

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

Hydrogen Exchange of Phenols and Phenol Ethers with Deutero-alcohol¹BY PHILIP F. TRYON,² WELDON G. BROWN AND M. S. KHARASCH

The experiments described herein were performed in an attempt to set up a quantitative basis for the comparison of variously constituted phenols and phenol ethers in respect to the rates of exchange of nuclear hydrogen atoms. Whereas previous investigators have examined the hydrogen exchange of phenol³ with aqueous alkali, and of anisole with aqueous sulfuric acid,^{3a} our work has been done with deutero-ethanol as solvent and reactant, thereby avoiding heterogeneous reaction mixtures. Moreover, although we have used sulfuric acid to promote the exchange of nuclear hydrogens, it has been under such mild conditions, as compared to the above-mentioned experiments on anisole, that the exchange is limited to those positions which are known to be active in ordinary electrophilic substitutions.

Briefly, the significant features of our results are the following. First, it is noted that the partition coefficient for the distribution of deuterium in a nuclear exchange reaction differs appreciably from unity, the deuterium favoring the hydroxyl group of ethanol as might be expected from zero-point energy considerations. Thus the limiting values of the "exchange number" in experiments on mixtures which were allowed to approach exchange equilibrium fall short of the integer representing the number of participating hydrogen atoms by nearly 10%. Such an effect is not observed in exchange reactions involving only the hydroxyl group of phenols (*cf.* Table I).⁴

TABLE I

EXCHANGE OF HYDROXYL HYDROGEN OF PHENOLS WITH DEUTEROALCOHOL^a

| Compound | Obs. exch. |
|-----------------------------|------------|
| <i>p</i> -Cresol | 1.02 |
| β -Naphthol | 1.01 |
| 3,5-Dimethyl-4-chlorophenol | 1.06 |
| 3,4-Dimethylphenol | 1.09 |
| 6-Hydroxytetralin | 1.10 |
| 5-Hydroxyhydrindene | 1.06 |

^a Experiments carried out by dissolving 0.008 mole of the phenol in 5 ml. of deuteroalcohol and recovering the alcohol immediately thereafter by vacuum distillation.

Referring next to the naphthols and naphthol ethers, the data presented in Table II show that

(1) Abstracted from a Ph.D. thesis by Philip F. Tryon, Chicago, 1939.

(2) Present address: Commercial Solvents Corporation, Terre Haute, Indiana.

(3) (a) Ingold, Raisin and Wilson, *J. Chem. Soc.*, 1637 (1936); (b) Small and Wolfenden, *ibid.*, 1811 (1936); (c) Best and Wilson, *ibid.*, 28 (1938); (d) Munzberg, *Z. physik. Chem.*, **B33**, 23, 39 (1936).

(4) This work was carried out prior to the discovery that significant changes in isotopic composition occur when ethanol is fractionally distilled and that precautions are necessary to avoid errors due to this effect (Brown and Widiger, *THIS JOURNAL*, **61**, 2453 (1939)). The exchange numbers herein reported, being subject to such errors, may be too high by as much as 5%.

whereas α -naphthol and its ethyl ether exchange two nuclear hydrogens, β -naphthol and its ether exchange only one. That this is the α -hydrogen is strongly supported by the observation that α -methyl- β -naphthyl ethyl ether exhibits no exchange under comparable conditions. The non-occurrence of exchange at the 3-position of β -naphthol and derivatives is readily explained on the basis of a mechanism similar to that established for the acid-catalyzed exchange reactions of tertiary aromatic amines.⁵ Of the two possible transition states which could arise from the attachment of a deuteron at a carbon atom adjacent to the hydroxyl or alkoxy group, I is fixed in electronic configuration and must correspond to an activation energy several kilocalories higher than II in which a benzenoid ring is preserved.

