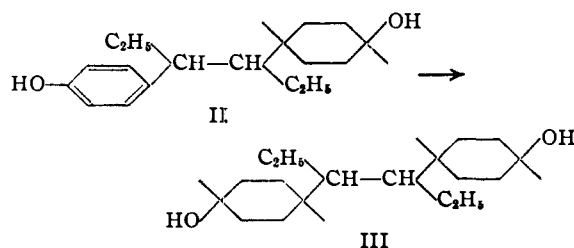


[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

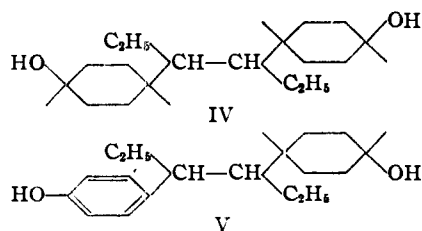
Hydrodiethylstilbestrol Compounds. II. The Racemic Octahydro Compounds

BY HERBERT E. UNGNADE AND ANNA LUDUTSKY^{1,2}

The partial hydrogenation of diethylstilbestrol at 210° (265 atm.) leads to a mixture of phenolic and non-phenolic compounds which can be separated by extracting with alkali.³ When the crystallized phenolic material (I) is adsorbed on alumina an octahydrodiethylstilbestrol compound, m. p. 147–148° (II) is obtained in the lower zones. This compound belongs to the racemic series and is assigned the *trans* configuration because it gives a good yield of a single perhydro compound, *dl*-3,4-di(4^t-hydroxycyclohexyl)-hexane (III)³ on hydrogenation with nickel catalyst.⁴



Attempts to separate the remaining low-melting material from the upper zones of the chromatogram by adsorption, crystallization, distillation, extraction or distribution between solvents have failed. Upon hydrogenation with Raney nickel catalyst this material gives a mixture of about equal amounts of (III) and its isomer (IV), *dl-r*-3-(4^t-hydroxycyclohexyl)-4-(4^c-hydroxycyclohexyl)-hexane, which is regarded as evidence that the low-melting substance is largely a mixture of (II) and the corresponding *cis*-isomer (V).⁴



Benzoylation of the mixture (I) by the procedure of Schotten-Baumann gives two monobenzoates which can be separated by adsorption on alumina. One of these is the monobenzoate of compound (II). The other is regarded as the benzoate of the *cis*-isomer (V) which it gives on hydrolysis.

Minute amounts of an octahydro isomer (VI), m.p. 142–143° have been isolated by chromato-

(1) George Breon Fellow, 1943–1946.

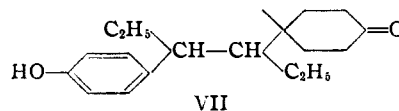
(2) Present address: Rockefeller Institute for Medical Research, New York, N. Y.

(3) Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 307 (1945).

(4) It is assumed that the reduction takes place without affecting the configuration of (II).

graphing mixture (I) on sucrose. This substance is identical with the octahydro compound melting at 144–145° described previously,⁵ and probably belongs to the meso series.

The mixture (I) of the octahydro compounds can be converted to the phenolic ketone (VII).



Reduction of this glassy material (VII) with sodium and alcohol gives the low melting mixture (VIII) of the octahydro compounds (II) and (V). The reduction of the ketone (VII) with platinum in acetic acid affects mainly the phenolic ring so that it is not a suitable method for the preparation of the *cis*-isomer (V).

The compound melting at 92–94° described earlier⁵ as an octahydrostilbestrol isomer has now been established as a complex consisting of the perhydrodiethylstilbestrol isomer (IV) and *dl*-dihydrodiethylstilbestrol.

Experimental⁶

Partial Hydrogenation of Diethylstilbestrol.—Diethylstilbestrol (50 g.) dissolved in 100 cc. of methyl alcohol was reduced at 210° under an initial pressure of 270 atm. until one half of the amount of hydrogen was absorbed which is required for complete saturation. The reaction mixture was filtered and freed from solvent. The remaining glass (51 g.) was dissolved in 200 cc. of peroxide-free ether. The *dl*-3,4-di(4^t-hydroxycyclohexyl)-hexane (2.5 g.) which crystallized out on standing over night was filtered, the ether was removed from the filtrate, and the residue was refluxed on a water-bath for eight hours with a sodium methoxide solution prepared from 2.5 g. of sodium and 50 cc. of methanol. Most of the methanol was distilled off, 200 cc. of water was added to the residue, the mixture was thoroughly stirred and extracted with benzene.⁷ Distillation of the benzene gave 13 g. of alkali-insoluble glass. The aqueous solution was acidified to congo red with concentrated hydrochloric acid and extracted with ether. The glass (29 g.) obtained from the ether extract was crystallized from benzene giving 15 g. of colorless crystals, m. p. 55–60° (I). This material contained 0.75 mole of benzene of crystallization. The loss in weight on heating to 100° at 3 mm. was 17.20%. Calcd. for C₁₈H₂₈O₂·³/₄C₆H₆: 17.36.

