

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP & DOHME, INC.]

PALLADIUM CATALYST. II. THE EFFECT OF HYDROGEN CHLORIDE IN THE HYDROGENATION OF ISONITROSO KETONES

BY WALTER H. HARTUNG

RECEIVED MARCH 9, 1931

PUBLISHED JUNE 8, 1931

It has been shown that benzaldoxime and benzonitrile when reduced catalytically, with palladium on charcoal, form pure primary benzylamine if the proper amount of hydrogen chloride is present, whereas in the absence of the acid a mixture of primary and secondary bases results.¹

Profiting by this knowledge it has been possible to prepare a series of amino alcohols of considerable physiological interest by reducing isonitroso ketones of the general formula $\text{ARCOCR}=\text{NOH}$ under similar conditions. The oximino ketone is dissolved in absolute alcohol containing three equivalents of hydrogen chloride and is then agitated with the catalyst in an atmosphere of hydrogen until reduction practically ceases. Under these conditions all isonitroso ketones in which the aromatic portion is a hydrocarbon radical, that is, is phenyl, *m*- and *p*-tolyl, naphthyl, the reduction goes smoothly and completely to the corresponding amino alcohol.² In those cases where the aromatic portion of the molecule is substituted by a phenolic hydroxyl or its methyl ether, the reduction stops at the amino ketone stage and the resulting compound may be isolated and purified, as its salt, and then in aqueous solution and with new catalyst reduced to the corresponding amino alcohol. The reduction of the phenolic compounds will be described in a subsequent paper, the reason for mentioning them at this time being to emphasize the fact that in each case pure primary amine is obtained.

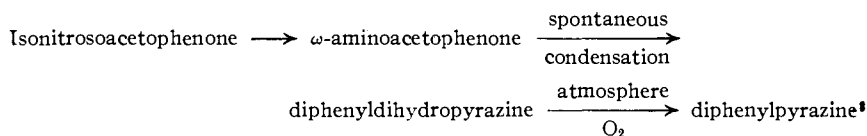
A second point is that under the conditions employed the oximino group apparently is a readier receptor for hydrogen than is the ketonic portion. This is shown not only in the case of the phenolic derivatives but also with isonitrosoacetophenone and in isolated cases with isonitrosopropiophenone.

Isonitrosoacetophenone, as already described,² is as a rule first hydrogenated to the corresponding intermediate amino ketone stage. With isonitrosopropiophenone the rule is for the reduction to proceed to the corresponding amino alcohol, but in several instances out of many only two-thirds of the calculated hydrogen was taken up and the product when isolated proved to be pure hydrochloride of phenyl- α -aminoethyl ketone, $\text{C}_6\text{H}_5\text{COCH}(\text{CH}_3)\text{NH}_2\cdot\text{HCl}$. Hence the evidence would seem quite conclusive that under the conditions here employed, of the two groups capable of being hydrogenated the oximino is the more susceptible.

¹ Hartung, *THIS JOURNAL*, **50**, 3370 (1928).

² Hartung and Munch, *ibid.*, **51**, 2262 (1929); Hartung, Munch, Deckert and Crossley, *ibid.*, **52**, 3317 (1930).

In neutral alcoholic solution, that is, in the absence of hydrogen chloride, the product isolated from the reduction of isonitrosoacetophenone was 2,5-diphenylpyrazine. But as already explained² this end-product results in the following manner



that is to say, reduction in this case takes place at the oximino group, which is quite what one might expect in view of the foregoing discussion.

The hydrogenation of higher homologs in the absence of acid, however, follows a course that is most strikingly different, one which while theoretically possible was not anticipated because of the results already described.

A product obtained by the reduction of isonitrosopropiophenone, melting at 108–110° has been described as of unknown composition.² In a personal communication Dr. D. Holroyde Hey, of the University of Manchester, suggested that this product might be the oxime of phenylacetylcarbinol. Comparison with known phenylacetylcarbinol oxime supplied by him⁴ indicated the correctness of this suggestion and preparation of the corresponding semicarbazone lent confirmation. This could mean only one thing, *viz.*, that in this instance the ketonic carboxyl was affected and the oximino group remained unchanged. Further proof of this was found in the fact that products similarly obtained from isonitrosobutyrophenone and isonitrosohexanophenone, hitherto also unidentified, turned out to be the oximes of phenylpropionylcarbinol and phenylvalerylcarbinol, respectively.

