The *p*-nitrophenylhydrazone appeared as golden yellow needles from alcohol; m.p. 172.5–175°.

Anal. Calcd. for $C_{18}H_{21}O_5N_3$: C, 60.16; H, 5.89. Found: C, 59.68; H, 6.01.

Permanganate oxidation of IIi gave **2-ethoxy-3,4-dimethoxybenzoic acid** as colorless fine thin prisms from cyclohexane; m.p. 77.5–80.5°.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.32; H, 6.26.

The amide, sublimed at 150° (bath temperature) (0.05 mm.), melted at 100–103°.

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.56; H, 6.71. Found: C, 58.43; H, 6.59.

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A New Synthesis of *dl*-Arterenol[1]

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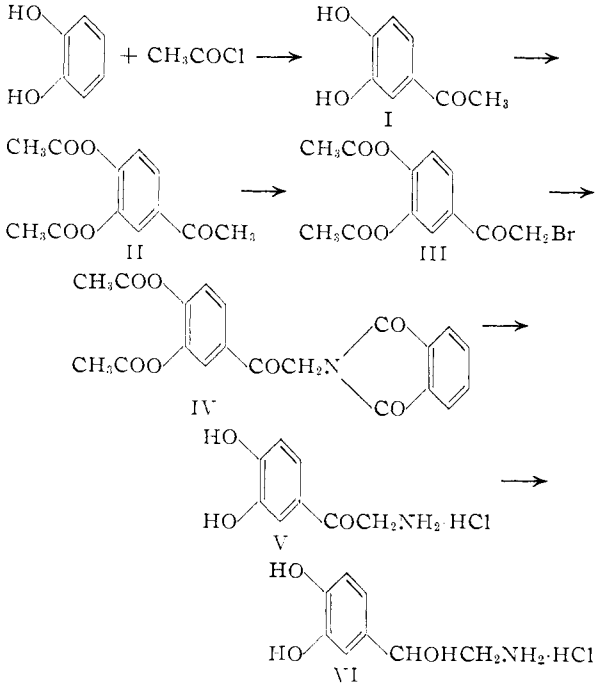
In order to implement the preparation of α-C^{14}-*dl*-arterenol,[2] a new synthesis of this important pressor substance has been devised which avoids oxidative losses (or the rather elaborate precautions necessary to prevent them) by employing intermediates in which the sensitive 3,4-dihydroxyphenyl moiety is protected by acetylation. The steps involved in the procedure are outlined below (in practice, neither I nor V was isolated).



On a 5–10 mM. scale, the procedure diagrammed above and described in detail below gave *dl*-arterenol as the hydrochloride (VI) in 6–15% over-all yield based on sodium acetate (*cf.* 5% on the same basis obtained[4] by the older method[3]).

Experimental

All melting points are corrected. Microanalyses were performed by Dr. A. Elek of the Elek Microanalytical Laboratories, Los Angeles.

3,4-Dihydroxyacetophenone (I) was prepared by a modification of the procedure of Miller, *et al.*[5] After standing at room temperature for 15 minutes, a mixture of 0.70 g. (6.4 mM.) of catechol and 2.55 g. (19.1 mM.) of anhydrous aluminum chloride in 7.5 ml. of carbon disulfide was heated for one hour at 40°; 0.50 g. (6.8 mM.) of acetyl chloride[6] then was added dropwise. The mixture next was heated to about 70°, the carbon disulfide being permitted to distil out, and finally to 140°, where it was maintained for 3.5 hours. The resulting buff or light-brown solid then was cooled in ice, treated with ice and 20 ml. of 3 *N* HCl and shaken vigorously with 5 ml. of ice-cold ethyl acetate until the solid reaction product dissolved completely. Two additional 5-ml. ethyl acetate extracts were combined with the first and washed with two 1-ml. portions of water (excess water is to be avoided since I has a moderate water solubility); the crude dihydroxyacetophenone was acetylated directly (see below). Samples of I isolated at this point in earlier experiments and recrystallized from benzene melted higher (119.2–119.7°) than has been reported previously (lit. 116°,[8] 115–116°,[9] 114–115°[10]). Use of ethyl acetate instead of butanol[5] as an extracting solvent for I is not only dictated by the conditions of the acetylation reaction (see below), but also is preferred if I is to be isolated; butanol is difficult to remove completely and the persistence of even small amounts affects the crystallizing power of the product adversely.

