The Chemistry of Carbanions. XVI. The Stereochemistry of Alkylation of the 1-Acetyl and 1-Cyano Derivatives of 4-(*t*-Butyl)cyclohexane[1a]

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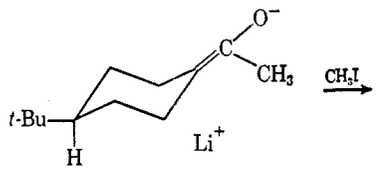
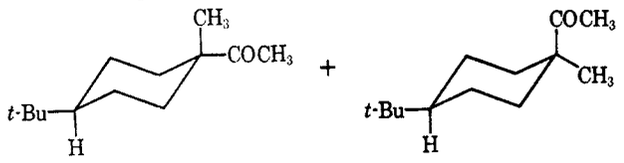
Received August 4, 1967

The lithium enolate anions **1** and **26** from methyl 4-*t*-butylcyclohexyl ketone (**9**) and 1-cyano-4-*t*-butylcyclohexane (**21**) were alkylated with methyl iodide in 1,2-dimethoxyethane solution. In each case, the major monoalkylated product was the material containing an equatorial methyl group. These results are discussed in light of earlier N-methylation of 1-ethyl-4-*t*-butylpiperidine (**4**) to form a mixture of salts in which the stereoisomer with an axial methyl group predominated.

As part of an exploration of the various structural features which control the stereochemistry of enolate anion C alkylation,[2] we have examined the stereochemistry of methylation of the enolate **1** to form

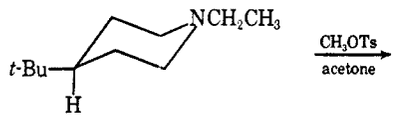


1

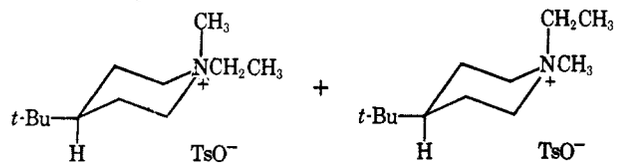


2 **3**

ketones **2** and **3**. The stereochemical problem posed by this reaction differs from the extensively studied[2b] alkylation of cyclohexanone derivatives in that the only portion of the enolate anion contained within the cyclohexane ring is the carbon atom undergoing alkylation. Consequently, the steric interactions incurred by an alkylating agent approaching the enolate anion **1** are related to those which influence the previously studied[3] methylation of the piperidine derivative **4** in which the



4

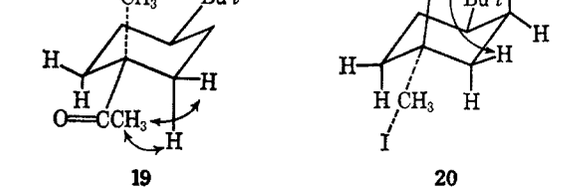


5, 80% of the product **6**, 20% of the product

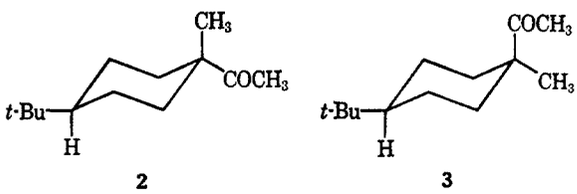
introduction of an axial methyl group to form **5** is approximately four times as rapid as the introduction of a methyl group to form **6**.

A solution of the enolate anion **1** was obtained by reaction of the enol acetate **7** with methyllithium in 1,2-dimethoxyethane (DME)[4] as illustrated in Scheme I. Under these conditions, varying amounts of the dialkylated by-products **13** and **14** were obtained. However, neither of the ethyl ketones **11**, the products expected if equilibration of the enolate anion **1** had occurred prior to alkylation, could be detected. The equations in Scheme II illustrate the procedures used to establish the stereochemistry of the alkylated products **2** and **3** by conversion into the known[5] alcohols **15** and **16**. The stereochemistry of the major dialkylated product **13** was established by the indicated synthesis from the known[6] acid **17**. The results indicate that introduction of an equatorial methyl group to form **3** is approximately five times as fast as introduction of an axial methyl group to form **2**.

It seemed possible that different stereochemical preferences found for the alkylation of the piperidine derivative **4** (introduction of an axial methyl group favored) and the enolate anion **1** (introduction of an equatorial methyl group favored) could be attributed to the stereoelectronic factor requiring a specific orientation of the acetyl group during alkylation of the enolate **1**. In particular, the necessity for the acetyl group to lie in a plane perpendicular to the forming methyl–carbon bond[2] leads to the conclusion that the transition states for alkylation should be portrayed by structures **19** and **20**. In these structures nonbonding



19 **20**



2 **3**

(1) (a) This research has been supported by research grants from the National Institutes of Health (Grant No. 08761) and from the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant No. AF-AFOSR-573); (b) National Institutes of Health Predoctoral Fellow, 1965–1966.

(2) For reviews of this subject, see (a) J. M. Conia, *Rec. Chem. Progr.* (Kresege-Hooker Sci. Lib.), **24**, 43 (1963); (b) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965).

