[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF OKLAHOMA]

Ketimines. I. Alkyl-Aryl Type[1]

BY P. L. PICKARD AND D. J. VAUGHAN

In 1891, Hantzch and Kraft[2] described the production of the hydrochlorides of ketimines by the reaction between urethan and the dichlorides produced from ketones and phosphorus pentachloride. Moureu and Mignonac[3] published the results of a study of eleven ketimines prepared from aromatic nitriles and organomagnesium compounds. The compounds produced in both investigations were readily hydrolyzed to ketones in dilute acid.

Other authors[4,5,6,7,8,9,10] have since described the preparation of ketimines or their salts by the action of Grignard reagents on nitriles. These compounds are reported either non-hydrolyzable or hydrolyzed with difficulty.

It is the object of this investigation to prepare and investigate the properties of a number of ketimines. Inasmuch as there has been no systematic study of these compounds since the work of Moureu and Mignonac,[3] it was deemed advisable to work first with compounds prepared from readily available reagents. This has enabled us to determine optimum conditions and preferred technique for synthesis of ketimines by action of Grignard reagents on nitriles. Although addition of nitrile to the organomagnesium compound in ether causes considerable heating and almost instantaneous formation of a precipitate, the only product obtained upon working up the mixture at this point is unreacted nitrile. Two methods for the preparation of ketimines by the Grignard reaction in toluene have been developed. The first involves decomposition of the addition compound with anhydous hydrogen chloride. This procedure, which very closely parallels that of Moureu and Mignonac,[3] has proved feasible and provides fair yields of product. It has been modified, however, to require less time and to produce higher yields. The bases may be produced directly in toluene solution by decomposition of the addition compound with anhydrous ammonia. Not only does ammonia decompose the addition compound more rapidly, but it also produces an inorganic magnesium compound more easily filtered from the toluene solution of ketimine than is magnesium halide from the hot chloroform solution of ketimine hydrochloride.

The compounds thus far produced are high boiling liquids with a penetrating odor. At atmospheric pressure over Adams platinum catalyst they absorb one mole of hydrogen. It is not surprising that the ketimines behave as secondary amines by producing alkali-insoluble benzenesulfonamides; however, the primary amines from catalytic reduction also form alkali-insoluble benzenesulfonamides. The ketimines, with one exception, are at least partially hydrolyzed to ketones, which have been characterized by physical constants and derivatives. It is noted that the semicarbazones of two of the ketones exhibit different melting points from those listed in the literature,[11] but analysis of these derivatives as well as the 2,4-dinitrophenylhydrazones indicates that the compounds are uncontaminated.

All compounds produced, physical properties and analyses are given in Tables I–III.

Experimental

Preparation of Ketimines.—A Grignard reagent was prepared from 0.75 mole of alkyl halide and 0.76 g. atom of magnesium in 300 cc. of ether. After the halide had been added and reaction had ceased, 150 cc. of ether was distilled and an equal amount of anhydrous toluene added. The mixture was then distilled until the distillate temperature reached 100°; the distillate was replaced by an equal amount of toluene. The aromatic nitrile (0.50 mole) was added dropwise over a period of one hour and the mixture stirred and refluxed for forty-eight hours. Following this reaction period, the product was worked up by one of the methods given below.

a. Hydrogen Chloride Method.—The reaction mixture was distilled to remove toluene until a thick viscous solution remained. Anhydrous chloroform was added and hydrogen chloride bubbled into the solution for three hours. The mixture was refluxed during the last hour of this addition and filtered hot through a fritted glass funnel. The chloroform filtrate was cooled and treated for an hour with a stream of ammonia, the precipitated ammonium chloride filtered and the chloroform distilled. The residual ketimine was distilled in vacuum. By this method, *o*-tolyl *t*-butyl ketimine and *p*-tolyl *t*-butyl ketimine were prepared in yields of 50 and 49%, respectively.

b. Ammonia Method.—Anhydrous ammonia was bubbled through the toluene solution for one hour. The mixture was filtered through a fritted glass funnel, the toluene distilled and the ketimine distilled in vacuum. By this procedure, *m*-tolyl *t*-butyl ketimine and *o*-, *m*- and *p*-tolyl *s*-propyl ketimines were prepared in yields of 86, 83, 79 and 50%, respectively.

Hydrochlorides of the ketimines were prepared by bubbling anhydrous hydrogen chloride through an ether solution of the base. Recrystallization was accomplished

(1) This research was carried out with the support of the Office of Naval Research and the University of Oklahoma Research Institute Project No. 45.

(2) A. Hantzsch and F. Kraft, *Ber.*, **24**, 3516 (1891).

