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The Cyclization of 3,3-Dimethyl-5-keto-hexanoic Acid to Dimedone by Sulfuric Acid

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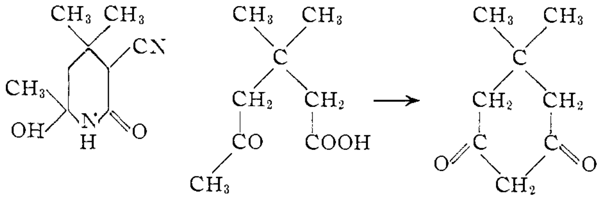
From a hydrolysis of 6-hydroxy-3-cyano-2-keto-4,4,6-trimethylpiperidine[1] (I) by a mixture of aqueous acetic and sulfuric acids, instead of the expected 3,3-dimethyl-5-keto-hexanoic acid (II), a non-ketonic, acidic crystalline compound was obtained whose equivalent weight suggested that it might have been produced from II by loss of the elements of water.



I II III

Infrared analysis showed two main bands, one at 1700 cm.$^{-1}$ and another at 1605 cm.$^{-1}$ The compound was recognized[2] as 3,3-dimethylcyclohexanedione-1,5 (dimedone) (III), and confirmation was obtained by a direct comparison of the spectrum with that of an authentic sample, and then by the preparation of derivatives with formaldehyde and acetaldehyde.

Preliminary experiments soon established that the reaction proceeded through the δ-keto-acid II and accordingly an investigation was undertaken of the reaction mechanism involved. The reaction is of first order with respect to the δ-keto-acid II, is strongly influenced by acid concentration and has an activation energy of 23.4 kcal. over the temperature range 100 to 131° in solutions containing between 50 and 72% w./w. sulfuric acid.

The effect of acidity on the reaction was studied by measuring the variation in the specific rate constant, k, in aqueous sulfuric acid solution over the range 50% (w./w.) to 75% (w./w.). Within the range 64% (w./w.) to 75% (w./w.), log k appears to be a sensibly linear function of both Hammett's acidity function H_0[3] and of the logarithm of the stoichiometric concentration of acid. The respective slopes, however, are 0.35 and 4.6 and hence, unlike the cyclization of o-benzoylbenzoic acid[3] this reaction does not conform to any simple mechanism. Over a more extended acid range, however, the plot of log k against H_0 shows pronounced curvature, whilst the plot against the stoichiometric acid concentration is linear over the whole range. In this connection it must be noted that values of k measured at 100° have here been correlated with values of H_0 at 25°; where the cyclization of o-benzoylbenzoic acid has been considered[3] a similar temperature differential exists.

Further investigations into the functional dependence of k on acid strength and on modifications in the structure of the δ-keto-acid are being actively pursued. The results of such experiments will be communicated.

Experimental

6-Hydroxy-2-keto-3-cyano-4,4,6-trimethylpiperidine (I).—This was prepared as described by Khuda,[1] that is, by the interaction of equivalent quantities of mesityl oxide and cyanoacetamide in absolute alcoholic solution containing a catalytic (0.1 M) amount of sodium ethoxide.

3,3-Dimethyl-5-keto-hexanoic Acid (II).—The alkaline hydrolysis procedure described by Khuda was found to be slow and unsatisfactory; hydrolysis under acid conditions is to be preferred.

The condensation product (I) (182 g.) was vigorously boiled under reflux with excess (1.5 liters) of concentrated hydrochloric acid for 12 hours. The aqueous hydrolysate was concentrated, saturated with ammonium sulfate and extracted with ether until a test portion failed to react with 2,4-dinitrophenylhydrazine. The ether extract was dried, the ether removed and the residual brown oil distilled under diminished pressure; the fraction (98.5 g.) of b.p. 152.5–154.5° (22.5 mm.) was collected. On standing, a white solid separated which was identified as the dilactone.[1] Accordingly, the whole was boiled vigorously with excess sodium hydroxide solution for 2 hours, then cooled in ice-water, acidified to congo red with hydrochloric acid, saturated with ammonium sulfate and again thoroughly extracted with ether. Distillation this time gave a colorless oily liquid of b.p. 155° (24 mm.) (84 g.).

Solution in light petroleum (40–60°) and cooling to −10° gave the keto-acid, which had been reported previously[1,4] as a colorless oil, as colorless flat prisms of m.p. 28.2°. The recovery was almost quantitative. Analysis by potentiometric titration with carbonate-free sodium hydroxide gave an equivalent weight of 158.5; $C_8H_{14}O_3$ requires 158.2; semicarbazone, m.p. 170–172° (dec.) (Khuda[1] gives 172° (dec.)).

