melting point now found for the Schmidt reaction sample (110.5° cor.) as well as that obtained from 3,4-dimethylacetanilide differs from the 111–111.5° previously reported, which was determined using a Fisher–Johns apparatus. The present melting points were obtained in capillary tubes using a Hershberg type apparatus.

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.6; H, 6.2; N, 29.8.

The methiodides were best prepared by heating the tetrazole in a sealed tube with an excess of methyl iodide at 80–90° for 1.5 hours. The precipitate which formed was collected on a filter and recrystallized twice from ethanol. Both methiodides melted at 206° cor. The melting point of their mixture showed no depression.

Anal. Calcd. for $C_{11}H_{15}N_4I$: C, 40.01; H, 4.58; N, 16.97. Found (A) methiodide from tetrazole prepared from 3,4-dimethylacetanilide: C, 39.8; H, 4.6; N, 17.2. (B) methiodide from tetrazole from Schmidt reaction: C, 39.5; H, 4.9; N, 16.8.

The absorption spectra were determined with a Model DU Beckman quartz spectrophotometer. Absolute ethanol was used as solvent; the following concentrations of tetrazole were employed for the wave lengths in question: 7.969×10^{-5} *M* for 215–260 mμ; 1.594×10^{-4} *M* for 260–270 mμ; 1.328×10^{-3} *M* for 270–280 mμ; 1.198×10^{-2} *M* for 285 mμ.

The authors are indebted to Dr. Paul D. Sternglanz and Miss Ruth C. Thompson for the analytical and ultraviolet absorption spectra data presented in this note.

LABORATORY OF ADVANCED RESEARCH
REMINGTON RAND, INC.
SOUTH NORWALK, CONNECTICUT RECEIVED MAY 3, 1951

Some Aryloxyaliphatic Acids

BY L. F. BERHENKE, L. E. BEGIN, B. M. WILLIAMS AND F. L. BEMAN

Several aryloxyaliphatic acids, not previously reported, have been made and are reported in Table I. The aryloxyacetic acids have been proposed as identifying derivatives for phenols[1] and can be made by the method there given or by modifications thereof.[2] In addition to the purification schemes described, we have found that crystallization of the acid from chlorobenzene or of the sodium salts from water at *p*H 10–13 are also effective methods for separating the acids from unreacted phenols.

The α- and β-substituted propionic acids and the α-substituted butyric acids were similarly prepared from α- and β-chloropropionic acid and α-bromobutyric acid, respectively.

The γ-substituted butyric acid was prepared by a modification of the method previously reported.[3] Two hundred thirty-two grams of *p*-phenylphenol was neutralized with 55 g. of sodium hydroxide in 1.5 l. of water and 148 g. of γ-bromobutyronitrile added over one hour, then the mixture was refluxed for two hours. Sixty-eight grams of sodium hydroxide was added as 10 *N* solution and the nitrile hydrolyzed by refluxing overnight. The reaction mixture (*p*H about 11) was cooled, filtered, washed with water and the moist cake resuspended in 10 l. of water, acidified with concentrated hydrochloric acid, digested on the steam-bath for several hours, cooled and filtered. The crystals were dried and recrystallized from 2 l. of chlorobenzene; yield 190 g., 74%, m.p. 151–155°. Further recrystallization gives material m.p. 158.5–160°.

