15 ml. of water which caused precipitation of a white product. The combined fractions were recrystallized from ethanol to give white crystals, m.p. 201.5–202°. The total yield was 0.8 g. (77%).

Anal. Calcd. for $C_{20}H_{20}N_2O_8S_4$: C, 44.06; H, 3.70; N, 5.14. Found: C, 44.09; H, 3.82; N, 4.95.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

Quinol Intermediates in the Oxidation of Phenols and Their Rearrangements[1]

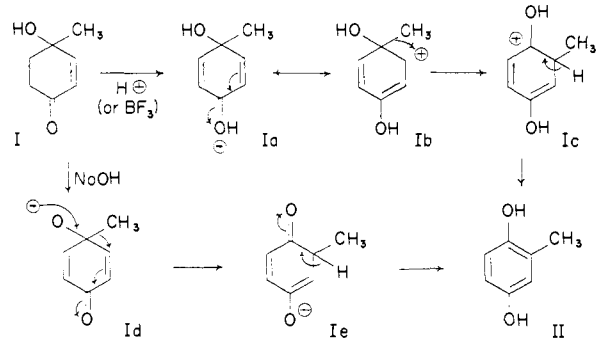
BY SIDNEY GOODWIN AND BERNHARD WITKOP

RECEIVED APRIL 5, 1956

The *p*-quinols and their O-acetates obtained from *p*-cresol, methyl *p*-hydroxyphenylacetate and 6-hydroxytetralin were rearranged to derivatives of hydroquinone under aqueous acidic or basic conditions and to resorcinols under the conditions of the Thiele reaction or by the use of boron trifluoride in ether. The rearrangements are pictured as acyloin shifts, and mechanisms are proposed for the alternate alkyl or acyloxy migrations. Homogentisic acid (XVII) was shown to be the product of the action of alkali on 4-carbomethoxymethyl-4-acetoxy-2,5-cyclohexadien-1-one (XVI). The *o*-quinoid diacetate XX yielded the triacetate of 5-methylpyrogallol (XXI) under the conditions of the Thiele reaction. The implications of these rearrangements are discussed in connection with biological oxidation mechanisms.

The oxidation of *p*-alkylated phenols with peracids in acidic solution[2] leads to alkylhydroquinones. Under neutral conditions the labile intermediates in this reaction can be isolated,[3] namely *p*-alkylquinols, originally obtained by the anionotropic, acid-catalyzed *inter*molecular rearrangement[4,5] of *p*-alkylhydroxylamines.[6] The analogy of these rearrangements to the metabolic sequence tyrosine → homogentisic acid was recognized by several investigators[7,8]; however, attempts to prepare the intermediate quinol in this series failed.[8–10] In this paper the preparation and various rearrangements of a number of free and O-acetylated simple mono- and bicyclic quinols as well as of the quinol precursor of homogentisic acid are described following up a preliminary communication published several years ago.[11]

p-Toluquinol (I) and the homologous xyloquinol have been rearranged by the action of aqueous acid and by aqueous alkali.[6,12]

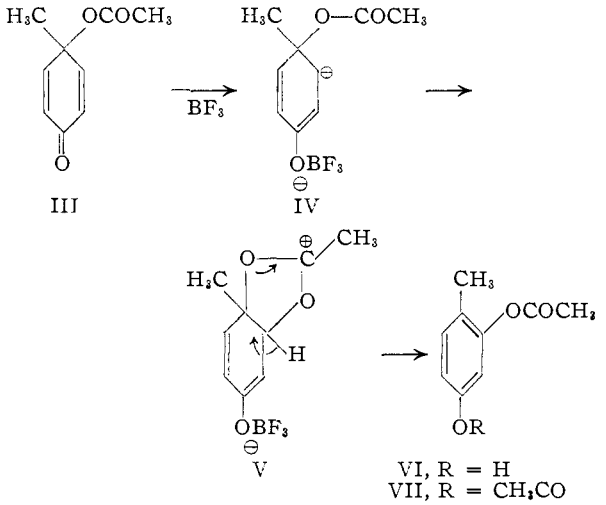


The rearrangements can best be pictured as vinylogous acyloin shifts.[13] Normally an α-hydroxyketone (or aldehyde) by the action of acid or base[14,15] is converted to the isomeric α-hydroxyketone with concomitant interchange of the oxygen functions and migration of one alkyl group. The quinols will not stop at this stage (Ie or Ic) but aromatize to hydroquinones. Such rearrangements are of importance in the biosynthesis of isoleucine and valine and in the formation of uranes in the metabolism of 17-hydroxy-20-ketosteroids.[16]

Whereas gentle acetylation of *p*-toluquinol with ketene (see Experimental) leads to the O-acetate III, which is more easily prepared by the action of lead tetraacetate on *p*-cresol,[17] rearrangement to the liquid cresorcinol diacetate VII occurs under the conditions of the Thiele reaction (acetic anhydride with concd. sulfuric acid). The same cresorcinol diacetate VII is obtained from the quinol acetate III in the Thiele reaction. Since the methyl group migrates more readily than a hydroxyl group, under Thiele conditions acetylation of the tertiary hydroxyl group of I[18] by acetylium ion probably precedes attack of the ion on the carbonyl oxygen followed by migration of the tertiary acetoxyl group (IV → V with acetoxyl instead of $-OBF_3^-$). Whereas the ordinary Thiele reaction proceeds with *external* addition of acetoxyl ion,[19] the cresorcinol diacetate VII arises probably by an

(1) Labile Metabolites. IV. Preceding paper in this series, B. Witkop and T. Beller, THIS JOURNAL, **78**, 2882 (1956).
(2) T. Kumazi and R. Wolffenstein, *Ber.*, **41**, 297 (1908).
(3) E. Bamberger, *ibid.*, **36**, 2028 (1903).
(4) E. A. Braude, *Quart. Rev. Chem. Soc.*, **4**, 423 (1950); *Nature*, **169**, 80 (1952).
(5) H. E. Heller, E. D. Hughes and C. K. Ingold, *Nature*, **168**, 909 (1951).
(6) E. Bamberger, *Ber.*, **33**, 3600 (1901).
(7) E. Mayer, *Deutsch. Arch. Klin. Med.*, **70**, 443 (1901).
(8) E. Friedmann, *Beitr. Chem. Physiol. Pathol.*, **11**, 304 (1908).
(9) O. Neubauer, *Deutsch. Arch. Klin. Med.*, **95**, 211 (1909).
(10) H. D. Dakin, *J. Biol. Chem.*, **8**, 13 (1910).
(11) *Cf.* B. Witkop and S. Goodwin, *Experientia*, **8**, 377 (1952).
(12) E. Bamberger, *Ann.*, **390**, 164 (1912).
(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 479.
(14) D. B. Sharp and E. L. Miller, THIS JOURNAL, **74**, 5643 (1952).
(15) R. B. Turner, *ibid.*, **75**, 3484 (1953).
(16) For a more complete survey of the literature, *cf.* M. Strassman, A. J. Thomas and S. Weinhouse, *ibid.*, **77**, 1261 (1955); S. Weinhouse, Amino Acid Biogenesis and Protein Synthesis Symposium, University of California, Los Angeles, April 18 and 19, 1955, Proceedings, pp. 1–45.
(17) F. Wessely and F. Sinwell, *Monatsh.*, **81**, 1055 (1950).
(18) The acetylation of tertiary hydroxyls of acyloins, even of highly hindered ones, is remarkably facile under acid conditions: Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, THIS JOURNAL, **74**, 5394 (1952), and ref. 15.
(19) H. A. E. Mackenzie and E. R. S. Winter, *Trans. Faraday Soc.*, **44**, 159, 171, 243 (1948); H. Burton and P. F. G. Praill, *Chemistry & Industry*, 92 (1950); *Quart. Revs.*, **6**, 316 (1952).

