# Steric Effects in Ambident Ions. The Acylation of Cyclic β-Keto Esters[1]

JAMES P. FERRIS, CHARLES E. SULLIVAN,[2] AND BETH GEORGE WRIGHT

*Department of Chemistry, Florida State University, Tallahassee, Florida*

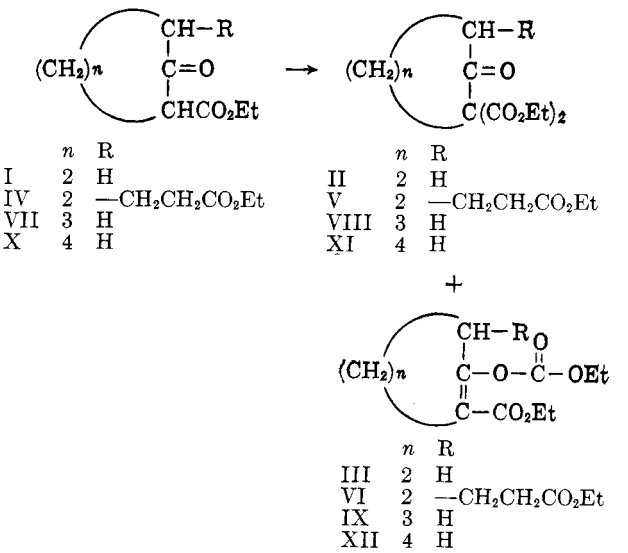
*Received February 4, 1963*

Acylation of five-, six-, and seven-membered cyclic β-keto esters with ethyl chloroformate yields both carbon- and oxygen-acylated products. The greatest proportion of carbon-acylation was observed with the seven-membered ring compound and the least in the six-membered ring compound. The preponderance of oxygen-acylated product in the 2-carbethoxycyclohexanone reaction is ascribed to hindrance to axial attack of the ethyl chloroformate on the carbocyclic ring. Such hindrance, due to the ring hydrogens, is less in the five- and seven-membered rings, thereby accounting for the greater proportion of carbon-acyl product.

The alkylation of ambident ions has been the topic of extensive recent investigation and the reaction conditions which direct alkylation on carbon or oxygen have been well defined in certain systems.[3] The corresponding acylation reaction has not been studied in a systematic manner, although in several instances it is known that solvent, reaction temperature, and the cation accompanying the anion exert considerable effect on the proportion of carbon- and oxygen-acylation.[4-6] It was hoped that a systematic investigation of the acylation of β-keto esters would clarify previous literature reports, point to a method of obtaining better yields of the synthetically more useful carbon-acylated product, and contribute to the general understanding of the factors which direct the point of attack in an ambident ion.[7]

We chose to study the reaction of ethyl chloroformate with cyclic β-keto esters. The anions of the cyclic compounds would be expected to be planar about the carbon atoms joined to the ester and carbonyl groups so that the most favored conformation of the ring would be the same as that in the corresponding cycloalkenes. The latter have been investigated extensively and the most stable conformations are known.[8] The mechanism of the reaction of ethyl chloroformate with various nucleophiles has been examined and it was found to be a second-order reaction displacement in every instance.[9] This combination of reactants requires a transition state which involves axial attack[10] of the ethyl chloroformate on the anion of the keto ester. Equipped with this knowledge it should be possible to discern the more subtle factors which effect the geometry of the transition state so as to tilt the balance in favor of either carbon- or oxygen-acylation. In this work we planned to explore the effect of systematically changing the ring size of the β-keto ester.

A few literature reports are available describing the acylation of cyclic β-keto esters. Komppa and Talvitie[11] reported the preparation of 2,2-dicarbomethoxycyclopentanone (II, Et = Me) by the reaction of the sodium salt of 2-carbomethoxycyclopentanone with methyl chloroformate. Hydrolysis of this product yielded adipic acid. However, an equally plausible reaction product, consistent with the structure proof given, is the enol carbonate III (Et = Me). The report that ethyl camphorcarboxylate yields the oxygen-acylated product (XIII) on treatment with ethyl chloroformate[12] would provide a precedent for structure III.

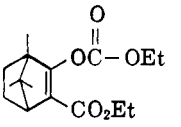



| | n | R |
|---|---|---|
| I | 2 | H |
| IV | 2 | —$CH_2CH_2CO_2Et$ |
| VII | 3 | H |
| X | 4 | H |

| | n | R |
|---|---|---|
| II | 2 | H |
| V | 2 | —$CH_2CH_2CO_2Et$ |
| VIII | 3 | H |
| XI | 4 | H |

+

| | n | R |
|---|---|---|
| III | 2 | H |
| VI | 2 | —$CH_2CH_2CO_2Et$ |
| IX | 3 | H |
| XII | 4 | H |




XIII

More recently Plesek[13] has reported that carbon-acylated products are formed from the reaction of the magnesium salt of 2-carbethoxycyclopentanone with various acid chlorides. However, the acylated product was not isolated, but instead the cyclopentanone ring of the crude product was cleaved to the corresponding keto acid with sodium carbonate. This reaction does not prove that the carbon-acylated product was initially obtained since there remains the possibility that the oxygen-acylated product was originally formed and

(1) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Abstracted in part from the M.S. thesis of C. E. Sullivan.

