. Chem. Soc.*, 1838 (1939).

(4) T. A. Geissman and R. Tess, THIS JOURNAL, **62**, 514 (1940).

(5) J. Bougault, *Compt. rend.*, **159**, 745 (1915); K. von Auwers and K. Möller, *J. prakt. Chem.*, **109**, 124 (1925).

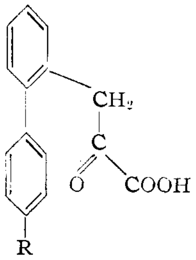
(6) Throughout this paper, R groups not otherwise designated are hydrogen.

(7) W. E. Bachmann, G. I. Fujimoto and L. B. Wick, THIS JOURNAL, **72**, 1995 (1950).

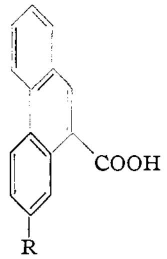
(8) *E.g.*, K. Fries, H. Herring, E. Hemmicken and G. Sichert, *Ann.*, **527**, 83 (1937); H. Lempert and R. Robinson, *J. Chem. Soc.*, 1419 (1934); P. Fritsch, *Ann.*, **286**, 1 (1895); R. Robinson and E. Schlittler, *J. Chem. Soc.*, 1288 (1935).

(9) M. S. Newman, H. V. Anderson and K. H. Takemura, THIS JOURNAL, **75**, 347 (1953).

acids[10] yielding an easily separable mixture containing 2-methoxyphenanthrene-9,10-dicarboxylic acid anhydride (VI) and 2-methoxyl-10-phenanthroic acid (XIX). This parallels the observations of Geissman and Tess[4] that the parent keto-ester I yielded some 9-phenanthroic acid (XVIII) in addition to the expected anhydride IV. Since none of the known[11] 2-methoxy-9-phenanthroic acid was obtained in the reaction, it seems quite certain that the phenanthroic acids XVIII and XIX do not arise from partial decarboxylation of the 9,10-dicarboxylic acids but, as suggested earlier,[12] are formed through the cyclization of (2-biphenylyl)-pyruvic acids (XVI, XVII).[13]



XVI
XVII, R = OCH_3



XVIII
XIX, R = OCH_3

The preparation of ethyl α-(3-methoxy-2-biphenylyl)-propionate (XV) was carried out starting with 2-(*m*-methoxyphenyl)-cyclohexanone (VIII). When XV was acylated with acetyl chloride, and the product treated with hydrobromic and acetic acids, a compound believed to be 3-methoxy-9,10-dimethylphenanthrene was obtained (as the picrate).

Experimental[14]

2-(*m*-Methoxyphenyl)-1-cyclohexenylacetic Acid (X).—In a three-necked flask, equipped with a stirrer and two reflux condensers, 87 g. of α-(*m*-methoxyphenyl)-cyclohexanone[7] in 400 ml. of benzene was placed, with 36 g. of well-cleaned zinc foil. After distilling a small quantity of the benzene to remove any traces of water, 85 g. of ethyl bromoacetate and a crystal of iodine were added. After the initial exothermic reaction, the mixture was refluxed for four hours. Dilute hydrochloric acid was added and the benzene layer separated and washed with water and sodium thiosulfate. The benzene solution was dried and concentrated and the residue distilled, b.p. 172–180° (3 mm.). The distillate (93 g.) was dissolved in 300 ml. of dry ether, 50 ml. of dry pyridine was added, and the mixture cooled to 5° while 50 g. of thionyl chloride was added in small portions. After the mixture had stood for an additional two hours at room temperature, water was added and the ethereal layer separated. The ether solution was concentrated and the residual oil was refluxed for one hour with 250 ml. of claisen alkali to which 100 ml. of methanol had been added. The alkaline solution was poured into an equal volume of ice-water and the resulting solution washed with ether. The aqueous layer was acidified and the resulting oil taken up in ether. Upon evaporation of the ether and distillation of the residue the desired acid X was obtained, b.p. 199–200° (3 mm.), n^{25}_{D} 1.5561, yield 50.9 g. (50%).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.24; H, 7.42.

From the ether used in washing the alkaline solution above, 12.3 g. of α-(*m*-methoxyphenyl)-cyclohexanone (identified by formation of the phenylhydrazone[7]) was isolated, making the yield of the acid X 55%, on the basis of ketone consumed.

Ethyl 2-(*m*-Methoxyphenyl)-1-cyclohexenylacetate.—The free acid (X, 50.9 g.) was esterified by refluxing with 500 ml. of absolute ethanol containing 8 ml. of sulfuric acid.

