[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Mechanism of the Stobbe Condensation

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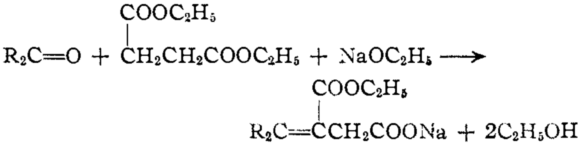
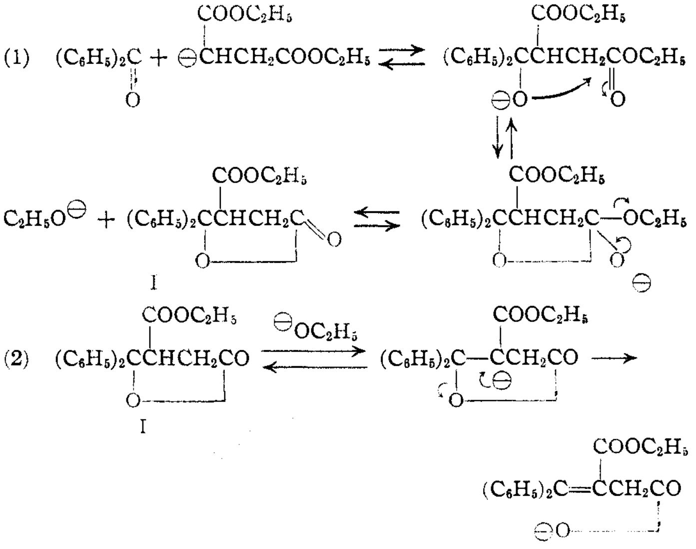
In 1893 Hans Stobbe[1] demonstrated that when acetone and diethyl succinate were treated with sodium ethoxide, the expected product of an acetoacetic ester type of condensation was not obtained, but instead teraconic acid, $(CH_3)_2C{=}C(COOH)CH_2COOH$, was produced by an aldol type of condensation between the carbonyl group of the ketone and an α-methylene group of the ester. This reaction was indeed surprising in view of the numerous precedents from the work of Claisen for the former type of behavior. Stobbe and his collaborators, therefore, undertook an extensive study which revealed that both aldehydes and ketones generally condense with succinic esters in this special manner. One mole of alkoxide is required for each of ketone and ester, and the primary product is the salt of the half-ester, *i. e.*



$$R_2C{=}O + \overset{COOC_2H_5}{CH_2}CH_2COOC_2H_5 + NaOC_2H_5 \longrightarrow R_2C{=}\overset{COOC_2H_5}{C}CH_2COONa + 2C_2H_5OH$$

In his early work Stobbe postulated that this unusual behavior of succinic ester might be attributable to the formation of an intermediary paraconic ester (I). Since then considerable evidence has accumulated confirming this view and the purpose of the present communication is to summarize the available data, and to present new evidence in support of the paraconic ester mechanism.

It is striking that this strong susceptibility to undergo an aldol type of condensation with ketones is limited almost exclusively to esters of the succinic acid type. While benzophenone, thus, condenses with diethyl succinate to give crystalline β-carbethoxy-γ,γ-diphenylvinylacetic acid, $(C_6H_5)_2C{=}C(COOC_2H_5)CH_2COOH$, in 90% yield,[2] under the same conditions this ketone failed altogether to react with ethyl or *t*-butyl acetate. That the success of the Stobbe condensation is not attributable solely to a high reactivity of the α-methylene groups of succinic ester, is demonstrated by the failure of diethyl malonate with its even more reactive α-methylene group to condense to any appreciable extent with benzophenone under comparable conditions.[3] The specificity of succinic esters in this reaction may possibly be associated with the juxtaposition of a carbethoxyl group for easy ring formation by reaction at the center of aldol addition as indicated in reaction sequence (1). The postulation of an intermediary paraconic ester (I)[4] is reasonable in view of the fact that such substances have been isolated particularly when shorter reaction periods were employed (see below), and that paraconic esters are cleaved by alkoxides in excellent yield to salts of the unsaturated half-esters.[5] This cleavage, a β-elimination, may be represented by reaction sequence (2) and the combined steps (1) and (2) thus constitute a satisfactory rationalization of the course of the Stobbe condensation, the irreversibility of the second step driving the reaction to completion.



