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Thermochemical Studies of Carbonyl Compounds. 3. Enthalpies of Hydrolysis of Ortho Esters

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The enthalpies of hydrolysis of a series of ortho esters have been measured in aqueous dioxane. The largest effect on ΔH_r was found with α-branching, in contrast to the previously reported hydrolysis of ketals which gave the larger effect with β-branching. Possible reasons for this difference in behavior are discussed.

As part of a study of the enthalpy component of steric effects, we have reported the enthalpies of hydrolysis of a series of acetals[1] and ketals,[2] in which the alkyl group attached to the substituted center was varied from methyl and ethyl through *tert*-butyl and neopentyl. The relative changes in the hydrolysis enthalpies for the acetals and ketals bearing smaller alkyl groups were found to be much less than the corresponding free energy changes, indicating that the effect of the alkyl group on the equilibrium constant appeared largely in the entropy term. With the larger alkyl groups, significantly larger enthalpy contributions were found.

In a continuation of this study, we have examined the enthalpies of hydrolysis of a series of ortho esters. The symmetry of the substitution at the functional group will minimize the possibility of finding a conformation in which the alkyl group can avoid interaction with one of the methoxy groups and may lead to larger effects than found in the other series (Scheme I).

The ortho esters were prepared by the conventional Pinner reaction starting with the corresponding nitriles.[3] It was successful where R = methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, 2-butyl, and isobutyl. However, no ortho ester could be obtained in the cases where R = *tert*-butyl or neopentyl. Attempts to prepare these compounds by transferring CH_3^+ from a dimethylbromonium salt[4] to the corresponding esters, followed by trapping with methanol or methoxide ion failed.

The enthalpies of hydrolysis were determined by using a modified version of the automated calorimeter previously described.[2,5] A typical set of results is shown in Table I. The observed enthalpies of reaction, along with the enthalpies of solution of the products, are given in Table II. From these data, we calculate the enthalpies of hydrolysis with all species in the pure liquid phase. The values are given in the last column of Table II. The enthalpies of hydrolysis of three of the ortho esters have previously been investigated. The values are compared in Table III. The best agreement is found with the more precise of the earlier studies, that for trimethyl orthoacetate. Somewhat larger deviations are found with the other two ortho esters, but the present values are far more precise than the others.

The enthalpies of hydrolysis are compared with the results of our studies of acetal and ketal hydrolysis in Table IV. In the present case, we also examined the ortho ester where R = *n*-butyl. Therefore, the hydrolyses of the corresponding ketal and acetal also were examined (Table V) and are included in Table IV.

Scheme I

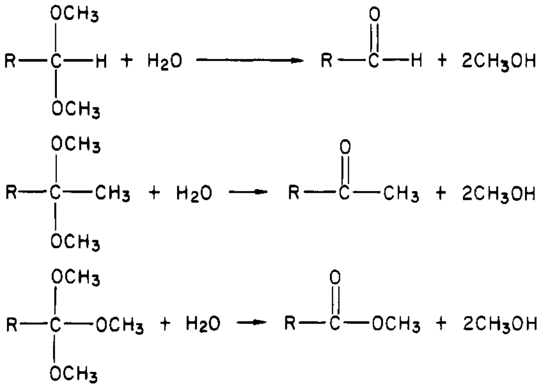

Table I. Enthalpy of Hydrolysis of Trimethyl Orthovalerate

run	mmol	ϵ,[a] cal/K	ΔT	Q, cal	ΔH_r, cal/mol
1	2.3119	73.60	0.1430	10.525	−4552
2	2.1616	73.60	0.1338	9.847	−4556
3	2.4081	73.56	0.1489	10.953	−4548
4	2.1956	73.84	0.1354	9.998	−4554

$\Delta H(\text{av}) = -4553 \pm 4$ cal/mol[b]

[a] Effective heat capacity of the calorimeter as determined via an electrical calibration. [b] Uncertainties are given as two times the standard deviation from the mean ($2\bar{s}$).

With the ortho esters, all of the *n*-alkyl groups led to an increase in ΔH_r over that for a methyl group (i.e., a less exothermic reaction). Thus, compared to methyl, these groups stabilize the ortho ester relative to the ordinary ester and provide a small inverse steric effect. The alkyl groups which were branched at the α-position gave a considerable decrease in ΔH_r and thus a large normal steric effect. The changes in ΔH_r observed for these groups in ortho ester hydrolysis are much larger than those observed in the hydrolysis of either ketals or acetals.

