chloride was dissolved in 75 ml. of benzene, and this solution was added to a solution of 10.4 g. (0.075 mole, plus 10%) of freshly distilled dimethyl sulfate in 25 ml. of benzene, with mild cooling in water. After 1.5 hours stirring at room temperature, the mixture was heated just to refluxing to dissolve the precipitate, and the white crystals (40 g.) which formed on cooling were collected on a filter and recrystallized from 100 ml. of benzene. The yield was 36.0 g. (70% calculated from lead chloride), m.p. 137–138°.

Anal. Calcd. for $C_{27}H_{37}O_4NSPb$: Pb, 30.5; S, 4.7. Found: Pb, 30.2; S, 4.9.

This derivative was very soluble in methanol or ethanol, soluble in hot benzene, insoluble in cold benzene or in petroleum ether. It was very soluble in water. A sample of the solid moistened with even a few drops of water passed into a clear solution which foamed on shaking. The *p*H of a solution of 5 g. of the material in 100 ml. of water was 5.7 immediately after preparation, 6.9 after 4 days, and 7.2 after 11 days. After 3 months this solution showed no precipitate.

Methyl Sulfate Derivative from Triphenyl-*p*-dimethylaminophenyllead.—Triphenyl-*p*-dimethylaminophenyllead,[6] 8.4 g. (0.015 mole), in 25 ml. of benzene was added rapidly with shaking to 1.9 g. (0.015 mole plus 10%) of dimethyl sulfate in 10 ml. of benzene. After one hour at room temperature and 20 minutes under reflux, the product precipitated as a bulky solid, which was filtered out, washed with ether, and recrystallized from ethanol. The yield was 3.5 g. (34%) of white, pearly, very fine fibers or needles, m.p. 241–243°. The solubility in water was less than 0.1 g. per 100 ml., although the material nevertheless caused foaming when shaken with water.

Anal. Calcd. for $C_{28}H_{31}O_4NSPb$: S, 4.7; Pb, 30.3. Found: S, 4.6; Pb, 29.8.

Diphenyl-γ-diethylaminopropyllead Chloride Hydrochloride.—Triphenyl-γ-diethylaminopropyllead, 30.0 g., was dissolved in 20 ml. of ether and washed twice with 100-ml. portions of cold 5% aqueous hydrochloric acid. The oil which formed was withdrawn with the aqueous layers, and the combined aqueous layers were shaken until crystallization of the oil was complete (about 30 minutes). The product was filtered out and recrystallized from 450 ml. of 95% ethanol; yield 18.2 g. (61%).

Anal. Calcd. for $C_{19}H_{27}NCl_2Pb$: Cl, 12.9; Pb, 37.8. Found: Cl, 12.9; Pb, 38.0.

Heated in a capillary tube, this material gradually turned brown, but did not melt up to 240°.

This preparation was repeated several times, always with essentially the same result.

Of this product, 1.1 g. (0.002 mole), was suspended in 35 ml. of ether and cooled in ice while 0.004 mole of phenyllithium in ether was added with stirring. After 20 minutes refluxing, the mixture was worked up, and gave as product a yellow oil. This was treated with 1 g. of dimethyl sulfate in benzene, and there resulted 0.4 g. of white solid, m.p. 139–140°, which did not depress the melting point of a sample of the methyl sulfate derivative of triphenyl-γ-diethylaminopropyllead.

In a similar way, a reaction was carried out between diphenyl-γ-diethylaminopropyllead chloride hydrochloride (5.5 g., 0.01 mole) and ethylmagnesium bromide (0.02 mole, plus 10%). The product was again an oily liquid, and could not be caused to crystallize. It was dissolved in ether and treated in a separatory funnel with two portions of cold 5% hydrochloric acid. As in the case of triphenyl-γ-diethylaminopropyllead, an insoluble layer separated immediately, and this was withdrawn with the water layer. In this case, the product would not crystallize on cooling, shaking, scratching, or standing in the refrigerator.

A corresponding reaction was carried out between diphenyl-γ-diethylaminopropyllead chloride hydrochloride and benzylmagnesium chloride. The oily product from this reaction was divided into portions which were treated, respectively, with methyl iodide, dimethyl sulfate or 5% hydrochloric acid. None of the products were crystalline.

