Synthesis and Cyclization of the Three Isomeric 2-Benzylphenyl Pyridyl Ketones

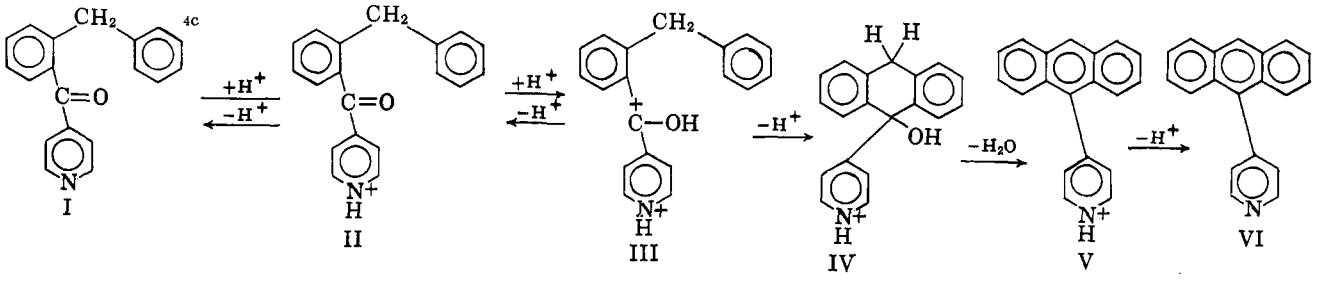
FRANK A. VINGIELLO AND MELVIN M. SCHLECHTER[1-3]

Department of Chemistry, Virginia Polytechnic Institute, Blacksburg, Virginia

Received December 26, 1962

Although a considerable number of studies have been made[4] regarding the rates of the acid-catalyzed aromatic cyclodehydration of ketones, these studies included only ketones containing one basic group, the carbonyl function of the ketone. Substituents on the ketone were restricted to alkyl groups and halogen atoms. The cyclization behavior of ketones containing a group more strongly proton accepting than the ketonic carbonyl would test a possible limitation of the Bradsher-type[5] aromatic cyclodehydration reaction. Protonation of the substituent might retard formation of the carbonium ion needed for cyclization. This inference actually does not exist since all three isomeric 2-benzylphenyl pyridyl ketones are cyclized at a faster rate than 2-benzylbenzophenone by the usual hydrobromic acid–acetic acid–water mixture. The data suggest that the diprotonated species (III, see Chart I) is involved in the reaction and that this species undergoes rapid aromatic cyclodehydration.

CHART I



The three isomeric pyridyl ketones needed for this study were prepared through the interaction of the Grignard reagent of 2-bromodiphenylmethane[6] and the appropriate cyanopyridine followed by hydrolysis to the final product. Only the 2-pyridyl ketone was obtained in pure crystalline form. The 3- and 4-pyridyl isomers were obtained as distillable oils which were characterized *via* their picrates and by essentially quantitative cyclodehydration to their corresponding 9-pyridylanthracenes. Cyclization was effected by using a mixture of hydrobromic and acetic acids under reflux conditions, or in a sealed tube at elevated temperatures, or by using hot phenyl acid phosphate, or hot benzenesulfonic acid.

The specific rates of aromatic cyclodehydration of each of the three isomeric ketones (I) to the corresponding 9-pyridylanthracene (VI) was measured in acid solution at 100° using a spectrophotometric method. For comparison purposes, the rate of cyclization of 2-benzylbenzophenone to 9-phenylanthracene also was measured under the same experimental conditions. The rates of cyclization, which are tabulated in the Experimental section of this paper, reveal a pseudo first-order reaction with respect to ketone. All three of the pyridyl ketones cyclize at a slightly greater rate than the corresponding phenyl ketone (2 - benzylbenzophenone). This may be due to the fact that in the case of 2-benzylbenzophenone the intermediate corresponding to III is only monoprotonated. In the case of the pyridyl ketones, III is a diprotonated species and would be expected to effect a more rapid electrophilic attack on the point of cyclization. These views are in consonance with the current views[7] on the mechanism of aromatic cyclodehydration and are illustrated in Chart I. It is not clear at this time why the rates of cyclization of the three isomeric pyridyl ketones vary slightly from one another. It may be significant that, in the case of the 4-pyridyl ketone, the pyrotonated species corresponding to II has its positive charge at a greater distance from the carbonyl group, and this may favor, relative to the other isomers, the formation of the diprotonated species and account for its relatively faster rate of reaction. It also should be noted that the 2-pyridyl ketone, in forms corresponding to III and IV, may form a five-membered intramolecular hydrogen bonded ring structure with resulting stabilization of these structures.