Anal. Calcd. for C₁₈H₂₈O₂: C, 78.20; H, 10.21; mol. wt., 276. Found: C, 78.18; H, 10.51; mol. wt. (cryoscopic, in dioxane), 314.

dl-r-(*p*-Hydroxyphenyl)-4-(4^t-hydroxycyclohexyl)-hexane (II).—The crystalline benzene complex (I) (1.0 g., m. p. 55–60°) was dissolved in 20 cc. of benzene and

(5) Hoehn and Ungnade, *This Journal*, **67**, 1617 (1945).

(6) Semi-micro analyses by Anna Ludutsky. Best results were obtained with the simple band filling described by Niederl and Niederl. "Micromethods of Quantitative Organic Analysis," 2nd Ed., John Wiley and Sons, New York, N. Y., 1942, p. 107, and doubled combustion time.

(7) Ordinary extraction of the mixture by means of aqueous alkali or Claisen alkali fails to give a complete separation of phenolic and non-phenolic substances.

adsorbed on a column of alumina. The first 5 cc. of benzene eluate contained 0.1 g. of crystalline material which melted at 138–140° after crystallization from benzene. Several crystallizations from benzene or chloroform-Skellysolve A mixtures raised the melting point to 147–148° (II). The mixture with the octahydro compound (VI), m. p. 144–145°⁶ melted at 120–125°.

Anal. Calcd. for C₁₈H₂₀O₂: C, 78.20; H, 10.21. Found: C, 78.21; H, 10.46.

Monobenzoate.—Benzoylation of the above compound (II) (0.2 g.) dissolved in 20 cc. of 5% aqueous sodium hydroxide solution with 0.1 cc. of benzoyl chloride gave 0.25 g. of a glass. Crystallization from Skellysolve B gave 0.1 g. of the monobenzoate melting at 73–75°. Another crystallization from Skellysolve F raised the melting point to 77–78°.

Anal. Calcd. for C₂₅H₂₈O₃: C, 78.90; H, 8.47. Found: C, 78.90; H, 8.82.

Further elution of the original chromatogram with benzene gave 0.05 g. of a substance melting at 50–55°. Subsequent extraction with ether yielded 0.6 g. melting at 38–40°.

In one case, 0.5 g. of a mixture (I), m. p. 35–40°, dissolved in 10 cc. of benzene was adsorbed on sucrose. The first 5 cc. of benzene eluate gave 0.05 g. of material (VI) which melted at 125–129°. Several crystallizations from benzene raised the melting point to 142–143°. The substance did not depress the melting point of the octahydro compound melting at 144–145°.⁶

Hydrogenation of *dl*-3-(*p*-Hydroxyphenyl)-4-(4'-hydroxycyclohexyl)-hexane (II).—The pure *trans*-isomer (II) (1.0 g.) dissolved in 100 cc. of methanol was reduced with 3 g. of Raney nickel at 210° (270 atm.). The glassy product (0.90 g.) obtained after removing catalyst and solvent was refluxed with a solution of sodium methoxide in methanol (0.15 g. of sodium in 20 cc. of methanol). The mixture was diluted with water and extracted with benzene. The extract contained 0.78 g. of substance which melted at 180–185°. The mixed melting point with *dl*-3,4-di-(4'-hydroxycyclohexyl)-hexane (m. p. 188–189°) was 183–185°. No other product could be isolated.