TABLE I

Compound	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
Acetic acid										
p-Acetylphenoxy-	$C_{10}H_{10}O_4$	172.5–174.5	61.84	61.77	5.19	5.18			194.2	195.5
4-*s*-Butyl-2,6-dichlorophenoxy-	$C_{12}H_{14}Cl_2O_3$	78.4–80					25.62	25.60	277.1	276.0
3-Chloro-4-biphenylyloxy-	$C_{14}H_{11}ClO_3$	158–159					13.50	13.53	262.7	263.8
5-Chloro-2-biphenylyloxy-	$C_{14}H_{11}ClO_3$	123–125					13.50	13.58	262.7	265.2
4-Chloro-*o*-cumyloxy-	$C_{11}H_{13}ClO_3$	170–171					15.50	15.37	228.7	231.7
2,6-Dichlorophenoxy-	$C_8H_6Cl_2O_3$	134.7–135					32.10	32.27	221.0	221.0
3,5-Dichlorophenoxy-	$C_8H_6Cl_2O_3$	116–116.5					32.10	32.18	221.0	221.0
2,3,6-Trichlorophenoxy-	$C_8H_5Cl_3O_3$	147–148					41.60	41.59	255.5	261.8
Butyric acid										
γ-(4-Biphenylyloxy)-	$C_{16}H_{16}O_3$	158.5–160	74.97	74.90	6.29	6.31			256.3	265.2
α-(*p*-*t*-Butylphenoxy)-	$C_{14}H_{20}O_3$	89–90.5	71.15	71.06	8.53	8.49			236.3	238.7
α-(*o*-Chlorophenoxy)-	$C_{10}H_{11}ClO_3$	80–80.5					16.53	16.43	214.6	212.3
α-(*p*-Chlorophenoxy)-	$C_{10}H_{11}ClO_3$	77.5–78							214.6	213.7
α-(2,4,5-Trichlorophenoxy)-	$C_{10}H_9Cl_3O_3$	140–141					37.52	37.36	283.5	282.3
Propionic acid										
α-(*p*-*t*-Butylphenoxy)-[a]	$C_{13}H_{18}O_3$	89–90.5	70.26	70.08	8.16	8.20			222.2	218.6
β-(2,4,5-Trichlorophenoxy)-	$C_9H_7Cl_3O_3$	143–144							269.5	269.1

[a] Preparation reported by Salminen and Weissberger, U. S. Patent 2,423,730, but no constants are given.

(1) Koelsch, THIS JOURNAL, **53**, 304 (1931).
(2) Hayes and Branch, *ibid.*, **65**, 1555 (1943).
(3) Lohman, *Ber.*, **24**, 2631 (1891).

DOW CHEMICAL CO.
MIDLAND, MICHIGAN RECEIVED FEBRUARY 23, 1951

The Conversion of Δ⁴-Cholestene-3-one to Cholesterol[1]

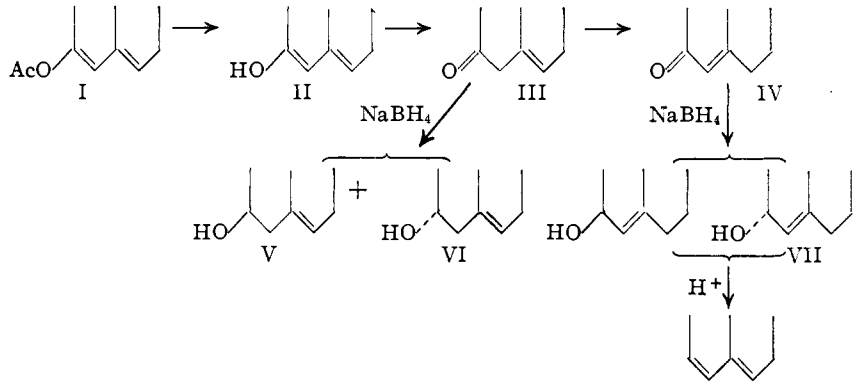
BY B. BELLEAU AND T. F. GALLAGHER

Because of our need for effecting the transformation of cholestenone to cholesterol in the maximum yield for partial synthesis of the isotopically labelled sterol we have investigated the action of sodium borohydride on the enol acetate of cholestenone and have obtained cholesterol in 70 to 85% yield. Dauben and Eastham[2] with lithium aluminum hydride reduced cholestenone enol acetate to

(1) This investigation was supported by grants from the Lillia Babbitt Hyde Foundation, and the National Cancer Institute, United States Public Health Service.
(2) W. G. Dauben and J. F. Eastham, THIS JOURNAL, **72**, 2305 (1950).

cholesterol in 34% yield and Birch[3] by an alternative method prepared cholesterol from the same compound in somewhat lower yield. Earlier Reich and Lardon,[4] through an extended sequence, had developed a procedure for the conversion of Δ^4-3-ketosteroids to Δ^5-3-hydroxy compounds.