(3) Recent developments in this area have been reviewed by C. F. Hobbs, C. K. McMillin, E. P. Papdopoulos, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **84**, 43 (1962).

(4) The older literature on the alkylation and acylation of β-keto esters is reviewed by A. Brändström, *Arkiv Kemi*, **6**, 155 (1953).

(5) H. D. Murdoch and D. C. Nonhebel, *J. Chem. Soc.*, 2153 (1962); D. C. Nonhebel, *ibid.*, 738 (1963).

(6) W. J. Barry, *ibid.*, 670 (1960).

(7) A recent review has pointed out the need for such a study: D. P. N. Satchell, *Quart. Rev.* (London), **17**, 161 (1963) (see especially pp. 194–195).

(8) K. Pitzer and W. G. Dauben, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 38; N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5729 (1959).

(9) H. K. Hall, Jr., *ibid.*, **77**, 5993 (1955); **79**, 5438 (1957); H. K. Hall, Jr., and P. W. Morgan, *J. Org. Chem.*, **21**, 249 (1956).

(10) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); G. Stork and S. D. Darling, *ibid.*, **82**, 1512 (1960).

(11) G. Komppa and A. Talvitie, *Ann. Acad. Sci., Fennicae Ser.*, **A57**, **No. 15**, 3 (1941); *Chem. Abstr.*, **38**, 5496 (1944).

(12) J. W. Bruhl, *Ber.*, **24**, 3391, 3709 (1891).

(13) J. Plesek, *Collection Czech. Chem. Commun.*, **21**, 1312 (1956); **22**, 49 (1957); **22**, 1661 (1957).

then rearranged to the carbon-acylated product before ring cleavage.[14]

The results of our study, summarized in Table I, show that the proportion of carbon-acylation decreases as the ring size changes from $C_7$ to $C_5$ to $C_6$. The relative proportion of carbon- and oxygen-acylated product was determined by vapor phase chromatography (v.p.c.) and by the extinction coefficient of the $\alpha,\beta$-unsaturated ester chromophore (oxygen-acylated product) in the ultraviolet spectrum. Pure samples of the carbon- and the oxygen-acylated products of IV and X were not obtained, but the composition of the reaction mixture may be calculated from the extinction coefficient of the mixture, if one makes the reasonable assumption that the pure oxygen-acylated derivatives would have the same extinction coefficients as the oxygen-acylated derivatives of I and VII.

TABLE I

PRODUCTS OF THE REACTION OF ETHYL CHLOROFORMATE WITH CYCLIC $\beta$-KETO ESTERS

| Keto ester | Temp., °C. | Solubility of chelate salt | Total yield, % | % C- and O-acylation Ultraviolet C:O | V.p.c. C:O |
|---|---|---|---|---|---|
| I | 80 | Insoluble | 62 | 24:76 | 23:77 |
| I | R.T.[a] | Insoluble | 57 | 19:81 | 17:83 |
| IV | 80 | Soluble | 68 | 20:80 | 10:90 |
| VII | 110 | Insoluble | 60 | | 1:99 |
| VII | R.T.[a] | Insoluble | 61 | | 1:99 |
| X | 80 | Soluble | 67 | 57:43 | 50:50[b] |
| X | R.T.[a] | Soluble | 54 | 62:38 | 50:50[b] |

[a] Room temperature. [b] Peaks were of equal height but overlapped so that accurate integration was not possible.

The reactions were carried out at room temperature and at reflux temperatures (with the exception of IV which reacted at reflux only) with no appreciable variation in the yield or proportion of carbon- and oxygen-acylated product. The composition of the crude reaction products and the distilled product were shown to be the same by comparison of infrared spectra and vapor phase chromatograms before and after distillation. The distilled products were shown to be stable when heated for 30 min. at 200° in sealed tubes. These data show that oxygen-acylated material was not rearranging to carbon-acylated material either during the reaction or in any of the subsequent work-up and analysis steps.[15]

The structures of the reaction products were proved by spectral and chemical means. The oxygen-acylated product exhibited maxima ascribed to the enol carbonate carbonyl and double bond at 1765 and 1660 cm.$^{-1}$, respectively. The carbonyl group for the $\alpha,\beta$-unsaturated ester appeared at 1720 cm.$^{-1}$. In the cases where appreciable amounts of carbon-acylated product were formed the maxima for the ring carbonyl also was observed. The ultraviolet spectra of the products all exhibited maxima in the 220–230-m$\mu$ region consistent with the enol ester chromophore.[16] The carbon-acylated product would not be expected to have appreciable absorption in that region of the ultraviolet.