Hydrogenation of Mixture (I).—The mixture of octahydro isomers (I), m. p. 62–66°, was freed from the *trans*-compound (II) by chromatographing on alumina. The resulting glass (0.6 g.) was dissolved in 100 cc. of methanol and reduced with 3 g. of Raney nickel at 210° (270 atm.). The reduction product, worked up as usual, gave 0.5 g. of alkali-insoluble glass and 0.1 g. of alkali-soluble glass. The alkali-insoluble fraction yielded 0.2 g. of *dl*-3,4-di-(4'-hydroxycyclohexyl)-hexane (III), m. p. 185–187°, mixed melting point with an authentic sample (188–189°) 185–187°, and 0.2 g. of *dl*-3-(4'-hydroxycyclohexyl)-4-(4'-hydroxycyclohexyl)-hexane (IV), m. p. 129–130°, mixed melting point with an authentic specimen of (IV) (m. p. 129–130°) 129–130°. The alkali-soluble glass was crystallized from benzene and melted at 62–64°.

Attempted Separations of Mixture (I): Digitonides.—The digitonide of mixture (I), (0.1 g., m. p. 62–66°) precipitated only after considerable dilution of the reaction mixture with water. It melted at 165–175° (yield 0.18 g.) and gave back 0.1 g. of the starting material, m. p. 60–65°.

Monobenzoates.—The Schotten-Baumann reaction with benzoyl chloride converted the mixture (I) (1.0 g., m. p. 55–60°) to a glassy mixture of benzoates (yield 1.25 g.).

Anal. Calcd. for C₂₅H₂₈O₃: mol. wt., 380. Found: (from sapon. equiv.) mol. wt., 403.

Crystallization of this mixture gave traces of the dibenzoate of *meso*-dihydrodiethylstilbestrol, m. p. 234–235°, which did not depress the melting point of an authentic specimen melting at 236–237°,⁸ and traces of the dibenzoate of *dl*-dihydrodiethylstilbestrol, m. p.

121–123°, mixed melting point with an authentic specimen (m. p. 123–124°) m. p. 122–124°.

Anal. Calcd. for C₃₂H₃₆O₄: C, 80.33; H, 6.27. Found: C, 80.56; H, 6.56.

The remaining mixture of benzoates was adsorbed on alumina from Skellysolve B solution. The column was eluted with the same solvent and the fractions crystallized. The upper zones contained 0.1 g. of the monobenzoate of (II), melting point and mixed melting point 77–78°. The lower zones gave 0.25 g. of a monobenzoate melting at 114–115°.

Anal. Calcd. for C₂₅H₂₈O₃: C, 78.90; H, 8.47. Found: C, 78.90; H, 8.56.

Hydrolysis of the monobenzoate of (II), m. p. 77–78°, with alcoholic sodium hydroxide gave a good yield of *dl*-*r*-3-(*p*-hydroxyphenyl)-4-(4'-hydroxycyclohexyl)-hexane, m. p. 144–145° which did not depress the melting point of an authentic sample.⁹

Hydrolysis of the benzoate, m. p. 114–115°, under the same conditions gave a glass which melted at 34–40° after crystallization from benzene. The melting point could be raised to 47–50° by recrystallization from a chloroform-Skellysolve mixture.

Mono-*p*-phenylazobenzoates.—The mixture (I) (1 g., m. p. 65–68°) dissolved in 100 cc. of 5% aqueous sodium hydroxide was shaken for two hours with 1 g. of *p*-phenylazobenzoyl chloride¹⁰ in 20 cc. of ether. The product (1.3 g.) melted at 97–103° after crystallization from Skellysolve B.

The esters were adsorbed on silicic acid from acetone solution according to the procedure of Coleman.¹¹ The chromatogram was uniform. Three arbitrary fractions gave products with the same melting point 96–100° (from aqueous acetone).

Anal. Calcd. for C₃₁H₃₆O₃N₂: C, 76.81; H, 7.49. Found: C, 76.48; H, 7.63.

Upon hydrolysis of this material with sodium hydroxide in aqueous alcohol the mixture (I) was regenerated, m. p. 53–57° (from benzene-Skellysolve B mixture).

Dibenzoate.—The mixture (I) (0.3 g., m. p. 45–50°) when benzoylated with 1 g. of benzoic anhydride and 5 cc. of pyridine gave 0.2 g. of a benzoate melting at 100–110°. After several crystallizations from Skellysolve B the melting point remained constant at 117–118°.

Anal. Calcd. for C₃₂H₃₆O₄: C, 79.33; H, 7.43. Found: C, 79.09; H, 7.63.

Hydrolysis of this dibenzoate (m. p. 117–118°) with aqueous alcoholic potassium hydroxide gave back mixture (I), m. p. 35–40° (from Skellysolve B).

