

*Anal.* Calcd. for  $C_8H_7NOBr_2$ : C, 19.58; H, 2.86; N, 5.71; Br, 65.31. Found: C, 19.73; H, 2.78; N, 5.44; Br, 65.25.

**N-Methylol-2,3-dibromoisobutyramide (V).**—To a mixture consisting of 12.5 g. (0.05 mole) of 2,3-dibromoisobutyramide, 5 ml. (0.062 mole) of 37% formalin solution and three pellets of sodium hydroxide was added sufficient ethanol to dissolve the amide. After standing at 25° for 16 hours, the solution was concentrated *in vacuo* and the solid residue was crystallized from ethyl acetate or acetone to give 7 g. (50.9%) of pure product, m.p. 125–126°.

*Anal.* Calcd. for  $C_8H_9NO_2Br_2$ : C, 21.82; H, 3.27; N, 5.09. Found: C, 21.87; H, 3.28; N, 5.11.

**Reactions of N-Methylol-2,3-dibromoisobutyramide.** (a) **With Hydrochloric Acid.**—A mixture consisting of 1.4 g. (0.005 mole) of N-methylol-2,3-dibromoisobutyramide, 10 ml. of ethylene chloride and two drops of 38% hydrochloric acid was refluxed for 20 minutes, filtered from gummy matter, and cooled to yield 0.7 g. (81.3%) of 2,3-dibromoisobutyric acid,<sup>8</sup> m.p. 48–49°. A mixed melting point determination with an authentic sample of the acid was 48–49°.

(b) **With Hydrogen Bromide.**—A mixture of 2 g. (0.0073 mole) of N-methylol-2,3-dibromoisobutyramide and 100 ml. of ethylene chloride was saturated with hydrogen bromide at 25° and allowed to stand for one hour. After filtration, which yielded 0.8 g. of starting material, dry air was bubbled through the solution to remove hydrogen bromide and to concentrate the solution. This procedure afforded 0.6 g. (33% conversion 55% yield) of N,N'-methylenebis-(2,3-isobutyramide),<sup>2</sup> m.p. 205° after recrystallization with ethylene chloride.

(c) **With Sulfuric Acid.**—A mixture consisting of 1 g. (0.0036 mole) of N-methylol-2,3-dibromoisobutyramide, 20 ml. of ethylene chloride and one drop of concd. sulfuric acid was refluxed for 15 minutes. The mixture was concentrated to a volume of 10 ml. and decanted from a small amount of gum. Upon cooling, 0.85 g. (94%) of N,N'-methylenebis-(2,3-dibromoisobutyramide) was obtained.

(d) **With Bromine.**—N-Methylol-2,3-dibromoisobutyramide (2 g., 0.0073 mole) and 1 g. (0.006 mole) of bromine were allowed to react in the dark for 12 hours in a closed flask at 25°. The bromine was then removed in the dark and the remaining residue (1.85 g.) melted at 188–196°. Recrystallization from ethylene chloride raised the melting point to 204–206°. A total of 1.6 g. (86%) of crystals was obtained and identified as N,N'-methylenebis-(2,3-dibromoisobutyramide).<sup>2</sup> A mixed melting point determination with an authentic sample was 205°.

(e) **With Iodine.**—A mixture consisting of 2.75 g. (0.01 mole) of N-methylol-2,3-dibromoisobutyramide, 0.25 g. of iodine and 200 ml. of dry ethylene chloride was kept in a closed

container for 12 hours at 25°. After evaporation, 2.6 g. (94.2%) of the starting material was recovered.

**Hydrolysis of N,N'-Methylenebis-(2,3-dibromoisobutyramide) (IV).**—A mixture consisting of 5.0 g. (0.01 mole) of N,N'-methylenebis-(2,3-dibromoisobutyramide) and 175 ml. of concd. hydrochloric acid was refluxed until dissolution was complete (22 hours). The mixture was then cooled and extracted with three 50-ml. portions of carbon disulfide. Evaporation of the solvent and cooling of the residual oil yielded 1.5 g. (30%) of crystals, m.p. 46–47°, which were identified as 2,3-dibromoisobutyric acid.<sup>8</sup> A mixed melting point determination with an authentic sample showed no depression.