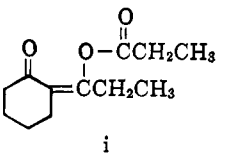
We carried out some degradative reactions on the product obtained from the acylation of 2-carbethoxycyclopentanone to verify the aforementioned spectral assignments. Acid- and base-catalyzed ethanolysis (the product was stable in ethanol alone) yielded diethyl adipate as the principal product. Diethyl carbonate as well as trace amounts of 2-carbethoxycyclopentanone also were found in the base-catalyzed reaction. More definitive evidence for the enol carbonate structure (III) was obtained by reaction with sodium borohydride in ethanol, a procedure which is known to cleave enol esters.[17] Diethyl carbonate was observed as a product of this reaction, a result consistent with the proposed structure. The reaction of sodium borohydride with the carbon-acylated product would not be expected to give diethyl carbonate under such mild reaction conditions.[18]

A sample of the pure III was prepared using pyridine as the reaction solvent.[19] The v.p.c. retention times for the principal product (93%) of this reaction and that from the reaction of the sodio derivative with ethyl chloroformate were identical. The infrared and ultraviolet spectral data of the two products were quite similar except for a more intense ultraviolet absorption for the product from the pyridine reaction and the presence of a weak carbonyl maxima in the infrared at 1740 cm.$^{-1}$ (cyclopentanone carbonyl from product of sodium in benzene reaction). Surprisingly, only starting material was recovered when the acylation of 2-carbethoxycycloheptanone was attempted in pyridine solution. Attempted preparation of pure samples of the carbon-acylated products by treatment of the magnesium salts[20] of 2-carbethoxycyclopentanone and 2-carbethoxycyclohexanone with ethyl chloroformate yielded only starting material and diethyl carbonate.

All this evidence clearly shows that the principal product obtained from the reaction of ethyl chloroformate with 2-carbethoxycycloheptanone is that of oxygen-acylation and not the carbon-acylated product reported by Komppa and Talvitie.[11]

## Discussion

The mechanism of the reactions studied must involve axial attack[10] of the ethyl chloroformate on the $\pi$-electron system of the anion of the $\beta$-keto ester. This is essentially an irreversible process since nonpolar solvents were used and no evidence was found for rearrangements when the reactions were carried out at higher temperatures and longer reaction times. In some cases the salt of the $\beta$-keto ester was insoluble in



i

(14) H. Henecka, *Ber.*, **81**, 196 (1948). This possibility currently is being investigated in our laboratory.

(15) F. Gogan, A. E. O'Brian, E. M. Philbin, N. S. O'Connor, F. R. F. Timoney, and T. S. Wheeler, *Tetrahedron*, **3**, 140 (1958).

(16) The enol acetate of ethyl acetoacetate has a maximum at 212 m$\mu$ (log $\epsilon$ 3.90); R. Richter, *Helv. Chim. Acta*, **35**, 1115 (1952). Compound i has a maximum at 234 m$\mu$ ($\epsilon$ 7800); S. Hunig, E. Benzing, and L. Lucke, *Ber.*, **90**, 2833 (1957).

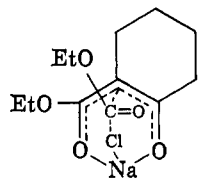
(17) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

(18) Mr. C. Crawford recently has prepared 2,2-dicarbethoxycyclopentanone. It exhibits strong bands in the infrared at 1773 and 1739 cm.$^{-1}$ and a $\lambda_{max}$ at 287 m$\mu$ ($\epsilon$ 54) in the ultraviolet. No diethyl carbonate is formed when it is treated with sodium borohydride (see Experimental).

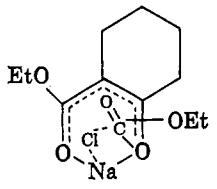
(19) L. Claisen and E. Hasse, *Ber.*, **33**, 1242 (1900); P. E. Wright and W. E. McEwen, *J. Am. Chem. Soc.*, **76**, 454 (1954).

