3-Methyl-1-phenyl-4-phenylhydrazono-5-pyrazolone. Following the procedure of Buchka and Sprague,[6] 1.3 g. of α-bromoacetoacetic ester gave 1.5 g. (50%) of the pyrazolone derivative: m. p. 154° (Buchka and Sprague[6] reported the m. p. at 157°).

Chlorination of Ketene Dimer.—In a flask protected against atmospheric moisture there was placed a solution of 8.4 g. (0.1 mole) of ketene dimer in 100 cc. of chloroform, a solution of 23.8 g. (0.1 mole) of N,2,4-trichloroacetanilide in 200 cc. of chloroform was added, and the mixture refluxed for twenty hours. The reaction mixture was then reduced to a volume of 150 cc., cooled in an ice–salt-bath, the precipitated 2,4-dichloroacetanilide filtered, and 4.6 cc. of absolute alcohol added to the chloroform solution. This mixture was then refluxed for six hours, concentrated to 50 cc., and again cooled to precipitate additional dichloroacetanilide. The liquid residue was then fractionated under reduced pressure giving 6.0 g. (35% based on ketene dimer) of α-chloroacetoacetic ester: b. p. 100–110° (25 mm.).

This chloroester was characterized in the same manner as described for α-bromoacetoacetic ester: ethyl 2-amino-4-methylthiazole-5-carboxylate, m. p. 172–173°; 3-methyl-1-phenyl-4-phenylhydrazono-5-pyrazolone, m. p. 155–157°.

Summary

Chemical evidence, based on halogenation of the allyl position, is presented in support of that lactone structure for ketene dimer which has the exocyclic carbon–carbon double bond.

ITHACA, N. Y. RECEIVED JUNE 6, 1947

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

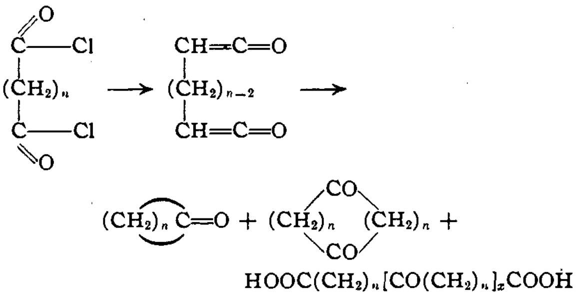
Many-membered Carbon Rings. I. Cyclization of Some Bifunctional Ketenes[1]

BY A. T. BLOMQUIST AND R. D. SPENCER[2]

In the course of investigations in this Laboratory with respect to certain derivatives of many-membered carbon rings it was decided to investigate the possibilities of a new method of cyclization involving bifunctional ketenes. Sauer[3] in his investigation of ketene dimers from acid halides observed that the bifunctional ketene derived from adipyl chloride gave a 40% yield of α-carbethoxycyclopentanone when treated with ethyl alcohol while sebacyl chloride yielded only a polymeric ketene derivative with no evidence of the formation of cyclic compounds. In these experiments no attempt was made to achieve significantly greater dilution than that employed in the preparation of monofunctional ketene dimers. Ziegler[4] and subsequently Hunsdiecker[5] have shown that high dilution is essential for the formation of many-membered rings in satisfactory yields by their methods. Ruzicka's method[6] was not adaptable to the application of the dilution principle and, consequently, the yields of the larger rings formed by his method were quite low.

We reported in a recent communication[7] the results obtained when the dilution principle was applied to the formation of the bifunctional ketene prepared from sebacyl chloride by dehydrohalogenation with triethylamine. There was some evidence for the formation of traces of cyclononanone as a product of the reaction, but none was isolated. A 16% yield of crude 1,10-cycloöctadecanedione was obtained. We have now prepared cycloheptanone and 1,8-cyclotetradecanedione from suberic acid as well as cyclopentadecanone and 1,16-cyclotriacontanedione from thapsic acid.