The Cyclization of 3,3-Dimethyl-5-keto-hexanoic Acid to Dimedone.—The keto-acid II (1.0 g.) was dissolved in 10 ml. of aqueous sulfuric acid (72% w./w.) and the solution held at 130° for 1.5 hour. The yellow reaction mixture was poured into water (75 ml.) cooled in ice-water and the solid which separated was filtered (0.66 g.). Extraction of the aqueous solution with chloroform gave a further 0.18 g.; over-all yield 92%.

The product was identified by comparison with authentic material, and by the condensation products with formaldehyde and acetaldehyde.

Kinetic Studies. (a) **Analytical Procedure.**—An analytical method was developed for dimedone based on its absorption spectrum in the ultraviolet; a solution of dimedone in 0.1 N NaOH showed an absorption maximum at 282 mμ (2820 Å.). All quantitative measurements were carried out in 1.0-cm. quartz cells with correction for imperfect matching of the cells. The instrument used was a Unicam S.P. 500 photoelectric quartz spectrophotometer (Cambridge Instrument Co.).

Optical density measurements on two series of standard solutions of dimedone in 0.1 N sodium hydroxide confirmed that Beer's law was obeyed over the whole range of measurement, and from the slope of the linear plot of optical density against concentration in g. moles liter^{-1} a value of log ϵ 4.418 was obtained. Blout gives log ϵ 4.42 for solutions in ethanol.

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(1) Quadrat-i-Khuda, *J. Chem. Soc.*, 202 (1929).

(2) L. J. Bellamy, "Infrared Spectra of Complex Molecules," Methuen, London, 1955, p. 123.

(3) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932).

(4) L. Ruzicka, *Helv. Chim. Acta*, **2**, 154 (1919).

Solutions of the δ-keto-acid II in 0.1 N sodium hydroxide solution also absorb in the ultraviolet; the absorption band corresponds both in shape and position with that of dimedone, but the intensity is considerably reduced. The slope of the linear plot of optical density against concentration gave log ε 2.5, and hence in estimating dimedone by the absorptiometric procedure a simple correction was made for the keto-acid present.

The analytical procedure was then tested by means of a number of synthetic mixtures of known dimedone content. Very satisfactory agreement was found in all cases. In all the kinetic measurements, the dilution of the samples was so adjusted that the optical density fell within the range of greatest sensitivity of the instrument.

(b) **Order of Reaction with Respect to Keto-acid.**—The reactions were carried out in 20-ml. glass-stoppered Pyrex tubes, surrounded by vapor from boiling pure chlorobenzene so that the reaction temperature could in general be held constant at 130.7 ± 0.1°.

A known volume of aqueous sulfuric acid (64.6% w./w.) was allowed to attain thermal equilibrium in the vapor-bath in each of two tubes. To these were added known quantities of a preheated standard aqueous solution of keto-acid from a calibrated pipet and the reaction mixtures rapidly and thoroughly shaken. The times of transfer and mixing were small; the reaction time was taken from the moment of mixing in each case. At suitable intervals of time 1-ml. samples were withdrawn, alternately from one tube and then the other, by means of a calibrated pipet, and discharged into 500 ml. of standard 0.1 N sodium hydroxide solution. After mixing thoroughly the alkaline solutions (pH 12–12.5) were analyzed for dimedone by comparing the optical density with that of a standard blank solution containing the same amount of sulfuric acid and sodium hydroxide as in the test sample.

The graph of log C_t against time (t) establishes the order of reaction as unity with respect to the keto-acid II; this result is also shown in Table I.

TABLE I

Concentrations in g. moles liter^{-1} at 130.7°; sulfuric acid 64.6% w./w.

Time, sec. (t)	Obsd. optical density	Corr. optical density	Concn. of dimedone	Concn. of keto-acid (C_t)	$k = \frac{2.303 \log (C_0/C_t)}{t}$ sec.$^{-1}$ × 10^4
0	...	...	0.0	0.02384	..
648	0.379	0.362	.00692	.01692	5.30
1002	.487	.472	.00903	.01481	4.75
1500	.693	.680	.0130	.01084	5.25
1800	.755	.743	.0142	.00964	5.03
2280	.870	.859	.0164	.00744	5.10
2700	.930	.920	.0176	.00624	4.96
3120	.992	.983	.0188	.00504	4.98
3600	1.045	1.036	.0198	.00404	4.94
3960	1.070	1.062	.0203	.00354	4.82
4530	1.110	1.102	.0211	.00274	4.79

(c) **The Effect of Acid Concentration.**—Trial experiments showed that the reaction was markedly influenced by sulfuric acid concentration. In view of the speed of reaction at high acid concentrations, the effect of acid was studied at a lower temperature, 100 ± 0.1°, using water vapor in the heating jacket.

Also in view of the fact that at high acid concentrations the heat of mixing, which is produced on addition of aqueous samples of keto-acid, caused unstable conditions at the beginning of the reaction, the experimental procedure was slightly modified and then applied to all ranges of acid concentration.

