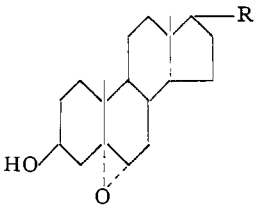
A Method for Reduction of Steroid Oxides

BY L. CARROLL KING AND J. ALLAN CAMPBELL

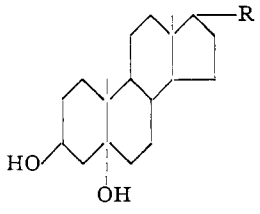
Recent interest in the reduction of steroid oxides[1] impels us to record a method for reduction of these substances which has been under investigation in this Laboratory.

(α)-Cholesteryl oxide (I) reacts with thiourea and *p*-toluenesulfonic acid in alcoholic solution to give 3(β),5(α)-dihydroxycholestanyl-6-isothiuronium tosylate (II) in 73–92% yield. An alcoholic solution of II on shaking with an equivalent amount of sodium hydroxide and an excess of standard nickel catalyst[2] was reduced to 3(β),5(α)-dihydroxycholestane (III), yield 88–95%. The identity of III was established by conversion to 3(β)-acetoxy-5(α)-hydroxycholestane.

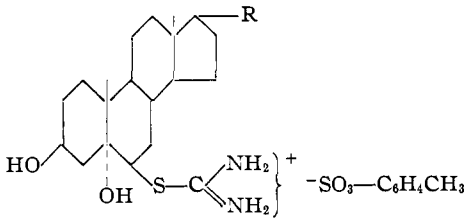
The application of this method of reduction to the preparation of 17-hydroxysteroids from the corresponding 16,17- or 17,20-oxido compounds is in progress.



I



III



II

3(β),5(α)-Dihydroxycholestane-6-isothiuronium Tosylate (II).—Prepared from (α)-cholesteryl oxide by refluxing with thiourea and *p*-toluenesulfonic acid in alcoholic solution; yield 73–92%, m. p. 228–229°. *Anal.* Calcd. for $C_{35}H_{58}N_2O_5S_2$: C, 64.57; H, 8.98. Found: C, 64.57; H, 8.39%.

3(β),5(α)-Dihydroxycholestane (III).—Prepared from II by action of standard nickel catalyst and an equivalent of sodium hydroxide in alcoholic solution; yield 88–95%, m. p. 222–224°. *Anal.* Calcd. for $C_{27}H_{48}O_2$: C, 80.13; H, 11.96. Found: C, 80.03; H, 11.93.

3(β)-Acetoxy-5(α)-hydroxycholestane.—From III by warming with acetic anhydride; m. p. 182–184°. *Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 76.94; H, 10.91.

(1) Plattner, Heusser and Feurer, *Helv. Chim. Acta.*, **31**, 2210 (1948); *ibid.*, **32**, 587 (1949); Julian, Meyer and Ryden, THIS JOURNAL, **71**, 756 (1949).

(2) Adkins, "Reactions of Hydrogen with Organic Compounds, etc.," The University of Wisconsin Press, Madison, Wis., 1937, p. 20.

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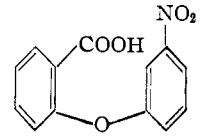
Camps Reaction with 1-Xanthonamine[1]

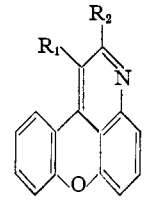
BY C. F. KOELSCH AND F. J. LUCHT

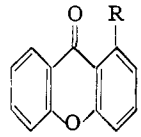
This paper describes a synthesis of [1]benzopyrano[4,2,de]quinoline (IX) and some reactions designed to yield its 6-methoxy derivative. It is planned to use these substances in experiments which it is hoped will furnish 4-*o*-hydroxyphenylquinolinic acid and ultimately morphine analogs.[2]

The synthesis involved intermediates I–VIII, formulated below. The route from VI to IX through X and XI instead of VII and VIII gave poorer yields. Yield of each substance is indicated by the figure in parentheses.



