Formation of Derivatives of Cyclopentane-1,3-dione from Oxazolones

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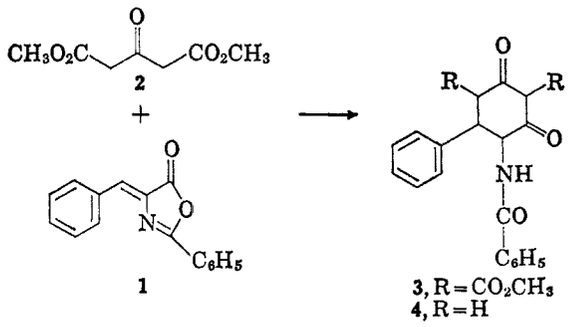
It has recently been shown[1] that the oxazolone **1** reacts with dimethyl 3-oxoglutarate (**2**) to give the dihydroresorcinol **3** in 90% yield. This reaction has

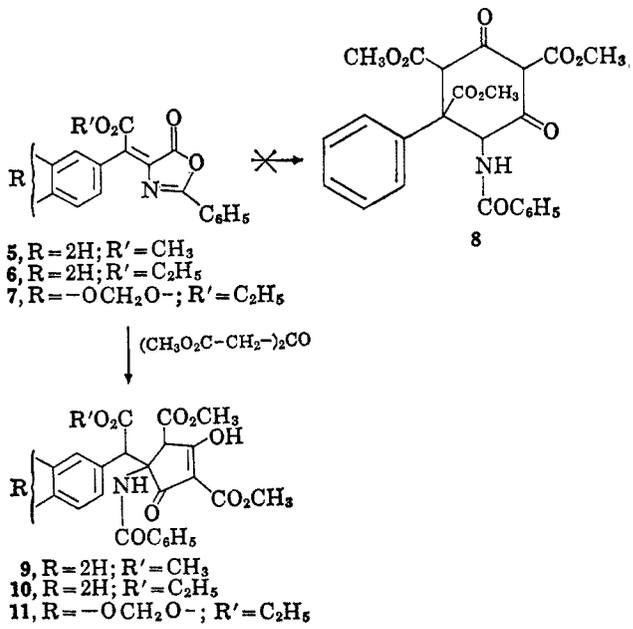


2 + **1** → **3**, R = CO_2CH_3; **4**, R = H

been successfully applied in the synthesis of the polyfunctional 6-deoxy-6-demethyltetracycline.[2]

In the course of an attempted application of this reaction to the now completed total synthesis of the Amaryllidaceae alkaloid crinine,[3] the oxazolone **5** was prepared. When this compound was allowed to react with dimethyl 3-oxoglutarate (**2**) and sodium hydride in tetrahydrofuran, conditions which previously had been used in the preparation of **3**, a single crystalline product was isolated in 44% yield. This compound had the elemental composition ($C_{25}H_{23}NO_9$) of a 1:1 adduct of oxazolone **5** to dimethyl 3-oxoglutarate as required for a dihydroresorcinol derivative of structure **8**. In addition, like **3**, it gave a brownish ferric chloride test. However, a comparison of the ultraviolet spectra between **3** and the condensation product seemed to exclude such a possibility. The dihydroresorcinol **3** had an absorption maximum at 250 mμ in methanol which was not altered on addition of acid but was shifted to 277 mμ on addition of base. In contrast, the condensation product from **5** had an absorption maximum at 254 mμ in methanol which was shifted to 225 mμ on addition of acid but remained at 254 mμ when base was added. This showed that the new reaction product had to be a considerably stronger acid than the dihydroresorcinol **3**. The compound seemed to be almost completely dissociated in neutral methanol, since upon addition of base only very minor spectral changes were observed. Upon addition of acid, the absorption maximum of the undissociated species at 225 mμ was observed. Therefore, it was evident that the new compound could not be a derivative of a dihydroresorcinol. This information, plus that derived from the nmr spectrum, led to the assignment of structure **9**, with a cyclopentane-1,3-dione chromophore, to the condensation product from the oxazolone **5**.