internal migration of the acetoxyl group.[20] This concept was supported when the quinol acetate III in boron trifluoride–ether solution showed the expected 1,2-shift of the acetoxyl rather than the methyl group. The quasi-cyclic five-membered intermediate structure V has its analogy in the cyclic carbonium ions postulated in reactions where neighboring groups participate.[21] The exothermic reaction led to the new resorcinol 2-acetate VI, m.p. 102–104°, in 70% yield.

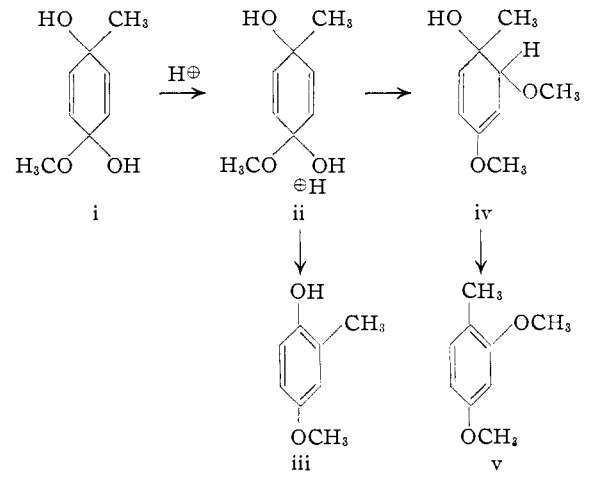


Further examples on the dualism of rearrangement of quinol acetates to derivatives of hydroquinone and resorcinol[22] were studied in the tetralin series.[23] The quinol acetate VIII, prepared from 6-hydroxytetralin with lead tetraacetate in acetic acid, rearranged to 5,7-diacetoxytetralin (XII) under the conditions of the Thiele reaction and to 5-acetoxy-7-hydroxytetralin (XI) when boron trifluoride in ether was used. The migration of the ring system to 5,8-diacetoxytetralin (XIV) was observed by Asahina[24] when he subjected the free quinol XIII to the conditions of the Thiele reaction. A similar dualism of rearrangement is known for the dienone–phenol rearrangement in this series (angular methyl instead of acetoxyl)[25,26] where the manner in which the reaction medium (aqueous acid or acetic anhydride)[27] influences the course of the rearrangement is not clear and where special environmental factors may lead to concurrent methyl and methylene migration. With the quinol XIII and its acetate VIII *both rearrangements occur under anhydrous conditions*. Possibly the hydroxyl group of XIII is more hindered than that of I and does not become acetylated before the rearrangement.

Finally the liquid *p*-quinol acetate XVI was prepared in small yield from methyl *p*-hydroxyphenylacetate[28] by the method of Wessely.[17] Since tyrosinase is most effective at an optimal *p*H of 7.4, mild basic conditions were employed for the rearrangement. After treatment of the quinol for 30 min. with 0.7 *N* NaOH at 50° under nitrogen, the presence of homogentisic acid (XVII) in the reaction mixture was proved by the method of Knox.[29] These experiments confirm only that in a quinol of type XVI or XVIII a side chain carrying a carboxyl group can migrate as had to be postulated by experiments with radioactive carbon.[30,31] No agreement exists on the exact nature of the quinolic precursor of homogentisic acid (XVII). Since 2,5-dihydroxyphenylpyruvic acid[32] was recently abandoned as a metabolic precursor of homogentisic acid,[33] the quinol with a pyruvic side chain XVIII may not be the actual intermediate. A hydroperoxide XIX may also be possible. Internal addition to XIXa, side chain migration coupled with decarboxylation (XIXa), and intramolecular oxidation–reduction and the possible role of heavy metals (copper) in stabilizing the quinolic intermediates are attractive aspects in need of clarification.

Rearrangements of *o*-Quinoid Intermediates.—The *o*-quinoid *gem*-diacetate XX was also subjected to conditions of acid-catalyzed rearrangements. No crystalline product could be obtained in the reaction with boron trifluoride where the 2,3-diacetate of 4-methylpyrogallol might be expected. The conditions of the Thiele reaction led to a triacetoxy compound, m.p. 101.5–102.5°, in 90% yield. The free trihydroxytoluene XXII which was obtained on hydrolysis had m.p. 126–127°,

(20) This dualism of external *vs.* internal reaction is also reflected in the rearrangements of *p*-toluquinol in acidic methanol (ref. 12), where the presumable intermediate i, the hemiacetal of *p*-toluquinol, can either undergo methyl migration to 4-methoxy-2-methylphenol (iii), the



major product, or add methanol *via* iv to give resorcinol dimethyl ether (v).

(21) *Cf.* S. Winstein and R. E. Buckles, THIS JOURNAL, **65**, 613 (1943); H. Meerwein, *Angew. Chem.*, **67**, 374 (1955).

(22) *Cf.* F. Wessely and W. Metlesics, *Monatsh.*, **85**, 637 (1954). The objection raised there (p. 644) against a part of our mechanisms (ref. 11) rests on a misunderstanding. The symbol A⊕ was used by us in the sense of a general Lewis acid and was not meant to represent the acetyl cation.

(23) *Cf.* F. Wessely, J. Kotlan and W. Metlesics, *ibid.*, **85**, 69 (1954).

(24) Y. Asahina, *Ber.*, **71**, 1421 (1938).

(25) R. B. Woodward and T. Singh, THIS JOURNAL, **72**, 494 (1950).

(26) Y. Abe, T. Harukawa and T. Toga, *J. Pharm. Soc. Japan*, **71**, 474 (1951); *C. A.*, **46**, 4518 (1952).

(27) A. S. Dreiding, W. J. Pummer and A. J. Tomasewski, THIS JOURNAL, **75**, 3159 (1953).

(28) *Cf.* A. Siegel and H. Keckeis, *Monatsh.*, **84**, 910 (1953).