I (85)





II, R = NO_2 (35)
III, R = NH_2 (100)
IV, R = $NHCOCH_2$-$COOC_2H_5$ (86)

	R_1	R_2
V	$COOC_2H_5$	OH (90)
VI	COOH	OH (94)
VII	H	OH (98)
VIII	H	Cl (89)
IX	H	H (28 from VIII; good from XI
X	COOH	Cl (25)
XI	COOH	H (59)

Experimental

***o*-(*m*-Nitrophenoxy)-benzoic Acid, I.**—The substance has been prepared but not isolated by Dhar.[3] In the present work it was obtained by heating and stirring a mixture of 62 g. of *o*-chlorobenzoic acid, 63 g. of *m*-nitrophenol, 50 g. of sodium carbonate, 5 g. of copper filings, 0.2 g. of cuprous chloride, and 150 ml. of *n*-amyl alcohol for three hours in an oil-bath at 160–170°. The crude crystalline product (55 g.) was suitable for cyclization. Crystallization from benzene gave pale yellow prisms, m. p. 138–139°.

Anal. Calcd. for $C_{13}H_9NO_5$: C, 60.2; H, 3.5. Found: C, 60.2; H, 3.8.

Xanthone Ring Closure.—A solution of 55 g. of crude nitrophenoxybenzoic acid in 300 ml. of sulfuric acid was heated on a steam-bath for thirty minutes and then poured into water. Acidic materials were removed, and the crude neutral residue (25 g., m. p. 160–170°) was separated by crystallization from acetic acid into 18 g. of 1-nitroxanthone (II), pale yellow prisms m. p. 206–207° (reported[3] 210°), and 7 g. of brown crystalline material, m. p. 155–160°. The latter contained the still unknown 3-nitroxanthane, for by reducing it with stannous chloride and alcoholic hydrochloric acid, and fractionally crystallizing the product from alcohol, there was obtained 3.7 g. of 3-xanthonamine, m. p. 231–232° (reported[4] 232°).

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3. Found: C, 74.0; H, 4.4.

1-Xanthonamine, III.—Reduction of 11.5 g. of 1-nitroxanthone with 45 g. of stannous chloride in 115 ml. of alcohol containing 50 ml. of hydrochloric acid and crystallization of the product from alcohol gave 9.5 g. of yellow prisms, m. p. 150–151°.

(1) From the Ph.D. Thesis of Fred J. Lucht, submitted to the Graduate Faculty of the University of Minnesota, September, 1946.

(2) Koelsch, THIS JOURNAL, **67**, 569 (1945).

(3) Dhar, *J. Chem. Soc.*, **117**, 1061 (1920).

(4) Ullmann and Wagner, *Ann.*, **355**, 359 (1907).

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3. Found: C, 73.9; H, 4.5.

All the isomeric xanthonamines are now known: 2 (m. p. 205°),[5] 3 (m. p. 232°),[4] and 4 (m. p. 201°).[6] The structure of the substance, m. p. 175°, formerly thought to be a xanthonamine of uncertain orientation,[7] is thus rendered still more uncertain.

1-(Carbethoxyacetamido)-xanthone, IV.—A solution of 12.5 g. of 1-xanthonamine in 125 ml. of ethyl malonate was boiled for twenty minutes, then most of the ester was removed by rapid distillation. Crystallization of the residue from alcohol gave 16.5 g. of pale tan powder, m. p. 122–123°.

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.4; H, 4.7. Found: C, 66.5; H, 4.7.

Pyridone Ring Closure.[8]—A solution of sodium ethoxide from 3 g. of sodium in 100 ml. of alcohol was added during fifteen minutes to a boiling suspension of 16 g. of IV in 300 ml. of alcohol. The mixture was boiled for an additional fifteen minutes and then cooled. The solid product was stirred for some time with dilute hydrochloric acid, then washed and dried, giving 13.5 g. of ethyl 2-hydroxy[1]-benzopyrano[4,2-de]quinoline-1-carboxylate (V), m. p. 279–282°. Recrystallization from acetic acid gave fine pale yellow plates, m. p. 285–287°.

Anal. Calcd. for $C_{18}H_{13}NO_4$: C, 70.3; H, 4.3. Found: C, 70.3; H, 4.2.

2-Hydroxy[1]benzopyrano[4,2-de]quinoline-1-carboxylic Acid, VI.—The ester (3.4 g.) was saponified by boiling it six hours with excess 5% aqueous sodium hydroxide. The solution was then poured into excess hot dilute hydrochloric acid and the product was crystallized from acetic acid, giving 2.9 g. of small yellow plates. It began to lose carbon dioxide and change its appearance at 270°; the residue melted at 350–352° without effervescence.