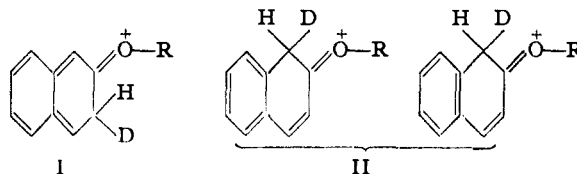


TABLE II

ACID CATALYZED EXCHANGE OF HYDROGEN ATOMS OF PHENOLS AND PHENOL ETHERS WITH DEUTEROALCOHOL AT 110°

| Compound | Reaction time, hours | Observed exchange | Active H atoms (theor.) |
|-------------------------------|---|-------------------|-------------------------|
| α -Naphthol | 0.25 | 1.74 | |
| | 0.5 | 2.67 | |
| | 3.5 | 2.93 | |
| | 9 | 2.85 | |
| | 22 | 2.89 | 3 |
| β -Naphthol | 0.25 | 1.80 | |
| | 0.5 | 2.10 | |
| | 3.5 | 2.01 | |
| | 16.5 | 1.90 | |
| | 51.5 | 1.97 | 2 |
| <i>p</i> -Cresol | 24 | 1.63 | |
| | 52 | 2.63 | |
| | 213 | 2.82 | |
| | 235 | 2.80 | 3 |
| | α -Naphthyl ethyl ether | 22 | 0.18 |
| 83 | | 1.46 | |
| 119 | | 1.72 | |
| 206 | | 1.89 | 2 |
| β -Naphthyl ethyl ether | | 24 | 0.49 |
| | 112 | 0.92 | |
| | 190 | 1.00 | |
| | 410 | 0.97 | 1 |
| | α -Methyl- β -naphthyl ethyl ether | 142 | 0.03 |

(5) Brown, Widiger and Letang, *ibid.*, **61**, 2597 (1939).

In experiments which were carried out at a lower temperature (Table III), and in which exchange equilibrium was not attained, there is revealed the rather surprising effect of the β -methyl group in ethers of β -methyl- α -naphthol. The lower reactivity of these compounds, in which the hydro-

TABLE III

ACID CATALYZED EXCHANGE OF HYDROGEN ATOMS AT 60°

| Compound | Reaction time, hours | Observed exchange | Active H atoms (theor.) |
|---|----------------------|-------------------|-------------------------|
| <i>p</i> -Cresol | 15 | 1.11 | |
| | 20 | 1.15 | 3 |
| α -Naphthyl methyl ether | 70 | 0.36 | |
| | 238 | 1.15 | 2 |
| α -Naphthyl isopropyl ether | 213 | 1.18 | 2 |
| β -Methyl- α -naphthyl methyl ether | 238 | 0.08 | 1 |
| | | | |
| β -Methyl- α -naphthyl isopropyl ether | 213 | 0.07 | 1 |
| | | | |

gen atoms in the 4-position should still be active, is perhaps an example of a steric effect which should arise in di-*ortho*-substituted phenol ethers because of hindrance to coplanarity in the quinonoid transition state.⁶

The results shown in Table IV for phenols having two non-equivalent free *ortho* positions are of interest in connection with the Mills-Nixon effect. It is clear from these results that each of these substances exchanges two nuclear hydrogen atoms, and if one exchanges faster than the other the differences are not great enough to be readily discernible in the rate curves. These curves are similar in form to that shown by the symmetrical phenol, 3,5-dimethyl-4-chlorophenol, except that the time scale is somewhat more extended for this compound because of its lower reactivity.

Experimental

The experimental procedure employed in this Laboratory for following exchange reactions with deuterioalcohol has been described in previous papers.⁷ In all of the experiments here reported the extent of exchange has been determined from the decrease in deuterium content of the alcohol.

The experiments on sulfuric acid catalyzed reactions fall into two groups according to the temperature employed. At 60° the acid is present as ethyl hydrogen sulfate and it was determined that there is no loss of catalyst by further reaction to form diethyl sulfate within a period of eight days. At 110° the loss of catalyst is appreciable within a few hours and the experiments carried out at this temperature therefore do not represent steady conditions with respect to catalyst concentration.

In the presence of small amounts of sodium ethylate, neither α -naphthyl ethyl ether nor β -naphthyl ethyl ether showed any measurable exchange in periods up to twelve days at 110°.

The reaction mixtures generally contained 5 cc. of deuterioalcohol (0.085 mole) and about 0.009 mole of

(6) Further evidence concerning possible steric effects was sought by examining the hydrogen exchange of 2-methylanisole and 2,6-dimethylanisole, but both of these compounds showed some decomposition (positive ferric chloride test) under the conditions of the exchange experiments and the results were therefore inconclusive.

(7) (a) Kharasch, Brown and McNab, *J. Org. Chem.*, **2**, 36 (1937); (b) Brown, Kharasch and Sprows, *ibid.*, **4**, 442 (1939).

the phenol or ether. Where sulfuric acid was to be used, it was added to the alcohol so as to provide a stock solution containing 10 mg. of sulfuric acid per 5 cc. of alcohol. However, in the series of experiments summarized in Table IV, a more dilute stock solution, containing 0.5 mg. of sulfuric acid per 5 cc. of alcohol, was used and the quantity of phenol was accurately adjusted to 0.00818 mole.