The effects observed in the three series are best seen diagrammatically as shown in Figure 1 where the enthalpies of hydrolysis are plotted against the Taft steric parameter, E_s, which represents the steric free energy contribution from the groups in ester hydrolysis. In the case of acetals, there is a slow increase in ΔH_r with increasing steric bulk, but it is much smaller than the change in E_s. With the ketals, an irregular change is found, and the largest effects are observed with β-branched alkyl substituents. This is in contrast to the present results in which ortho ester hydrolysis leads to the larger effects with the α-branched alkyl groups. The reversal of effects between isobutyl and 2-butyl on going from the ketals to the ortho esters made us concerned that an error might have been made in our earlier study. The ketals were reexa-

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(3) Pinner, A. *Chem. Ber.* **1883**, *16*, 352. Cf. DeWolf, R. H. "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970.
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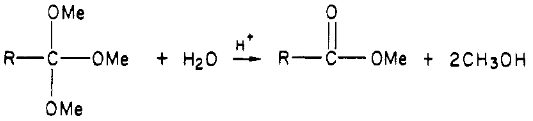
Table II. Ortho Ester Hydrolysis in the Pure Liquid Phase



$$R{-}C(OMe)_2{-}OMe + H_2O \xrightarrow{H^+} R{-}C(=O){-}OMe + 2CH_3OH$$

R	ester,[a] %	ΔH_{obsd},[b] cal/mol	ΔH_{soln},[c] cal/mol	ΔH_{corr},[d] cal/mol	ΔH_r,[e] cal/mol
Me	0.40	−5682 ± 6[g] (6)[f]	689 ± 1 (4)	−5708 ± 7	−6426 ± 7
Et	0.0	−5297 ± 14 (5)	917 ± 7 (6)	−5297 ± 14	−6244 ± 16
n-Pr	0.0	−5048 ± 12 (6)	1195 ± 8 (8)	−5048 ± 12	−6272 ± 14
n-Bu	0.0	−4553 ± 4 (3)	1520 ± 11 (6)	−4553 ± 4	−6101 ± 12
i-Pr	2.37	−6458 ± 11 (4)	1179 ± 7 (6)	−6591 ± 15	−7799 ± 17
2-Bu	0.34	−6658 ± 13 (5)	1413 ± 7 (4)	−6699 ± 14	−8140 ± 16
i-Bu	0.0	−5758 ± 10 (4)	1507 ± 13 (5)	−5758 ± 10	−7295 ± 16

[a] Mole percent of corresponding ester (impurity) in sample of orthoester. In the case where R = 2-Bu, the sample also contained 0.67 mol % methanol. [b] Heat due to breaking ampule of ortho ester into solution of 65/35 dioxane/water (v/v). [c] Heat of solution of corresponding ester. [d] Heat of reaction corrected for the ester impurity including ester ΔH_{soln}. Standard state for ortho esters is the pure liquid phase. For all other reaction components the standard state is 65/35 dioxane/water. [e] Standard state for all components is the pure liquid phase. ΔH_{soln} for H_2O and CH_3OH = −219 ± 1 and −95 ± 1 cal/mol, respectively. [f] Number of runs in parentheses. [g] All errors are given as $2\bar{s}$.

Table III. Comparison of Enthalpies of Hydrolysis of Ortho Esters

R	this work	lit. (ref)
Me	−6.426 ± 0.014	−6.29 ± 0.13 (16)
Et	−6.224 ± 0.032	−6.57 ± 0.29 (17)
i-Pr	−7.799 ± 0.034	−7.05 ± 0.59 (17)

[a] Uncertainties are 2*s* (not $2\bar{s}$) corresponding to the 95% confidence level.

mined and gave values in good accord with the previous results. Thus, the unusual variation in substituent effect between ketals and ortho esters is correct.

