Aspects of Catalytic Hydrogenation with a Soluble Catalyst

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The use of tristriphenylphosphinerhodium chloride as a soluble catalyst for hydrogenation has been further investigated, and some of its specificities have been examined in systems containing more than one double bond. Its properties include the ability to add deuterium specifically to the double bonds of cyclohexene, oleic and linoleic acids, and ergosterol without introduction of additional labelling. Some hydrogenations without hydrogenolysis have been carried out (that of ω-nitrostyrene into phenylnitroethane and of cinnamyl chloride in part into phenylpropyl chloride).

HETEROGENEOUS hydrogenation catalysts have some disadvantages. They may show lack of selectivity when more than one double bond is present, including the production of 1,2- and 1,4-dihydro-derivatives from conjugated dienes; they may cause double-bond migration, and they usually cause allylic interchanges with deuterium, resulting in unspecific labelling. With 1,4-dihydrobenzenes they usually cause disproportionation rather than hydrogenation, and stereochemistry, despite a number of rules, is difficult to predict since it depends on chemisorption and not on reactions between molecules.

Some at least of the difficulties might be overcome by a soluble catalyst which acts as a single molecular donor of a hydrogen molecule. A possible catalyst is tristriphenylphosphinerhodium chloride, whose catalytic properties were first described by Wilkinson and his coworkers.[1] It does not appear to have been examined from the point of view of preparative organic chemistry, and we have used it with some olefins of interest in connection with other work, particularly with a view to obtaining specifically deuterated substances.

Cyclohexene, which was readily hydrogenated, after reaction with deuterium gave a dideuterocyclohexane, presumably the 1,2-compound, shown by mass spectrometry to contain no extra deuterium. Methyl oleate gave methyl stearate containing only two deuterium atoms, presumably the 9,10-dideutero-compound, and methyl linoleate a tetradeutero-derivative, presumably 9,10,12,13; in each case the number of deuterium atoms in the product was defined by mass spectrometry. Ergosterol gave, on hydrogenation, the 5α,6-dihydro-derivative, and, on deuteration, a dideutero-derivative (mass spectrum), presumably the 5,6-compound. Neither the 7- nor the 22-double bond was affected. Deuteration may well be stereospecific, in this case 5α,6α, but attempts to confirm this by examination of the n.m.r. spectrum failed because of its complexity. The situation is being further examined in a number of steroids.

A double bond in the 1-position of a steroidal 1,4-dien-3-one was specifically reduced, leaving the 4-en-3-one structure. A 4-en-3-one could, however, be hydrogenated, although more slowly; testosterone gave eventually the 4,5α-dihydro-derivative. Hydrogenation of pregna-5,16-dien-3β-ol-20-one acetate gave pregnenolone acetate in very good yield; the 16-double bond is specifically and rapidly reduced.

(+)-Carvone (I) was rapidly and specifically hydrogenated on the isopropylidene group, giving carvotanacetone. Geraniol (II) and its *cis*-isomer, nerol, were examined to determine whether selective hydrogenation of a double bond could be accomplished. The reaction began rapidly, but soon slowed, and a yellow crystalline substance was isolated, identified as bistriphenylphosphinerhodium carbonyl chloride. This abstraction of carbon monoxide occurred very rapidly from the corresponding aldehyde, citral, which consequently could not be hydrogenated. Similar loss of carbon monoxide from aldehydes has been observed [2] by other workers; possibly the allylic nature of the geraniol facilitates the process here. The hydrogenated products from both geraniol and nerol showed hydrogenation of both double bonds (n.m.r.) in the ratio of 1·7—1·8 for the 2- compared with the 6-position. Neryl acetate showed a similar lack of specificity, but could be converted eventually without loss of carbon monoxide into 3,7-dimethyloctyl acetate.

Linalool (III) was hydrogenated selectively on the vinyl group, to give the 1,2-dihydro-derivative at least 96·5% pure. Dehydrolinalool, the acetylenic analogue, was converted with 1 mol. of hydrogen into a mixture of linalool (50%), dihydrolinalool (25%), and unchanged material (25%). The acetylenic bond was therefore reduced only to a slighly greater extent than the ethylenic one.