A small sample of solid keto-acid was weighed out into a small glass thimble, which, together with its contents, was dropped into the sulfuric acid solution and the whole thoroughly shaken.

The specific rate constant of the reaction was determined for each of ten solutions of sulfuric acid within the range 50 to 92% w./w. The sulfuric acid content was checked by titration of a sample of the reaction mixture at the end of the reaction.

The results are summarized in Table II and are also exhibited graphically, Fig. 1.

TABLE II

k, sec.$^{-1}$ × 10^5 (100°)	% H_2SO_4 (w./w.)	$-H_0$ (25°)	Reacn. vol., ml.	$C_{H_2SO_4}$
4.91	64.6	4.53	12.4	9.94
12.35	75.0	5.83	12.5	12.30
22.30	91.6	8.06	10.5	16.40[a]
14.64	86.4	7.50	10.5	15.10[a]
9.13	72.1	5.44	10.5	11.50
6.25	68.5	5.00	11.5	10.70
2.98	61.4	4.19	13.6	9.06
2.25	59.0	3.93	11.3	8.56
1.285	53.9	3.37	11.3	7.57
0.887	50.8	3.02	12.3	6.98

[a] Not plotted; product decomposes.

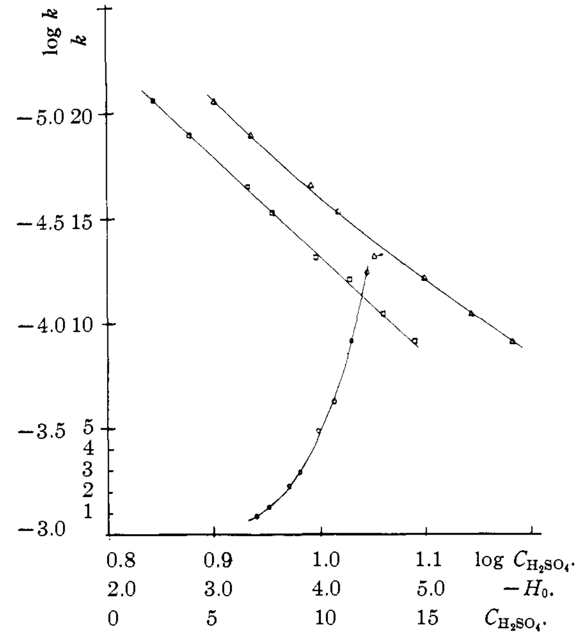

Fig. 1.—Showing effect of sulfuric acid strength on rate of cyclization at 100°: k, specific rate constant (per sec.); H_0, Hammett's acidity function; $C_{H_2SO_4}$, concentration of H_2SO_4 (g. moles per 1000 cc.); △, log $k \sim H_0$; □, log $k \sim$ log $C_{H_2SO_4}$; ○, $k \sim C_{H_2SO_4}$.

In the two solutions of highest acid strengths, considerable charring and the production of a red color resulted, presumably due to progressive decomposition; the results from these experiments do not conform to the general trend shown by the remainder.

(d) **Activation Energy.**—The specific rate constant was measured at each of four temperatures (i) in 72.3% sulfuric acid solutions and (ii) in 50.6% sulfuric acid solutions. Temperature constancy to within ±0.1° was obtained as in previous experiments. The temperature recorded is that shown by a sensitive mercury thermometer kept in a liquid-filled tube suspended next to the reaction tube. (The absence of significant temperature gradients in both the vertical and the horizontal direction had been ascertained previously under representative conditions.)

The results are summarized in Table III.

TABLE III

72.3% H_2SO_4		50.6% H_2SO_4	
Temp., °C. abs.	k, sec.$^{-1}$ × 10^5	Temp., °C. abs.	k, sec.$^{-1}$ × 10^5
373.2	9.13	373.2	0.887
383.7	22.05	383.9	2.183
390.4	37.6	389.8	3.86
404.0	101.3	379.7	1.52

Arrhenius plots of ln k against $1/T$ gave the following activation energies: (i) at 72.3% acid, 23400 cal. mole^{-1}; (ii) at 50.6% acid, 23800 cal. mole^{-1}. (These figures are subject to an estimated uncertainty of 300 cal. mole^{-1}.) (Note: The range of temperature in which the rate of reaction can be investigated in solutions of low acidity is limited at the upper end by the vapor pressure of the solution and at the lower end by the slowest rate which can be measured conveniently using the thermostat arrangement described. The rate at temperatures below 100° may, however, be measured with the aid of a suitable thermostat which can be left unattended for longer periods).