The more obvious mechanism involving the postulation of an intermediary unsaturated di-ester—*i. e.*, the ketone first condenses with the succinate eliminating water which then reacts with the alkoxide to form hydroxide, this in turn effecting partial saponification of the di-ester—is not tenable in view of (1) the failure to isolate any such unsaturated ester even when a large excess of diethyl succinate was employed in the condensa-

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* Harvard University Ph.D. 1940.

(1) Stobbe, *Ber.*, **26**, 2312 (1893).

(2) Johnson, Petersen and Schneider, THIS JOURNAL, **69**, 74 (1947).

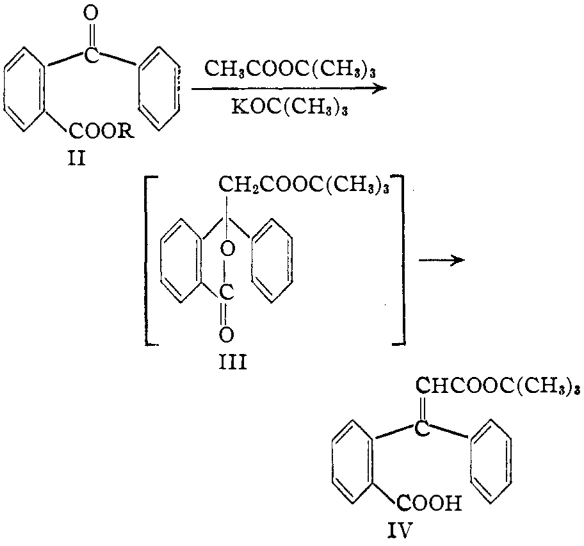
(3) With the even more reactive ethyl cyanoacetate, condensation with benzophenone is realized to the extent of 66% in the presence of ammonium acetate and acetic acid, a catalyst which does not promote the condensation of diethyl malonate at all; Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

(4) Stobbe, *Ann.*, **282**, 280 (1894).

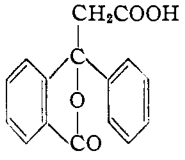
(5) Roser, *ibid.*, **220**, 258 (1883); Fittig, *ibid.*, **256**, 50 (1890); Fittig, *Ber.*, **27**, 2681 (1894).

tion thus affording a highly competitive source of ester groups to react with the limited amount of hydroxide[6]; (2) the failure of other esters with comparably reactive methylene groups to condense readily (see above); (3) the failure of partial saponification of the appropriate unsaturated di-ester to give a good yield of half-ester,[7,8] and (4) the fact that isomers of the citraconic and mesaconic acid type, which would be expected tautomers of certain alkylidenesuccinic di-esters,[9] have never been found as products of the Stobbe condensation.

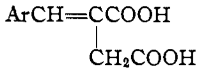
The importance of an appropriately situated carbalkoxyl group is strikingly illustrated by the experiments with *o*-benzoylbenzoate (II) described in the present paper. This ester condensed readily with *t*-butyl acetate in the presence of sodium hydride[10] or potassium *t*-butoxide to give the crystalline half-ester IV, m.p. 180°. The methyl, ethyl and *t*-butyl esters (II, R = CH_3, C_2H_5 or *t*-C_4H_9) were used, the best yields (64%) being obtained with the last. Since the condensation fails without the COOR group (the case of benzophenone), the participation of an intermediary lactone ester III is suggested. It seems unlikely that the effect of the carbalkoxy group is to so activate the keto groups that the condensation proceeds without participation.