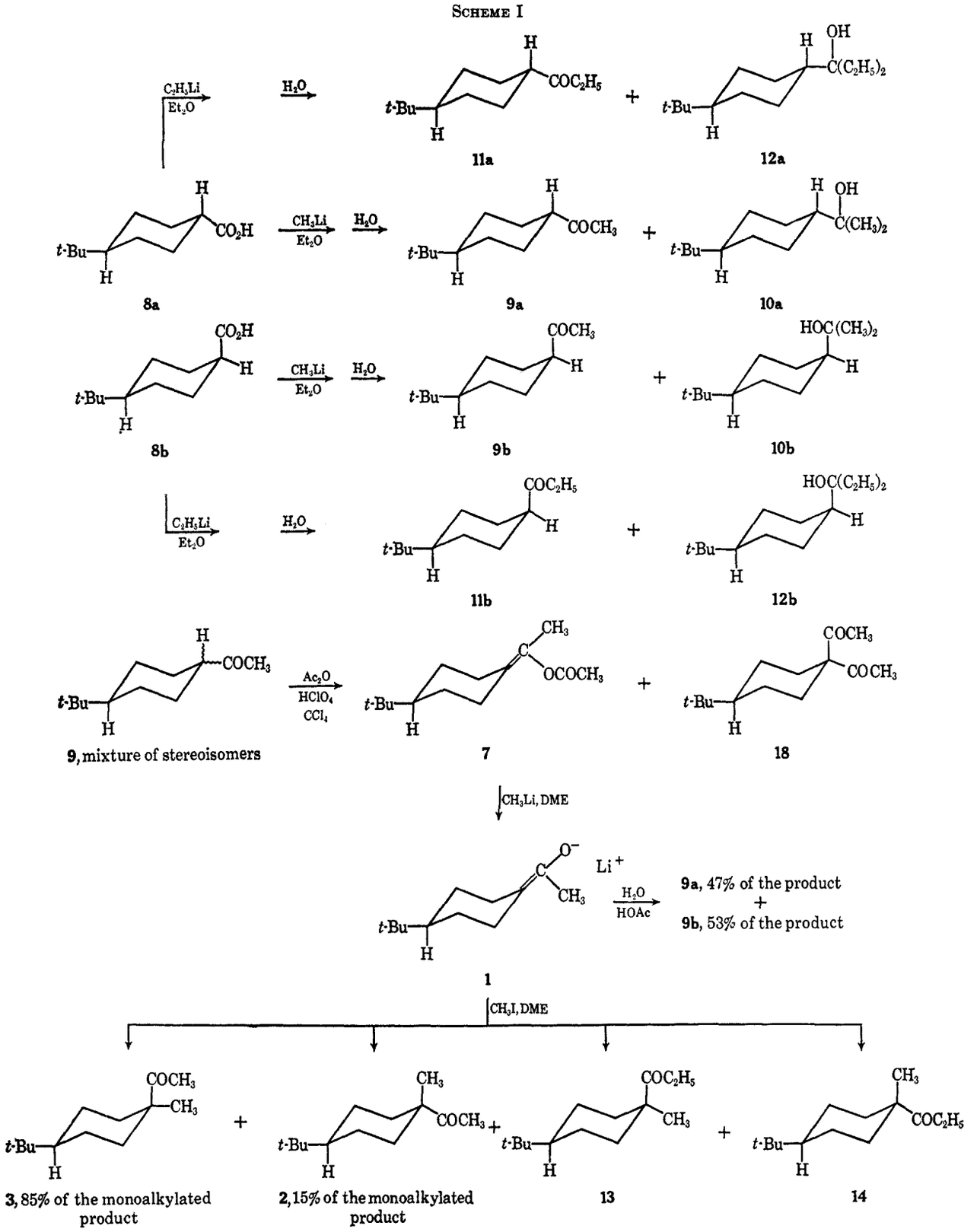
(3) (a) H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966); (b) also see D. R. Brown, B. G. Hutley, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 719 (1966); (c) D. R. Brown, J. McKenna, J. M. McKenna, J. M. Stuart, and B. G. Hutley, *ibid.*, 380 (1967).

(4) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341, 2502 (1965); (b) H. O. House and C. J. Blankley, *ibid.*, **32**, 1741 (1966); (c) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *ibid.*, **32**, 935 (1966).

(5) For leading references, see H. O. House and W. L. Respess, *J. Org. Chem.*, **30**, 301 (1965).

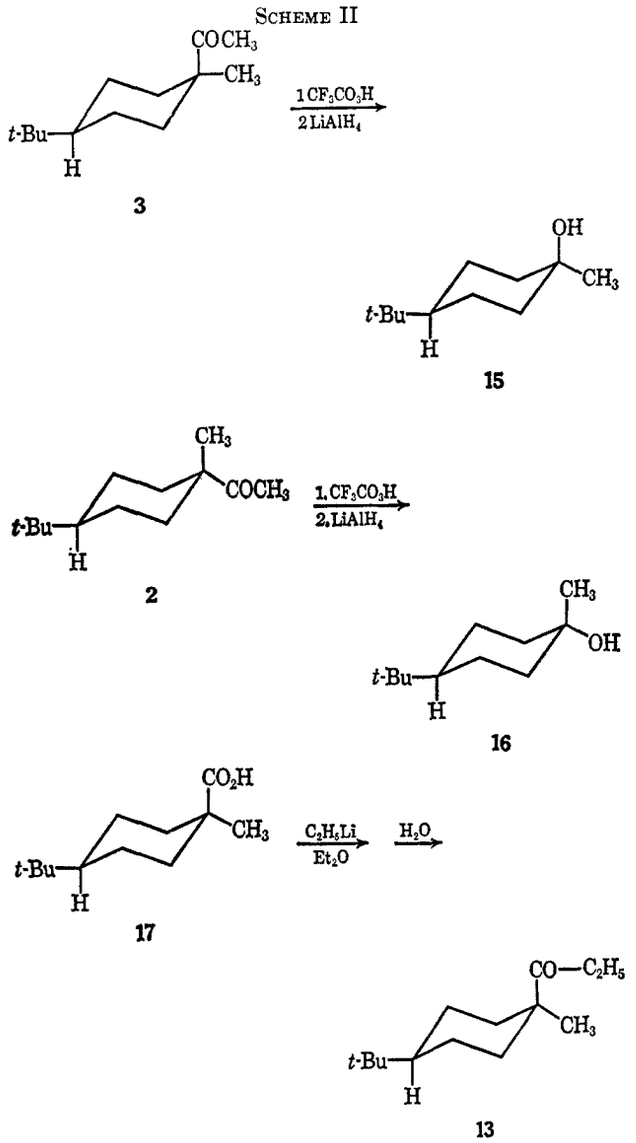
(6) F. D. Greene and A. Fang, unpublished work.

