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The Vicinal Orientation. I. The Pivaloylation of Polymethylbenzenes[1)]

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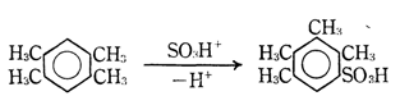
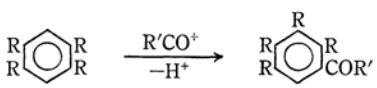
The direct introduction of a pivaloyl group by Friedel-Crafts acylation has been carried out with the following polymethylbenzenes: *o*-xylene, *m*-xylene, hemimellitene, pseudocumene, mesitylene, prehnitene and durene. The decarbonylation was not very significant, and seven new polymethylpivalophenones were prepared in fairly high yields. The hydrocarbon mixtures obtained simultaneously in these reactions usually consisted of at least four or five substances. In the pivaloylation of durene, the Jacobsen-type migration (vicinal orientation) of a methyl group was observed.

The introduction of a bulky group into the nucleus of polyalkylbenzenes often brings about the migration of alkyl groups, and results in the formation of unexpected products in which all the alkyl groups occupy the vicinal positions. The most typical of these anomalous reactions is the Jacobsen reaction.



This reaction has long been the object of many investigators' interest, but in spite of several recent proposals,[2)] its mechanism still remains uncertain. In order to get more precise knowledge about the puzzling features of this reaction, it seems pertinent to investigate some other reactions in which similar phenomena (vicinal orientation) are observed.

In the Friedel-Crafts acylation of polymethylbenzenes, one can sometimes observe unusual reactions in which the alkyl group migrates to the position meta to the entering acyl group, thus yielding the vicinal compounds[3,4)]:



This anomaly is generally attributed to steric stress and may be interpreted as follows: the migration of the alkyl group occurs in order to reduce the overcrowding caused by the introduction of the bulky acylium ion, while the entering acyl group, strongly electron-attracting in its nature, directs the migrating methyl group to the position meta to its original position.

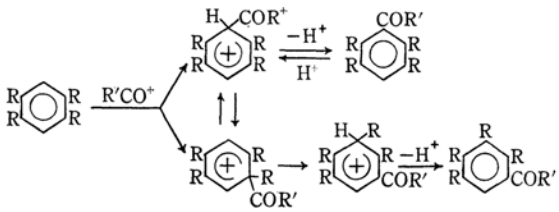
1) The Reaction of Polysubstituted Aromatics. Part IX; Part VIII: This Bulletin, **39**, 128 (1966).

* For the numbering by Roman numerals, refer to the Experimental section.

2) M. Kilpatrick and M. W. Meyer, *J. Phys. Chem.*, **65**, 1312 (1961); H. Suzuki, This Bulletin, **36**, 1642 (1963); F. Bohlmann and J. Riemann, *Chem. Ber.*, **97**, 1515 (1964).

3) G. Baddeley and A. G. Pendleton, *J. Chem. Soc.*, **1952**, 807.

4) W. L. Mosby, *J. Am. Chem. Soc.*, **74**, 2564 (1952); *J. Org. Chem.*, **18**, 483 (1953); G. M. Badger, W. Carruthers and J. W. Cook, *J. Chem. Soc.*, **1949**, 2044; R. R. Aitken, G. M. Badger and J. W. Cook, ibid., **1950**, 331; B. J. Abadir, J. W. Cook and D. T. Gibson, ibid., **1953**, 8.