**N,N'-Methylenebis-(2,3-dibromopropionamide) (VI).**—A solution of 0.2 g. (0.77 mmole) of N-methylol-2,3-dibromopropionamide<sup>2</sup> in 20 ml. of ethylene chloride, to which one drop of concd. sulfuric acid had been added, was boiled for 15 minutes. Upon cooling, 0.1 g. (55%) of N,N'-methylenebis-(2,3-dibromopropionamide) was obtained, m.p. 207–208° after recrystallization with ethylene chloride.

*Anal.* Calcd. for  $C_7H_{10}O_2N_2Br_2$ : C, 17.72; H, 2.11; N, 5.91. Found: C, 18.0; H, 2.39; N, 5.46.

**2,3-Dibromopropionamide.**—A slurry of 35 g. (0.57 mole) of acrylamide in 100 ml. of carbon tetrachloride was treated with 80 g. (0.5 mole) of bromine. The precipitate was filtered off, washed with carbon tetrachloride and recrystallized from absolute ethanol. A yield of 70 g. (63%) of 2,3-dibromopropionamide, m.p. 132–133°, lit. value<sup>9</sup> 130–133°, resulted.

**Attempted Methylation of 2,3-Dibromopropionamide.**

(a) **With Sodium Hydroxide.**—A solution of 23 g. (0.1 mole) of 2,3-dibromopropionamide and 3 g. (0.1 mole) of 37% formalin solution in ethanol was basified with sodium hydroxide. The solution became neutral on standing and additional base was added to maintain a pH of 9–10. After 12 hours, the solvent was removed *in vacuo* at 25° and filtration yielded 10.3 g. of sodium bromide dihydrate (73% based on removal of one mole of hydrobromic acid per mole of dibromopropionamide), m.p. 51°. Distillation of the filtrate yielded 4.5 g. of unreacted starting material.

(b) **With Potassium Carbonate.**—The experimental procedure was the same as above except that potassium carbonate was used instead of sodium hydroxide. Pure potassium bromide was isolated in 30% conversion and a tough, slightly tacky translucent polymer in 60% conversion if the material is considered to be a polymer of  $\alpha$ -bromoacrylamide.

**Acknowledgments.**—The authors are indebted to Professor Herbert C. Brown for many stimulating discussions and to the Office of Naval Research for the financial support of this work.

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LAFAYETTE, INDIANA

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## The Stereochemistry of Raney Nickel Action. VII. Catalytic Hydrogen-Deuterium Exchange in the 2-Phenylpropionamide Series

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The relative rates of racemization and hydrogen-deuterium exchange when (+)-2-phenylpropionamide is treated with deuterated Raney nickel in refluxing deuterio-ethanol have been investigated. Isotope exchange occurs at the  $\alpha$ -hydrogen, in the  $\alpha$ -methyl group and in the aromatic ring considerably more rapidly than racemization occurs, results which may be rationalized in terms of a stereospecifically adsorbed carbonium ion intermediate. 1-Phenylethanol and ethylbenzene similarly underwent isotope exchange in both the side chain and nucleus.

It has recently been reported<sup>1</sup> that both  $\alpha$ -hydrogen atoms and nuclear hydrogen atoms in mandelamide and phenylacetamide undergo exchange with deuterium when treated with deuterated Raney nickel in refluxing deuterioethanol. Similarly, the slow racemization of compounds such as ethyl (+)-

2-phenylpropionate and (+)-2-phenylpropionamide under the influence of Raney nickel in refluxing ethanol has been reported.<sup>2</sup> It seemed to us of considerable interest to investigate quantitatively any relationship which might exist in the rate of

(2) W. A. Bonner, J. A. Zderic and G. A. Casaletto, *ibid.*, 74, 5086 (1952).

(1) W. A. Bonner, *THIS JOURNAL*, 76, 6350 (1954).

TABLE I  
 HYDROGEN-DEUTERIUM EXCHANGE AND RACEMIZATION OF (+)-2-PHENYLPROPIONAMIDE

Time, hr.	$[\alpha]^{27D}$ , °	Recovered 2-phenylpropionamide		D, g. at./mol.	Benzoic acid		Deuterium distribution	
		% Racemization	% D <sub>2</sub> O <sup>a</sup>		% D <sub>2</sub> O <sup>a</sup>	D, g. at./mol.	α-Methyl <sup>b</sup>	Phenyl nucleus
2.2	51.8	2	18.0	1.81	12.5	0.68	0.13	0.68
8.5	45.6	14	28.1	2.86	22.0	1.22	0.64	1.22
24.5	44.5	16	26.6	2.70	23.0	1.26	0.44	1.26