Some cyclohexa-1,4-dienes were hydrogenated without disproportionation. The compound (IV), kindly supplied by Mr. K. S. J. Stapleford, was converted into its tetrahydro-derivative with 2 mol. of hydrogen. 1-Methoxycyclohexa-1,4-diene absorbed 1 mol. of hydrogen, and the product gave rise to pure cyclohexanone 2,4-dinitrophenylhydrazone. However, it was only partly the expected 1-methoxycyclohexene, and contained some ketal produced by reaction with ethanol in the solvent. Repetition in pure benzene gave a mixed product containing 1-methoxycyclohexene and cyclohexanone (about 25%); the reason for this "hydrolysis" is not clear. However, the yield of cyclohexanone 2,4-dinitrophenylhydrazone was 95%, and there is no doubt that no disproportionation had occurred, and that the

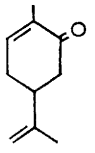
[1] J. W. Young, J. A. Osborn, F. H. Jardine, and G. Wilkinson, *Chem. Comm.*, 1965, 131.

[2] J. Tsuji, K. Ohno, *Tetrahedron Letters*, 1965, 3969; M. C. Baird, D. N. Lawson, J. T. Mague, J. A. Osborn, G. Wilkinson, *Chem. Comm.*, 1966, 129.

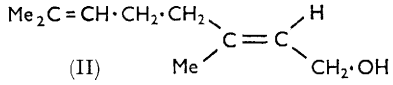
unsubstituted double bond alone had been hydrogenated. In view of the much higher activity of the enol ether double bond to electrophilic attack, either the reagent is nucleophilic or it is dominated by the steric factor, a likely possibility in view of its bulk. The enol ether 2,3-dihydropyran was readily hydrogenated, so this structure is not itself inhibitory; 1-methoxy-5-methylcyclohexa-1,4-diene reacted some forty times more slowly than the compound lacking the methyl group, although the product was eventually 3-methylcyclohexanone. Substitution is therefore inhibitory but methyl is less effective than methoxyl.

In contrast to hydrogenation of the conjugated system of ergosterol, that of α-phellandrene (5-isopropyl-2-methylcyclohexa-1,3-diene) did not occur. The result seemed surprising, so another complex diene, thebaine, was examined and found to be hydrogenated readily on the conjugated bond adjacent to the enol ether, to give, in 77% yield, 8,14-dihydrothebaine (V), identified by mass spectrometry and n.m.r. spectrum. This contrasts with previously recorded hydrogenations, which have given mixtures containing tetrahydrothebaine and dihydrothebaine. The phellandrene result may be due to stable complex formation with the diene. Indeed, the failure of the 5-double bond in cholesterol to be hydrogenated, compared with the reaction of the 5-double bond of the 5,7-diene system of ergosterol, suggests that conjugation assists the process in more complex molecules.

A reagent which can hydrogenate double bonds without hydrogenolysis of other groups would have wide applications. Benzyl bromide was found to be unaffected, so cinnamyl chloride was examined. After



(I)



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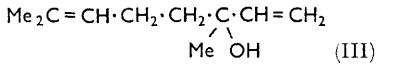

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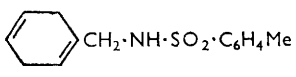

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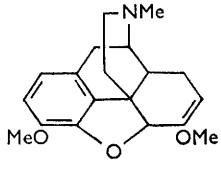

(V)

uptake of about 1 mol. of hydrogen, the total product, examined by n.m.r., was found to be a mixture of phenylpropyl chloride (38%), propenylbenzene (35%), propylbenzene (19%), and starting material (10%). Although experimentally unsatisfactory, the result is of interest in showing that the reaction goes to some extent in the desired direction. It is even more interesting that ω-nitrostyrene was hydrogenated to phenylnitroethane.

EXPERIMENTAL

The Process.—The catalyst was prepared [1] by refluxing rhodium chloride trihydrate (1 g.) and triphenylphosphine (6 g.) in ethanol (120 ml.). The tristriphenylphosphine-rhodium chloride (3·5 g.) was filtered off and washed with ethanol and with ether.

All reactions were carried out at atmospheric pressure and temperature in a normal hydrogenator. The solvent was AnalaR benzene unless otherwise indicated. Catalyst of about 10—20% of the weight of the compound being hydrogenated was employed, with 20 ml. of solvent for 100 mg. of catalyst. Cyclohexene was used to test the catalyst; it was normally hydrogenated within 15 min., after a brief induction period. Although the initial catalyst is insoluble in ethanol or ether, the hydrogenated catalyst is soluble, and is best removed by distillation of the product in the case of volatile compounds, or filtration in ether through alumina or Florisil.

Products of Hydrogenation.—Cyclohexene was treated with deuterium (98%) and the solution used directly in the mass spectrometer; the parent peak (14 ev) at *m/e* 86 for dideuterocyclohexane was unaccompanied by higher or lower peaks due to incorporation of 1 or 3 deuterium atoms. At higher voltages lower peaks were noted due to hydrogen loss.