The following general equation indicates the products obtained upon hydrolysis and decarboxylation of the ketene derivatives without making any attempt to show the structure of these intermediates themselves. The structure of ketene dimer and the aldoketene dimers is still a controversial issue.[8,9]



In the course of the cyclization reaction much ketene polymer is formed. Part of this is ether insoluble and remains with the triethylamine hydrochloride. The ether soluble polymeric material is easily separable from the desired cyclic products after the mixture has been hydrated and decarboxylated with alcoholic potassium hydroxide. Presumably the polymers afford polyketodibasic acids which are soluble in aqueous alkali.

The original experimental procedure has been

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(1) Abstracted from a dissertation submitted by R. D. Spencer in June, 1947, to the Graduate Faculty of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) du Pont Postgraduate Fellow in Chemistry, 1946–1947.

(3) Sauer, THIS JOURNAL, **69**, 2444 (1947).

(4) Ziegler, Eberle and Ohlinger, *Ann.*, **504**, 94–130 (1933), and succeeding papers by Ziegler and his co-workers.

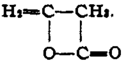
(5) Hunsdiecker, *Ber.*, **75B**, 1190–1197 (1942), and succeeding papers.

(6) Stoll and Rouve, *Helv. Chim. Acta*, **27**, 1570–1583 (1944).

(7) Blomquist and Spencer, THIS JOURNAL, **69**, 472 (1947).

(8) Hanford and Sauer, "Organic Reactions," John Wiley and Sons, New York, Vol. III, 1946, pp. 127–128.

(9) Recent work in this Laboratory, *cf.* Blomquist and Baldwin, THIS JOURNAL, **69**, 29 (1947), supports the following structure for ketene dimer



$CH_2=C—CH_2$, $O—C=O$.

simplified by using crude acid chlorides.[10] Traces of thionyl chloride have no apparent effect on the reaction but the presence of larger amounts are undesirable.

Three tertiary amines have been tried as the dehydrohalogenating and condensing agents. Triethylamine gave the best yields, even though it was possible to achieve considerably greater dilution with N-ethylpiperidine by using apparatus (B) (see Experimental). Tributylamine of uncertain purity gave negative results in a cyclization of sebacyl chloride. However, even with carefully purified tributylamine, low yields of the desired product were obtained with pelargonyl chloride and with the crude acid chloride from lauric acid and thionyl chloride.

A second approach to the problem of formation of macrocyclic ketene dimers is under study at the present time. It is known that several keto- and aldoketene dimers can be reconverted to the monomers by heat.[11] On the other hand, Sauer has reported[3] that the ketene derivative obtained from adipyl chloride resinified when its distillation was attempted. An analogous observation was made by Hill and Carothers,[12] when they attempted to depolymerize a linear polyanhydride (sebacic "α-anhydride") by heating it under greatly diminished pressure in a Claisen flask; but, by molecular distillation at 200°, they obtained a twenty-two-membered cyclic dimer. Preliminary experiments in this Laboratory on the ketene polymer from sebacyl chloride indicate that it does indeed depolymerize on heating. The results of these investigations will be the subject of a future communication. In addition to the high temperature depolymerization there is some evidence that the "dimerization" reaction is reversible or, possibly, that a further condensation of some sort occurs even at the temperature of refluxing ether.

Comparison to Other Methods of Formation of Large Ring Ketones

In the cyclization step the yields of large ring ketones by the ketene method are generally superior to those of Ruzicka, but inferior to those of Ziegler and Hunsdiecker. The discrepancy is not so great, however, when the over-all yields are compared, since the synthesis of dibasic acids generally involves fewer steps than do the syntheses of the corresponding nitriles and ω-iodo-β-keto-esters. The lower yields obtained by the ketene method are probably due very largely to the lower dilution employed. It is shown in the experimental section that an increase in the reaction time during the cyclization step has the effect of materially reducing the yield. This phenomenon could be caused either by reversibility of the ketene dimerization reaction in the presence of the catalyst or by a further condensation of the dimer. The authors favor the first explanation and experiments are under way to test this theory. It can readily be seen that if the dimerization reaction is appreciably reversible under the conditions of the cyclization, a point of diminishing returns may be reached. At this point the cyclic dimers open up and react with the linear ketene polymer (present in solution in ever-increasing concentration) more rapidly than they are formed by the intramolecular condensation of the monomer. Consequently, with this in mind, it was necessary to avoid prolonging the reaction time. This was accomplished partly by making small runs, but, nevertheless, the advantages of extremely high dilution had to be sacrificed.