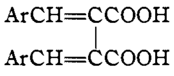
The structure of the condensation product IV was confirmed by the following experiments. On heating in benzene solution with a trace of *p*-toluenesulfonic acid,[11] isobutylene was lost readily giving the crystalline dibasic acid corresponding to IV. More vigorous treatment with hot hydrobromic–acetic acid mixture effected further reaction involving lactonization, and the product, V, proved to be identical with material prepared from II (R = C_2H_5) by the Reformatsky reaction with methyl α-bromoacetate. It is noteworthy that the Reformatsky reaction gave very poor yields compared with the new method involving the aldol type of condensation.


V

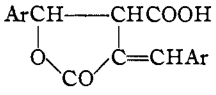
The behavior of piperonaldehyde in the Stobbe condensation with diethyl succinate affords further support for the paraconic ester mechanism. When the reaction was carried out in refluxing ethanol, piperonylidenesuccinic acid VI was obtained in 90% yield.[12] At low temperature (−10 to 0°), however, the condensation of two moles of aldehyde with one of ester is favored, and yields as high as 36% of the dipiperonylidenesuccinic acid VII were realized.[13] By the use of short reaction periods in addition to low temperatures the lactonic acid VIII was isolated in yields as high as 30%[14] and it was clearly demonstrated moreover that the proportion of dibasic acid VII to lactone acid VIII was higher with longer reaction periods. This behavior suggests that the condensation of the second molecule of aldehyde occurs with an intermediary paraconic ester IX which would have a longer life at lower temperatures, higher temperatures promoting conversion to the half-ester salt which would not be expected to condense further because of the less reactive methylene group. It is possible that a dilactone is the primary product of the condensation with IX.

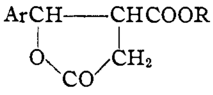

$\mathrm{ArCH{=}C(COOH)CH_2COOH}$

VI


$\mathrm{ArCH{=}C(COOH)\text{–}C(COOH){=}CHAr}$

VII


VIII


IX

The structures proposed for the lactonic acids obtained by the condensation of cuminaldehyde with diethyl isopropylidenesuccinate,[15] of fluorenone with diethyl phenylitaconate,[16] and of benzophenone with diethyl phenylitaconate,[17] are not those expected from the mechanism advanced

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[6] See for example Johnson and Miller, THIS JOURNAL, **72**, 511 (1950).

[7] Stobbe, *Ber.*, **41**, 4350 (1908).

[8] Johnson and Johnson, unpublished observation; Johnson and Goldman, THIS JOURNAL, **66**, 1030 (1944); Johnson and Graber, *ibid.*, **72**, Feb. (1950).

[9] *Cf.* Coulson and Kon, *J. Chem. Soc.*, 2568 (1932).

[10] *Cf.* Daub and Johnson, THIS JOURNAL, **72**, 501 (1950).

[11] *Cf.* Breslow, Baumgarten and Hauser, *ibid.*, **66**, 1286 (1944).

[12] Cornforth, Hughes and Lions, *J. Proc. Roy. Soc.*, *N. S. Wales*, **72**, 228 (1939).

[13] Haworth and Woodcock, *J. Chem. Soc.*, 1985 (1938).

[14] Stobbe, Vieweg, Eckert and Reddelien, *Ann.*, **380**, 78 (1911).

[15] Stobbe and Leuner, *Ber.*, **38**, 3897 (1905).

[16] Stobbe, Badenhausen, Hennicke and Wahl, *Ann.*, **380**, 120 (1911).

[17] Stobbe and Badenhausen, *Ber.*, **39**, 769 (1906).

above. The evidence for these structures, however, is inconclusive and further study is indicated.

Diethyl glutarate might be expected to react like the lower homolog in a Stobbe type of condensation, since it too should give rise to an aldol intermediate capable of lactonization. Surprisingly we have found that this ester is relatively unreactive, which may possibly be due to a sufficiently lower susceptibility to formation of the δ- in comparison with γ-lactone ring so that competing reactions such as self-condensation take precedence. Diethyl glutarate, thus, failed to condense to any appreciable extent with benzophenone under those conditions which promoted condensation with succinate in 90% yield.[2] When di-*t*-butyl glutarate was substituted for the diethyl ester with the hope of inhibiting self-condensation, the half-ester, $(C_6H_5)_2C{=}C(COO\text{-}t\text{-}C_4H_9)CH_2CH_2COOH$, was indeed obtained, but in poor yield. With ketones containing a reactive methylene group diethyl glutarate reacted preferentially by an acetoacetic ester type of condensation.[18,19]

