attack at C_3 in the bile esters, no. 8, 9 and 10, contrasts with preferential attack at other positions when chromic acid[16] and N-bromosuccinimide[17] are used. Oxidation of both cholestan-3β-ol and cholestan-3α-ol (no. 5 and 6, respectively) to cholestan-3-one suggests that orientation of the hydroxyl group is not a determining factor, at least as far as C_3 is concerned.

Our attempts to oxidize cholesterol by the above procedure have met with conspicuous failure.[18] Whether the presence of a double bond at the 5,6-position imposes a structural limitation on the method, or whether our cholesterol contained traces of a poison has not been ascertained as yet.

Experimental[19]

Oxidation of *n*-Octyl Alcohol.—A suspension of 250 mg. of platinum oxide in 5 ml. of ethyl acetate was stirred magnetically in an atmosphere of hydrogen until reduction to platinum was complete. The hydrogen in the system was then replaced with air by careful and repeated evacuation.[20] Oxygen was admitted and stirring continued until no further oxygen was absorbed. A solution of 580 mg. of redistilled *n*-octyl alcohol in 10 ml. of ethyl acetate was then added through an attached dropping funnel, and the mixture was stirred for 20 hours, at the end of which time the uptake of oxygen had ceased. The catalyst was removed by filtration and, after distillation of the bulk of the solvent, the residual material was treated with a solution of 1.2 g. of 2,4-dinitrophenylhydrazine in methanolic sulfuric acid. Three hundred mg. of *n*-octyl aldehyde 2,4-dinitrophenylhydrazone, m.p. 100–101°, was obtained in this way, corresponding to an over-all yield from *n*-octyl alcohol of 21%.

Oxidation of Benzyl Alcohol.—A solution of 627 mg. of redistilled benzyl alcohol in 10 ml. of ethyl acetate was added to a suspension of platinum (prepared from 250 mg. of platinum oxide as described in the preceding experiment) in 5 ml. of ethyl acetate under an atmosphere of oxygen. After stirring for 24 hours the absorption of oxygen had ceased. The reaction product, isolated as described above, furnished 1.18 g. of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 227–228° dec.; yield 72% based on benzyl alcohol.

Oxidation of Cyclohexanol.—Cyclohexanol (577 mg.), was treated as described in the preceding experiment. Oxidation was complete in 18 hours. Isolation of the product in the usual way furnished 1.05 g. of the 2,4-dinitrophenylhydrazone of cyclohexanone as yellow plates, m.p. 160°; yield, 68% based upon cyclohexanol.

In a second experiment 962 mg. of cyclohexanol in 100 ml. of water was oxidized as previously described with the exception that air was used in place of oxygen. After 24 hours the reaction mixture was continuously extracted with ether, and the ether was finally removed by distillation through a short column. The residual material furnished 1.98 g. (74%) of cyclohexanone 2,4-dinitrophenylhydrazone, m.p. 159–160°.

Oxidation of 2-Methylcyclohexanol.—The 2-methylcyclohexanol employed in this experiment was a redistilled sample of commercial material which must be presumed to contain both *cis* and *trans* isomers. Oxidation of 414 mg. of alcohol by the standard procedure, furnished, after distillation from a Hickman flask, 220 mg. (50%) of 2-methylcyclohexanone, identified by its quantitative conversion into the corresponding 2,4-dinitrophenylhydrazone, m.p. 230–232°.

Oxidation of Cholestan-3β-ol.—A solution of 600 mg. of cholestan-3β-ol in 45 ml. of ethyl acetate was added to a suspension of platinum (from 200 mg. of platinum oxide) in 10 ml. of ethyl acetate. The mixture was stirred in an atmosphere of oxygen; after 7 hours the oxidation was complete. The yield of cholestan-3-one, m.p. 128–129°, was 435 mg. (72%).

Oxidation of Cholestan-3α-ol.—Cholestan-3α-ol (160 mg., m.p. 182–184°) in 15 ml. of ethyl acetate was oxidized as described above with platinum derived from 100 mg. of platinum oxide. Crystallization of the reaction product from acetone furnished 80 mg. (50%) of cholestan-3-one, m.p. 128–130°.

Oxidation of Methyl 3α-Hydroxycholanate.—Methyl 3α-hydroxycholanate (450 mg., m.p. 126–127°) and platinum from 200 mg. of platinum oxide in 20 ml. of ethyl acetate were stirred under oxygen according to the usual procedure. Crystallization of the crude product from methanol gave 330 mg. (73%) of methyl 3-ketocholanate, m.p. 118–120°.

