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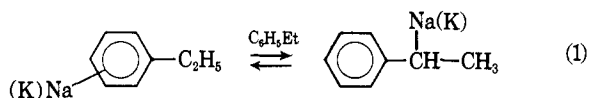
Factors Governing Orientation in Metalation Reactions. II. The Metalation of Isopropylbenzene with *n*-Amylsodium and *n*-Amylpotassium

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The metalation of isopropylbenzene (cumene) with *n*-amylsodium and *n*-amylpotassium has been studied in detail. The *n*-amylsodium and *n*-amylpotassium were prepared from *n*-amyl chloride as well as from di-*n*-amylmercury. It was found that the aromatic ring of cumene is metalated both *meta* and *para* in a kinetically controlled sequence by both metalating agents regardless of their mode of preparation. The *m*- and *p*-isopropylphenylpotassium isomers are converted fairly rapidly (in the presence of excess cumene) to the more thermodynamically stable α -cumylpotassium. The *m*- and *p*-isopropylphenylsodium isomers convert more slowly than the potassium compounds (but equally as surely) to α -cumylsodium also *via* a transmetalation process in the presence of excess cumene. The α -cumylsodium (unlike α -cumylpotassium) is relatively unstable and decomposes to α -methylstyrene. The formation of the latter material triggers a series of side reactions (*e.g.*, dimer formation leading to 1,1,3-trimethyl-3-phenylindane and metalation resulting in the formation of 3-phenyl-3-butenic acid upon carbonation) which lower the yield of cumene acids obtained initially from the metalation and tend to becloud the basic metalation sequence.

In the first paper in this series¹ it was shown that ethylbenzene is metalated in the aromatic ring by both *n*-amylsodium and *n*-amylpotassium in a kinetically controlled sequence. In the presence of excess ethylbenzene, the ring isomers equilibrate to the more thermodynamically stable α -isomer.



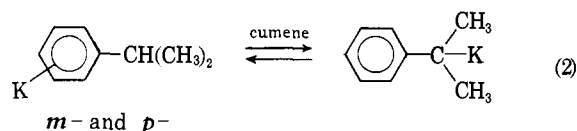
These results were essentially the same when the metalating agent was prepared from either *n*-amyl chloride or di-*n*-amylmercury.

In view of the above findings, it was of interest to note the conflicting results which had been published concerning the metalation of isopropylbenzene (cumene) by alkyl alkali reagents. One laboratory reported^{2,3} that *n*-amylsodium metalated cumene predominantly *para* and some *ortho* to the isopropyl group, while another claimed⁴ nearly a 1:1 *meta/para* ratio. Very little side-chain metalation was observed with *n*-amylsodium by either laboratory. On the other hand, another report⁵ claimed that metalation of cumene with ethylsodium produced 40% of α -cumylsodium. *n*-Amylpotassium was reported to give almost exclusive side-chain metalation when the potassium reagent was prepared from *n*-amyl chloride and potassium,⁶ but only 13% α -product when it was prepared from *n*-amylsodium and a sodium-potassium alloy.⁴

An attempt⁶ was made to explain these puzzling discrepancies on the basis that each laboratory had prepared their organoalkali reagents by different methods. It was reasoned that different modes of preparation (*e.g.*, from the alkyl chloride or dialkylmercury) might well result in different surface characteristics of these relatively insoluble organometallics and hence metalations involving these reagents could result in different orientations.⁷

These discordant results were resolved in part by our earlier disclosure⁸ that cumene (like ethylbenzene) is metalated by both *n*-amylsodium and *n*-amylpotassium

(regardless of their mode of preparation) in the aromatic ring in a kinetically controlled process. The highly energetic *m*- and *p*-isopropylphenylpotassium revert quickly (*via* trans-metalation in the presence of excess cumene) to the more thermodynamically stable α -isomer.



However, our results⁸ for *n*-amylsodium metalations of cumene were unusual, since, under conditions identical with the *n*-amylpotassium metalations, a maximum of only about 3% α -product was obtained after 20 hr. On the basis of thermodynamic control, one would expect, intuitively at least, similar stabilities for the α -sodium and α -potassium species. Presumably factors (*e.g.*, benzylic resonance) operating to stabilize the latter should likewise accommodate the former. Nevertheless, the dramatic differences⁸ between alkylsodium and alkylpotassium metalations of cumene prompted us to investigate these reactions thoroughly, as well as the related question of the stability of cumyl carbanions. This paper reports the results of this study.

The isomer distributions obtained by metalating cumene with *n*-amylsodium and *n*-amylpotassium were determined by carbonating the intermediates to carboxylic acids. The latter were esterified with diazomethane and the products analyzed by vapor phase chromatography. In order to establish that the analytical procedure was reliable, a synthetic mixture consisting of *o*-, *m*-, and *p*-isopropylbenzoic acid and 2,2-dimethylphenylacetic acid was prepared. This mixture was subjected to treatment with diazomethane and the resulting methyl esters were analyzed by vapor phase chromatography. The results indicated the method⁹ was reliable to $\pm 0.6\%$.

It will be noted in Table I (entries 1, 2, 4, and 5) that again the mode of preparing the metalating agent (from either RCl or R₂Hg) had practically no effect on the final isomer distributions. In the case of the *n*-amylpotassium metalations, the α -isomer predominated after 20 hr. In the case of *n*-amylsodium, the ring isomers were still predominant after 20 hr.

Entries 6 and 7 in Table I are equally revealing. When the metalating agent was changed to *n*-propyl-

(1) R. A. Benkeser, A. E. Trevillyan, and J. Hooz, *J. Am. Chem. Soc.*, **84**, 4971 (1962).

(2) A. A. Morton, J. T. Massengale, and M. L. Brown, *ibid.*, **67**, 1620 (1945).

(3) A. A. Morton and C. E. Claff, Jr., Abstracts, 119th National Meeting of the American Chemical Society, Boston, Mass., 1951, p. 11M.

(4) D. Bryce-Smith, *J. Chem. Soc.*, 1079 (1954).