In neutral absolute alcoholic solution hydrogen absorption does not, as a rule, cease when one molar equivalent has been taken up, nor does it continue until three molar equivalents, the amount necessary for complete reduction to the amino alcohol, have been used. However, when reduction is stopped, of itself or deliberately, after somewhat more than one equivalent of hydrogen has been taken up, the yield of carbinol ketoxime is a maximum, approaching theory, although other products are also formed. On the other hand, if hydrogenation proceeds to any great extent beyond this point, the amount of carbinol ketoxime becomes proportionately less and the quantity of other products becomes correspondingly greater. These other products have been identified as an ammonia (odor) and a mixture of primary, secondary and tertiary amines, separated according to Hinsberg's classical method with benzenesulfonyl chloride.

Such results indicate that under these conditions the first product is that in which the ketonic carbonyl is reduced to the carbinol, and then if further

² Compare also references 16, 17, 18 and 19 cited in Ref. 2.

⁴ Hey, *J. Chem. Soc.*, 232 (1930).

reduction does occur, the oximino group is affected, and it, in the absence of hydrogen chloride, behaves quite as one might expect from the results of previous experimenters with oximes,⁵ that is, it forms primary contaminated with secondary and tertiary amines.⁶

Another striking difference between reduction in neutral medium as compared to that in a solution containing hydrogen chloride is in the rate of hydrogen absorption. This is shown in Fig. 1, by the two representative curves. The conditions were identical except that in one three equivalents of hydrogen chloride were used, and in this one practically three times as much hydrogen was taken up in about one-third the time as in the other.

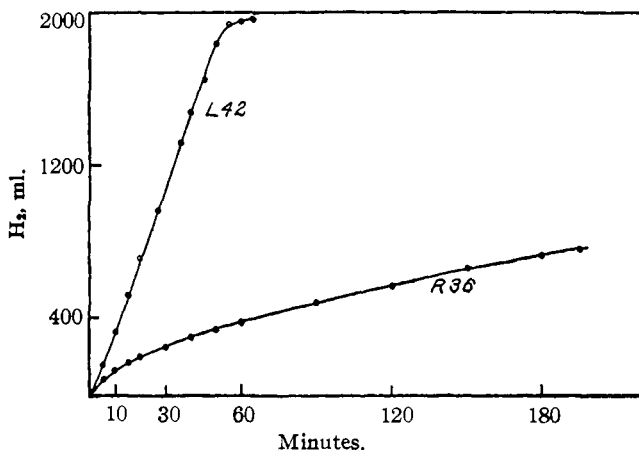
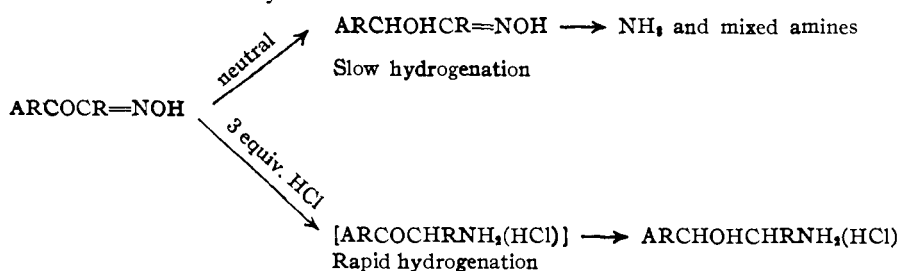


Fig. 1.—Curves showing difference in rates and extent of hydrogenation in absence and presence of hydrogen chloride. In each instance 4.9 g. of isonitrosopropiophenone (0.03 mole) in 100 ml. of absolute alcohol was used. R36 represents reduction in neutral medium and L42, in presence of 0.09 mole of hydrochloric acid.

In substance, then, the reduction of isonitroso ketones in absolute alcoholic solution may follow one of two courses

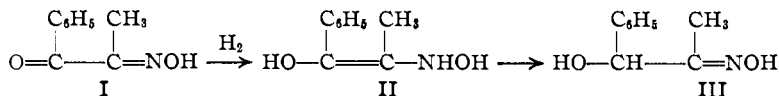


⁵ See references 1, 2, 3, 4 and 5 in Ref. 1.

⁶ It is of interest to note, in this connection, that Adkins and Cramer [THIS JOURNAL, 52, 4349 (1930)], with their nickel catalyst in neutral solvent, obtained pure primary amines from *o*-tolunitrile and isonitrosopropiophenone.

and the influence of the hydrogen chloride becomes apparent in three distinct ways. First, it is responsible for the hydrogenation of the oximino portion; second, it has a marked effect on the rate of hydrogenation; and, third, it prevents formation of contaminating secondary and tertiary bases.