Oxidation of Methyl 3α,6α-Dihydroxycholanate.—Methyl 3α,6α-dihydroxycholanate (500 mg., m.p. 86–89°) was treated as described in the preceding experiments. The product was an oil, which failed to crystallize. The material was accordingly saponified for 0.5 hour with 100 mg. of sodium hydroxide in 10 ml. of methanol containing 2 ml. of water. Crystallization of the free acid from acetone–petroleum ether furnished 279 mg. of material, m.p. 199–201°, $[\alpha]_D$ +14.2° (methanol), that did not depress the melting point of an authentic sample of methyl 3-keto-6α-hydroxycholanate supplied through the courtesy of Dr. T. F. Gallagher. A second crop, 80 mg., m.p. 197–200°, was obtained from the mother liquors making a total yield of 75%.

Oxidation of Methyl 3α,12α-Dihydroxycholanate.—Oxidation of methyl 3α,12α-dihydroxycholanate (500 mg.) in ethyl acetate solution was carried out in the usual way. The product, 350 mg. (70%), crystallized from aqueous methanol and melted at 142–144°. The substance was identified as methyl 3-keto-12α-hydroxycholanate by a mixed melting point determination with an authentic sample.

Oxidation of Methyl 3α,7α,12α-Trihydroxycholanate.—Methyl 3α,7α,12α-trihydroxycholanate (410 mg., m.p. 151–153°) was oxidized in 25 ml. of ethyl acetate. Absorption of oxygen ceased after 16 hours. Crystallization of the crude reaction product from dilute ethanol furnished 290 mg. (70%) of methyl 3-keto-7α,12α-dihydroxycholanate, m.p. 173–175° (lit.[21] 171–172°). The diacetate prepared as a derivative melted at 192–194° (lit.[21] 190–191°).

(16) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N.Y., 1949, p. 126.

(17) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3935 (1949).

(18) The capricious behavior of cholesterol in catalytic *hydrogenation* is well known. *Cf.* E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, THIS JOURNAL, **73**, 1144 (1951); H. R. Nace, *ibid.*, **73**, 2379 (1951).

(19) All melting points are corrected.

(20) In the course of this work we experienced one fire, which was traceable to incomplete removal of hydrogen at this stage. Care should be exercised to wash all catalyst from the walls of the vessel by gentle swirling prior to admitting oxygen.

(21) A. S. Jones, M. Webb and F. Smith, *J. Chem. Soc.*, 2164 (1949).

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Alkyl Derivatives of Iminodiacetic Acid

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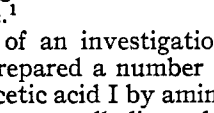
RECEIVED JUNE 8, 1954

Replacement of amino hydrogen atoms by carboxymethyl groups has been shown to produce compounds which form highly stable chelates with alkaline earth and transition group metals. This augmented tendency to combine with metal ions has been ascribed both to the increased ionic charge of the donor molecule and to the well-known stabilizing effect of added rings within a chelate structure.[1]

In the course of an investigation of the above effect we have prepared a number of alkyl derivatives of iminodiacetic acid I by amination of chloroacetic acid in aqueous, alkaline solution (Table I).



I

(1) P. Pfeiffer and H. Simons, *Ber.*, **76B**, 847 (1943).

TABLE I

DERIVATIVES OF IMINODIACETIC ACID $R—N(CH_2COOH)_2$

R	Method	Composition	M. p.,[a] °C.	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
$(CH_3)_2CH$	A	$C_7H_{13}NO_4$	230–231 d.	47.99	47.81	7.48	7.63	7.99	7.87
$(CH_3)_3C$	A	$C_8H_{15}NO_4$	199–200.5 d.	50.78	50.88	7.99	8.09	7.41	7.50
$CH_3(CH_2)_3$	A	$C_8H_{15}NO_4$	184–185.5	50.78	50.93	7.99	8.12	7.41	7.53
$CH_3(CH_2)_4$	A	$C_9H_{17}NO_4$	156–158	53.3	53.33	8.45	8.54	6.92	6.95
$CH_3(CH_2)_5$—	B	$C_{10}H_{19}NO_4$	130–131	55.28	55.44	8.82	8.89	6.44	6.55
$CH_3(CH_2)_6$—	B	$C_{11}H_{21}NO_4$	133–134	57.12	57.06	9.15	9.03	6.05	6.00
$CH_3(CH_2)_7$—	B	$C_{12}H_{23}NO_4$	137–137.5	58.75	58.88	9.45	9.50	5.71	5.64
$CH_3(CH_2)_8$—	B	$C_{13}H_{25}NO_4$	159.5–161.5	60.2	60.17	9.72	9.88	5.40	5.41
$CH_3(CH_2)_9$—	C	$C_{14}H_{27}NO_4$	135–136	61.51	61.62	9.96	10.10	5.12	5.23
$CH_3(CH_2)_{11}$—	C	$C_{16}H_{31}NO_4$	135.5–136.5					4.63	4.69
$CH_3(CH_2)_{15}$—	C	$C_{20}H_{39}NO_4$	128.2–129.3	67.19	67.24	10.92	11.06	3.97	4.03

[a] All melting points uncorrected. [b] Analyses by Dr. Ritter, Basel, Switzerland.