If the reaction occurs for such a sterical reason, the bulky tertiary acylium ion would be more effective in inducing these phenomena. In the literature, however, reactions are limited only to those with the primary acyl group; the direct introduction of the tertiary acyl group into the nucleus of polymethylbenzenes seems never to have been attempted. The use of a tertiary acyl halide as the acylating agent, however, creates some complications. Tertiary acyl halides, such as pivaloyl chloride, often decarbonylate in the presence of the Friedel-Crafts catalysts and act as an alkylating agent.[5] With such highly-reactive substrates as anisole or phenol, the acylation takes place almost exclusively. If the aromatic nucleus is more weakly activated, as in benzene and in toluene, both processes occur simultaneously, yielding the corresponding acylation and alkylation products. An increase in the number of the methyl groups attached to the ring would activate the nucleus and so favor the attack of the tertiary acylium ion upon it. This advantage would, however, be in part counterbalanced by the opposite effect — an increased resistance to the entrance of the bulky tertiary acyl group into the crowded nucleus. Furthermore, the tertiary alkyl cation formed by the decomposition of the tertiary acylium ion is also bulky, and in some cases brings about the alkyl migration.[6] Thus, in the Friedel-Crafts acylation of polyalkylbenzenes with tertiary acyl halides, one might expect the possibility of an alkyl migration analogous to the Jacobsen reaction, regardless of whether the reaction proceeds mainly through the acylation or through the alkylation.

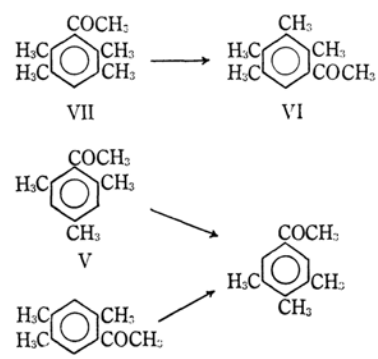
Results

In the present work, we used pivaloyl chloride as the acylating agent; the non-vicinal polyalkylbenzenes used were pseudocumene, mesitylene and durene. *o*- and *m*-Xylene hemimellitene and prehnitene were also acylated for the sake of comparison. Aluminum chloride, titanium chloride and stannic chloride were employed as the catalysts, and carbon disulfide or nitromethane as the solvents. Preliminary experiments proved aluminum chloride to be the most effective catalyst; the other two brought about the decomposition of pivaloyl chloride to a great extent. Carbon disulfide was preferred to nitromethane, because the latter also favored the decarbonylation of the acid chloride.

On treatment with pivaloyl chloride in carbon disulfide at a low temperature, all the polymethylbenzenes used underwent acylation without any remarkable decarbonylation, although with less activated *o*- and *m*-xylene, or with mesitylene and durene, in which only the hindered positions were available, decarbonylation leading to the formation of a complex mixture of polymethylbenzenes was observed to a certain extent. The hydrocarbon mixtures simultaneously obtained in the reactions were found by gas chromatography to contain at least four or five, and in some cases even seven or eight, substances. Most of them, however, could not be identified. As the original hydrocarbons had little tendency toward disproportionation under the experimental conditions employed, the formation of various polyalkylbenzenes is probably to be attributed both to the alkyl migration caused by the introduction of the bulky pivaloyl group into the ring, and to the alkylation of polymethylbenzenes with isobutylene or its condensate products, formed by the decomposition of pivaloyl chloride.

Contrary to our expectations, most of the acylation, except in the case of durene, proceeded without any rearrangement. Only durene underwent an anomalous acylation to yield the vicinal product, 2, 3, 4, 5-tetramethylpivalophenone (VI).* A prolonged reaction time or an elevated temperatures resulted in an increased formation of the hydrocarbon parts and resinous matter, with a consequent decrease in the yield of the ketonic products.

The hindered ketones are generally known, in the presence of aluminum chloride, to isomerize



5) E. Rothstein and R. W. Saville, ibid., **1949**, 1946, 1950, 1954, 1959, 1961; E. Rothstein and M. A. Saboor, ibid., **1943**, 425; E. Rothstein, ibid., **1951**, 1459; M. E. Grundy, W. H. Hsü and E. Rothstein, ibid., **1952**, 4136; M. E. Grundy, E. Rothstein and W. H. Hsü, ibid., **1956**, 4558, 4561; M. E. Grundy, W. H. Hsü and E. Rothstein, ibid., **1958**, 581; D. E. Pearson, *J. Am. Chem. Soc.*, **72**, 4169 (1950).