(5) H. Gilman, H. Pacevitz, and O. Baine, *J. Am. Chem. Soc.*, **62**, 1514 (1940).

(6) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **23**, 1636 (1958).

(7) The assumption was made here that these metalations are occurring on the surface of the undissolved alkyl alkali reagents.

(8) R. A. Benkeser and T. V. Liston, *J. Am. Chem. Soc.*, **82**, 3221 (1960).

(9) This analytical method assumes that carbonation provides an accurate probe for the position of the metal atom. We believe this to be true, since in a few cases we employed trimethylchlorosilane to trap the anion and obtained quite comparable isomer distributions.

TABLE I
METALATION OF CUMENE WITH *n*-AMYLSDIUM AND
n-AMYL POTASSIUM

Metalating agent	Method ^a of prepn.	Reaction time, hr.	Yield, %, of methyl esters ^b	Product composition, % ^c		
				α	<i>meta</i>	<i>para</i>
1 <i>n</i> -AmNa	I	20	48	2	55	43
2 <i>n</i> -AmNa	II	20	42	1	56	43
3 <i>n</i> -AmK ^d	I	3	..	42	39	19
4 <i>n</i> -AmK	I	20	49	88	4	8
5 <i>n</i> -AmK	II	20	43	92	..	8
6 <i>n</i> -PrNa	II	20	51	4	47	48
7 EtNa	II	20	54	2	50	48
8 <i>n</i> -AmNa ^e	I	48	10	10	27	27
9 <i>n</i> -AmK	I	48	56	100

^a Method I employed RCl + metal; method II employed R₂Hg + metal. ^b The yields are based on weight of starting RCl or R₂Hg. ^c The α , *meta*, and *para* refer to the methyl esters obtained after carbonation and treatment with diazomethane. ^d The *n*-AmK in this run was prepared in heptane. In all other entries in this table the metalating agent was prepared directly in cumene. ^e There was also detected in this run α -methylstyrene, α -methylstyrene dimers, and 36% methyl 3-phenyl-3-butenate. The isomer distributions listed are the average of three runs.

sodium and ethylsodium, the isomer ratios were comparable to those obtained with *n*-amylsodium (*cf.* entry 2), particularly with respect to the low percentage of α -isomer obtained. This result is at variance with an earlier report⁵ dealing with the metalation of cumene by ethylsodium, in which a 40% yield of α -isomer was claimed. In view of the demonstrated reliability of our analytical method we are inclined to question the accuracy of this earlier report.

At this point in the investigation it appeared, superficially at least, that alkylsodium reagents indeed favored metalating cumene in the aromatic ring, since these isomers predominated even after 20-hr. reaction time. The alkylpotassium reagents, on the other hand, after 20 hr. had reverted to the α -cumyl isomer (eq. 2). Hence, the results obtained with the alkylpotassium reagents paralleled exactly those observed in the metalation of ethylbenzene¹ (eq. 1).

Corroborative evidence for the equilibrium depicted in eq. 2 was obtained by treating highly purified *p*-chlorocumene (free of *o*- and *m*-isomers) with potassium in solvents of cumene and heptane (see Table II). Carbonation and esterification with diazomethane resulted in a progressive increase in α -ester with time. After 20 hr. only α -isomer was present (entry 1, Table II), while at the end of 4 hr. (entry 2, Table II), α as well as *meta* and *para* isomers could be detected. The equilibrium shown in eq. 2 seems to offer the best explanation for these results.

TABLE II
REACTION OF HIGHLY PURIFIED *p*-CHLOROCUMENE WITH POTASSIUM

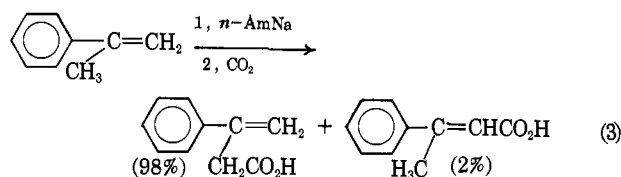
Solvent	Reacn. time, hr.	Product composition, %		
		α	<i>meta</i>	<i>para</i>
1 Cumene	20	100
2 Cumene	4	60	23	17
3 Heptane ^a	5	56	20	24

^a Contained a twofold excess of cumene.

The apparent failure of the *m*- and *p*-cumylsodium to equilibrate to α -cumylsodium in the manner of the potassium compounds (eq. 2) seemed attributable to at least one of two effects: (1) The α -cumylsodium is not as thermodynamically stable as the *m*- and *p*-cumylsodium and hence the equilibrium depicted in eq. 2 lies to the left, or (2), the equilibrium depicted in eq. 2 requires longer than 20 hr. to establish itself. In order to test the latter possibility, the metalation of cumene

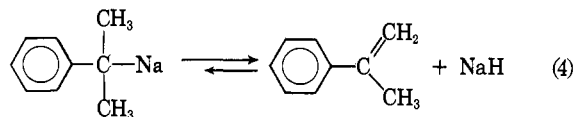
with *n*-amylsodium was allowed to proceed for 48 hr. (entry 8, Table I). It was apparent immediately that the yield of cumene acids from this run was considerably lower than that obtained in the 20-hr. reaction. In addition, a new acid comprising 36% of the product (later identified as 3-phenyl-3-butenic acid) was isolated. The isomer distribution was such that ring substitution still predominated. An investigation of the neutral materials obtained from this run disclosed the presence of α -methylstyrene as well as polymeric materials derived from α -methylstyrene (*e.g.*, a dimer). When the same reaction time was employed utilizing *n*-amylpotassium (entry 9, Table I) instead of *n*-amylsodium, an excellent yield of cumene acids was realized. For all practical purposes, there was no α -methylstyrene or 3-phenyl-3-butenic acid found in the case of the potassium reaction.

The source of the 3-phenyl-3-butenic acid was ascertained when it was found that treatment of α -methylstyrene with *n*-amylsodium followed by carbonation produced this acid in considerable quantities.



