Preparation of α,α,ω,ω-Tetrahydroperfluoroalkanediol Di-*n*-perfluorobutyrates.—*n*-Perfluorobutyryl chloride (10% excess) was added dropwise to 13.2 g. (0.0623 mole) of 1,1,5,5-tetrahydro-1,5-perfluoropentanediol heated to above the melting point. The reaction was carried out for two days, the mixture being finally heated to 150°, and was followed by the rate of formation of hydrogen chloride gas. The product was then treated with 10% potassium carbonate solution until the upper aqueous layer gave a negative test for chloride ion. The lower layer was dried over anhydrous magnesium sulfate and was finally fractionally distilled under vacuum. No unreacted glycol was detected, and there were isolated 23.25 g. (62% yield) of 1,1,5,5-tetrahydro-1,5-perfluoropentanediol di-*n*-perfluorobutyrate, b.p. 131° at 30 mm.

In a similar manner, 26.2 g. (0.1 mole) of 1,1,6,6-tetrahydro-1,6-perfluorohexanediol reacted with 5% excess of perfluorobutyryl chloride to give 20 g. of the desired diester, b.p. 82–85° (mostly 85°) at 1.5 mm., as well as 15 g. of recovered glycol, most of which precipitated out on cooling the reaction mixture. This represented a 30.6% conversion and a 71.6% yield of 1,1,6,6-tetrahydro-1,6-perfluorohexanediol di-*n*-perfluorobutyrate.

Preparation of Bis-(*n*-1,1-dihydroperfluorobutyl) Perfluoroglutarate.—Fifty-two grams (0.234 mole) of perfluoroglutaric anhydride prepared as previously described[4] was allowed to react with *n*-1,1-dihydroperfluorobutanol (93.6 g., 0.468 mole) at 180° for two days. Upon rectification there were isolated two compounds, namely, bis-(*n*-1,1-dihydroperfluorobutyl) perfluoroglutarate, III (83.2 g., 58.8%), which was washed and dried prior to analysis, and mono-*n*-1,1-dihydroperfluorobutyl perfluoroglutarate, I (25.8 g., 26.1%). Thus the total yield of the two products based on the anhydride was 84.9% of theory. The acid-ester, I, (20.0 g., 0.0474 mole) reacted with 10% excess phosphorus pentachloride to yield 14.4 g. (69.0%) of mono-*n*-1,1-dihydroperfluorobutyl perfluoroglutaryl chloride (II). This acid chloride-ester reacted with equimolar quantities of 1,1-dihydroperfluorobutanol in the previously described fashion to yield additional diester III.

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[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF NORTH CAROLINA]

Palladium Catalysis. V.[1] The Hydrogenation of α-Oximino Ketones[2,3]

BY YEN-TSAI CHANG[4] AND WALTER H. HARTUNG

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A mechanism is proposed for the hydrogenation of α-oximino ketones which explains the stereospecificity of the reaction, whereby a single racemic modification is formed. The polar oxygen and nitrogen atoms of the substrate molecule adsorb on the catalyst to form a rigid ring-like structure. 1,4-Addition of hydrogen, followed by *cis*-addition of the second molecule of hydrogen, can give rise to only a single steric structure. Or, 1,2-addition to the same original ring-like complex forms an intermediate stage of which the steric structure determines the approach of the additional hydrogen molecule to the 3,4-double bond, giving rise to the same racemic modification.

The reduction of α-oximino ketones to the corresponding amino alcohols affords a convenient route to many compounds with pharmacological activity.[5] The mechanism by which these reactions proceed is of interest, first, because of the type of products that have been identified at the intermediate stages of hydrogenation and, second, because the amino alcohol is isolated always as a single racemic modification, although two diastereoisomeric racemates might be expected.