6) L. R. C. Barclay and E. E. Betts, *J. Am. Chem. Soc.*, **77**, 5735 (1955); L. R. C. Barclay and J. W. Hilchie, *J. Org. Chem.*, **22**, 633 (1957); P. C. Myhre and W. M. Schubert, ibid., **25**, 708 (1960). Also cf. R. M. Roberts and D. Schienthong, *J. Am. Chem. Soc.*, **86**, 2851 (1964).

gradually to the isomers of the less hindered structures. Thus acetodurene isomerizes to acetoprehnitene,[3,7] and acetomesitylene or acetopseudocumene, to acetohemimellitene.[8]

In expectation of such isomerization to the vicinal structure, 2, 3, 5, 6-tetramethylpivalophenone (VII) and 2, 4, 6-trimethylpivalophenone (V) were subjected to the action of an excess of aluminum chloride at room temperature. VII readily underwent a Jacobsen-type isomerization to give the vicinal isomer (VI). Such an easy transformation of VII into VI in comparison with that of the corresponding acetyl derivative[3,7] is no doubt due to the greater steric repulsion between the pivaloyl group and the adjacent ortho methyl group. In contrast to the tetramethyl compound, V was comparatively stable towards the action of aluminum chloride, and no alkyl migration was observed under ordinary condition even with a prolonged reaction time. The only reaction that took place was deacylation, followed by complicated side reactions involving alkylation by isobutylene or its condensates. This difference of ease between V and VII towards the vicinal orientation may be attributed to the buttressing effect of the methyl groups at the meta positions to the pivaloyl group.

In the hydrocarbon mixtures obtained by the rearrangement of VII, no noticeable amount of isodurene was found. This suggests that the Jaccobsen-type isomerization occurs via a direct rearrangement of the hindered ketone VII. If the vicinal product VI were formed through the step-by-step 1, 2-alkyl migration, as has been explained by Dewar,[9] with the intermediary formation of 2, 3, 4, 6-tetramethylpivalophenone, much isodurene would be detected in the hydrocarbon fraction, because the pivaloyl group in the highly-hindered position would readily be removed from the ring in the presence of a large excess of aluminum chloride. This however, did not happen. Durene was the only main tetramethylbenzene isolated.

Experimental

Materials. — Pivalic acid, prepared from *t*-butyl chloride by the Grignard reaction,[10] was carefully fractionated twice; the product had a b. p. of 159.5—161.5°C and an m. p. of 31—33°C. Freshly-distilled thionyl chloride was used for preparing the pivaloyl chloride, which, after careful distillation, had a b. p. of 104—106°C. Durene (m. p. 79—80°C) and prehnitene (b. p. 80—82°C/18 mmHg) were prepared as has been described by Smith and his co-workers.[11,12] Pseudocumene (b. p. 166—167°C) was prepared by the lithium hydride reduction[13] of 2, 5-dimethylbenzyl chloride (b. p. 99—102°C/15 mmHg), which in turn was obtained by the chloromethylation of *p*-xylene[14]. The *o*-xylene, *m*-xylene, mesitylene and hemimellitene were commercial products.

Measurements.—The infrared spectra were determined on liquid films or on potassium bromide disks, with a Perkin-Elmer Model 021 spectrophotometer. The ultraviolet absorption spectra (above 220 mμ) were measured in methanol solutions with a Hitachi EPS-30 automatic recording spectrophotometer. The NMR spectra were obtained in carbon tetrachloride solutions, with tetramethylsilane as the internal reference, using a JNM-3H 60 spectrometer manufactured by the Japan Electron Optics Laboratory Co., Ltd. The chemical shifts are expressed in τ-units. The NMR spectrum was very helpful in the structure assignment of each isomer obtained; in most cases it permitted an unequivocal choice (Fig. 1).