As depicted in eq. 3, a small amount of 3-phenyl-2-butenic acid was also formed. Obviously the 3-phenyl-3-butenic acid was produced by the metalation of α -methylstyrene at its allylic position. Hence, all by-products observed in the 48-hr. metalation of cumene by *n*-amylsodium were derived from α -methylstyrene and significantly α -methylstyrene itself was detected among these by-products. The origin of the α -methylstyrene as a consequence became a pivotal issue since its formation was clearly responsible for the lowered yield of cumene acids.

It must be concluded that the α -methylstyrene arose in some manner from α -cumylsodium. Significantly, only traces of α -methylstyrene were produced from α -cumylpotassium. While we have not investigated the mechanism by which α -methylstyrene arises from α -cumylsodium, one might envision a thermal decomposition of the latter (*via* either a four-center or radical process) leading to α -methylstyrene and sodium hydride.¹⁰ Since we have demonstrated that α -cumyl-



potassium is essentially stable under conditions where α -cumylsodium decomposes to α -methylstyrene (eq. 4), one is faced with the problem of explaining why the equilibrium depicted in eq. 4 lies to the right in the case of sodium but to the left in the case of potassium. Possibly the higher heat of formation of sodium hydride compared to potassium hydride¹¹ affords a greater driving force for decomposition in the case of the sodium compound, or possibly the increased contribution of benzylic resonance stabilization afforded by the greater

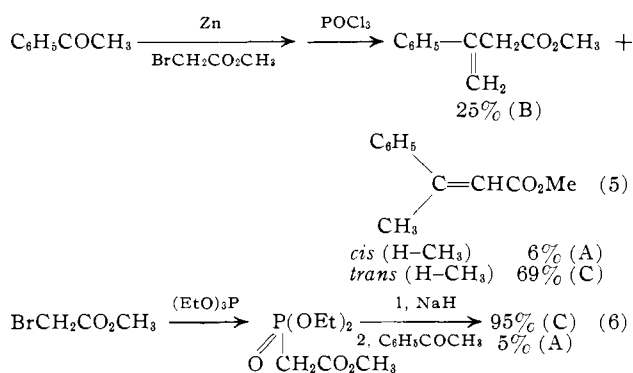
(10) An equilibrium of this sort has been proposed involving α -cumylpotassium. See H. Pines and L. Schaap, *J. Am. Chem. Soc.*, **80**, 4378 (1958). An extensive study of such hydride eliminations from organosodium and organopotassium compounds has been made by Professor R. A. Finnegan (see, for example, *Tetrahedron Letters*, **13**, 851 (1963), and references contained therein). In general, the results of these interesting studies indicate that RK compounds are less thermally stable than RNa types.

(11) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. I, Oxford Press, Oxford, 1950, p. 67.

ionic character of the carbon-potassium bond compared to the carbon-sodium bond¹² provides an answer. It is also conceivable that the greater reduction potential of potassium metal compared to sodium plays a role. *Whatever the reason, the facts clearly indicate that α -cumylsodium is relatively unstable compared to α -cumylpotassium.*

Structure Determination of By-products Arising from the *n*-Amylsodium Metalation of Cumene. (1) **Methyl 3-Phenyl-3-butenolate.**—When the metalation of cumene with *n*-amylsodium was carried out at room temperature for 48 hr., a new ester (in addition to the expected esters derived from the isomeric cumene acids) was produced upon carbonation and treatment with diazomethane. The retention time of this new ester by vapor phase chromatography was identical with that of an authentic sample of methyl 3-phenyl-3-butenolate. Likewise, when the ester mixture obtained from the above cumene metalation was hydrogenated catalytically, the peak ascribed to methyl 3-phenyl-3-butenolate disappeared, and a new peak identical in retention time with an authentic sample of methyl 3-phenylbutyrate made its appearance. There can be little doubt that the prolonged metalation of cumene by *n*-amylsodium results in the formation of 3-phenyl-3-butenic acid upon carbonation of the products. When α -methylstyrene was deliberately treated with *n*-amylsodium, this same acid was produced upon carbonation¹³ (eq. 3).

An authentic sample of methyl 3-phenyl-3-butenolate was obtained by the independent synthesis shown below in eq. 5.



In the first sequence (eq. 5), the Reformatsky product obtained from acetophenone, methyl bromoacetate, and zinc was dehydrated with phosphorus oxychloride. Vapor phase chromatography disclosed that the product of the dehydration was a mixture of three materials (compounds A, B, and C shown in eq. 5). The structural assignments were based on their n.m.r. spectra (Table III).

Corroborative evidence for the structural assignments of compounds A, B, and C was obtained by an alternative synthesis shown in eq. 6. Triethyl phosphite was treated with methyl bromoacetate (Michaelis-Arbusov reaction)¹⁴ to form methyl diethylphosphonoacetate. Treatment of the latter with sodium hydride followed by acetophenone produced only compounds A and C but not B in accord with theoretical predictions.

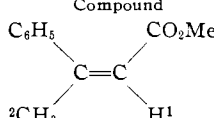
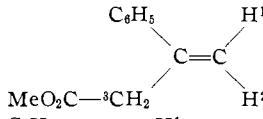
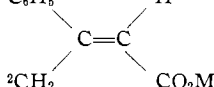
(2) **Dimer of α -Methylstyrene (1,1,3-Trimethyl-3-phenylindane).**—When cumene was metalated with

(12) E. G. Rochow, D. T. Hurd, and R. N. Lewis, "The Chemistry of Organometallic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 16.

(13) The metalation of α -methylstyrene by *n*-amylsodium was reported previously. See A. A. Morton and E. Grovenstein, Jr., *J. Am. Chem. Soc.*, **74**, 5437 (1952). These authors suggest (with essentially no structure proof) that the product was 3-phenyl-2-butenic acid.

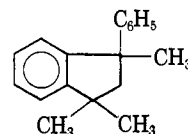
(14) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter 7.