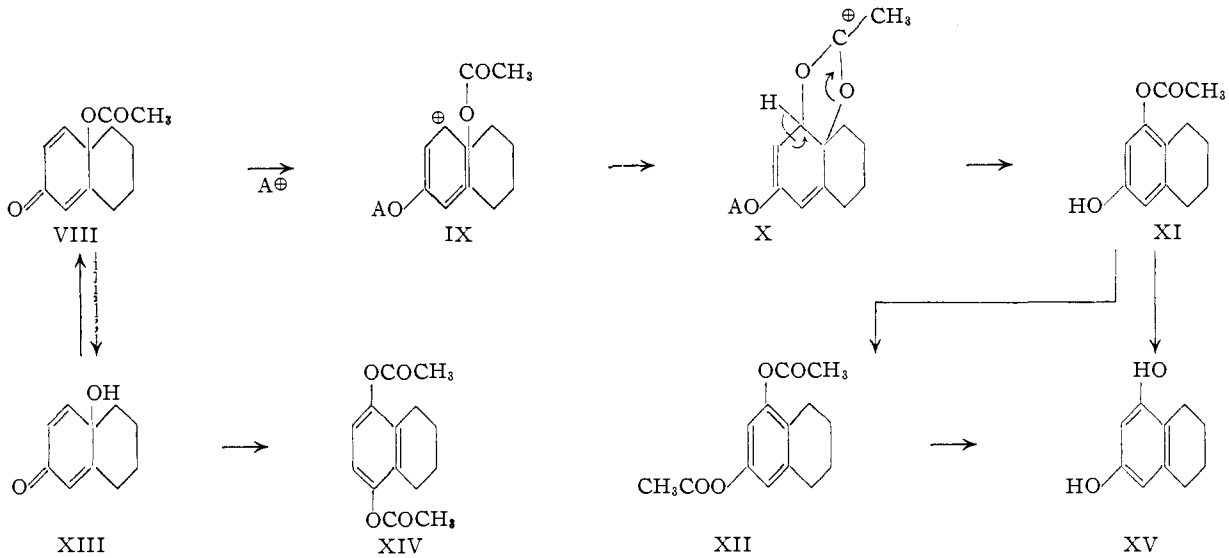
(29) W. E. Knox and M. Le May-Knox, *Biochem. J.*, **49**, 687 (1952).

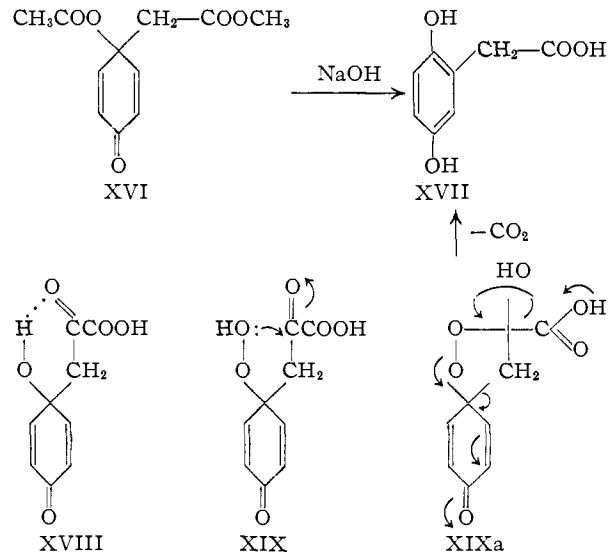
(30) S. Weinhouse and R. H. Millington, *J. Biol. Chem.*, **175**, 995 (1948).

(31) B. Schepertz and S. Gurin, *ibid.*, **180**, 663 (1949).

(32) For a recent review *cf.* M. Uchida, S. Suzuki and K. Ichihara, *J. Biochem. (Japan)*, **41**, 41 (1954).

(33) S. W. Edwards, D. Y. Y. Hsis and W. E. Knox, *Federation Proc.*, **14**, 206 (1955).





was characterized by its complex with methylstrychnine[34] and found to be identical with 5-methylpyrogallol.[35] This was further confirmed by methylation to the liquid 3,4,5-trimethoxytoluene (XXIII) and oxidation to the well known trimethylgallic acid (XXIV). The presumable mechanism of this rearrangement is pictured in the sequence XX → XXI. The *o*-quinoid oxidation product XXV from methyl *p*-hydroxyphenylacetate was likewise rearranged to methyl homogallate triacetate XXVI. No ring closure to a coumarone was noticed. The *o*-quinone *gem*-diacetate XXVII from α-naphthol[36] in the Thiele reaction gave the same 1,2,4-triacetoxynaphthalene (XXVIII) as 1,2- or 1,4-naphthoquinone.[37] If the *p*-position is blocked by an alkyl substituent as in XXIX, or in 4-methyl-1,2-naphthoquinone, the product of the Thiele rearrangement is XXXI.[38] For the first rearrangement the possible intermediates XXVIIa,b,c are reminiscent of the "second path" proposed for the dienone–phenol rearrangement of 2,2-dimethyl-1-oxodihydronaphthalene.[39] For the second rearrangement a quinonemethide intermediate XXX may be written.

The conversion of simple phenols to derivatives of hydroquinone, resorcinol and pyrogallol by oxidation and rearrangement of the quinolic intermediates open interesting aspects of biological oxidation. It must, of course, be remembered that biogenetically the sequence shikimic → prephenic → phenylpyruvic acids or the condensation of polyketonic acids[40] may lead to polyphenolic plant products by retention of hydroxyl groups. Whether the introduction of phenolic hydroxyl groups into aromatic substrates by the pathways discussed in this investigation is of general significance must still be shown.

Experimental[41]

p-**Toluquinol** (I).—The original procedure of Bamberger[12] was modified in the following way. To a partially frozen solution of 22.5 cc. of sulfuric acid and 450 cc. of water in a 1-liter flask was added 30 g. of *p*-tolylhydroxylamine in three portions. The stoppered flask was placed on "wrist action" shaker set for very slow agitation. Some solid material remained undissolved. After 16 hr. at room temperature, the original yellow, milky mixture had become a clear dark brown solution. An insoluble tan substance (4.3 g.) was removed by filtration. It had the properties of *p*-azoxytoluene, forming, after two crystallizations from ethanol, bright yellow needles, m.p. 69–70°. The residue was a dark brown oil weighing 21.8 g. (theoretical yield of toluquinol 30.2 g.). The ether-soluble reaction product (21.8 g.) was purified by chromatography over alumina in benzene solution followed by sublimation *in vacuo*. The yield of pure *p*-toluquionol, m.p. 76–78° (reported m.p. 75–76°[17]) was 33%; $\lambda_{max}^{CHCl_3}$ 2.77, 2.90–2.95, 5.98s (conjugated carbonyl), 6.19s μ (conjugated ethylene).