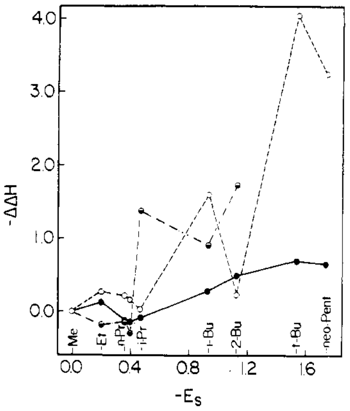
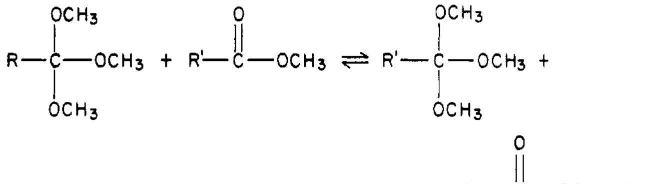


Figure 1. Relationship between the changes in enthalpies of hydrolysis with respect to R = CH_3 (kcal/mol) and the Taft steric parameter, E_s. The data for acetals are given by the solid circles, those for ketals by the open circles, and those for the ortho ester by the half filled circles. The points for *n*-butyl are between those for *n*-propyl and isopropyl.

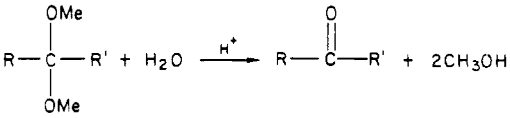
In our earlier study of the hydrolysis of acetals and of ketals, additional information was obtained by comparing free energies derived from equilibrium studies with the enthalpies of hydrolysis. We should like to make a similar comparison in the present case. It seemed likely that the *n*-alkyl groups would show their normal steric effect in the equilibrium between the ester and the ortho ester. The direct measurement of the equilibrium constant was not possible because it appears to be so small that no measurable amount of ortho ester was present at equilibrium. Thus, we attempted to measure the following trans-orthoesterification equilibrium (eq 1). Unfortunately, it was not possible to find conditions under which this equilibrium could be achieved. An acid catalyst is needed, and the ortho ester appears to esterify the catalyst at a rate competitive with the trans-orthoesterification.



$$R{-}C(OCH_3)_2{-}OCH_3 + R'{-}C(=O){-}OCH_3 \rightleftharpoons R'{-}C(OCH_3)_2{-}OCH_3 + R{-}C(=O){-}OCH_3 \quad (1)$$

We shall now attempt to rationalize the substituent effects which we have observed. Here, it is helpful to consider groups of substituents which represent a given type of structural change. The introduction of methyl groups at the α-position (Figure 2a) leads to only a small change for the acetals and only a small change for the first

Table IV. Enthalpies of Hydrolysis of Ortho Esters, Ketals, and Acetals (25 °C)



$$R{-}C(OMe)_2{-}R' + H_2O \xrightarrow{H^+} R{-}C(=O){-}R' + 2CH_3OH$$

	ortho esters (R′ = OCH_3)		ketals (R′ = CH_3)		acetals (R′ = H)		
R	Δ*H*	ΔΔ*H*	Δ*H*	ΔΔ*H*	Δ*H*	ΔΔ*H*	E_s
Me	−6426 ± 7	0	4858 ± 7	0	8566 ± 15	0	0.00
Et	−6244 ± 16	182	4609 ± 8	−249	8432 ± 17	−134	−0.20
n-Pr	−6272 ± 14	154	4655 ± 14	−203	8745 ± 23	179	−0.36
n-Bu	−6101 ± 12	325	4724 ± 18	−134	8700 ± 13	134	−0.39
i-Pr	−7799 ± 17	−1373	4844 ± 9	−14	8629 ± 16	63	−0.47
2-Bu	−8140 ± 16	−1714	4749 ± 11	−109	8066 ± 33	−500	−1.13
i-Bu	−7295 ± 16	−869	3268 ± 13	−1590	8272 ± 23	−294	−0.93
t-Bu			805 ± 13	−4053	7863 ± 19	−703	−1.54
neopent			1628 ± 21	−3230	7906 ± 35	−660	−1.74

[a] All enthalpies are in cal/mol. [b] Uncertainties are given as two times the standard deviation from the mean ($2\bar{s}$). [c] Standard state is the pure liquid phase.