TABLE III
N.M.R. SPECTRA OF ISOMERIC UNSATURATED ESTERS^a

Compound	Chemical shift, τ (rel. intens.)		
	H ¹	H ²	H ³
A 	4.20 (1)	7.85 (3)	...
B ^b 	4.57 (1)	4.87 (1)	6.62 (2)
C ^c 	3.88 (1)	7.45 (3)	...

^a Spectra were determined in carbon tetrachloride solution using tetramethylsilane as internal standard. A Varian A-60 n.m.r. spectrometer was employed. Chemical shifts are measured to the estimated center of a singlet or multiplet. ^b It will be noted that only compound B contains two (nonequivalent) vinylic protons at 4.57 and 4.87 τ and a methylene resonance at 6.62 τ . ^c It is well established that β -methyl groups located *cis* to carbomethoxy consistently exhibit lower chemical shift values than when they are *trans*. See L. M. Jackman, "Application of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, London, 1959, pp. 119-125; L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881 (1960); T. R. Fukuto, E. O. Hornig, R. L. Metcalf, and M. Y. Minton, *J. Org. Chem.*, **26**, 4620 (1961). On this basis, the *trans* isomer C is deshielded (7.45 τ) by a *cis*-carbomethoxy group whereas that in the *cis* structure (A) is not (7.85 τ).

n-amylsodium for 48 hr. at room temperature only a 10% yield of acids derived from cumene was obtained. In addition to 3-phenyl-3-butenic acid, α -methylstyrene and higher molecular weight aggregates of the latter could be detected. When the higher molecular weight materials were distilled, a cut boiling at 141-143° (2 mm.) was collected. Vapor phase chromatography disclosed that this material contained at least two components (two poorly resolved peaks were obtained). The first of these peaks was identified as 1,1,3-trimethyl-3-phenylindane (a dimer of α -methylstyrene) by comparing its infrared and n.m.r. spectrum and retention



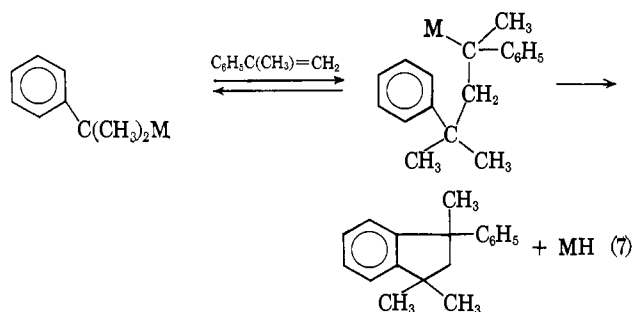
time with an authentic sample. The authentic sample was prepared by dimerizing α -methylstyrene with stannic chloride¹⁵ and by treating α -methylstyrene with α -cumylpotassium. Rather interestingly, we were also able to isolate 1,1,3-trimethyl-3-phenylindane from the reaction of α -methylstyrene with benzylium-sodium catalyst according to the method of Pines.¹⁶

The mechanism for the formation of 1,1,3-trimethyl-3-phenylindane under the basic conditions which were employed was not investigated. However, since it was also produced from the reaction of α -methylstyrene and α -cumylpotassium, it is attractive to think of α -cumylsodium as a key intermediate.

Conclusions.—It must be concluded that cumene, like ethylbenzene, undergoes ring substitution during metalation by *n*-amylsodium and *n*-amylpotassium in a kinetically controlled process. The *meta* and *para* (and perhaps *ortho*) substituted isopropylphenylpotas-

(15) H. Staudinger and F. Breusch, *Ber.*, **62**, 442 (1929).

(16) M. Kolobinski and H. Pines, *J. Am. Chem. Soc.*, **79**, 5820 (1957), identified one of the products arising from this reaction as 1-methyl-1,3-diphenylcyclopentane. It is possible that 1,1,3-trimethyl-3-phenylindane was also present in their mixture, but escaped detection. Since a study of the dimerization of α -methylstyrene was not our objective, we made no attempt to investigate all the products of this reaction.



sium revert rather rapidly to the more thermodynamically stable α -isomer via a transmetalation process in the presence of excess cumene (eq. 2). The isopropylphenylsodium isomers also revert to α -cumylsodium, but at a slower rate than the corresponding potassium compounds. However, α -cumylsodium is relatively unstable (compared to α -cumylpotassium) and decomposes to α -methylstyrene.¹⁷ The formation of the latter compound then triggers several side reactions, all of which ultimately consume α -cumylsodium. Thus, α -methylstyrene is metalated at its allylic position and is dimerized (possibly by reaction with α -cumylsodium itself) to 1,1,3-trimethyl-3-phenylindane. As in the ethylbenzene study,¹ the above results were independent of the two different methods employed for making the n -amylsodium and n -amylpotassium.

It should be noted at this point that in our metalation studies involving n -amylsodium and n -amylpotassium, thus far we have uncovered no experimental evidence which requires the concept of heterogeneity for explanation. Thus, the kinetically controlled ring isomer distributions we have observed (though complicated by continual reversion to α) can generally be explained in terms of the inductive effect of the substituent alkyl group. No essential differences have been noted when the metalating agents have been prepared from RCl or R₂Hg. Finally, the apparent differences in orientation between the metalation of cumene by n -amylsodium and n -amylpotassium has now been shown not to be due to heterogeneity effects, but to differences in the stability of α -cumylsodium and α -cumylpotassium. In short, all the evidence except for alkoxide effects¹⁸ which has been advanced thus far to support the concept of heterogeneity in these metalation reactions has now been refuted. In a subsequent paper in this series we will report in detail our investigation of the metalation of *t*-butylbenzene by n -amylsodium and n -amylpotassium and our assessment of the influence of metal alkoxides on the course of these metalations.

Experimental

Preparation of Authentic Samples of *o*-, *m*-, and *p*-Isopropylbenzoic Acids.—The *o*- and *m*-acids were prepared by carbonating the Grignard reagent derived from the corresponding bromides. The pure *o*-acid melted at 63–64° (lit.¹⁹ 63–63.5°) and the *m*- at 49–50° (lit.¹⁹ 51–52°). The *p*-acid was a commercial product (Eastman Kodak Co.).