SCHEME I

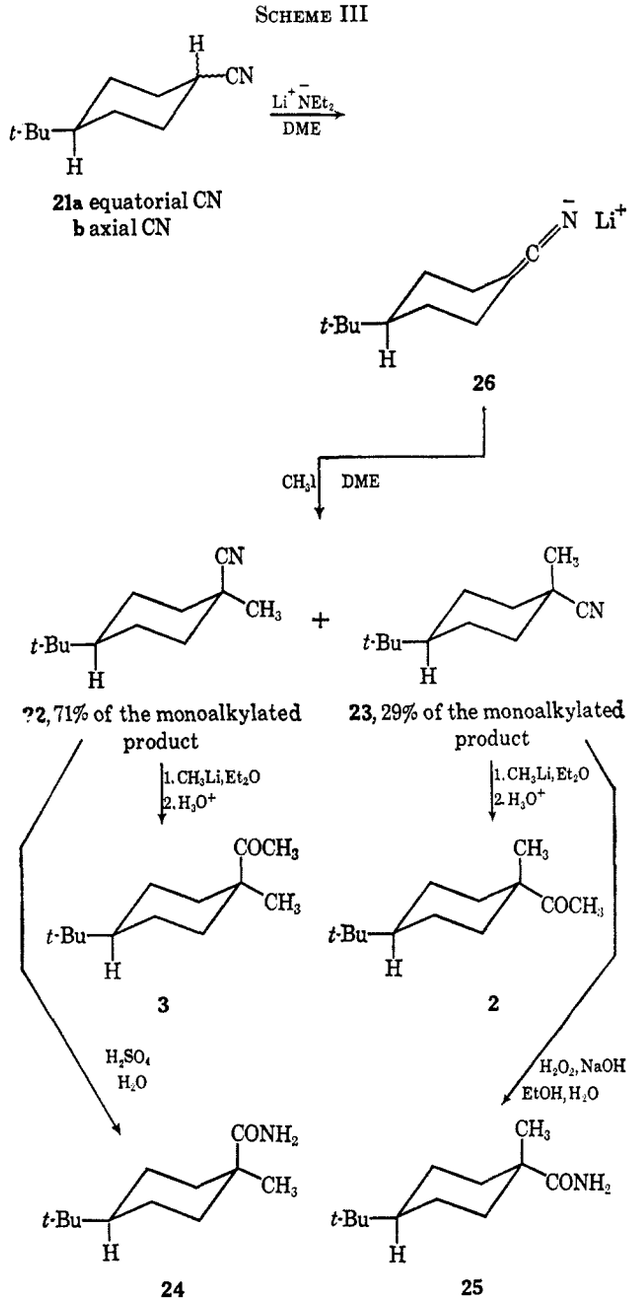


interactions which interfere with the necessary conformation of the acetyl group (represented by heavy arrows in **19** and **20**) appear to be more severe in structure **19** leading to the ketone **2** with an axial methyl group. This consideration does not arise in the alkylation of the related N-ethylamine **4** since no particular orientation of the N-ethyl group is required. To test this hypothesis, the related nitrile **21** was alkylated under comparable conditions. The relatively small, linear cyano function would appear much less subject to the types of nonbonding interactions represented in structures **19** and **20** and, consequently, might be expected to exhibit a stereochemical preference in alkylation similar to that seen for the amine **4**. In fact, the stereochemical results of this alkylation (Scheme III) correspond to the results obtained on alkylation of the

SCHEME II



SCHEME III



enolate anion **1** in that introduction of an equatorial methyl group was approximately three times as rapid as introduction of an axial methyl group.[7] The reactions used to establish the stereochemistry of the alkylated products **22** and **23** are summarized in Scheme III.

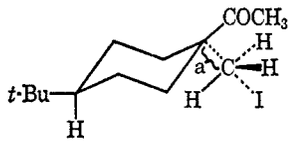
These results indicate that, in the absence of serious opposing steric factors, the methylation of stabilized cyclohexyl carbanion derivatives such as **1** and **26** gives predominantly products with equatorial methyl groups. The corresponding amine **4**, which might be considered as a crude model for such carbanions, yields predominantly the product with an axial methyl group and protonation of the enolate **1** with aqueous acetic acid shows little evidence of any stereoselectivity.[8]

The equilibrium concentrations of the ketones **9** (90% of **9a** and 10% of **9b** in 1,2-dimethoxyethane at 25°) indicate that the free-energy difference between axial and equatorial acetyl groups is approximately 1.3 kcal/mol. The energy difference between these values and the value (1.8 kcal/mol)[7b] for an ethyl group is not sufficient that one can account for the different stereochemical paths for C and N alkylation with differences in stabilities of alkylated products. Consequently, the energy differences between axial and equatorial alkylation at carbon or at nitrogen must be greater in the transition states than in the alkylated products. More specifically, the results suggest that an entering pentacoordinate methyl group has a greater effective steric bulk than an acetyl or nitrile function when it is becoming bonded to carbon (*i.e.*, **27a** of lower energy than **27b**) but has a smaller effective steric bulk than a fully

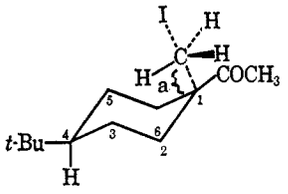
(7) (a) Methylation of the enolate anion derived from a cyclohexanecarboxaldehyde derivative has also been found to result in predominant formation of the product with an equatorial methyl group: R. E. Ireland and L. N. Mander, *Tetrahedron Lett.*, 3453 (1964). (b) The free-energy differences between axial and equatorial substituents are reported to be 1.7 kcal/mol for a methyl group (E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N.Y., 1966, p 44) and 1.3–1.4 kcal/mol for a formyl group (G. W. Buchanan and J. B. Stothers, *Chem. Commun.*, 179 (1967)).

(8) Studies of the stereochemistry of enolate protonation are complicated by the fact that the rates of protonation at carbon and at oxygen are presumably both diffusion controlled and, consequently, approximately equal; see M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964). As a result, approximately half of the mixture of stereoisomeric ketones **9** is derived not from the enolate but from subsequent protonation of the enol at carbon.

