Catalytic Hydrogenations of Cyclic Imides and Anhydrides

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The carbonyl functions in phthalimide and succinimide are unaffected on attempted hydrogenation in ethyl acetate at room temperature and atmospheric pressure over platinum oxide catalyst. Hydrogenation in the imide ring in these compounds can be accomplished under such conditions if an acetyl or other acyl group is attached to the imide nitrogen atom. An important alternative reaction, competitive hydrogenolytic cleavage of the acyl group, can be eliminated by using an alkoxycarbonyl or dimethylcarbamoyl substituent. The stereochemistry of the products obtained from *N*-acylphthalimides and the effect of varying the nature of the acyl substituent on reaction rate and product composition have been determined. On the basis of these and previously reported results on the hydrogenation of a series of cyclic anhydrides under similar conditions a mechanism is proposed for the hydrogenation of cyclic imides and anhydrides.

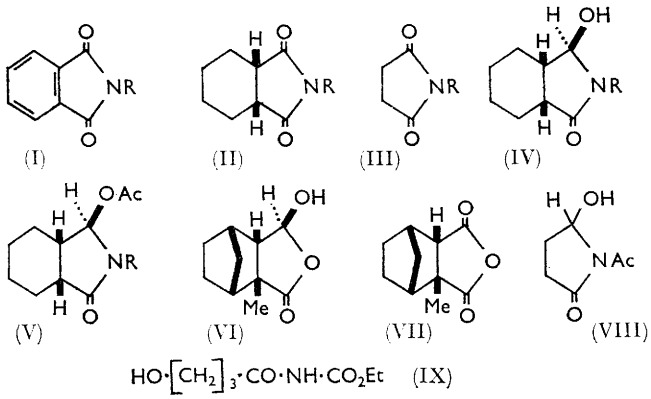
The catalytic hydrogenation of certain *N*-acylphthalimides, in ethyl acetate or ethanol at room temperature and atmospheric pressure over 10% palladium on carbon catalyst, gives the corresponding 2-acyl-3-hydroxydihydroisoindol-1-ones in high yield.

Cyclic anhydrides (CO·O·CO) hydrogenated [1] over Adams platinum oxide at room temperature and atmospheric pressure (r.t.p.) in ethyl acetate or acetic acid, take up 1, 2, or 3 mol. of hydrogen to give, respectively, the corresponding hydroxy-lactone (CH(OH)O·CO), lactone [(CH_2·O·CO), or hydroxy-acid (CH_2(OH)·HO_2C)] or acid (CH_3 and HO_2C); the nature of the product(s) obtained depends on the starting material, the solvent employed, and the reaction time. Cyclic imides bearing an electron-withdrawing group on the imide nitrogen atom can also be hydrogenated under similar conditions.[2] Here we describe work on the hydrogenation of a series of cyclic imides; the mechanism of this reaction and the related reaction of anhydrides is discussed.

Hydrogenation of various classes of carbonyl compounds reveals the following order of reactivity; acid chlorides > aldehydes, ketones > anhydrides > esters > carboxylic acids > amides.[3] As this sequence parallels the order of susceptibility to nucleophilic attack at the carbonyl function, it might be expected that imides will be less readily hydrogenated than anhydrides. Indeed, in contrast to phthalic and succinic anhydrides,[1] phthalimide (I; R = H) on attempted hydrogenation over Adams platinum oxide in ethyl acetate at r.t.p. gave only *cis*-octahydroisoindole-1,3-dione (II; R = H), while succinimide (III; R = H) was unaffected.

[1] R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1962, 4798.
[2] A. J. McAlees and R. McCrindle, *Chem. and Ind.*, 1965, 1869.
[3] See, for example, G. Lanchec, B. Blouri, and P. Rumpf, *Bull. soc. chim. France*, 1966, 3978.

N-Alkylimides undergo hydrogenation over Raney nickel (in dioxan 200—220°, 200—400 atm.) [4] to give lactams, or over copper–chromium oxide (in dioxan, 250°, 200—300 atm.) [4,5] to give cyclic amines, more readily than the *N*-unsubstituted analogues. Under our conditions, however, *N*-alkyl substitution was insufficient to promote hydrogenation at the imide carbonyl groups. Thus, hydrogenation of *N*-methylphthalimide (I; R = Me) over Adams platinum oxide in ethyl acetate gave 2-methyloctahydroisoindole-1,3-dione (II; R = Me) which led us to investigate the possibility of activating the imide carbonyl function to hydrogenation



Only relative configurations are implied throughout.

with electron-withdrawing acyl groups on the imide nitrogen atom.

Hydrogenation of *N*-acetylphthalimide (I; R = Ac), (PtO_2–ethyl acetate, r.t.p.) proceeded with the uptake of 4·25 mol. of hydrogen during 10 hr. to give two principal products (t.l.c.) which were separated by chromatography (SiO_2 gel). The minor component, identified by comparison with an authentic specimen, was *cis*-octahydroisoindole-1,3-dione (II; R = H). The i.r. spectrum of the major product, lacked aromatic absorption but had strong peaks at 3450, 1748, and 1693 $cm.^{-1}$ which suggested that it was 2-acetyl-3-hydroxyoctahydroisoindol-1-one (IV; R = Ac) and that reduction of the imide ring had taken place. This conclusion was supported by the n.m.r. spectrum in which the low-field proton (C*H*OH) appeared at τ 4·61 as a doublet (*J* 3 Hz) which collapsed to a singlet on equilibration with D_2O. The product was readily converted into the acetate (V; R = Ac) the n.m.r. spectrum of which showed the low-field proton as a singlet at τ 3·60. The absence of observable coupling between the low-field proton of 2-acetyl-3-hydroxyoctahydroisoindol-1-one, or its acetate, and the neighbouring ring-junction proton suggested a dihedral angle between them of *ca.* 90°.[6] If the stereochemistry of the ring junction in these compounds is *cis*, by analogy with the formation of *cis*-octahydroisoindole-1,3-dione on hydrogenation of phthalimide, this requirement is fulfilled only if the hydroxy or acetate group is *cis* with respect to the adjacent proton as indicated in formulae (IV) and (V). The assumption of *cis* ring-fusion is reinforced by the following: (*a*) a dihedral angle of 90° could not be accommodated in a *trans*-fused system, and (*b*) 2-acetyl-3-hydroxyoctahydroisoindol-1-one (IV; R = Ac) was also obtained on hydrogenation of 2-acetyl-*cis*-octahydroisoindole-1,3-dione (II; R = Ac) (see below). The stereochemistry shown in formulae (IV) and (V) is in agreement with that assigned [7] to the hydroxy-lactone (VI) obtained [1] by hydrogenation of the Diels–Alder adduct (VII) the entering hydrogen being *trans* to the neighbouring proton in both cases.

In the hydrogenation of *N*-acetylphthalimide, the acetyl group, as well as the imide ring, is susceptible to attack, hydrogenolysis of the former giving octahydroisoindole-1,3-dione and, presumably, ethanol.

N-Ethoxycarbonylphthalimide (I; R = CO_2Et), in which the electron-withdrawing power of the acyl substituent is less than in *N*-acetyl phthalimide, was next investigated, as it was anticipated that the ethoxycarbonyl group should not itself be susceptible to hydrogenation. Indeed, *N*-ethoxycarbonylphthalimide absorbed 4 mol. of hydrogen during 24 hr. under the conditions employed for the *N*-acetyl analogue and yielded essentially a single product, an oil, the i.r. and n.m.r. spectra of which suggested its formulation as (IV; R = CO_2Et) with the same stereochemistry as its *N*-acetyl analogue. In the n.m.r. spectrum of the derived acetate (V; R = CO_2Et) the low-field proton appeared as a singlet at τ 3·60. The hydrogenation of *N*-methoxycarbonylphthalimide (I; R = CO_2Me) proceeded similary to give 2-methoxycarbonyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO_2Me).

In the next derivative studied the electron-withdrawing power of the substituent was even further reduced. Hydrogenation of *N*-dimethylcarbamoylphthalimide (I; R = $CONMe_2$), prepared from phthaloyl chloride and 1,1-dimethylurea in pyridine, proceeded more slowly than that of its *N*-acetyl or *N*-alkoxycarbonyl analogues; less than 4 mol. of hydrogen was absorbed during 24 hr., after which the uptake of hydrogen virtually ceased. The two products, separated by column chromatography, were 2-dimethylcarbamoyloctahydroisoindole-1,3-dione (II; R = $CONMe_2$) and 2-dimethylcarbamoyl-3-hydroxyoctahydroisoindol-1-one (IV; R = $CONMe_2$). The rate of hydrogenation of the *N*-acylphthalimides thus examined decreases in the order *N*-acetyl > *N*-alkoxycarbonyl > *N*-dimethylcarbamoyl.