The ketene method is surpassed in convenience only by that of Ruzicka. The necessity of maintaining rigorously anhydrous conditions makes the ketene method somewhat more tedious. However, this inconvenience is offset by the greater ease of separating the cyclic ketones from the accompanying by-products. In this respect the ketene method far surpasses the other three. Although the cyclic diketones have been somewhat difficult to purify (possibly because of the presence of small amounts of the cyclic tri- and polyketones), the cyclic monoketones have been obtained in a relatively high state of purity after simple vacuum distillation.

Experimental[13]

Materials.—The thionyl chloride used in the cyclization step was carefully purified.[14] Commercial anhydrous ether was further purified by distillation from an ether solution of *n*-butylmagnesium bromide. A good grade of commercial triethylamine was purified by drying over potassium hydroxide pellets, refluxing over successive portions of sodium wire until a fresh portion retained its luster and, finally, fractioning it from the sodium wire through a 50-cm., vacuum-jacketed column packed with glass helices. The main fraction boiled at constant temperature. It was stored in a glass-stoppered bottle over sodium wire. N-Ethylpiperidine was prepared from piperidine by alkylation with ethyl iodide, and freed from the secondary amine by treatment with benzoyl chloride followed by fractional distillation. It was stored over sodium wire in the dark, but after about a month it had become light yellow in color.

The sebacyl chloride used in these experiments was prepared from commercial acid which had been purified through the ethyl ester. The suberic acid was from old Kahlbaum stock, m. p. 139.5–141°. The thapsic acid was prepared by the saponification of dimethyl thapsate.[15]

Apparatus.—(A) The apparatus which gave the most satisfactory results was very unpretentious. A one-liter, three-necked flask with ground joints was used. When in operation one neck was stoppered with a glass stopper. In the center neck was an efficient, all-glass stirrer equipped with a small condenser which effectively prevented the ether from distilling up into the mercury seal during the long periods of continuous operation. To the third neck was attached, by means of a bent adapter tube, a 30-cm. bulb condenser. The adapter was used simply to place the

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[10] This was first tried in the preparation of civetone. Blomquist, Holley and Spencer, THIS JOURNAL, 70, 34 (1948).

[11] Ref. 8, p. 119.

[12] Hill and Carothers, THIS JOURNAL, 54, 1574 (1932).

[13] Boiling points are uncorrected. Melting points are corrected.

[14] "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, New York, 1943, p. 570.

[15] This ester was prepared by Mr. George Kossel by electrolysis of methyl hydrogen azelate.

TABLE I

SUMMARY OF PROPERTIES OF CYCLIC KETONES

Cyclic ketone	M. p., °C. Found[a]	M. p., °C. Reported	B. p., °C. Found[b]	B. p., °C. Reported	M. p. semicarbazone, °C. Found[a]	M. p. semicarbazone, °C. Reported	M. p. oxime, °C. Found[a]	M. p. oxime, °C. Reported	Yield of cyclic ketone, %
Cycloheptanone			176[c]	179–180[d]	163.5–164.5	163–164[d]	Not prepd.	23[d]	33
1,8-Cyclotetradecanedione[e]	147.5–148				261 dec.		234–235 dec.		10
1,10-Cycloöctadecanedione	96–97	96–97[f]			225–227 dec.[g]	>230 dec.[f]	163–165[g]	166–168[f]	16[h]
Cyclopentadecanone	Not detd.	63[i]	107–108[j]	*ca.* 120[i,k]	190.5–191.5	187–188[i]			14–20
1,16-Cyclotriacontanedione	77–78	74–75[l]			216.5–219	218–219[l]	144.5–145.5	141–142[m]	1.3–5.3

[a] Melting points are corrected. [b] Boiling points are uncorrected. [c] At 735 mm. [d] Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1934. [e] Not previously reported. [f] Ruzicka, *et al.*, *Helv. Chim. Acta*, 11, 506 (1928). [g] Ref. 7. [h] This yield is on once-crystallized diketone. The crude yield was 22.5%. [i] Ref. 21. [j] At 0.25 mm. [k] At 0.3 mm. [l] Ref. 20. [m] Ruzicka, *et al.*, *Helv. Chim. Acta*, 16, 1342 (1933).

condenser and the dropping funnel at a convenient distance from the stirring motor. At the top of the condenser, by means of a well-rolled cork, was attached a U-tube bearing a calcium chloride drying tube and a Hershberg–Hinman dropping funnel.[16] The dropping funnel was protected with a calcium chloride tube.