Experimental[20]

***t*-Butyl Acetate**.—This substance was prepared conveniently by a modification of the procedure of Altschul.[21] Although the yield is lower, the new procedure is somewhat simplified in that no solvent is employed, the reaction being conducted in a pressure bottle. To 26 g. of glacial acetic acid and 2 ml. of concentrated sulfuric acid contained in a 500-ml. Pyrex pressure bottle was added 50 g. of liquefied (by passage through a dry-ice trap) isobutylene. The bottle was stoppered, allowed to stand at room temperature overnight, chilled in an ice-salt-bath, opened, and poured into a cold solution of 40 g. of sodium hydroxide in 500 ml. of water containing ice. The organic layer was separated, washed with dilute sodium hydroxide and dried over anhydrous potassium carbonate. Distillation through a 6-inch Vigreux column gave 26.5 g. of *t*-butyl acetate, b. p. 94-97° at 738 mm., n^{25}_D 1.3820 (reported n^{25}_D 1.3838).[22]

***t*-Butyl *o*-Benzoylbenzoate**. (*a*) *By Ester-Exchange*.—Two grams of ethyl *o*-benzoylbenzoate,[23] m. p. 56–58°, was added to a solution of 1 g. of potassium in 75 ml. of dry *t*-butyl alcohol and the mixture was boiled under reflux for forty-five minutes. After chilling the solution was diluted with water and ice. Upon stirring the ester solidified and was separated by filtration; yield, 1.40 g. (63%); m. p. 64–68°. Recrystallization from petroleum ether (40–60°) gave colorless prisms, m. p. 68–69.2°. Further recrystallization did not raise the m. p.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.33; H, 6.47.

(*b*) *By the Isobutylene Method*.—A solution of 10.00 g. of *o*-benzoylbenzoic acid,[23] m. p. 127–129°, in 70 ml. of ether containing 1 ml. of concentrated sulfuric acid was treated with 100 g. of liquid isobutylene in a 500-ml. pressure bottle as described above for the preparation of *t*-butyl acetate. After the alkali treatment the ether layer was dried over anhydrous potassium carbonate. Evaporation of the ether gave 8.81 g. (70% yield) of fairly pure colorless ester, m. p. 66–70°.

Pseudo *t*-Butyl *o*-Benzoylbenzoate.—In order to demonstrate that the ester prepared above was indeed the normal product, the pseudo ester was prepared by an established method.[24]

The chloride prepared from 5.00 g. of *o*-benzoylbenzoic acid[23] and 15 ml. of thionyl chloride was treated in the cold with 25 ml. each of pyridine and *t*-butyl alcohol. After several days at room temperature, excess cold dilute hydrochloric acid and ether were added. The ether layer was separated, washed thoroughly with saturated sodium bicarbonate solution and dried over anhydrous potassium carbonate. Evaporation of the ether gave 3.70 g. (59% yield) of crude pseudo ester, m. p. 80–84°, which after repeated recrystallization from petroleum ether (60–68°) was obtained as colorless prisms, m. p. 92.6–94.2°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.93; H, 6.25.