The reaction mechanism with sodium borohydride is essentially different from the reduction of an enol ester by lithium aluminum hydride, since sodium borohydride does not reduce esters. However, an aqueous alcoholic solution of sodium borohydride is alkaline, so that rapid and complete hydrolysis of an enol ester (I) occurs and the enol



form of the ketone is obtained as the primary product. The enol of an α,β-unsaturated ketone (II) then rearranges in two stages: (1) by rapid transformation to a ketone with an unconjugated double bond (III) and (2) by a markedly slower shift of the isolated double bond to a position of conjugation (IV). That the first stage of the reaction involved saponification of the ester to the enol was shown by the recovery of unchanged enol acetate after treatment with sodium borohydride in anhydrous pyridine; a carbonyl group is readily and completely reduced by sodium borohydride in this solvent. Since there is an excess of reducing agent at all times during these reactions, the intermediate Δ^5-cholesten-3-one (III) is almost completely reduced before shift of the double bond occurs as evidenced by the formation of a very small amount of (1–3%) of the Δ^4-stenols (VII). The principal product other than cholesterol is its 3α epimer (VI) obtained in 7.5% yield from the digitonin nonprecipitable fraction.

With the preceding reaction sequence in mind, a means for the elimination of the enol ester was sought. Grignard and Blanchon[5] have shown that ketones enolize and form salts readily in the presence of tertiary alkyl magnesium halides. Since the ketone regenerated from cholestenone enolate upon hydrolysis could be reduced to cholesterol, it was possible that this route might be advantageous. It was, in fact, possible to obtain cholesterol in 37% yield from cholestenone upon treatment with *t*-butyl magnesium chloride followed by hydrolysis and reduction with sodium borohydride in aqueous ethanol and it is quite likely that under the most suitable experimental conditions this yield could be appreciably bettered. It is noteworthy that a similar isomerization of the double bond was effected by Kharasch and Tawney[6] when isophorone was treated with methyl magnesium bromide in the presence of ferric chloride. Unquestionably, the explanation for their results is that the ferric ion converted the α,β-unsaturated ketone to the enol which, as the magnesium halide salt, was incapable of adding Grignard reagent. The enol was then hydrolyzed to the ketone without rearrangement of the double bond, precisely as in our experiments with cholestenone. In both instances the relative stability of the unconjugated system permitted isolation of the β,γ-unsaturated ketone.

Acknowledgments.—We wish to express our appreciation to Dr. K. Dobriner and Mrs. Phyllis Humphries of this institute, who determined and interpreted the infrared spectra for us.

Experimental[7]

Cholesterol from Δ^4-Cholestene-3-one Enol Acetate.—Five hundred milligrams of cholestenone enol acetate[8] was dissolved in 200 ml. of redistilled 95% ethanol and after cooling to 5° was added to a solution of 1 g. of sodium borohydride in 25 ml. of 70% aqueous ethanol. The mixture was stored at 5° for two hours. The solution was then heated to boiling, 25 ml. of 5% aqueous sodium hydroxide was added and most of the ethanol evaporated *in vacuo*. The residual solution was poured into excess dilute hydrochloric acid and extracted with ether. The ether extract was dried and evaporated, and the crystalline residue heated under reflux for two hours in 30 ml. of ethanol containing 4 drops of concentrated hydrochloric acid.[9] The solution was evaporated to dryness *in vacuo*, the residue dissolved in ethanol and treated with excess digitonin in ethanol. The digitonide was collected and, after washing with ether, was dissolved in pyridine.[10] The digitonin was precipitated with ether and removed by filtration. The filtrate was washed with dilute hydrochloric acid and with water and dried over sodium sulfate. Evaporation of the solvent yielded 385 mg. ((85%) of cholesterol m.p. 138–145°, which was chromatographed on 40 g. of silica gel. The first portions of ether-petrol ether 1:3 eluted 12 mg. of material melting from 130–140°, followed by 326 mg. of cholesterol m.p. 144–148°. Recrystallization from ethanol afforded 317 mg. m.p. 146–148°, identical in all respects with authentic cholesterol.

The filtrate from the cholesterol digitonide together with the ether washings was diluted with ether and the digitonin removed by filtration. The filtrate was evaporated to an oil which exhibited an absorption maximum at 235 mμ and, from the molar extinction coefficient 20,700, contained 6.5 mg. of Δ 3,5-cholestadiene. The oil was chromatographed on 2 g. of alumina. Petroleum ether eluted 17 mg. of amorphous material which contained all of the Δ3,5-cholestadiene. Ether–petrol ether 1:4 eluted 32 mg. (7.4%) of crystalline material which from the infrared spectrum was identical with 3α-cholesterol. Sublimation followed by recrys-

(3) A. J. Birch, *J. Chem. Soc.*, 2325 (1950).