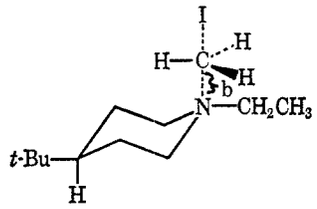
bonded alkyl group (*e.g.*, methyl, ethyl, benzyl)[3] when it is becoming bonded to nitrogen (*i.e.*, **28a** of lower energy than **28b**). Two general explanations for



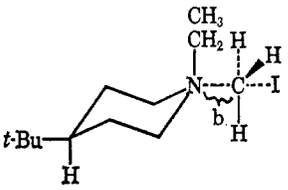
27a



27b



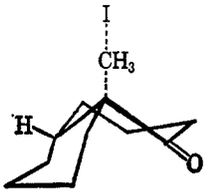
28a



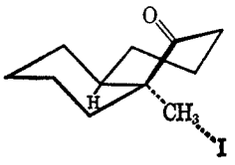
28b

this apparent difference in the effective size of an entering methyl group can be considered. (1) The forming bond to the alkylating agent is more completely formed, and consequently shorter, in carbon alkylation (bond a in **27**) than is the case in the nitrogen alkylation (bond b in **28**). (2) The direction of attack by the entering methyl group is different in the two types of alkylation. Specifically, in the axial nitrogen alkylation the entering group presumably approaches the tetrahedral nitrogen atom from a direction essentially perpendicular to the plane of the piperidine ring as indicated in structure **28a**. Since the nucleophilic centers in initial enolate anions **1** and **26** (and their associated cations) are not tetrahedral but planar, the entering axial methyl group will presumably approach C-1 on a path which is not perpendicular to the plane of the cyclohexane ring but rather tilted back toward C-3 and C-5 as illustrated in structure **27b**. This reaction path will bring the entering methyl group closer to the axial hydrogens at C-3 and C-5 (structure **27b**) than is the case in the corresponding N alkylation (structure **28a**) and would serve to destabilize this reaction path leading to axial C alkylation. As formation of the new C–C bond at the transition state becomes more complete, this latter factor will become less important since with complete C–C bond formation the C-1 carbon will be tetrahedral and the methyl group will be perpendicular to the cyclohexane ring. At the present time our available data[4] are most consistent with the idea that the transition states for both amine and enolate alkylations resembled the starting materials more than the products. Consequently, we favor the second explanation in which the orientation of the entering alkyl group rather than the length of the forming bond is assigned primary importance. We hope to obtain information bearing on these questions from experiments currently in progress.

Finally, it should be noted that the preference for alkylation of a cyclohexyl ketone to introduce an equatorial alkyl group agrees very well with the observation that bridgehead alkylation of 1-decalone derivatives[2,4a] and 1-keto perhydroindan derivatives[2,4b] favors the production of *cis*-fused products. In either of the probable[4c] transition states (**29** or **30**)



29



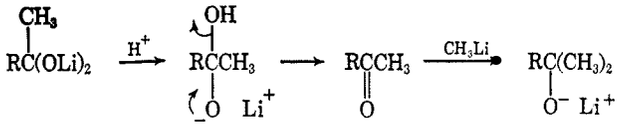
30

leading to 9-methyl-*cis*-1-decalone, it will be noted that the entering methyl group is equatorial with respect to the nonoxygenated cyclohexane ring.

Experimental Section[9]

Preparation of the Starting Materials.—The *cis* (**8b**, mp 116–117.5°, lit.[10a] mp 117–118°) and *trans* (**8a**, mp 175–176°, lit. mp 176–177°,[10b] 174.5–175°[10a]) acids were prepared and separated as previously described.[10] The purity of each acid was verified by esterification of each isomer with excess ethereal diazomethane followed by gas chromatographic analysis;[11,12] the *cis*-methyl ester was eluted more rapidly than the *trans* isomer. Ethereal solutions of methyllithium were prepared and analyzed as previously described.[13]

Preparation of the Ketones 9 and 11.—Since our initial reaction of the acid **8** with ethereal methyllithium led to mixtures which contained both the expected ketones **9** and variable amounts of the alcohols, we studied various methods to diminish the proportion of alcohol formed in the reaction. We concluded that the bulk of the alcohol by-product was formed during the quenching procedure when the ether solution containing the lithium alkoxide[14] and methyllithium was added to aqueous acid. Evidently the indicated reactions occur sufficiently rapidly that they may compete with the rate of mixing of the ethereal solution containing excess methyllithium with aqueous acid. The



initial addition of methyllithium to the carboxylic acid was less critical since small amounts (1–3%) of alcohol were formed by dropwise addition of methyllithium to either the free acid **8** or to its lithium salt (prepared from **8** and lithium hydride), provided that mixing was sufficiently rapid during the subsequent quenching procedure. The following procedure was found to be reproducible and to give small amounts of alcohol by-product.

To a cold (0°), vigorously stirred solution of 7.235 g (37.9 mmol) of a mixture of stereoisomeric acids **8** in 250 ml of ether was added, dropwise over a period of 0.75 hr, 60 ml of an ethereal solution containing 76.9 mmol of methyllithium. During the addition a voluminous white precipitate (the lithium salt of the acid) separated and then redissolved as the addition was continued. The resulting faintly turbid solution was stirred at

(9) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian Model A-60 nmr spectrometer. The chemical shift values are expressed either in cycles per second or δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a CEC Model 21-130 mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. All reactions utilizing organolithium reagents were conducted under a nitrogen atmosphere.

(10) (a) H. H. Lau and H. Hart, *J. Amer. Chem. Soc.*, **81**, 4897 (1959); (b) R. D. Stolow, *ibid.*, **81**, 5806 (1959); (c) M. Tichý, J. Jonas, and J. Sicher, *Coll. Czech. Chem. Commun.*, **24**, 3434 (1959).

(11) A gas chromatography column packed with silicone fluid, no. 710, suspended on Chromosorb P was employed for this analysis.

(12) The *cis*-methyl ester is reported to melt at 26.1–26.7° and the *trans*-methyl ester is reported to boil at 84° (0.9 mm): E. A. S. Cowell, N. B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960).

(13) H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

(14) H. F. Bluhm, H. V. Donn, and H. D. Zook, *J. Amer. Chem. Soc.*, **77**, 4406 (1955).

room temperature for 4 hr and then 50-ml aliquots were removed from the reaction mixture and added, dropwise and with stirring, to fresh portions of ice and dilute aqueous hydrochloric acid. The combined ether layers were washed with aqueous sodium carbonate and with water and then were dried and concentrated. Distillation of the residual liquid (6.59 g) separated 6.54 g (94.8%) of colorless liquid, bp 67–72° (0.57 mm), $n^{25}D$ 1.4593, which contained[15] 9% of the *cis* ketone **9b** (eluted first) and 91% of the *trans* ketone **9a** (eluted second). Neither of the alcohols **10** was detected. Acidification of the aqueous sodium carbonate washings afforded 0.24 g of the starting acid **8**.