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Palladium Catalysis. IV.[1] Change in the Behavior of Palladium-on-Charcoal in Hydrogenation Reactions[2]

BY WALTER H. HARTUNG AND YEN-TSAI CHANG[3]

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During the past 18 years there developed a change in the qualitative behavior of palladium-on-charcoal catalysts which has been difficult to demonstrate convincingly. Previous results, for example, with α-oximino ketones showed that when three moles of hydrogen was taken up practically quantitative yields of the corresponding amino alcohol were formed; or if two moles of hydrogen was taken up, practically pure amino ketone was formed. Now with catalysts similarly prepared from pure palladium chloride, α-oximinopropiophenone takes up about two moles of hydrogen, but the product consists of approximately equal amounts of amino alcohol and oximino alcohol. The addition of platinum or rhodium to the palladium gives catalysts which, judging by results, somewhat approximate those employed earlier. α-Oximinopropiophenone reduced in alkaline medium forms good yields of amino alcohol.

It has been impossible until now to confirm by convincing experiments the suspicion, which developed shortly after the last paper in this series was published,[1] that the character of hydrogenation reactions in which palladium-on-charcoal was employed was changing. This has now been shown for α-oximinopropiophenone, and the results with this compound lend support to the belief that it may be true in other respects also.

The conversion of α-oximino ketones of structure Ar–CO–CR:NOH with palladium catalysts to the corresponding physiologically active amino alcohols, Ar–CHOH–CHR–NH_2, has become an accepted procedure.[4,5] If the Ar group is phenyl or tolyl the amino alcohol is formed directly unless the reaction is stopped earlier; at 2 moles of hydrogen, practically pure almost quantitative yields of amino ketone are formed. If the aromatic portion is substituted with hydroxyl or alkoxyl the reaction stops at the amino ketone, which may then be further hydrogenated with fresh catalyst in aqueous solution to the amino alcohol. It is to be stressed here that when two molar equivalents of hydrogen was taken up and the reaction was carried out in acidic medium only the amino ketone was identified

(1) For no. III see W. H. Hartung and F. S. Crossley, THIS JOURNAL, **56**, 158 (1934).

(2) The authors are grateful to Sharp and Dohme for a grant to the North Carolina Pharmaceutical Research Foundation for assistance in these studies.

(3) Fellow, American Foundation for Pharmaceutical Education, 1948–1951.

(4) W. H. Hartung, J. C. Munch and others, THIS JOURNAL, **51**, 2262 (1929); **53**, 4149 (1931).

(5) R. Baltzly and J. S. Buck, *ibid.*, **62**, 164 (1940).

among the products; in neutral solvent poor yields of oximino alcohol were isolated.[6]

In the recent studies of the probable mechanism by which α-oximino ketones are converted into a single racemic modification of the amino alcohol, Chang and Hartung[7] employed pure palladium chloride for preparing catalysts.[8] It was now found that, even in the usual ethanolic hydrogen chloride solvent, although 1.8 to 2.2 moles of hydrogen was taken up, the product was not the expected practically pure amino ketone hydrochloride, which has heretofore been obtained, but consisted of approximately equimolar amounts of oximino alcohol and amino alcohol, for the production of which 2 moles of hydrogen is required.

It may be argued that in the early experiments the presence of the oximino alcohol, Ar–CHOH–CR:NOH, was overlooked, for it, too, might be a likely intermediate stage in the reduction of oximino ketones to amino alcohols. However, experiments show that the oximino alcohol is resistant to further hydrogenation in the presence of fresh catalysts, stronger catalysts or even catalysts to which promoters have been added. Hence it is unlikely that this intermediate was overlooked in the earlier work.

In the past 20 years there has also been a change in the properties of the charcoal available as carrier for these catalysts. Evidence thus far shows that the character of the carrier has a marked effect on the course of the hydrogenation reaction. These studies are not yet complete but thus far they give no indication that the carrier is responsible for the change reported here.

Laboratory representatives of the suppliers reluctantly concede that the palladium salts available 20 years ago may not have been so pure as now. To us, unfamiliar with the technology of the platinum metals, it seemed not unreasonable that traces of other metals may have been present, and a study of their effects was indicated. α-Oximinopropiophenone was used as the substrate.