Table V. Enthalpies of Hydrolysis of Ketal and Acetal Where R = Butyl

parent	ketal/acetal hydrolysis	ketone/aldehyde heat of soln
2-hexanone[b]	5841 ± 17 (5)	1088 ± 17 (8)
water[b]		−219 ± 1 (6)
methanol[b]		−95 ± 1 (6)
valeraldehyde[c]	2155 ± 1 (3)	−6275 ± 13 (5)
water[c]		−196 ± 1 (4)
methanol[c]		−233 ± 2 (5)

[a] All values are given in cal/mol. Uncertainties are given as twice the standard deviation of the mean ($2\bar{s}$). The number of runs is given in parentheses. [b] Breaking an ampule of the compound into 65% dioxane–water. [c] Breaking an ampule of the compound into 50% methanol–water.

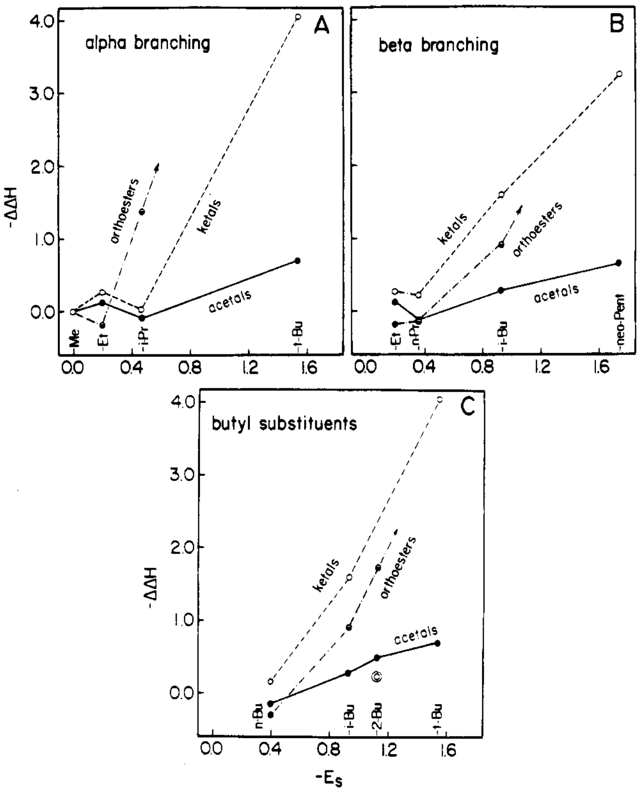


Figure 2. Relationships between the changes in enthalpies of hydrolysis (kcal/mol) and E_s for selected groups of substituents. Note the anomalous position of the ketal of *n*-butyl methyl ketone in C (double circle).

two substitutions for the ketals. A large change is first found on going to R = *tert*-butyl. With the ortho esters, a large change is found with the second substitution (i.e., with R = isopropyl). The introduction of methyl groups in the β-position (Figure 2b) leads to a large change with the second substitution (R = isobutyl) for both the ketals and ortho esters, with the larger effect found with the ketals.

When only isomeric alkyl substituents are considered, the trends are simplified. The subset of butyl groups is large enough to include both α- and β-branching. Figure 2c is analogous to Figure 1 except that only the C4 substituents have been included. (The fact that trimethyl orthopivalate is too strained to be prepared by known reactions suggests that its value, although unknown, would be large.) All of the acetals and ortho esters, and three of the four ketals, show roughly linear relationships with E_s. Thus, some factor which complicates the relationships in Figure 1 is apparently held constant when only isomeric groups are compared. The notable exception is the ketal of 2-butyl methyl ketone which lies some 3000 cal/mol below the value anticipated by the other data in this plot. A comparison of the *n*-propyl- and isopropyl-substituted compounds shows that a similar exception is found with the ketal of isopropyl methyl ketone.

One would reasonably expect that α-branching (R = isopropyl or 2-butyl) would lead to a steric interaction in these rather crowded ketals. However, since no large effect is seen in the hydrolysis enthalpies, then α-branching must destabilize the corresponding ketone by a similar amount. A suggestion that this may be the case is found in a comparison of the enthalpies of formation of aldehydes and ketones. The difference in liquid-phase enthalpies of formation between isobutyraldehyde and *n*-butyraldehyde is reported to be 2.8 ± 0.50 kcal/mol,[6] with the former having the lower energy as is generally observed for chain branching.[7] On the other hand, the enthalpy difference between isopropyl methyl ketone and *n*-propyl methyl ketone is reported to be only 0.5 ± 0.3 kcal/mol.[6] The determination of enthalpies of combustion for compounds such as these is fraught with difficulties, and the errors in the reported values may be considerably larger than the reported uncertainty intervals. Nevertheless, the difference is interesting.