(4) H. Reich and A. Lardon, *Helv. Chim. Acta*, **29**, 671 (1946).

(5) V. Grignard and H. Blanchon, *Roczniki Chem.*, **9**, 547 (1929); *C. A.*, **24**, 1342 (1930).

(6) M. S. Kharasch and P. O. Tawney, THIS JOURNAL, **63**, 2308 (1941); *ibid.*, **67**, 128 (1945).

(7) The phrase "in all respects identical" refers particularly to the coincidence of (a) infrared spectra, (b) the melting point of mixtures, and (c) the optical rotation when compared with an authentic sample prepared by an independent method. All melting points are corrected; ultraviolet spectra were determined with a Cary recording spectrophotometer.

(8) U. Westphal, *Ber.*, **70**, 2128 (1937).

(9) R. Schoenheimer and E. A. Evans, Jr., *J. Biol. Chem.*, **114**, 567 (1936).

(10) R. Schoenheimer and H. Dam, *Z. physiol. Chem.*, **215**, 59 (1933).

tallization from acetone afforded colorless needles of 3α-cholesterol melting at 140–142° identical in all respects with an authentic sample.

When 50 mg. of the enol acetate of cholestenone was dissolved in 20 ml. of dry pyridine containing 100 mg. of sodium borohydride and the mixture stored at room temperature for two hours, 25 mg. of crystalline enol acetate was recovered after addition of ether followed by washing with hydrochloric acid and water. The mother liquors were essentially pure enol acetate as judged by infrared spectrometry. Under similar conditions 17β-hydroxyetiocholan-3-one was reduced to the 3α and β diols in almost quantitative yield.

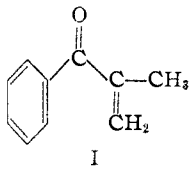
Cholesterol from Δ⁴-Cholesten-3-one.—A solution of 766 mg. of cholestenone in ether was added to a Grignard reagent prepared from 1.9 g. of *t*-butyl chloride and 480 mg. of magnesium. The solution was heated under reflux for 20 min. and then poured into a stirred and cooled solution of 1.20 g. of sodium borohydride in 200 ml. of 80% aqueous ethanol. The mixture was allowed to stand for 30 min. and cholesterol was isolated as described in the preceding experiment. From the digitonin precipitate 290 mg. (37%) of pure cholesterol melting at 146–148° was obtained after two crystallizations from acetone.

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
NEW YORK, N. Y. RECEIVED APRIL 9, 1951

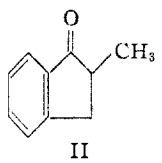
A Thiophene Isostere of 2-Methyl-1-indanone

BY J. H. BURCKHALTER AND JOSEPH SAM

It has been demonstrated that α-methylacrylophenone (I), obtained from steam distillation of β-dimethylamino-α-methylpropiophenone hydrochloride,[1] will undergo ring closure to form 2-methyl-1-indanone (II).[2] Later studies have shown that α-methyl-2-acrylothienone (III), an analog of I, can

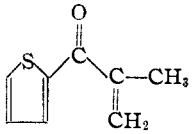


I

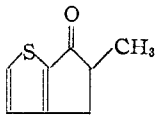


II

be readily obtained from the analogous Mannich base.[3] The present report records the ring closure of III to form IV. Proof that a substance of struc-



III



IV

ture IV has been obtained was afforded by a comparison of the 2,4-dinitrophenylhydrazine derivatives of III and IV. Further confirmatory evidence is supplied by the molecular refractivity of IV and by a distinctive odor which is also characteristic of the benzene isostere of IV.

We are grateful to Dr. Austin M. Patterson, of Xenia, Ohio, for advice on the systematic naming of IV (see Experimental part).

Experimental[4]

4,5-Dihydro-5-methyl-6*H*-cyclopenta[*b*]thiophen-6-one (IV).—Eighteen grams of α-methyl-2-acrylothienone (III)[3] was poured slowly with stirring into 100 ml. of concentrated sulfuric acid which had been at room temperature. The mixture turned to a clear reddish color and became slightly warm. After the liquid had been allowed to cool to room temperature, it was poured with stirring into a liter of cold water. The milky oil which separated was extracted with three portions of ether and the extract dried over sodium sulfate. After removal of the ether, 14 g. (78% yield) of cyclic ketone (IV) was distilled at 95.5° (2 mm.); $n^{20}D$ 1.5808, d^{20}_{20} 1.1890, M_D calcd. 41.80, found 42.48.