The reaction of 165.7 mg (0.90 mmol) of the *trans* acid **8a** with 3.46 mmol of methyllithium in 6.7 ml of ether was performed following the above procedure except that special precautions to obtain rapid mixing during the addition and quenching steps were not observed. The crude neutral product, an oil, contained[16] the *trans* ketone **9a** (46%, first eluted) and the *trans* alcohol **10a** (54% eluted second). Samples of each of these components were collected.[16] The *trans* **ketone 9a** was obtained as a colorless liquid: ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$), δ 0.88 (9 H singlet, $(CH_3)_3C$), 2.20 (3 H singlet, $COCH_3$), and 1.0–2.5 multiplet (10 H, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 57 ($(CH_3)_3C^+$), 43 ($CH_3C{\equiv}O^+$), and 41.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.14; H, 12.16.

The *trans* **alcohol 10a** was obtained as a solid which was sublimed (75° at 0.15 mm) to separate white needles: mp 101–102°; ir (CCl_4), 3590 cm^{-1} (OH); nmr ($CDCl_3$), δ 0.87 (9 H singlet, $(CH_3)_3C$), and 1.19 (6 H singlet, $(CH_3)_2C$); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 59 ($(CH_3)_2C{=}O^+H$) and 57 ($(CH_3)_3C^+$).

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.83; H, 13.21.

Similarly, reaction of 111.2 mg (0.603 mmol) of the *cis* acid **8b** with 2.18 mmol of methyllithium in 4.7 ml of ether yielded a crude neutral product which contained[16] the *cis* ketone **9b** (58%, eluted first) and the *cis* alcohol **10b** (42%). A collected[16] sample of the *cis* **ketone 9b** was a colorless liquid: ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$), δ 0.84 (9 H singlet, $(CH_3)_3C$), 2.22 (3 H singlet, CH_3CO), and 1.0–2.8 multiplet (10 H, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 71, 57 ($(CH_3)_3C^+$), 43 ($CH_3C{\equiv}O^+$), and 41.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.85; H, 12.08.

A collected[16] sample of the *cis* **alcohol 10b** was a colorless oil: ir (CCl_4), 3600 (unassociated OH) and 3420 cm^{-1} (broad, associated OH); nmr ($CDCl_3$), 0.87 (9 H singlet, $(CH_3)_3C$) and 1.22 (6 H singlet, $(CH_3)_2C$); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 59 ($(CH_3)_2C{=}^+OH$) and 57 ($(CH_3)_3C^+$).

Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.69; H, 13.15.

After a mixture of 99.4 mg (0.54 mol) of the *trans* acid **8a** and 1.08 mmol of ethyllithium in 5.3 ml of benzene had been allowed to react for 2 hr, the resulting solution was added, dropwise and with stirring, to dilute aqueous hydrochloric acid. The crude neutral product, isolated as previously described, contained[15] the *trans* ketone **11a** (*ca.* 60%, eluted first) and a product thought to be the *trans* alcohol **12a** (*ca.* 40%, eluted second): ir (CCl_4), 3600 and 3460 cm^{-1} (OH). A collected[15] sample of the *trans* **ketone 11a** was obtained as a colorless liquid: ir (CCl_4), 1715 cm^{-1} (C=O); nmr (CCl_4), δ 2.37 (2 H quadruplet, J = 7 cps, $COCH_2$–), 0.97 (3 H triplet, J = 7 cps, CH_3C), and 0.84 (9 H singlet, $(CH_3)_3C$–); mass spectrum, molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 139, 83, 57, 55, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.60; H, 12.41.

The same procedure was repeated with 47.6 mg (0.258 mmol) of the *cis* acid **8b** and 0.516 mmol of ethyllithium in 4.1 ml of benzene to yield a crude neutral product which contained[15] the *cis* ketone **11b** (*ca.* 70%, eluted first) and a component believed to be the *cis* alcohol **12b** (*ca.* 30%, eluted second): ir (CCl_4), 3600 and 3470 cm^{-1} (OH). A collected sample of the *cis* **ketone 11b** was obtained as a colorless liquid: ir (CCl_4), 1715 cm^{-1} (C=O); nmr (CCl_4), δ 2.38 (2 H quadruplet, J = 7 cps, $CO-CH_2$–), 0.99 (3 H triplet, J = 7 cps, CH_3C), and 0.81 (9 H singlet, $(CH_3)_3C$–); mass spectrum, molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 139, 111, 85, 83, 57, 55, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.65; H, 12.39.

Examination of the gas chromatographic behavior[16] of the ethyl ketones **11** established that the *cis*-ethyl ketone **11b** was eluted more rapidly than the *trans*-ethyl ketone **11a** and that each of the ethyl ketones **11** was resolved from the subsequently described alkylation products **2**, **3**, **13**, and **14**.

Preparation of the Enol Acetate 7.—A solution of 19.19 g (0.0968 mol) of the ketone **9** (a mixture of stereoisomers), 100 g (0.978 mol) of acetic anhydride, and 0.5 ml of aqueous 70% perchloric acid in 300 ml of carbon tetrachloride was stirred at room temperature for 1.5 hr and then diluted with 500 ml of pentane. The resulting solution was stirred with 200 ml of saturated aqueous sodium bicarbonate to which additional portions of solid sodium bicarbonate were added periodically until the evolution of carbon dioxide ceased. After the organic layer had been separated, dried, and concentrated, the residual oil (22.3 g) was distilled through a 90-cm spinning-band column. Fractions collected at 143–148° (10 mm), $n^{29}D$ 1.4689, amounted to 10.26 g (47%) and contained[15] the **enol acetate 7** (eluted first) contaminated with 1.5% of the diketone **18** (eluted second). The spectra of the enol acetate **7** indicate it to be the more highly substituted isomer: ir (CCl_4), 1755 (enol ester C=O) and 1690 cm^{-1} (enol C=C); nmr (CCl_4), δ 2.06 (3 H singlet, CH_3COO–), 1.82 (3 H broad singlet, $CH_3C{=}C$), 0.86 (9 H singlet, $(CH_3)_3C$–), and 1.0–2.7 multiplet (9 H, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 224 with abundant fragment peaks at *m/e* 182 (M − $CH_2{=}C{=}O$), 57, 43, and 41.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.77; H, 10.84.