Methyl oleate (500 mg.) reacted readily with deuterium to give methyl 9,10-dideuterosterate (500 mg.), purified on Florisil with benzene as eluant. The parent peak (*m/e* 300) was accompanied by minor peaks at 301 and 302 of the same relative intensities as those in the product obtained by hydrogenation.

Methyl linoleate (500 mg.) was deuterated as above to methyl 9,10,12,13-tetradeuterostearate (443 mg.) (*m/e* 302, again with negligible higher peaks).

Ergosterol rapidly took up 1 mol. of hydrogen. The 5α,6-dihydroergosterol, m. p. 173—174°, acetate m. p. 176—178° (lit.,[3,4] 174 and 174·6—177·4°, respectively), $[\alpha]_D$ −17·8° (lit.,[3] −20°), was obtained in 68% yield after two crystallisations. It showed no ultraviolet absorption above 230 mμ. Deuteration similarly gave 5α,6(α?)-dideuteroergosterol, m. p. 172—174·5° (from methanol–chloroform), *m/e* 400.

17α,21-Dihydroxypregna-1,4-diene-3,20-dione 21-acetate (100 mg.) and catalyst (100 mg.) took up 1 mol. of hydrogen in 3 hr. The product crystallised from acetone to give 17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate (56 mg.), m. p. 236—240°, $\nu_{max.}$ 1749, 1720, 1657, and 1617 cm.$^{-1}$, *m/e* 388 (lit.,[5] m. p. 236—238°); the n.m.r. spectrum was in agreement with the assigned structure.

Testosterone (500 mg.) was hydrogenated for 5 days. Chromatography and recrystallisation gave 17β-hydroxy-5α-androstan-3-one (268 mg.), m. p. 176—178°, *m/e* 290, $\nu_{max.}$ 1715 cm.$^{-1}$ (lit.,[6] m. p. 178°).

Pregna-5,16-dien-3β-ol-20-one acetate (400 mg.) was allowed to react for 3 days. The resulting pregnenolone acetate was recrystallised twice from hexane, rods (354 mg., 88%), m. p. 146·5—147·5° (lit.,[6] m. p. 146—147°, $\nu_{max.}$ 1730, 1702, and 1236 cm.$^{-1}$).

(+)-Carvone hydrogenation practically ceased after absorption of 1 mol.; the product showed loss of $=CH_2$ ($\nu_{max.}$

[3] Fieser and Fieser, "Steroids," Reinhold, New York, 1957 p. 112.
[4] G. D. Landbach and K. J. Brunings, *J. Amer. Chem. Soc.*, 1952, **74**, 705.
[5] K. Miescher and J. Schmidlin, *Helv. Chim. Acta*, 1950, **33**, 1840.
[6] I. Heilbron, H. M. Bunbury, "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1953.

895 cm.$^{-1}$) and the presence of only αβ-unsaturated ketone (1675 cm.$^{-1}$).

Geraniol (1·0 g.) and catalyst (95 mg.) were shaken in benzene–ethanol (3 : 2) for 2 days under hydrogen, uptake being 0·85 mol. Evaporation, removal of the rhodium carbonyl derivative, and distillation gave an oil (653 mg.). Nerol similarly took up 0·7 mol.; neryl acetate after 24 hr. had taken up 1·31 mol., and after 2 days no olefinic material could be recognised from the n.m.r. spectrum. The n.m.r. spectra of geraniol and nerol contain a multiplet τ 4·5—5·2 due to vinylic protons, and a doublet at 6·04 (2H) and a singlet due to CH_2·OH. In the reduced products the doublet was partly replaced by a triplet at 6·48, one peak of which coincided with the OH proton; the degree of hydrogenation was calculated by comparing the areas under the doublet and triplet. The neryl acetate hydrogenation product was examined similarly.

Linalool (1·0 g.) and catalyst (100 mg.) took up 1 mol. of hydrogen in 260 min., and the product was chromatographed on Florisil in ether, and distilled. The product (804 mg.) showed complete absence of vinylic protons in its n.m.r. spectrum but an extra Me at τ 9·14 and one major peak on g.l.c.; a minor one corresponded to about 3·5% of another compound. Dehydrolinalool was treated similarly. The mixture was analysed by examining the relative intensities of the proton absorption due to the acetylenic proton at τ 7·72, a quartet at 4·14 due to linalool, and a triplet at 9·4 due to the new Me in dihydrolinalool.