Di-*p*-phenylazobenzoates.—Mixture (I) was esterified with *p*-phenylazobenzoyl chloride in pyridine. The product, worked up as usual, was adsorbed on silicic acid.¹¹ Two arbitrary fractions of the uniform chromatogram both melted at 167–169°.

Anal. Calcd. for C₄₄H₄₄O₄N₄: C, 76.25; H, 6.40. Found: C, 76.00; H, 6.60.

Hydrolysis of the di-*p*-phenylazobenzoate gave back mixture (I), m. p. 55–65° (from benzene and Skellysolve B).

***dl-r*-3-(*p*-Hydroxyphenyl)-4-(4'-ketocyclohexyl)-hexane (VIII).**—This ketone was obtained from the oxidation of the mixture (I), m. p. 55–60° by Oppenauer's method¹² and by oxidation of the glassy monobenzoate derived from the mixture (I) (0.6 g.) with chromic anhydride (0.1 g.) in acetic acid (5 cc.) at 60° and subsequent hydrolysis of the oxidation product. The crude ketone

(9) It is thus shown that benzoylation and hydrolysis of the benzoate under the conditions described do not involve a stereochemical inversion at the alcoholic hydroxyl group.

(10) Ansporn, "Organic Syntheses," Vol. 25, p. 86; Coleman, Nichols, McCloskey and Ansporn, *ibid.*, Vol. 25, p. 87.

(11) Coleman, Rees, Sundberg and McCloskey, *THIS JOURNAL*, **67**, 385 (1945).

(12) Oppenauer, "Organic Syntheses," Vol. 21, p. 18; Wayne and Adkins, *ibid.*, Vol. 21, p. 8.

(8) Foreman and Miller, *THIS JOURNAL*, **68**, 2240 (1941).

was separated from by-products and unchanged starting material by means of Girard reagent.¹³ The glassy product was soluble in benzene, insoluble in Skellysolve B.

Anal. Calcd. for C₁₈H₂₀O₂: C, 78.83; H, 9.48. Found: C, 79.13; H, 9.23.

The benzoate, oxime, semicarbazone and benzoate oxime of this substance were obtained only in the glassy state and were not further investigated.

Reduction of the purified ketone (VII) (1.0 g.) dissolved in 15 cc. of absolute alcohol with 1 g. of sodium gave 0.2 g. of a mixture of octahydro compounds (VIII), m. p. 45-50° which was separated from glassy by-products by adsorption on alumina.

Identification of the Compound Melting at 92-94°.⁵—This compound¹⁴ was characterized by two benzoates⁵ melting at 113-114° and at 123-124°. The benzoate melting at 113-114° has now been identified as the dibenzoate of *dl-r-3*-(4^r-hydroxycyclohexyl)-4-(4^c-hydroxycyclohexyl)-hexane (IV).³ It did not depress the melting point of an authentic sample. The benzoate melting at 123-124°⁵ has been identified as the dibenzoate of *dl*-dihydrodiethylstilbestrol since it did not depress the melting point of an authentic specimen (m. p. 123-124°) and upon hydrolysis gave a good yield of *dl*-dihydrodiethylstilbestrol, m. p. and mixed m. p. 125-126°. Compound formation between these hydrodiethylstilbestrol compounds has been reported previously.¹⁵

Infrared Absorption Spectra¹⁶

Analytically pure samples of substances (II), (V) and (VI) were run as Nujol mulls in a Perkin Elmer infrared spectrometer with rocksalt optics. Because mixture (VIII) did not powder well, it was used as a glass by melting it between two rock-salt plates and cooling to room temperature. The thickness of the samples was not known. The conclusions were based on comparisons of the relative intensities of bands within one spectrum with the relative intensities of the same bands in another spectrum.

The results (Table I) show that the spectra of (II), (V) and (VI) are all different. Each contains bands which are absent, or extremely weak, in the other two, and each also fails to exhibit bands which are possessed by the other two. Compounds (II), (V) and (VI) must therefore be regarded as spectroscopically different substances. The fourth sample (VIII) gives a spectrum indicating that it is a mixture of (VI), somewhat less of (II) and a small amount of (V).

The four possible racemates of the octahydro compounds will have different spectra. Since the structure of (II) has been established as a *trans*-alcohol belonging to the racemic series, and since (I) is largely a mixture of *cis*- and *trans*-isomers, (V) would be expected to be the corresponding *cis*-alcohol. Compound (VI), which is in small amounts, could belong to the meso series.¹⁷

(13) Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936); Smith, Chase and Rhodes, *This Journal*, **66**, 1547 (1944).