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Heterocyclic Organophosphorus Compounds. I. Pentamethylenephosphinic Acid

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Cyclic compounds in which an atom of phosphorus forms a part of the ring are of obvious interest in studies of physico-chemical properties of substances in which the hetero-atom is varied. Although several compounds have been reported in the literature, in the past forty years, in which phosphorus is a part of the ring, most of these substances have been truly cyclic amides or esters, with nitrogen or oxygen being integral parts of the ring along with phosphorus. A few carbocyclic phosphorus compounds have been reported as well, but all of these have been either phosphines or phosphonium compounds. It was of considerable interest to prepare a phosphorus-containing acid in which the phosphorus atom is a part of an otherwise carbocyclic ring. Obviously, a true carbon analog of such a substance is impossible for it would demand a carboxylic acid group being a part of a ring structure. Phenphosphazinic acid[1] is the only acid of the type described above that has been reported to date; however, in this compound a nitrogen atom is also present in the carbon–phosphorus ring.

Examination of the possible routes to such a substance indicated that the most probable synthesis could be developed by either or both of the schemes

$$(CH_2)_x(MgX)_2 + (RO)_2P(O)H \longrightarrow$$

$$(CH_2)_xP(O)MgX \xrightarrow{HOH} (CH_2)_xP(O)H \xrightarrow{(O)} (CH_2)_xP(O)OH \quad (I)$$

$$(CH_2)_x(MgX)_2 + R_2NP(O)Cl_2 \longrightarrow (CH_2)_xP(O)NR_2 \longrightarrow (CH_2)_xP(O)OH \quad (II)$$

Obviously, both of these routes could be expected to produce many other substances. Thus, in route I the intermediate compound with PMgX link could be expected to react with any, as yet unreacted, dialkyl phosphite, thus forming a phosphine oxide. At the same time the reaction of the bifunctional Grignard reagent could be expected to involve not one but two phosphorus-bearing molecules, thus leading to formation of a polymeric substance based on the unit

$$-P(O)H-(CH_2)_xP(O)H-(CH_2)_x-$$

which, in turn, could react further with the intermediate mentioned above. In route II the most serious obstacle is the reaction of the latter type, *i.e.*, reaction of the bifunctional Grignard reagent not only with one molecule of the phosphorus dihalide, but with two of these, thus forming a polymeric substance of the phosphinic amide type

$$-(CH_2)_xP(O)(NR_2)-(CH_2)_xP(O)(NR_2)-$$

Both routes were explored with pentamethylene-bis-magnesium bromide which was selected as a desirable starting material in order to prepare a cyclic compound with a six-membered ring. A shorter chain of the Grignard reagent, such as that with tetramethylene radical, could not be expected to give high yields of the desired cyclic product; this was observed previously in the synthesis of five- and six-member ring cyclic phosphines.[2]

Route I failed to yield any detectable amounts of the desired acid, the products being polymeric substances with and without acidic properties. Route II, however, yielded some 10% of the desired cyclic product, pentamethylenephosphinic acid, along with considerable amounts of acidic polymeric material. This yield of the product was attained by a form of "infinite dilution" technique, since conventional addition of one reagent to the other gave only the polymeric materials, as could be expected from consideration of the nature of the probable reactions.

The procedure used in the isolation of the product may be expected to be useful for the removal of magnesium from Grignard reactions with organophosphorus compounds, and for separation of some phosphinic acids from mixtures. Details are given in the Experimental part.

Experimental

Pentamethylene bromide was prepared conventionally from tetrahydropyran, but the product was steam distilled from the mixture, instead of the recommended mechanical separation[3]; the modification improved the yield by some 10%, to 91–93%.

The Grignard reagent was prepared from 98 g. of pentamethylene bromide and 20.8 g. of magnesium in 400 ml. of dry diethyl ether. Traces of unreacted magnesium were separated by decantation and filtration. One pound of dry diethyl ether was brought to reflux and the Grignard reagent and a solution of 81.0 g. of N,N-diethylamidophosphoryl dichloride in 100 ml. of dry diethyl ether were slowly and simultaneously dropped into the stirred refluxing ether over a period of seven hours. Our previous experience indicated that reflux temperature is necessary to complete the reaction of an amido dichloride with a Grignard reagent. The addition was made in such a manner that the dichloride solution was kept slightly "ahead" of the Grignard reagent. The mixture in the reaction flask separated into two layers during the reaction, the bottom layer being a yellowish, relatively viscous liquid. After addition the mixture was stirred with refluxing for a further period of three hours and was then allowed to stand overnight. The bottom layer had set by this time to a semi-solid mass. The mixture was added gradually to 300 g. of ice-water and was treated with 150 ml. of concentrated hydrochloric acid to yield two clear phases. The ether layer was evaporated,

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(1) P. G. Sergeev and D. G. Kudryashov, *J. Gen. Chem. USSR*, **8**, 266 (1938).

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(3) "Organic Syntheses," Coll. Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 692.