(B) A more complicated cyclization apparatus was devised in which ether was distilled from the reaction flask through a short fractionating column and condensed into a second flask where it was used to further dilute the solution of the acid chloride before eventually returning to the reaction flask. It was estimated that fifty-fold dilution was easily realized by this arrangement. However, triethylamine distilled too readily with the ether despite the fractionation employed and, consequently, could not be used successfully as the condensing agent with this apparatus. A condensing agent of higher molecular weight, N-ethylpiperidine, although it did not distil appreciably with the ether (of the order of one part of amine per one hundred thousand parts of ether)[17] gave a much lower yield than that obtained when triethylamine was used in apparatus (A).

(C) When the simplified Ziegler apparatus[18] was used, with triethylamine and three times as much ether in the reaction flask, there was troublesome clogging of the dropping funnel and the yield was not improved over (A). The clogging was probably due to the greater ease of diffusion of triethylamine vapor to the funnel tip, with consequent formation of the hydrochloride in the capillary.

General Procedure.—A cyclization run is conveniently made with from 3–5 g. of dibasic acid or a correspondingly larger amount of the bifunctional acid chloride. If the acid is used it is first converted to the crude acid chloride by the following procedure. To the acid is added one and one-half to two times the theoretical amount of purified thionyl chloride.[19] The mixture is heated in a water-bath maintained at about 55° for two hours and is then heated on the steam-bath until evolution of hydrogen chloride and sulfur dioxide has ceased. This usually requires from one to three hours longer. When the reaction is complete the excess thionyl chloride is removed as completely as possible without subjecting the acid chloride to excessive heating. This is best accomplished by applying cautiously the direct suction of a good glass aspirator (10–15 mm.) shaking and swirling gently for three to four minutes at room temperature and for four to five minutes more on the steam-bath. The flask must be swirled constantly in order to prevent bumping and should be protected with a small Kjeldahl safety trap. If a sufficiently efficient aspirator is not available, addition of a small amount of anhydrous ether and repetition of the above evacuation is suggested. As previously mentioned, a large excess of thionyl chloride present in the crude acid chloride causes the cyclization mixture to become orange or brown in color and seems to reduce the yield materially. If the removal of thionyl chloride has been essentially complete, the cyclization mixture is almost colorless or is a very light yellow. The crude acid chloride which is usually a light yellow color, is transferred by means of a pipet to a carefully dried Hershberg–Hinman dropping funnel to which 200–300 cc. of dry ether has previously been added. The two liquids must be thoroughly mixed before the addition is started.

While the acid chloride is being prepared, the apparatus for the cyclization is assembled and thoroughly dried for one to two hours with air or nitrogen which has previously passed through an efficient drying tower. To the flask is added 500–600 cc. of dry ether and 10–20 cc. (three to four times the calculated amount) of pure triethylamine. Stirring is started and the "glass-col" heating mantle adjusted to a temperature which causes the ether to reflux gently. Addition is started at such a rate that it is usually complete at the end of twenty–forty hours. (Longer periods were sometimes required because of the occasional clogging of the dropping funnel.) The dropping funnel is rinsed with 50 cc. of dry ether and this is run in rapidly and is used to rinse down the sides of the condenser. Refluxing is continued for an hour longer. The subsequent operations differ somewhat and will be discussed under the individual cases.