Osmium was not tried since it showed inhibitory effects when used with palladium on other substrates. Iridium also showed adverse effects. The results with ruthenium were not clear cut. Platinum with palladium was encouraging, forming good yields of amino alcohol, although in some experiments appreciable amounts of oximino alcohol were still obtained; and if the catalyst was used a second time the ratio of oximino alcohol was larger. When rhodium was used with palladium the reduction never went completely to the amino alcohol; but it is surprising that when the catalyst was used a second time, or if the reaction with a fresh catalyst was interrupted when 2 moles of hydrogen was taken up, the product was substantially pure amino ketone hydrochloride and contained no detectable amounts of oximino alcohol.

The reduction of 1,3-diphenyl-2-oximino-1-propanone reveals an analogous pattern, as described in the experimental portion.

The hydrogenation of α-oximino ketones in alkaline medium has been deliberately avoided until now for it was believed, in the light of previous results, that the route to the amino alcohol proceeded always *via* the amino ketone intermediate, and free α-amino ketones readily cyclize into dihydropyrazines. It is now found that good yields of amino alcohols may be obtained in alkaline medium. The results for two substrates are given under the experimental portion.

Experimental

Catalysts.—The general method of preparing the catalysts has already been described.[9] For the present studies the catalyst was prepared from 2 g. of Nuchar, 200 mg. of pure $PdCl_2$, the metal being deposited on the carrier from a solution containing 10 g. of hydrated sodium acetate.[10] When other metals were added, the addition was in the form of solutions of their chlorides, in which the following molar ratios were employed: Pd:Pt::100:1.45, Pd:Rh::100:1.4, Pd:Ru::100:1.3.

Reduction of α-Oximinopropiophenone (Recent Experiments) (i).—A solution of 16.3 g. of α-oximinopropiophenone[11] (0.1 mole), in 100 ml. of 3 *N* absolute ethanolic HCl was shaken on the Parr apparatus with 2 g. of Pd–C "acetate" catalyst at an initial hydrogen pressure of 4 atm. Reduction stopped when 0.214 mole of hydrogen was taken up, in about 1 hour. The catalyst was removed, washed with 100 ml. of water; filtrate and washings were combined, and the *p*H adjusted to about 5 by addition of 20% NaOH solution, then concentrated under reduced pressure to about 100 ml., cooled and extracted with three 100-ml. portions of ether. The solvent from the ethereal extract was volatilized, leaving a residue which, purified by crystallization from water, formed colorless crystals, m.p. 112°, soluble in alcohol and ether; it was identical with the oxime of phenylacetylcarbinol, previously obtained by reduction of the oximino ketone in neutral solution.[6] The aqueous layer, *p*H 5, was made alkaline and extracted with three 100-ml. portions of ether; volatilization of the ethereal solvent gave a basic residue weighing 8.5 g., which was the amino alcohol. During the isolation of these products there was always formed some colored, tarry material; it is possible that this had its origin in amino ketone, which is unstable as free base. The general character of these reductions was not changed by employing dilute ethanolic HCl or glacial acetic acid as solvents.

(ii).—A tenth mole of α-oximinopropiophenone in 100 ml. of 3 *N* absolute ethanolic HCl reduced with 2 g. of the Pd–Pt-on-C "acetate" catalyst took up 0.28 mole of hydrogen in 25 minutes; the yield of purified amino alcohol was 11.2 g., 74%. When the catalyst was used a second time, reduction stopped after about 25 minutes, after taking up 0.213 mole of hydrogen; from the product there was isolated 4.3 g. of oximino alcohol and 7.5 g. of amino alcohol. Some Pd–Pt catalysts, even when used for the first time, gave lower yields of amino alcohol, and a by-product of oximino alcohol was isolated.

(iii).—A tenth mole of α-oximinopropiophenone reduced with 2 g. of Pd–Ru catalyst took up 0.212 mole of hydrogen in less than half an hour. The product was not pure; from it was isolated 6.7 g. of purified norephedrine; the by-product was not identified, but it exhibited the properties of oximino alcohol. The formation of oximino alcohol is indicated also by the fact that such a high yield of amino alcohol was formed although only slightly more than 2 molar equivalents of hydrogen was absorbed.

(6) W. H. Hartung, *ibid.*, **53**, 2248 (1931).

(7) Y. T. Chang and W. H. Hartung, in press.