(14) The isolation of this compound, m. p. 92-94° was purely accidental and is due to the fact that the extraction of the phenolic fraction with aqueous alkali was incomplete.

(15) Ungnade and Morriss, *This Journal*, **69**, 1545 (1947).

(16) This work was done by Agatha R. Johnson and Foil A. Miller, Department of Chemistry, University of Illinois.

(17) The other alternative, which appears less likely, that (VI) is the *cis*-isomer while (V) belongs to the meso series can be definitely ruled out when the meso compounds are available. They are now under investigation.

TABLE I
WAVE NUMBERS OF THE ABSORPTION BANDS^a

II ^b	V ^b	VI ^b	VIII ^b
686	705 m	717	677
720 s	743	732 s	705
735	769	781	720
777	797	805	735
796	817 m	824 s	781
814	828	834 s	796
833 s	841 s	846	833 s
853	859	904	880
882	901 m	948	900 m
903	908	966 m	947
914	946	995	961 m
929	962	1007	1003
949 s	971 m	1016	1016
959 s	1006	1055 s	~1051 s
1021	1016 m	1073	1174 m
1034 s	1035 sh	1098	{ 1220
1057	1051 s	1109	{ 1260
1081	1085	1127	{ 1296
1103	1093	1143	{ 1363 s
1120	1113 m	1174 m	{ 1376 s
1150	1150	1212	1457 s
1174	1177	1232 s	1514 s
1183	1202	1253 s	1598 s
1215 s	{ 1236 s	1298	1613 s
1229	{ 1245 s	1331	1884
1250 s	1295	1376 s	2505
1261 sh	1339	1459 s	2712
1293	1376 s	1513 s	{ 2865 s
1310	1407	1598	{ 2950 s
1334	1457 s	1613 s	~3340 s
1366 s	1513	1885	
1376 s	1600 s	2490	
~1443 sh	1611 s	2585	
1459 s	1890	2687	
1512 s	2494	{ 2875 s	
1595 s	~2605	{ 2955 s	
1613 s	{ 2880 s	3164	
1892	{ 2951 s	3390	
2454	3025 sh		
2570	3255 s		
2687	3444		
{ 2880 s			
{ 2950 s			
3110 s			
3405 s			

^a The wave numbers are estimated to have the following accuracy: 650-1000, ±1; 1000-1600, ±2; 1600-2000, ±5; 2000-3000, ±15; 3000-3500, ±20. ^b s = strong; m = medium; sh = shoulder.

Preliminary biological tests indicate that the octahydro compounds of the racemic series do not possess any appreciable androgenic activity.¹⁸

Summary

The partial hydrogenation of diethylstilbestrol gives a complex mixture of products. The alkali soluble portion contains mainly two racemic octahydro compounds along with traces of the two dihydrodiethylstilbestrol isomers.

(18) The biological results will be reported elsewhere.

dl-r- (*p*-Hydroxyphenyl) - 4 - (4^t-hydroxycyclohexyl)-hexane has been isolated from the alkali soluble material and its structure has been established. The remaining mixture of *cis*- and *trans*-

isomers appears to be resistant to the usual methods of separation. It contains small amounts of isomers belonging to the meso series.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE]

Oxidation-Reduction Potentials of Thiol-Disulfide Systems. II. Dithiobiuret-3,5-Diimino-1,2,4-dithiazoline

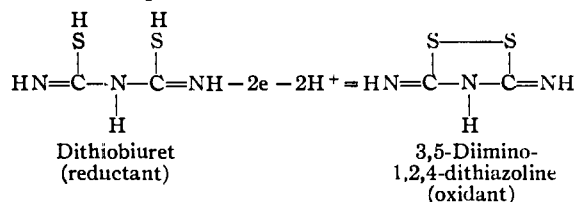
BY PAUL W. PREISLER AND MARGARET M. BATEMAN

The activation of certain enzymes by the formation or liberation of the thiol (—SH) groups of the enzyme molecule or their inactivation by alteration or blocking of these groups has been indicated in the recent literature.

Since the reduction of (—SS—) to two (—SH) is a possible mode of activation and the reverse oxidation a possible mode of inactivation, the oxidation-reduction potentials of these components of the enzyme molecule or the potentials of the reagents which react with them are of interest.