α -Phenylisobutyric acid was prepared by an adaptation of the method of Hauser²⁰ utilizing α -phenylpropionic acid. It melted at 79–80° in agreement with the literature value.²¹

Preparation of Authentic Methyl Esters.—Each of the above acids was converted to the corresponding methyl ester by treat-

ment with diazomethane in ether. The physical constants of the esters thus produced agreed well with the literature values (all have been previously reported).

Analytical Method.—A synthetic mixture of the four isomeric cumene carboxylic acids of known composition was converted to the methyl esters by excess diazomethane.²² The methyl esters were then analyzed by vapor phase chromatography²³ with the following results.

Isomer	Synthetic mixture of acids, %	Methyl esters, %
α	4.5	3.9; 3.9
<i>ortho</i>	4.5	4.8; 3.9
<i>meta</i>	45.4	45.5; 45.9
<i>para</i>	45.4	45.7; 45.2

The analyses were accurate therefore to $\pm 0.6\%$, indicating that conversion to the methyl esters was essentially quantitative.

Preparation of Pure *p*-Chlorocumene.—An attempt was made to prepare pure *p*-chlorocumene by treating chlorobenzene with isopropyl alcohol and boron trifluoride.²⁴ The product, however, was badly contaminated with *o*- and *m*-isomers. Quite pure *p*-chlorocumene was obtained by the following sequence. *p*-Chloroacetophenone, when treated with methylmagnesium iodide followed by acid hydrolysis and treatment with potassium bisulfate and hydroquinone, gave a 75% yield of *p*-chloro- α -methylstyrene (b.p. 86°, n_{D}^{20} 1.5560). Catalytic reduction of the latter material in a Parr hydrogenator using a 10% platinum-on-charcoal catalyst gave an 80% yield of essentially pure *p*-chlorocumene (b.p. 74° (10 mm.), n_{D}^{20} 1.5109).

Reaction of *p*-Chlorocumene with Potassium in Excess Cumene (Table II).—A solution of pure *p*-chlorocumene (13.9 g., 0.09 mole) in 20 ml. of cumene was added slowly (2.5 hr.) to potassium sand (7.8 g., 0.2 g.-atom) in 100 ml. of cumene at 25°. The reaction mixture was a deep red color. High speed stirring²⁵ was continued for 20 hr. at room temperature. This was followed by the usual carbonation and esterification technique. Entry 1 in Table II lists the results of this run.

The results of a duplicate experiment except for a reaction time of 4 hr. is listed as entry 2 in Table II.

A third experiment containing a twofold excess of cumene dissolved in heptane was also carried out (entry 3, Table II).

Metalation of Cumene with *n*-Amylsodium (Method I).—*n*-Amylsodium was prepared by the dropwise addition (1 hr.) of *n*-amyl chloride (21.3 g., 0.2 mole) in 25 ml. of cumene to a sodium dispersion (10.4 g., 0.45 g.-atom) in 100 ml. of cumene at -10° with high speed stirring under a blanket of nitrogen. The mixture was stirred for an additional hour at -10° and then stirred at room temperature for 20 hr. The carbonation, esterification, and general work-up are identical with that described in paper I of this series.¹ The results are listed in Table I.

Metalation of Cumene with *n*-Amylsodium (Method II).—*n*-Amylsodium was prepared by the dropwise addition (1.5 hr.) of di-*n*-amylmercury (34.2 g., 0.1 mole) in 45 ml. of cumene to a sodium dispersion (8.02 g., 0.35 g.-atom) in 80 ml. of cumene. High speed stirring was continued for 20 hr. The carbonation and esterification procedure have been described previously.²² The results are listed in Table I.

Metalation of Cumene with Ethylsodium and *n*-Propylsodium.—The procedure was essentially identical with that described under method II above for *n*-amylsodium. The results are listed as entries 6 and 7 in Table I.

Metalation of Cumene with *n*-Amylpotassium (Method I).—To *n*-amylpotassium (from 16 g., 0.15 mole, of *n*-amyl chloride and potassium sand, 11.8 g., 0.30 g.-atom) in 75 ml. of cumene was added an additional 50 ml. of cumene with high speed stirring. Stirring was continued at room temperature for 20 hr. The usual carbonation and esterification sequence afforded 13 g. (49%) of methyl esters (entry 4, Table I).

Metalation of Cumene with *n*-Amylpotassium (Method II).—To potassium sand (11.8 g., 0.3 g.-atom) in 75 ml. of cumene was added di-*n*-amylmercury (31.8 g., 0.09 mole) in 50 ml. of cumene dropwise at room temperature. High speed stirring was continued at room temperature for 20 hr. Carbonation and esterification gave 14 g. (43%) of methyl esters (entry 5, Table I).

By-products from Metalation of Cumene by *n*-Amylsodium.—*n*-Amylsodium was prepared in the usual manner from *n*-amyl

(17) It is now clear that the statement which has been quoted on numerous occasions in the literature [see, for example, A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **23**, 1636 (1958)] that metalation of cumene by sodium reagents yields predominantly nuclear substituted products while metalation by potassium reagents leads to side-chain substitution is misleading and requires revision.

(18) A. A. Morton, C. E. Claff, Jr., and F. W. Collins, *J. Org. Chem.*, **20**, 428 (1955).

(19) W. E. Harvey, *Acta Chem. Scand.*, **8**, 692 (1954).

(20) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956).

(21) A. Bistrzycki and L. Mauron, *Ber.*, **40**, 4370 (1907).

(22) See paper I in this series for more complete experimental details of this procedure.

(23) A Perkin-Elmer Model 154C vapor fractometer was used with a column "R" (polypropylene glycol) at 175°; 20 p.s.i. In subsequent experiments, an F and M Model 500 unit was employed with a 2-m. Carbowax 20M column at 175° and helium flow of 60 cc./min. for more rapid analyses. The results of both methods concur.