The character of the isolable intermediate stages, where more than one molecule of hydrogen is taken up, as well as of the final product itself, is a function of the catalytic process, as Linstead and co-workers have shown.[6] These authors, who reduced diphenic acid and phenanthrene derivatives over platinum oxide, explain the formation of perhydro products by postulating complete saturation at a single contact of the substrate molecule with the catalyst, that is, there is minimum desorption at partially hydrogenated stages; and they account for the predominant formation of a single racemic product on the basis of specific steric structure of the substrate–catalyst complex. Experimental results with α-oximino ketones suggest that somewhat analogous phenomena obtain; not all the hypothetical intermediate products have been obtained, and the final amino alcohol possesses a single steric structure.

The oximino ketones used in this study may be divided into three types, as in Table I, depending

TABLE I

α-OXIMINO KETONES

For types B and C the indicated likely pathways come into consideration.

Ar—CO—C—R
‖
NOH

	Ar =	R =	M.p. (uncor.), °C.	Ref.
Type A	C_6H_5	$COOC_2H_5$	118–119	5d
Type B	C_6H_5	H	124–126	7
	p-HOC_6H_4	CH_3	178–179	5a
	3,4-$(HO)_2C_6H_3$	CH_3	161–162	5a
Type C	C_6H_5	CH_3	113–114	8
	C_6H_5	$CH_2C_6H_5$	125–126	1

(1) For No. IV see W. H. Hartung and Y. T. Chang, THIS JOURNAL, **74**, 5927 (1952).

(2) Also No. XIX in Amino Alcohol Series; for No. XVIII see J. P. LaRocca and W. H. Hartung, *J. Am. Pharm. Assoc.*, **40**, 140 (1951).

(3) Presented before the Medicinal Chemistry Section, XIIth International Congress of Pure and Applied Chemistry, New York, September 12, 1951.

(4) Fellow, American Foundation for Pharmaceutical Education, 1948-1951.

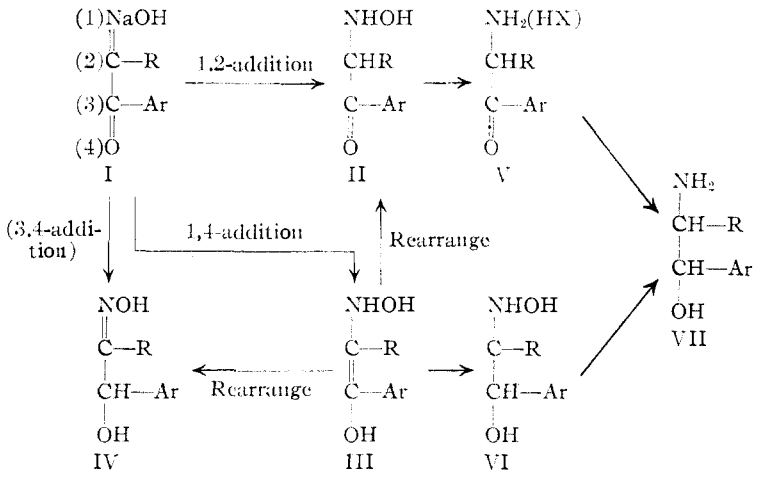
(5) (a) W. H. Hartung, J. C. Munch, E. Miller and F. S. Crossley, THIS JOURNAL, **53**, 4149 (1931); (b) H. K. Iwamoto and W. H. Hartung, *J. Org. Chem.*, **9**, 513 (1944); (c) B. L. Zenitz and W. H. Hartung, *ibid.*, **11**, 444 (1946); (d) W. H. Hartung, T. T. Dittrich and Y. Chang, THIS JOURNAL, **75**, 238 (1953); (e) R. Baltzly and J. S. Buck, *ibid.*, **62**, 164 (1940).

(6) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. H. Whetstone, *ibid.*, **64**, 1985 (1942).

(7) W. M. Whaley, thesis, University of Maryland, 1947.

(8) Obtained from Sharp and Dohme through the courtesy of Dr. James M. Sprague.

on the partially hydrogenated intermediate products which have been isolated and identified.