The measurement of the simpler systems involving (—SH) and (—SS—) has been undertaken as one approach to the study of the mechanism of such reactions. A further aim is to establish a graded series of reagents which might be useful for such studies.

The following simple type system is the first to be reported which involves the opening and closing of a ring structure as part of the oxidation-reduction equilibrium.



The potentials, within the pH range studied, are stable and follow the equations applicable to systems of the type: reductant - 2 H⁺ = oxidant. The relatively low position of the system on the oxidation-reduction scale ($E_0' = +0.251$ at pH 0 and $E_0' = +0.102$ at pH 5) indicates that dithiobiuret is a moderately strong reducing agent and suggests its use for this purpose.

Experimental

The oxidation-reduction potential apparatus and procedure generally used for such measurements were employed. The potentials of platinum wire electrodes immersed in the test solution were measured against a saturated potassium chloride calomel half-cell connected by a saturated potassium chloride-4% agar bridge. A Leeds and Northrup Type K potentiometer and a No. 2420-C galvanometer were used. Liquid junction potentials were considered negligible. The electrode, vessel and calomel cell were kept in a water-bath at 30° and the test solution was deoxygenated and stirred with cylinder nitrogen gas previously purified by passing over hot copper

The recorded potentials have been converted into E_h values (normal hydrogen electrode taken as zero). The potentials of the two electrodes usually were within 0.0001 volt and, after the first two minutes allowed for mixing and reaction, did not change more than 0.0002 in thirty minutes.

The materials and solutions were prepared from commercial analytical grade reagents.

Dithiobiuret¹ was recrystallized from hot 0.01 *N* hydrochloric acid. At this acidity the slight amount of oxidized product formed by air oxidation remains in solution and does not decompose significantly into sulfur and other undesired products. Analysis of the material showed: N, 30.5, 30.7; calculated, 31.1.

3,5-Diimino-1,2,4-dithiazoline, the oxidation product of dithiobiuret was isolated as the hydrochloride. Twenty-five grams of recrystallized dithiobiuret was suspended in 350 cc. of *N* hydrochloric acid. While cooling in an ice-bath, 21.5 cc. of 30% hydrogen peroxide was added dropwise and stirring was continued for about a half-hour or until, by microscopic examination, all of the needle-like crystals of dithiobiuret had disappeared and only the granular crystals of the oxidation product hydrochloride were present. These were filtered off by suction, washed with cold *N* hydrochloric acid, acidified ethanol, ethanol, and finally ether. The 5% water remaining after drying over calcium chloride was removed by heating at 110° for about two hours. Analyses showed: N, 24.4, 24.4; Cl, 21.1, 21.0; calculated N, 24.7; Cl, 20.9, indicating the monohydrochloride, C₂H₄N₃S₂Cl.

Ceric or thallic sulfate solutions in sulfuric acid were prepared from the corresponding oxides and standardized. Formamidine disulfide solutions in *N* hydrochloric acid were prepared from weighed amounts of the di-trichloroacetate.

The pH of the acid solutions or buffers were calculated from their corresponding quinhydrone electrode potentials. Their composition, within 1% accuracy, was as follows: pH 0.05—1 *N* HCl; pH 0.73—0.2 *N* HCl, 0.8 *M* KCl; pH 1.32—0.05 *N* HCl, 0.95 *M* KCl; pH 1.99—0.1 *N* HCl, 0.1 *M* glycine, 0.9 *M* KCl; pH 2.60—0.06 *N* HCl; 0.14 *M* glycine, 0.94 *M* KCl; pH 3.36—0.02 *N* HCl, 0.18 *M* glycine, 0.98 *M* KCl; pH 3.97—0.16 *N* HAc, 0.04 *M* KAc, 0.96 *M* KCl; pH 4.58—0.1 *N* HAc, 0.1 *M* KAc, 0.9 *M* KCl; pH 5.19—0.04 *N* HAc, 0.16 *M* KAc, 0.84 *M* KCl.

Quantitative solutions of the reductant or oxidant were made with deoxygenated solvents and protected by the passage of a stream of purified nitrogen. Moderate heating was usually necessary to facilitate solution of the reductant.

Calculations

The mathematical equations applicable to the potentials of the system may be developed in the conventional manner² from the fundamental electrode equations.

(1) Obtained through the courtesy of the American Cyanamid Company, 30 Rockefeller Plaza, New York 20, N. Y.

(2) W. M. Clark and B. Cohen, U. S. Public Health Repts., **38**, 670 (1923); **40**, 1158 (1925).