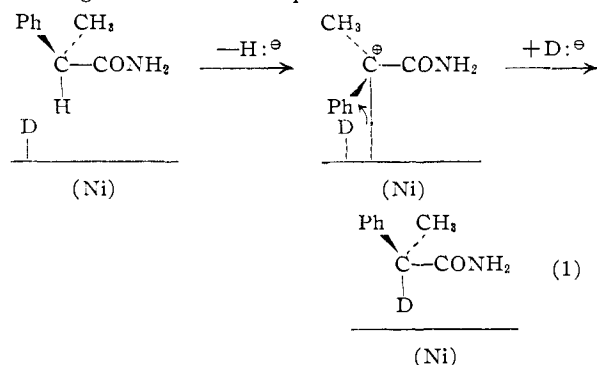
<sup>a</sup> In water obtained by combustion. <sup>b</sup> Assuming complete exchange of α-hydrogen with deuterium. Calculated by difference.

racemization and the rate of hydrogen-deuterium exchange in substances such as (+)-2-phenylpropionamide.

(+)-2-Phenylpropionamide,  $[\alpha]^{27D}$  52.5°, was treated with deuterated Raney nickel<sup>1</sup> in refluxing absolute deuterio-ethanol. At measured time intervals, aliquots of the reaction mixture were removed and processed for the recovery of 2-phenylpropionamide. The specific rotation and the deuterium content of each recovered sample was determined. The sample was then oxidized to benzoic acid, and the deuterium content of the latter was determined. The data pertaining to these experiments are summarized in Table I.

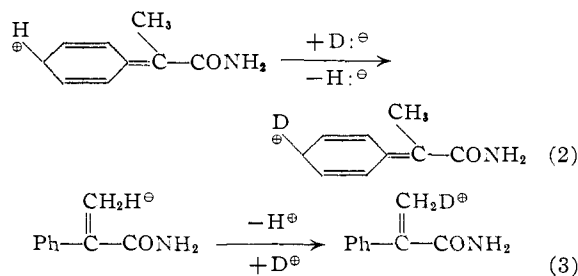
Several conclusions follow from Table I. In the first place it is clear that deuterated Raney nickel in deuterio-ethanol engenders hydrogen-deuterium exchange not only at the α-carbon and in the aromatic nucleus as reported before, but also in the α-methyl group of 2-phenylpropionamide. Secondly, the extent of hydrogen-deuterium exchange exceeds the extent of racemization, arguing for a certain stereospecificity of the exchange process. Thus after 8.5 hr. 24.4% of ring hydrogens, 21.3% of α-methyl hydrogens and, presumably,<sup>1</sup> all of the α-hydrogen have been exchanged for deuterium, while the product is only 7% inverted. In the third place, both exchange and racemization reactions appear to reach a saturation value sometime before 8.5 hr., beyond which both processes essentially stop. The slightly lower deuterium assays after the 24.5 hr. period are at present unexplained, since they appear to be beyond experimental error.<sup>1</sup>

To rationalize the occurrence of hydrogen-deuterium exchange in the absence of extensive racemization, a stereospecifically adsorbed carbonium ion<sup>2</sup> may be postulated, (1) with deuteride ion attacking from below the plane of the adsorbed ion.



Exchange in the nucleus and α-methyl group might occur as the result of resonance (2) and hyperconjugative (3) stabilization of such an adsorbed ion.

(3) W. A. Bonner and J. A. Zderic, *THIS JOURNAL*, **78**, 3218 (1956).



The reason for the attainment of a saturation value with respect to both exchange and racemization is not at present clear, although experiments described below exclude incomplete catalyst deuteration as an explanation for the saturation phenomenon with respect to deuterium exchange.

Because the racemization observed in the above reaction was less than that previously noted<sup>2</sup> for 2-phenylpropionamide, we were concerned that residual alkali in the Raney nickel sample might be responsible for the racemization. A sample of (-)-2-phenylpropionamide in ethanol was treated with a trace of 0.04 *N* sodium hydroxide. No rotational change was observed after refluxing during 6 hr., nor after refluxing 21 hr. after adding 10 times as much 0.04 *N* alkali. Since the rinse deuterium oxide from the preparation of the deuterated Raney nickel above showed *pH* 7.3, it is highly improbable that residual alkali on the Raney nickel engendered the racemization. Similarly, when 2-phenylpropionamide was heated in refluxing deuterio-ethanol containing 1.1 ml. of 0.04 *N* sodium hydroxide for 2 days, the recovered amide was found to contain only 0.5 g. at./mole deuterium, thus precluding the possibility that the isotope exchange above was alkali engendered.