(3) C. Moureu and G. Mignonac, *Ann. chim.*, [9] **14**, 322 (1920).

(4) Ramart-Lucas and Salmon Legagneur, *Compt. rend.*, **184**, 103 (1927).

(5) N. R. Easton, J. H. Gardner and J. R. Stevens, THIS JOURNAL, **69**, 976 (1947).

(6) E. M. Schultz, C. M. Robb and J. M. Sprague, *ibid.*, **69**, 2454 (1947).

(7) N. R. Easton, J. H. Gardner, M. L. Evanick and J. R. Stevens, *ibid.*, **70**, 76 (1948).

(8) H. L. Lochte, Joe Horeczy, P. L. Pickard and A. D. Barton, *ibid.*, **70**, 2012 (1948).

(9) L. F. Fieser and A. M. Seligman, *ibid.*, **61**, 136 (1939).

(10) L. F. Fieser and D. M. Bowen, *ibid.*, **62**, 2103 (1940).

(11) Heilbron, "Dictionary of Organic Compounds," Vol. II, Eyre and Spotteswoode, London, 1936, p. 463, gives the melting point of the semicarbazone of *m*-tolyl *s*-propyl ketone as 120° and the semicarbazone of *p*-tolyl *s*-propyl ketone as 101°. Our values are 126 and 171°, respectively.

TABLE I

KETIMINES

$R_1C(=NH)R_2$ R_1	R_2	B. p., °C. 740 mm.	5 mm.	d^{20}_4	$n^{20}D$	N %	Benzenesulfonamide M. p., °C.	N, %	Hydrochloride M. p., °C.	N, %	Picrate M. p., °C.	N, %
s-Propyl	*o*-Tolyl	224	86–87	0.9535	1.5300	8.78[a]	Liq.		155	7.05[d]	249	14.62[f]
s-Propyl	*m*-Tolyl	227	87–88	.9499	1.5349	8.74[a]	Liq.		249	7.11[d]	270 dec.	14.55[f]
s-Propyl	*p*-Tolyl	228	86–87	.9511	1.5374	8.75[a]	Liq.		275	7.11[d]	223	14.54[f]
t-Butyl	*o*-Tolyl	235	93–94	.9337	1.5140	7.84[b]	77	4.59[c]	183	6.65[e]	187	13.92[g]
t-Butyl	*m*-Tolyl	238	91–93	.9240	1.5118	7.83[b]	90	4.58[c]	178	6.69[e]	236	14.04[g]
t-Butyl	*p*-Tolyl	235	93–95	.9338	1.5122	7.81[b]	119	4.52[c]	229	6.63[e]	232 dec.	14.07[g]

Theoretical values: [a] 8.70; [b] 7.99; [c] 4.44; [d] 7.09; [e] 6.62; [f] 14.37; [g] 13.89.

TABLE II

AMINES

$R_1CH(NH_2)R_2$ R_1	R_2	B. p., °C. 740 mm.	Red. p.	Mm.	d^{20}_4	$n^{20}D$	N, %	Benzenesulfonamide M. p., °C.	N, %	Picrate M. p., °C.	N, %
s-Propyl	*o*-Tolyl	243	107–108	4	0.9426	1.5214	8.57[a]	Liq.	...	203	14.14[d]
s-Propyl	*m*-Tolyl	231	104–105	3	.9275	1.5151	8.51[a]	Liq.	...	164	14.31[d]
s-Propyl	*p*-Tolyl	238	106–107	4	.9386	1.5200	8.52[a]	Liq.	...	244	14.17[d]
t-Butyl	*o*-Tolyl	243	104–105	1	.9317	1.5165	7.78[b]	151	4.40[c]	216	13.66[e]
t-Butyl	*m*-Tolyl	243	105–106	1	.9224	1.5125	7.79[b]	128	4.49[c]	231[f]	13.72[e]
t-Butyl	*p*-Tolyl	253	107–108	1	.9298	1.5130	7.86[b]	128	4.55[c]	241	13.69[e]

Theoretical values: [a] 8.58; [b] 7.90; [c] 4.41; [d] 14.28; [e] 13.78. [f] The mixed melting point of this picrate and the corresponding ketimine picrate is below 200°.