The General Procedure for Pivaloyl Chloride Acylations.—In a three-necked flask fitted with a thermometer, a reflux condenser and a dropping funnel, finely-powdered aluminum chloride was covered with small amounts of carbon disulfide and then cooled to the temperature of ice-water. The mixture was magnetically-stirred and a solution of pivaloyl chloride and a polymethylbenzene dissolved in carbon disulfide was added drop-by-drop over a period of 20—30 min. As the pivaloyl chloride entered the aluminum chloride suspension, gas evolved immediately. The gas was a mixture of hydrogen chloride, carbon monoxide and isobutylene, the proportions varying markedly with the structure of the aromatic hydrocarbon and the experimental conditions used. After the addition of the pivaloyl chloride, the mixture was stirred for half an hour at room temperature and then decomposed with dilute hydrochloric acid mixed with crushed ice. The organic layer was separated, carbon disulfide was removed by passing a current of air through it, and the residual dark oil was subjected to steam distillation. The oily layer of the steam-distillate was extracted with ether and dried over anhydrous calcium chloride. The ether extract was concentrated, and the residue was fractionated at reduced pressure.

In the distillation of VII, however, so much foaming was encountered that this compound was first chromatographed on a short alumina column, using petroleum ether as an eluant, and then repeatedly crystallized from light-boiling ligroin.

Compounds I, II and V have already been synthesized by Nightingale and his co-workers[15] through quite the same procedure, but the precise physical constants of them have not been described. Compounds III, IV and VII were first synthesized by the present authors.

2, 4-Dimethylpivalophenone (I).—To the stirred suspension of aluminum chloride (30 g.) in carbon disulfide (40 ml.), pivaloyl chloride (10 g.) and *m*-xylene (13.0 g.) dissolved in carbon disulfide (30 ml.) were added at 0—5°C over a 30-min. period. After

7) M. Lukin and B. B. Carson, *J. Org. Chem.*, **23**, 1007 (1958).
8) G. Baddeley and S. Varma, *J. Chem. Soc.*, **1957**, 2727.
9) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford Press, London (1956).
10) "Organic Syntheses," Coll. Vol. 1, 524. 2nd ed. (1956).
11) "Organic Syntheses," Coll. Vol. 2 (1948), p. 248.
12) "Organic Reactions," Vol. 1, John Wiley & Sons, Inc., New York, N. Y. (1942), p. 382.
13) J. E. Johnson, R. H. Blizzard and H. W. Carhart, *J. Am. Chem. Soc.*, **70**, 3664 (1948).
14) J. Von Braun and J. Nelles, *Ber.*, **67**, 1096 (1934); D. A. Shirley, "Preparation of Organic Intermediates," John Wiley & Sons, Inc., New York, N. Y. (1951), p. 129.
15) D. V. Nitingale, R. L. Sablett, R. A. Capenter and H. D. Radford., *J. Org. Chem.*, **16**, 655 (1951).