The nmr spectrum of the new compound, recorded in deuteriochloroform, revealed four sharp singlets at δ 3.49, 3.66, 3.69, and 3.90 which integrated for nine protons and were assigned to the three methyl ester groups.[4] The multiple peaks assigned to the ester protons may be interpreted in terms of an acid–base equilibrium and a tautomeric equilibrium of the acid which was set up in solution. Eleven protons absorbed as a multiplet at δ 7.1–9.8 (ten aromatic protons and one amide proton). The integration in this area dropped to ten protons upon addition of D_2O due to facile exchange of the amide proton. A broad singlet at δ 11.68 (enolic OH) also disappeared on addition of D_2O. This singlet always integrated for less than one proton (dissociation). Finally, two singlets integrating for one proton each were observed at δ 4.68 and 3.82. The signal at δ 4.68 was assigned to the benzylic hydrogen in **9**, and the remaining signal at δ 3.82 was assigned to the lone ring hydrogen in the



5, R = 2H; R′ = CH_3
6, R = 2H; R′ = C_2H_5
7, R = $-OCH_2O-$; R′ = C_2H_5

$(CH_3O_2C-CH_2-)_2CO$

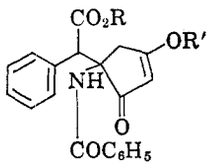
9, R = 2H; R′ = CH_3
10, R = 2H; R′ = C_2H_5
11, R = $-OCH_2O-$; R′ = C_2H_5

cyclopentanedione ring. This proton was exchanged more rapidly than the proton at δ 4.68 when **9** was treated with alkaline D_2O.

The structure of **9** was further substantiated by chemical transformations. Compound **9** was saponified with barium hydroxide and then decarboxylated with warm hydrochloric acid to give the acid **12** in 74% yield. The ultraviolet spectrum of **12** is similar to that of cyclopentane-1,3-dione and distinctly different from the corresponding degradation product **4**[1] of the cyclohexane-1,3-dione derivative **3**. On treatment with 1 equiv of diazomethane, **12** was transformed into its methyl ester **13**, but both **12** and **13**, when treated with excess diazomethane, were converted into the enol ether methyl ester **15** or its isomer. Further, the conversion of the acid **12** into the enol ether **14** proceeded under the conditions described by Wenkert.[5]

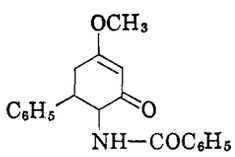
(1) H. Muxfeldt, J. Behling, G. Grethe, and W. Rogalkski, *J. Amer. Chem. Soc.*, **89**, 4991 (1967).
(2) H. Muxfeldt and W. Rogalski, *ibid.*, **87**, 933 (1965).
(3) H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *ibid.*, **88**, 3670 (1966).
(4) In other solvent systems (methanol-d_4 and D_2O–sodium carbonate) the esters were never observed as three singlets but rather as four or five lines.
(5) E. Wenkert and D. P. Strike, *ibid.*, **86**, 2044 (1964).

On treatment of **14** with diazomethane, **15** was formed in high yield. The ultraviolet spectrum of enol ethers **14** and **15** no longer exhibit the bathochromic shift



12, R = R′ = H
13, R = CH_3; R′ = H
14, R = H; R′ = CH_3
15, R = R′ = CH_3

characteristic of β-diketones upon addition of base. Furthermore, their absorption maximum was different from that of the cyclohexane derivative **16**.