In discussing the formation of the oxime of phenylacetylcarbinol, Hey⁴ suggests that this need not "necessarily signify that the oximino group is less susceptible to the action of the reducing agent," for he postulates 1,4-addition with a subsequent rearrangement of the intermediate hydroxyl-amino-alkenol (II) to the carbinol oxime (III)



Such an hypothesis is inadequate in that it does not show how the first intermediate (II) rearranges to form, in the presence of hydrogen chloride and after addition of another mole of hydrogen, the amino ketone (ArCO-CHRNH₂·HCl); and it fails to take into account the difference in rates of hydrogen absorption in neutral and acid media.

An explanation, not inconsistent with experimental results, might be given as follows. The oximino ketone and the hydrogen chloride form a complex or compound in which the electronic structure is so shifted as to make the oximino portion very susceptible to the entry of hydrogen. In the case where the aryl is a hydrocarbon, the susceptibility of the ketonic carbonyl may be unaffected or possibly also increased. If the aryl contains a phenolic hydroxyl or a methoxy group, this group may modify the degree but not the nature of this shift induced by the acid, so that the susceptibility of the carbonyl to reduction is reduced. Such an explanation is conceivable and does not complicate the picture.

Experimental

The apparatus and procedure for reduction have been described in the preceding papers. The only modification that need be mentioned is that the reaction flask was wrapped in a towel so that hydrogenation proceeded in the dark. Evidence, not yet conclusive, indicates that light may have an inhibiting effect; hence, in order to maintain external conditions as reproducible as possible the reduction was carried out in the wrapped flask.

Oxime of Phenylpropionylcarbinol, C₆H₅CHOHC(=NOH)C₂H₅.—Isonitrosobutyrophenone, 8.9 g., in 100 ml. of absolute alcohol, took up 950 ml. of hydrogen during 445 minutes. The catalyst was filtered off and the solvent evaporated under reduced pressure over sulfuric acid, leaving a yellow crystalline residue. After crystallization first from benzene and then from benzene-petroleum ether (60:40), the gray crystals began to sinter at 92° and melted at 97°.⁷

⁷ Tiffeneau and Lévy, *Bull. soc. chim.*, 37, 1247 (1925).

Oxime of Phenylvalerylcarbinol, $C_6H_5CHOHC(=NOH)C_4H_9$.—Products obtained four years ago by the hydrogenation of isonitrosohexanophenone in neutral absolute alcoholic solution were recrystallized from toluene and melted at 97° (corr.).⁸

Oxime of Phenylacetylcarbinol, $C_6H_5CHOHC(=NOH)CH_3$.—Only two representative experiments will be given.

Experiment R 36 (see Fig. 1). Three-hundredths mole (4.9 g.) of isonitrosopropiophenone in 100 ml. of absolute alcohol absorbed 760 ml. of hydrogen (0.0338 mole) during the course of 195 minutes. The catalyst was filtered off and the solvent evaporated. The larger portion of the residue, after recrystallization from toluene, was identified as the oxime of phenylacetylcarbinol, m. p. 113° (corr.). The toluene mother liquors were extracted with dilute hydrochloric acid; the acid extract on benzoylation formed a small amount of crystals which were very soluble in toluene, but could be forced from it by means of excess petroleum ether. These crystals formed an opaque melt at 164° (corr.) and are suspected of being a derivative of secondary amine. The benzoyl derivative of phenylpropanolamine melts at 143.5° (corr.).⁹

Experiment R 53. A twentieth mole (8.2 g.) of isonitrosopropiophenone in 100 cc. of absolute alcohol behaved as follows.

Hydrogen, ml.	Time, min.	Rate/min.	Hydrogen, ml.	Time, min.	Rate/min.
190	10	19	Fortified catalyst by adding 0.1 g. of $PdCl_2$		
410	30	10	1520	300	4
610	60	6	1900	450	3
870	120	4	Added 0.1 g. of $PdCl_2$		
1170	210	3	2010	480	3.7
			2060 (0.0915 mole)	510	1.7

The catalyst was filtered off. The filtrate had in it the odor of ammonia. The solvent was evaporated and the residue was taken up in hot toluene. On cooling, crystals settled out (4.1 g.), which were identified as phenylacetylcarbinol oxime. The toluene mother liquors were extracted with dilute hydrochloric acid to extract the bases. These were treated with benzenesulfonyl chloride in order to separate them by the well-known method of Hinsberg.¹⁰ The derivative of the primary amine (1 g. isolated) after crystallization from toluene melted at 127° (corr.), agreeing with the corresponding derivative prepared from known phenylpropanolamine. The derivative which should be from the secondary amine was a brown, amorphous solid. By filtering it in hot dilute alcoholic solution through charcoal, it was possible to obtain a yellow-brown product of indefinite crystalline form that melted at 110° (uncorr.). The composition of this substance is unknown. Analysis showed it to contain 4.42% nitrogen, whereas $(C_6H_5CHOHCH-CH_3)_2NSO_2C_6H_5$ should contain but 3.3% nitrogen.