(20) M. Viscontini and N. Merckling, *Helv. Chim. Acta*, **35**, 2280 (1952).

benzene and in others it was soluble. One might expect that a different mechanism would be operative in the two different cases.[21] However, essentially the same proportion of carbon- and oxygen-acylation was obtained when 2-carbethoxycyclopentanone was acylated, the sodium salt of which is insoluble in benzene, as was obtained from diethyl cyclopentanone-2-carboxylate-5-β-propionate (IV),[22] the sodium salt of which is soluble in benzene. If the heterogeneous reactions were proceeding by a mechanism that was considerably different from the homogeneous reactions one would expect to see a significant difference in the reaction products.[23] Other factors found by previous workers to effect course of reaction of an ambident ion—*e.g.*, solvent[21,24] and the metal ion used[25]—were held constant in this work so that the principal factor which governs the course of these acylations must be the different steric requirements of the anions being acylated.[5]



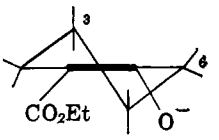

XIV



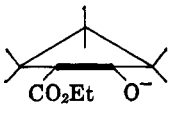

XV

Brändström[4] originally postulated that the transition state for the carbon-acylation reaction is best represented by XIV. The attack of the acylating agent is facilitated by polarization of the carbon–halogen bond by the metal of the chelate ring. Nonhebel,[5] using Brändström's model, suggested, as shown in XV, that the oxygen-acylation reaction involves a four-centered transition state for carbon acylation. Therefore, one would expect that only a small change in the steric requirements of the anion being acylated would change the nature of the transition state from one favoring carbon-acylation to one favoring oxygen-acylation.

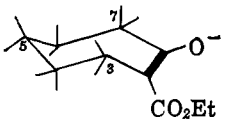
Models of the anions studied reveal that axial attack on the 2-carbethoxycyclohexanone chelate XVI (shown without the chelated metal ion for clarity) is highly hindered by the axial hydrogen at C-4 and the quasi-axial hydrogen at C-6. This hindrance is somewhat less in the cyclopentanone chelate (XVII) where the ring hydrogens are not perpendicular to the plane of the ring and, therefore, are not in direct interference with an entering group. One finds the least hindrance of all in the cycloheptanone ring where the plane described by the chelate system (XVIII) is inclined away from any interference with the quasi-axial hydrogens at C-3, C-5, and C-7.




XVI




XVII




XVIII

The rate of nucleophilic displacement at carbon should be faster than that at oxygen[26] so that the carbon-acylated product would be expected to form more rapidly. However, as the hindrance in the vicinity of the carbon atom increases, the acylation takes place on the more accessible oxygen atom.[27]

## Experimental[29]

**Reaction of 2-Carbethoxycyclopentanone with Ethyl Chloroformate. A. At Room Temperature.**—2-Carbethoxycyclopentanone (31.2 g., 0.2 mole) was added dropwise with stirring and heating to 4.6 g. (0.2 g.-atom) of powdered sodium in 600 ml. of dry benzene. The mixture was refluxed and stirred for 5 hr. with the formation of a white pasty solid. Ethyl chloroformate (33.0 g., 0.3 mole) was added dropwise with stirring to the mixture; it was then stirred at room temperature for 4 hr. The benzene solution was washed twice with water, dried over sodium sulfate, and the benzene distilled *in vacuo*. Distillation of the residue at 82–84° (0.05 mm.) yielded 26 g. (57%); $\lambda_{max}$ 228 mμ (ε 7420); $\nu_{max}$ 1765, 1725, 1660, 1740 (shoulder) cm.$^{-1}$; v.p.c. retention times for the crude reaction mixture, 4.3 (4%), 5.7 (16%), and 6.8 (78%) min. A peak with the retention time of 2.5 min. was observed for the starting β-keto ester. The distilled product had peaks of retention time, 5.4 (17%) and 6.6 (83%) min.

*Anal.* Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.65; H, 7.21.

**B. In Refluxing Benzene.**—The sodium salt of 2-carbethoxycyclopentanone (31.2 g., 0.2 mole) was prepared as previously described. Ethyl chloroformate (33 g., 0.3 mole) was added dropwise with stirring to the sodium salt at room temperature and the mixture was then refluxed and stirred for 5 hr. After the usual work-up, 28.2 g. (62%) of product distilled at 82–84° (0.05 mm.), $\lambda_{max}$ 228 mμ (ε 7010). The crude reaction product exhibited v.p.c. retention times of 5.7 (23%), 6.7 (73%), and 8.1 (2%) min. A peak with retention time of 2.3 min. was observed for starting β-keto ester. The distilled product had peaks of retention time, 5.6 (20%), 6.7 (79%), and 7.9 (1%) min.

**C. With Sodium Hydride in Refluxing Benzene.**—The sodium salt of 2-carbethoxycyclopentanone (144 g., 0.9 mole) was pre-

(21) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).

(22) N. N. Chatterjee, B. K. Das, and G. N. Barpujari, *J. Indian Chem. Soc.*, **17**, 161 (1941).

(23) Evidence has been cited[4,5] which suggests that the sodium salts of β-keto esters and β-diketones have the sodium bound in a chelate ring and not as the enolate salt. We have assumed the sodium to be chelated even though it has been suggested that such salts may be recognized by solubility in nonpolar solvents and the predominent formation of carbon-acylated products on treatment with acid halides. We feel that the binding in the salts of I and IV should be the same (chelate) even though one is soluble and the other insoluble in benzene. The greater solubility of the salt of IV in nonpolar solvents is undoubtedly only a reflection of its greater molecular weight. The proponderance of oxygen-acylation with these chelates is dealt with later in this paper.