We next studied the corresponding derivatives of succinimide. Hydrogenation (PtO_2–EtOAc, r.t.p.) of *N*-acetylsuccinimide (III; R = Ac) proceeded with the uptake of 2 mol. of hydrogen to give a mixture containing succinimide as the major product. Chromatography of the residue (*ca.* 15% by weight of the total product)

[4] B. Wojcik and H. Adkins, *J. Amer. Chem. Soc.*, 1934, **56**, 2419.
[5] J. H. Paden and H. Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2487.
[6] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
[7] R. F. C. Brown, S. Sternhell, and R. N. Warrener, *Austral. J. Chem.*, 1965, **18**, 731.

and examination of the fractions by n.m.r. (see Experimental section) suggested the presence of 5-hydroxy-*N*-acetylbutyrolactam (VIII), butyrolactone, γ-acetoxypropionamide, and *N*-acetyl-γ-hydroxypropionamide. This result * contrasts with that for the hydrogenation of *N*-acetylphthalimide, where hydrogenation occurred preferentially in the imide ring. As anticipated however, the sole product isolated from the hydrogenation of *N*-ethoxycarbonylsuccinimide was identified as *N*-γ-hydroxybutyryl-*O*-ethylcarbamate (IX). Since hydrogenation in the imide ring is more favoured in *N*-acetylphthalimide than in *N*-acetylsuccinimide preference for reaction at a benzylic carbonyl function [if carbonyl reduction precedes saturation of the benzene ring (see below)], might be expected, if it is remembered that palladium catalysts, for example, are effective [9] for the hydrogenation of aromatic but not aliphatic ketones at r.t.p. However, that the presence of a benzene ring adjacent to the carbonyl function has little influence on the course of reaction in hydrogenations carried out over platinum under our conditions is shown by the results obtained from the following series; *N*-benzoylphthalimide (I; R = Bz), *N*-cyclohexylcarbonylphthalimide (I; R = CO·C_6H_{11}), and *N*-benzoylsuccinimide (III; R = Bz). Hydrogenation of the two phthalimide derivatives gave cyclohexylmethanol, octahydroisoindole-1,3-dione, and 2-cyclohexylcarbonyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO·C_6H_{11}). The amounts of octahydroisoindole-1,3-dione recovered (0·27 and 0·26 g. from 1·00 g. *N*-benzoyl and *N*-cyclohexylcarbonyl derivatives respectively) suggest that the benzene ring has little directing effect on the site of reaction. Further, hydrogenation of *N*-benzoylsuccinimide gave a similar ratio of products arising from (i) *N*-acyl cleavage (succinimide and cyclohexylmethanol) and (ii) hydrogenation in the imide ring (cyclohexanecarboxamide) to that already observed for *N*-acetylsuccinimide.

The possibility of reducing the amount of acyl group cleavage by using sterically hindered acyl groups was next examined. However, *N*-pivaloylsuccinimide (III; CO·CMe_3), on hydrogenation in ethyl acetate over platinum oxide at r.t.p. gave succinimide and neopentyl alcohol by almost exclusive cleavage of the acyl substituent. Only a trace of a third product, pivalamide, arising from hydrogenation in the imide ring, was isolated. Similarly, the principal product (*ca.* 75%) on hydrogenation of *N*-pivaloylphthalimide (I; R = CO·CMe_3) was octahydroisoindole-1,3-dione. However, in contrast to other *N*-acylphthalimides, t.l.c. indicated the presence of at least five accompanying products; † the two principal components, isolated by preparative t.l.c., were identified as pivalamide and octahydrobenzo[*c*]furan-1-one. The expected product, 2-pivaloyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO·CMe_3) could not be detected in the chromatographic fractions of the mixture by n.m.r. spectroscopy. This apparent increased tendency to cleavage of bulky acyl groups led us to study the hydrogenation of *N*-isobutyrylphthalimide (I; R = $COCHMe_2$) in which the quantity of octahydroisoindole-1,3-dione (*ca.* 40%) recovered was intermediate between that obtained from the *N*-acetyl (*ca.* 30%) and *N*-pivaloyl analogues. Also obtained in this reaction was the expected 3-hydroxy-2-isobutyryloctahydroisoindol-1-one (IV; R = $COCHMe_2$) the structure of which was confirmed by its i.r. (**3425**, **1736**, and **1675** $cm.^{-1}$, aromatic peaks absent) and n.m.r. (low field proton, τ 4·60 d, *J* 3 Hz, s on D_2O equil.) spectra. The methyl groups of the isobutyryl moiety are magnetically non-equivalent and appear as a pair of doublets (*J* 6·5 Hz) centred at τ 8·85 and 8·83.

The catalytic hydrogenation of *N*-acylphthalimides might proceed *via* either the corresponding 2-acyl-3-hydroxydihydroisoindol-1-ones (X) or the 2-acyloctahydroisoindole-1,3-diones (II; R = acyl) depending on whether hydrogenation at the carbonyl group precedes or follows saturation of the benzene ring. To determine which, if either, of these intermediates is involved two approaches were adopted: (*a*) partial hydrogenation of the *N*-acylphthalimides and attempted isolation of the intermediates, and (*b*) synthesis and hydrogenation of possible intermediates. The substituted phthalimides examined were the *N*-acetyl, *N*-ethoxycarbonyl, and *N*-dimethylcarbamoyl derivatives.

N-*Acetylphthalimide* (I; R = Ac).—When the hydrogenation of *N*-acetylphthalimide was stopped after *ca.* 3 mol. of hydrogen had been absorbed, fractional crystallisation of the product gave 2-acetyl-3-hydroxyoctahydroisoindol-1-one (IV; R = Ac), octahydroisoindole-1,3-dione, and 2-acetyl-3-hydroxyoctahydroisoindol-1-one (X; R = Ac); the other possible product of partial hydrogenation, 2-acetyloctahydroisoindole-1,3-dione (II; R = Ac) could not be detected in the reaction mixture (t.l.c.). Since this result suggested that the catalytic hydrogenation of *N*-acetylphthalimide proceeds largely, or entirely, through initial reduction at the imide carbonyl group, the hexahydro-derivative was hydrogenated to determine whether or not the product has the same stereochemistry as that already obtained. Hydrogenation (PtO_2–EtOAc) of 2-acetyloctahydroisoindole-1,3-dione (II; R = Ac), prepared from *cis*-octahydroisoindole-1,2-dione and acetic anhydride, was complete after the absorption of rather more than 1 mol. of hydrogen; the resulting mixture contained (t.l.c.) octahydroisoindole-1,3-dione and the known 2-acetyl-3-hydroxyoctahydroisoindole-1-one (IV; R = Ac). Thus the stereochemistry of the final product (IV; R = Ac) is the same, irrespective of whether it is derived *via*

* Hydrogenation of *N*-stearoylsuccinimide in ether over 10% Pd–$BaSO_4$ also largely results [8] in acyl group cleavage.

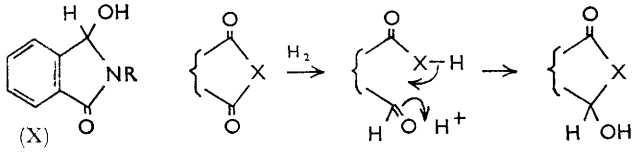
† Traces of by-products were also observed on t.l.c. in the reaction mixtures obtained from the other *N*-acyl phthalimides, but they were not isolated. They constituted about 2—5% of the total reaction mixture in these cases.

[8] E. S. Rothman, S. Serota, and D. Swern, *J. Org. Chem.*, 1964, **29**, 646.

[9] See, for example, E. Breitner, E. Roginski, and P. N. Rylander, *J. Org. Chem.*, 1959, **24**, 1855.

2-acetyl-3-hydroxydihydroisoindol-1-one or 2-acetyloctahydroisoindole-1,3-dione. In addition, the amount of octahydroisoindole-1,3-dione recivered from this reaction was only slightly greater than that obtained on hydrogenation of *N*-acetylphthalimide, indicating, as has already been concluded, (see above) that the presence of a benzene ring adjacent to the carbonyl function has little activating influence on the hydrogenation of the latter over platinum.

N-*Ethoxycarbonylphthalimide* (I; R = CO_2Et).—The partial (2 mol. of hydrogen) hydrogenation (PtO_2) of *N*-ethoxycarbonylphthalimide gave four products which appeared on t.l.c. as two pairs of close-running spots. The mixture was chromatographed into two fractions each containing two components. The less-polar fraction contained starting material and 2-ethoxycarbonyloctahydroisoindole-1,3-dione (II; R = CO_2Et). Fractional crystallisation of the more-polar fraction gave 2-ethoxycarbonyl-3-hydroxydihydroisoindol-1-one (X; R = CO_2Et) while the n.m.r. spectrum of the residual oil from the mother liquors showed the fourth component to be the already characterised 2-ethoxycarbonyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO_2Et). The identity of these products, and the relative quantities obtained, suggest that in the hydrogenation of *N*-ethoxycarbonylphthalimide, the competing initial reactions of carbonyl reduction and benzene ring saturation take place at similar rates.



