oxalic, succinic and adipic derivatives were synthesized. Here, too, bis-methyl and ethyl iodides were easily prepared.

In the morpholinoethyl series (see Table IC), amides were made from all the simple aliphatic dicarboxylic acids, oxalic through adipic, and sebacic. The bis-methiodides were also prepared but attempts to obtain bis-ethiodides gave as products viscous oils in some cases and there seemed to be some difficulty in attaining satisfactory carbon and hydrogen analyses with these higher alkyl quaternary ammonium salts.

These amides and their quaternary ammonium salts showed no curare-like activity at the dose levels at which many of them showed powerful activity in prolonging the duration of neuromuscular block produced by diacetylcholine in the cat. In the dimethylaminoethyl amide series this latter activity persisted in all members of the group above oxalic regardless of chain length. The bis-methiodide of the succinic amide derivative was about 1.5 times as active in its potentiating action as the tertiary base while both the tertiary base and bis-methiodide of the adipic amide were of nearly equal activity. Both the bis-morpholinoethyl amides and their bis-methiodides were inactive as potentiators of diacetylcholine.

At very much higher dose levels some of the bis-methiodides of the bis-amides exhibited weak curare-like activity.

A detailed report on the pharmacology of these compounds will be made later from these laboratories.

Acknowledgment.—The author is indebted to Messrs. Samuel W. Blackman and N. Martinez, Jr., for the microanalyses included. The dimethylethylenediamine, diethylethylenediamine and morpholinoethylamine were supplied through the courtesy of Mr. J. Conway of the Fine Chemicals Division, Carbide and Carbon Chemical Corporation.

Experimental

The general method of preparation of the bis-tertiary-aminoethyl amides and of their bis-quaternary ammonium salts is illustrated below by an example of each.

N,N'-Bis-(β-dimethylaminoethyl)-succinamide.—A mixture of 18 g. (0.1 mole) of ethyl succinate and 35 cc. (28 g., 0.32 mole) of dimethylethylenediamine was refluxed for four hours in a metal-bath at 150°. After removal of excess amine and alcohol 26 g. (100%) of white crystalline product remained. Recrystallized from ethyl acetate the pure product melted at 134–135°.

N,N'-Bis-(β-dimethylaminoethyl)-succinamide Bis-methiodide.—A solution of 5.2 g. (0.02 mole) of the bis-amino-amide just described in 50 cc. of methanol was treated with 6 cc. of methyl iodide and the mixture was refluxed for one hour. A solid crystalline cake resulted in two minutes. Upon cooling 10.8 g. (100%) of product was obtained and after recrystallization from methanol this melted at 251-252°.

TUCKAHOE 7, NEW YORK RECEIVED JUNE 26, 1951

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

The Reduction of Cholestanone by Lithium Aluminum Hydride and Aluminum Alkoxides[1]

BY HAROLD R. NACE AND GEORGE L. O'CONNOR

Reduction of cholestanone by lithium aluminum hydride or a Meerwein-Ponndorf reaction is shown to give a mixture of α- and β-cholestanol. The ratio of isomeric stanols produced is a function of the size of the reducing agent and the temperature of reaction. With sterically larger aluminum alkoxides the production of α-cholestanol is favored.

Catalytic hydrogenation[2] of cholestanone for preparing α-(epi)-cholestanol is inconvenient and not entirely satisfactory. The purpose of this investigation was to determine whether the reduction of cholestanone by aluminum alkoxides would provide a new and more convenient route to α-cholestanol. Shoppee and Summers[3] reported that lithium aluminum hydride reduction of cholestanone gave 4% α-cholestanol, the remainder of the reduction product being the β-isomer. Noyce and Denney have pointed out[4] that the Meerwein-Ponndorf reduction of sterically hindered ketones with aluminum isopropoxide or reduction with lithium aluminum hydride yields a mixture of epimeric carbinols, and that aluminum isopropoxide yields more of the *cis*-carbinol than lithium aluminum hydride. They concluded that aluminum isopropoxide reduction produced more *cis*-alcohol because the bulky alkoxide group was more sensitive to steric requirements than an incipient AlH_4^- ion. The Meerwein-Ponndorf reduction has been pictured[5,6,7] as proceeding through a pseudo-six membered ring transition state. Ring formation would be favored on the less hindered side leading to a *cis*-carbinol, with the hydroxyl being formed on the hindered side.