(24) N. Kornblum, P. Berrigan, and W. Le Noble, *J. Am. Chem. Soc.*, **82**, 1257 (1960).

(25) D. Y. Curtin, R. J. Crawford, M. Wilhelm, *ibid.*, **80**, 1391 (1958); I. Forsblad, *Arkiv Kemi*, **15**, 403 (1960).

(26) E. S. Gould, "Mechanism and Structure in Organic Chemistry," H. Holt and Co., New York, N. Y., 1959, p. 259.

(27) Brändström[4] explains the formation of oxygen-alkylated products with 2-cyanocyclohexanone and exclusive formation of carbon-alkylated products of 2-cyanocyclopentanone on the greater degree of enolization of the former. Such rationalization is inconsistent with our data as it would predict that 2-carbethoxycycloheptanone (12% enolized[28]) would give more oxygen-acylation than 2-carbethoxycycloheptanone (5% enolized[28]), but actually the opposite is observed.

(28) G. Schwarzenbach, M. Zimmerman, and V. Prelog, *Helv. Chim. Acta*, **34**, 1954 (1951).

(29) Infrared spectra were determined on a Perkin-Elmer Model 137 in carbon tetrachloride. Ultraviolet spectra were determined on a Cary Model 14 in 95% ethanol by Mrs. K. Osmond, Mrs. D. DeTar, and Mrs. P. Ward. V.p.c. analyses were performed on an F and M Model 500 chromatograph equipped with Disc Integrator. A 2-ft. silicone rubber column was used with helium flow rate of 50 ml./min. The column was programmed at 11 deg./min. starting at 90°. Powdered sodium was prepared in toluene and then the toluene was decanted and the solvents and reactants listed were added. In each acylation the infrared spectrum of the reaction product before distillation was determined and it was found to be virtually identical with that of the distilled product. Analyses were performed by F. Pascher, Bonn, West Germany; Midwest Microlab, Indianapolis; and Scandanavian Microanalytical Laboratory, Copenhagen, Denmark.

pared by refluxing with 50 g. (1 mole) of 53% sodium hydride–mineral oil dispersion in 2 l. of dry toluene. Ethyl chloroformate (108 g., 1 mole) was added dropwise with stirring and the mixture was stirred and refluxed an additional 5 hr. Distillation after the usual work-up yielded 153 g. (75%) of a product that was identical in all respects with that prepared in B.

**D. In Pyridine[19] at Room Temperature.**—2-Carbethoxycyclopentanone (31.2 g., 0.2 mole) was dissolved in 32 g. of pyridine, ethyl chloroformate (32.4 g., 0.3 mole) was added slowly, and the mixture was allowed to stand at room temperature for 2 days. Water was added and the mixture was extracted with ether, the ether extracts were washed with cold 10% potassium hydroxide, dried over sodium sulfate, and the ether distilled to yield 12.3 g. of a red oil. Vacuum distillation at 84–86° (0.1 mm.) yielded 4.0 g.; $\lambda_{max}$ 228 mμ (ε 9115); $\nu_{max}$ 1765, 1725, and 1660 cm.$^{-1}$; v.p.c. retention times, 5.4 (7%) and 6.6 (93%) min.

**E. With Magnesium Ethoxide.**[20]—Magnesium turnings (13.25 g.-atom) were converted to magnesium ethoxide by refluxing with 200 ml. of absolute ethanol. Dry ether (500 ml.) was then added to the solution followed by dropwise addition of 78 g. of 2-carbethoxycyclopentanone. The mixture was stirred for an hour, ethyl chloroformate (54 g.) was added dropwise, and the stirring was continued overnight. Acetic acid and water were added to the mixture and the ether layer was separated and washed with water. The ether solution was dried over sodium sulfate, concentrated, and the residue was vacuum distilled to yield 5 g. of diethyl carbonate and 40 g. of starting keto ester (identified *via* the infrared spectra).

**Reaction of Diethyl Cyclopentanone-2-carboxylate-5β-propionate[22] with Ethyl Chloroformate.**—The title compound (111 g., 0.43 mole) was added dropwise with stirring to 10 g. (0.44 g.-atom) of powdered sodium suspended in 0.5 l. of toluene and 1 l. of benzene. The solution was stirred and refluxed for 5 hr. The solution was cooled to room temperature and 57 g. (0.53 mole) of ethyl chloroformate was added; then the mixture was stirred and refluxed for an additional 5 hr. The benzene solution was washed with water and sodium carbonate solution, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue distilled at 155–157° (0.2–0.3 mm.) to yield 95.5 g. (68%). A sample was redistilled for analysis at 155° (0.25 mm.); $\lambda_{max}$ 229 mμ (ε 6371); $\nu_{max}$ 1765, 1740, 1725 (shoulder), and 1650 cm.$^{-1}$; v.p.c. retention times, 10.3 (10%) and 12.7 (90%) min.