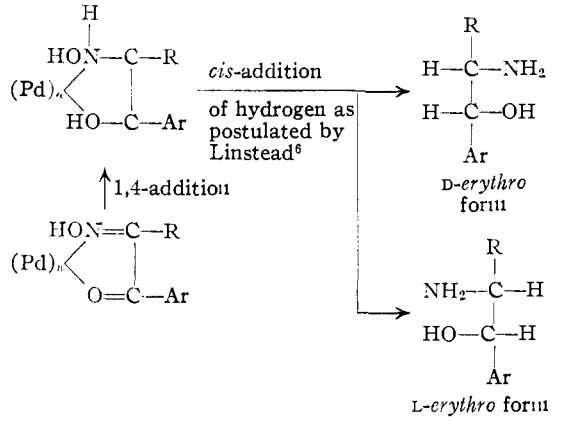
Type A is represented by ethyl benzoyloximinoacetate, which yields the ethyl ester of β-phenylserine in only one racemic form with no evidence of the corresponding amino ketone or amino alcohol. When the hydrogenation was interrupted before it stopped of its own accord, only the ester of phenylserine and unchanged starting oximino ketone were isolated. These observations do not illuminate the hydrogenation route, except that they indicate predominantly a transfer of three molecules of hydrogen within the substrate–catalyst–hydrogen complex before the reduced molecule is desorbed.

Type B α-oximino ketones in acidic medium yield only amino ketones, structure V, as the first stage of reduction. Their formation may be explained by having the first molecule of hydrogen add to the conjugated system by either the 1,2-route, or by the 1,4-path followed, as indicated, by rearrangement. Hydrogenation in alkaline medium gives poor or negligible yields of amino alcohol; hence no further light is obtained here.

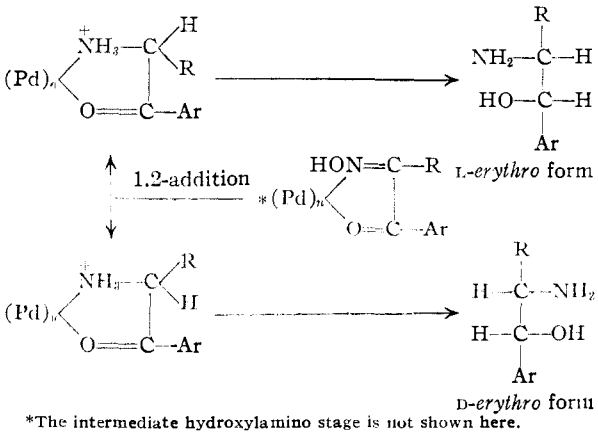
Type C compounds yield, depending on the catalyst[1] and the *p*H of the medium, amino ketone, oximino alcohol and amino alcohol. In alkaline medium, which results in good yields of amino alcohol, the 1,2-addition, *i.e.*, *via* I–II–V–VII in the hypothetical pathways, is hardly likely since the free amino ketones of structure V readily form dihydropyrazines; unless, of course, the adsorption of V on the catalyst surface lends it stability. The formation of the oximino alcohol, structure IV, may be explained by 3,4-addition to the conjugated system; it may also have its origin in a rearrangement of the 1,4-addition intermediate, structure III. The formation of approximately equal amounts of oximino alcohol, IV, and of amino alcohol, VII, with pure palladium-on-charcoal[1] is adequately explained by 1,4-addition of the first hydrogen molecule, then rearrangement in both directions, to II which proceeds *via* V to VII, and to IV which is resistant to further hydrogenation. If this assumption is correct, then the question arises as to the function of the promoters such as rhodium and platinum, which eliminate the formation of IV; do they act by influencing the direction of the rearrangement of III or do they favor 1,2-addition?

Whatever may be the actual mechanism, the sequence of the addition of the hydrogen molecules still does not explain the stereospecificity of the reaction. On the basis of present information it appears established that phenylpropanolamine and the ethyl ester of β-phenylserine formed by catalytic hydrogenation of the intermediate oximino ketones are of the *erythro* configuration.[9] It is reasonable to believe that the other compounds are of the same series.