TABLE III

KETONES

$R_1—CO—R_2$ R_1	R_2	B. p., °C. 740 mm.	Red. p.	Mm.	d^{20}_4	$n^{20}D$	C, %	H, %	2,4-Dinitrophenylhydrazone M. p., °C.	N, %	Semicarbazone M. p., °C.	N, %
s-Propyl	*o*-Tolyl	237	79–80	3	0.9771	1.5131	81.49[a]	8.93[c]	91	16.29[e]	177	19.24[g]
s-Propyl	*m*-Tolyl	239	86–87	5	.9714	1.5171	81.49[a]	8.76[c]	109	16.27[e]	126	19.19[g]
s-Propyl	*p*-Tolyl	242	85–86	3	.9712	1.5202	81.55[a]	8.93[c]	122	16.39[e]	171	19.18[g]
t-Butyl	*m*-Tolyl	240	84–85	2	.9770	1.5085	81.75[b]	9.11[d]	171	15.79[f]	...	....
t-Butyl	*p*-Tolyl	247	85–86	2	.9616	1.5129	81.63[b]	9.36[d]	165	15.76[f]	...	....

Theoretical values: [a] 81.44; [b] 81.77; [c] 8.70; [d] 9.15; [e] 16.36; [f] 15.72; [g] 19.16.

by solution in warm chloroform and precipitation with ether. Picrates were prepared by adding a few drops of ketimine to an alcoholic solution of picric acid and warming. The salt usually separated as pure crystals within thirty minutes. Recrystallization from alcohol or alcohol–water yielded a constant melting product. Benzenesulfonamides were prepared by adding a few drops of ketimine to an excess of benzenesulfonyl chloride and warming gently. A solution of 20% sodium hydroxide was then added slowly to destroy the excess acid chloride. The sulfonamides are insoluble in basic solution and could be recrystallized from 95% alcohol.

Hydrogenation of Ketimines.—A 1.0–2.0-g. sample was dissolved in anhydrous methanol and hydrogenated quantitatively over prereduced Adams platinum catalyst at room temperature and atmospheric pressure. In each case the hydrogen absorbed was the theoretical amount; however, in both the *s*-propyl and *t*-butyl series, the time necessary for reduction decreased from *o*- to *m*- to *p*-tolyl. The amines were purified by distillation in vacuum. All picrates were prepared by adding the primary amine to a saturated alcoholic solution of picric acid. These derivatives gave a constant melting point after a single recrystallization from alcohol. Benzenesulfonamides were prepared by the usual method and are solids or liquids, insoluble in alkaline solution. Examination of the benzenesulfonamides indicates that they do not react with sodium hydroxide to form insoluble sodium salts, as was first suspected.

Hydrolysis of Ketimines.—Each ketimine was subjected to both acidic and basic hydrolysis with the following results.

a. In 10% Sodium Hydroxide.—*o*-, *m*- and *p*-tolyl *s*-propyl ketimines were partially hydrolyzed after ten hours reflux. Extraction with ether and washing with dilute hydrochloric acid to remove the ketimine as hydrochloride yielded small amounts of ketone. *o*- and *m*-tolyl *t*-butyl ketimines were recovered essentially unchanged after refluxing twenty hours. *p*-Tolyl *t*-butyl ketimine was partially hydrolyzed after twenty hours of refluxing.

b. In 18% Hydrochloric Acid.—*o*-, *m*- and *p*-tolyl *s*-propyl ketimines dissolved in the acid and an oily product began to separate after four hours refluxing. Hydrolysis was complete after twelve hours refluxing. *o*-Tolyl *t*-butyl ketimine precipitated as a hydrochloride insoluble in hydrochloric acid. Upon heating, the salt apparently melted and remained insoluble. After twenty-four hours refluxing and allowing to stand for another twenty-four hours the ketimine was recovered unchanged as its hydrochloride. *m*-Tolyl *t*-butyl ketimine precipitated as a hydrochloride insoluble in hydrochloric acid. Upon heating, the salt melted. After twenty-four hours reflux and twenty-four hours standing, the mixture was filtered to recover approximately 50% of the ketimine as its hydrochloride. The filtrate, upon ether extraction, yielded the ketone.

p-Tolyl *t*-butyl ketimine precipitated as an insoluble hydrochloride which became molten during the early stages of refluxing. After twenty-four hours refluxing and twenty-four hours standing the mixture was ether extracted to obtain the ketone. No ketimine hydrochloride was obtained. Semicarbazone and 2,4-dinitrophenylhydrazone derivatives were prepared according to directions in Shriner and Fuson.[12]

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1948.

Summary

1. An improved method of synthesis of ketimines is reported.
2. Six ketimines have been prepared and characterized by their physical constants and derivatives.
3. Five ketones have been produced by hydrolysis of ketimines.
4. Six primary amines have been prepared by low pressure catalytic reduction of ketimines.