(24) G. F. Hennion and V. R. Pieronek, *J. Am. Chem. Soc.*, **64**, 2751 (1942); G. F. Endres and C. G. Overberger, *ibid.*, **77**, 2201 (1955).

(25) The high speed stirring apparatus used can be purchased as a unit from LaPine Scientific Co. under the name "Stir-O-Vac."

chloride (28.8 g., 0.27 mole) in 30 ml. of cumene and sodium dispersion (15.0 g., 0.65 g.-atom) in 150 ml. of cumene. High speed stirring was continued for 1 hr. at -10° , 21 hr. at room temperature, and 22 hr. at 90° . The usual carbonation and esterification procedure afforded the methyl esters but only in 6–16% yield.

The neutral organic layer was dried over Drierite and then distilled through a Todd column. A fraction boiling at $43\text{--}45^{\circ}$ (10 mm.) was collected and analyzed by v.p.c. (2-m. column "R," 140° , 15 p.s.i. He). It contained cumene, *n*-decane, and a trace of α -methylstyrene (the starting cumene was vapor chromatographically free of α -methylstyrene).

The residue was distilled on a micro column to give 7.0 g. of material boiling at $141\text{--}143^{\circ}$ (2 mm.), n_D^{20} 1.5561. When analyzed by v.p.c. (2-m. column R, 200° , 20 p.s.i. He) it showed two peaks. Its infrared spectrum (bands at 3.4, 3.5, 6.3, 6.7, 6.8, 7.0, 7.4, 9.7, 13.2, and $14.4\ \mu$) was identical to the spectrum of the material obtained by treating α -methylstyrene with benzylsodium-sodium catalyst (see below). The material responsible for the first peak in the chromatogram was isolated by preparative scale v.p.c. (Aerograph Autoprep, Model A-700, 10 ft. \times $\frac{3}{8}$ in. poly-*m*-phenyl ether column, 225°). It proved to be a solid melting at $50\text{--}52^{\circ}$ and identical in all respects (n.m.r. and infrared spectra as well as v.p.c. retention time) with an authentic sample of 1,1,3-trimethyl-3-phenylindane.

Anal. Calcd. for $C_{15}H_{20}$: C, 91.47; H, 8.53; mol. wt., 236. Found: C, 91.81; H, 8.45; mol. wt. (osmometer in $CHCl_3$), 236.

When the above reaction was repeated under identical conditions except that the metalation mixture was stirred at high speeds for 48 hr. at room temperature, the neutral fraction again contained trace amounts of α -methylstyrene in addition to 1,1,3-trimethyl-3-phenylindane. Also, the acidic fraction was found to contain significant quantities (36%) of 3-phenyl-3-butenic acid. The latter material was isolated (as its methyl ester) from a mixture by v.p.c. (Carbowax 20M, 4 ft. \times 0.25 in., 150°) and identified by comparing its infrared spectrum with an authentic sample of methyl 3-phenyl-3-butenate. Likewise, when the crude ester mixture was reduced catalytically (Parr hydrogenator, Raney Ni catalyst) the peak for methyl 3-phenyl-3-butenate disappeared and a new peak appeared which had a retention time identical with that of an authentic sample of methyl 3-phenylbutanoate.

Reaction of α -Methylstyrene with Benzylsodium-Sodium Catalyst.—The procedure is essentially that described by Pines.¹⁶ *o*-Chlorotoluene (1.5 g., 0.12 mole) and sodium (2.0 g., 0.09 g.-atom) were refluxed in 13 ml. toluene for 4 hr. The black suspension was freed from excess toluene (vacuum) and the residue cooled under nitrogen. α -Methylstyrene (53.0 g., 0.45 mole) was added and the mixture was refluxed for 24 hr. Low boiling materials were removed (flash distillation at *ca.* 1 mm.). The residue was extracted with benzene, filtered, and the benzene removed (vacuum). Short path distillation gave 22.6 g. (43%) of material boiling at $106\text{--}114^{\circ}$ (0.7 mm.). This was shown by v.p.c. analysis to be a mixture of at least two components which had the same retention time and infrared spectrum as the neutral materials isolated from the metalation of cumene by *n*-amylsodium (48-hr. reaction time). Upon long standing (>6 months), a solid separated from this material. Upon purification, it melted at $50\text{--}52^{\circ}$ and corresponded in retention time to the first of the two peaks obtained from the crude product. It was identical in all respects with the compound isolated from the neutral material of the amylsodium-cumene metalation (see above). An n.m.r. spectrum²⁶ confirmed the identity of this material as 1,1,3-trimethyl-3-phenylindane.

Reaction of Phenylisopropylpotassium with α -Methylstyrene.—*n*-Amylpotassium was prepared by the dropwise addition of *n*-amyl chloride (10.7 g., 0.10 mole) in 30 ml. of dry cumene to a potassium dispersion (11.7 g., 0.30 g.-atom) covered by 150 ml. of dry cumene with high speed stirring at -10° under an atmosphere of dry nitrogen. Stirring was continued for 1 hr. at -10° and 16 hr. at room temperature. α -Methylstyrene (11.8 g., 0.10 mole) was added and stirring continued for 5 hr. Evolution of heat was apparent shortly after the addition. The temperature was maintained at 90° for 8 hr. Carbonation and esterification with diazomethane was accomplished in the usual fashion. There was obtained 5.5 g. (31%) of methyl esters which v.p.c. analysis indicated were over 95% α .

Distillation of the neutral layer yielded 9.0 g. of material boiling at $118\text{--}140^{\circ}$ (1 mm.). A vapor phase chromatogram indicated at least three peaks. The first two of these were identical in retention time with those obtained by treating α -methylstyrene with benzylsodium-sodium (see above).