Cyclization of Thapsic Acid.—The apparatus used were those described under (A), (B) and (C). The procedure for working up the reaction product was essentially the same in all three cases. In each run 4.00 g. (0.014 mole) of thapsic acid was used. The addition time varied from thirty-eight hours for (A) to forty-eight and fifty-three hours for (B) and (C), respectively. The reaction mixture was distilled until about 300 cc. of solution remained. This was decanted from the precipitated amine salt and ketene polymer and shaken with a slight excess of dilute hydrochloric acid in a separatory funnel to remove the excess amine. The ether solution was washed with water, dried and distilled on the steam-bath. The viscous orange or amber oil was refluxed for three hours with a solution of 1.5 g. (0.027 mole) of potassium hydroxide in 25 cc. of alcohol. During the first hour, an incrustation, presumably potassium carbonate, formed around the sides of

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(16) "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, 1943, p. 129. The capillary stem of Hershberg's funnel was modified by L. Hinman as follows. A tungsten wire (about 0.5–0.6 mm. in diameter) with a sharpened tip was placed in a lathe and used as the grinding tool to enlarge a capillary of smaller diameter. The stem was 7 cm. long and the wire, when completely seated, extended slightly beyond the glass tip, thus making it possible to clear the capillary when it became clogged. This modification permitted a very fine adjustment of flow ranging from complete stoppage to a steady stream.

(17) This was determined by a simple test. A 1-cc. portion of the ether solution of N-ethylpiperidine is placed in a small test-tube containing a piece of red litmus paper about 5 mm. square. One drop of boiled, distilled water is allowed to fall through the ether solution onto the litmus paper. The tube is shaken gently and the time required for the paper to become perceptibly blue (as compared with a blank) serves as a rough indication of the concentration of N-ethylpiperidine in the solution. The test was sensitive enough to detect one part by volume of the amine in at least two hundred thousand parts of ether.

(18) Schroeder, Ph.D. Dissertation, Harvard University, 1938.

(19) An equal volume of anhydrous ether may also be added to accelerate the solution of the acid and thereby speed the reaction. If this is done the ether is allowed to distil slowly through the uncooled condenser during the first hour.

the flask. The reaction mixture was diluted with 50 cc. of water and thoroughly extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and distilled. Removal of the ether left an aqueous-alcoholic residue which deposited 1,16-cyclotriacontanedione in needles. The yield ranged from 1.3% of tan crystals sintering at 68° and melting at 74–76° when apparatus (C) was used, to 5.3% of white crystals melting at 76–77° when apparatus (B) was used. Apparatus (A) gave 2.9% m. p. 76.5–78°. Recrystallization from alcohol did not appreciably raise the melting points, 77–78° (Ruzicka reports 74–75°[20]). The yield of diketone obtained seemed to bear no relation at all to the yield of monoketone.

The cyclopentadecanone (Exaltone) was isolated by distillation of the filtrate from the diketone in a 5-cc. flask provided with a sausage side arm. The white, waxy ketone distilled at 107–108° (0.25 mm.). The yields ranged from 14 (B) to 20% (C) and (A). The ketone was converted directly to the semicarbazone, which, after one crystallization from methanol melted at 190.5–191.5° (Ruzicka gives 187–188°).[21]

Cyclization of Suberic Acid.—The apparatus was that described under (A). The addition of the solution of crude acid chloride from 3.00 g. of suberic acid required twenty-six hours. The ether solution from the cyclization was decanted from the precipitated triethylamine hydrochloride and trace of insoluble polymer into a separatory funnel. After shaking with a slight excess of dilute hydrochloric acid, it was washed with water until the washings were neutral to congo red. The solution was dried over magnesium sulfate and then fractionally distilled through a 50-cm., vacuum-jacketed column packed with glass helices. To the residual light yellow oil was added 5 cc. of alcohol, and, *very slowly*,[22] with cooling, a solution of 1.8 g. (0.032 mole) of potassium hydroxide in 20 cc. of alcohol. The solution was allowed to stand at room temperature for ten hours and was then refluxed for two hours more. A precipitate, presumably potassium carbonate, started to form shortly after addition of the alcoholic potassium hydroxide. The mixture was worked up in the same manner as the thapsic acid cyclization product with the exception that the ether solution was fractionally distilled through the above-mentioned fractionating column. From the alcoholic solution which remained was isolated 93 mg. of shining white plates, m. p. 144–145.5°. Distillation of the filtrate gave 642 mg. (33.3%) of cycloheptanone, b. p. 176° (735 mm.). An additional 100 mg. of slightly yellow crystals, m. p. 143–146.5°, was isolated by crystallization from alcohol of the residue from the distillation of the cycloheptanone. The two crops represent a yield of 10% of 1,8-cyclotetradecanedione. Crystallization from alcohol raised the melting point to 147.5–148° and this was not changed by a vacuum sublimation.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78; mol. wt., 224.34. Found: C, 74.89; H, 10.89; mol. wt., 231 (micro Rast).