As the pyridyl ketones (I) presumably exist in acid environment primarily as pyridinium ions (II), acid in excess of that required to protonate the basic nitrogen should be required to effect cyclization. This was shown to be the case. 2-Benzylphenyl 3-pyridyl ketone under a five-hour reflux with an equimolar amount of 48% hydrobromic acid in acetic acid gave no 9-pyridylanthracene, whereas an 88% yield resulted when excess acid was used.

(1) Presented before the Division of Organic Chemistry at the Southeastern Regional Meeting of the American Chemical Society, Richmond, Va., November, 1959.

(2) Abstracted in part from the *Masters thesis of Melvin M. Schlechter* presented to the Virginia Polytechnic Institute in 1958.

(3) Supported by a research grant (AP-88) from the Division of Air Pollution, Bureau of State Services, National Institutes of Health, U. S. Public Health Service.

(4) For recent work, see (a) L. K. Brice and R. D. Katstra, *J. Am. Chem. Soc.*, **82**, 2669 (1960), and (b) F. A. Vingiello, M. O. L. Spangler, and J. E. Bondurant, *J. Org. Chem.*, **25**, 2091 (1960). (c) The mechanism is shown only for 2-benzylphenyl 4-pyridyl ketone; however, it presumably would be essentially the same for the two isomeric pyridyl ketones and it is very similar to a previously published mechanism for the cyclization of 2-benzylbenzephenones.[4b]

(5) C. K. Bradsher, *Chem. Rev.*, **38**, 447 (1946).

(6) For a greatly improved preparation, see P. Polss, Ph.D. thesis, Virginia Polytechnic Institute, Blacksburg, Va., December, 1962, p. 109.

(7) C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, **71**, 1434 (1949).

TABLE I

NEW PYRIDYLANTHRACENES (VI)

Isomer	Method of cyclization	Yield, %	M.p., °C.	Analyses, % Carbon Calcd.[a]	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2-Pyridyl	A	92	163–165	89.38	89.25	5.13	5.31	5.49	5.61
2-Pyridyl	B	Quant.	163–165						
2-Pyridyl	C	62	163–165						
2-Pyridyl	D	Quant.	163–165						
3-Pyridyl	A	93	197–198	89.38	89.52	5.13	5.26	5.49	5.40
3-Pyridyl	B	Quant.	197–198						
3-Pyridyl	C	60	197–198						
3-Pyridyl	D	Quant.	197–198						
4-Pyridyl	A	97	199–200	89.38	89.16	5.13	5.18	5.49	5.54
4-Pyridyl	B	Quant.	199–200						
4-Pyridyl	C	65	199–200						
4-Pyridyl	D	Quant.	199–200						

[a] Calcd. for $C_{19}H_{13}N$.

Experimental[8-10]

2-Benzylphenyl 2-Pyridyl Ketone.—A Grignard reagent was prepared from 21.1 g. (0.086 mole) of 2-bromodiphenylmethane and 2.1 g. (0.086 mole) of magnesium in 75 ml. of anhydrous ether. The Grignard reagent was stirred and a solution of 8.0 g. (0.084 mole) of 2-cyanopyridine[11] in 30 ml. of anhydrous ether was added dropwise over a period of 90 min.; a slight amount of heat was evolved. The resultant dark brown solution was heated under reflux for 8 hr. during which time small portions of solvent were added to prevent the stirrer from being stopped. The mixture was then carefully decomposed with cold concentrated hydrochloric acid and the two layers which formed were stirred at room temperature for 8 hr. The organic layer was discarded and the aqueous portion was heated under reflux for 4 hr., cooled to room temperature, and made alkaline with dilute sodium hydroxide solution. The basic solution was extracted several times with an ethyl ether–acetone mixture, and the combined organic extracts were dried over anhydrous magnesium sulfate. The solution was concentrated and the residual oil distilled. The fraction distilling between 208–211° (3 mm.) was collected; 12 g. (59%). The distillate crystallized on cooling and on recrystallization from ethanol yielded white prisms, m.p. 61–62°.