By-product.—After several days large prismatic colorless crystals appeared in the brown oil of a benzene–alcohol fraction from the chromatography of 6 g. of crude toluquinol reaction mixture. The crystals were separated mechanically. Crystallization from benzene failed to remove brown impurity, but sublimation *in vacuo* yielded a colorless solid, m.p.

(34) J. T. Edward and R. Robinson, *J. Chem. Soc.*, 1080 (1952).

(35) A. W. Hofmann, *Ber.*, **12**, 1376 (1879), m.p. 129°; (b) O. Rosauer, *Monatsh.*, **19**, 557 (1898), m.p. 119°.

(36) F. Wessely, J. Kotlan and F. Sinwell, *ibid.*, **83**, 902 (1952).

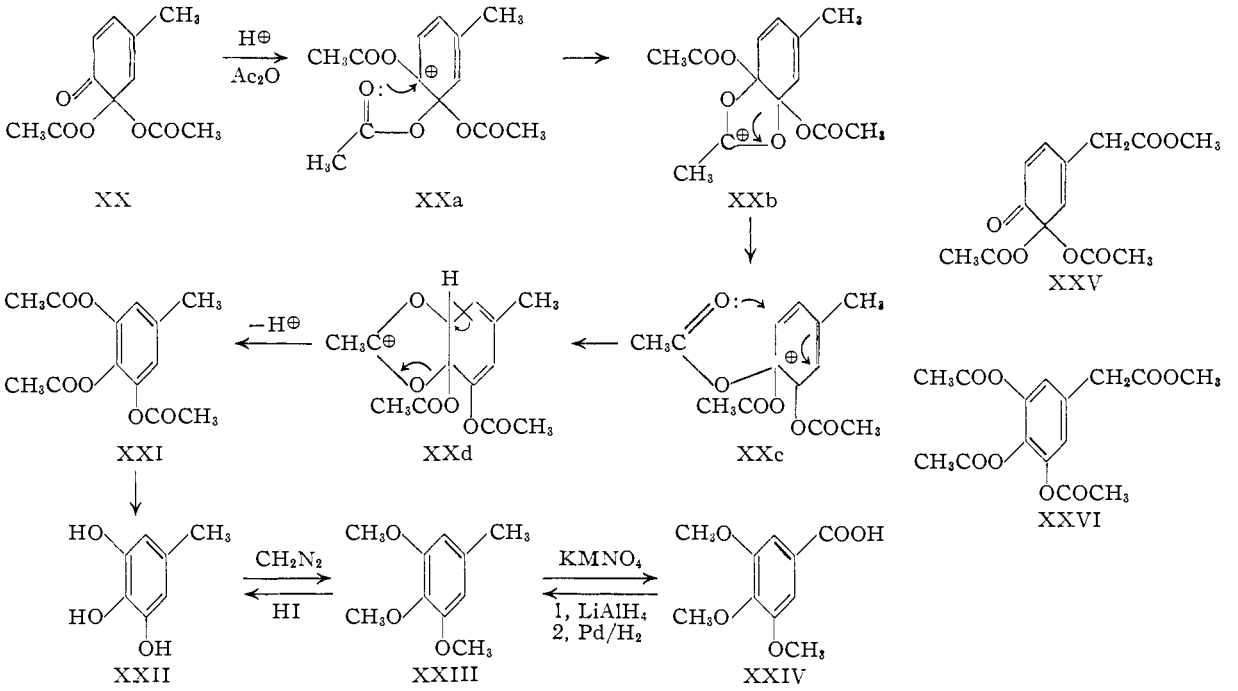
(37) J. Thiele and E. Winter, *Ann.*, **311**, 341 (1900).

(38) A. Ebnöther, Th. M. Meijer and H. Schmid, *Helv. Chim. Acta*, **35**, 910 (1952).

(39) E. N. Marvel and E. Magoon, THIS JOURNAL, **76**, 5118 (1954).

(40) *Cf.* R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956).

(41) All melting points are corrected, all boiling points uncorrected. The microanalyses were performed by Dr. W. C. Alford and associates, Microanalytical Service Laboratories, National Institutes of Health.



108–109°, very soluble in methanol and in water, sparingly soluble in ethyl acetate, somewhat less soluble in benzene and insoluble in chloroform. The substance is not acidic; λ_{max} (log ϵ) 216 mμ (4.01), 325 mμ (1.6) in ethanol, 3.05 μ, 5.98 μ (in Nujol).[42]

Anal. Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.10; H, 6.88.

***p*-Toluquinol-3,5-dinitrobenzoate.**—To a solution of 0.20 g. (1.61 mmoles) of *p*-toluquinol in 1 cc. of dry pyridine 0.39 g. (1.65 mmoles) of 3,5-dinitrobenzoyl chloride was added. The solution was warmed on the steam-bath for 15 minutes and, after cooling, 10 cc. of 10% potassium bicarbonate added. The yellow precipitate was collected, dried and crystallized from benzene. Shiny, white plates were obtained melting sharply at 161–162°.

Anal. Calcd. for $C_{14}H_{10}N_2O_7$: C, 52.83; H, 3.17; N, 8.80. Found: C, 52.82; H, 3.25; N, 8.92.

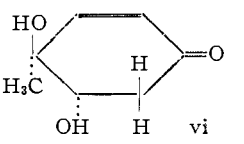
***p*-Toluquinol N-Phenylcarbamate.**—A mixture of 0.20 g. of *p*-toluquinol, 0.20 g. of phenyl isocyanate and 2 drops of pyridine was allowed to stand for 2 days. The resulting colorless solid, after washing with warm cyclohexane, melted at 150–160°. Crystallization from methyl alcohol yielded glistening stubby colorless needles, m.p. 180–181°.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.42; H, 5.40; N, 5.81.

***p*-Toluquinol acetate** (III) was obtained by allowing ketene to bubble through an acetone solution of *p*-toluquinol. The product, obtained first as a light yellow oil, crystallized on seeding, m.p. 40°,[17] λ_{max}^{EtOH} 236 mμ (4.16).

***p*-Cresol by Lithium Aluminum Hydride Reduction of *p*-Toluquinol.**—Two hundred milligrams of *p*-toluquinol was added to a solution of 100 mg. of powdered lithium aluminum hydride in 25 cc. of ether. There was an immediate white precipitation. The mixture, on being worked up in the usual manner, yielded a yellow-brown oil which was treated with 3,5-dinitrobenzoyl chloride in pyridine. Recrystallization of the product from benzene afforded yellow-tinged flakes melting at 181–182° undepressed on ad-

(42) As suggested by the referee, the composition and properties would correspond to an addition product vi of water to *p*-toluquinol, still retaining some moisture.



mixture with the 3,5-dinitrobenzoate (m.p. 182–183°) of *p*-cresol.