TABLE IV

UPTAKE OF DEUTERIUM FROM DEUTEROALCOHOL, AT 60°, BY 3,4-DIMETHYLPHENOL (I), 5-HYDROXYHYDRINDENE (II), 6-HYDROXYTETRALIN (III) AND 3,5-DIMETHYL-4-CHLOROPHENOL

| Time, hours | Exchange number ^a | | | |
|----------------|------------------------------|------|-------|------|
| | (I) | (II) | (III) | (IV) |
| 0 ^b | 1.05 | 1.02 | 1.06 | 1.02 |
| 1 | 1.11 | 1.16 | 1.18 | |
| 3 | 1.26 | 1.37 | 1.40 | |
| 5 | 1.60 | 1.56 | 1.56 | |
| 6 | | | | 1.13 |
| 10 | 1.70 | 1.85 | 1.99 | |
| 13 | | | | 1.26 |
| 15 | 1.99 | 1.99 | 2.15 | |
| 20 | 2.25 | 2.09 | 2.27 | 1.34 |
| 25 | 2.40 | 2.21 | 2.28 | |
| 30 | 2.39 | 2.25 | 2.41 | 1.46 |
| 35 | 2.52 | 2.28 | 2.47 | |
| 40 | 2.54 | 2.40 | 2.44 | 1.54 |
| 45 | 2.60 | 2.43 | 2.54 | |
| 50 | | 2.49 | 2.56 | |
| 55 | | 2.50 | | |
| 60 | | | 2.56 | 1.68 |
| 90 | | 2.63 | | |
| 100 | | | | 1.97 |
| 120 | 2.71 | | | |
| 140 | 2.70 | 2.68 | | 2.25 |
| 180 | | | 2.68 | |
| 200 | | | 2.68 | |
| 216 | | | | 2.39 |
| 265 | | | | 2.49 |
| 342 | | | | 2.56 |

^a For each experiment a solution was prepared containing 0.085 mole of deuterioalcohol (14.77 mole % C₂H₅-OD), 0.001 equivalent of sulfuric acid, and 0.00818 mole of phenol. The exchange numbers were calculated from the analyses on recovered alcohol, taking into account dilution of deuterium by hydrogen from the sulfuric acid.

^b The experimental results entered for zero time were obtained by recovering the alcohol, by distillation, immediately after preparing the mixture. Actually the separations required several minutes to perform. The observed exchange is obviously the exchange of the hydroxyl hydrogen atoms of the phenols.

Except as noted below the materials used were prepared and purified by methods described in the literature.

β -Methyl- α -naphthyl Methyl Ether.—This compound was obtained in 50% yield on treatment of an alkaline solution of β -methyl- α -naphthol⁸ with dimethyl sulfate: colorless liquid, b. p. 129–130° at 9 mm., n_D^{20} 1.6007, d_4^{25} 1.056. It was characterized by nitration, following a procedure similar to that used by Heermann⁹ in the nitration of α -naphthol ether, which furnished a mononitro derivative (1-methoxy-2-methyl-4-nitronaphthalene), light yellow needles, m. p. 104°. *Anal.* Calcd. for C₁₂H₁₁O₂N: N, 6.45; Found: N, 6.82.

β -Methyl- α -naphthyl Isopropyl Ether.—A suspension of the sodium salt of β -methyl- α -naphthol in a solution

(8) Prepared by the method of Lesser, *Ann.*, **402**, 38–43 (1914).

(9) Heermann, *J. prakt. Chem.*, **44**, 238 (1891).

containing 150 cc. of dioxane, 32 g. of isopropyl bromide, and 2 g. of potassium iodide was refluxed for fourteen hours. After distilling off most of the dioxane, ether and water were added, and the ether layer, after washing with alkali and with water and then drying over calcium chloride, yielded on distillation 13 g. (38% yield) of the desired product; b. p. 147–148° at 12 mm., n_D^{20} 1.5764, d_4^{25} 1.017. Nitration yielded a mononitro derivative (1-isopropoxy-2-methyl-4-nitronaphthalene), light yellow needles, m. p. 45°. *Anal.* Calcd. for $C_{14}H_{16}O_2N$: N, 5.71; Found: N, 5.69.

α -Naphthyl Isopropyl Ether.—This was prepared by a procedure similar to the preceding, from the sodium salt of α -naphthol and isopropyl bromide in 21% yield; b. p. 139–140° at 9 mm., n_D^{20} 1.5848, d_4^{25} 1.025. On nitration a mononitro derivative was obtained which yielded 4-nitro-1-naphthol on treatment with alcoholic potassium hydroxide for one hour on the steam-bath and is thus identified as 1-isopropoxy-4-nitronaphthalene; dark

yellow needles, m. p. 69°. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: N, 6.06; Found: N, 6.15.