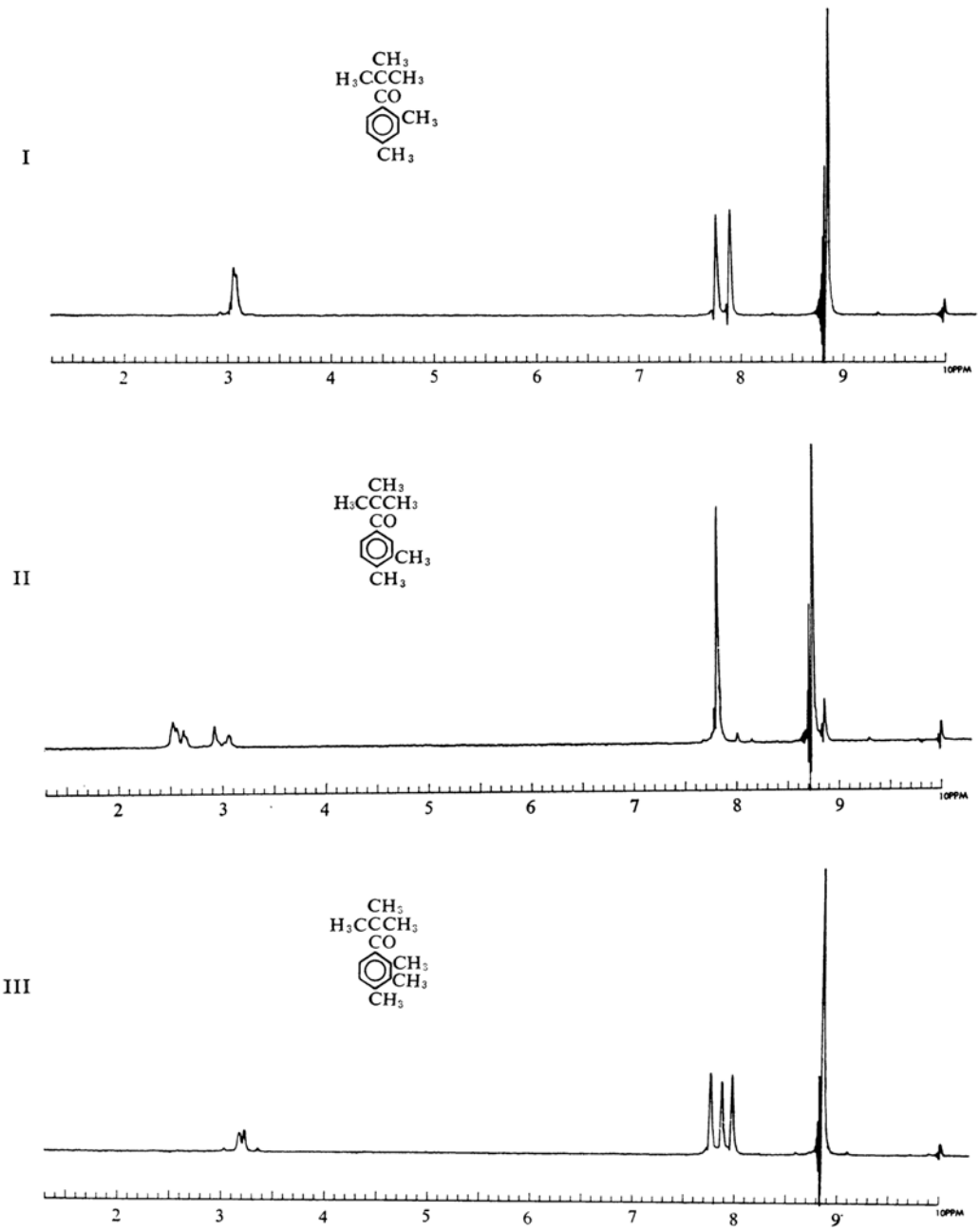


Fig. 1. NMR spectra of polymethylpivalophenones.

1 hr., the mixture was worked up as described above. The distillation of the oily product gave three hydrocarbon fractions: b. p. —90°C/22 mmHg, 1.5 g.; b. p. 93—95°C/22 mmHg, 7.7 g. (5-*t*-butyl-*m*-xylene); b. p. 121—122°C/22 mmHg, 1.5 g., and a ketonic fraction (b. p. 132—133°C/22 mmHg, 6.6 g.). The redistillation of the ketonic fraction yielded 5.6 g. of I, boiling at 131—132°C/21 mmHg.

Found: C, 82.18; H, 9.80. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54%.

Its infrared bands were at 867 (isolated ring hydrogen), 827 (two adjacent ring hydrogen) and 1664 cm^{-1} (carbonyl). The ultraviolet absorption bands were at 244.5, 271—272 (*infl*)** and 310 mμ (*s*)**. The NMR methyl peaks at were 7.91 (*o*-methyl), 7.76 (*p*-methyl) and 8.85 (*t*-butyl).

3, 4-Dimethylpivalophenone (II).—II was prepared in the manner described above. B. p. 141—143°C/20—21 mmHg. The yield of steam-distilled ketone was a little lower than that of I. The hydrocarbon