(8) The palladium chloride used for these studies is graciously supplied by the American Platinum Works, Newark. Mr. F. A. Meyer of that Company states that the material is the purest he ever prepared; that its method of preparation permits only gold to be present but that the test for it is negative. The same Company also supplied the chlorides of platinum, iridium, ruthenium and rhodium.

(9) W. H. Hartung, THIS JOURNAL, **50**, 3370 (1928).

(10) The favorable effect of sodium acetate solution in preparing palladium-on-charcoal catalysts was observed by Reeve and Hartung (unpublished, 1935) and its use has been recommended a number of times; see, for example, (a) E. R. Alexander and A. C. Cope, *ibid.*, **66**, 888 (1944), note 7; (b) R. Mozingo, *Org. Syntheses*, **26**, 77 (1946), method D.

(11) Supplied through courtesy of Dr. James M. Sprague of Sharp and Dohme.

(iv).—A tenth mole of α-oximinopropiophenone in 100 ml. of 3 *N* absolute ethanolic HCl in the presence of 2 g. of Pd–Rh catalyst took up 0.272 mole of hydrogen in 40 minutes, and 0.0729 mole of purified amino alcohol was isolated. When this catalyst was used a second time, 0.200 mole of hydrogen was taken up in about 2 hours; and from the product was isolated 0.069 mole of the hydrochloride of α-aminopropiophenone. Other reductions with fresh Pd–Rh catalyst did not give such good yields of amino alcohol. For example, in one experiment 0.200 mole of hydrogen was absorbed in 90 minutes, and it was possible to isolate 0.080 mole of amino ketone hydrochloride. However, in none of these reductions was oximino alcohol isolated.

(v).—A solution of 16.3 g. (0.1 mole) of α-oximinopropiophenone in 100 ml. of 5% ethanolic NaOH was hydrogenated in the presence of 2 g. of Pd "acetate" catalyst; 0.265 mole of hydrogen was taken up in about 75 minutes. The catalyst was removed and washed; filtrate and washings were made neutral to congo red by the addition of HCl and evaporated to dryness. The residue was taken up in 150 ml. of water and filtered to remove insoluble material and then the solution was made strongly alkaline with 20% NaOH and extracted with ether. The residue after removal of the ether weighed 12.3 g. (80%); crystallization from 100 ml. of benzene gave 10.1 g. (66.9%) of pure norephedrine.

Reduction of 1,3-Diphenyl-2-oximino-1-propanone[12] (i).—Twelve grams of the oximino ketone (0.05 mole) in 100 ml. of 1.5 *N* absolute ethanolic HCl was hydrogenated with 2 g. of Pd catalyst. After 45 minutes reduction ceased, when 0.082 mole of hydrogen had been absorbed. In the reaction mixture considerable crystallization had taken place. All the solid was collected on a buchner funnel, and the crystals were removed from the charcoal by extracting with 100 ml. of boiling water. The filtrate and washing were combined and evaporated to dryness on a water-bath and under reduced pressure. The residue was dissolved in 200 ml. of boiling water; on cooling an oil separated out, which later crystallized, forming a greenish mass weighing 7.5 g. Recrystallized from alcohol, it formed a colorless product, m.p. 114–116°, which contained neither halogen or nitrogen; it formed a semicarbazone, m.p. 188–189°. The product was identified as 1,3-diphenylpropan-1-ol-2-one, previously prepared by Stoermer and Tier[13] who report the keto alcohol m.p. 116–117°, and its semicarbazone m.p. 189–190°. The precursor of this compound is presumably the oxime, which is hydrolyzed either during the hydrogenation reaction or the isolation process. Addition of 15 ml. of concd. NH_3 to the aqueous solution liberated a base, which was extracted with ether; yield 2.5 g., m.p., 117–118°; calcd. for $C_{15}H_{17}ON$: N, 6.16; found: N, 6.28, 6.35. Hydrochloride is colorless silky crystals, m.p. 185–186°; calcd. for $C_{15}H_{17}ON\cdot HCl\cdot H_2O$: N, 4.97; found: N, 4.90, 5.08.

(ii).—From a similar experiment in which 0.05 mole of oximino ketone was hydrogenated with Pd–Pt catalyst, 0.10 mole of hydrogen taken up in 45 minutes, there was isolated 3.5 g. of amino alcohol and 5.8 g. of keto alcohol.