(XI) X = O or NCOR

The formation of the same product on hydrogenation of both 2-ethoxycarbonyl-3-hydroxydihydroisoindol-1-one (X; R = CO_2Et) and 2-ethoxycarbonyl-*cis*-octahydroisoindole-1,3-dione (II; R = CO_2Et) was confirmed by the synthesis and hydrogenation of these compounds. The latter was obtained by reaction of ethyl chloroformate and the potassium salt of octahydroisoindole-1,3-dione in refluxing benzene while hydrogenation of *N*-ethoxycarbonylphthalimide, in ethyl acetate or ethanol at r.t.p. over 10% palladium on carbon, gave an excellent yield of the former. The generality of this hydrogenation with palladium was shown by the preparation of the 3-hydroxydihydroisoindolones from *N*-acetyl, *N*-isobutyryl, and *N*-methoxycarbonylphthalimides.

The hydrogenation of *N*-pivaloylphthalimide (I; R = $COCMe_3$ (proceeded noticeably more slowly than that of the other analogues, to give 2-pivaloyl-3-hydroxydihydroisoindol-1-one in only 30% yield. Although *N*-dimethylcarbamoylphthalimide (I; R = $CONMe_2$) could not be hydrogenated over palladium in either ethyl acetate or ethanol the hydroxydihydroisoindolone (X; R = $CONMe_2$) was obtained with a platinum catalyst. In one hydrogenation of *N*-dimethylcarbamoylphthalimide (I; R = $CONMe_2$) in which platinum oxide catalyst from a new source was used the uptake of the first mol. of hydrogen was notably faster than later ones. Indeed, after 24 hr. the reaction had virtually stopped with the uptake of only *ca.* 2 mol. of hydrogen. T.l.c. of the reaction mixture showed the presence of a minor component with a mobility identical to that of 2-dimethylcarbamoyloctahydroisoindole-1,3-dione (II; R = $CONMe_2$), but the principal product was 2-dimethylcarbamoyl-3-hydroxydihydroisoindol-1-one (X; R = $CONMe_2$). When this latter hydrogenation was stopped after the uptake of 1 mol. of hydrogen (X) was isolated in 65% yield. The increased activity of this catalyst * for carbonyl group hydrogenation, but marked decrease in both activity for benzene ring hydrogenation and extent of acyl group cleavage, was confirmed for other *N*-acylphthalimides (see Experimental section).

The stereochemistry of the 2-acyl-3-hydroxyoctahydroisoindol-1-ones (IV; R = acyl) obtained in these hydrogenations and the observed order of susceptibility to cleavage of acyl substituents (acetyl < isobutyryl < pivaloyl) is the same as found previously. The times taken for absorption of 1 mol. of hydrogen by the *N*-acetyl, *N*-ethoxycarbonyl, and *N*-dimethylcarbamoyl derivatives of phthalimide over this catalyst (1·0 g. substrate, 0·3 g. PtO_2) were respectively <30 min., 35—40 min., and 50—55 min.

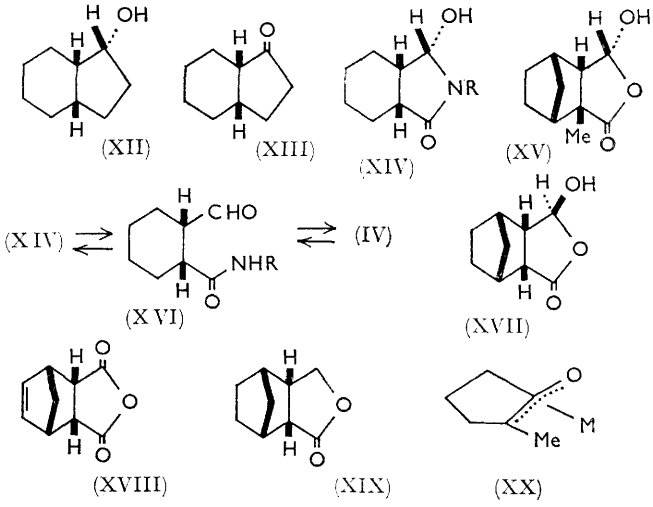
N-*Dimethylcarbamoylphthalimide* (I; R = $CONMe_2$).—As previously discussed, the hydrogenation (PtO_2) of this compound gave the hexahydro-derivative (II; R = $CONMe_2$) as well as the main product, 2-dimethylcarbamoyl-3-hydroxyoctahydroisoindol-1-one (IV; R = $CONMe_2$). The former compound accounted for *ca.* 25% by weight of the total product and since reaction appeared to have stopped at this point, it appeared possible that the hexahydro-compound was, in fact, resistant to hydrogenation and not an intermediate in the formation of 2-dimethylcarbamoyl-3-hydroxyoctahydroisoindol-1-one. However, hydrogenation of 2-dimethylcarbamoyloctahydroisoindole-1,3-dione (II; R = $CONMe_2$) did proceed slowly over fresh platinum oxide catalyst to give the expected product (IV; R = $CONMe_2$). These results suggested that with *N*-dimethylcarbamoylphthalimide, saturation of the benzene ring takes place more rapidly than carbonyl group reduction.

DISCUSSION

The Mechanism of the Catalytic Hydrogenation of Cyclic Imides and Anhydrides over Adams Platinum Oxide.—The order of susceptibility of carbonyl compounds to catalytic hydrogenation described earlier suggests that their hydrogenation may involve a nucleophilic attack at

* We are unable to account for the difference in activity and selectivity found but the suppliers of this catalyst have informed us that tests performed by them on samples from this particular batch have shown it to have an activity below their normally accepted standard.

the carbonyl carbon atom. Similarly, the observation that in a series of *N*-acyl-imides the ease of hydrogenation increases with increasing electron-withdrawing power of the acyl substituent (acetyl > ethoxycarbonyl > dimethylcarbamoyl) leads to the same conclusion. The decrease in rate of hydrogenation of the *N*-acylphthalimides in this order might be ascribed not only to a decrease in the inductive effect of the acyl substituent, but also to an increase in the strength of adsorption of starting material, intermediates, and products on the catalyst surface. The dimethylcarbamoyl group would be expected to be the most strongly adsorbed of the three, and thus the most effective in decreasing the overall rate of hydrogenation, both by competition with other groups in the substrate and with hydrogen for catalyst sites, and by retarding the rate of desorption of products. However, since these effects should lead to a concomitant reduction in the rate of hydrogenation of the benzene ring in the *N*-acylphthalimides, it is considered that the decrease in the rate of carbonyl group relative to benzene ring hydrogenation found for these derivatives is evidence for a significant contribution from the electron-withdrawing effect of the acyl groups. The catalytic hydrogenation of cyclic imides and anhydrides to the corresponding hydroxy-lactams and hydroxy-lactones may be envisaged as proceeding by one of two routes analogous to those outlined, *e.g.* by Adkins,[10] for the hydrogenation of esters, *viz.*, (*a*) direct addition of hydrogen across a carbonyl group, as may occur with ketones, or (*b*) hydrogenolysis to give a free aldehydo-function followed by rapid recyclisation before further reduction of the latter can occur (XI; arrows). If route (*a*) represents the correct mechanism, then the stereochemistry of the products might be expected to be subject to control by steric factors as is found in the hydrogenation of ketones to alcohols. Thus, by an analogy with the formation of *cis-cis*-hydrindan-1-ol (XII) as the major product on hydrogenation of *cis*-hydrindan-1-one (XIII) over platinum,[11] which involves preferential addition of hydrogen from the less-hindered side of the molecule, 2-acyloctahydroisoindole-1,3-diones (II; R = acyl) and the Diels–Alder adduct (VII) should give the all-*cis* hydroxy-lactams (XIV) and hydroxy-lactone (XV) respectively. In fact, the sole products (IV) and (VI) isolated from these reactions have the hydroxy-group in the opposite configuration. If the hydrogenation of cyclic imides and anhydrides proceeded by route (*a*), these results could however be explained in the two ways (i) and (ii) discussed below. (i) The expected products (XIV) and (XV) may indeed be formed initially, but subsequent ring opening to the aldehydo-form occurs, followed by reclosure to the tautomer (XVI; arrows) in which the configuration of the hydroxy-group is inverted and less hindered. Against this explanation is our observation that neither prolonging the time of hydrogenation of the *N*-acylphthalimides, nor attempting further hydrogenation of the 2-acyl-3-hydroxyoctahydroisoindol-1-ones (IV; R = acyl) with fresh catalyst,



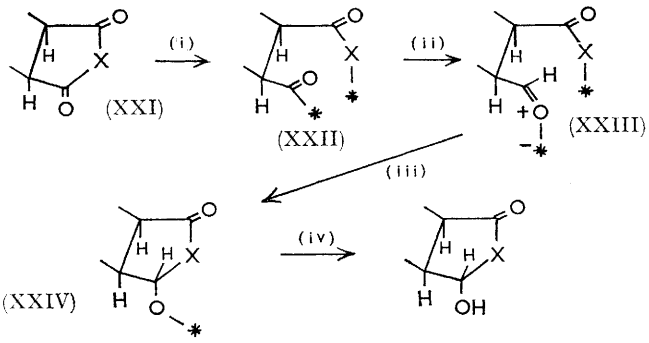
results in further uptake of hydrogen, whereas if reversible ring-opening to the aldehydo-form occurred, it should be subject to further attack. On the other hand, the hydroxy-lactone (XVII) obtained by hydrogenation of *endo*-norborn-5-ene-1,2-dicarboxylic acid anhydride (XVIII) [1,7] for example, can be hydrogenated to the lactone (XIX).[1] This may reflect a more ready ring-opening for hydroxy-lactones than for hydroxy-lactams and, indeed, the fact that the ease of further hydrogenation of different hydroxy-lactones varied considerably with their structure [1] may indicate that prior ring-opening is an essential step in this reaction. Indeed, the equilibrium between the open and closed forms of hydroxy-lactones has been studied.[12–14] No observation of an equilibrium between hydroxy-lactams and the corresponding aldehydo- (or keto) amides appears to have been recorded in the literature,[15–22] but the somewhat meagre information available on hydroxy-lactams indicates that such compounds are less subject to ring-opening than hydroxy-lactones.