RECEIVED AUGUST 22, 1949

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Stereochemistry of the Peracid Oxidation of Ketones[1]

BY RICHARD B. TURNER

The conversion of cyclic ketones into lactones by the action of persulfuric acid was first observed by Baeyer and Villiger[2] in 1899. The general applicability of the reaction has since been demonstrated by many investigators, and numerous examples of the formation of esters from acyclic ketones, both aliphatic and aromatic, are recorded in the literature. Peracetic and perbenzoic acids have been employed successfully in place of persulfuric acid. The stereochemistry of the reaction, however, has not hitherto been explored, and a study of the steric course of the oxidation was undertaken in this Laboratory in conjunction with Gallagher's[3] investigation of the behavior of epimeric 17-acetyl steroid derivatives.

cis- and *trans*-1-acetyl-2-methylcyclohexane (II and III) were chosen as suitable model substances. Although only the *trans* isomer (III) had been prepared previously,[4] a satisfactory synthesis of the *cis* derivative was achieved by catalytic hydrogenation of 1-acetyl-2-methyl-Δ^1-cyclohexene (I). The crude hydrogenation product was purified as the semicarbazone (m. p. 182–182.5°), from which the ketone was regenerated by steam distillation in the presence of phthalic acid.[5] Evidence for the absence of inversion in the latter transformation was provided by reconversion of the purified ketone into a semicarbazone identical in melting point and mixed melting point with the starting material. The *cis* ketone (II) proved rather stable toward acid, but isomerization could be effected without difficulty by the use of sodium ethoxide. The rearrangement product was likewise purified as the semicarbazone (m. p. 177–178.5°, marked depression with the *cis* semicarbazone), which, after hydrolysis, furnished a pure sample of *trans*-1-acetyl-2-methylcyclohexane (III). Structures assigned to the isomeric ketones are based on the methods of synthesis[6,7] and on correlation of the physical constants[8] recorded in Table I.

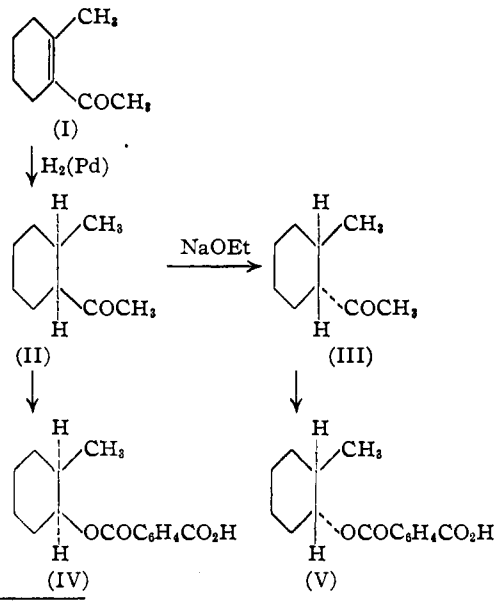

TABLE I

Compound	B. p. °C.	Mm.	d^{25}	$n^{25}D$	$M^{25}D$
II (*cis*)	67–68	10	0.9169	1.4532	41.36[a]
III (*trans*)	64–65	10	.8951	1.4464	41.80
VI (*cis*)	53–53.5	14	.9043	1.4418	36.91[b]
VII (*trans*)	53.5–54	14	.8923	1.4383	37.06

[a] Calcd. 41.59. [b] Calcd. 36.97.

Both substances (II and III) were subjected to oxidation with perbenzoic acid in chloroform solution according to the procedure employed by Gallagher.[3] The products, *cis*- and *trans*-2-methylcyclohexanyl acetate, were saponified directly and converted into the corresponding acid phthalates, which were separated from the non-alcoholic fraction by extraction with dilute alkali. From *cis*-1-acetyl-2-methylcyclohexane (II) a product (IV), m. p. 102–103°, was obtained that did not depress the melting point of an authentic sample of *cis*-2-methylcyclohexanyl acid phthal-

(1) This work was supported by funds provided by the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

(2) Baeyer and Villiger, *Ber.*, **32**, 3625 (1899); **33**, 858 (1900).

(3) Gallagher and Kritchevsky, THIS JOURNAL, **72**, 882 (1950).

(4) Darzens, *Compt. rend.*, **144**, 1124 (1907).

(5) Naves and P. Bachmann, *Helv. Chim. Acta*, **26**, 2151 (1943).

(6) *Cf.* Linstead, Doering, Davis, Levine and Whetstone, THIS JOURNAL, **64**, 1985 (1942).

(7) *Cf.* Hückel and Goth, *Ber.*, **58**, 447 (1925).

(8) Hückel, "Theoretische Grundlagen der organischen Chemie," 5th ed., Vol. II, p. 154, Akademische Verlagsgesellschaft, Leipzig, 1948.