TABLE II

α-IODOESTERS

Ester	B.p. °C.	B.p. Mm.	$n^{20}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ethyl iodoacetate[a]	60	3	1.5045				
Ethyl α-iodopropionate	49	7	1.4963	26.33	26.21	3.98	3.93
Ethyl α-iodobutyrate	46	1	1.4923	29.77	30.04	4.55	4.74
Ethyl α-iodocaproate	84	4	1.4873	35.37	35.87	5.60	5.90

[a] W. H. Perkin [*J. Chem. Soc.*, **65**, 402 (1894)] reports b.p. 142.5–143.5° (250 mm.), $n^{12.7}D$ 1.5079.

filtrate and washings were concentrated *in vacuo* and the residual pale blue oil was distilled; yield 35.3 g. (80%) of pure ethyl α-nitropropionate (b.p. 75–76° (9 mm.), $n^{20}D$ 1.4210).

This α-nitroester dissolves readily in saturated aqueous sodium bicarbonate solution and from the resulting yellow solution ethyl α-nitropropionate ($n^{20}D$ 1.4210) is recovered in 90% yield by acidification with aqueous acetic acid containing urea.[8] The other α-nitroesters listed in Table I also dissolve readily in saturated aqueous bicarbonate and, of course, they are also easily soluble in 10% aqueous sodium hydroxide.

Rate Measurements.—A solution consisting of 5.95 g. (0.035 mole) of 2-iodopropane and 200 ml. of anhydrous diethyl ether was stirred and cooled in an ice-bath. After one hour duplicate 1-ml. samples were withdrawn to give the initial concentration of iodide. Then 53.9 g. (0.35 mole) of silver nitrite was added as rapidly as possible and the reaction followed by withdrawing 1-ml. samples. The unreacted 2-iodopropane was converted to ionic iodide by the use of Raney nickel and alkali[9] and titrated as such with silver nitrate. The reaction of ethyl α-iodopropionate was followed in exactly the same way using 7.98 g. (0.035 mole) of the ester. Duplicate runs gave times of half-reaction which agreed within 1%.

The rates with α-bromoesters were determined as above (except for operating at room temperature) and also by recovery of the α-bromoesters. In a typical experiment 50.1 g. (0.30 mole) of ethyl bromoacetate was treated, at 25–28°, with 48.5 g. (0.315 mole) of silver nitrite. After 6.5 days 40.1 g. (80%) of the ethyl bromoacetate was recovered.

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Triolein-H^3

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To obtain a triglyceride of an unsaturated acid labeled with tritium, which was required for other studies, we undertook the preparation of triolein-H^3 by isotope exchange involving a sealed-tube reaction of the fat with labeled water in the presence of reduced platinum and a small quantity of base.[1] Although the over-all yield of isotopic exchange was low, it was possible to obtain tritium-labeled triolein in good yield and of a specific activity (16.9 μc./g.) sufficient for our further work.

Upon saponification, the oleic acid moiety was found to contain 14.8 μc./g. and the glycerol 0.10 μc./g., using calculations correcting for the hydrogen atoms gained during saponification. About 16% of the activity was lost during the saponification. Heating the triolein-H^3 with dilute base for a short time resulted in no loss of activity.

To ascertain that none of the activity was due to hydrogenation of the double bonds present in triolein, the acid recovered after saponification was subjected to paper chromatography using the method of Savary[2] which gives wide separation of oleic and stearic acids. No stearic acid could be detected by spray with Rhodamine B solution and activity was recovered only from the oleic acid area when the strips were subjected to radioactive assay in a windowless counter.[3] Additional proof of the absence of stearic acid was the demonstration that the iodine number of the radioactive product was identical with that of the starting material.

Experimental

Triolein-H^3.—One gram of platinum oxide and 1 ml. of tritiated water were introduced into a glass tube and the catalyst was reduced in a stream of hydrogen gas. After the tube had been thoroughly flushed with nitrogen, 6 g. of triolein (hydroxyl value 0.7, free fatty acid content 0.15%, iodine number 85.3 (theory 86),[4] 15 mg. of KOH and an additional 5 ml. of tritiated water (8.8 mc./ml.)) were added, the tube was evacuated and sealed, then maintained at 130° for 28 hours with constant shaking. After the shaking period the organic layer was taken up in ether and the acidic material separated from the neutral triolein on an IRA-400 ion exchange column.[5] The specific activity of the eluted triolein (5.2 g.) measured by gas counting[6] was 16.9 μc./g. The iodine number of the eluted material was 85.0. It is possible that some of the triglyceride was hydrolyzed during the course of the isotopic exchange, but any appreciable amounts of mono- or diglyceryl oleate would cause considerable lowering of the iodine number; the $d^{20}{}_4$ 0.915 $\frac{20^\circ}{4^\circ}$ (lit. 0.915 (15°),[7] 0.9152 (20°)[8]). Since the specific gravity of glyceryl monoöleate is 0.947, appreciable quantities of this material in our final product would have resulted in an elevation of the observed value.

Saponification.—The radioactive triolein was saponified by refluxing with concd. alcoholic KOH for 5 hours in an atmosphere of nitrogen. After acidification and extraction, the ether solution was passed over a column of IRA-400 resin, the oleic acid being eluted with alcoholic HCl. The aqueous layer was distilled to dryness at reduced pressure and the residual salt extracted with hot acetone to obtain the glycerol. The corrected activity of the oleic acid was 14.8 μc./g. (4.2 $\times$ 10^3 μc./mole) and that of the glycerol was 0.10 μc./g. (9 μc./mole). Partial saponification was carried out using dilute alcoholic KOH and only 1 hour reflux. There was no change in the activity of the recovered triolein.

Paper Chromatography.—Descending chromatography on single strips of Whatman No. 1 paper was used, with methanol–water 8:2 as the developing solvent. In model experiments with mixtures of oleic and stearic acids, the stearic acid remained at or near the origin (R_f 0.00–0.05) and the oleic acid had an R_f of 0.60–0.90, measuring from the origin to the foremost point of the spot. The spots were actually wide streaks about 6 cm. in length, but showing no overlap if the solvent front was allowed to travel at least 25 cm. In two representative runs, 150 c.p.m. were applied to the origin. After development of the chromatogram no color and no counts were found at the origin. The oleic acid gave R_f values of 0.58 and 0.93, respectively, with recovery of most of the counts from the area detected using the Rhodamine B spray.

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

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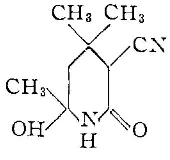
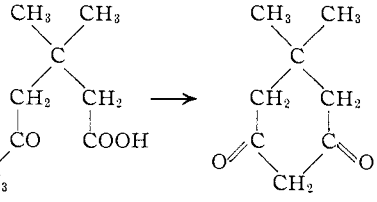
From a hydrolysis of 6-hydroxy-3-cyano-2-keto-4,4,6-trimethylpiperidine[1] (I) by a mixture of aqueous acetic and sulfuric acids, instead of the expected 3,3-dimethyl-5-keto-hexanoic acid (II), a non-ketonic, acidic crystalline compound was obtained whose equivalent weight suggested that it might have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