4-Methyl-2,2-diacetoxy-3,5-cyclohexadiene-1-one (XX).—The oxidation of *p*-cresol (10.8 g., 0.1 mole) in glacial acetic acid with lead tetraacetate (89 g., 0.2 mole) according to Wessely and Sinwell[17] yielded 6.6 g. (29.4%) of 4-methyl-2,2-diacetoxy-cyclohexadiene-1-one, obtained as an orange crystalline solid, m.p. 128–134°. This material crystallized from the red oily residue after the evaporation of the ethereal extract and was separated from the oily portion by filtration and washing with small portions of ether. The material could be recrystallized from either benzene or methanol but the orange discoloration was not removed by this means. Purification was easily achieved by vacuum sublimation. The yield of white sublimate from 4.00 g. of orange solid was 3.64 g. Crystallization of the sublimate from methanol afforded stout colorless needles, m.p. 141–142° (reported m.p. 140°);[14] λ_{max}^{EtOH} 314 mμ (3.42), 5.67 μ (ester carbonyl), 5.88 μ (conj. carbonyl), 6.01 μ (conj. double bonds).

4-Methyl-4-acetoxy-2,5-cyclohexadiene-1-one (III).—The *para*-oxidation product, *p*-toluquinol acetate, remaining in the oily red mother liquors after the removal of the *o*-quinoid oxidation product was obtained pure by distillation; b.p. 87° at 1.1 mm. The pale yellow oily distillate was redistilled twice and finally solidified to clear colorless prisms, m.p. 39.5–40.5° after washing with cold ether–pentane (1:1); λ_{max}^{EtOH} 237 mμ (4.08); in chloroform: 5.67 μ (ester carbonyl), 5.98 μ (conj. carbonyl), 6.10 μ (conj. double bonds).

Toluhydroquinone. A. From *p*-Toluquinol (I) with Boron Trifluoride in Ether.—A solution of 5 cc. of boron trifluoride etherate in 10 cc. of dry ether was added to a solution of 500 mg. of toluquinol in 25 cc. of dry ether. The light brown solution was refluxed for 20 minutes, then cooled, diluted with ether, washed with small volumes of water and sodium bicarbonate solution, dried over sodium sulfate and evaporated to a dark residue containing shiny grayish crystals (270 mg., 54%, m.p. 110–122°). Recrystallization from benzene gave colorless needles, m.p. 125–127° (not depressed on admixture with a sample of authentic toluhydroquinone, m.p. 124–127°). The infrared spectra of the two samples were identical.

B. From *p*-Toluquinol Acetate (III) **with Aqueous Base.**—On the addition of 1.2 g. of *p*-toluquinol acetate in 2 cc. of methanol to 10 cc. of 10% NaOH an exothermic reaction occurred. The mixture which became dark after refluxing for 15 minutes under nitrogen was cooled, acidified with 20% sulfuric acid and extracted with ether. The ether was evaporated leaving a red oil in which crystals appeared on standing. A little benzene was added and the almost colorless crystals were collected, m.p. 124–126°, mixed m.p. with toluhydroquinone 125–128°. The yield was about 4% of the theoretical. The infrared spectrum was identical with that of toluhydroquinone.

Cresorcinol Diacetate (VII) **by the Thiele Reaction of *p*-Toluquinol** (I).—A solution of 0.1 cc. of concentrated sulfuric acid in 1 cc. of acetic anhydride was added to a solution of 3.0 g. of *p*-toluquinol in 30 cc. of acetic anhydride. After the vigorous exothermic reaction had subsided the initially yellow solution became greenish-black. After standing for several hours at room temperature the solution was poured into 300 cc. of water and allowed to stand for an hour with occasional shaking. The oil which separated was taken up in ether and the aqueous phase extracted with ether. The ethereal extracts were washed successively with water, bicarbonate solution and water, dried over magnesium sulfate and evaporated leaving a fragrant yellow oil which could not be made to crystallize. The oil was miscible with benzene, methanol, ether, ethyl acetate and chloroform, immiscible with hexane and water. On distillation at a bath temperature of 130–150° and pressure of 0.1–0.2 mm. a water-clear liquid was obtained in good yield which became pale yellow on standing; $\lambda_{max}^{CHCl_3}$ 5.65 μ.

Cresorcinol by Hydrolysis of the Diacetate VII.—A mixture of 0.43 g. of the diacetate VII and 20 cc. of 5% sodium hydroxide solution was refluxed under nitrogen for 2 hr. The resulting red solution was cooled, acidified and extracted with ether. The ether extract was washed with a small volume of water, dried and concentrated. The infrared spectrum of the resulting red oil showed absorption at 2.78 and 3.0 μ and no absorption in the region of carbonyl absorption, indicating complete hydrolysis. The oil, on distillation *in vacuo*, gave a colorless viscous liquid which crystallized on standing, m.p. 102–103°. Four crystallizations from benzene gave colorless crystals, m.p. 102.5–104.0°; reported m.p. 83–84°,[43] 104–105°,[44] 70 to 104°,[45] 104–105°.[46] The product was identical (m.m.p., infrared spectrum) with a sample of cresorcinol (m.p. 95–96°) prepared by Clemmensen reduction of 2,4-dihydroxybenzaldehyde.

Cresorcinol-2-acetate (VI).—A solution of 2.4 g. of *p*-toluquinol acetate (III) in 10 cc. of dry ether was treated with 2 cc. of boron trifluoride etherate. The solution darkened considerably and the heat of reaction caused the temperature to rise to about 60°. The reaction mixture, after standing for a day, was diluted with 100 cc. of ether and washed twice with 100 cc. of water. The brown ethereal solution was dried over anhydrous sodium sulfate and evaporated yielding a brown oil which was dissolved in benzene. On addition of pentane the brown solid crystallized (1.7 g., 70% yield), m.p. 93–102°, after sublimation m.p. 99–102°. The analytical sample crystallized from benzene in lustrous white needles, m.p. 102–104°; λ_{max}^{ether} 289 mμ (3.35), λ_{max}^{EtOH} 279 mμ (3.40), $\lambda_{max}^{CHCl_3}$ 2.78, 3.02 μ (broad, hydroxyl group), 5.70 μ (ester carbonyl) 6.14, 6.25 μ (phenyl).

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 64.86; H, 6.16.

Cresorcinol-2-acetate on hydrolysis and by the usual procedure, after sublimation and recrystallization from benzene, gave tiny colorless needles, m.p. 105–107°, with crystalline transformation at 86°, undepressed on admixture with cresorcinol (m.p. 105–106°), obtained from hydrolysis of the Thiele reaction product of *p*-toluquinol (see above); λ_{max}^{EtOH} 283 mμ (log ε 3.48). The monoacetate on treatment with acetic anhydride–pyridine yielded an oily diacetate VII whose infrared spectrum was essentially superimposable on that of cresorcinol diacetate from the Thiele reaction of *p*-toluquinol; λ_{max}^{EtOH} (log ε) 265 mμ (2.77), 271 mμ (2.73).