Citral (1·00 g.) and catalyst (500 mg.) in 2 : 1 benzene–ethanol (40 ml.) was shaken with hydrogen for 20 min. The solvent was removed, ethanol (10 ml.) added, and the product (356 mg., 95%) filtered off and recrystallised from benzene. The bistriphenylphosphinerhodium carbonyl chloride, m. p. 179·5—180·5°, was identical with an authentic specimen. The same product was obtained in the absence of hydrogen after 18 hr.; n-butyraldehyde gave similar results.

2,5-Dihydrobenzylamine toluene-*p*-sulphonate (400 mg.) took up 2 mol. of hydrogen in 8·5 hr.; the benzene solution was passed through Florisil, and the product eluted with ether. The resulting cyclohexylmethylamine toluene-*p*-sulphonate crystallised from hexane, m. p. 79—80° (369 mg.), *m/e* 267. The n.m.r. spectrum agreed with that expected for the product and showed predictable differences from that of the starting material, in particular olefinic resonances at τ 4·35 and allylic resonances at 7·43 had disappeared, and that due to CH_2N became a triplet, reconverted into a doublet by D_2O.

1-Methoxycyclohexa-1,4-diene took up 0·85 mol. of hydrogen and the reaction stopped. The product after distillation at 14 mm. (bath 40°) (700 mg.) had $\nu_{max.}$ 1664 cm.$^{-1}$, and gave rise to cyclohexanone 2,4-dinitrophenylhydrazone, m. p. 160—160·5°. The n.m.r. spectrum showed resonances due to OMe at τ 6·96 and to OEt at 6·54 and 8·88. Lack of a band at 1715 cm.$^{-1}$ indicated absence of cyclohexanone. In ethyl acetate or in pure benzene the product was similar, except for a cyclohexanone band at 1715 cm.$^{-1}$. The diene (1·00 g.) after hydrogenation gave cyclohexanone 2,4-dinitrophenylhydrazone (2·394 g.), $\lambda_{max.}$ 365 mμ, after chromatography on alumina. Before hydrogenation the diene (1·00 g.) gave cyclohex-2-enone 2·4-dinitrophenylhydrazone (2·392 g.).

1-Methoxy-5-methylcyclohexa-1,4-diene (1·00 g.) took up 1 mol. in 91 hr. The product, $\nu_{max.}$ 1714, 1670, and 1225 cm.$^{-1}$, gave 3-methylcyclohexanone 2,4-dinitrophenylhydrazone, $\lambda_{max.}$ 365 mμ, m. p. 153—156° (lit.,[7] 155°).

Thebaine (1·00 g.) in benzene ceased to take up hydrogen 1·12 mol.) in 20 hr. Chromatography on alumina and recrystallisation from ethyl acetate gave 8,14-dihydrothebaine (771 g.), m. p. 164—164·5° (lit.,[8] 162—163°), *m/e* 313. The n.m.r. spectrum of thebaine itself contains doublets at τ 4·49 and 5·01 due to H-7 and H-8 of the diene enol ether structure, and a singlet at 4·75 due to H-5 of the –CH–O– group. The spectrum of the product shows τ 5·45 due to the remaining olefinic proton of the enol ether and that due to H-5 has moved to 5·37 (slight splitting).

Cinnamyl chloride (1·00 g.), with catalyst (100 mg.), was hydrogenated for 24 hr., and further catalyst (70 mg.) added. After 36 hr. the reaction was stopped (1·06 mol. absorbed), and the product passed through alumina and distilled. The total oil (745 mg.) was analysed by its n.m.r. spectrum; triplet at τ 6·65 (CH_2Cl in propyl chloride), doublet at 5·95 (CH_2Cl in cinnamyl chloride), triplet at 7·33 (benzyl CH_2), quartet at 8·00 (middle CH_2 in propyl chloride), doublet at 8·20 (Me of 1-phenylpropene), triplet at 9·10 (Me of phenylpropane). Quantitative estimation was possible using the bands at 5·95, 6·65, 9·10, and 8·20.

ω-Nitrostyrene (1·0 g.) was hydrogenated for 2 days, the solution passed through Florisil in benzene, and the product distilled; it was a pale yellow oil (501 mg.), identified as 2-phenylnitroethane by spectra; 1604, 1550, 1495, 1381, 752, and 698 cm.$^{-1}$; τ (CCl_4 solution) 2·79s (5H), 5·55t (2H), and 6·81t (2H).

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[7] A. I. Vogel, "Practical Organic Chemistry," Longmans, London, 1957.
[8] M. Freund, E. Speyer, and E. Guttmann, *Ber.*, 1920, **53**, 2250.