(iii).—Twelve grams of the oximino ketone (0.05 mole) in 100 ml. of 1.5 *N* absolute ethanolic HCl hydrogenated with 2 g. of Pd–Rh catalyst took up 0.087 mole of hydrogen in about 2 hours. The product consisted of 3.3 g. of crystalline 1,3-diphenylpropan-1-ol-2-one and 7.4 g. of the hydrochloride of 1,3-diphenyl-2-amino-1-propanone, m.p. after three crystallizations from alcohol, 225–226° (dec.). Amino ketone hydrochloride: calcd. for $C_{15}H_{15}ON\cdot HCl$: N, 5.38; found, N, 5.48 and 5.26. Further reduction of the amino ketone hydrochloride in aqueous solution with Pd catalyst formed the amino alcohol.

(iv).—Twelve grams of the oximino ketone dissolved in 100 ml. of 2.5% ethanolic NaOH hydrogenated with Pd catalyst absorbed 0.154 mole of hydrogen. The catalyst was removed, the filtrate and washings were diluted with 50 ml. of water and the solution made acid to congo red and evaporated to dryness; the residue was taken up in water, filtered and basified, thus liberating a quantitative yield of amino alcohol which, recrystallized from benzene, gave 8.8 g. (77.5%) of 1,3-diphenyl-2-amino-1-propanol, m.p. 118°.

(12) This oximino ketone prepared by the regular nitrosation[14] of 1,3-diphenylpropanone, recrystallized from benzene, formed white crystals, m.p. 126–127°. It is known from the work of W. Schneidewind, *Ber*, **21**, 1326 (1888).

(13) R. Stoermer and C. Tier, *ibid.*, **58**, 2613 (1925).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC.]

Hydrogenation of $\Delta^{5,7}$-Sterol Derivatives

BY W. V. RUYLE, E. M. CHAMBERLIN, J. M. CHEMERDA, G. E. SITA, L. M. ALIMINOSA AND R. L. ERICKSON

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A smooth, generally applicable method for the hydrogenation of $\Delta^{5,7}$-steroids to Δ^{7}-allosteroids with Raney nickel in benzene is described. By this procedure the isomerization of Δ^{7}-allosteroids to $\Delta^{8(14)}$-allosteroids encountered with the use of platinum and palladium catalysts is avoided and pure Δ^{7}-allosteroids are obtained in 80–90% yields.

During the course of an investigation which led to the utilization of plant steroids for the synthesis of cortisone,[1] we studied the hydrogenation of a number of steroid derivatives. As some of the procedures described in the literature were frequently inadequate with respect to reproducibility or to optimum yields, at least in our hands, we wish to report our experience in this field.

Following the procedures of earlier investigators we were unable to bring about the satisfactory hydrogenation of ergosterol acetate[2] or methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate[3] to $\Delta^{7,22}$-ergostadiene-3β-ol acetate and methyl Δ^{7}-3β-acetoxyallobisnorcholenate, respectively.[4] In practically every experiment in which platinum catalysis was used in accordance with previously described directions, the absorption of hydrogen was erratic and pure products were difficult to obtain. In the case of ergosterol acetate even when one mole of hydrogen was absorbed, a practically inseparable mixture was obtained in which considerable $\Delta^{5,7}$-diene was still present as judged from the ultraviolet absorption spectrum. Hydrogenation of methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate with one mole of hydrogen with the aid of platinum in ethyl acetate evidently afforded the same methyl Δ^{7}-3β-acetoxyallo-

(1) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951); J. M. Chemerda, E. M. Chamberlin, E. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951).

(2) I. M. Heilbron and W. A. Sexton, *J. Chem. Soc.*, 921 (1929); H. Wieland and W. Benend, *Ann.*, **554**, 1 (1943).

(3) W. Bergmann and P. G. Stevens, *J. Org. Chem.*, **13**, 10 (1948).

(4) Since the completion of our work, three reports have appeared on the hydrogenation of ergosterol and its derivatives; R. C. Anderson, R. Budizarek, G. T. Newbold, R. Stevenson and F. S. Spring; *Chemistry and Industry*, 1635 (1951); H. Heusser, K. Eichenberger, P. Kurath, H. R. Dallenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2123 (1951); G. D. Laubach and K. J. Brunings, THIS JOURNAL, **74**, 705 (1952).