** *infl* denotes inflection; *s*, shoulder.

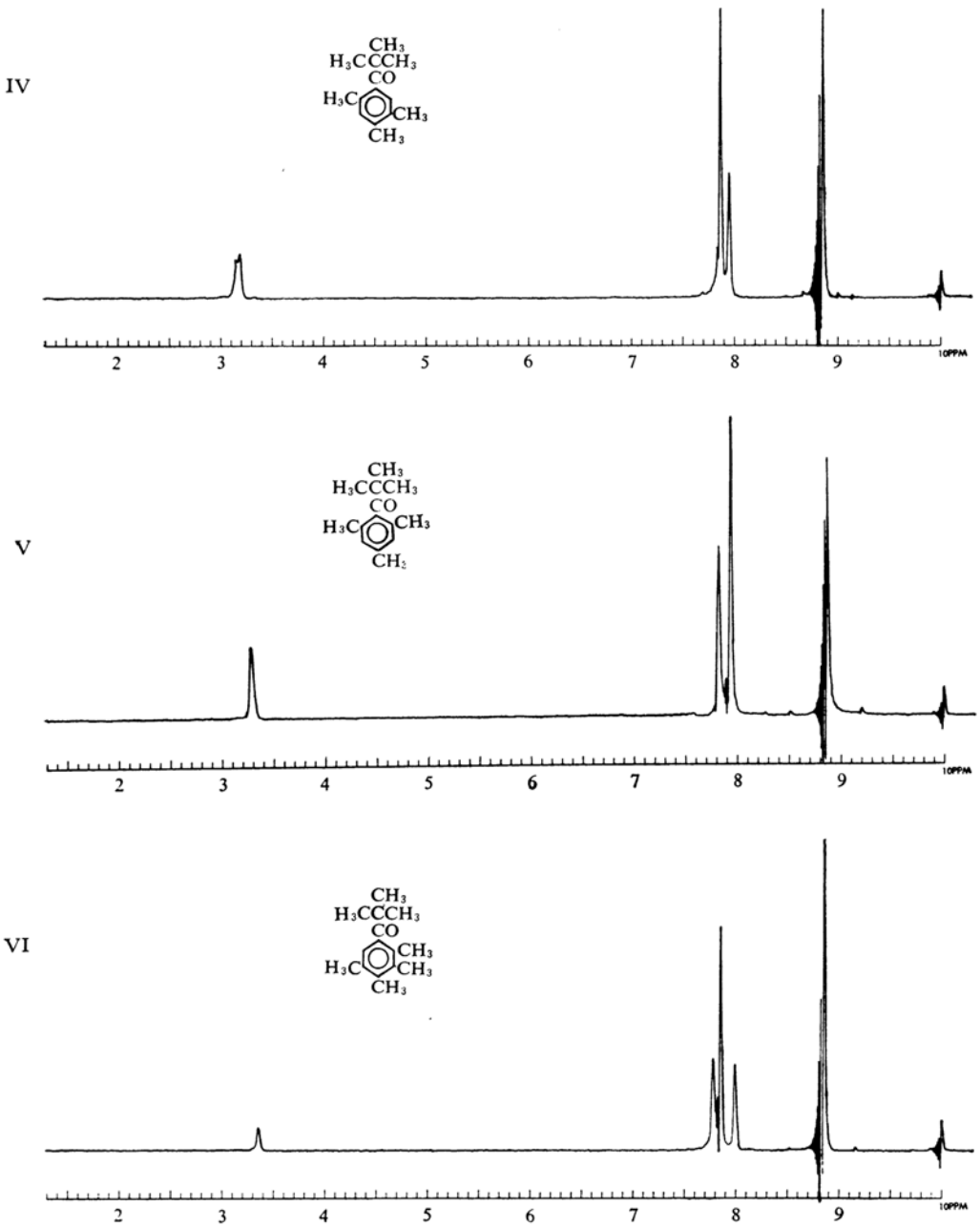


Fig. 1. Continued

fraction was mainly composed of 4-*t*-butyl-*o*-xylene, b. p. 102—103°C/22 mmHg.

Found: C, 82.33; H, 9.65. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54%.

Strong infrared bands were found at 867 (isolated ring hydrogen), 827 (two adjacent ring hydrogens) and 1665 cm^{-1} (carbonyl). The ultraviolet absorption bands were at 252, 276—277 (*infl*) and 317—318 mμ (*s*). The NMR methyl peaks were at 7.81 (*m*- and *p*-methyl) and 8.74 (*t*-butyl).