5-Methylpyrogallol Triacetate (XXI). A. By Rearrangement of 4-Methyl-2,2-diacetoxy-3,5-cyclohexadiene-1-one (XX) in the Thiele Reaction.—A suspension of 1.35 g. (6.02 mmoles) of 4-methyl-2,2-diacetoxy-cyclohexadien-1-one (XX) in 10 cc. of acetic anhydride was treated with a solution of 3 drops of concentrated H_2SO_4 in 3 cc. of acetic anhydride. On mixing an exothermic reaction occurred producing a clear deep yellow solution. The color faded within about one minute leaving an almost colorless solution which was allowed to stand overnight. The addition of 30 g. of ice led to the formation of a colorless crystalline solid, which was collected after 30 minutes, washed well with water and dried. The colorless plates (1.44 g., 90%), m.p. 97–101°, were recrystallized from aqueous methanol; m.p. 101.5–102.5°. The infrared spectrum showed a maximum at 5.64 μ and phenyl bands at 6.17 and 6.23 μ. The substance was readily soluble in chloroform, benzene, ether and alcohol.

The triacetate XXI (2.9 g.) was hydrolyzed by refluxing in a mixture of 10 cc. of acetic acid and 100 cc. of 2 *N* HCl for 3 hr. under nitrogen. The ether-soluble 5-methylpyrogallol (XXII) eventually was obtained as 1.13 g. of feathery colorless blades, m.p. 126–127°. The conversion to the oily trimethyl ether XXIII was done with diazomethane in ether. A solution of 181 mg. of XXIII in 15 cc. of acetone and 5 cc. of water was treated with 3 g. of potassium permanganate and 10 cc. of water. The reaction mixture was stirred under reflux for 1 hr. Sulfur dioxide was bubbled through the cooled reaction mixture until a clear colorless solution was obtained which was then diluted with water and extracted with ether. Acidic material in the ether extract was extracted with 1 *N* NaOH. Acidification of the alkaline extract with 2 *N* H_2SO_4 followed by ether extraction gave on evaporation 50 mg. of a white solid, m.p. 134–155°. Two sublimations of this material *in vacuo* raised the melting point to 163–166°, undepressed on admixture with a sample of authentic trimethylgallic acid (Eastman) melting at 167°. The infrared spectra of the authentic sample of trimethylgallic acid and the material obtained as described from the rearrangement product were identical.

B. Synthesis of 5-Methylpyrogallol Triacetate (XXI).—Trimethylgallyl alcohol was obtained in 37% yield (14.7 g. from 45.2 g.) by lithium aluminum hydride reduction of methyl 3,4,5-trimethoxybenzoate (m.p. 80–82°) in ether.

(43) E. Clemmensen, *Ber.*, **47**, 62 (1914).

(44) O. Wallach, *ibid.*, **15**, 2835 (1882).

(45) T. B. Johnson and F. W. Lane, THIS JOURNAL, **43**, 341 (1921).

(46) J. C. Bell, W. Bridge and A. Robertson, *J. Chem. Soc.*, 1542 (1937).

The reaction mixture was stirred with excess hydride under reflux for 2 hr. and worked up in the usual manner. The product was a colorless, viscous oil, b.p. 133° (0.25 mm.) (reported b.p. 228° (25 mm.)).[47] The low yield is attributed to partial ether cleavage indicated by the fact that the ethereal solution of the reaction product on washing with 10% sodium hydroxide produced a deep red alkaline phase. A mixture of 12.0 g. (0.06 mole) of the alcohol, 5 g. of Pd/C (10%) and 100 cc. of glacial acetic acid was hydrogenated at a pressure of 40 lb. The mixture was shaken at room temperature until no more pressure drop was observed. After removal of the catalyst by filtration, the solution was concentrated *in vacuo* at 50° to about 30 cc., diluted with five volumes of water and extracted with ether. The ethereal extracts were washed with water and 5% NaOH, dried over Na_2SO_4 and concentrated. The yield of pale yellow liquid boiling at 95° (1 mm.) was 10.3 g. (94%). The infrared spectrum of the product was identical with that of the trimethoxytoluene obtained from the rearrangement of XX. A mixture of 8.4 g. (0.046 mole) of XXIII and 30 cc. of hydriodic acid (d. 1.70) was heated in an oil-bath. Methyl iodide started to be evolved at 115°. The bath temperature was allowed to rise to 135°. After 2 hr. 15.8 g. of methyl iodide (80%) had been collected. Heating was continued for one more hour. The light-yellow reaction mixture was cooled, diluted with water and extracted with three 150-cc. portions of ether. The ethereal extracts were washed with water, sodium bicarbonate solution and saturated sodium chloride solution, dried over sodium sulfate and evaporated. The residual, nearly colorless oil solidified on scratching, yielding 4.6 g. (72% yield) of tan solid. Recrystallization from benzene gave tan crystals, m.p. 125–126°. Colorless crystalline material was obtained by sublimation at 100° (0.3 mm.). The sublimate melted at 125–126°, undepressed on admixture with 5-methylpyrogallol (XXII) from the rearrangement of XX. The triacetate, prepared by standard methods, crystallized from benzene in colorless plates, m.p. 100–101° (reported[35] 99°), undepressed on admixture with the compound obtained by rearrangement from XX.

Complex of the 5-Methylpyrogallol with Methylstrychnine.—Following the directions of Robinson[34] a solution of 437 mg. (1 mmole) of methylstrychnine in 14 cc. of warm water was mixed with a solution of 140 mg. (1 mmole) of 5-methylpyrogallol. On cooling, colorless needles formed. The analytical sample was dried for 24 hr. *in vacuo*, m.p. 232–233°.

Anal. Calcd. for $C_{29}H_{33}O_6N_2 \cdot {}^1/_2H_2O$: C, 67.68; H, 6.67; N, 5.44. Found: C, 67.62; H, 6.83; N, 5.49.

