(28°, 60 atm.) was still an equilibrium mixture of end-product and intermediate peroxides. The most obvious interpretation of the data obtained in this investigation would favor the latter conclusion.

The writer takes this opportunity to thank Professor H. S. Lukens for help and suggestions obtained from him during the course of this work. Thanks are also due Mr. J. G. Butz for helpful suggestions.

Summary

A study has been made of some of the factors which influence the composition of the precipitate formed by adding the solution of a lead salt to sodium rosinate solution.

An apparatus has been devised in which all the steps in the preparation of the rosinate may be carried out in an inert atmosphere.

A method for the analysis of the metal content of rosinates has been proposed.

The course, extent and reversibility of the autoxidation of lead rosinate has been studied, using a carefully prepared rosinate of known composition.

The results have been discussed from the viewpoint of the theory suggested by Dupont and Lévy for the autoxidation of abietic acid.

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COMPETITIVE HYDROGENATIONS. II

BY F. F. DIWOKY AND HOMER ADKINS

Recently it was shown that there was no apparent relationship between the relative rates of the hydrogenation over platinum of pure compounds taken separately and their relative rates of hydrogenation in mixtures.[1] For example, d-α-pinene was much more rapidly hydrogenated than was cinnamic acid and yet in a mixture of pinene and cinnamic acid the latter was completely hydrogenated before the former took up any hydrogen. It was also ascertained that a reducible substance not undergoing hydrogenation may greatly accelerate the hydrogenation of another compound. For example, pure pinene, which was much more rapidly hydrogenated than was pure allyl alcohol, increased the rate of hydrogenation of allyl alcohol almost seven-fold without itself being hydrogenated to any considerable extent. The results given in this paper are concerned with an extension of this study to the use of nickel catalysts in the hydrogenation of mixtures of reducible compounds.

Originally it was intended to determine (a) the time required for hy-

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[1] Adkins, Diwoky and Broderick, THIS JOURNAL, **51**, 3418 (1929).

drogenation of certain representative compounds over a nickel catalyst; (b) the time required for the absorption of one-half the quantity of hydrogen necessary for the complete hydrogenation of the components of equimolecular mixtures of two compounds; (c) the distribution of hydrogen between the components of the mixture; (d) the time required for the absorption of all the hydrogen necessary for the complete hydrogenation of the components of the mixtures of compounds. However, the last of these objectives was reached in the case of only four mixtures (benzene with toluene, with diphenylamine and with phenol and of pyridine with phenol) because the hydrogenations could not be made complete under conditions which were comparable with those used for the pure com· pounds and the half hydrogenation of mixtures.

There are recorded in Table I the time required and the proportion of products in the hydrogenation of ten compounds and of thirty-two mixtures of these compounds with each other. The amount of each compound used in each experiment was 0.5 mole except for the mixtures containing acetanilide, for which the quantities were cut in half. A temperature of 175° was used for the hydrogenations involving aniline, acetanilide and diphenyl, and for the mixture of pyridine and toluene. A temperature of 132° was used for pure benzyl alcohol and .125° for the mixture of benzyl alcohol and benzene; while 150° was used for all the other hydrogenations. Two grams of catalyst was used for diphenylamine and the mixture of it with toluene. One gram of catalyst was used in all other experiments. The initial pressure (at 20°) in all experiments was 136 atmospheres; the hydrogenations took place at pressures from 125 to 200 atmospheres.

TABLE I

HYDROGENATION OF PURE COMPOUNDS AND MIXTURES

Hydrogen acceptors	% H_2	Time. min.	Product(s) and % yields
Benzene	100	0	Cyclohexane
Toluene	100	60	Methylcyclohexane
Pyridine	100	480	Piperidine
Phenol	100	120	Cyclohexanol
Aniline	69	1500	Cyclohexylamine (52); dicyclohexylamine (5)
Benzyl alcohol	100	230	Toluene (84); cyclohexylcarbinol (16)
Acetanilide	68	640	N-Acetylcyclohexylamine
Quinoline	100	0	Tetrahydroquinoline
Diphenylamine	100	960	Dicyclohexylamine
Acetone	100	26	Propanol-2
Benzene + toluene	100	34	Cyclohexane (56); methylcyclohexane (31)
Benzene + pyridine	94	510	Cyclohexane (0); piperidine (100)
Benzene + phenol	100	86	Cyclohexane (46); cyclohexanol (51)
Benzene + aniline	21	1010	Cyclohexane (0); cyclohexylamine (17)
Benzene + benzyl alcohol	70	250	Cyclohexane (9); toluene (65); cyclohexylcarbinol (35)