Although formation constants have been reported for isopropyl- and *t*-butyliminodiacetic acids,[2] and the synthesis of the isopropyl and *n*-butyl compounds has been mentioned in the patent literature,[3,4] no characterization of the compounds has been given.

The procedure used to obtain the pure acids varied with the water solubility of the acid. The less soluble acids were precipitated by direct acidification of the reaction mixture of the amine and sodium chloroacetate, and were purified by fractional crystallization from water or aqueous alcohol (procedure B). Those acids which were quite soluble in water were obtained pure by precipitation of the barium salt followed by sulfuric acid decomposition[5] (procedure A). The high molecular weight amines required use of an aqueous alcoholic solvent (procedure C).

Preliminary studies indicate that these compounds behave similarly to imino-[6] and methyliminodiacetic acid[7] as regards reactions with metal ions in solution. Further work is in progress and results will be published at a later date.

Experimental

Isopropyliminodiacetic Acid. Procedure A.—Distilled isopropylamine (7.4 g., 0.125 mole) was added to 24 g. (0.25 mole) of chloroacetic acid neutralized to phenolphthalein with 5 *N* sodium hydroxide in a 250-ml. flask equipped with thermometer, dropping funnel and reflux condenser. The temperature was maintained at 50° for 10 hours, during which time 5 *N* alkali was added so as to keep the solution alkaline to phenolphthalein; the alkali was consumed rapidly initially but more slowly as the reaction progressed.

Addition of 32.0 g. (0.13 mole) of barium chloride dihydrate dissolved in 60 ml. of hot water caused immediate precipitation. The mixture was warmed, with stirring, on a steam-bath for 30 minutes, and the precipitate was collected on a suction filter. The dry barium salt was added to 75 ml. of boiling water, and a stoichiometric amount of 5 *N* sulfuric acid was added slowly (30 minutes) to the well-stirred mixture. The mixture was then suction filtered through a layer of Super-Cel filter aid, and the filtrate evaporated to dryness in vacuum. Alternatively, the mixture was concentrated to a sirup in vacuum and crystallization was induced by addition of absolute methanol and cooling in ice. Recrystallization from a small quantity of hot water gave pure, white, crystalline product.

Procedure B.—Direct acidification of the reaction mixture with concentrated hydrochloric acid rather than precipitation of the barium salt differentiates procedure B from A. Longer reaction times were necessary with the higher molecular weight amines. The precipitated acids were purified by fractional recrystallization from boiling water.

Dodecyliminodiacetic Acid. Procedure C.—A solution of 24 g. (0.25 mole) of chloracetic acid in 100 ml. of alcohol and 10 ml. of water was neutralized to phenolphthalein with 10 *N* sodium hydroxide. Twelve grams (0.065 mole) of dodecylamine was added and the solution was allowed to stand 3 days at room temperature, and finally 5 hours at 80–95°; over this entire period of time there were added 30 ml. of 10 *N* alkali. Acidification of the solution with concentrated hydrochloric acid gave a crude product which was purified by several recrystallizations from 95% alcohol.

The authors wish to thank the Office of Naval Research for the support given this study.

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Steroids. LXII.[1] Synthesis of Progesterone 3-Cycloethylene Ketal

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RECEIVED JULY 26, 1954

We have been interested in these Laboratories in carrying out certain transformations involving the side-chain of progesterone. In this connection it was necessary to make available a progesterone derivative appropriately protected at C-3 and progesterone 3-monocycloethylene ketal (I) seemed to be a suitable compound.[2] In the present communication we describe the formation of this substance by three different routes.[3]

(1) Paper LXI, A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **77**, 148 (1955).

(2) *Cf.*, the conversion of the 3-monocycloethylene ketal of 11-ketoprogesterone to 11-dehydrocorticosterone and cortisone [L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *ibid.*, **74**, 4974 (1952); G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, *ibid.*, **76**, 5031 (1954)].

(3) Since this manuscript was prepared, A. Ercoli and P. de Ruglieri [*Gazz. chim. ital.*, **84**, 312 (1954)] have described the preparation of the ketal I [m.p. 171–173°, $[\alpha]^{18}D$ +54° (pyridine)] by an independent method as well as its conversion to desoxycorticosterone acetate.