Condensation of *t*-Butyl Acetate with Alkyl *o*-Benzoylbenzoates.—Sodium hydride (0.59 g.) was added to a solution of 3.10 g. of *t*-butyl *o*-benzoylbenzoate, m. p. 66–69°, in 25 ml. of dry benzene contained in a 3-necked round-bottomed flask equipped with a rubber slip-sealed Hershberg wire stirrer, a condenser and dropping funnel. The flask was immersed in an oil-bath at 80° and a mixture of 25 ml. of *t*-butyl acetate and 2 ml. of dry *t*-butyl alcohol was added dropwise over a period of one hour with stirring. After heating for an additional four hours the dark reaction mixture was chilled, and 3 ml. of acetic acid was added followed by about 0.5 ml. of concentrated hydrochloric acid. Ether and water were added, the layers separated, and the organic layer extracted with successive 50-ml. portions of 2% sodium bicarbonate solution until the amounts of acidic material being removed, as determined qualitatively by the precipitate obtained on acidification, began to diminish. The total material in these extracts amounted to 0.66 g. of oily product which probably consisted mainly of *o*-benzoylbenzoic acid. The organic layer was next washed thoroughly with portions of 5% potassium carbonate solution. Acidification of these extracts gave 2.30 g. (64% yield) of crude, tan, crystalline ***t*-butyl β-(*o*-carboxyphenyl)-cinnamate** (IV), m. p. 170–175°. A sample after repeated recrystallization from petroleum ether (90–100°) was obtained as colorless needles, m. p. 175.5–177°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22; neut. equiv., 324.4. Found: C, 74.04; H, 6.15; neut. equiv., 327.8.

When the condensation was carried out with ethyl and with methyl *o*-benzoylbenzoate[23] essentially as described above, the crude half-ester IV was produced in 56% (m. p. 160–165°) and 55% (m. p. 158–160°) yields, respectively. The condensation of *t*-butyl acetate and ethyl *o*-benzoylbenzoate was also carried out with potassium *t*-butoxide in *t*-butyl alcohol according to the procedure for the modified Stobbe condensation,[2] and afforded the crude half-ester, m. p. 158–160° in 40% yield. The remainder of the material was accounted for as *o*-benzoylbenzoic acid except for a 5% yield of *t*-butyl *o*-benzoylbenzoate which was found in the neutral fraction. It was from this discovery that the procedure described above for the preparation of *t*-butyl ester by ester-exchange was developed.

When an attempt was made to effect condensation between benzophenone and *t*-butyl acetate by the potassium *t*-butoxide method, the ketone was recovered in practically quantitative yield. The starting ketone was similarly essentially completely recovered in attempts to bring about condensation between benzophenone and diethyl malonate either with potassium *t*-butoxide in *t*-butyl alcohol or with sodium ethoxide in ethanol.

β-(*o*-Carboxyphenyl)-cinnamic Acid.—A solution of 2.135 g. of the *t*-butyl ester IV and 0.1 g. of *p*-toluenesulfonic acid in 20 ml. of dry benzene was boiled under reflux for one hour during which isobutylene was evolved and the

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[18] Robinson and Seijo, *J. Chem. Soc.*, 582 (1941).

[19] Johnson, Johnson and Petersen, THIS JOURNAL, **67**, 1360 (1945).

[20] All melting points are corrected.

[21] Altschul, *ibid.*, **68**, 2605 (1946).

[22] Norris and Rigby, *ibid.*, **54**, 2088 (1932).

[23] *o*-Benzoylbenzoic acid was prepared by the method of Fieser, "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Company, New York, N. Y., 1941, p. 183. The methyl and ethyl esters were obtained by direct esterification; *cf. idem.*, *ibid.*, p. 65.

[24] Newman and McCleary, THIS JOURNAL, **63**, 1537 (1941).

dibasic acid gradually precipitated from the hot solution. This product amounted to 1.705 g. (96% yield) of colorless crystals, m. p. 194–198°. After two recrystallizations from isopropyl alcohol the acid was obtained as small colorless prisms, m. p. 196.5–199°.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51; neut. equiv., 134.1. Found: C, 71.18; H, 4.73; neut. equiv., 132.5.

3-Phenylphthalide-3-acetic Acid (V). (*a*) *From t-Butyl β-(o-Carboxyphenyl)-cinnamate.*—A solution of 0.670 g. of the half-ester in 20 ml. of a solution of 48% hydrobromic acid, acetic acid and water in the ratio of 2:6:3 by volume was boiled under reflux for one hour. The solvents were evaporated at the steam-bath in a current of air and the residue dissolved in excess saturated sodium bicarbonate. The solution was filtered and acidified with hydrochloric acid to give 0.504 g. (91% yield) of colorless lactone acid, m. p. 175–179°. A sample purified by repeated recrystallization from benzene–petroleum ether (90–100°) was obtained as colorless needles, m. p. 179–181°.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51; neut. equiv., 268.3. Found: C, 71.71; H, 4.48; neut. equiv., 268.0.