Anal. Calcd. for C_8H_8OS: C, 63.13; H, 5.30. Found: C, 62.83; H, 5.47.

A red **2,4-dinitrophenylhydrazone** of IV decomposed at 248°, after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{14}H_{12}N_4O_4S$: C, 50.59; H, 3.64. Found: C, 50.81; H, 3.64.

A derivative of α-methyl-2-acrylothienone (III), considered to be **1-(2,4-dinitrophenyl)-3-(2-thienyl)-4-methylpyrazoline** by analogy with other results,[3] was prepared as a red crystalline product from III and 2,4-dinitrophenylhydrazine, m.p. 222°, after recrystallization from ethyl acetate. A mixed melting point with the 2,4-dinitrophenylhydrazone of IV showed a decided depression.

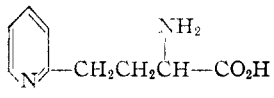
Anal. Calcd. for $C_{14}H_{12}N_4O_4S \cdot {}^1/_2H_2O$: C, 49.26; H, 3.84. Found: C, 49.12; H, 3.90.

DEPARTMENT OF PHARMACEUTICAL CHEM.
UNIVERSITY OF KANSAS
LAWRENCE, KANSAS RECEIVED MARCH 26, 1951

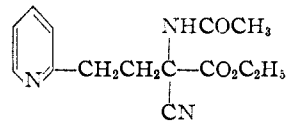
α-Amino-γ-2-pyridinebutyric Acid

BY J. H. BURCKHALTER AND VERLIN C. STEPHENS[1]

As a part of a study of unnatural amino acids as possible antimetabolites,[2] α-amino-γ-2-pyridinebutyric acid (I) was prepared. Ethyl α-acetamido-α-cyano-γ-2-pyridinebutyric acetate (II) was ob-



I



II

tained in 53% yield by a base-catalyzed condensation of 2-vinylpyridine with ethyl acetamidocyanoacetate.[3] Acid hydrolysis of II gave I in only 51%yield, because its extensive solubility in water made separation from the by-product ammonium chloride rather difficult.

Experimental[4]

Ethyl α-Acetamido-α-cyano-γ-2-pyridinebutyrate (II).—To a boiling solution of 17 g. (0.1 mole) of ethyl acetamidocyanoacetate, 2 g. of sodium ethoxide and 200 ml. of benzene, 10.5 g. (0.1 mole) of 2-vinylpyridine[5] was added dropwise with vigorous stirring. The solution was maintained at reflux temperature for seven hours under a slow stream of nitrogen. After cooling and filtering, the benzene solution was concentrated *in vacuo* until solid began forming. A saturated solution of sodium bisulfite was added, and the mixture of liquids was allowed to stand for two hours with occasional shaking. The solid which had gradually formed was collected by filtration. A little more product was obtained by further concentration. The yield of crude ester was 14.5 g. (53%), m.p. 116–120°. Recrystallization from aqueous methanol gave 12 g., m.p. 120–122°.

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.07; H, 6.23. Found: C, 60.88; H, 6.13.

(1) Mannich and Heilner, *Ber.*, **55**, 356 (1922).
(2) Burckhalter and Fuson, THIS JOURNAL, **70**, 4184 (1948).
(3) Blicke and Burckhalter, *ibid.*, **64**, 453 (1942).
(4) Microanalyses by Mr. Charles Beazley, Skokie, Illinois.

(1) Fellow of the American Foundation for Pharmaceutical Education, 1948–1950.
(2) Burckhalter and Stephens, THIS JOURNAL, **73**, 56 (1951).
(3) Doering and Weil, *ibid.*, **69**, 2461 (1947), have used the same general method for the preparation of γ-2-pyridinebutyric acid.
(4) C and H analyses by Mr. C. W. Beazley, Skokie, Illinois.
(5) Obtained through the courtesy of Reilly Tar and Chemical Co., Indianapolis, Indiana.