TABLE I   (*Concluded*)

Hydrogen acceptors	% H$_2$	Time, min.	Product(s) and % yields
Benzene + acetanilide	100	360	Cyclohexane (71); N-acetylcyclohexylamine (20)
Benzene + quinoline	100	0	Cyclohexane (0); tetrahydroquinoline (100)
Benzene + diphenylamine	100	300	Cyclohexane (24); dicyclohexylamine (24); phenylcyclohexylamine (16)
Toluene + pyridine	100	420	Methylcyclohexane (0); piperidine (100)
Toluene + phenol	100	82	Methylcyclohexane (30); cyclohexanol (68)
Toluene + aniline	17	450	Methylcyclohexane (0); cyclohexylamine (11)
Toluene + acetanilide	91	480	Methylcyclohexane (38); N-acetylcyclohexylamine (50)
Toluene + quinoline	100	0	Methylcyclohexane (0); tetrahydroquinoline (100)
Toluene + diphenylamine	108	670	Methylcyclohexane (8); dicyclohexylamine (46); phenylcyclohexylamine (8)
Pyridine + phenol	88	1600	Piperidine (92); cyclohexanol (8)
Pyridine + aniline	100	630	Piperidine (96); cyclohexylamine (0)
Pyridine + benzyl alcohol	98	1000	Piperidine (100)
Pyridine + acetanilide	107	550	Piperidine (100); N-acetylcyclohexylamine (5)
Pyridine + quinoline	114	1000	Piperidine (50); tetrahydroquinoline (67)
Pyridine + diphenylamine	95	1200	Piperidine (100)
Phenol + aniline	98	410	Cyclohexanol (24); dicyclohexylamine (33); cyclohexylamine (35)
Phenol + benzyl alcohol	106	280	Cyclohexanol (51); toluene (72); cyclohexylcarbinol (28)
Phenol + acetanilide	103	280	Cyclohexanol (87); N-acetylcyclohexylamine (8)
Phenol + quinoline	101	7	Cyclohexanol (0); tetrahydroquinoline (100)
Phenol + diphenylamine	101	220	Cyclohexanol (56); dicyclohexylamine (16); phenylcyclohexylamine (5)
Aniline + benzyl alcohol	94	1440	Cyclohexylamine (22); dicyclohexylamine (34); toluene (16); cyclohexylcarbinol (19)
Aniline + acetanilide	52	1200	Cyclohexylamine (45); N-acetylcyclohexylamine (0)
Aniline + quinoline	98	5	Cyclohexylamine (0); tetrahydroquinoline (100)
Aniline + diphenylamine	25	1000	Cyclohexylamine (24); dicyclohexylamine (3)
Benzyl alcohol + quinoline	103	0	Tetrahydroquinoline (100)
Benzyl alcohol + diphenylamine	62	170	Toluene (66); cyclohexylcarbinol (16); dicyclohexylamine (17)
Benzyl alcohol + acetanilide	100	60	Toluene (58); cyclohexylcarbinol (42); N-acetylcyclohexylamine (20)