The disemicarbazone of 1,8-cyclotetradecanedione was prepared by treating 50 mg. of the diketone in 3 cc. of warm methanol with semicarbazide reagent. A yield of 75 mg. of fine, white powder was obtained (the theoretical yield on the basis of disemicarbazone). This, being very insoluble in the common solvents, was purified by extraction with two portions of boiling alcohol, m. p. 261° dec. in a copper block with rapid heating (about five degrees per minute).

Anal. Calcd. for $C_{16}H_{30}O_2N_6$: N, 24.83. Found: N, 23.73, 23.84.

The dioxime of 1,8-cyclotetradecanedione was prepared by the pyridine method.[23] The white material was crystallized from a large volume of alcohol, m. p. 234–235° dec.

Anal. Calcd. for $C_{14}H_{26}O_2N_2$: N, 11.01. Found: N, 11.10, 10.93.

Evidence for Reversibility of the Dimerization Reaction.—The stability of the cyclic ketene derivatives was tested in the following manner. To a solution of 50 cc. (36.5 g., 0.36 mole) of triethylamine in 100 cc. of dry ether was added over a period of fifty-seven hours a solution of 11.90 g. (0.0498 mole) of sebacyl chloride in 600 cc. of dry ether. The apparatus described under (A) was used. The funnel was rinsed with dry ether and the mixture allowed to stand overnight at room temperature. The ether was siphoned into a one-liter graduated cylinder through a glass tube in the end of which was placed a plug of fine glass wool. Care was taken to minimize the exposure of the ether solution to the atmosphere. Half of the ether was returned to the flask by means of a pipet and refluxed for three more days. The other half was worked up as follows.

Most of the ether was distilled on the steam-bath. When the volume became small the remainder of the ether and most of the excess triethylamine was removed with suction at room temperature and finally for a short period at 50–60°. A solution of 3 g. (0.053 mole) of potassium hydroxide in 50 cc. of alcohol was added and the resulting solution was refluxed on the steam-bath for three hours. A precipitate, presumably potassium carbonate, started to come down at once. Upon the addition of 50 cc. of water the potassium carbonate readily dissolved, but the 1,10-cycloöctadecanedione was precipitated. This solution was steam distilled until 200 cc. of liquid had been collected in the distillate. This was acidified to congo red. A pronounced sweetish odor was detected, but extraction with ether and fractionation through a 12-cm., helix-packed column, followed by treatment with semicarbazide reagent, failed to yield any cyclononanone semicarbazone. Filtration of the residue from the steam distillation gave 783 mg. (22.5%) of crude, faintly brown 1,10-cycloöctadecanedione, m. p. 80–90° with sintering at about 75°. One crystallization from ether gave 446 mg. of almost white cubes, m. p. 93–96°. Concentration of the mother liquor yielded an additional 117 mg., m. p. 92.5–95°. This represents a yield of 16% of relatively pure diketone. The melting point can be raised to 96–97° by sublimation at 110° (0.45 mm.).

The ether solution which had been returned to the flask for further refluxing was worked up the same way as the first half. The crude diketone weighed 478 mg. (13.7%) and melted at 75–85° with previous sintering at about 70°.

Summary

Acid chlorides of suberic, sebacic and thapsic acids have been dehydrohalogenated by tertiary aliphatic amines to form the bifunctional ketene derivatives. These condense linearly to give ketene polymers, but under conditions of high dilution, moderate yields of macrocyclic compounds are obtained. Hydrolysis and decarboxylation of these cyclic ketene derivatives gives the large ring ketones and diketones.

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(20) Ruzicka, *et al.*, *Helv. Chim. Acta*, **11**, 509–510 (1928).

(21) Ruzicka, *ibid.*, **9**, 260 (1926).

(22) A vigorous exothermic reaction ensues and if great care is not taken there is likely to be a loss of product.

(23) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., p. 167.