Summary

It is shown that hydrogen atoms *ortho* and *para* to the hydroxyl or alkoxy group in phenols and phenol ethers exchange with deuterioalcohol in the presence of small amounts of sulfuric acid. Exceptions are β -naphthol and derivatives thereof in which exchange occurs only at the α -position. The unsymmetrical phenols, 5-hydroxyhydrindene and 6-hydroxytetralin, which couple at a preferred *ortho* position (Mills–Nixon effect), show two active nuclear hydrogens in the exchange reaction.

CHICAGO, ILLINOIS

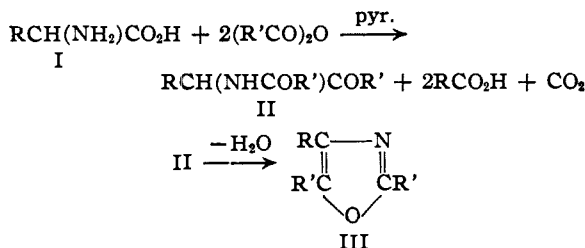
RECEIVED DECEMBER 31, 1947

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Conversion of α -Amino Acids to Acylamido Ketones and Oxazoles

BY RICHARD H. WILEY AND OLIN H. BORUM¹

A previous communication² described a method for the conversion of α -amino acids (I) to acetamidoketones (II, $R' = CH_3$) by reaction with acetic anhydride in pyridine, and of the acetamidoketones to oxazoles (III).



The present paper describes the anomalous course of this reaction with glycine, the substitution of propionic for acetic anhydride in the formation of a propionamidoketone, and a modified procedure for obtaining yields of 70–90% of the acylamidoketone.

The reaction product obtained on refluxing glycine and acetic anhydride in pyridine can be fractionated to give a principal fraction boiling at 105–108° at 2 mm. The analytical data show that this compound is not acetamidoacetone, the product which would be formed if the reaction were analogous to that with alanine. The data agree with values calculated for an acetyl derivative of acetamidoacetone. This is substantiated by the hydrolysis of this acetyl derivative to acetamidoacetone b. p. 101–105° (0.5 mm.) in 76% yield. The structure of the acetyl derivative cannot be assigned on the basis of the available information. It is noted in this connection that previous at-

tempts to bring about this reaction with glycine³ were less successful because the reaction is very slow at steam-bath temperatures.

Improved yields of 3-acetamido-2-butanone are obtained by stirring during the reaction period to aid in evolution of carbon dioxide. The preferred procedure, in which the product is separated by fractionation of the reaction mixture, gives 88% of redistilled product as described in the experimental part. Using this procedure aminophenylacetic acid and propionic anhydride give a 75% yield of 1-phenyl-1-propionamido-2-butanone.

Dehydration of the acylamidoketones to oxazoles with potassium bisulfate and other reagents has been accomplished but with no advantage over the previously described² sulfuric acid dehydration.

Experimental Part

3-Acetamido-2-butanone (II, $R = CH_3$, $R' = CH_3$).—A mixture of 159 ml. (1.98 moles) of pyridine (J. T. Baker C. P.), 224 ml. (2.35 moles) of acetic anhydride (95% min. assay), and 35.11 g. (0.39 mole) of vacuum-dried alanine (Merck) was heated with stirring on the steam-bath for six hours after solution was complete. The excess pyridine and acetic anhydride were removed at reduced pressure and the residue distilled through a short column to obtain 47.5 g., 93.2% of the theoretical amount of crude 3-acetamido-2-butanone, b. p. 110–125° at 3 mm. On refractionation 88% of the theoretical amount, 45 g., b. p. 102–106° at 2 mm., was obtained, n_D^{20} 1.4558.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.81; H, 8.48; N, 10.90.

Without stirring the yield dropped to 46%. Reducing the molar ratio of pyridine or anhydride also reduced the yield.

1-Phenyl-1-propionamido-2-butanone (II, $R = C_6H_5$, $R' = C_2H_5$).—A mixture of 60 g. (0.4 mole) of aminophenylacetic acid (E. K. Co.), 250 ml. (2.0 moles) of propionic anhydride (Carbide and Carbon Co.), and 165

(1) The work reported in this paper was taken in part from the Master's Thesis submitted by Olin H. Borum to the Graduate School of the University of North Carolina.

(2) Richard H. Wiley, *J. Org. Chem.*, **12**, 43 (1947).

(3) Dakin and West, *J. Biol. Chem.*, **78**, 91–105 (1928).