3,4-Diacetoxyacetophenone (II).—The ethyl acetate extracts of I obtained above were carefully floated on an ice-cold solution of 1.66 g. of potassium hydroxide pellets in 24 ml. of water and 2.07 g. of acetic anhydride was added to the upper phase. (The anhydride employed had been shown[11] previously to contain about 34% acetic acid by weight; the amount of KOH used was adjusted to provide a 10% excess over that required to neutralize any acetic acid in the acetic anhydride and to complete the acetylation.) After adding a few pieces of ice, the mixture was shaken vigorously; initially dark green, it soon turned pale brown, indicating completion of the desired acetylation. The ethyl acetate phase was washed with 5% aqueous sodium carbonate, dried ($MgSO_4$), and evaporated to give 1.335 g. of yellow-brown solid residue. II was obtained best from this material by dissolving in a little benzene, evaporating on a steam-bath, and rapidly diluting the residual oil with 4 ml. of boiling isopropyl ether; on cooling and standing, beautiful clusters of near-colorless slats emerged, weighing 0.605 g. (40.3% from catechol; other experiments run in apparently identical manner gave yields varying between this figure and 22.1%) and melting at 87.8–88.2° (lit. 84–85°,[10] 91°,[12] 86°[13]). Further processing of the mother liquors yielded 0.39 g. of crude catechol diacetate, but no appreciable additional amounts of II.

3,4-Diacetoxy-α-bromoacetophenone (III) was prepared by blowing bromine vapors with nitrogen into a concen-

(1) Supported by Grant No. 9, 1951–1952, from the Los Angeles County Heart Association to W. G. C. Grateful acknowledgment also is made to the Atomic Energy Commission for the 200 mc. of $BaC^{14}O_3$, contributed under the free distribution cancer plan, authorization No. 11260, Nov. 6, 1951.

(2) Synthesis of this radioactive substance by known procedures[3] was reported[4] during completion of the work presently described.

(3) W. Langenbeck and F. Fischer, *Pharmazie*, **5**, 56 (1950).

(4) R. W. Schayer, THIS JOURNAL, **75**, 1757 (1953).

(5) E. Miller, W. H. Hartung, H. J. Rock and F. S. Crossley, *ibid.*, **60**, 7 (1938).

(6) Radioactive acetyl chloride was prepared by the action of benzoyl chloride on sodium 1-C^{14}-acetate, prepared in turn from $BaC^{14}O_3$ by the procedure of Spector.[7]

(7) *Cf.* H. J. Strecker and L. B. Spector, cited in Calvin, *et al.*, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 176–177.

(8) V. S. Dzierzgovski, *J. Russ. Phys. Chem. Soc.*, **25**, 157 (1893).

(9) E. Clemmensen, *Ber.*, **47**, 56 (1914).

(10) L. S. Birnbaum and G. Powell, *J. Org. Chem.*, **4**, 139 (1939).

(11) L. F. Fieser, "Experiments in Organic Chemistry," Part II, Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 380. In determining amounts of acetic acid in samples of acetic anhydride, ethyl bis-(2,4-dinitrophenyl)-acetate is employed as indicator, since phenolic indicators are acetylated rapidly and thus rendered nonfunctional under these conditions.

(12) P. W. Neber, A. Burgard and W. Thier, *Ann.*, **526**, 277 (1936).