If, from a consideration of the surface activity of the catalyst and the polarity of the nitrogen and oxygen atoms of the substrate molecule, one postulates a rigid ring-like complex, then the substituents of this cycle occupy positions which favor, on addition of hydrogen from the catalyst below the plane of the adsorbed molecule, the formation of a single racemic isomer of the amino alcohol, thus



Or, if the first molecule of hydrogen adds 1,2- to the conjugate system, the mechanism becomes



*The intermediate hydroxylamino stage is not shown here.

(9) The configurational correlation studies are quite extensive, for which the following are particularly pertinent: (a) W. J. Close, *J. Org. Chem.*, **15**, 1131 (1950); (b) K. N. F. Shaw and S. W. Fox, abstracts, p. 28N, Chicago Meeting American Chemical Society, September, 1950; (c) G. Carrara and G. Weitnauer, *Gazz. chim. ital.*, **79**, 856 (1949); (d) D. Billet, *Compt. rend.*, **230**, 1074 (1950); (e) K. Vogler, *Helv. Chim. Acta*, **33**, 2111 (1950); (f) M. C. Rebstock, H. M. Crooks, J. Controulis and Q. R. Bartz, THIS JOURNAL, **71**, 2458 (1949).

After the addition of hydrogen to the C:N bond the R group is no longer in the plane of the cycle; further addition of hydrogen across the carbonyl double bond from the side opposite R, either with or without catalyst hindrance,[6] gives rise to the same racemic configurations as before.

These explanations are more clearly appreciated when seen with models. And an adaptation of these postulates explains the formation of (−)-ephedrine by the hydrogenation of (−)-phenylacetylcarbinol in the presence of methylamine.[10]

Experimental

The hydrogenation results with α-oximinopropiophenone and 1,3-diphenyl-2-oximino-1-propanone are described elsewhere.[1]

The reduction of oximinoacetophenone, and of the phenolic oximinopropiophenones in ethanolic HCl was repeated, the results agreeing substantially with those already published.[5a] Oximinoacetophenone hydrogenated in alkaline medium gave only small yields of phenylethanolamine, and there is indication that an appreciable amount of 2,5-diphenylpyrazine was formed.

Ethyl Ester of *erythro*-β-Phenylserine.—One-tenth mole (22.1 g.) of ethyl benzoyloximinoacetate was dissolved in 100 ml. of 3 *N* absolute ethanolic HCl and shaken with 2 g. of catalyst prepared from pure palladium and Nuchar as described by Hartung and Chang.[1] The reaction proceeded smoothly until 0.269 mole hydrogen was taken up. Crystals had formed in the flask. Crystals and catalyst were collected on a buchner funnel. The filtrate was allowed to evaporate to dryness in the open. The catalyst was extracted with hot water, first with 100 ml. and then 50 ml. The aqueous extracts were allowed to cool, and then used to dissolve the residue from the alcoholic filtrate, then treated with 30 ml. of concd. NH_3. The crystals which formed were filtered off and the filtrate was extracted with three 100-ml. portions of ether. The ether was volatilized and the residue added to the crystals, and the total crude base was crystallized from benzene crystals, m.p. 83–84°; obtained 15.4 g. Further recrystallization from dilute alcohol gave colorless crystals m.p. 85–86° (dec.); hydrochloride m.p. 170° (dec.). Reported values for *erythro*-phenylserine ethyl ester,[9a] base 85–86°, hydrochloride 176°.

Ten grams of phenylserine ethyl ester hydrochloride was dissolved in 20 ml. of warm water and to the solution was slowly added 40 ml. of 10% NaOH solution. A white crystalline mass separated, which quickly dissolved on shaking. The mixture was boiled for 2 minutes, cooled and carefully neutralized to litmus with dilute HCl, and then placed in a refrigerator overnight. Colorless, feather-like crystals were collected, dry weight 6.0 g. (82%), m.p. 180–184° (dec.). Recrystallization from 50% alcohol gave crystals m.p. 184–188° (dec.). Shaw and Fox[9b] report the free acid as m.p. 189–192° (dec.). A careful examination of all the hydrogenation products failed to reveal the presence of *threo*-isomer.