*Anal.* Calcd. for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.75; H, 7.43.

**Reaction of 2-Carbethoxycyclohexanone with Ethyl Chloroformate. A. At Room Temperature.**—The sodium salt (34 g., 0.2 mole) of 2-carbethoxycyclohexanone was prepared by refluxing with 4.6 g. (0.2 mole) of powdered sodium for 10 hr. Ethyl chloroformate (33 g., 0.3 mole) was added to the cooled solution and the mixture was stirred at room temperature for 4 hr. The mixture was washed with water, dried over sodium sulfate, and the benzene distilled. Distillation of the residue at 97–98° (0.05 mm.) yielded 29.5 g. (61%); $\lambda_{max}$ 222 mμ (ε 8558); $\nu_{max}$ 1765, 1720, 1660 cm.$^{-1}$. The v.p.c. of the crude reaction mixture exhibited peaks of retention time, 6.1 (1%) and 7.9 (99%) min. A peak of retention time of 3.4 min. was observed for starting material. The distilled product exhibited only one peak with a retention time of 7.2 min.

*Anal.* Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.89; H, 7.51.

**B. In Refluxing Toluene.**—The aforementioned reaction was carried out by refluxing in toluene for 35 hr. A 60% yield of product was obtained that was identical in all respects with that prepared in A.

**C. With Magnesium Ethoxide.**[20]—Magnesium turnings (2.7 g., 0.11 g.-atom) were converted to magnesium ethoxide with 15 ml. of ethanol. Ether (100 ml.) was added and then 17.4 g. (0.1 mole) of 2-carbethoxycyclohexanone in 20 ml. of ether. The mixture was stirred at room temperature for 30 min., then 10.9 g. (0.1 mole) of ethyl chloroformate in 20 ml. of ether was added, and the mixture was allowed to stir at room temperature overnight. At the end of this time the mixture was refluxed for 1 hr., ice and dilute sulfuric acid were added until the water solution was distinctly acid, and the ether layer was separated, washed with water, dried over sodium sulfate, and concentrated. The crude reaction product exhibited v.p.c. peaks of 0.4 (27%), 3.7 (62%), and 11.4 (11%) min. The peaks at 0.4 and 3.7 min. were shown to be diethyl carbonate and 2-carbethoxycyclohexanone, respectively. Distillation of the residue yielded 10 g. of starting keto ester as well as diethyl carbonate. Both were identified *via* infrared spectra.

**Reaction of 2-Carbethoxycycloheptanone[30] with Ethyl Chloroformate. A. At Room Temperature.**—The sodium salt (31.8 g., 0.17 mole) of 2-carbethoxycycloheptanone was prepared by refluxing with 4.6 g. (0.2 g.-atom) of powdered sodium for 5 hr. Ethyl chloroformate (33 g., 0.3 mole) was added dropwise with stirring to the solution of the sodium salt and the mixture was stirred for 4 hr. at room temperature. The benzene solution was washed with water, dried with sodium sulfate, and the benzene was distilled. The residue distilled at 105–108° (0.3 mm.) to yield 23.9 g. (54%); $\lambda_{max}$ 223 mμ (ε 3590); $\nu_{max}$ 1760, 1730, 1715 (shoulder), and 1660 cm.$^{-1}$. The crude reaction mixture exhibited v.p.c. peaks of retention time, 0.8 (7%), 7.7 (45%), and 7.8 (45%) min. A peak of retention time 4.1 min. was observed for the starting material. The distilled product had peaks of retention time, 8.6 (50%) and 8.8 (50%), min.

*Anal.* Calcd. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.40; H, 8.09.

**B. In Refluxing Benzene.**—The sodium salt (92 g., 0.5 mole) of 2-carbethoxycycloheptanone was prepared by refluxing with 13.8 g. (0.6 g.-atom) of powdered sodium suspended in 0.5 l. of toluene and 1 l. of benzene for 4 hr. The reaction mixture was allowed to cool to room temperature and 64.8 g. (0.6 mole) of ethyl chloroformate was added and the mixture was refluxed for an additional 4 hr. The solution was then washed with water, dried over sodium sulfate, and the solvent distilled *in vacuo*. Distillation of the residue at 99–100° (0.1 mm.) yielded 86 g. (67%) of product ($\lambda_{max}$ 223 mμ, ε 4100) that was identical with that from the room temperature reaction.

**C. In Pyridine at Room Temperature.**—The reaction was carried out in exactly the same way as with 2-carbethoxycyclopentanone, but only starting material was isolated on work-up.