(13) C. Schöpf, E. Brass, E. Jacobi, W. Jorde, W. Mocnik, L. Neuroth anh W. Salzer, *ibid.*, **544**, 30 (1940).

trated solution of II in chloroform; instances of bromination of isomeric diacetoxyacetophenones are reported by Mosimann and Tambor[14] and by Shriner and Witte.[15] Thus 0.41 g. (2.57 mM.) of bromine was passed into a solution of 0.605 g. (2.57 mM.) of recrystallized II in 3.5 ml. of chloroform (reagent grade, 0.75% ethanol) at room temperature under anhydrous conditions. The velocity of the nitrogen stream was controlled in such a way that no appreciable amounts of free bromine emerged from the solution. When, at the start of the reaction, the solution had become colored with bromine, the nitrogen stream was interrupted and the mixture was allowed to decolorize before proceeding; reaction with bromine occurred rapidly after this induction period. After all the bromine had been consumed (an hour was usually required), the nitrogen stream was quickened to sweep out hydrogen bromide and most of the solvent, solvent removal being facilitated by warming the reaction vessel finally to about 40°. On completion of evaporation *in vacuo*, the crude product solidified. Recrystallization from isopropyl ether–ethanol gave pure III, clusters of colorless needles, m.p. 96–98°, weighing 0.575 g. (71.1%; yields in other runs varied only from 70 to 72%). Mother liquors yielded no further amounts of III. The analytical sample, after repeated recrystallization, melted at 99.2–99.8°.

Anal. Calcd. for $C_{12}H_{11}BrO_5$: C, 45.73; H, 3.52; Br, 25.36. Found: C, 45.67; H, 3.55; Br, 25.30.

3,4-Diacetoxy-α-phthalimidoacetophenone (IV).—Conversion of an α-haloacetoxyacetophenone to an α-aminohydroxyacetophenone *via* the α-phthalimido ketone has been described by Tutin, *et al.*[16] A mixture of 0.575 g. (1.827 mM.) of recrystallized III, 0.37 g. (10% excess) of potassium pthalimide and 1 ml. of dimethylformamide[17] (freed of traces of moisture by azeotropic distillation with benzene) was heated in steam for about one minute, cooled in ice, and the product partitioned between chloroform and water. Washed with 0.2 *N* sodium hydroxide, dried ($MgSO_4$), and freed of solvent, the chloroform extracts gave crude solid IV (0.655 g.). Recrystallization from ethanol–ethyl acetate yielded 0.36 g. (43.1%) of pure IV, clustered colorless slabs, m.p. 156–157°. A sample of IV obtained in another experiment melted slightly higher, at 156.8–157.8°. Yields of pure IV (based on III) in other experiments were as high as 58%; model experiments on phenacyl bromide gave comparable yields of α-phthalimidoacetophenone, in contrast to the near-quantitative yields reported.[17]

Anal. Calcd. for $C_{20}H_{15}NO_7$: C, 62.99; H, 3.97; N, 3.67. Found: C, 62.83; H, 4.04; N, 3.61.

***dl*-α-(Aminomethyl)-3,4-dihydroxybenzyl Alcohol (*dl*-Arterenol) Hydrochloride (VI).**—IV (0.64 g.) was hydrolyzed by heating with a mixture of 1.5 ml. each of 12 *N* HCl and glacial acetic acid sealed in a nitrogen-filled tube at 100° for seven days. The contents of the tube then were diluted with distilled water to 25 ml., filtered from a small amount of phthalic acid, and hydrogenated over 10% Pd-on-charcoal (American Platinum Works) at 25° and at atmospheric pressure. A total of 48 ml. of moist hydrogen was absorbed (theory 43 ml.). Filtered free of catalyst, extracted with ether to remove residual traces of phthalic acid and evaporated to dryness from the frozen state, the mixture gave the theoretical yield (0.32 g.) of crystalline, near-colorless VI. For analysis, a sample of the salt was precipitated from an absolute ethanol solution by addition of anhydrous ether.

Anal. Calcd. for $C_8H_{12}ClNO_3$: C, 46.72; H, 5.88; Cl, 17.24; N, 6.81. Found: C, 46.61; H, 6.00; Cl, 17.20; N, 6.77.

The ultraviolet absorption spectrum of VI dissolved in 0.1 *N* HCl corresponded closely with another of authentic *dl*-arterenol hydrochloride, showing a maximum at 279 and a minimum at 252 mμ.