(ii) The observed products (IV) and (VI) could have been formed directly if hydrogen addition to the carbonyl group proceeds by an Eley–Rideal type of mechanism, whereby hydrogen adds to the adsorbed molecule on the side remote from the catalyst rather than the adsorbed

[10] H. Adkins, ' Organic Reactions,' vol. VIII, 1954, p. 1.
[11] W. Huckel and M. Hanack, *Annalen*, 1957, **610**, 106.
[12] See, *e.g.*, B. H. Korsch and N. V. Riggs, *Austral. J. Chem.*, 1963, **16**, 709.
[13] E. Bernatek, *Acta. Chem. Scand.*, 1960, **14**, 785.
[14] J. Kagan, *J. Org. Chem.*, 1967, **32**, 4060.
[15] R. Lukes, *Coll. Czech. Chem, Comm.*, 1929, **1**, 119.
[16] R Lukes and V. Prelog, *Coll. Czech. Chem. Comm.*, 1929, **1**, 282.
[17] R. Lukes and V. Prelog, *Coll. Czech. Chem. Comm.*, 1929, **1**, 617.
[18] W. Flitsch and R. Heidues, *Angew. Chem. Internat. Edn.*, 1965, **4**, 1085.
[19] A. Queen and A. Reipas, *J. Chem. Soc.* (*C*), 1967, 245.
[20] P. C. Jocelyn and A. Queen, *J. Chem. Soc.*, 1957, 4437.
[21] E. G. Havard, R. V. Lindsay, jun., and C. W. Theobald, *J. Amer. Chem. Soc.*, 1959, **81**, 4355.
[22] E. Tagmann, E. Sury, and K. Hoffmann, *Helv. Chim. Acta*, 1954, **37**, 185.

side. The intervention of such a process has been proposed [23] to account for the results of a study of the hydrogenation of 2-methylcyclopentanone and the concomitant isomerisation of the 2-methylcyclopentanols. The authors suggest the involvement of a triadsorbed intermediate (adsorbed *via* carbonyl oxygen, carbonyl carbon, and either α-carbon atom), *e.g.* (XX), comparable with hydrocarbon π-allylic species, which could react both with atomic hydrogen (on that side of the ring adsorbed on the catalyst) and with molecular hydrogen (from the top side of the adsorbed molecule). Formation of the 2-acyl-3-hydroxyoctahydroisoindol-1-ones (IV; R = acyl) from the 2-acyloctahydroisoindole-1,3-diones (II; R = acyl) *via* a triadsorbed intermediate involving a ring-junction carbon atom would require that hydrogen addition at that carbon atom takes place specifically from the adsorbed side of the molecule (assuming this to be adsorbed on its less-hindered side), while addition to the carbonyl carbon atom takes place specifically from the free side. The involvement of such an intermediate is excluded, however, by the requirement in the proposed mechanism [23] that either addition to *both* sides of *each* of the carbon atoms involved in adsorption may occur, which would give *mixtures* of isomers, or addition to both carbon atoms must occur from the same side, which would give products in which the hydroxy-function was *trans* rather than *cis* to the adjacent proton. Hydrogenation by an Eley–Rideal type of mechanism could give the observed products only if a diadsorbed species (adsorbed *via* the carbonyl carbon and oxygen atoms) were involved. In a study of the hydrogenolysis of benzylic alcohols and their derivatives, such a model has been advanced to account for the inversion of configuration observed when hydrogenolyses are carried out over palladium.[24] However, against any hydrogen addition type of mechanism is the observation in the present investigation that the amount of competitive cleavage of acyl groups from *N*-acyl-imides increases with increasing bulk of these substituents, whereas increasing steric hindrance might be expected to result in a decrease of such competition.

We now propose that the products obtained by hydrogenation of 2-acyloctahydroisoindole-1,3-diones (and hence of the other *N*-acyl-imides) and of cyclic anhydrides, could be accounted for if reaction proceeded by initial hydrogenolysis, as in route (*b*) above, by the mechanism outlined in Scheme 1, the individual steps of which are as follows. (i) Nucleophilic attack of the catalyst on an imide (or anhydride) carbonyl carbon atom of the substrate molecule adsorbed on the catalyst surface on its less-hindered side [as in (XXI)] with concomitant ring opening, gives the species (XXII). This acyl group cleavage step is analogous to that proposed [25,26] as the initial step in the Rosenmund hydrogenation of acid halides, and in the catalytic decarbonylation of acyl halides and aldehydes, over palladium. Further analogies can be found in recent examples of oxidative addition of acyl halides to square-

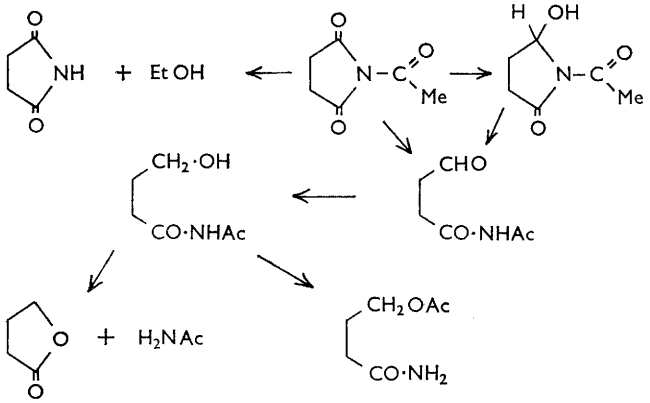


SCHEME 1 The mechanism proposed to account for the products of hydrogenation of *N*-acyl cyclic imides and of cyclic anhydrides. X = O or NCOR. * Denotes an adsorption site on the catalyst surface. Charges are formal.

planar transition-metal complexes with the d^8 configuration of electrons, and the use of such complexes as catalysts for the decarbonylation of acyl halides and aldehydes.[27–29] Nucleophilic attack by the catalyst has been suggested [30] to occur in the hydrogenolysis of certain α-halogeno-ketones and -lactones over palladium, and it has been observed [29] that the ease of decarbonylation of aldehydes with tris(triphenylphosphine)halogenorhodium (I) complexes [$RhX(PPh_3)_3$; X = Cl, Br, and I] increases both with increasing electrophilicity of the aldehyde, and with increasing nucleophilicity of the catalyst (X = I > Br > Cl). The observation [27] that the reaction of $RhCl(PPh_3)_3$ with acyl halides, to give the five-co-ordination species $RCORhCl_2(PPh_3)_2$, proceeded most readily with higher n-acyl halides appears to parallel our finding of increased susceptibility to cleavage of bulkier *N*-acyl substituents in hydrogenation of both *N*-acylphthalimides and *N*-acylsuccinimides over platinum. (ii) Hydrogenolysis of the metal–carbon bond to give the aldehydo-function is followed by rotation of this function through 180° to give a species (XXIII) adsorbed through the aldehyde carbonyl oxygen atom. The formulation of this intermediate is analogous to that already suggested [31] for the initial adsorbed intermediate in the hydrogenation of ketones. (iii) Ring closure of the aldehydo-intermediate (XXIII) gives an oxygen-bound species (XXIV). The rate of this step compared with the rate of further hydrogenation of the aldehydo-function generated in step (ii) may determine whether products of further reduction are obtained. Thus, for

[23] D. Cornet and F. G. Gault, *J. Catalysis*, 1967, **7**, 140.
[24] A. M. Khan, F. J. McQuillin, and I. Jardine, *J. Chem. Soc.* (*C*), 1967, 136.
[25] J. Tsuji, K. Ohno, and T. Kajimoto, *Tetrahedron Letters*, 1965, 4565.
[26] J. Tsuji and K. Ohno, *J. Amer. Chem. Soc.*, 1968, **90**, 94.
[27] K. Ohno and J. Tsuji, *J. Amer. Chem. Soc.*, 1968, **90**, 99.
[28] M. C. Baird, J. T. Mague, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc.* (*A*), 1967, 1347.
[29] M. C. Baird, C. J. Nyman, and G. Wilkinson, *J. Chem. Soc.*, (*A*), 1968, 348.
[30] D. A. Denton, F. J. McQuillin, and P. L. Simpson, *J. Chem. Soc.*, 1964, 5535.
[31] J. Newham and R. L. Burwell, *J. Amer. Chem. Soc.*, 1964, **86**, 1179.

the *N*-acylphthalimide series, with the exception of the *N*-pivaloyl-derivative, ring closure must be relatively fast, so that little or no hydrogenation beyond the hydroxy-lactam stage is observed. In the *N*-acyl-succinimide series, where ring closure would be expected to be slower since the aldehydo- and imide groups of the intermediate (XXIII) are not rigidly constrained in a manner favouring interaction, the main product of reaction is an alcohol, or products derived therefrom. Thus, the products of hydrogenation of *N*-acetyl-succinimide may be rationalised as outlined in Scheme 2. In the hydrogenation of cyclic anhydrides (and possibly of *N*-pivaloylphthalimide *), an additional complication comes into play, namely that the derived hydroxy-lactones (or hydroxy-lactams) may be in equilibrium with the tautomeric open-forms. In this case, further hydrogenation may occur not only of the adsorbed intermediate (XXIII) formed directly from the substrate, but



SCHEME 2 A reaction scheme which accounts for the products of hydrogenation of *N*-acetyl succinimide

also of the hydroxy-lactone (or hydroxy-lactam), at a rate depending on how rapidly ring opening of the latter occurs as the open, aldehydo-form is removed from the equilibrium by hydrogenation. (iv) Hydrogenolysis of the oxygen-bound species (XXIV) and desorption gives a hydroxy-lactone or hydroxy-lactam in which the hydroxy-function has the stereochemistry required by formulae (IV), (VI), and (XVII).