A twentieth mole of ethyl benzoyloximinoacetate in 100 ml. of 1.5 *N* absolute ethanolic HCl was reduced with 2 g. of Pd-on-Nuchar catalyst, as before. The reaction was interrupted when 0.104 mole of hydrogen had been taken up. Considerable crystallization had taken place, catalyst and crystals were removed by filtration; isolation and purification of product as before, showed presence of only unchanged oximino ketone and hydrochloride of the ethyl ester of *erythro*-β-phenylserine.

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(10) C. Neuberg and co-workers, *Biochem. Z.*, **115**, 282 (1921); **128**, 610 (1922).

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY]

The Polymerization of Allyl Compounds. VI. The Polymerization of Allyl-1-d_2 Acetate and the Mechanism of its Chain Termination

BY PAUL D. BARTLETT AND FRED A. TATE[1]

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Allyl acetate having deuterium at the α-position of the allyl group was polymerized by benzoyl peroxide in amounts from 0.25 to 2.00% by weight. The rates of polymerization were from 1.93 to 2.89 times those observed in identical experiments with undeuterated allyl acetate, and the average molecular weight of all the polymer so produced was 2.38 times as great for the deuterated as for the undeuterated material. These results confirm the conclusion previously reached on kinetic grounds that the chain terminating step in the polymerization of allyl acetate involves the transfer of hydrogen from the α-position of allyl acetate to a chain-carrying free radical. Assuming that all chains are terminated in this way, light hydrogen is estimated to be transferred in this atomic displacement reaction about three times as fast as deuterium. Chain transfer in the polymerization of allyl acetate must also proceed through the α-acetoxyallyl free radical.

The polymerization of allyl acetate shows a linear relation between the concentrations of monomer and of initiator throughout the consumption of the latter,[2] a behavior since observed also for α-methylstyrene,[3] isopropenyl acetate[4a,b] and vinylmesitylene.[5] The explanation originally suggested[2] appears to have gained general acceptance, although the evidence for it is entirely indirect. The kinetic chain is considered to be terminated by the transfer of a hydrogen atom to a growing radical from a monomer molecule with the formation of an acetoxyallyl radical, I

$$CH_2{=}CHCHOOCCH_3 \longleftrightarrow CH_2CH{=}CHOOCCH_3$$
$$\text{I}$$

which is so stabilized by virtue of its allylic structure that it resists reacting with a monomer long enough to combine instead with another radical either of its own or of the chain-propagating kind.

Through the use of the isotope-rate effect a tool has recently become available for testing the participation of a particular hydrogen atom in a hydrogen-transfer process. In a number of examples in which hydrogen is transferred as a proton, the rate of transfer for protium is found to be from four to ten times as great as for deuterium.[6a,b] Although this rate ratio for the hydrogen isotopes has not been thoroughly investigated for the

(1) U. S. Rubber Company Fellow at Harvard University, 1950–1951.

(2) P. D. Bartlett and R. Altschul, THIS JOURNAL, **67**, 816 (1945).

(3) G. Smets and L. de Haes, *Bull. soc. chim. Belg.*, **59**, 13 (1950).

(4) (a) R. Hart and G. Smets, *J. Polymer Sci.*, **5**, 55 (1950); (b) N. G. Gaylord and F. R. Eirich, *ibid.*, **5**, 743 (1950).

(5) A. de Pauw and G. Smets, *Bull. soc. chim. Belg.*, **59**, 629 (1950).

(6) (a) See W. F. K. Wynne-Jones, *J. Chem. Phys.*, **2**, 381 (1934); (b) F. H. Westheimer and N. Nicolaides, THIS JOURNAL, **71**, 25 (1949), and references there cited.