Radioactivity of the sample of α-C^{14}-VI was determined (by conventional methods) to be 16 mc./mM. (calcd. from $BaC^{14}O_3$ 17.6). Biological activity of the radioactive substance was determined using a pithed male cat. The carotid artery was cannulated for recording arterial pressure changes *via* the Statham pressure transducer and an Offner oscillograph. A three-point standard curve of authentic VI was obtained by injecting increasing amounts of the substance up to but not including decreased linearity of response; the presence of 70 ± 14 mg. of VI in a solution containing 55 mg. of the synthetic radioactive material was thus indicated.

Dilute solutions of C^{14}-VI undergo appreciable deterioration even when stored under mild conditions. Thus after several months' storage at 0° of a solution of 55 mg. of the substance in 50 ml. of 0.001 *N* HCl, 0.001 *N* $NaHSO_3$ under nitrogen, its ultraviolet spectrum was noted to have changed; the change was manifest principally by a decrease in the absorptivity ratio ($a_{max}:a_{min}$), presumably as a consequence of increased end absorption attributed to decomposition products. Paper chromatography of the altered solution indicated the presence of several labeled contaminants, two (about 10 and 20% of the total counts) with R_f's smaller and one (about 5%) with an R_f greater than that of VI.[18]

A chromatographically pure sample of C^{14}-VI was obtained by placing a sample of the storage-deteriorated solution on Whatman No. 1 paper presprayed with ascorbic acid (50 mg./100 ml.) and developing with phenol (85 g.)–0.1 *N* HCl (15 ml.) in an SO_2 atmosphere. After removing the phenol by washing the paper with benzene, it was dried at room temperature and the C^{14}-VI area cut out and extracted with 0.2 *N* formic acid (recovery > 90%). Rechromatography showed no persistent contamination.

(14) W. Mosimann and J. Tambor, *Ber.*, **49**, 1263 (1916).

(15) R. L. Shriner and M. Witte, THIS JOURNAL, **61**, 2328 (1939).

(16) F. Tutin, F. W. Caton and A. C. O. Hann, *J. Chem. Soc.*, **95**, 2113 (1909).

(17) J. C. Sheehan and W. A. Bolhofer, THIS JOURNAL, **72**, 2786 (1950).

(18) The possibility is not excluded that some of these contaminating substances are present in the freshly-prepared product; thus one (tentatively identified by its R_f) appeared to be dopamine β-(3,4-dihydroxyphenyl)-ethylamine, which might well have been produced by hydrogenolysis of VI. The authors are indebted to Dr. David Masuoka for these chromatographic studies.

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Reactions of Haloketones, Allylic Chlorides and N-Chlorosuccinimide with Ketene Acetal. Orthoester Reactions *via* Chloroacetone[1]

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The reactions of many organic halides with ketene acetal have been reviewed by McElvain.[3] We have studied the reactions of a number of halides of diverse type with this substance and are reporting our results here.

The action of chloroacetone and of bromoacetone on ketene acetal leads mainly to polymerization of the latter, although small amounts of ethyl levulinate are formed, as are ethyl acetate, ethyl orthoacetate and ethanol, known decomposition products of ketene acetal. Ethyl orthoacetate at 110° with chloroacetone likewise gives ethyl levulinate and normal decomposition products of ketene acetal. It is possible that ketene acetal is an intermediate in this reaction. Since the action of chloroacetone on ketene acetal leads to isolation of ketene acetal dimer (16%) and trimers (15%), this polymerization is similar in effect to that brought about by hydrogen fluoride.[4,5]

(1) Abstracted in part from the Ph.D. thesis of Eugene E. Richardson submitted to the Graduate Faculty of Kansas State College, Manhattan, as partial fulfillment for the Degree, Doctor of Philosophy in Chemistry.

(2) Research Corporation Research Assistant.

(3) S. M. McElvain, *Chem. Revs.*, **45**, 453 (1949).

(4) S. M. McElvain and D. Kundiger, THIS JOURNAL, **64**, 254 (1942).

(5) S. M. McElvain and J. W. Langston, *ibid.*, **65**, 2239 (1943).