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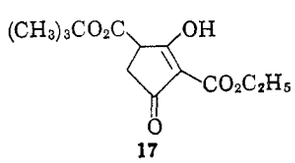
All the reported data are in good agreement with structure **9** for the condensation product. The strong acidity of **9** and its effect on the pH dependency of the ultraviolet spectrum was very similar to the behavior of compound **17**.[6] The only significant



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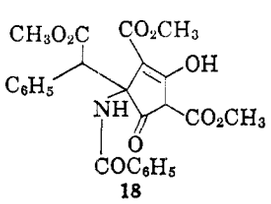
difference being that **17** had an absorption maximum at 248 mμ (ε 21,000) in acidic solution, whereas the absorption maximum of compound **9** appeared at 225 mμ (ε 23,000) with a shoulder at approximately 250 mμ. This may be explained best by the assumption that tautomer **18** contributed substantially to the tautomeric mixture of **9** since **18** appeared to have minimal nonbonded interactions. Therefore, it might appear to a much larger extent in the equilibrium of **9** than the corresponding tautomer **19** does in the equilibrium of **17**. The oxazolones **6** and **7** condensed in the same way that oxazolone **5** condensed with dimethyl 3-oxoglutarate (**2**), and the cyclopentane-1,3-dione derivatives **10** and **11** were obtained in 55 and 35% yields, respectively.



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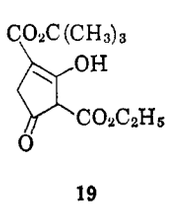

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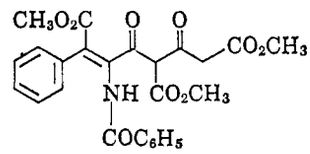
One way of rationalizing the formation of a cyclopentane-1,3-dione instead of a cyclohexane-1,3-dione is to assume that the oxazolone (for example, **5**) is first opened by the anion of dimethyl 3-oxoglutarate (**2**) to form the β-keto ester **20**. Then **20** could undergo



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an intramolecular Michael addition to give **9**. On the basis of the available experimental data other reasonable pathways cannot, of course, be excluded.

(6) G. Büchi and E. C. Roberts, *J. Org. Chem.*, **33**, 460 (1968). We thank these authors for communicating their data to us prior to its publication.

Experimental Section[7]

Preparation of Oxazolone 5.—To a solution of 765 mg (4.61 mmol) of methyl benzoyl formate, bp 85–88° (3.5 mm), and 825 mg (4.61 mmol) of hippuric acid in 1.4 ml of acetic anhydride and 10 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was added 870 mg (2.3 mmol) of lead acetate trihydrate, and the reaction was boiled under reflux for 6 hr and then stirred at room temperature for 10 hr. The solution was diluted with methylene chloride and washed with water. After drying of the organic phase over sodium sulfate and evaporation of the solvent *in vacuo*, 1.58 g of a red oil was obtained, which upon addition of ethanol and ether gave 577 mg (33% of theory) of **5**: mp 124–125°; λ_{max}^{KBr} 5.60, 5.70, 5.75, and 6.15 μ; $\lambda_{max}^{95\%\ ethanol}$, mμ (ε), 365 (33,050), sh 385 (21,000), sh 350 (29,000), and 261 (14,650).

Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.23; N, 4.55; mol wt, 307. Found: C, 70.61; H, 4.45; N, 4.88.

The preparation of oxazolone 6 was similar to that described for the preparation of the oxazolone **5**; the ethyl ester oxazolone **6** was prepared from 4.44 g (24.7 mmol) of ethyl benzoyl formate and 1 equiv each of hippuric acid and lead acetate trihydrate. The mixture was boiled under reflux for 19 hr. After crystallization from ether 2.3 g (29% of theory) of **6** was isolated. A sample was recrystallized for analysis from ether: mp 122–123°; λ_{max}^{KBr} 5.55, 5.65, 5.75, and 6.05 μ; $\lambda_{max}^{95\%\ ethanol}$, mμ (ε), 365 (32,800), sh 385 (21,580), sh 350 (28,400), 261 (13,220), and sh 248 (11,900).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.35; mol wt, 321. Found: C, 71.00; H, 4.71; N, 4.34.