2, 3, 4-Trimethylpivalophenone (III).—Hemimellitene (10 g.) was acylated with a mixture of pivaloyl chloride (6.6 g.) and aluminum chloride (20 g.) at 0—3°C by the procedure used above. An ordinary work-up followed by the distillation of the residual oil, gave two hydrocarbon fractions (b. p. 78—79°C/31 mmHg, 2.0 g.; b. p. 125—127°C/31 mmHg, 3.5 g.), a ketonic fraction (b. p. 149—151°C/21 mmHg, 9.5 g.), and a residue (ca. 1.0 g.). After redistillation, the ketone (b. p. 151—152°C/20—21 mmHg, 8.5 g.) solidified to white prisms melting at 39—40°C.

Found: C, 82.47; H, 10.11. Calcd. for $C_{14}H_{20}O$:

VII

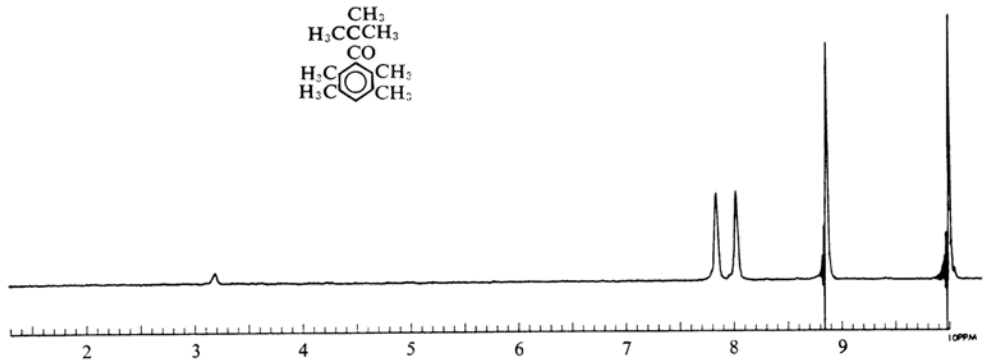


Fig. 1. Continued

C, 82.30; H, 9.87%.

The infrared bands were at 832 (two adjacent hydrogens) and 1685 cm^{-1} (carbonyl). The ultraviolet absorption bands were at 238—242 (broad) and 301—303 mμ (s). The NMR methyl peaks were at 7.76 (*p*-methyl), 7.87 (*m*-methyl), 7.97 (*o*-methyl) and 8.84 (*t*-butyl).

2, 4, 5-Trimethylpivalophenone (IV).—IV was prepared from pseudocumene (15 g.), pivaloyl chloride (10 g.) and aluminum chloride (30 g.). The fractionation of the oily product gave the hydrocarbon mixture (b. p. chiefly 66—68°C/22 mmHg. 2.0 g.) and the ketone (b. p. 152—154°C/30—31 mmHg, 13.7 g.). On standing, the ketone solidified to white prisms melting at 32—33°C.

Found: C, 82.17; H, 9.87. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87%.

Its infrared bands were at 874 (isolated ring hydrogen) and 1691 cm^{-1} (carbonyl). The ultraviolet absorption bands were at 250, 278 (*s*) and 307 mμ (*infl*). The NMR peaks were at 7.86 (*m*- and *p*-methyl), 7.95 (*o*-methyl) and 8.85 (*t*-butyl).

2, 4, 6-Trimethylpivalophenone (V).—Mesitylene (15.0 g.) was acylated using pivaloyl chloride (10.0 g.) and aluminum chloride (30.0 g.) at 0—5°C. The distillation of the oily product gave two hydrocarbon fractions (b. p. 61—63°C/22 mmHg, 4.5 g.; b. p. chiefly 91—92°C/22 mmHg, 0.5 g.), a ketonic fraction (b. p. 141—143°C/22 mmHg, 10.2 g.) and a residue (ca. 1.0 g.). The redistillation of the ketonic fraction gave 9.5 g. of V, boiling at 142—143°C/22 mmHg, which, on standing in the refrigerator, solidified to white crystals, m. p. 19—21°C.

Found: C, 82.50; H, 10.08. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87%.