The later fractions from the fractional distillation contained increasing amounts of the solid diketone **18** which could be separated by recrystallization from methanol. The pure **diketone 18** separated as white plates: mp 82.0–82.5°; ir (CCl_4), 1695 and 1715 cm^{-1} (shoulder) (C=O of nonenolized β-diketone); nmr ($CDCl_3$), δ 2.10 and 2.05 (two 3 H singlets, CH_3CO–), 0.80 (9 H singlet, $(CH_3)_3C$–), and 1.0–2.7 multiplet (9 H, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 224 with abundant fragment peaks at *m/e* 182, 57, 43, and 41.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.77; H, 10.60.

From reactions of the methyl ketone **9** with isopropenyl acetate and *p*-toluenesulfonic acid,[4] mixtures of enol acetates were obtained which contained[16] both the more highly substituted enol acetate (eluted first) and a more slowly eluted component believed to be a mixture of the stereoisomeric less highly substituted enol acetates. The infrared and nmr spectra of this mixture were consistent with this assignment. Acid-catalyzed isomerization[4] of this mixture converted the material into a mixture of enol acetates which contained[16] *ca.* 95% of the more highly substituted enol acetate **7**. As had been noted previously,[4b] formation of the C-acetylated product **18** was not a significant side reaction when the isopropenyl acetate procedure was employed for the preparation of the enol acetate.

Methylation of the Enolate Anion 1.—Following previously described procedures,[4] the enol acetate **7** was added to solutions of methyllithium in 1,2-dimethoxyethane until the triphenylmethyl anion indicator was almost decolorized. The resulting solutions of enolate anion were stirred vigorously at room temperature and methyl iodide was added in one portion. After each reaction mixture was stirred for the time specified in Table I, a 10-ml aliquot of dilute, aqueous hydrochloric acid was added, followed by a weighed sample of tetralin (as an internal standard). The reaction mixtures were partitioned between water and ether

TABLE I

METHYLATION OF THE ENOLATE ANION 1 IN DIMETHOXYETHANE SOLUTION

Concn of enolate anion, *M*	Concn of methyl iodide, *M*	Reaction time, sec	Products, % yield					
			9a	**9b**	**2**	**3**	**14**	**13**
0.088	0.36	30	3.3	2.1	7.2	54.8	1.8	15.5
0.096	0.44	10	4.6	5.0	10.2	56.8	1.9	8.3
0.089	0.35	*Ca.* 2	13.2	13.2	8.1	47.2	...	2.5

(15) A gas chromatography column packed with LAC-728 (diethylene glycol succinate) suspended on Chromosorb P was employed for this analysis.

(16) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

and the ethereal layer was washed with aqueous sodium bicarbonate, dried, concentrated, and analyzed by gas chromatography.[16] The gas chromatography equipment was calibrated with known mixtures of collected samples to permit the yield calculations listed in Table I. The retention times[16] of the components being analyzed follow: tetralin, 27.2 min; monoalkylated ketone **3**, 38.2 min; starting ketone **9b**, 41.4 min; dialkylated ketone **13**, 43.2 min; starting ketone **9a**, 51.6 min; monoalkylated ketone **2**, 56.4 min; and dialkylated ketone **14**, 68.0 min.

In another experiment a solution of the enolate anion **1**, from 0.568 mmol of the enol acetate **7** and 1.32 mmol of methyllithium, in 6.6 ml of 1,2-dimethoxyethane containing a weighed amount of tetralin was added dropwise to a solution of 1.29 mmol of acetic acid in 63 ml of water. The ethereal extract from this mixture contained[15] (average values from two runs) 47% of the equatorial ketone **9a** and 53% of the axial ketone **9b**; the calculated recovery of the ketone **9** was 72%.

To determine the equilibrium composition of the ketones **9**, a weighed sample (*ca.* 0.1 mmol) of each pure ketone was added to 2.00 ml of 1,2-dimethoxyethane which contained a weighed amount (*ca.* 10 mg) of tetralin as an internal standard and 0.05 mmol of alcohol-free potassium *t*-butoxide. Each solution was stirred at room temperature for 2 hr and then partitioned between ether and dilute aqueous hydrochloric acid. The neutral product recovered from each ether solution contained[15] 90% of the equatorial ketone **9a** and 10% of the axial ketone **9b**; the calculated recovery of ketones **9** exceeded 90% in each case.

Identification of the Alkylation Products from Ketone 9.—Each component was collected from the gas chromatograph[15,16] of an appropriate alkylation reaction. The **monoalkylated ketone 3** was separated as a crystalline solid which was sublimed (40° at 10 mm) to separate white needles: mp 46.5–47°; ir (CCl_4), 1705 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.05 (3 H singlet, CH_3CO), 0.98 (3 H singlet, CH_3C), and 0.73 (9 H singlet, $(CH_3)_3C$–); mass spectrum, weak molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 97, 57, 55, 43, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.52; H, 12.21.

The **monoalkylated ketone 2**, a crystalline solid, was sublimed (60° at 20 mm) to afford white plates: mp 45.5–46.5°; ir (CCl_4), 1705 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.10 (3 H singlet, CH_3CO), 1.10 (3 H singlet, CH_3C), and 0.85 (9 H singlet, $(CH_3)_3C$–); mass spectrum, weak molecular ion peak at *m/e* 196 with abundant fragment peaks at *m/e* 97, 83, 69, 57, 55, 43, and 41.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.77; H, 12.35.

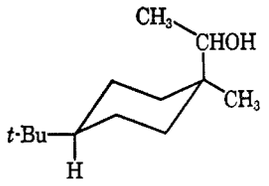
The dialkylated ketone **13** was obtained as a colorless liquid: ir (CCl_4), 1710 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.48 (2 H quadruplet, J = 7 cps, $-CH_2CO-$), 1.03 singlet superimposed on the center peak of a triplet with J = 7 cps, (6 H, two CH_3C groups), and 0.81 (9 H singlet, $(CH_3)_3C$–); mass spectrum, weak molecular ion peak at *m/e* 210 with abundant fragment peaks at *m/e* 97, 83, 69, 57, 55, and 41.

Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.95; H, 12.37.

A previously characterized[6] sample (65.4 mg or 0.329 mmol) of the *cis* acid **17** (mp 129–130.5°) was allowed to react with 0.658 mmol of ethyllithium in 4.4 ml of benzene following the previously described procedure. The crude neutral product exhibited only a single gas chromatographic peak[15] corresponding to the ketone **13**. A collected[15] sample was identified with ketone **13** by comparison of infrared spectra.