Finally, the stereochemistry of hydrogenation of the 2-acyl-3-hydroxydihydroisoindol-1-ones (X; R = acyl) requires comment, these derivatives giving only one of the two possible hexahydro-compounds on hydrogenation over platinum. In order to account for this, it seems necessary to assume that the stereochemistry of addition of hydrogen to the benzene ring is controlled by the adsorption of the substrate molecules onto the catalyst surface through the hydroxy-function. Such control of the direction of addition of hydrogen has been suggested in numerous cases [32] to account for the stereochemistry of products obtained on hydrogenation of double bonds having a hydroxy-function in their vicinity.

* The hydrogenation (PtO_2–EtOAc) of 2-pivaloyl-3-hydroxydihydroisoindol-1-one (X; R = $COCMe_3$) gave products similar to those obtained directly from *N*-pivaloylphthalimide, in which further attack had taken place in the hydroxy-lactam ring in addition to saturation of the benzene ring. 2-Pivaloyl-3-hydroxyoctahydroisoindol-1-one (IV; R = $COCMe_3$) was not detected in the reaction mixture.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded for Nujol mulls, unless otherwise stated, on a Unicam SP200 spectrophotometer and ^1H n.m.r. spectra on a Perkin-Elmer R10 and a Varian Associates HA-100 spectrometer in deuteriochloroform with *ca.* 0·3M-solutions and tetramethylsilane as internal standard. Microanalyses were by Mr. J. M. L. Cameron, Glasgow, and his staff. Plates for analytical and preparative t.l.c. were spread with Kieselgel G. (Merck) and developed, unless specified, with ethyl acetate–light petroleum (2 : 3); spots were located in iodine vapour. Light petroleum refers to the fraction b.p. 60—80°, unless otherwise specified. Hydrogenations were carried out at 20° and atmospheric pressure (or slightly above) in a sloping manifold hydrogenator. Volumes were recorded at r.t.p. AnalaR grade ethyl acetate was used as solvent. Platinum oxide and 10% palladium on carbon catalysts were obtained from Engelhard Industries Ltd., Baker Platinum Division, 52 High Holborn, London, W.C.1.

Hydrogenations over Adams Platinum Oxide.—In general, the substrate (1·0 g.) was shaken in ethyl acetate (100 ml.) with the catalyst (0·3 g.) under hydrogen for 24 hr., during which time hydrogenation was usually complete, no further absorption being observed either on prolonging the time of reaction or after the addition of fresh catalyst.

Phthalimide. The imide absorbed 3 mol. (460 ml.) of hydrogen and t.l.c. of the product showed the presence of one component. Removal of the catalyst and solvent and crystallisation of the residue from ethyl acetate gave *cis*-hexahydrophthalimide (0·80 g.), m.p. 135—136°.

Succinimide. Succinimide was recovered quantitatively from reaction conditions similar to those used for hydrogenation of phthalimide.

N-*Methylphthalimide.* The hydrogenation of *N*-methylphthalimide [33] was complete within 10 hr. with the uptake of 3 mol. (410 ml.) of hydrogen. T.l.c. showed the presence of essentially a single product and a minor amount of polar material. On removal of the catalyst and solvent the residual oil gradually crystallised to give *N*-methyl-*cis*-hexahydrophthalimide,[33] m.p. 48—50°.

N-*Acetylphthalimide.* This compound [34] absorbed just over 4 mol. (490 ml.) of hydrogen in 8 hr. and *ca.* 4·25 moles (510 ml.) in 24 hr. The two products (t.l.c.) were separated by column chromatography over silica gel (40 g.). Elution with ethyl acetate–benzene (1 : 9) gave 2-*acetyl*-3-*hydroxy*-*octahydroisoindol*-1-*one* (IV; R = Ac) (0·62 g.), m.p. 81° (from light petroleum) (Found: C, 60·8; H, 7·35. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·65%); $\nu_{max.}$ 3450, 1748, and 1693 $cm.^{-1}$; τ 7·5—9·1 (m, 9H), 7·45 (s, 3H), 6·92 (m, 1H), 6·01 (d, *J* 3 Hz; lost on D_2O equil.), and 4·61 (d, *J* 3 Hz, 1H; s on D_2O equil.). Further elution, first with ethyl acetate–benzene (3 : 22) gave *cis*-octahydroisoindole-1,3-dione (0·17 g.) and then with ethyl acetate a mixture

[32] See, for example, Y. Watanabe, Y. Mizuhara, and M. Shiota, *J. Org. Chem.*, 1966, **31**, 3785, and refs. therein.

[33] L. M. Rice, E. E. Reid, and C. H. Grogan, *J. Org. Chem.*, 1954, **19**, 884.

[34] O. Aschan, *Ber.*, 1886, **19**, 1400.

(30 mg.) of octahydroisoindole-1,3-dione and more polar material (t.l.c.). This last fraction was not further investigated.

The isoindolone (IV; R = Ac) (111 mg.) was heated with acetic anhydride (0·2 ml.) in refluxing pyridine (2 ml.) for 1 hr. Water (10 ml.) was added to the cooled reaction mixture. The solid obtained, on recrystallisation from light petroleum, gave clear tablets of *2-acetyl-3-acetoxyoctahydroisoindol-1-one* (V; R = Ac), m.p. 106° (Found: C, 60·4; H, 7·15. $C_{12}H_{17}NO_4$ requires C, 60·25; H, 7·15%); $\nu_{max.}$ 1706 (several shoulders to higher frequencies) and 1722 cm.$^{-1}$ (complex band); τ 7·5—9·1 (m, 9H), 7·93 (s, 3H), 7·43 (s, 3H), 7·00 (m, 1H), and 3·60 (s, 1H).

N-*Ethoxycarbonylphthalimide*.—This imide [35] took up 4 mol. (400 ml.) of hydrogen within 24 hr. T.l.c. of the resulting solution indicated the presence of a single product and traces of polar material. Work up furnished *2-ethoxycarbonyl-3-hydroxyoctahydroisoindol-1-one* (IV; R = CO_2Et) (0·71 g.) as an oil [after purification by column chromatography over silica gel (40 g.) and elution with ethyl acetate–benzene (1 : 9)] (Found: C, 57·2; H, 7·6. $C_{11}H_{17}NO_4$ requires C, 58·15; H, 7·55%); $\nu_{max.}$ (liquid film) 3490, 1785, and 1725 cm.$^{-1}$; τ 7·5—9·1 (m, 9H), 8·65 (t, *J* 7 Hz, 3H), 7·01 (m, 1H), 5·71 (q, *J* 7 Hz, 2H), 5·09 (d, *J* 3 Hz, 1H; lost on D_2O equil.), and 4·72 (d, *J* 3 Hz, 1H; s on D_2O equil.).

The hydroxyoctahydroisoindolone (200 mg.) was acetylated as above. Recrystallisation of the product from light petroleum furnished *3-acetoxy-2-ethoxycarbonyloctahydroisoindol-1-one* (V; R = CO_2Et) as long needles, m.p. 115° (Found: C, 58·25; H, 6·9. $C_{13}H_{19}NO_5$ requires C, 58·0; H, 7·1%); $\nu_{max.}$ 1788 and 1736 cm.$^{-1}$; τ 7·5—9·1 (m, 9H), 8·66 (t, *J* 7 Hz, 3H), 7·93 (s, 3H), 7·06 (m, 1H), 5·60 (q, *J* 7 Hz, 2H), and 3·60 (s, 1H).