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53. Found: C, 83.26; H, 5.65.

Picrate of 2-Benzylphenyl 3-Pyridyl Ketone.—A Grignard reagent was prepared from 37 g. (0.15 mole) of 2-bromodiphenylmethane in 100 ml. of anhydrous ether and 3.78 g. (0.16 mole) of magnesium. A solution of 15.5 g. (0.15 mole) of 3-cyanopyridine[12] in 30 ml. of anhydrous ether was added dropwise over a period of 3 hr. The reaction was worked up as was described for the isomeric 2-pyridyl ketone. The fraction distilling between 204–207° (3 mm.) was collected; 14 g. (33%). This pale yellow oil resisted all attempts at crystallization and darkened after several days.

A hot solution of 1 g. of the prior, freshly distilled ketone in 6 ml. of ethanol was added to a hot solution of 1 g. of picric acid in 3 ml. of ethanol. The solution was then cooled and the precipitate which formed was recrystallized from ethanol, yielding yellow flakes, m.p. 116–118°.

Anal. Calcd. for $C_{25}H_{18}N_4O_8$: C, 59.76; H, 3.61; N, 11.15. Found: C, 59.83; H, 3.71; N, 11.26.

Picrate of 2-Benzylphenyl 4-Pyridyl Ketone.—This compound was prepared in a manner similar to that described before for the isomeric 3-pyridyl compound. The Grignard reagent, prepared from 24.7 g. (0.10 mole) of 2-bromodiphenylmethane and 2.5 g. (0.10 g.-atom) of magnesium, was allowed to react with 10 g. (0.10 mole) of 4-cyanopyridine[13]; the product was worked up as previously described. The fraction distilling between 207–212° (3 mm.) was collected; 14 g. (53%). The oil behaved as did the 3-pyridyl isomer and again the picrate was prepared, m.p. 165–167°.

Anal. Calcd. for $C_{25}H_{18}N_4O_8$: C, 59.76; H, 3.61; N, 11.15. Found: C, 59.53; H, 3.75; N, 11.36.

9-(2-Pyridyl)anthracene. A. *Via* **Hydrobromic and Acetic Acid Cyclization.**—A mixture of 4.5 g. (0.017 mole) of 2-benzylphenyl 2-pyridyl ketone, 25 ml. of 48% hydrobromic acid, and 50 ml. of glacial acetic acid was heated under reflux for 52 hr. The solution was neutralized with dilute sodium hydroxide solution, and the resultant precipitate was collected, washed with water, and dried. The yield was 3.9 g. (92%) and recrystallization from a mixture of ethyl and methyl alcohol afforded light yellow-green crystals, m.p. 163–165°.

Anal. Calcd. for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.25; H, 5.31; N, 5.61.

B. *Via* **Phenyl Acid Phosphate Cyclization.** A mixture of 1.0 g. (0.0037 mole) of the ketone and 7.0 g. of phenyl acid phosphate was heated for 5 hr. at 190°. The mixture was worked up as described in method A. The yield of identical product was quantitative.

C. *Via* **Benzenesulfonic Acid Cyclization.**—A mixture of 1.0 g. (0.0037 mole) of the ketone and 5.0 g. of benzenesulfonic acid was heated for 5 hr. at 150°. The mixture was worked up as described in method A. The yield of identical product was 0.58 g. (62%).

D. *Via* **a Sealed Tube Hydrobromic and Acetic Acid Cyclization.**—A mixture of 0.5 g. (0.0018 mole) of the ketone, 8 ml. of 48% hydrobromic acid, and 15 ml. of glacial acetic acid was heated for 6 hr. at 180° in a Carius tube. The mixture was worked up as described in method A. The yield of identical product was quantitative.