Preparation of 1,1,3-Trimethyl-3-phenylindane.—To 250 g. (2.1 moles) of α -methylstyrene was added 20 g. of stannic chloride

at room temperature. After stirring for 24 hr., the viscous mixture was taken up in 300 ml. of benzene. After several extractions with dilute hydrochloric acid, followed by dilute sodium hydroxide solution, it was concentrated (steam bath) and dried over Drierite. A rapid, short-path distillation gave a fraction boiling at $140\text{--}142^{\circ}$ (4 mm.). This was redistilled three times and a fraction boiling at 141° (4 mm.) was collected. When this was seeded with a crystal of 1,1,3-trimethyl-3-phenylindane, obtained, as described above, from the reaction of α -methylstyrene-benzylsodium-sodium, it solidified. It proved identical in every respect with the 1,1,3-trimethyl-3-phenylindane obtained from the other reactions.

***cis*- and *trans*-Methyl 3-Phenyl-2-butenate and Methyl 3-Phenyl-3-butenate.**²⁷—A Reformatsky reaction was carried out in the usual manner using acetophenone (120 g., 1 mole), methyl bromoacetate (153 g., 1 mole), and zinc dust (65 g., 1 g.-atom). The latter had been conditioned by rapid washing with 5% hydrochloric acid, followed by water, alcohol, and acetone. It was then dried in an oven at 105° for 1 hr.

The crude benzene solution of the hydroxy ester was refluxed with phosphorus oxychloride for 1 hr. and then poured onto crushed ice. The organic layer was extracted, washed with water several times, then dried over Drierite. Solvent removal and rapid distillation from a short column afforded 70.4 g. of product boiling at $103\text{--}106^{\circ}$ (1.5 mm.). Analysis of this material by v.p.c. revealed three products: A, 6%, B, 25%; C, 69%.

An Aerograph Autoprep Model A-700 equipped with a 20 ft. \times $\frac{3}{8}$ in. poly-*m*-phenyl ether column (30% liquid phase on $42/60$ Chromosorb P at 200°) was employed to separate compound C from A and B. Compound C melted at $32\text{--}33^{\circ}$ (uncor.), $\lambda_{\text{max}}^{\text{isooctane}}$ 261 μ and was identified as methyl 3-phenyl-2-butenate. From its n.m.r. spectrum the methyl and carbomethoxy groups were *cis* (Table III).

Anal. Calcd. for $C_{11}H_{22}O_2$ (compound C): C, 74.97; H, 6.87. Found: C, 75.20; H, 6.86. Calcd. for mixture of A and B, $C_{11}H_{22}O_2$: C, 74.97; H, 6.87. Found: C, 74.78; H, 6.60.

The Aerograph Autoprep equipped with a 10 ft. \times $\frac{3}{8}$ in. Carbowax 20M column at 150° was used to separate A from B. Both were pale yellow liquids when analytically pure. Compound A ($\lambda_{\text{max}}^{\text{isooctane}}$ 242 μ) was identified by n.m.r. (Table III) as methyl 3-phenyl-2-butenate with the methyl and carbomethoxy groups *trans*. Compound B was also identified by its n.m.r. spectrum (Table III) as methyl 3-phenyl-3-butenate.

The *cis*- and *trans*-methyl 3-phenyl-2-butenate were also prepared by the following independent synthesis.²⁸

To a slurry of sodium hydride (50%, 2.4 g., 0.05 mole) in 100 cc. of dry 1,2-dimethoxyethane was added a solution of methyl diethylphosphonoacetate²⁹ (10.5 g., 0.05 mole) in 10 ml. of 1,2-dimethoxyethane dropwise with stirring. After addition was complete, the solution was stirred for 1.5 hr. at room temperature. Acetophenone (6.0 g. 0.05 mole) was added dropwise, whereupon the solution was stirred at room temperature for 2 hr. and refluxed for 1 hr. After cooling, the solution was poured into a large excess of water and the product extracted with ether. The organic layer was dried over Drierite and the solvent removed under vacuum. Only a portion of the crude reaction mixture was distilled to give 2 g. of product boiling at $108\text{--}109^{\circ}$ (2 mm.). Analysis of this cut by vapor phase chromatography indicated that it was a mixture of 95% compound C and 5% A (see Table III).

Reduction of Reformatsky Products.—A solution of 8.8 g. (0.05 mole) of the initial mixture of compounds A, B, and C in 200 ml. of absolute methanol was hydrogenated over Raney nickel (Parr hydrogenator) until the uptake of hydrogen ceased (4 hr.). There was obtained 8.2 g. (92%) of a *single* product, methyl 3-phenylbutyrate, boiling at $87\text{--}88^{\circ}$ (1.5 mm.) (lit.³⁰ $133\text{--}134^{\circ}$ (22 mm.)). It was identified by its anilide which melted at $137\text{--}138^{\circ}$ (lit.³¹ $136\text{--}137^{\circ}$).

Metalation of α -Methylstyrene by *n*-Amylsodium.—To *n*-amylsodium (from 0.2 mole of *n*-amyl chloride and 0.45 g.-atom of sodium in 100 ml. of decane was added α -methylstyrene (23.6 g., 0.2 mole) at -50° with high speed stirring. The reaction mixture was maintained at -50° for 3 hr., then warmed to -20° for 2 hr. The standard carbonation and diazomethane

(27) D. J. A. Johnson and G. A. R. Kon, *J. Chem. Soc.*, 2748 (1926).

(28) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(29) Prepared by the Michaelis-Arbuzov reaction¹⁴ from triethyl phosphite and methyl bromoacetate in refluxing tetrahydrofuran.

(30) I. M. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., Vol. 3, 1953, p. 429.

(31) J. F. Eijkman, *Chem. Weekblad.*, **5**, 655 (1908); *Chem. Zentr.*, **79** II, 1100 (1908).

(26) The n.m.r. spectrum shows three nonequivalent methyl groups at δ 3.33, 8.66, and 8.96 τ (intensities 3:3:3), a methylene group at 7.71 τ (intensity 2), and phenyl resonance at 2.87 τ (intensity 9).

treatment gave 11.6 g. of methyl esters. Analysis by v.p.c. indicated the presence of methyl caproate as well as methyl 3-phenyl-3-butenate (98%) and methyl 3-phenyl-2-butenate (2%).