Anal. Calcd. for $C_{16}H_9NO_4$: C, 68.8; H, 3.2. Found: C, 68.6; H, 3.4.

2-Hydroxy[1]benzopyrano[4,2-de]quinoline, VII.—The acid VI (2.9 g.) left a residue of nearly pure decarboxylation product (2.4 g.) when it was heated at 360°. Sublimation gave long yellow needles, m. p. 350–352°.

Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.6; H, 3.9. Found: C, 76.8; H, 3.8.

2-Chloro[1]benzopyrano[4,2-de]quinoline, VIII.—A solution of 2.4 g. of VII in 10 ml. of phosphorus oxychloride was heated on a boiling water-bath for thirty minutes, then cooled and poured on ice. The mixture was neutralized and the product was crystallized from benzene, giving 2.3 g. of yellow crystals, m. p. 179–180°.

Anal. Calcd. for $C_{15}H_8ClNO$: C, 71.0; H, 3.2. Found: C, 70.9; H, 3.2.

[1]Benzopyrano[4,2-de]quinoline, IX.—A solution of 2 g. of VIII and 1 g. of sodium acetate in 100 ml. of acetic acid was shaken with 0.1 g. of platinum oxide and hydrogen at two atmospheres for twenty minutes. Treatment of the product with hydrochloric acid left 0.54 g. of unchanged chloro compound and dissolved the desired dehalogenated substance. The latter formed fine yellow needles (0.5 g.) from ligroin; m. p. 138–140°.

Anal. Calcd. for $C_{15}H_9NO$: C, 82.2; H, 4.1. Found: C, 82.2; H, 4.2.

2-Chloro[1]benzopyrano[4,2-de]quinoline-1-carboxylic Acid, X.—A solution of 0.9 g. of VI in 5 ml. of phosphorus oxychloride was heated for thirty minutes, then poured into water and allowed to stand overnight. The bicarbonate soluble product crystallized from alcohol in the form of a bright yellow powder (0.25 g.), m. p. 221–222° with decomposition.

Anal. Calcd. for $C_{16}H_8ClNO_3$: C, 64.5; H, 2.7. Found: C, 64.6; H, 2.7.

The corresponding **ethyl ester**, yellow crystals from benzene–ligroin, m. p. 177–179°, was obtained in a yield of 80% from 3.3 g. of V, with 10 g. of phosphorus oxychloride.

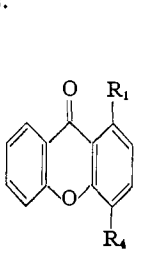
Anal. Calcd. for $C_{18}H_{12}ClNO_3$: C, 66.3; H, 3.7. Found: C, 66.6; H, 3.8.

[1]Benzopyrano[4,2-de]quinoline-1-carboxylic Acid, XI.—Dehalogenation of 0.24 g. of X was accomplished by shaking its solution in dilute alkali with Raney nickel and hydrogen at three atmospheres for ninety minutes. The product formed yellow crystals from alcohol, m. p. 265° dec., yield, 0.125 g.

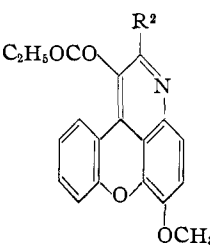
Anal. Calcd. for $C_{16}H_9NO_3$: C, 73.0; H, 3.4. Found: C, 72.8; H, 3.6.

The residue left from the melting of the acid was nearly pure decarboxylation product (IX), yellow needles from alcohol, m. p. 138–139° alone or mixed with the previously described substance.

Preceding the work described above, experiments designed to furnish the 6-methoxy derivative of IX and involving compounds XII–XVI, were undertaken. Because of poor yields of intermediates, the objective was not reached. These experiments are outlined in the following paragraphs.