In the case of the mixtures the reaction was allowed to proceed (when possible) until the amount of hydrogen absorbed was approximately equal to the amount of hydrogen required for the complete hydrogenation of one of the components. The bomb was then allowed to cool to room temperature and the amount of hydrogen actually absorbed determined. The amount of hydrogen actually absorbed is given in the

second column of the table. One hundred per cent. hydrogen adsorption is that required for the complete hydrogenation of one of the two components of a mixture. In the case of mixtures this in general means 1.5 moles of hydrogen. For mixtures containing quinoline or acetanilide the amount is 1.0 and 0.75 mole of hydrogen, respectively. Benzyl alcohol presents a unique case since there are two reactions, one of which requires 3 moles and the other 1 mole of hydrogen for 1 mole of the alcohol. In the case of mixtures containing benzyl alcohol 100% absorption means 3 moles of hydrogen per mole of alcohol. The time (in minutes) given in column 3 of the table is that elapsing between the time at which the designated temperature was reached and the time at which the hydrogenation was stopped. The hydrogenation was stopped either because the desired amount of hydrogen had been taken up or because the catalyst had become inactive. A zero in this column means that hydrogenation was complete at the time that the designated temperature was reached. Eighty minutes were required to heat the bomb from 20 to 150° and fifteen minutes from 150 to 175°. There are given in column 4 of the table the name and yield of the various products of hydrogenation.

The rate of hydrogenation of phenol and quinoline at 2 to 3 atmospheres' pressure was determined for the sake of comparison with those at 125 to 200 atmospheres. Two grams of catalyst with 0.2 mole of each compound was used at 135°. Phenol was completely reduced in about two hundred and fifty minutes while quinoline was completely converted into tetrahydroquinoline in two hundred minutes.

If the nine compounds which were hydrogenated are listed in the order of decreasing rate of hydrogenation, the order is (1) quinoline, (2) benzene, (3) toluene, (4) phenol, (5) benzyl alcohol, (6) pyridine, (7) diphenylamine, (8) acetanilide and (9) aniline. (This order is not independent of the pressure of hydrogen at which reaction occurs because phenol for example reduces readily at 2 or 3 atmospheres while some of the other compounds are not hydrogenated at all over the nickel catalyst at the lower pressures.) The relative rates of hydrogenation of these compounds in a mixture are in many cases very different from that which would be expected from the relative rates of hydrogenation of the single compounds. If the compounds are listed in the order of preferential hydrogenation in mixtures the sequence is (and using the numbers assigned to each compound above) (1) quinoline, (6) pyridine, (9) aniline, (5) benzyl alcohol, (4) phenol, (7) diphenylamine, (2) benzene, (8) acetanilide, (3) toluene. That is, if a mixture of any two compounds in the above list is partially hydrogenated under the experimental conditions used in this investigation, the compound which is higher in the list just given will receive the greater proportion of the hydrogen.

In the case of mixtures of some compounds having the same functional

groups, the relative rates of hydrogenation of the components of a mixture are qualitatively what would be expected from a knowledge of the rates of hydrogenation of the single compounds. This is true for the mixture of benzene and toluene and for the one of quinoline and pyridine. The increased proportion of cyclohexanol from phenol in toluene as compared with the results in benzene is in agreement with the relative rates of hydrogenation of toluene and benzene. However, the relative rates of hydrogenation of benzene and phenol in a mixture are not at all what would be anticipated from a knowledge of the rates of hydrogenation of the compounds taken singly.

It appears that a compound such as aniline which is very slowly and never completely hydrogenated and which shows every sign of poisoning the catalyst for its own hydrogenation, may yet be almost without effect upon the hydrogenation of another compound. Quinoline for example hydrogenated practically as rapidly in the presence as in the absence of aniline. In a similar way aniline was almost without effect upon the hydrogenation of pyridine. In contrast with this is the effect of aniline, quinoline or pyridine in inhibiting completely the hydrogenation of the easily reduced benzene or toluene.

The time for the hydrogenation of a mixture of quinoline and pyridine was more than twice the sum of the times for the hydrogenation of the components, that is to say, each compound was inhibiting the hydrogenation of the other.

The hydrogenation of diphenylamine over nickel was accelerated by benzene and toluene although not so markedly as was the hydrogenation of allyl alcohol by pinene over platinum. The hydrogenation of aniline was also accelerated by the presence of phenol. Phenol and benzene in these experiments were also hydrogenated to the extent of 24% but toluene was almost completely resistant to hydrogenation just as was pinene in the mixture with allyl alcohol.