The minor dialkylated ketone **14** was separated as a colorless liquid which still contained an impurity which was only partially resolved by gas chromatography.[15,16] Although we were unsuccessful in obtaining a pure sample of this minor product, the spectroscopic properties of the crude material leave little doubt as to its identity: ir (CCl_4), 1705 cm^{-1} (C=O); nmr (CCl_4), δ 2.41 (2 H quadruplet, $-CH_2CO-$), 0.86 (9 H singlet, $(CH_3)_3C$–), and 0.8–2.0 multiplet (aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 210 with abundant fragment peaks at *m/e* 97, 83, 69, 57, 55, and 41.

Baeyer–Villiger Oxidation of the Ketones 2 and 3.—A mixture of 76.3 mg (0.39 mmol) of the ketone **3**, 447 mg of disodium hydrogen phosphate, and *ca.* 1.9 mmol of peroxytrifluoroacetic acid[17] in 1.2 ml of methylene chloride was stirred at room temperature for 3 days. Since the crude neutral product had infrared absorption indicative of a mixture of trifluoroacetate (1780 cm^{-1}), acetate (1730 cm^{-1}), and ketone (1700 cm^{-1}) functions, the material was treated with additional portions of peroxytrifluoroacetic acid and disodium hydrogen phosphate and stirring was continued for an additional 2 days. The resulting neutral product, which still contained some unchanged ketone, was treated with a mixture of 34.5 mg (0.908 mmol) of lithium aluminum hydride and 1.6 ml of ether. The resulting mixture was stirred at room temperature for 1.5 hr and then treated with sufficient dilute aqueous sodium hydroxide to precipitate the aluminum and lithium salts as a granular precipitate. After the precipitate had been separated and washed with ether, the combined ether solutions were concentrated. The residual liquid contained[15] a mixture of the tertiary alcohol **15** (eluted first) and the secondary alcohol **31** (eluted second, from reduction of the unchanged ketone **3**). A sample of the alcohol **31**, obtained by reduction of the



31

ketone **3** with ethereal lithium aluminum hydride, was identified with a collected[15] sample of the above component by comparison of infrared spectra, mass spectra, and gas chromatographic retention times. A collected[15] sample of the tertiary alcohol **15** was identified with a previously described[5] sample by comparison of gas chromatographic retention times and infrared spectra.

Reaction of 22.1 mg (0.113 mmol) of the ketone **2** with *ca.* 0.67 mmol of peroxytrifluoroacetic acid[17] and 129 mg of disodium hydrogen phosphate in 0.43 ml of refluxing methylene chloride for 1.5 hr afforded a crude neutral product which no longer contained any starting ketone. Reduction with 25.6 mg (0.676 mmol) of lithium aluminum hydride in 1.0 ml of ether as previously described yielded a crude neutral product which exhibited a single gas chromatographic peak[15] corresponding to the tertiary alcohol **16**. A collected sample was identified with a previously described[5] sample of the alcohol **16** by comparison of gas chromatographic retention times and infrared spectra.

Preparation of the Nitrile 21.—Following previously described procedures,[18] 6.0 g of a mixture of stereoisomeric acids **8** was converted into 5.35 g (89.5%) of a mixture of stereoisomeric amides, mp 156.5–159° (lit.[18] melting point of *cis* isomer, 162.7–163.9°; *trans*, 134.2–135.8°), and 3.00 g of this amide mixture was dehydrated to yield 2.50 g (92.3%) of a mixture of stereoisomeric nitriles **21**, bp 117.5–119° (12 mm). This mixture contained[15] *ca.* 58% of the axial nitrile **21b** (eluted first) and *ca.* 42% of equatorial nitrile **21a** (eluted second). Collection[15] from the gas chromatograph afforded pure samples of the *cis*-nitrile **21b**, mp 54–55° (lit.[18] mp 56.3–57.3°) and the *trans*-nitrile **21a**, mp 31–32° (lit.[18] mp 33.4–34.7°).

Methylation of the Nitrile 21.—To a solution of 21.6 mmol of methyllithium and several milligrams of triphenylmethane (as an indicator) in 35 ml of 1,2-dimethoxyethane was added 2.15 ml (20.4 mmol) of diethylamine. To the resulting red solution was added a solution of 2.80 g (17.0 mmol) of the nitrile **21** (mixture of stereoisomers) in 3.0 ml of 1,2-dimethoxyethane. After the pale red solution had been warmed to 50° for 10 min and then cooled to room temperature, 5.45 ml (87.2 mmol) of methyl iodide was added to the mixture rapidly with stirring. After the exothermic reaction subsided, the mixture was stirred for 25 min and then partitioned between ether and aqueous hydrochloric acid. The ethereal layer was washed with water and aqueous sodium thiosulfate, dried, and concentrated. Distillation in a short-path still separated 2.92 g (95.7%) of alkylated product which contained (in order of increasing retention time)[15] the axial nitrile **22** (*ca.* 68%), the axial nitrile **21b** (*ca.* 2%), the equatorial nitrile **23** (*ca.* 29%), and the equatorial nitrile **21a** (*ca.* 3%). This alkylation was repeated on a smaller scale in the presence of an internal standard (biphenyl). Utilizing previously calibrated gas chromatography apparatus,[15] the calculated yields were 68% of the *cis*-nitrile **22** and 28% of the

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trans-nitrile **23** corresponding to a 71:29 ratio of the monoalkylated products.

To examine the effect of using a less reactive alkylating agent, a cold (−70°) solution of methyl chloride (*ca.* 16 mmol) in 2.0 ml of 1,2-dimethoxyethane was treated with a solution of the anion **26**, prepared from 1.08 mmol of the nitrile **21** and 1.40 mmol of lithium diethylamide in 3.8 ml of 1,2-dimethoxyethane. After the addition was complete, the solution was allowed to warm to room temperature and was stirred for 23 hr and then subjected to the previously described isolation procedure. After a weighed amount of internal standard had been added, analysis[15] indicated the yields of alkylated products to be 67% of **22** and 13% of **23** corresponding to an 84:16 ratio of monoalkylated products.