4-Carbomethoxymethyl-2,2-diacetoxy-2,4-cyclohexadiene-1-one (XXV).—Methyl *p*-hydroxyphenylacetate was prepared *via* diazotized *p*-aminophenylacetic acid followed by esterification. The fraction boiling at 132–134° (0.7 mm.), $n^{19}D$ 1.5369, was used. A solution of 4.2 g. (0.025 mole) of methyl *p*-hydroxyphenylacetate in 125 cc. of glacial acetic acid was treated with successive portions of 24.4 g. (0.055 mole) of lead tetraacetate with agitation. After standing at room temperature for 24 hr., the dark-red reaction mixture was concentrated *in vacuo* to 20 cc. and poured into 300 cc. of water. The brown solid precipitate and tar were removed by filtration, dried *in vacuo* and extracted with ether in a soxhlet. The aqueous filtrate was extracted with ether. The ether extracts were washed with water and sodium bicarbonate and dried over magnesium sulfate. Both the red oily residue from the extraction of the filtrate and the red tarry residue from the soxhlet extraction gave crystalline material (280 mg., λ_{max}^{alc} 312 mμ (log ε 2.76))[11] which was purified by repeated recrystallization from methanol to give prismatic colorless crystals, m.p. 103–104°; λ_{max}^{alc} 310 mμ (log ε 3.49), λ_{min}^{alc} 268 mμ (log ε 2.91); $\lambda_{max}^{CHCl_3}$ 5.70 μ ($OCOCH_3$), 5.75 ($-COOCH_3$), 5.90 (conj. CO), 6.04 μ (conj. C=C).

Anal. Calcd. for $C_{13}H_{14}O_7$: C, 55.31; H, 4.99. Found: C, 55.25; H, 5.06.

4-Carbomethoxymethyl-4-acetoxy-2,5-cyclohexadiene-1-one (XVI).—Attempted chromatography on alumina of the red oily mother liquor did not afford any identifiable materials. However, the quinol acetate XVI was obtained on distillation of the combined mother liquors from five 4.2-g. runs. The fraction (0.7 g.) distilling at 135–155° (2 mm.) was re-distilled. The analytical sample, a pale yellow oil, boiled at 152° (3 mm.), $\lambda_{max}^{C_2H_5OH}$ 234 mμ (log ε 4.03); $\lambda_{max}^{CHCl_3}$ 5.68 (shoulder, $-OCOCH_3$), 5.74 ($-COOCH_3$), 5.96 (conj. CO), 6.11 μ (C=C). The forerun had λ_{max} 224 mμ (log ε 3.86), a somewhat higher boiling fraction had λ_{max} 228 (log ε 3.90).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.06; H, 5.65.

Base-catalyzed Rearrangement of 4-Carbomethoxymethyl-4-acetoxy-2,5-cyclohexadiene-1-one (XVI) to Homogentisic Acid (XVII).—After nitrogen had been bubbled through 40 cc. of 0.7 *N* NaOH for 30 minutes, 0.36 g. of 4-carbomethoxymethyl-4-acetoxy-2,5-cyclohexadien-1-one (XVI) was added. The reaction mixture was warmed at 50° for 1.5 hr. during which time the oil dissolved giving a brown solution. After cooling the reaction mixture was acidified with 2 *N* H_2SO_4 and extracted continuously with ether for 12 hr. The ether extract was concentrated to about 20 cc. and extracted with water (3 × 50 cc.). The combined water extracts were then extracted with ether (6 × 50 cc.). An aliquot of the red oil obtained on evaporation was subjected to paper chromatography according to Knox[29] using 1-butanol-water with a few drops of formic acid as the descending solvent. An authentic sample of homogentisic acid was also applied to the paper. The spots were located by spraying with ammoniacal silver nitrate. The reaction mixture gave only *one spot* which had the same *Rf* value as authentic homogentisic acid on the same paper.

Methyl 3,4,5-Triacetoxyphenylacetate (XXVI).—A suspension of 1.55 g. (0.0055 mole) of XXV in 5 cc. of acetic anhydride was treated with a solution of 1 drop of concd. H_2SO_4 in 1 ml. of acetic anhydride. The instantaneous exothermic reaction gave a clear red solution in a few seconds. In less than a minute the color faded leaving a pale yellow solution. After 1 hour 30 cc. of ice-water was added. The glistening white solid which separated was collected and washed well with water. The product (1.41 g., 79% yield) melted at 135–136°. From the aqueous solution an additional 0.16 g. (increasing the yield to a total of 88%) of crystalline material was obtained by chloroform extraction. The analytical sample crystallized from benzene as glistening, colorless, thin, rectangular plates melting sharply at 138.8–139.7°; $\lambda_{max}^{CHCl_3}$ 5.65 μ ($C_6H_5-OCOCH_3$), 5.76 μ ($CH_2-COOCH_3$); 6.19, 6.25 μ (phenyl).

Anal. Calcd. for $C_{15}H_{16}O_8$: C, 55.55; H, 4.97. Found: C, 55.82; H, 4.99.

1,2,4-Triacetoxynaphthalene (XXVIII) from the Parent *o*-Quinol *gem*-Diacetate (XXVII) by a Thiele Reaction.—A suspension of 0.55 g. of the *o*-quinol diacetate[36] (XXVII, m.p. 169°) in 1.5 cc. of acetic anhydride was treated with a mixture of 2 drops of concentrated sulfuric acid in 0.2 cc. of acetic anhydride. The clear solution became deep orange immediately and then changed to green-brown. The reaction mixture was allowed to stand for 1 hr. at room temperature during which time a crystalline precipitate formed. Following the addition of ice-water the yellowish solid was collected, m.p. 115–125°. The product crystallized from methanol as colorless blades, m.p. 137–139°, not depressed on admixture with an authentic sample of the same triacetate XXVIII prepared from naphthoquinone. The infrared spectra of the products from the *o*-quinol diacetate and from 1,4-naphthoquinone were superimposable.

10-Acetoxy-2-keto-$\Delta^{1,9,3,1}$-hexahydronaphthalene (VIII).—A mixture of 28.8 g. (0.2 mole) of β-naphthol, 200 cc. of ethanol, 8 cc. of 6 *N* hydrochloric acid and 1 g. of platinum oxide was shaken under a pressure of 45 lb. of hydrogen with warming.[48] The reaction stopped after the uptake of 0.2 mole of hydrogen and was started again by the addition of 0.5 g. of platinum oxide and 4 cc. of 6 *N* hydrochloric acid. After the required pressure drop the reaction mixture was worked up in the usual manner. The purified 6-hydroxytetralin, m.p. 58–59°, was obtained in 92% yield by either distillation (b.p. 121–124° (2.5 mm.)) or crystallization from benzene–hexane (1:10). To a solution of 7.4 g. (0.05 mole) of 6-hydroxytetralin in 250 cc. of glacial acetic acid was added 45 g. (0.10 mole) of lead tetraacetate in small portions with swirling after each addition. A mildly exothermic reaction led to a deep red solution which was allowed to stand at room temperature for 24 hr. About three-fourths of the

(47) M. Marx, *Ann.*, **263**, 252 (1891).