In addition to 4.7 g. of unchanged acid, 47.2 g. (93%) of a very viscous pale yellow oil, b.p. 170–172° (2–3 mm.), was obtained, n^{25}_{D} 1.5298.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.51; H, 8.14.

Ethyl (3′-Methoxy-2-biphenylyl)-acetate (XIII).—Dehydrogenation of 77.8 g. of ethyl 2-(*m*-methoxyphenyl)-1-cyclohexenyl acetate was effected by heating (225–235°) and stirring it with 18.2 g. of sulfur for three hours. The reaction mixture was then mixed with 200 ml. of benzene, 20 ml. of mercury was added and the whole vigorously stirred and refluxed for 34 hours. The mercury and mercury sulfide were filtered off, and the benzene evaporated. Distillation of the residue yielded 54.3 g. (72%) of a light yellow oil, b.p. 174–180° (2–3 mm.). The analytical sample boiled at 178° (3 mm.), n^{25}_{D} 1.5568.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.22; H, 6.66.

(3′-Methoxy-2-biphenylyl)-acetic Acid.—Hydrolysis of the above ester XIII was effected, in essentially quantitative yield, by refluxing it for three hours with claisen alkali. The white solid crystallized from petroleum ether (70–90°) as rhombic crystals, m.p. 85.5–86.5°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.34; H, 5.83. Found: C, 74.25; H, 6.11.

1-Methoxy- and 3-Methoxyphenanthrene-9,10-dicarboxylic Acid Anhydrides (V and VII).—Potassium ethoxide was prepared from 1.95 g. of potassium and 9.2 ml. of absolute ethanol in 150 ml. of anhydrous ether, and to this mixture 14.6 g. of diethyl oxalate was added. After 15 minutes, a solution of 13.5 g. of ethyl (3′-methoxy-2-biphenylyl)-acetate in 50 ml. of dry ether was added and the mixture refluxed for 51 hours. The reaction mixture was cooled, and extracted with 5% sodium hydroxide solution. The aqueous layer was saturated with carbon dioxide, and the precipitated oil taken up in ether. The residue obtained by evaporating the dried ether solution (10.6 g.) was crude diethyl α-keto-α'-(3-methoxy-2-biphenylyl)-succinate (II) which was used in subsequent experiments without purification. From the alkali-insoluble fraction, 4.2 g. of starting material XIII was recovered.

Cyclization of 5.9 g. of the keto-ester II was effected by stirring it vigorously with 30 ml. of 80% sulfuric acid for ten minutes on the steam-bath. By dilution of the reaction mixture with 300 ml. of water, 5.4 g. of dark yellow solid was obtained. This solid dissolved in 400 ml. of benzene leaving only a small quantity of a black residue. The benzene solution contained two isomeric compounds. The lower melting isomer, which was more abundant, was slightly less soluble in benzene and crystallized in fairly pure form from the dilute solution. When the lower melting compound no longer crystallized in pure form, the solvent was evaporated, and the residue taken up in glacial acetic acid. The higher melting compound crystallized from acetic acid in a fairly pure condition as a flocculent mass. When hard kernels of impure material began to form, the acetic acid was replaced by benzene. The alternation between solvents was continued until there was no residue left on evaporation. After a total of 37 crystallizations 2.36 g. of **3-methoxyphenanthrene-9,10-dicarboxylic acid anhydride** (V) was obtained as yellow needles, m.p. 221.5–222°.

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(10) The frequently reported inhibition of cyclization *meta* to a methoxyl group (*e.g.*, L. F. Fieser and C. K. Bradsher, THIS JOURNAL, **58**, 1738 (1936); G. Graves and R. Adams, *ibid.*, **45**, 2439 (1923); R. Jacobsen and R. Adams, *ibid.*, **45**, 2455 (1923); W. Johnson, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 120; P. Mitter and S. De, *J. Indian Chem. Soc.*, **16**, 35 (1939); G. Walsh and C. Weizmann, *J. Chem. Soc.*, **97**, 685 (1910); W. Koenigs and G. Jaegle, *Ber.*, **28**, 1046 (1895); W. Koenigs and A. Mengel, *ibid.*, **37**, 1322 (1904); E. Roberts and E. Turner, *J. Chem. Soc.*, 1832 (1927); E. Thielepape, *Ber.*, **55**, 127 (1922); W. S. Johnson and W. E. Shelberg, THIS JOURNAL, **67**, 1853 (1945); L. A. Wiles, *Chem. Revs.*, **56**, 329 (1956); J. E. Davies, F. E. King and J. C. Roberts, *Chemistry & Industry*, 1110 (1954)) was not observed in this case.