The tertiary amine was isolated by extracting it from ethereal solution with dilute hydrochloric acid and evaporating this *in vacuo* over sulfuric acid and finally over phosphorus pentoxide. The residue began to sinter at 82° and melted at 88° (corr.). Its identity is also unknown. It contained 4.63% nitrogen, while the calculated nitrogen content for $(C_6H_5CHOHCH-CH_3)_3N \cdot HCl$ is 3.07%.

Hydrolysis of the oxime of phenylacetylcarbinol by warming with dilute acid gave good yields of the corresponding ketone alcohol.

Phenyl- α -aminoethyl ketone hydrochloride was obtained in one instance in very

⁸ Tiffeneau and Lévy give the melting point $95-96^\circ$.

⁹ Schmidt, *Arch. Pharm.*, **255**, 147 (1917), describes $C_6H_5CHOHCH(CH_3)NH-COC_6H_5$ as melting at 142° .

¹⁰ Hinsberg, *Ber.*, **23**, 2962 (1890); **33**, 3526 (1900).

pure form. A catalyst, double the regular size, was being used for the third time to reduce 65.2 g. of isonitrosopropiophenone; initial hydrogen absorption was 90 ml./min.; at the end of 220 minutes the rate was still 30 ml./min., but since 18,400 ml. of hydrogen had been taken up, that is, a slight excess over that calculated to give amino ketone, the reduction was purposely stopped at this point. The resulting product was purified by forcing it out of absolute alcoholic solution with ether and formed the characteristic red decomposing melt at 183.5° (corr.).¹¹

Summary

The effect of the presence of hydrogen chloride during the hydrogenation of α -oximino ketones, by means of palladium catalyst, has been described. The effect is manifested in three distinct ways. (1) It promotes the reduction of the oximino group. (2) It increases many fold the rate of hydrogenation. (3) It prevents the formation of contaminating secondary and tertiary bases.

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

DERIVATIVES OF OPTICALLY ACTIVE TRIARYLCARBINOLS AND THEIR HALOCHROMIC SALTS¹

BY EVERETT S. WALLIS

RECEIVED MARCH 12, 1931

PUBLISHED JUNE 8, 1931

Shortly after Gomberg's discovery of triphenylmethyl, Norris and Sanders² made the interesting observation that colorless triphenylchloromethane forms a dark brown crystalline salt with aluminum chloride of the formula $(C_6H_5)_3CCl \cdot AlCl_3$. Kehrman and Wentzel³ soon showed that this was a general property of triphenylchloromethane and they prepared double compounds with other metallic salts. Since then many investigators⁴ have studied these halochromic salts, and today we have a large number of colored double compounds of triarylmethyl halides with metallic salts, acids and halogens.

The question as to the constitution of these compounds and related substances such as the triarylmethyls and triphenylmethane dyes has long been debated. The problem has been approached both from the experimental and theoretical sides in the hope that a simple explanation for the color and salt-like nature of these compounds could be found. Following the observation that colorless triphenylchloromethane dis-

¹¹ Beilstein, 3d ed., Vol. III, supplement, p. 112.

¹ Presented before the Organic Division of the American Chemical Society in Indianapolis, Indiana, April, 1931.

² Norris and Sanders, *Am. Chem. J.*, **25**, 54, 117 (1901).

³ Kehrman and Wentzel, *Ber.*, **34**, 3818 (1901).

⁴ Gomberg, *ibid.*, **35**, 1822 (1902); Baeyer, *ibid.*, **38**, 1162 (1905); Tschitschibabin, *ibid.*, **40**, 1817 (1907); Meyer, *ibid.*, **41**, 2576 (1908); Wieland, *ibid.*, **42**, 3024 (1909); Gomberg and Cone, *Ann.*, **370**, 142 (1909); Schlenk, *ibid.*, **372**, 9, 25 (1910).