XII, R_1 = H, R_4 = OH
XIII, R_1 = NH_2, R_4 = OCH_3
XIV, R_1 = $NHCOCH_2COOC_2H_5$, R_4 = OCH_3



XV, R_2 = OH
XVI, R_2 = Cl

4-Hydroxyxanthone, XII.—The Ullmann reaction between guaiacol and *o*-chlorobenzoic acid gave *o*-(*o*-methoxy)-phenoxybenzoic acid in yields of 36% when no solvent was used, and 43% when *n*-amyl alcohol was used.[6] Cyclization by sulfuric acid in acetyl chloride[9] and subsequent demethylation using aluminum chloride[4] in benzene gave nearly quantitative yields.

4-Methoxy-1-xanthonamine, XIII.—4-Hydroxyxanthone (23.4 g.) suspended in cold aqueous soda coupled with diazotized sulfanilic acid to give an azo compound in nearly quantitative yield. This dye was dried and mixed with 100 ml. of methyl sulfate. The mixture was treated with 300 g. of 20% aqueous sodium hydroxide, added with shaking and cooling (70°) during thirty minutes. The resulting material was diluted, treated with more sodium hydroxide and boiled to destroy excess methyl sulfate, and then treated with excess sodium hydrosulfite. The part of the product soluble in hydrochloric acid was crystallized from methanol, giving 14 g. (52%) of yellow prisms, m. p. 169–169.5°. In most preparations the yields were much smaller (5–20%), but the reason was never found.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6. Found: C, 69.9; H, 4.4.

The acetyl derivative, from the amine and acetic anhydride in 90% yield, formed yellow crystals from benzene, m. p. 234–234.5°. No pyridone ring closure[8] could be effected using sodium hydroxide in water, or sodium alkoxide in butyl or ethyl alcohol; from these experiments, the acetyl derivative was recovered largely unchanged.

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6. Found: C, 67.8; H, 4.6.

1-(Carbethoxyacetamido)-4-methoxyxanthone, XIV.—From 4 g. of XIII and 100 ml. of malonic ester, there was

(5) Purgotti, *Gazz. chim. ital.*, **44**, i, 641 (1914).

(6) Ulmann and Zickasoff, *Ber.*, **38**, 2111 (1905).

(7) DeTurski, German Patent 287,756; *Frdl.*, **12**, 120 (1914).

(8) Camps reaction: for a summary and references, see Hollins, "The Synthesis of Nitrogen Ring Compounds," E. Benn, Ltd., London, 1924.

(9) Gottesmann, *Ber.*, **66**, 1168 (1933).

obtained 5 g. (85%) of pure product, pale yellow crystals from ethanol, m. p. 154–155°.

Anal. Calcd. for $C_{19}H_{17}NO_6$: C, 64.2; H, 4.8. Found: C, 64.5; H, 4.7.

Ethyl 2-Hydroxy-6-methoxy[1]benzopyrano[4,2-de]-quinoline-1-carboxylate, XV.—From 4 g. of XIV, with 450 ml. of 1% alcoholic sodium ethoxide, there was obtained 3.4 g. (89%) of product, yellow needles from alcohol, m. p. 272–274°.

Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.6; H, 4.5. Found: C, 67.5; H, 4.4.

Ethyl 2-Chloro-6-methoxy[1]benzopyrano[4,2-de]-quinoline-1-carboxylate, XVI.—From 2 g. of XIV, treated with 10 ml. of phosphorus oxychloride, there was obtained 1.7 g. of product, yellow crystals from benzene–ligroin, m. p. 161–162°.

Anal. Calcd. for $C_{19}H_{14}ClNO_4$: C, 64.1; H, 4.0. Found: C, 63.8; H, 4.0.

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Chemical Degradation of Isotopic Succinic Acid[1]

BY MORTON KUSHNER AND SIDNEY WEINHOUSE

In connection with biochemical studies it was necessary to determine the distribution of isotopic carbon in samples of succinic acid isolated from biological sources. It has been found that pyrolysis of the barium salt in a high vacuum at 500° results in a satisfactory conversion of the carboxyl carbon of succinic acid to barium carbonate. The course of this reaction is uncertain. In addition to barium carbonate and some carbon, products such as carbon dioxide, carbon monoxide, methane, ethane, ethylene and hydrogen were identified by mass-spectrometric analysis.