N-*Methoxycarbonylphthalimide*.—The hydrogenation of this derivative [35] proceeded with the uptake of 450 ml. of hydrogen. The reaction mixture was warmed to 50—60° on a water-bath at the start of the reaction to keep the substrate in solution. T.l.c. (ethyl acetate) of the product showed it to be essentially one compound accompanied by traces of both less and more polar materials. Work-up and crystallisation from ethyl acetate gave *2-methoxycarbonyl-3-hydroxyoctahydroisoindol-1-one* (IV; R = CO_2Me) (0·80 g.), m.p. 105° (Found: C, 56·6; H, 7·4. $C_{10}H_{15}NO_4$ requires C, 56·3; H, 7·1%); $\nu_{max.}$ 3495, 1780, and 1697 cm.$^{-1}$; τ 8·04—9·16 (m, 7H), 7·5—8·0 (m, 2H), 7·06 (m, 1H), 6·20 (s, 3H), 6·04 (d, *J* 3·5 Hz, 1H; lost on D_2O equil.), and 4·78 (d, *J* 3·5 Hz, 1H; s on D_2O equil.).

N-*Dimethylcarbamoylphthalimide*.—The substrate was prepared by the dropwise addition of phthaloyl chloride (7·7 g.) to a suspension of 1,1-dimethylurea (3·2 g.) in pyridine (15 ml.) at 0°. The resulting mixture was set aside at 20° for 24 hr. and then poured into water (250 ml.) with vigorous stirring; a reddish-brown oil separated, which soon precipitated flakes. Recrystallisation of the product from ethyl acetate gave N-*dimethylcarbamoylphthalimide* (5·6 g.) as lustrous, white leaflets, m.p. 158° (Found: C, 60·35; H, 4·65. $C_{11}H_{10}N_2O_3$ requires C, 60·55; H, 4·6%); $\nu_{max.}$ 1794, 1767, 1736, 1675, 1614, 723, and 705 cm.$^{-1}$; τ 6·95 (s, 3H), 6·82 (s, 3H), and 2·08 (m, 4H). The hydrogenation of this compound appeared complete after 24 hr. when *ca.* 4 mol. (405 ml.) of hydrogen had been absorbed. The product contained (t.l.c.) two major components and minor amounts of polar material. The mixture was chromatographed over silica gel (40 g.), elution with ethyl acetate–benzene (1 : 9) giving the *2-dimethylcarbamoyloctahydroisoindole-1,3-dione* (II; R = $CONMe_2$) (0·21 g.); this crystallised from benzene–light petroleum as white leaflets, m.p. 114—115° (Found: C, 59·15; H, 7·1. $C_{11}H_{16}N_2O_3$ requires C, 58·9; H, 7·2%); $\nu_{max.}$ 1725 and 1701 cm.$^{-1}$ (shoulders to higher and lower frequencies); τ 7·9—8·8 (m, 8H), 7·07 (s, 3H), and 6·90 (s, 3H) (these two singlets are superimposed on resonances from a further 2H). Elution with ethyl acetate–benzene (3 : 17) gave *2-dimethylcarbamoyl-3-hydroxyoctahydroisoindol-1-one* (IV; R = $CONMe_2$) (0·75 g.) as a viscous oil which crystallised from light petroleum as small, white prisms, m.p. 95—97° (Found: C, 58·2; H, 7·9. $C_{11}H_{18}N_2O_3$ requires C, 58·4; H, 8·0%); $\nu_{max.}$ 3350 and 1679 cm.$^{-1}$ (latter has shoulders to higher frequencies); τ 7·5—9·2 (m, 9H), 7·00 (s, 6H; superimposed on resonance from further 1H), 5·21 (broad s, 1H; lost on D_2O equil.), and 4·84 (s, 1H).

N-*Acetyl succinimide*.—The substrate [36] was prepared by the reaction of succinimide with acetic anhydride and fractional distillation of the product. Its hydrogenation appeared to be complete within 24 hr. during which time *ca.* 2 mol. (327 ml.) of hydrogen had been absorbed. T.l.c. (ethyl acetate) of the resulting mixture showed the presence of a principal component with a mobility identical to that of succinimide and small quantities of at least one less and three more polar products. Succinimide (0·36 g., m.p. 125°) was recovered by crystallisation from ethyl acetate and the residue from the mother liquors was separated into three fractions (a)—(c) by column chromatography over silica gel. Fraction (a) (60 mg.) eluted with ethyl acetate–benzene (1 : 1) had n.m.r. resonances at τ 7·23 (s) and 2·85 (broad s) (succinimide?), 7·48 (s) and 4·10 (q, *J* 5·5, 3 Hz) [*N*-acetyl-5-hydroxy-2-pyrrolidone (VIII)?], 5·63 (t, *J* 7 Hz) (γ-butyrolactone?). Fraction (b) (0·14 g.), eluted with ethyl acetate–benzene (3 : 2) was almost pure (t.l.c.; n.m.r.) succinimide. The most polar fraction (c) (30 mg.) was eluted with ethyl acetate and had n.m.r. resonances at τ 7·98 (s), 5·61 (t, *J* 7 Hz), and 4·0 (broad s) ($MeCO_2$·$[CH_2]_3$·CO·NH_2?); τ 7·64 (s), 6·28 (t, *J* 6 Hz), and 0·25 (broad s) (HO·$[CH_2]_2$·CO·NHAc?)

N-*Ethoxycarbonylsuccinimide*.—The hydrogenation of *N*-ethoxycarbonylsuccinimide [36] was complete after 48 hr. when 2 mol. (272 ml.) of hydrogen had been taken up. The resulting solution contained only one product [t.l.c.; ethyl acetate–light petroleum (3 : 2)]. Work-up and crystallisation from ethyl acetate–light petroleum gave the *hydroxyamide* (IX) (0·85 g.) as white needles, m.p. 71—72° (Found: C, 48·2; H, 7·3. $C_7H_{13}NO_4$ requires C, 48·0; H, 7·5%); $\nu_{max.}$ 3275, 3205, 1753, and 1693 cm.$^{-1}$; τ 8·70 (t, *J* 7 Hz, 3H), 8·08 (quintet, *J* 6·5 Hz, 2H), 7·17 (t, *J* 6·5 Hz, 2H: superimposed on resonance at 7·05, 1H; lost on D_2O equil.), 5·77 (q, *J* 7 Hz, 2H), and 1·48 (broad s, 1H; lost on D_2O equil.).

N-*Benzoylphthalimide*.—This compound [37] absorbed *ca.* 7·5 mol. (700 ml.) of hydrogen during 36 hr. T.l.c. indicated two principal products and a small amount of polar material. Column chromatography over silica gel (40 g.) and elution with ethyl acetate–benzene (3 : 47) gave a fraction (0·59 g.) in which the characteristic odour of cyclohexylmethanol was readily detected. A pure sample of this compound was

[35] G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. trav. chim.*, 1960, **79**, 688.

[36] G. Heller and P. Jacobsohn, *Ber.*, 1921, **54**, 1107.

[37] A. W. Titherley and W. L. Hicks, *J. Chem. Soc.*, 1906, **89**, 708.

obtained by the following sequence. The chromatographic fraction was extracted with cold, light petroleum (b.p. 40—60°); and the solvent was evaporated; the residual oil was heated on a steam-bath with dilute aqueous sodium hydroxide for 1 hr.; the organic material, isolated with ether was distilled on a sublimation block at 190°. The oil was identical with an authentic sample of cyclohexylmethanol (i.r. and conversion to the α-naphthylurethane, m.p. 109—110°). The residue from extraction of the cyclohexylmethanol on crystallisation from light petroleum gave 2-*cyclohexylcarbonyl*-3-*hydroxyoctahydroisoindol*-1-*one* (IV; R = $CO{\cdot}C_6H_{11}$), m.p. 118—120° (Found: C, 67·85; H, 8·8. $C_{15}H_{23}NO_3$ requires C, 67·9; H, 8·75%); $\nu_{max.}$ 3480, 1746, and 1678 cm.$^{-1}$; τ 7·50—9·10 (m, 19H), 6·97 (m, 1H), 6·50 (m, 1H), 6·05 (d, *J* 3 Hz, 1H; lost on D_2O equil.), and 4·60 (d, *J* 3 Hz, 1H; s on D_2O equil.). Further elution, with ethyl acetate–benzene (3 : 17), gave octahydroisoindole-1,3-dione (0·27 g.) and with ethyl acetate, a fraction (30 mg.) containing (t.l.c.) a further amount of octahydroisoindole-1,3-dione and polar material.

N-*Cyclohexylcarbonylphthalimide*.—This *acyl imide* synthesised by the procedure described [37] for its *N*-benzoyl analogue, was obtained from ethanol as white needles, m.p. 113—114° (Found: C, 69·95; H, 6·0. $C_{15}H_{15}NO_3$ requires C, 79·0; H, 5·9%); $\nu_{max.}$ 1790, 1765, 1736, 1705, and 1608 cm.$^{-1}$. On hydrogenation it absorbed 4·5 mol. (400 ml.) of hydrogen and furnished the same products (t.l.c.) as those obtained from *N*-benzoylphthalimide. Column chromatography as before gave a fraction (0·73 g.) containing cyclohexylmethanol and 2-cyclohexylcarbonyl-3-hydroxyoctahydroisoindol-1-one and a second fraction (0·26 g.) containing octahydroisoindole-1,3-dione.