The reduction of keto-steroids with aluminum isopropoxide has been reported in a few instances to give mixtures of the isomeric stanols,[8,9] but in-

(1) This paper is based on a portion of the thesis to be submitted by George L. O'Connor in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Brown University.

(2) (a) G. Vavon and B. Jakubowicz, *Bull. soc. chim.*, **53**, 584 (1933); (b) L. Ruzicka, H. Brüngger, E. Eichenberger and J. Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934).

(3) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(4) D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).

(5) R. Woodward, N. Wendler and F. Brutschy, *ibid.*, **67**, 1425 (1945).

(6) M. Dewar, "Electronic Theory of Organic Chemistry," Oxford at the Clarendon Press, 1949, p. 136.

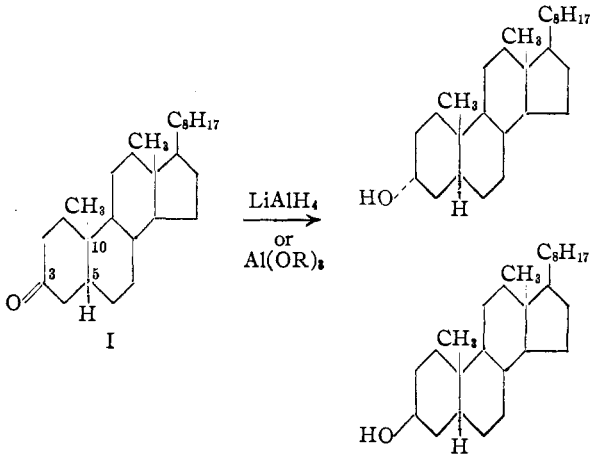
(7) W. von E. Doering and R. W. Young, THIS JOURNAL, **72**, 630 (1950).

(8) (a) R. Marker, D. Turner and E. Wittbecker, *ibid.*, **64**, 221 (1942); (b) R. Marker, H. Crooks, R. Wagner and E. Wittbecker, *ibid.*, **64**, 2089 (1942).

(9) "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 142.

adequate quantitative data were presented on the percentage of isomers formed. No examples could be found of the use of other aluminum alkoxides.

Cholestanone (I) and the alcohols derived from it, α-(II) and β-cholestanol (III) are members of the allo-series with the hydrogen at position 5, *trans* to the methyl group at position 10. The



hindrance at the 3-position in the allo-series is not pronounced but inspection of models shows that there is more hindrance on the "lower" (α) side of the molecule than on the "upper" (β) side, mainly due to the 5 hydrogen. That this slight hindrance can be important was shown by Ruzicka, *et al.*,[10] who found that the hydrolysis of β-cholestanol acetate was more rapid than that of α-cholestanol acetate.

In the reduction of cholestanone it would be expected that as the size of the reducing group was increased, the formation of the ring intermediate on the unhindered (β) side would be favored, resulting in a higher percentage of α-cholestanol.

The results reported here are in accord with this prediction, the yield of α-cholestanol increasing from 12% with lithium aluminum hydride, to 28% for the aluminum salt of isopropyl alcohol, 35% for diethylcarbinol, 45% for diisopropylcarbinol and 55% for di-*t*-butylcarbinol.

On the basis of a purely random reduction of the carbonyl, the epimeric alcohols should be produced in equal amounts. The question then arises as to why the α-cholestanol is not produced in greater quantity than the β-isomer, since the hindrance favors the formation of the former. The answer appears to lie in the fact that the stanols produced differ in stability, and in so far as the transition states partake of the character of the products, the more stable isomer will predominate. Thus the α-producing transition states may rearrange to produce the more favorable β-producing transition states. Windaus[11] observed that the epimerization of β-cholestanol (III) in the presence of sodium alkoxides gave an equilibrium mixture of about 10% α-(II) and 90% β-cholestanol (III), showing that the β-isomer represents the more stable form. This epimerization involves an equilibrium analogous to the oxidation–reduction system present in the Meerwein–Ponndorf–Oppenauer scheme as shown by Doering.[12] Additional evidence for the greater stability of the β-isomer has been obtained by treating β-cholestanol with aluminum alkoxide solutions containing a small amount of cyclohexanone, whereby a mixture of 84% β- and 16% α-cholestanol was obtained.