To see if activation of the α-hydrogen in 2-phenylpropionamide by the carboxamide function was essential for hydrogen-deuterium exchange, we have also investigated the behavior of 1-phenylethanol and ethylbenzene under catalytic exchange conditions. When (-)-1-phenylethanol was treated with deuterated Raney nickel in hot deuterio-ethanol, racemic deuterio-ethylbenzene resulted. The experiment was duplicated using *rac*-1-phenylethanol, and the ethylbenzene produced was found to contain 2.0 gram atoms deuterium per mole. A similar experiment with ethylbenzene gave an impure product, oxidation of which yielded benzoic acid containing 1.5 gram atoms deuterium per mole. Thus an α-activating function is not a prerequisite for the occurrence of either chain or ring isotope exchange.

The efficacy of our procedure<sup>1</sup> for deuterating Raney nickel by equilibration with heavy water has been tested by removing the adsorbed gas from

deuterated nickel by baking *in vacuo*. The desorbed gas was investigated mass spectrometrically and found to be 89% deuterium and 11% hydrogen, indicating the reasonable effectiveness of the catalyst deuteration method and excluding incomplete catalyst deuteration as an explanation for the exchange saturation noted above.

### Experimental

**Deuterated Raney Nickel.**—This was prepared by equilibration of Raney nickel, filtered just free of ethanol, with 99% deuterium oxide in the manner previously described.<sup>1</sup> The pH of each deuterium oxide rinse was measured. When the catalyst was sucked too dry on the sintered funnel, especially after dioxane was used as an intermediate rinse,<sup>1</sup> the pH of the deuterium oxide filtrate was 3 to 4.5. In such cases the catalyst was not effective in deuterating the aromatic nucleus of mandelamide or similar compounds during dehydroxylation. If care was exercised not to let the catalyst become dry during filtration, and if the intermediate dioxane rinse was eliminated, the pH of the deuterium oxide filtrates was 6.3 to 7.3, and the resulting catalyst readily effected the isotope exchange reactions below. The reason for the above behavior of the catalyst is not understood, has been merely observed empirically and is under present investigation.

**Isotope Content of Deuterated Raney Nickel.**—A deuterated catalyst sample (*ca.* 8 g.) was prepared using two 36 hr. rinses with heavy water recovered from previous deuterations, then one 48 and one 96 hr. rinse with 99% deuterium oxide. A portion of this catalyst was filtered almost dry, then placed in a small flask connected to a gas bulb and a vacuum line. The system was evacuated below 0.1 mm. for a short time, then closed. The catalyst sample was heated gradually in an oil-bath, and the pressure rise noted manometrically. Pressure in the system rose insignificantly until the bath temperature reached approximately 200°, whereupon the catalyst degassed very abruptly. Further baking at 205° produced no additional pressure increase. The gas bulb was closed and the system was allowed to cool. The gas free catalyst was emptied onto a watch glass and weighed *ca.* 5 g. It gained weight rapidly, became red hot and reverted from gray to black, presumably on reacting with atmospheric oxygen. Rough calibration of the vacuum system indicated that 16.3 mmoles of gas was liberated, corresponding to about 73 ml. gas/g. of catalyst. Mass spectrometric assay of the gas sample collected<sup>4</sup> indicated it to be 11.2% hydrogen and 88.8% deuterium.

**Action of Deuterated Raney Nickel on (+)-2-Phenylpropionamide.**—About 4 g. of deuterated Raney nickel was mixed with deuterio-ethanol<sup>1</sup> (34 ml.) containing 806 mg. (+)-2-phenylpropionamide, m.p. 96.5–98.5°,  $[\alpha]^{27D}$  52.5° (*c* 3.16, chloroform). The mixture was heated under reflux for 2.1 hr., when one-third of the reaction slurry was removed by pipetting. The remainder was refluxed further.

The aliquot was filtered, and the catalyst was rinsed with hot ethanol (50 ml.), then the solvent was distilled. The residue was treated with absolute ethanol, and the solution was again boiled dry (100°) to ensure replacement of amide deuterium by hydrogen.<sup>1</sup> In this manner Amide I, 162 mg., m.p. 96.5–102.5°,  $[\alpha]^{27D}$  51.8° (*c* 3.39, chloroform), was obtained.