**Hydrolysis of the Reaction Product Obtained from the Acylation of the Sodium Salt of 2-Carbethoxycyclopentanone. A. With Acetic Acid.**[31]—The reaction product (8 g.) was dissolved in a solution of 100 ml. of water, 100 ml. of glacial acetic acid, and 5 ml. of hydrochloric acid, and stirred at room temperature overnight. The solution was poured into 1 l. of water and extracted thoroughly with ether. The ether extracts were combined and washed with water and sodium carbonate solution, dried over sodium sulfate, and the ether removed under vacuum. An infrared spectrum of the residue showed it to be starting material.

**B. With Hydrochloric Acid.**—The reaction product (16 g.) was dissolved in a mixture of 75 ml. of concentrated hydrochloric acid and 200 ml. of ethanol and stirred at room temperature overnight. Work-up as in A gave 5 g. of an oil whose infrared spectrum was identical with that of diethyl adipate.

**C. With Sodium Ethoxide.**—The reaction product (16 g.) was added to 250 ml. of 0.28 *M* sodium ethoxide and the mixture was refluxed overnight. The dark brown solution was cooled and poured into 200 ml. of concentrated hydrochloric acid. Water (1.5 l.) was then added and the mixture extracted with ether. The ether extracts were washed with water and sodium carbonate solution, dried over sodium sulfate, and the ether removed on the steam bath. Distillation of the residue at atmospheric pressure yielded 2 g. of a liquid whose infrared spectrum was identical with that of diethyl carbonate. The remainder was too badly charred for further investigation.

A repetition of this experiment followed by distillation under vacuum yielded two fractions. Fraction 1 gave a positive ferric chloride test (violet color) and its infrared spectrum showed it to be mainly diethyl adipate with some 2-carbethoxycyclopentanone (weak infrared bands at 1760, 1660, and 1620 cm.$^{-1}$). Fraction 2 did not give a positive ferric chloride test and its infrared spectrum identified it as diethyl adipate.

**Sodium Borohydride Reduction of the Reaction Product Obtained from the Acylation of the Sodium Salt of 2-Carbethoxycyclopentanone.**—The reaction product (8 g., 0.035 mole) was added dropwise with stirring to 2.6 g. (0.07 mole) of sodium borohydride in 250 ml. of absolute ethanol and the mixture was stirred for 24 hr. at room temperature. Dilute hydrochloric acid (1 l.) was added and the aqueous solution was extracted with ether. The ether extract was washed with sodium carbonate solution, dried over sodium sulfate, and the ether was distilled to yield 0.96 g. of product. The infrared spectrum of this

(30) Prepared by an unpublished procedure of Professor W. Herz and L. Glick.

(31) J. C. Sheehan and C. E. Mumaw, *J. Am. Chem. Soc.*, **72**, 2127 (1950).

material was essentially that of diethyl carbonate; v.p.c. analysis confirmed the presence of diethyl carbonate by a peak of retention time 0.4 (13%) min. However the following peaks also were present, 1.5 (1%), 2.4 (11%), 3.3 (53%), 3.7 (1%), 4.7 (15%), 6.3 (1%), 7.3 (3%), and 8.0 (1%) min.

**Sodium Borohydride Reduction of 2,2-Dicarbethoxycyclopentanone.**[18]—2,2-Dicarbethoxycyclopentanone (8 g., 0.035 mole) was added dropwise with stirring to 2.6 g. (0.07 mole) of sodium borohydride in 250 ml. of absolute ethanol and the mixture was stirred for 24 hr. at room temperature. Dilute hydrochloric acid (1 l.) was added and the aqueous solution was extracted with ether. The ether extract was washed with sodium carbonate solution, dried over sodium sulfate, and the ether was distilled to yield 0.85 g. of product. The infrared spectrum of this material was not at all similar to diethyl carbonate and no peak in the v.p.c. corresponding in retention time to this compound was observed. Peaks of retention times of 4.5 (11%), 6.2 (10%), 7.9 (74%), and 8.3 (5%) min. were observed.

**Attempted Thermal Rearrangement of the Acylation Products.**—One-milliliter samples of the acylation products of 2-carbethoxycyclopentanone, 2-carbethoxycyclohexanone, and 2-carbethoxycycloheptanone were heated in sealed tubes at 200° for 30 min. V.p.c. and infrared analysis indicated no rearrangement took place.

**Acknowledgment.**—The authors wish to thank Professor Werner Herz and Mr. Laverne Glick for communicating the results of unpublished work and for determining several of the vapor phase chromatograms.

# Highly Substituted Aromatics. The Synthesis and Nuclear Magnetic Resonance Spectrum of 2,4,6-Tri-*t*-butyl-3-fluorophenol[1]

BRUCE RICKBORN, DONALD A. MAY, AND ANTONI A. THELEN

*The Department of Chemistry, University of California, Santa Barbara, California*

*Received August 16, 1963*

The low steric requirements of the fluoro substituent allow the insertion of a *t*-butyl group in the 2-position of 3-fluorophenol, as evidenced by the preparation of the title compound. The n.m.r. spectra of this material and some analogs were used for structure proof; long-range H–F spin–spin coupling between the protons of the 2- and 4-*t*-butyl groups and the adjacent fluorine was observed.