N-*Benzoylsuccinimide*.—This compound [38] absorbed less than 5 mol. (540 ml.) of hydrogen. Extraction of the products with ice-cold light petroleum gave an oil (0·48 g.) from which pure cyclohexylmethanol was recovered as above. The solid residue (0·46 g.) from the extraction yielded, on fractional crystallisation from ethyl acetate, succinimide (0·34 g.) and cyclohexanecarboxamide (33 mg.). The latter was identified by direct comparison with an authentic sample.

N-*Pivaloylsuccinimide*.—Pivaloyl chloride (4·0 g.) was added dropwise to succinimide (3·2 g.) in pyridine at 0° and the resulting solution was left at 20° for 12 hr. Dilution with water precipitated an oil, which slowly solidified. Crystallisation from methanol gave N-*pivaloylsuccinimide* (2·5 g.) as large flakes, m.p. 100° (Found: C, 58·9; H, 7·25. $C_9H_{13}NO_3$ requires C, 59·0; H, 7·15%); $\nu_{max.}$ 1792, 1733, and 1706 cm.$^{-1}$. Hydrogenation of this compound proceeded with the uptake of 2 mol. (243 ml.) of hydrogen. Only one product, succinimide, was visible on t.l.c. (ethyl acetate). Removal of the catalyst and most of the solvent gave succinimide (0·35 g.) and a further amount (0·13 g.) was recovered after the addition of light petroleum. Evaporation of the solvent left an oil which was substantially neopentyl alcohol (i.r. and n.m.r.).

N-*Pivaloylphthalimide*.—Pivaloyl chloride (4·0 g.) was added dropwise to a suspension of phthalimide (4·9 g.) in pyridine (10 ml.) at 0° and this mixture was left for 24 hr. at 20°. Addition of water precipitated N-*pivaloylphthalimide* (5·4 g.), which crystallised from light petroleum as large flakes, m.p. 84–85° (Found: C, 67·8; H, 5·6. $C_{13}H_{13}NO_3$ requires C, 67·5; H, 5·65%); $\nu_{max.}$ 1784, 1733, 1711, 1609, and 728 cm.$^{-1}$. On hydrogenation, *N*-pivaloylphthalimide absorbed *ca.* 4·5 mol. (430 ml.) of hydrogen. T.l.c. of the resulting mixture showed the presence of one major and four (less polar) minor products and also traces of polar material. Removal of the catalyst and solvent and extraction of the residue with boiling light petroleum left octahydroisoindole-1,3-dione (0·48 g.), m.p. 132—134°. Preparative t.l.c. [ethyl acetate–light petroleum (3 : 7)] of the soluble material gave the principal of the less-polar products, *cis*-octahydrobenzo[*c*]furan-1-one and the polar product, pivalamide, both of which were identified by comparison with authentic samples.

N-*Isobutyrylphthalimide*.—This compound [39] absorbed less than 4·5 mol. (460 ml.) of hydrogen. The resulting mixture contained (t.l.c.) two major products and a small amount of polar material. Removal of the catalyst and solvent and extraction with boiling light petroleum left octahydroisoindole-1,3-dione (0·28 g.). The petroleum-soluble fraction (0·53 g.), on crystallisation from that solvent, gave 2-*isobutyryl*-3-*hydroxyoctahydroisoindol*-1-*one* (IV; R = $COCHMe_2$), m.p. 104—105°, as white needles (Found: C, 64·1; H, 8·5. $C_{12}H_{19}NO_3$ requires C, 63·95; H, 8·5%); $\nu_{max.}$ 3425 1736, and 1675 cm.$^{-1}$; τ 7·5—9·2 (m, 9H), 8·85 (d, *J* 6·5 Hz, 3H), 8·83 (d, *J* 6·5 Hz, 3H), 6·97 (m, 1H), 6·28 (septet, *J* 6·5 Hz, 1H), 6·00 (d, *J* 3 Hz, 1H; lost on D_2O equil.), and 4·60 (d, *J* 3 Hz, 1H; s on D_2O equil.).

Partial Hydrogenations: N-*Acetylphthalimide*.—This acyl imide (1·00 g.) in ethyl acetate (100 ml.) was hydrogenated in the presence of PtO_2 (0·20 g.); the reaction was stopped when *ca.* 3 mol. (350 ml.) of hydrogen had been absorbed. T.l.c. of the reaction mixture showed the presence of 2-acetyl-3-hydroxyoctahydroisoindol-1-one (IV; R = Ac) and more polar products; 2-acetyloctahydroisoindole-1,3-dione or other less-polar compounds were absent. Work-up and crystallisation of the residue from ethyl acetate–light petroleum gave first the hydroxyoctahydroindolone (IV; R = Ac) (0·28 g.) and then 2-acetyl-3-hydroxyoctahydroisoindol-1-one [40] (X; R = Ac) (0·16 g.), m.p. 162°, which was identified by elemental analysis and by i.r. and n.m.r. spectroscopy. Octahydroisoindole-1,3-dione (70 mg.) was recovered from the mother liquors.

2-*Acetyloctahydroisoindole*-1,3-*dione*.— Octahydroisoindole-1,3-dione (3·0 g.) was heated in refluxing acetic anhydride (15 ml.) for 16 hr. Work-up gave a yellow oil which slowly solidified and furnished, after several recrystallisations from ethyl acetate–light petroleum, white needles of 2-*acetyloctahydroisoindole*-1,3-*dione* (0·90 g.), m.p. 69° (Found: C, 61·5; H, 6.6. $C_{10}H_{13}NO_3$ requires C, 61·5; H, 6·7%); $\nu_{max.}$ 1795, 1745, and 1707 cm.$^{-1}$. This derivative (0·50 g.) with PtO_2 (0·17 g.), in ethyl acetate (25 ml.) absorbed hydrogen (72 ml.) and produced a mixture containing (t.l.c.) two major components and a little polar material. Removal of the catalyst and solvent and extraction of the residue with warm light petroleum left octahydroisoindole-1,3-dione (0·13 g.). The petroleum-soluble fraction (0·33 g.) yielded 2-acetyl-3-hydroxyoctahydroisoindol-1-one (IV; R = Ac) on crystallisation from that solvent.

N-*Ethoxycarbonylphthalimide*.—The hydrogenation of this compound (1·00 g.) with PtO_2 (0·13 g.) in ethyl acetate (50 ml.) was stopped when less than 2 mol. (200 ml.)

[38] A. W. Titherley, *J. Chem. Soc.*, 1904, **85**, 1679.

[39] C. D. Hurd and M. F. Dull, *J. Amer. Chem. Soc.*, 1932, **54**, 2432.

[40] R. D. Reynolds and R. J. Conboy, *J. Org. Chem.*, 1965. **30**, 2251.

of hydrogen had been absorbed. T.l.c. showed the presence of two pairs of close-running products, having mobilities similar to those of starting material (less polar pair) and 2-ethoxycarbonyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO_2Et) (more polar pair). Column chromatography over silica gel and elution with ethyl acetate–benzene (1 : 19) gave a fraction (0·45 g.) containing the two less-polar components. Crystallisation from ethyl acetate–light petroleum afforded *N*-ethoxycarbonylphthalimide while the mother liquors contained the second component, 2-ethoxycarbonyloctahydroisoindole-1,3-dione (n.m.r.). Further elution, first with ethyl acetate–benzene (2 : 23), gave a fraction (0·18 g.) containing all four components, and subsequently with ethyl acetate–benzene (1 : 9) a fraction (0·31 g.) containing the two polar components. Crystallisation of this last fraction from ethyl acetate–light petroleum gave *2-ethoxycarbonyl-3-hydroxydihydroisoindole-1,3-dione* (X; R = CO_2Et), m.p. 137° (from ethyl acetate) (Found: C, 59·65; H, 5·0. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0%); $\nu_{max.}$ 3460, 1772, 1692, 1618, and 702 $cm.^{-1}$; τ 8·61 (t, *J* 7 Hz, 3H), 5·59 (q, *J* 7 Hz, 2H), 5·44 (d, *J* 4 Hz, 1H; lost on D_2O equil.), 3·56 (d, *J* 4 Hz, 1H; s on D_2O equil.), and 2·05—2·65 (m, 4H). The mother liquors contained the second component, 2-ethoxycarbonyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO_2Et) (n.m.r.).

2-Ethoxycarbonyloctahydroisoindole-1,3-dione.—The potassium salt of octahydroisoindole-1,3-dione (3 g.) was heated with ethyl chloroformate (2 g.) in refluxing dry benzene for 6 hr. Insoluble salts were filtered off and the benzene was evaporated to give a yellow oil. Chromatography of this over silica gel and elution with ethyl acetate–benzene (3 : 97) gave *2-ethoxycarbonyloctahydroisoindole-1,3-dione* (0·46 g.), m.p. 71° (from chloroform–light petroleum) (Found: C, 58·3; H, 6·75. $C_{11}H_{15}NO_4$ requires C, 58·65; H, 6·7%); $\nu_{max.}$ 1805, 1785, and 1716 $cm.^{-1}$; τ 8·60 (t, *J* 7 Hz; superimposed on m, 7H), 8·13 (m, 4H), 7·02 (m, 2H), and 5.5 (q, *J* 7 Hz, 2H). Hydrogenation of this compound (0·25 g.), with PtO_2 (0·10 g.) in ethyl acetate (25 ml.) proceeded with the uptake of 30 ml. of hydrogen and formation of virtually pure (t.l.c. and n.m.r.) 2-ethoxycarbonyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO_2Et).