(*b*) *From β-(o-Carboxyphenyl)-cinnamic Acid.*—A 0.215-g. sample of the dibasic acid was heated with 10 ml. of the acid reagent described above (part *a*) until all of the suspended solid had dissolved (thirty minutes). The product was worked up as described above to give 0.202 g. (94% yield) of colorless lactone acid, m. p. 178–180°, undepressed on admixture with the material prepared from the half-ester (see above).

(*c*) *By the Reformatsky Reaction with Ethyl o-Benzoylbenzoate.*—According to a general procedure,[25] activated zinc foil (1 g.), methyl bromoacetate (2 ml.) and a crystal of iodine were added to a solution of 2.10 g. of ethyl *o*-benzoylbenzoate in 15 ml. of dry benzene. The mixture was boiled under reflux for two and one-half hours, then an additional charge of zinc (1 g.) with a crystal of iodine was added and heating continued for another one and one-half hours. The mixture was cooled, acidified with hydrochloric acid, and the product worked up in the conventional manner by saponification with dilute methanolic potassium hydroxide. The crude dark acidic material was shown to contain considerable *o*-benzoylbenzoic acid which could be removed most readily by trituration with hot benzene. The remaining insoluble material (possibly the hydroxy dibasic acid) was warmed with 5 ml. of 48% hydrobromic acid on the steam-bath until the mineral acid evaporated. The residue was crystallized from benzene–petroleum ether (90–100°) giving 0.15 g. of material, m. p. 177–180°, undepressed on admixture with the lactone acid described above (part *a*).

δ,δ-Diphenyl-γ-carbo-*t*-butoxyallylacetic Acid.—To a cooled solution of 5.04 g. of potassium in 75 ml. of dry *t*-butyl alcohol was added 14.56 g. of benzophenone and 27.36 g. of di-*t*-butyl glutarate, b. p. 124–126° (13 mm.).[26] The system was evacuated, filled with nitrogen and heated under reflux for one and one-half hours. Most of the alcohol was distilled off at reduced pressure and the residue acidified with dilute hydrochloric acid and extracted with ether. The ether layer was washed thoroughly with 5% sodium bicarbonate solution which yielded on acidification 0.56 g. of dark brown intractable oil. The ether solution was then washed thoroughly with 5% potassium carbonate solution, which gave after acidification, 2.90 g. (10% yield) of crude crystalline half-ester, m. p. 108–114°. Repeated recrystallization from benzene–petroleum ether (40–60°) gave colorless crystals m. p. 127–127.5°. No attempt was made to improve the yield.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86; neut. equiv., 352.4. Found: C, 74.78; H, 6.91; neut. equiv., 356.4.

Summary

Esters of *o*-benzoylbenzoic acid have been shown to condense with *t*-butyl acetate by an aldol type of reaction involving the keto group of the keto ester and the α-hydrogen atoms of the acetate. Since the less hindered keto group of benzophenone fails to condense with *t*-butyl acetate under the same conditions (alkoxide), it is concluded that the *o*-carbalkoxy group influences the course of the reaction by participating in the formation of an intermediary γ-lactone ring which is subsequently opened by an alkoxide-catalyzed, β-elimination to give the salt of the half-ester, *o*-HOOC-$C_6H_4C(C_6H_5)=CHCOOC(CH_3)_3$. The product of the condensation was proved to have this structure by its chemical behavior.

This discovery lends support to the postulation of an analogous intermediary γ-lactonic ester in the Stobbe condensation of a ketone or aldehyde with succinic esters. Other evidence in support of such a mechanism is reviewed.

Di-*t*-butyl glutarate and benzophenone have been shown to undergo a Stobbe type of condensation, but in poor yield.

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[25] Shriner in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 18.

[26] Prepared by the method of Backer and Homan, *Rec. trav. chim.*, **58**, 1048 (1939).