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE STATE UNIVERSITY OF IOWA, IOWA CITY, IOWA]

Benzopyrylium Salts. VII. Reaction of Flavylium Perchlorate with Ethyl Esters of α -Amino Acids

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Flavylium perchlorate reacted with the ethyl esters of glycine, alanine, and phenylalanine to form ethyl N-(2-phenyl-4H-1-benzopyran-4-ylidene)-amino acid ester hydroperchlorates, the hydroperchlorate of the amino acid ester, and a mixture of nonnitrogen-containing by-products which have been characterized as 2-hydroxychalcone, 2-phenyl-1,2-benzopyran-2-ol, and 2-phenyl-1,4-benzopyran-4-ol. The degradation of the new substituted benzopyranimines to 4-thioflavone and synthesis from this compound are described.

Since anthocyanins and α -amino acids occur in the aqueous cell sap of certain fruits, flowers, and leaves, it is of interest to determine whether there is any interaction between these two classes of compounds. When flavylium salts (which contain the skeletal structure of the anthocyanidines) were treated with glycine or phenylalanine, no reaction occurred. However, esters of the α -amino acids did react readily but yielded a mixture of products.

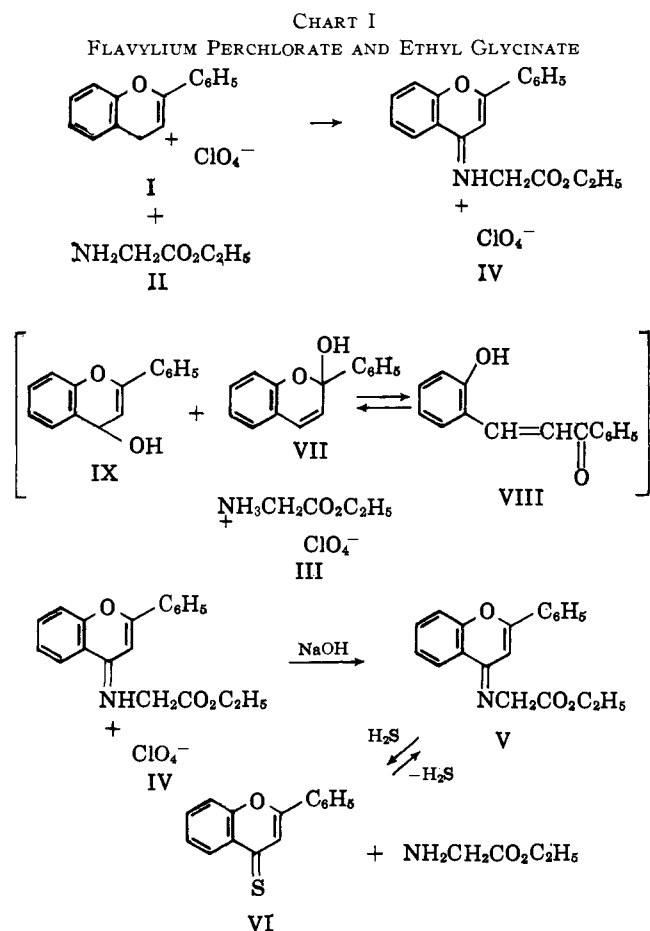
Chart I shows the five compounds formed from flavylium perchlorate (I) and one equivalent of ethyl glycinate (II). Over half of the latter appeared as the hydroperchlorate of ethyl glycinate (III); the other nitrogen-containing product, formed in 40% yield, has

been identified as ethyl N-(2-phenyl-4H-1-benzopyran-4-ylidene)-glycinate hydroperchlorate (IV).

The structure of the substituted ketimine salt (IV) was shown by: (1) Conversion by cold alkali to the free ketimine base V and re-formation of IV by perchloric acid. Flavylium perchlorate was not regenerated in sharp distinction from the behavior of 2- or 4-substituted aminoflavones.² (2) The infrared spectrum of V possessed an absorption band at 6.10 μ , indicative of substituted imino groupings, while the hydroperchlorate IV possessed an N-H band at 3.1 μ in addition to an imino band at 6.15 μ .³ (3) Treatment of an alcoholic solution of V with hydrogen sulfide produced red crystals of the known 4-thioflavone (VI), identical with a sample prepared by the action of phosphorus pentasulfide on flavone.⁴ (4) By boiling an alcoholic solution of 4-thioflavone (VI) with ethyl glycinate (II), a sample of V was obtained which was identical with that obtained from I plus II.

Reactions 3 and 4 parallel the degradations and syntheses described by Baker and co-workers⁵ on other N-alkyl-4H-1-benzopyran-4-imines.

It seems probable that the ketimine salt (IV) was produced by air oxidation of the initial adduct X to a carbinol XI which then lost water to give the ketimine



(1) E. I. du Pont de Nemours and Co. Postgraduate Fellow in Chemistry. From a thesis submitted to the Graduate School of the State University of Iowa in partial fulfillment of the requirements for the Ph.D. degree.

salt IV. Intermediates X and XI could not be found in the reaction mixture but similar oxidation of the reactive hydrogen in the 4-position to a carbinol has been demonstrated for the initial product from flavylium perchlorate and dimethylaniline.⁶

The water formed in conversion of XI to IV reacted with flavylium perchlorate in the presence of the ethyl

(2) R. L. Shriner in "Adams Symposium," John Wiley and Sons, Inc., New York, N. Y., 1955.

(3) F. A. Miller in "Organic Chemistry," Vol. III, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 140-150.

(4) W. Baker, G. G. Clark, and J. B. Harborne, *J. Chem. Soc.*, 998 (1954).

(5) W. Baker, J. B. Harborne, and W. D. Ollis, *ibid.*, 1294 (1952).

(6) R. L. Shriner and J. H. Shotton, *J. Am. Chem. Soc.*, **74**, 3622 (1952).