(11) R. P. Schorr, *Ber.*, **34**, 3998 (1901).

(12) C. K. Bradsher, *Chem. Revs.*, **38**, 477 (1946).

(13) It has been demonstrated that certain simple derivatives of XVI cyclize to yield 9-phenanthroic acid; C. K. Bradsher and R. S. Kittila, *J. Org. Chem.*, **15**, 374 (1950).

(14) All analyses are by Micro-Tech Laboratories, Skokie, Ill. All melting points are corrected.

Anal. Calcd. for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.58; H, 3.64.

In the same crystallization process, 0.89 g. of 1-methoxyphenanthrene-9,10-dicarboxylic acid anhydride as yellow needles, m.p. 235.5–236°, was obtained.

Anal. Calcd. for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.67; H, 3.63.

3-Methoxyphenanthrene.—Decarboxylation[9] of 300 mg. of 3-methoxyphenanthrene-9,10-dicarboxylic acid anhydride (V) was carried out by heating it for 30 minutes with 1.5 g. of barium hydroxide, 1.8 g. of iron filings and 0.1 g. of copper–bronze powder at 330–350° and 2 mm. pressure. The cooled residue was extracted with hot benzene, the benzene evaporated and the residue taken up in ethanol. To the ethanolic solution, a small quantity of picric acid in ethanol was added. Reddish needles, 97 mg., of a picrate, m.p. 124–125° (lit.[11] 124–125°), crystallized from the solution. The melting point of the picrate was not depressed by mixing with an authentic sample of the picrate of 3-methoxyphenanthrene.[15]

3-Hydroxyphenanthrene-9,10-dicarboxylic Acid Anhydride.—Ether cleavage of 3-methoxyphenanthrene-9,10-dicarboxylic acid anhydride (V) was accomplished by refluxing 0.3 g. for six hours in a solution containing 50 ml. of glacial acetic acid and 25 ml. of hydrobromic acid. The solid obtained by dilution and cooling of the reaction mixture was recrystallized from dioxane as yellow glistening plates, m.p. 395–396°, yield 265 mg. (92%).

Anal. Calcd. for $C_{16}H_8O_4$: C, 72.73; H, 3.05. Found: C, 72.41; H, 3.16.

Ethyl-2-(*p*-Methoxyphenyl)-cyclohexenyl-1-acetate.—The esterification of 2-(*p*-methoxyphenyl)-1-cyclohexenylacetic acid (XI)[7] was carried out essentially as in the case of the isomer X in a yield of 88%, b.p. 168–174° (2–3 mm.). The analytical sample, $n^{25}D$ 1.5303, was collected at 172° (2 mm.).

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.21; H, 7.93.

Ethyl (4′-Methoxy-2-biphenylyl)-acetate (XIV).—Dehydrogenation of 3.6 g. of ethyl 2-(*p*-methoxyphenyl)-1-cyclohexenylacetate with two equivalents of sulfur was carried out as in the preparation of the isomer XIII. Purified in the same way, it boiled at 166–170° (1 mm.), yield 1.9 g. (54%). The analytical sample boiled at 168° (1 mm.).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.25; H, 6.98.

2-(4′-Methoxy-2-biphenylyl)-acetic Acid.—Hydrolysis of 3.2 g. of the ethyl ester XIV above was effected by refluxing it for three hours with sodium hydroxide in ethanol–water; 96% yield. The analytical sample crystallized from benzene–ligroin as colorless blades, m.p. 108–109°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.56; H, 5.95.

Methyl (4′-Methoxy-2-biphenylyl)-acetate.—The acid (above) was esterified in methanol containing a small amount of sulfuric acid. The product, obtained in 91% yield, boiled at 146–147° (1 mm.), $n^{25}D$ 1.5768.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.82; H, 6.41.

2-Methoxyphenanthrene-9,10-dicarboxylic Acid Anhydride (VI) and 2-Methoxyphenanthrene-10-carboxylic Acid (XIX).—Condensation of 2.4 g. of methyl (4′-methoxy-2-biphenylyl)-acetate with 2.4 ml. of diethyl oxalate was carried out as in the case of the analog XIII except that refluxing was continued for a total of 91 hours. The acidic fraction yielded 2.9 g. of material (presumably like III) suitable for the cyclization reaction. The crude keto-ester (2.9 g.) was dissolved in 15 ml. of boiling acetic acid, and 10 ml. of 48% hydrobromic acid was added. Refluxing was continued for an additional ten minutes, and the greenish solid (1.5 g.) which separated was lixiviated with boiling glacial acetic acid. The monocarboxylic acid was more soluble and a partial separation could be effected. Separation was completed by evaporation of the acetic acid and solution of the residue in boiling 5% sodium hydroxide. When the cooled solution was acidified, a pale yellow precipitate was formed. This precipitate rapidly turned yellow-orange, presumably due to the loss of water from the dicarboxylic acid first formed. Dilute sodium hydroxide was then added to the precipitate, and the suspension filtered. In this manner, the 2 methoxyphenanthrene-9,10-dicarboxylic acid anhydride (total 0.4 g.) was collected and recrystallized from acetic acid as yellow needles, m.p. 274–275°.