(48) J. H. Brown, H. W. Durand and C. S. Marvel, THIS JOURNAL, **58**, 1594 (1936).

solvent was removed by distillation *in vacuo*. The temperature of the reaction mixture was not allowed to rise above 40°. The dark residues from four such runs were poured into 800 cc. of ice-water. The mixture was stirred for about 15 min. and filtered by suction. The orange-red filtrate was extracted with six 150-cc. portions of ether. The ethereal extracts were washed with water and with excess aqueous sodium bicarbonate. After a final washing with water and drying over anhydrous sodium sulfate, the solvent was evaporated and the red oily residue was distilled *in vacuo*. Three fractions were taken: 1, b.p. 109–116° (0.3 mm.), 1.52 g. of yellow oil which almost completely crystallized on seeding; 2, b.p. 118–122° (0.3 mm.), 3.88 g. of yellow oil which crystallized completely on seeding; and 3, b.p. 122–140° (0.3 mm.), 2.49 g. of viscous red oil in which a small amount of crystals formed. Fractions 1 and 2 were combined and crystallized from ether–pentane as colorless prismatic crystals (3.75 g.) melting at 75–76° (reported[24] 81°). The material was analytically pure; $\lambda_{max}^{C_2H_5OH}$ 245 mμ (4.16); $\lambda_{max}^{CHCl_3}$ 5.74, 6.00, 6.13 μ.

The black tar which separated when the reaction mixture was poured into water and which constituted the major portion of the organic reaction product was dissolved in ethyl acetate, washed with water, 0.1 *N* NaOH until alkaline (the alkaline solutions were deeply colored) and again with water. The dried solution on evaporation left 12 g. of a thick black tarry mass. A 5-g. portion of this tar was subjected to systematic chromatography on alumina. Infrared spectra were recorded for selected fractions. These data showed that the benzene eluates contained some of VIII contaminated with other materials. The chloroform and methanol fractions of the chromatogram gave no crystalline or identifiable materials.

5,7-Diacetoxytetralin (XII).—When a solution of 0.5 g. of VIII in 2 cc. of acetic anhydride was mixed with a solution of 2 drops of concd. sulfuric acid in 0.2 cc. of acetic anhydride, an immediate exothermic reaction occurred. After standing for 30 min. the slightly discolored reaction mixture was poured into ice-water. The product was extracted with ether in the usual manner. The analytical sample was distilled at 0.1 mm. and a bath temperature of 175–185°; reported[49] b.p. 196° (15 mm.), m.p. 39–40°. The diacetate of 5,8-dihydroxytetralin (m.p. 179–180°) melts at 188°.

5-Acetoxy-7-hydroxytetralin (XI).—When 800 mg. of VIII was dissolved in 5 cc. of freshly distilled boron trifluoride etherate, the initially clear colorless solution became progressively darker and slightly warm. After standing overnight the dark solution was poured into 100 cc. of water and extracted with ether in the usual manner. A red-brown oily residue (572 mg., 71% yield) remained on evaporation of the ether. On standing, needle-like crystals formed in the oil. Crystallization of the crude product from benzene–pentane gave 356 mg. of red crystalline material which was sublimed *in vacuo* at 0.3 mm. and a bath temperature of 110–115°. The colorless crystalline sublimate, on recrystallization from benzene–pentane, afforded long silky needles, m.p. 113–114°; $\lambda_{max}^{CHCl_3}$ 2.80, 3.04, 5.66, 6.19 μ.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.99; H, 6.93.

5,7-Dihydroxytetralin (XV).—A solution of 400 mg. of crude XI in 15 cc. of methanol and 20 cc. of 2 *N* hydrochloric acid was refluxed for 2 hr., diluted with 200 cc. of water and extracted with three 100-cc. portions of ether. The dried ethereal extracts were evaporated and the resulting oily residue was taken up in about 10 cc. of benzene. On addition of pentane and cooling, 297 mg. of brown crystals was obtained. Sublimation *in vacuo* (0.3 mm., bath temp. 160°) gave a pale-yellow solid sublimate which crystallized from benzene as a colorless crystalline powder, m.p. 119–120° (reported[49] 122°). Similarly XV from XII was a colorless solid melting at 120–121°, m.m.p. with XV from XI was 119–120°. Both compounds were analytically pure.

The infrared spectra were identical in all respects; λ_{max}^{CHCl} 2.79, 3.00, 6.17, 6.26 μ.

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(49) G. Schroeter, K. Erzberger and L. Passavant, *Ber.*, **71**, 1040 (1938).

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Studies on Hydroxyproline

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The N-carbobenzyloxy derivatives II and IV of natural hydroxy-L-proline (I), as well as of allohydroxy-D- (III) and -L-proline, have been prepared in a crystalline form and oxidized to N-carbobenzyloxy-4-keto-L- and -D-proline (V and VII). The stereospecific reduction of N-carbobenzyloxy-4-keto-L-proline with sodium borohydride led in good yield to the allohydroxy-L-proline derivative. 4-Keto-L-proline hydrobromide (VI) was prepared and investigated. The N-acetyl- and N-carbobenzyloxyallohydroxy-D- and -L-proline lactones (XIV, XV) were obtained by an internal displacement reaction, by dehydration of N-acylallohydroxyprolines with *p*-tolylsulfonyl chloride in pyridine and by the use of N,N'-dicyclohexylcarbodiimide. The solvolysis of the N-acetyl XIV as well as of the free lactone (XVI, hydrobromide) in aqueous buffer of varying *p*H was investigated. By opening of the lactones with esters of amino acids, peptides of allohydroxy-D- and -L-prolines were prepared. The rate of hydrolysis of allohydroxy-L-proline lactone hydrobromide (XVI) was followed by the mutarotation of its aqueous solution. The application of Hudson's rule confirmed the D_G configuration for C(4) in allohydroxy-L-proline. The general applicability of nucleophilic displacement reactions by suitable anions for the preparation of 4-substituted proline derivatives from the 4-tosylates was explored using sodium methyl mercaptide. The two diastereoisomeric 4-methylmercapto-L-prolines (XX and XVII) were prepared. The conversion of hydroxy-L-proline and of allohydroxy-D-proline into their betaines XXI and XXIII under non-epimerizing conditions led to conclusive stereochemical assignments for betonicine (XXI) and turicine (XXIII). The easy base-catalyzed epimerization of these betaines at room temperature casts some doubt upon the natural occurrence of turicine.

The most abundant protein in the body, collagen, is chemically distinguished from all other proteins by its high content of hydroxyproline.[1,2] The need for derivatives, analogs and antimetabolites of hydroxyproline for testing in collagen-producing tissue cultures[3] prompted the following study.

4-Ketoproline (VI) Hydrobromide.—The starting materials in this investigation were the carbobenzyloxy derivatives of natural and allohydroxy-

(1) K. H. Gustavson, "The Chemistry and Reactivity of Collagen," Academic Press, Inc., New York, N. Y., 1956.

(2) "Nature and Structure of Collagen," edited by J. T. Randall and S. F. Jackson, Academic Press, Inc., New York, N. Y., 1953.

(3) The results on this collaborative project with Prof. F. C. Steward and Drs. S. Udenfriend and C. Mitoma will be published separately.