2-Ethoxycarbonyl-3-hydroxyoctahydroisoindol-1-one (X; R = CO_2Et).—The hydrogenation of this compound (0·30 g.), with PtO_2 (0·10 g.) in ethyl acetate (25 ml.) proceeded with the uptake of 3 mol. (88 ml.) of hydrogen and the formation of a single (t.l.c.) product 2-ethoxycarbonyl-3-hydroxyoctahydroisoindol-1-one (IV; R = CO_2Et).

2-Dimethylcarbamoyloctahydroisoindole-1,3-dione.—The hydrogenation of 2-dimethylcarbamoyloctahydroisoindole-1,3-dione (0·10 g., with PtO_2 (0·10 g.) in ethyl acetate (25 ml.) proceeded very slowly and after 16 hr. was still incomplete; a mixture of starting material and 2-dimethylcarbamoyl-3-hydroxyoctahydroisoindol-1-one (IV; R = $CONMe_2$) was recovered.

The Preparation of 2-Acyl-3-hydroxydihydroisoindol-1-ones.—2-Ethoxycarbonylphthalimide (1·5 g.) was hydrogenated in dry ethanol (50 ml.) over Pd–C (10%; 1·0 g.); the reaction was stopped after 10 hr. when *ca.* 1 mol. (150 ml.) of hydrogen had been absorbed. Removal of the catalyst and solvent and crystallisation of the residue from ethyl acetate gave 2-ethoxycarbonyl-3-hydroxydihydroisoindol-1-one (X; R = CO_2Et) (1·2 g.), m.p. 137°. *N*-Ethoxycarbonylphthalimide under similar conditions but with ethyl acetate as solvent required 16 hr. for the absorption of 1 mol. of hydrogen. With a prolonged period of hydrogenation in either ethanol or ethyl acetate a very slow further uptake of hydrogen was observed.

N-Acetylphthalimide (1·0 g.) with 10% Pd–C (0·5 g.) in ethanol (100 ml.) absorbed 1 mol. of hydrogen in 6 hr. and gave 2-acetyl-3-hydroxydihydroisoindol-1-one (X; R = Ac) (0·70 g.), m.p. 162° (from ethyl acetate).

N-Isobutyrylphthalimide (1·0 g.), with 10% Pd–C (1·0 g.) in ethyl acetate (75 ml.) absorbed just over 1 mol. of hydrogen in 18 hr. The product, *3-hydroxy-2-isobutyryldihydroisoindol-1-one* (X; R = $COCHMe_2$) (0·76 g.) on crystallisation from light petroleum formed white prisms, m.p. 89—90° (Found: C, 65·7; H, 5·9. $C_{12}H_{13}NO_3$ requires C, 65·75; H, 6·0%); $\nu_{max.}$ 3460, 1717, 1691, 759, and 706 $cm.^{-1}$; τ 8·73 (d, *J* 6·5 Hz, 3H), 8·72 (d, *J* 6·5 Hz, 3H), 6·08 (septet, *J* 6·5 Hz, 1H), 5·21 (d, *J* 3 Hz, 1H; lost on D_2O equil.), 3·43 (d, *J* 3 Hz, 1H; s on D_2O equil.), and 2·00—2·60 (m, 4H).

N-Pivaloylphthalimide (1·0 g.), with 10% Pd–C (1·0 g.) in ethyl acetate (100 ml.) required 48 hr. for the uptake of 1 mol. of hydrogen. Work-up and crystallisation of the product from light petroleum gave large prisms of *3-hydroxy-2-pivaloyldihydroisoindol-1-one* (X; R = $COCMe_3$) (0·35 g.), m.p. 82—83° (Found: C, 66·95; H, 6·45. $C_{13}H_{15}NO_3$ requires C, 66·95; H, 6·5%); $\nu_{max.}$ 3495, 1736, 1688, 1619, 773, 744, and 708 $cm.^{-1}$; τ 8·58 (s, 9H), 5·22 (d, *J* 4 Hz, 1H; lost on D_2O equil.), 3·42 (d, *J* 4 Hz, 1H; s on D_2O equil.), and 2·0–2·6 (m, 4H).

N-Ethoxycarbonylphthalimide (1·0 g.), with 10% Pd–C (0·5 g.) in ethanol (100 ml.) absorbed 1 mol. of hydrogen during 8 hr. The reaction mixture was initially warmed to 50° on a water-bath to keep the substrate in solution. Removal of the catalyst and solvent and crystallisation of the residue from ethyl acetate gave *2-methoxycarbonyl-3-hydroxydihydroisoindol-1-one* (X; R = CO_2Me) (0·6 g.), m.p. 175—177° (Found: C, 57·9; H, 4·5. $C_{10}H_9NO_4$ requires C, 58·0; H, 4·4%); $\nu_{max.}$ 3460, 1765, 1694, 1615, and 708 $cm.^{-1}$.

Hydrogenation of Acyl Imides over Platinum Oxide Supplied by Johnson Matthey.—*N*-Dimethylcarbamoylphthalimide (1·0 g.) in ethyl acetate (50 ml.) was hydrogenated over this batch (no. 59M) of PtO_2 (0·3 g.). Approximately 1 mol. of hydrogen was absorbed during 1 hr. and a further 0·75 mole during 24 hr. T.l.c. showed the presence of one major and one minor product. Work-up and crystallisation of the mixture from ethyl acetate gave the major product, *2-dimethylcarbamoyl-3-hydroxydihydroisoindol-1-one* (X; R = $CONMe_2$) (0·42 g.) as needles, m.p. 169—171° (Found: C, 60·15; H, 5·35. $C_{11}H_{12}N_2O_3$ requires C, 60·0; H, 5·5%); $\nu_{max.}$ 3390, 1704, 1688, 1619, and 710 $cm.^{-1}$; τ 6·93 (s, 6H), 4·14 (d, *J* 6 Hz, 1H; lost on D_2O equil.), 3·35 (d, *J* 6 Hz, 1H; s on D_2O equil.), and 2·08—2·60 (m, 4H). This hydrogenation was repeated but the reaction was stopped when *ca.* 1 mol. (100 ml.) of hydrogen had been absorbed (55 min.). The major product (0·65 g., m.p. 169—171°) was again recovered by crystallisation from ethyl acetate. The mother liquors contained (n.m.r.) this major product, starting material, and the hexahydro-derivative of the latter in the *ca.* proportion of 1 : 1 : 1 (n.m.r.).

N-Acetylphthalimide (1·0 g.), with PtO_2 (0·3 g.) in ethyl acetate (100 ml.) took up less than 4 mol. (410 ml.) of hydrogen during 24 hr. Work-up and extraction of the residue with warm light petroleum left 2-acetyl-3-hydroxydihydroisoindol-1-one (0·16 g.), m.p. 162° (from ethyl acetate). The petroleum-soluble fraction on crystallisation

from that solvent gave 2-acetyl-3-hydroxyoctahydroisoindol-1-one (0·71 g.), m.p. 81°. When this hydrogenation was repeated and stopped when 1 mol. of hydrogen had been absorbed (30 min.) 2-acetyl-3-hydroxydihydroisoindol-1-one (0·55 g.; m.p. 162°) was obtained.

N-Methoxycarbonylphthalimide (1·0 g.), with PtO_2 (0·3 g.) in ethyl acetate (50 ml.) took up 1 mol. of hydrogen during 45 min. Work-up and crystallisation of the residue from ethyl acetate gave 2-ethoxycarbonyl-3-hydroxydihydroisoindol-1-one (0·6 g.), m.p. 137°.

N-Isobutyrylphthalimide (1·0 g.), with PtO_2 (0·3 g.) in ethyl acetate (75 ml.) absorbed 3·5 mol. (350 ml.) of hydrogen in 24 hr. Work-up and chromatography of the products over silica gel (50 g.) and elution with ethyl acetate–benzene (1 : 19) gave a mixture (t.l.c.) (0·79 g.) of 3-hydroxy-2-isobutyryldihydroisoindol-1-one (X; R = $COCHMe_2$) and its hexahydro-derivative. They were separated by fractional crystallisation from light petroleum, the former (0·21 g.) having m.p. 89—90° and the latter (0·26 g.) m.p. 104—105°. Elution with ethyl acetate–benzene (3 : 17) gave octahydroisoindole-1,3-dione (0·12 g.) m.p. 136°.

N-Pivaloylphthalimide (1·0 g.), with PtO_2 (0·3 g.) in ethyl acetate (50 ml.) required 24 hr. for the uptake of 3·5 mol. (340 ml.) of hydrogen. Work-up and chromatography of the products (6 components on t.l.c.) over silica gel (50 g.) gave octahydroisoindole-1,3-dione (230 mg.) and pivalamide (105 mg.).

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