Preparation of Oxazolone 7.—A mixture of 1.1 g (4.74 mmol) of ethyl piperonyl formate, 844 mg of hippuric acid, 1.80 g (4.74 mmol) of lead acetate trihydrate, and 1.45 g of acetic anhydride was dissolved in 10 ml of tetrahydrofuran and boiled under reflux in a manner similar to that described for the preparation of the methyl ester oxazolone **5**. After work-up, 1.9 g of a thick red oil was obtained, which could be partially crystallized upon addition of ether. A yield of 580 mg (33% of theory) of yellow crystalline **7** was isolated. An analytical sample was recrystallized from ether: mp 160–161°; λ_{max}^{KBr} 5.55, 5.65, 5.75, and 6.13 μ; λ_{max}^{ether}, mμ (ε), 410 (27,700), 396 (29,150), 334 (10,050), 295 (9,560), 268 (18,300), and 258 (15,220).

Anal. Calcd for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83; mol wt, 365. Found: C, 65.83; H, 4.09; N, 3.79.

Condensation of Oxazolone 5 with Dimethyl 3-Oxoglutarate.—To a solution of 309 mg (1.0 mmol) of **5** and 209 mg (1.2 mmol) of dimethyl 3-oxoglutarate dissolved in 10 ml of tetrahydrofuran was added 26.4 mg (1.1 mmol) of sodium hydride, and the solution was stirred under a nitrogen atmosphere for 18 hr at room temperature. The clear yellow solution was diluted with water and the resulting alkaline solution was washed with chloroform. The aqueous solution was then acidified and extracted with chloroform. This extract was dried over sodium sulfate and evaporated. A 364-mg portion of alkali soluble yellow oil was obtained, and upon addition of methanol–ether, 217 mg (44% of theory) of white crystalline solid **9** was precipitated. The remaining oil exhibited a maximum at 232 and a shoulder at 260 mμ in alkaline methanol. A sample of **9** was recrystallized from methanol–ether, mp 146–150°. A dilute solution of **9** in methanol gave an immediate orange coloration upon addition of ferric chloride: λ_{max}^{KBr} 2.95, 5.7–5.8 (broad), 6.0, and 6.22 μ; $\lambda_{max}^{0.4\ N\ HCl\text{-}MeOH}$, mμ (ε), sh 250 (19,250) and 225 (23,000); $\lambda_{max}^{0.1\ N\ HCl\text{-}MeOH}$, mμ (ε), 251 (21,250) and 226 (22,000); λ_{max}^{MeOH}, mμ (ε), 255 (25,550) and sh 227 (19,600); $\lambda_{max}^{0.1\ N\ NaOH\text{-}MeOH}$, mμ (ε), 253 (26,600) and sh 225 (20,900); $\lambda_{max}^{acetonitrile}$, mμ (ε), 250 (19,500), and 222 (23,950).

(7) Melting points were taken on a Kofler hot stage.

Anal. Calcd for $C_{25}H_{23}NO_9$: C, 62.36; H, 4.95; N, 2.91; mol wt, 481. Found: C, 62.40; H, 5.08; N, 2.82.

Condensation of Oxazolone 6 with Dimethyl 3-Oxoglutarate.—In a manner identical with that described for the reaction of oxazolone **5**, 878 mg (2.74 mmol) of **6** was allowed to react with 570 mg (3.28 mmol) of dimethyl 3-oxoglutarate and 75.5 mg (3.15 mmol) of sodium hydride. A yield of 1.27 g of a yellow oil was obtained which, upon addition of methanol–ether, gave 746 mg (55% of theory) of **10**: mp 140–144°. An analytical sample was obtained from methanol–ether: λ_{max}^{KBr} 2.9, 5.7, 5.75, 5.95, and 6.2 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 254 (23,000), and 227 (19,800); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 254 (24,900) and sh 227 (19,450); nmr ($CDCl_3$), δ 1.15 (t, J = 7 cps, 3 H, –O–CH_2–**CH_3**), 4.1 (q, J = 7 cps, 2 H, O–**CH_2**–CH_3), 3.52 (s, 3 H, methyl ester), 3.93 (3 H methyl ester), 3.76 (s, 1 H, methine), 4.70 (s, 1 H, benzylic methine), and 7.2–7.9 (m, 11 H, aromatic and N–H).

Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.02; H, 5.08; N, 2.82; mol wt, 495.5. Found: C, 63.13; H, 5.02; N, 2.74.

Condensation of Oxazolone 7 with Dimethyl 3-Oxoglutarate.—A 622-mg (1.7 mmol) sample of **7**, 355 mg (2.04 mmol) of dimethyl 3-oxoglutarate, and 46.5 mg (1.95 mmol) of sodium hydride were dissolved in 10 ml of tetrahydrofuran. After 3.5 days at room temperature the mixture was worked up in the usual fashion and gave 584 mg of a yellow oil. A yield of 308 mg (34% of theory) of a white solid (**11**) was obtained after crystallization from methanol–ether: mp 150–158°; λ_{max}^{KBr} 2.9, 5.7, 5.8, 6.0, 6.25, and 9.7 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 250 (24,570) and sh 290 (4700); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 251 (26,180) and sh 290 (5850); nmr ($CDCl_3$), δ 1.11 (t, J = 7 cps, 3 H, O–CH_2–**CH_3**), 4.1 (q, J = 7 cps, 2 H, O–**CH_2**–CH_3), 3.57 (s, 3 H, methyl ester), 3.95 (s, 3 H, methyl ester), 3.77 (s, 1 H, methine), 4.67 (s, 1 H, benzylic methine), 5.99 (s, 2 H, methylenedioxy), and 6.7–8.0 (m, 10 H, aromatic and N–H).

Anal. Calcd for $C_{27}H_{25}NO_{11}$: C, 60.11; H, 4.67; N, 2.59; mol wt, 539.5. Found: C, 60.03; H, 4.81; N, 2.54.

Hydrolysis and Decarboxylation of 9.—To a solution of 500 mg (1.04 mmol) of **9** in 10 ml of hot methanol, 100 ml of a 5% barium hydroxide solution in water was added. The mixture was heated on a steam bath for 2 hr. During this time a white precipitate formed from the initially colorless, homogeneous solution. The mixture was then acidified with 1 *N* HCl and heated for an additional 10 min. During this time the acid **12** crystallized. After cooling, 270 mg (74%) of **12** was collected, mp 261°. An analytical sample was recrystallized from methanol–ether: λ_{max}^{KBr} 3.0, 2.7–4.4 (broad), 5.9, 6.15, and 6.22 μ; λ_{max}^{MeOH}, mμ (ϵ), 249 (17,550) and 225 (17,550); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ) 268 (21,500) and 225 (15,780).

Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.98; mol wt, 351.4. Found: C, 68.37; H, 4.93; N, 3.93.

Preparation of the Ester Enol Ether 15 from 12.—To a cold solution of 130 mg (0.356 mmol) of **12** in 10 ml of ether was added a solution of diazomethane (0.80 mmol). Another portion of diazomethane was added after 4 hr and the mixture stirred at room temperature for 18 hr. The solvent was removed *in vacuo* and a sample of the recovered foam exhibited no bathochromic shift in alkaline methanol. A sample was crystallized from ether, mp 142–144°. Recrystallization of **15** from methanol–ether gave a 1:1 methanol adduct: mp 83–85°; λ_{max}^{KBr} 3.0, 5.8, 5.92, 6.05, and 6.3 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 243 (20,850) and sh 225 (18,900); $\lambda_{max}^{0.01\ N\ methanol\text{-}NaOH}$, m$\mu$ (ϵ), 243 (20,850) and sh 225 (18,900); nmr ($CDCl_3$), δ 3.22 (AB, J = 17 cps, 2 H, methylene), 3.75 (s, 6 H, enol ether and methyl ester), 4.02 (s, 1 H, benzylic methine), 5.23 (s, 1 H, vinyl), and 7.2–8.0 (m, 11 H, aromatic and N–H).

Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.95; H, 5.58; N, 3.69; mol wt, 379.4. Found: C, 69.89; H, 5.48; N, 3.72.

Preparation of the Acid Enol Ether 14.—A 378-mg (1.08 mmol) portion of **12** and 10 mg of *p*-toluenesulfonic acid was dissolved in 75 ml of benzene and 50 ml of methanol and distilled over 5 hr to a volume of 30 ml. The solution was diluted with ether and washed with dilute alkali. The organic phase was dried over sodium sulfate and evaporated to dryness under reduced pressure to give 41 mg (8% of theory) of the ester enol ether **15**, mp 140–144°. The alkaline solution was then acidified and washed with chloroform. The combined organic extracts were washed with water, dried over sodium sulfate, and evaporated to give 446 mg (62% of theory) of **14**: mp 125–128°; λ_{max}^{KBr} 2.95, 2.7–4.4 (broad), 5.85, 6.0, 6.3, and 7.35 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 243 (19,050) and sh 228 (18,050); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 228 (19,650) and sh 240 (18,900); nmr (D_2O–NaOD), δ 3.0 (d AB pattern, 2 H, methylene), 3.30 (s, 3 H, enol ether), 3.58 (s, 1 H, methine), 4.8 (s, HOD), 5.18 (s, 1 H, vinyl), and 7.0–8.0 (m, 10 H, aromatic).

Anal. Calcd for $C_{21}H_{19}NO_5 \cdot CH_3OH$: C, 66.48; H, 5.83; N, 3.54; mol wt, 402. Found: C, 66.71; H, 5.54; N, 3.61.

Preparation of the Ester Enol Ether 15 from 14.—To a suspension of 590 mg (1.61 mmol) of the acid enol ether **14** in 10 ml of cold ether was added a solution of diazomethane (4.8 mmol). Immediately upon addition of the diazomethane the solution became homogeneous. After 30 min a white solid crystallized from the cold solution. Stirring was continued for 12 hr and the excess diazomethane was removed by warming the solution slightly under reduced pressure. A 550-mg (86%) portion of the ester enol ether **15** was collected and shown to be identical with that prepared directly from **12**.

Registry No.—**5**, 15924-08-0; **6**, 15924-09-1; **7**, 15963-73-2; **9**, 15924-10-4; **10**, 15924-11-5; **11**, 15924-12-6; **12**, 15924-13-7; **14**, 15924-14-8; **15**, 15924-15-9.

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Preparation of Tertiary N,N-Dimethylamines by the Leuckart Reaction

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Introduction of alkyl groups into ammonia or a primary or secondary amine by means of certain aldehydes or ketones, when the reducing agent is ammonium formate, is known as the Leuckart reaction.[2,3] Later, Wallach[4] obtained better yields by using a mixture of ammonia or substituted amine with formic acid. The Leuckart reaction did not come into general use as a preparative method until 1936 when Ingersoll and coworkers[5] reviewed the subject and applied the reaction to the synthesis of a series of substituted β-phenylethylamines. Similarly, Novelli[6] showed that respectable yields of secondary amines could be obtained by the action of N-alkylformamides on some substituted acetophenones. When the carbonyl compound is formaldehyde, the transformation is termed the Clarke–Eschweiler[3] method.

The Leuckart reaction applied to the synthesis of tertiary amines has found only limited application to date. Early examples of the reaction where an aldehyde or ketone has been treated with a dialkylformamide include the reaction of benzaldehyde with formylpiperidine to give N-benzylpiperidine,[4] and the conversion

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(2) R. Leuckart, *Ber.*, **18**, 2341 (1885); R. Leuckart and E. Bach, *ibid.*, **19**, 2128 (1886).

(3) M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

(4) O. Wallach, *Ann.*, **343**, 54 (1905).

(5) A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp, and G. Jennings, *J. Amer. Chem. Soc.*, **58**, 1808 (1936).

(6) A. Novelli, *ibid.*, **61**, 520 (1939).