The ratio of isomers formed in the reduction was also observed to be subject to the temperature of reaction. This effect was quite pronounced with the aluminum salt of diisopropylcarbinol. The amount of α-cholestanol produced ranged from 22% at 40° to 45% at 100° and 23% at 140°. Reduction with aluminum isopropoxide gave 22, 28 and 27% of α-cholestanol at 25, 85 and 100°, respectively, with incomplete reduction at 25°. Trevoy and Brown[13] observed a similar effect of temperature on the steric course of reductions of 1,2-diketones with lithium aluminum hydride.

The total yield of epimeric alcohols was usually about 90% in the examples given here. The epimers were separated in all cases by chromatography over alumina according to the method of Galinovsky and Vogl.[14] The good yields obtained suggest the use of the sterically larger aluminum alkoxides in preparative work when the *cis*-carbinol is the desired product. In addition the results reported here are in accordance with the pseudo-six membered ring mechanism of the Meerwein–Ponndorf reduction.[5,6,7]

Experimental[15]

Reduction of Cholestanone by Lithium Aluminum Hydride.—One gram (26 millimoles) of lithium aluminum hydride was suspended in 30 ml. of dry ether and stirred for one hour. A solution of 500 mg. (1.29 millimoles) of cholestanone (m.p. 130°) in 10 ml. of benzene was added and a precipitate formed. The mixture was stirred at the reflux temperature for eight hours and then decomposed with 30 ml. of 6 *N* sulfuric acid without isolation of the precipitate. The organic layer was washed with three 50-ml. portions of water, dried over anhydrous sodium sulfate, and the solvent evaporated on a steam-bath. The residue was taken up in 2 ml. of a 1:1 benzene–petroleum ether (b.p. 30–60°) mixture and chromatographed on 10 g. of aluminum oxide (Merck suitable for chromatographic adsorption) in a column 1 × 12 cm. and 10-ml. eluates were collected.

Fraction	Eluant	Eluate	Weight, Mg.	%
1–4	1:3 benzene–petroleum ether			
5–13	1:1 benzene–petroleum ether	α-Cholestanol, m.p. 184–184.5°	53	12
14–20	Ether	β-Cholestanol, m.p. 142–143°	397	88
		Total yield	450	90

Reduction of Cholestanone by Aluminum Alkoxides.—The alkoxide solution was prepared in the case of isopropoxide by dissolving 3.0 g. (14.7 millimoles) of aluminum isopropoxide in 50 ml. of isopropyl alcohol (dried over calcium

(10) A. Ruzicka, M. Furter and M. W. Goldberg, *Helv. Chim. Acta*, **21**, 498 (1938).

(11) A. Windaus and C. Uibrig, *Ber.*, **47**, 2384 (1914).

(12) W. von E. Doering and T. Aschner, THIS JOURNAL, **71**, 838 (1949).

(13) L. W. Trevoy and W. G. Brown, *ibid.*, **71**, 1679 (1949).

(14) F. Galinovsky and O. Vogl, *Monatsh.*, **79**, 325 (1948).

(15) All melting points are corrected.

TABLE I

REDUCTION OF CHOLESTANONE BY LITHIUM ALUMINUM HYDRIDE AND ALUMINUM ALKOXIDES

Reducing agent	Temp., °C.	Time, hours	Yield, of α-cholestanol,[f] %	Total yield, %[g]
$LiAlH_4$	36[c]	8	12	80
$LiAlH_4$	36[c]	2	12	82
Aluminum-isopropoxide[a]	84[c]	7	28	93
	100[d]	7	27	92
	25[e]	7	22	56
Aluminum salt of diethylcarbinol[b]	115[c]	7	35	86
Aluminum salt of diisopropylcarbinol[b]	140[c]	7	22	93
	100[e]	7	45	95
	40[e]	7	23	68
Aluminum salt of di-*t*-butylcarbinol[b,h]	120[e]	7	55	90

[a] Distilled aluminum isopropoxide used. [b] Alkoxide solution prepared by dissolving aluminum with mercuric chloride and oxide in the carbinol. [c] Reflux temperature of solvent. [d] Carried out in a sealed tube. [e] Distillation carried out under reduced pressure in oil-bath at given temperature. [f] Yield based on amount of stanols isolated. [g] Based on cholestanone. [h] Di-*t*-butylcarbinol prepared in low yield using method in A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., 1943, p. 179, for preparation of di-*n*-butylcarbinol.