The infrared bands were at 875 (isolated ring hydrogen) and 1682 cm^{-1} (carbonyl). The ultraviolet absorption bands were at 274—276 (*infl*) and 305—306 mμ. The disappearance of the K-band indicates the steric inhibition of the conjugation due to the *o*, *o'*-disubstitution. The NMR methyl peaks were at 7.82 (*p*-methyl), 7.94 (*o*-methyl) and 8.86 (*t*-butyl).

2, 3, 4, 5-Tetramethylpivalophenone (VI).—Prehnitene (15.0 g.) was acylated with pivaloyl chloride (9.0 g.) and aluminum chloride (30 g.) at 0—5°C. The liberation of carbon monoxide was not significant. A similar work-up, followed by the distillation of the product, afforded hydrocarbon fractions (b. p. 85—89°C/25 mmHg, 1.6 g.; b. p. 90—130°C/25 mmHg, 1.0 g.), a ketone (b. p. 161—165°C/21 mmHg, 11.2 g.) and a residue (1.3 g.). The redistillation of the ketonic fraction gave 10.5 g. of pure VI, b. p. 162—163°C/21 mmHg, which readily solidified to prisms and melted at 37—39°C.

Found: C, 82.25; H, 10.45. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

There were strong infrared bands at 867 (isolated ring hydrogen) and 1691 cm^{-1} (carbonyl). The ultraviolet absorption bands were at around 240—250 (*s*), 275—280 (*infl*) and 310—314 mμ (*infl*). The NMR methyl peaks were at 7.79 (*p*-methyl), 7.86 (*m*-methyl), 7.99 (*o*-methyl) and 8.85 (*t*-butyl).

2, 3, 5, 6-Tetramethylpivalophenone (VII).—Durene (14.0 g.) was acylated with pivaloyl chloride (8.9 g.) and aluminum chloride (30 g.) at 5—10°C. A usual work-up followed by distillation under reduced pressure, was difficult because of the remarkable foaming; thus the oily product was subjected to chromatographic separation on an alumina column (1.8×30 cm.). Elution with petroleum ether afforded a hydrocarbon fraction (b. p. chiefly 98°C/37 mmHg, 2.5 g.), an oily mixture of VI and VII (11.0 g.), and small amounts of yellow needles of an unidentified ketonic substance. After the ketonic mixture had stood in the refrigerator, about 4.0 g. of white crystals separated out; on several recrystallizations from petroleum ether, these gave white needles melting at 104—105°C.

Found: C, 82.66; H, 10.25. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

The infrared bands were at 868 (isolated ring hydrogen) and 1685 cm^{-1} (carbonyl). The ultaviolet absorption bands were at 272—273 (*s*), 280 and 311 mμ (*s*). Its NMR methyl peaks were at 7.85 (*m*-methyl), 8.03 (*o*-methyl) and 8.86 (*t*-butyl).

The remaining oily part (b.p. 165—167°C/36 mmHg) was found by spectroscopic inspection to be mainly composed of the vicinal product VI.

The yellow needles, after recrystallization from boiling petroleum ether, melted at 183—185°C. They showed a strong absorption at 1685 cm^{-1} (carbonyl).

Found: C, 86.19; H, 8.92%.

The Isomerization of the Ketones.—A mixture of a ketone (3.3 or 4.0 g.), aluminum chloride (10 g.) and carbon disulfide (20 ml.) was agitated for 3—4 hr. at room temperatures and subsequently worked up in the manner described above. VII (4.0 g.) gave about 0.5 g. of a hydrocarbon fraction and 1.7 g. of a ketonic fraction. The spectral data of the latter nearly coincide

with those of the vicinal isomer VI. On the other hand, V (3.3 g.) gave 0.8 g. of the hydrocarbon fraction and 2.0 g. of the ketonic fraction (b. p. 144—146°C/22 mmHg, 2.0 g.). The spectral inspection of the latter disclosed that V was recovered unchanged. On the gas chromatograms of these hydrocarbon fractions simultaneously obtained there were found four or six peaks. In both cases some polymeric by-products were formed.