The large steric requirement of the *t*-butyl group has been the subject of a great deal of experimental and theoretical chemistry. The bulk effect of this substituent may be used to advantage or it may be the source of extreme synthetic difficulties. The latter are exemplified in the recent syntheses of *o*-di-*t*-butylbenzenes.[2] The strain energy involved in these systems, demonstrated by the apparent distortion of the benzene ring,[2a] supports Brown's earlier suggestion that these compounds are not to be expected from Friedel–Crafts type alkylation reactions.[3]

Extending the question of *ortho* steric effects of the *t*-butyl group, it is noted that innumerable compounds have been prepared by classical aromatic substitution methods which bear one substituent *ortho* to the bulky group.[4] In contrast, very few materials are known in which the *t*-butyl substituent is flanked by two groups other than hydrogen. Among these compounds are the "synthetic musks," in which both *ortho* groups are nitro.[5] Nitration appears generally to be less susceptible to bulk effects than many other electrophilic substitution reactions.[6] Kaeding[7] recently has prepared 4,6-dibromo-2-chloro-3-*t*-butylphenol. This compound, in which the *t*-butyl group is adjacent to bromine and chlorine, represents an extreme for halogenation.

In these examples the *ortho* groups were added after formation of a suitable *t*-butylbenzene derivative. The converse production of highly substituted aromatic *via* *t*-butylation was the object of the present study. The literature contains three reports of di-*ortho*-substituted *t*-butylbenzenes presumably prepared by direct alkylation. Katsui and Kuyama are quoted[8] as having examined the effect of 2,4-di-*t*-butylresorcinol on stabilization of vitamin A; the original literature indicates that the compound in question is the 4,6-derivative, instead, and that an error in translation is involved.

Dacre[9] has reported the preparation of 3,5-di-*t*-butyl-2,4-dihydroxytoluene from 2,4-dihydroxytoluene, but the only structure proof given was an acceptable carbon and hydrogen analysis. This, of course, would be identical for an isomeric O-butylated product, which is more likely the correct structure.[10]

Using the aluminum phenoxide-catalyzed alkylation reaction, which is noted for preferential *ortho* substitution,[11] Stroh, Seydel, and Hahn have reported the formation of 2,6-di-*t*-butyl-3-methylphenol from *m*-cresol.[12] However, it was subsequently shown that no substitution had taken place in the hindered *ortho* position and that the product was in reality 2,4-di-*t*-butyl-5-methylphenol.[13] Thus there are no clear-cut examples in the literature in which a *t*-butyl group has

(1) Work done in part at the University of California, Berkeley, Calif.

(2) (a) A. W. Burgstahler and M. O. Abdel-Rahman, *J. Am. Chem. Soc.*, **85**, 173 (1963); (b) L. R. C. Barclay, C. E. Milligan, and N. D. Hall, *Can. J. Chem.*, **40**, 1664 (1962); (c) E. M. Arnett, M. E. Strem and R. A. Friedel, *Tetrahedron Letters*, 658 (1961); (d) C. Hoogzand and W. Hübel, *ibid.*, 637 (1961).

(3) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 24 (1953).

(4) For a summary of the pertinent information, see G. S. Hammond and M. F. Hawthorne, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. 3.

(5) R. J. W. LeFevre, *J. Chem. Soc.*, 977 (1933).

(6) (a) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, **76**, 2349 (1954); (b) W. Rundel, *Ber.*, **96**, 636 (1963); (c) K. Ley and E. Müller, *ibid.*, **89**, 1402 (1956).

(7) W. W. Kaeding, *J. Org. Chem.*, **26**, 4851 (1961).

(8) G. Katsui and H. Kuyama, *Vitamins* (Kyoto), **5**, 342 (1952); *Chem. Abstr.*, **47**, 8316.

(9) J. C. Dacre, *Biochem. J.*, **78**, 758 (1961).

(10) Resorcinol itself gives a complex mixture of products under these reaction conditions. Although these have not been completely identified, some are definitely ethereal (unpublished results).

(11) (a) A. J. Kolka, J. P. Napolitano, and G. G. Ecke, *J. Org. Chem.*, **21**, 712 (1956); (b) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *ibid.*, **22**, 642 (1957).

(12) R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem.*, **69**, 699 (1957).

(13) R. Stroh, personal communication; see also R. Stroh, R. Seydel, and W. Hahn, "Neuer Methoden der Präparativen Organischen Chemie," Band II, Verlag Chemie, Weinheim, 1960, p. 231.