Aldehydes and ketones prefer to have an alkyl group eclipse the carbonyl group.[8] Aldehydes can easily accommodate an α-alkyl substituent, but in the case of methyl alkyl ketones, α-branching will lead to a gauche interaction with the methyl group and should raise the energy. There is a suggestion that branched alkyl groups may adopt a staggered conformation with respect to the carbonyl groups,[9] and this also would result in some loss of a stabilizing interaction.

If this were the case, why should the effect not be observed with the orthoesters? We have carried out some calculations concerning the origin of the conformational preference for aldehydes and found that a major component of the interaction of the carbonyl with the eclipsed alkyl group was a dipole-induced dipole interaction.[10] In the case of esters, such an interaction may be generated with both the carbonyl group and the C–O bond of the ester. This would allow a stabilizing interaction with the α-branched group, which may lead to a larger energy difference between *n*-propyl and isopropyl as was found with the aldehydes. The steric interaction in the ortho ester would not be cancelled by an effect in the ester, and α-branching would lead to a "normal" change in enthalpy of reaction as was observed. If this proposal were correct, one would expect to find the ΔH_f of methyl isobutyrate to be significantly more negative than that of methyl butyrate (i.e., similar to the isobutyraldehyde/butyraldehyde difference). However, the data required to test this hypothesis are not available.

It is unfortunate that so little is known about the conformations and energies of α-branched ketones and esters. Such information would be necessary if one is to achieve a detailed understanding of the enthalpy changes observed in this study. We have made a start at achieving an un-

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(6) Cox, J. D.; Pilcher, G. "Thermochemistry of Organic and Organometallic Compounds"; Academic Press: New York, 1970. Pedley, J. B.; Rylance, J. Sussex N. P. L. Computer Analyzed Thermochemical Data: Organic and Organometallic Compounds; University of Sussex, 1972.

(7) In the liquid phase, the ΔH_f of isobutyl alcohol is 1.7 kcal/mol more negative than that of n-butyl alcohol. Similarly, the ΔH_f of 2-methylbutane is 1.4 kcal/mol more negative than that of *n*-pentane.[6]

(8) For a review of the experimental data, see: Suter, U. *J. Am. Chem. Soc.* **1977**, *101* 6481.

(9) Cosse-Barbi, A.; Dubois, J. E. *Spectrochim. Acta, Part A* **1972**, *A28*, 561. Cosse-Barbi, A. *J. Mol. Struct.* **1978**, *49*, 181.

(10) Wiberg, K. B.; Martin, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 0000.

derstanding of the conformations and intramolecular interactions in these compounds,[10] and this investigation is continuing.

Experimental Section

Materials. Trimethyl orthoacetate and trimethyl orthovalerate were commercial samples (Kodak). The remaining ortho esters were prepared as described by McElvain and Nelson.[11] Each of the ortho esters was distilled from sodium through a 25-cm glass helix packed column, collecting a middle fraction. In some cases, it was necessary to repeat the distillation. The procedure was ineffective with trimethyl orthovalerate which could only be adequately purified via distillation through a spinning band column.

The ortho esters were analyzed by IR spectroscopy, gas chromatography, and NMR spectroscopy (500 MHz). In most case, the orthoesters were found to be >99.9% pure. In three cases, an impurity (the corresponding normal methyl ester) was found. They were trimethyl orthoacetate, trimethyl orthoisobutyrate, and trimethyl ortho-2-methylbutyrate. Analyses were carried out by GC by first examining the ortho ester and then a sample of ortho ester to which a known amount of the normal ester had been added. A comparison of the normal ester peak areas for the two samples allowed the concentration of the normal ester to be determined with a precision of ±0.1 %. The observed heats of reaction were corrected to the values expected for pure ortho esters (ΔH_{corr} in Table II).

The normal esters were commercial samples. They were purified by the procedure suggested by Perrin and Perrin[12] and then distilled through a 25-cm glass helices packed column taking a middle fraction. The process was repeated if necessary until both NMR spectroscopy and GC using an SE-30 or OV-101 column showed the sample to be at least 99.9% pure.