9-(3-Pyridyl)anthracene and 9-(4-Pyridyl)anthracene.—These compounds were prepared as was the 2-isomer. The data are summarized in Table I.

Kinetic Results.—The rates of cyclization of the three isomeric 2-benzylphenyl pyridyl ketones and 2-benzylbenzophenone to the corresponding anthracene derivatives were measured using a spectrophotometric method devised by Brice and Katstra[4a] and the specific rate constants were calculated in accordance with the

TABLE II

RATES OF THE HYDROBROMIC ACID-CATALYZED CYCLIZATION OF SEVERAL KETONES IN ACETIC ACID AT 100°

Ketone	Product	$K \times 10^2$ (hr.$^{-1}$)
2-Benzylbenzophenone	9-Phenylanthracene	0.727 ± 0.01
2-Benzylphenyl 2-pyridyl ketone	9-(2-Pyridyl)-anthracene	2.75 ± 0.02
2-Benzylphenyl 3-pyridyl ketone	9-(3-Pyridyl)-anthracene	2.69 ± 0.06
2-Benzylphenyl 4-pyridyl ketone	9-(4-Pyridyl)-anthracene	8.37 ± 0.15

(8) All melting points and boiling points are uncorrected.

(9) All analyses were carried out by Geller Microanalytical Laboratories, Bardonia, N. Y.

(10) The assistance of Mr. Thomas J. Delia in the preparation of both the analytical samples and the samples needed for carcinogenic activity testing is gratefully acknowledged.

(11) L. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).

(12) H. Adkins, *et al.*, *ibid.*, **66**, 1294 (1944).

(13) D. G. Leis and Br. C. Curran, *ibid.*, **67**, 79 (1945).

procedure given in ref. 4a. All reactions were performed in a stock solution similar to one previously used.[7,14] This solution was prepared by combining 700 ml. of redistilled glacial acetic acid, 166.4 ml. of redistilled hydrobromic acid, and 43.6 ml. of redistilled water. The ketone concentration was 500×10^{-5} *M*. The results are summarized in Table II.

(14) F. A. Vingiello, J. G. Van Oot, and H. H. Hannabass, *J. Am. Chem. Soc.*, **74**, 4546 (1952).

Comments on N.m.r. Spectra of Some Optically Active Dimethylcyclohexenes

GERARD V. SMITH AND PHILIP J. TROTTER

Department of Chemistry, Illinois Institute of Technology, Chicago 16, Illinois

Received January 21, 1963

We had occasion to prepare three isomeric optically active dimethylcyclohexenes: (+)-2,4-dimethylcyclohexene, (+)-1,3-dimethylcyclohexene, and (−)-3-methylmethylenecyclohexane. Confusion surrounded their identities, but we offer absolute proof of structure, n.m.r. proof which discloses methyl group positions on cyclohexene.

Experimental

(+)-3-Methylcyclohexanone was prepared by the method of Djerassi and Krakower[1] from pulegone (Eastman, $[\alpha]^{29}D$ +23.49). A portion of the product was purified ($[\alpha]^{25}D$ +13.09); the bulk, 0.815 mole, was dried, dissolved in 300 ml. of ether, and added dropwise to 1.23 moles of methylmagnesium iodide in 325 ml. of ether. After being stirred overnight the Grignard complex was decomposed as described. A distillation head was fitted to the reaction vessel and 100 ml. of 50 vol. % aqueous sulfuric acid was added with stirring over a period of 1.5 hr.[2]; immediately following addition of acid, 550 ml. of water was added with cooling and the olefin mixture was steam distilled.[3] The mixture, which contains 60% 2,4-, 38% 1,3-, and 2% *exo*-olefin, was separated by repeated fractionations through a 90 × 0.5 cm. spinning band column (Podbieliniak). On the basis of rated plates of the column[4] and compositions of several fractions we estimate the difference in boiling points between (+)-2,4-dimethylcyclohexene and (+)-1,3-dimethylcyclohexene to be less than 1° and probably less than 0.5°; we detected no difference in boiling points during fractionation, but gas chromatographic analyses of distillation fractions revealed the 2,4-olefin to be higher boiling. All analyses were done on a 73 ft. × 0.25 in. LAC-446 on firebrick (20% by weight) gas–liquid chromatographic column (Aerograph) from which the olefins emerge in the order: *exo*-; 1,3-; 2,4-. Table I compares some new and old physical constants.