Benzyl alcohol is hydrogenated to both toluene and cyclohexylcarbinol, so that with this compound there is a competitive hydrogenation even with a single compound. For the catalyst and conditions used in this investigation for the hydrogenation of benzyl alcohol the ratio of the products was about 5 moles of toluene to 1 of the cyclohexylcarbinol. The ratio of alcohol to toluene was increased by the presence of phenol and diphenylamine and especially by benzene and acetanilide, which were themselves only reduced to the extent of 10 to 20%. This is all the more remarkable since at the temperature used for the hydrogenation of the mixtures (175°) pure benzyl alcohol is quantitatively reduced to toluene.

It is generally accepted that the combination of the catalyst and at least one if not both of the reactants is an essential step in such reactions as are here under consideration. Preferential adsorption would thus

serve to account for many of the discrepancies in rate between the hydrogenation of single compounds alone and in mixture with other compounds. Upon this basis pyridine is preferentially hydrogenated in a mixture with the more easily hydrogenated benzene because it is adsorbed almost to the exclusion of benzene. It is noteworthy that the order of compounds quinoline, pyridine, aniline, benzyl alcohol, phenol, diphenylamine, benzene, acetanilide, toluene, which is the order of preferential hydrogenation in mixtures, is one which in general might reasonably be expected to hold for a tendency to form addition compounds.

Experimental Part

The apparatus and the general method of procedure were the same as those previously described.[2] The compounds submitted to hydrogenation were of the best grade sold by the Eastman Kodak Company and the Mallinckrodt Chemical Company and were in general not submitted to any purification other than a careful fractionation. The benzene and toluene were thiophene free. The catalysts were made as previously described. The values given for the hydrogen absorption are accurate to within plus or minus 4%. The accuracy of the values for the ratio of products varies a good deal in different analyses and in extreme cases may be as much as ±7%.

Analysis of Reaction Products.—The products of reaction were separated whenever possible by fractionations through a Widmer column at a suitable pressure. Whenever fractionation did not give a satisfactory separation of the components of a reaction mixture, advantage was taken of chemical as well as of physical differences between the components. The separation of cyclohexane from benzene, and methylcyclohexane from toluene was made with sulfuric acid containing 30% of sulfur trioxide. The separation of aniline, pyridine and piperidine from hydrocarbons was made by extracting a weighed portion of the product with a slight excess of hydrochloric acid, the extract made alkaline with solid sodium hydroxide, saturated with salt, extracted twice with 100 ml. of ether and the ethereal extract dried and fractionated. The absence of pyridine (except in one experiment) was shown by the test of Fülnegg and Riesenfeld.[3] Piperidine was identified by its benzene sulfone piperidine, m. p. 92–93°. When necessary pyridine and piperidine were separated as by Arndt and Nachway.[4] The products from the hydrogenation of phenol and aniline were separated as follows. A weighed sample was put into solution with ether, treated with an excess over the calculated amount of dilute sodium hydroxide solution to remove phenol, the ether

[2] Adkins and Cramer, THIS JOURNAL, **52**, 4349 (1930).

[3] Fülnegg and Riesenfeld, *Monatsh.*, **47**, 185 (1926).

[4] Arndt and Nachway, *Ber.*, **59B**, 448 (1926).

layer separated, dried over solid potassium hydroxide, separated again from the watery layer, the ether distilled off, product weighed and phenol calculated by loss in weight. This product consisted of cyclohexanol, cyclohexylamine, aniline and dicyclohexylamine. This weighed sample was extracted with dilute hydrochloric acid, extracted with two 75-ml. portions of ether and the layers separated. By the usual method cyclohexanol was obtained from the ether extract, the amines recovered from the hydrochloric acid extract and separated by fractional distillation. Cyclohexanol was separated from phenol by extracting a weighed amount with dilute sodium hydroxide, washing and drying the insoluble portion prior to distillation. Phenol was determined by difference. Mixtures of acetanilide and N-acetylcyclohexylamine were hydrolyzed as by Davis[5] and the amines separated by fractional distillation. Phenylcyclohexylamine and dicyclohexylamine were separated as by Fouque.[6] The former had a boiling point of 160–164° (22 mm.) and its picrate had a melting point of 163–164°.