Dioxane was distilled from benzophenone ketyl under an atmosphere of dry nitrogen. The solvent used for the calorimetric studies was 65% dioxane and 35% water (v/v) containing 0.001 N perchloric acid.

Calorimetry. The calorimetric experiments were carried out by using an automated reaction calorimeter which is similar to that previously described.[5] Some modifications were made. Instead of counting the 28-MHz signal from the quartz thermometer directly, the 28-MHz signal was mixed with a 30-MHz signal derived from the precision 10-MHz oscillator which is the master time base for the operations. The resultant 2-MHz difference frequency is more easily counted.[13] It is sent to one or the other of a pair of counters at 10-s intervals so that all of the input signal is counted, avoiding the quantization error normally encountered with counters. The heater power and timing circuits from the original LKB system were replaced. In doing so, it was found that there had been a systematic error associated with the earlier heater power circuit (it took a few seconds to reach the set voltage). It was equivalent to a heater circuit operating properly but starting 0.6 s late. All of the data from our previous studies of ketal and acetal hydrolysis were still available, and it was possible to correct for this problem. As a result, the values given in Table III are slightly different than those reported previously. Fortunately, the effect was rather small and leads to no significant change in the $\Delta\Delta H$ values resulting from changes in substituents.

The calorimeter was checked by measuring the enthalpy of reaction of TRIS (NBS standard reference material 724a) with 0.1 N hydrochloric acid. The average value for 26 runs carried out over a 3-month period was −7117 ± 5 cal/mol. The recommended value is −7116 ± 8 cal/mol.[14] The experimental uncertainties are reported as $2\bar{s}$, where $\bar{s}$ is the standard deviation from the mean ($\bar{s} = [\sum \delta^2/(n)(n-1)]^{1/2}$), in accord with the suggestion of Rossini.[15]

Acknowledgment. This investigation was supported by the Division of Basic Energy Sciences, U.S. Department of Energy.

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[11] McElvain, S. M.; Nelson, J. W. *J. Am. Chem. Soc.* **1942**, *64*, 1826.

[12] Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. "Purification of Laboratory Chemicals"; Pergamon Press: Oxford, 1980.

[13] The details of the modified calorimeter may be found in the Ph.D. thesis of E.J.M., 1984.

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Electron-Transfer Substitution Reactions of Anions Derived from Malonic Esters, β-Keto Esters, and β-Diketones[1]

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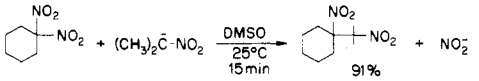
Electron-transfer substitution reactions of carbanions derived from malonic esters, β-keto esters, and β-diketones with α,α-dinitro compounds are compared with oxidative coupling of these carbanions to nitroparaffin salts using potassium ferricyanide; the former routinely give better yields.

In 1970 a new reaction of α,α-dinitro compounds was described;[2] when treated with nitroparaffin salts, these compounds undergo replacement of one of the geminal nitro groups in a manner shown by the example of eq 1.



(1)

The reactions occur readily at room temperature and give excellent yields of vicinal dinitro compounds. In the 1970 papers an electron-transfer chain mechanism was proposed, and evidence in its support was provided. In 1971 the displacement of one of the nitro groups of 2,2-dinitropropane by diethyl sodioethylmalonate, the sodium salt of ethyl 2-ethyl-3-ketobutyrate and sodio-3-methyl-

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[1] This is paper 28 in the series "Substitution Reactions which Proceed via Radical Anion Intermediates". It derives, in part, from the doctoral dissertation of M. M. Kestner, Purdue University, May 1973. For the preceding paper, see: Kornblum, N.; Singh, H. K.; Boyd, S. D. *J. Org. Chem.* **1984**, *49*, 358.

[2] Kornblum, N.; Boyd, S. D.; Stuchal, F. W. *J. Am. Chem. Soc.* **1970**, *92*, 5783. Kornblum, N.; Boyd, S. D. *Ibid.* **1970**, *92*, 5784. Also see: Kornblum, N. "The Chemistry of Functional Groups, Supplement F: The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives"; Patai, S., Ed.; Wiley: New York, 1982; pp 380–384.

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