Proton magnetic resonance spectra of the olefins were obtained with an A-60 n.m.r. spectrometer (Varian Associates); pertinent information is shown in Table II.

Discussion

Optical rotations of our 2,4- and 1,3-olefins differ considerably from previous reports. We believe this arises from different methods of establishing purity and not from racemization; *e.g.*, our 2,4-olefin has higher and our 1,3-olefin *lower* rotation than previously reported samples. We were able to establish compositions of mixtures by gas–liquid chromatography, an analytical tool not available to former workers. Because of their close boiling points, mixtures of these two olefins appear never to have been separated.

The proton magnetic resonance spectra offer absolute proof of methyl group position on cyclohexene rings Olefinic protons absorb in the usual region with exocyclic olefinic protons somewhat upfield.[5] Methyl bands occur around 91 and 50 c.p.s. Since those at 91 c.p.s. are less shielded and not split, they are attached to sp^2 hybridized carbons. Those at 50 c.p.s. are split into two peaks, the upfield one being less intense. In our case no ambiquity arises because comparison of the three spectra clearly reveals identical splitting of the 50-c.p.s. peaks of (+)-2,4-dimethylcyclohexene and

TABLE I

SOME PHYSICAL CONSTANTS OF THE CYCLOOLEFINS

Olefin	n_D	Temp., °C.	d_4	Temp., °C.	B.p., °C.	Press.	$[\alpha]$	λ	Temp., °C.	Ref.
2,4-Dimethylcyclohexene	1.4442	25.5	0.802	25	130–1	750	+135.16	589	29	[a]
	1.4467	25	.803	25	129	...	+112.90	579	25	[b]
	1.446	25	.801	25	128	760	Racemic			[c]
	1.4448	25	.806	27	124.5–125	719	+ 91.4	589	27	[d]
	1.4518	20	...	...	127–129	...	Racemic			[e]
1,3-Dimethylcyclohexene	1.4465	25.5	.799	25	130–131	750	+ 34.20	589	29	[a]
	1.4480	25	.807	25	127	...	+ 65.36	579	25	[b]
	1.443	25	.798	25	137	760	Racemic			[c]
	1.4493	20	.805	20	124.5	740	Racemic			[f]
	...	...	...	...	124–129	758	Racemic			[g]
3-Methylmethylenecyclohexane	1.4429	25.5	.783	25	121	750	− 45.93	589	29	[a]
	1.4434	25	.791	25	120.5	...	− 49.32	579	25	[b]

[a] This work; rotations of pure olefins were calculated from rotations and compositions of various binary mixtures assuming rotations are additive. For purities of samples, see Table II. [b] M. Mousseron, R. Richard, and R. Granger, *Bull. soc. chim. France*, **13**, 222 (1946). [c] "Physical Properties of Chemical Compounds," Vol. 1, R. R. Dreisbach, Ed., American Chemical Society, Washington, D. C., 1955, pp. 497, 499. [d] S. Siegel and M. Dunkel, "Advances in Catalysis," Vol. IX, Academic Press, Inc., New York, N. Y., 1956, p. 15. [e] J. Meinwald and R. F. Grossman, *J. Am. Chem. Soc.*, **78**, 992 (1956). [f] J. E. Nickels and W. Heintzelman, *J. Org. Chem.*, **15**, 1142 (1950). [g] K. W. Rosennund, H. Herzberg, and H. Schutt, *Ber.*, **87**, 1258 (1954).

(1) C. Djerassi and G. W. Krakower, *J. Am. Chem. Soc.*, **81**, 241 (1959).

(2) While sulfuric acid is being added, ether distils and must be replenished from time to time to maintain low viscosity and low temperature.

(3) Olefin removal temperature is critical; in previous preparations racemates were obtained when distillation temperature rose above 100°.

(4) "Technique of Organic Chemistry," Vol. IV, A. Weissberger, Ed. Interscience Publishers, Inc., New York, N. Y., 1961, p. 169.

(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959 p. 61.