The accompanying table, giving the results of the pyrolysis of carboxyl- and methylene-labeled succinates, shows that the barium carbonate satisfactorily represents the carboxyl carbon. Evidently there is some contamination of the carboxyl carbon by methylene carbon, but this is so small as to introduce only a negligible error. This slight enrichment of C^{13} in the non-labeled carboxyl position was not an artifact, since non-isotopic barium succinate invariably yielded barium carbonate with the normal C^{13} abundance. This enrichment may be due to oxidation of the methylene carbon by traces of oxygen; or possibly, to transfer of oxygen between barium carbonate and the accompanying residual carbon.

TABLE I

C^{13} DISTRIBUTION IN SYNTHETIC LABELED SUCCINIC ACIDS

Atom % C^{13} excess

	Over-all	Carboxyl carbon—Calcd.	Carboxyl carbon—Found
Carboxyl-labeled	2.41	4.82	4.80
Methylene-labeled	3.10	0.00	0.04 ± 0.02
Unlabeled	0.00	.00	.00 ± .01

(1) This work was sponsored by the Sun Oil Company and aided by a grant from the National Cancer Institute, U. S. Public Health Service.

Experimental

Preparation of Isotopic Succinic Acids.—Carboxyl-labeled succinic acid was prepared by refluxing ethylene dibromide with isotopic potassium cyanide, according to the procedure of Vanino.[2] The dinitrile was saponified with alkali without isolation, and after removal of neutral substances by extraction with ether, the succinic acid was isolated by acidification and continuous ether extraction. Yields ranged between 85 and 95%.

The methylene-labeled acid was prepared by a 4-step process giving an over-all yield of about 40%. Barium carbonate was reduced to the carbide according to the procedure of Cramer and Kistiakowsky[3] and the acetylene obtained therefrom reduced to ethylene by a modification of the method of Patterson and du Vigneaud.[4] This was converted to ethylene dibromide by addition of bromine and the former converted to succinic acid by the same procedure used for the carboxyl-labeled acid.

Preparation and Pyrolysis of Barium Salts.—About 20 mg. of the acid is dissolved in 1 ml. of water, 1 ml. of 20% barium chloride is added, and the solution brought to neutrality with dilute ammonia. Two volumes of 95% ethanol are added and the precipitated barium salt centrifuged, washed successively with alcohol and ether, and dried thoroughly in a vacuum.

The barium salt is transferred to a small glass tube, which is then sealed to the vacuum line or attached by means of a standard taper joint. After evacuation to a low pressure the salt is heated to 500° in an electric furnace. After about an hour the tube is cooled, the dark-colored residue is treated with dilute sulfuric acid and the evolved carbon dioxide collected for mass-spectrographic analysis.[5] It is important to avoid even traces of oxygen in this degradation since in its presence some of the methylene carbon will be oxidized to carbon dioxide and contaminate the carboxyl carbon.

Acknowledgment.—The authors express their appreciation to the Sun Oil Company for its support and interest, and to Mr. Arthur Kent for the C^{13} analyses.

(2) Vanino, "Handb. d. prep. Chem.," **3**, p. 263.
(3) Cramer and Kistiakowsky, *J. Biol. Chem.*, **137**, 549 (1941).
(4) Patterson and du Vigneaud, *ibid.*, **123**, 327 (1938).
(5) "Preparation and Measurement of Isotopic Tracers," Edwards Brothers, Ann Arbor, Mich., 1946, p. 43.

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Methoxyacetone

BY RAYMOND P. MARIELLA AND JOHN L. LEECH

In continuing our investigations of unsymmetrical ketones, it became necessary to prepare a large quantity of methoxyacetone.

It was found that the wet oxidation of the inexpensive and easily-available 1-methoxy-2-propanol (Dowanol 33B) with chromic acid at room temperature goes conveniently in one step to give methoxyacetone. The present method is adapted from that of Petrov[1] and gives methoxyacetone in much shorter time than other published methods[2–5] although in a somewhat lower yield.

(1) Petrov, *J. Gen. Chem., U. S. S. R.*, **16**, 1206 (1946); *cf. C. A.*, **41**, 3051 (1947).
(2) Henry, *Ann. chim.*, [8] **16**, 318 (1908).
(3) Henze and Rigler, THIS JOURNAL, **56**, 1350 (1934).
(4) Leonardi and diFranchis, *Gazz. Chim. Ital.*, **33**, I, 319 (1903)
(5) Traetta, Masca and Preti, *ibid.*, **51**, II, 275 (1921).