Samples of each of the alkylated nitriles **22** and **23** were collected[15] for characterization. Sublimation (65° at 10 mm) of the axial nitrile **22** afforded the material as white plates: mp 48.5–49.5°; ir (CCl_4), 2230 cm^{-1} (C≡N); nmr (CCl_4), δ 1.1–2.3 (9 H multiplet, aliphatic CH), 1.37 (3 H singlet, CH_3C), and 0.94 (9 H singlet, $(CH_3)_3C$); mass spectrum, weak molecular ion at *m/e* 179 with abundant fragment peaks at *m/e* 123, 108, 95, 57, 41, and 39.

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81. Found: C, 80.62; H, 12.04.

The equatorial nitrile **23** sublimed (80° at 10 mm) as white needles: mp 49.5–50°; ir (CCl_4), 2235 cm^{-1} (C≡N); nmr (CCl_4), δ 1.0–2.2 (9 H multiplet, aliphatic CH), 1.40 (3 H singlet, CH_3C), and 0.90 (9 H singlet $(CH_3)_3C$); mass spectrum, weak molecular ion peak at *m/e* 179 with abundant fragment peaks at *m/e* 124, 108, 95, 57, 56, 55, 41, and 39.

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81. Found: C, 80.55; H, 11.89.

The Stereochemistry of Nitriles 22 and 23. A. Conversion into Ketones 2 or 3.—A solution of 62.7 mg (0.35 mmol) of the nitrile **22** and 1.44 mmol of methyllithium in 3.6 ml of ether was refluxed with stirring for 15 hr and then poured into 50 ml of dilute, aqueous hydrochloric acid. The resulting mixture was heated on a steam bath overnight and then extracted with ether. The ethereal solution was dried and concentrated to leave the crude ketone **3**[15] as a residual solid. Sublimation (70° at 0.12 mm) afforded 62.1 mg (91.7%) of the ketone **3**, mp 47.5–48°, identified with the previously described sample by a mixture melting point determination and by comparison of gas chromatographic retention times[15] and infrared and mass spectra.

The comparable reaction of 46.3 mg (0.26 mmol) of the nitrile **23** with 1.3 mmol of methyllithium and subsequent hydrolysis yielded, after sublimation (70° at 10 mm), 44.1 mg (87%) of the ketone **2**, mp 45–46°, identified with the previous sample by all of the criteria listed above.

B. Conversion into Amides 24 and 25.—A mixture of 42.0 mg (0.23 mmol) of the nitrile **23**, 0.1 ml (0.87 mmol) of aqueous 30% hydrogen peroxide, 0.15 ml of absolute ethanol, and 9.6 μl (0.06 mmol) of aqueous 6 *N* sodium hydroxide was stirred at room temperature for 1 hr and at 50° for 2 hr. Upon dilution with water, the amide separated as a crystalline solid, mp 137–139°, yield 39.8 mg (86%). Recrystallization from aqueous ethanol afforded the pure equatorial amide **25** as white needles: mp 139.5–140° (lit.[6] mp 139.5–140°); ir ($CHCl_3$) 3510, 3480, and 3390 (NH), 1670 (amide C=O), and 1580 cm^{-1} (NH_2 bending).

Attempts to hydrolyze the axial nitrile **22** by the same procedure resulted in recovery of the starting nitrile, a result consistent with the more hindered nature of the axial cyano group. Consequently, an alternative hydrolysis procedure[19] was employed in which a solution of 26 mg (0.15 mmol) of the nitrile **22** in 0.17 ml of concentrated sulfuric acid was stirred at 60° for 6.5 hr and then diluted with water and extracted with ether. The crude neutral product was recrystallized from aqueous ethanol to separate 18.2 mg (64%) of the amide **24** as white needles: mp 131–132° (lit.[6] mp 129–130°); ir ($CHCl_3$), 3510, 3480, and 3390 (NH), 1670 (amide C=O), and 1585 cm^{-1} (NH_2 bending).

Registry No.—**2**, 15619-08-6; **3**, 15619-21-3; **7**, 15619-09-7; **9a**, 15619-10-0; **9b**, 15619-11-1; **10a**, 15619-12-2; **10b**, 15619-13-3; **11a**, 15619-14-4; **11b**, 15619-15-5; **13**, 15619-16-6; **18**, 15619-17-7; **21a**, 15619-18-8; **21b**, 15619-19-9; **22**, 15619-22-4; **23**, 15619-20-2.

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The Chemistry of Carbanions. XVII. The Addition of Methyl Organometallic Reagents to Cyclohexenone Derivatives[1a]

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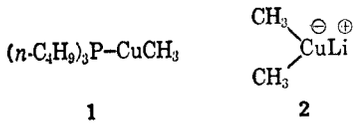
Received September 22, 1967

The additions of methylmagnesium and methylcopper derivatives to the α,β-unsaturated ketones **8**, **19**, and **21** have been studied. The stereochemistry of conjugate addition to the ketone **8** differs for methylcopper and methylmagnesium derivatives. When mixtures of these two metal derivatives are present, both contribute to the over-all stereochemistry of addition. Use of trimethylphosphite as a ligand for methylcopper to give relatively stable, ether-soluble complexes has been found advantageous in certain cases. Although the conjugate addition of lithium dimethylcuprate to α,β-unsaturated ketones appears to require no other species in the reaction solution, trimethyl phosphite and tri-*n*-butylphosphine complexes of methylcopper will undergo conjugate addition only if various salts such as lithium iodide, lithium bromide, magnesium bromide, or lithium cyanide are present in the reaction medium. A possible interpretation of this observation is presented.

Earlier studies of the copper-catalyzed conjugate addition of organomagnesium compounds and organolithium compounds to α,β-unsaturated ketones[2] had provided evidence supporting the idea that the actual reactants in these conjugate addition reactions are organocopper(I) compounds such as the materials



1 **2**

with the stoichiometric compositions **1** and **2**. Although it is probable that these copper(I) derivatives actually exist as associated structures (*e.g.*, tetramers) which may be bonded to solvent molecules as additional ligands, no compelling experimental evidence relating to these questions is currently available. The early data led to the hypothesis that the conjugate addition of the organocopper(I) reactants proceeded *via* a one-electron

(1) (a) This research has been supported by Grant No. AF-AFOSR-573 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research; (b) National Institutes of Health Predoctoral Fellow, 1966–1967.

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