hydride) or for the other alkoxides by dissolving 400 mg. (14.8 millimoles) of aluminum, 50 mg. of mercuric chloride and 10 mg. of mercuric oxide in 50 ml. of the proper alcohol (dried over calcium hydride) and refluxing the mixture four hours after the reaction began, as evidenced by darkening of the solution. These alkoxide solutions were used directly without further purification. To the alkoxide solution was added 250 mg. (0.65 millimole) of cholestanone and the mixture was heated in an oil-bath three hours at the desired temperature. Then the reaction mixture was slowly distilled at the same temperature over a period of four hours, under reduced pressure where necessary. A negative ketone test on the distillate with 2,4-dinitrophenylhydrazine reagent[16] was obtained after about two hours in most cases. At the end of the distillation period any remaining alcohol was removed by rapid distillation, the residue taken up in 50 ml. of benzene and decomposed with 50 ml. of 6 *N* sulfuric acid. The organic layer was washed with three 50-ml. portions of water, dried over anhydrous sodium sulfate, and chromatographed on 10 g. of aluminum oxide as above. The results are reported in Table I.

Epimerization of β-Cholestanol.—Aluminum alkoxide solutions of isopropyl alcohol and diisopropylcarbinol were prepared as above and 500 mg. of β-cholestanol added with 0.1 ml. of cyclohexanone. The mixture was heated on the steam-bath for one hundred hours and worked up as above. The mixture yielded 16% α- and 84% β-cholestanol in both cases.

(16) R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 200. For alcohols which are not completely soluble in water the modification applied to reactions run in toluene was used. See note p. 204.

PROVIDENCE, R. I. RECEIVED JUNE 2, 1951

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Glyoxylate Cyclizations. Methoxyindenes[1]

BY E. C. HORNING,[2] JOHN KOO[3] AND G. N. WALKER[4]

Applications of the Bougault cyclization in the preparation of methoxyindenes have been investigated. A new method of cyclization is described; the use of polyphosphoric acid as a cyclization agent leads to high yields of the indene ester, and the side reactions of sulfonation and ester-exchange are avoided. The indene esters are characterized by easy decarboxylation of the 3-carboxylic acid group during alkaline hydrolysis.

A method for preparing indenes involving the cyclization of a glyoxylate ester (derived from ethyl hydrocinnamate and ethyl oxalate) with sulfuric acid was first described by Bougault, and this general method was later extended by others to the synthesis of dihydronaphthalenes. In connection with studies on the structure of colchicine and its degradation products, particularly Windaus' anhydride,[5] we have used this approach for the synthesis of indenes, dihydronaphthalenes, and, in a new application, benzsuberenes. This paper describes the preparation of certain indenes.

The required ketoesters, IIA and IIB, were prepared by the condensation of ethyl oxalate with the corresponding hydrocinnamic esters IA and IB, using potassium or sodium ethoxides. The ketoester IIA was cyclized with sulfuric–phosphoric acids to yield the indene IIIA; this compound was a colorless diester which was converted on alkaline hydrolysis to the indene monocarboxylic acid VA. The acid IVA, corresponding to IIIA, would not be expected to undergo easy decarboxylation, but this result may be expected if the unsaturation in the five-membered ring of IIIA or IVA shifts, under the influence of alkali, to that indicated for V. A similar result was described by Bougault[6] for diethyl indene-2,3-dicarboxylate. The fact that the 3-carboxylic acid group was lost rather than the 2-group was demonstrated here by the independent synthesis of VA from the formyl derivative VIA by sulfuric–phosphoric acid cyclization, followed by hydrolysis. This result does not establish the validity of the bond shift, since VA is symmetrical; it does confirm the identity of VA.

When the ester IIB was subjected to Bougault conditions, the diester IIIB could not be obtained. Ester exchange or hydrolysis paralleled or followed cyclization, and the best conditions found gave an acid-ester. In searching for alternate methods of cyclization, polyphosphoric acid[7] was employed. With this reagent, the ester IIIB was obtained in 90% yield from IIB, indicating that polyphosphoric

(1) Supported in part by a grant-in-aid from the American Cancer Society, recommended by the Committee on Growth of the National Research Council.

(2) National Heart Institute, Bethesda, Md.

(3) American Cancer Society Postdoctoral Fellow, 1948–1950.

(4) Rohm and Haas Research Assistant, 1949–1950. du Pont Predoctoral Fellow, 1950–1951.

(5) A. Windaus, *Ann.*, **439**, 59 (1924).

(6) J. Bougault, *Compt. rend.*, **159**, 745 (1914).

(7) H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2962, 2965 (1950).