Anal. Calcd. for $C_{17}H_{10}O_4$: C, 73.38; H, 3.68. Found: C, 73.31; H, 3.87.

By acidification of the alkaline filtrate 2-methoxyphenanthrene-10-carboxylic acid (total 0.9 g.) was obtained. It was crystallized from ethanol as pale yellow needles, m.p. 236–237°.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 75.88; H. 4.80.

α-(2-(*m*-Methoxyphenyl)-1-cyclohexenyl)-propionic Acid (XII).—A Reformatsky reaction was carried out, essentially as before, using 61.2 g. of 2-(*m*-methoxyphenyl)-cyclohexanone (VIII) and 72.4 g. of ethyl α-bromopropionate. The crude β-hydroxy acid (73.5 g.) was dehydrated by treatment with thionyl chloride followed by alkali, as in the case of the homolog X. The product was a pale yellow oil, b.p. 187–192° (2–3 mm.), yield 36.7 g.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.65; H, 8.09.

Since 14.1 g. of 2-(*m*-methoxyphenyl)-cyclohexanone was recovered from the reaction mixture, the yield based on the ketone VIII consumed was 60%.

Ethyl α-(2-(*m*-methoxyphenyl)-1-cyclohexenyl)-propionate was prepared by esterification of the acid XII using ethanol–benzene and sulfuric acid. The product was a pale yellow liquid, b.p. 168–172° (3–4 mm.), yield 94%. The analytical sample was collected at 171° (3 mm.), $n^{25}D$ 1.5250.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.53.

Ethyl α-(3′-Methoxy-2-biphenylyl)-propionate (XV).—Dehydrogenation of ethyl α-(2-(*m*-methoxyphenyl)-1-cyclohexenyl)-propionate was carried out and the product worked up as in the case of the analogs XIII and XIV. From 35.4 g. of the cyclohexenyl ester, 25.2 g. (72%) of an almost colorless liquid, b.p. 158–162° (2–3 mm.), was obtained. The analytical sample was collected at 161° (3 mm.), $n^{25}D$ 1.5479.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.00; H, 7.30.

Picrate of 3-Methoxy-9,10-dimethylphenanthrene.[16]—A solution of 2.84 g. of the ester XV in 25 ml. of anhydrous ether was added to 0.011 mole of sodium triphenylmethide[17] in 55 ml. of ether. After 25 minutes, 1 g. of purified[18] acetyl chloride, dissolved in 25 ml. of anhydrous ether, was added. After one-half hour, wet ether and then water were added to the reaction mixture. The ether layer was washed, dried over magnesium sulfate, and finally concentrated. The residue was taken up in 50 ml. of benzene and the solution concentrated to 25 ml. This was then added to a mixture of 50 ml. of dry benzene and 420 ml. of dry petroleum ether. The solution was passed through a 20-mm. column containing 70 g. of activated alumina. An additional 250 ml. of the same solvent mixture was passed through eluting 2.8 g. of triphenylmethane. Elution with 200 ml. of benzene yielded 1.1 g. of the starting ester and finally 150 ml. of absolute ethanol was used to elute the keto-ester. This material (0.8 g.) was refluxed for ten minutes with equal volumes of acetic and 48% hydrobromic acids. The reaction mixture was cooled, diluted, and the product taken up in ether. The ethereal solution was washed, dried and evaporated, and the residue taken up in ethanol. Addition of an ethanolic solution of picric acid precipitated red needles, m.p. 157–159°. The analytical sample melted at 159–160°.

Anal. Calcd. for $C_{23}H_{19}O_7N_3$: C, 61.47; H, 4.26. Found: C, 61.22; H, 4.15.

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[15] A. Werner, *Ann.*, **321**, 276 (1902).

[16] While this is the most probable structure for this compound, there is a slight possibility that it is the picrate of the isomeric 1-methoxy-9,10-dimethylphenanthrene.

[17] W. B. Renfrow and C. R. Hauser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 609 (note 3).

[18] L. F. Fieser, "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 380.