Summary

The rates of hydrogenation of quinoline, benzene, toluene, phenol, benzyl alcohol, pyridine, diphenylamine, acetanilide and aniline have been determined over a nickel catalyst at 125–175° and under pressures of hydrogen from 125–200 atmospheres. The compounds have been listed in the order of decreasing rate of hydrogenation. Thirty-two mixtures of these compounds, each mixture containing two components, were subjected to the action of hydrogen over a nickel catalyst and the mixture allowed to take up as much hydrogen as would have been sufficient to completely hydrogenate one of the components of the mixture. The rate of absorption of the hydrogen and its distribution between the components of the mixture were determined by analysis of the reaction mixture. It was found that if the compounds were listed in the series, quinoline, pyridine, aniline, benzyl alcohol, phenol, diphenylamine, benzene, acetanilide and aniline, in any mixture containing two of them, the one higher in the series would receive the greater proportions of the hydrogen. Pyridine and quinoline in mixtures with other compounds took all, or practically all of the hydrogen. Apparently there is no relationship between the relative rates of hydrogenation of these compounds singly and in mixtures. The relative rates of hydrogenation of the components of a mixture are at least in part presumably dependent upon selective adsorption by the catalyst through two possible acceptors of hydrogen.

The hydrogenation of diphenylamine was accelerated by toluene and benzene, and the hydrogenation of aniline by the presence of phenol in the reaction mixture.

[5] Davis, *J. Chem. Soc.*, **95**, 1397 (1909).

[6] Fouque, *Ann. chim.*, **15**, 291–32 (1921).

The ratio of cyclohexylcarbinol to toluene produced in the hydrogenation of benzyl alcohol was increased by the presence of phenol or diphenylamine and especially of benzene or acetanilide in the reaction mixture.

MADISON, WISCONSIN

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

AMINO ALCOHOLS. VI. THE PREPARATION AND PHARMACODYNAMIC ACTIVITY OF FOUR ISOMERIC PHENYLPROPYLAMINES

BY WALTER H. HARTUNG AND JAMES C. MUNCH

The commoner hypertensive amines are derivatives of β-phenylethylamine, that is, compounds containing the aromatic nucleus separated from the amino group by two carbons of an aliphatic side chain; e. g., tyramine $HOC_6H_4CH_2CH_2NH_2$, epinephrine, $(HO)_2C_6H_3CHOHCH_2NHCH_3$, and ephedrine, $C_6H_5CHOHCH(NHCH_3)CH_3$, all have this common structure.

Recorded pharmacological studies with compounds in which the relative position of these two functional groups is modified are rare.

Barger and Dale,[1] in their classical study on the relationship between chemical structure and sympathomimetic action, included a series of compounds in which the relative position of the amino portion with respect to the phenyl group varied. They found that aniline has no specific action; benzylamine gives a trace of the desired activity, α-phenylethylamine is feebly active, β-phenylethylamine highly active and most active of the series, while γ-phenylpropylamine, $C_6H_5CH_2CH_2CH_2NH_2$, is again much less effective. While no allowance was made for any influence on the physiological activity that might be produced by the successive lengthening of the side chain, they nevertheless advanced the conclusion that "the optimum constitution of a fatty–aromatic amine for the production of sympathomimetic action is, therefore, that which is found in adrenaline itself, viz., a benzene ring with a side chain of two carbon atoms, of which the second bears the amino group."

Concerning the value of the two-carbon side chain these conclusions must, in the light of recent findings, be amended, for it has been amply demonstrated that amino alcohols of the ephedrine type, that is, compounds with three carbons in the side chain, are not only very active pharmacologically but may even possess physiological and therapeutic virtues not resident in the corresponding compounds with but two carbons.[2]

[1] Barger and Dale, J. Physiol., 41, 19 (1910). Cf. Pyman, J. Chem. Soc., 111, 1103 (1917).

[2] (a) Chen, Wu and Henriksen, J. Pharmacol., 36, 363 (1929); (b) Hartung and Munch, THIS JOURNAL, 51, 2262 (1929); (c) Hartung, Munch, Deckert and Crossley, ibid., 52, 3317 (1930); (d) Piness, Miller and Alles, J. Am. Med. Assn., 94, 790 (1930).