After 8.5 hr. one-half of the remaining refluxing reaction mixture was removed and processed similarly to give Amide II, 176 mg., m.p. 90–94°,  $[\alpha]^{24D}$  45.6° (*c* 3.34, chloroform). This material was recrystallized from a mixture of chloroform and ligroin to give Amide IIa, 144 mg., m.p. 90.5–93.5°,  $[\alpha]^{27D}$  49.1° (*c* 3.38, chloroform).

After 24.5 hr. the balance of the reaction mixture was treated as above to yield Amide III, 304 mg. This crystallized with difficulty to give a sample, m.p. 87.5–92.5°,  $[\alpha]^{26D}$  44.5° (*c* 3.37, chloroform). Recrystallization gave

Amide IIIa, 221 mg., m.p. 88.5–92.5°,  $[\alpha]^{30D}$  48.1° (*c* 3.39, chloroform). The above procedures account for 80% of the original (+)-2-phenylpropionamide.

Portions of Amides I, IIa and IIIa were oxidized to benzoic acid with alkaline potassium permanganate, and the product from each oxidation was purified by vacuum sublimation.

Each amide sample and the benzoic acid derived from it was combusted in oxygen in a semi-micro combustion apparatus, and the effluent water was collected and analyzed mass spectrographically for deuterium oxide,<sup>1,4</sup> thus providing the data in Table I.

**Racemization of (-)-2-Phenylpropionamide by Alkali.**—A solution of (-)-2-phenylpropionamide (0.4 g., m.p. 93.5–95°,  $[\alpha]^{22D}$  -29.5° (*c* 2.00, 75% ethanol)) in abs. ethanol (25 ml.) had  $\alpha^{28D}$  -0.49° (*l* = 1 dcm.). After a 20-hour reflux period the rotation was  $\alpha^{24D}$  -0.50°. To this solution was added 0.01 ml. of 0.04 *N* sodium hydroxide. Six hours of refluxing produced no rotational change, and 0.1 ml. 0.04 *N* sodium hydroxide was added. The rotation was unchanged after 21 hr. of refluxing. One ml. of 0.04 *N* base was then added, and after a 45-hour reflux period the solution was optically inactive.

**Deuteration 2-Phenylpropionamide by Alkali Catalysis.**—Racemic 2-phenylpropionamide (0.25 g.), 0.04 *N* sodium hydroxide (1.1 ml.) and deuterio-ethanol (27 ml.) were heated under reflux during 48 hr. Customary isolation and recrystallization as above yielded 0.05 g. of pure 2-phenylpropionamide, m.p. 93.5–95°. A sample of this was combusted in the usual manner, and the combustion water was found to contain 5.2% deuterium oxide, corresponding to 0.5 gram atom deuterium per mole.

**Deuterated Raney Nickel and 1-Phenylethanol.**—Fifteen grams of Raney nickel which had been in contact with deuterium oxide (30 ml.) for 1.5 months was filtered almost dry and transferred to deuterio-ethanol (40 ml.). 1-Phenylethanol (5.0 g.) was added, and the mixture was refluxed for 6 hr. It was then filtered and the catalyst was rinsed with 100 ml. of hot ethanol. The filtrate and rinse were treated with 250 ml. of water, and the small organic layer was separated. The aqueous layer was steam distilled until the distillate was clear, whereupon the distillate and above organic layer were combined and extracted with 50 ml. of ligroin. The extract was washed with water, dried and distilled, 2.7 g., b.p. 129–134°. On redistillation a fraction, b.p. 132°,  $n^{20D}$  1.4930, was removed for assay. The product appeared to be substantially pure dideterated ethylbenzene, as indicated by the reasonable similarity of its infrared spectrum to that of ethylbenzene, by the fact that its combustion water contained 21.9% deuterium oxide as determined mass spectrographically, and by its combustion analysis corrected for the D<sub>2</sub>O-content of the combustion water.

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>D<sub>2</sub>: C, 88.85; H + D, 11.15. Found: C, 87.89, 87.96; H + D, 11.21, 11.43.

In another experiment (-)-1-phenylethanol,  $[\alpha]^{28D}$  -42.5° (neat) (97% optically pure), resolved by the procedure of Downer and Kenyon,<sup>5</sup> was subjected to the action of deuterated Raney nickel as described above. The ethylbenzene from the reaction was indistinguishable from the sample isolated above, gave essentially identical combustion analyses and proved to be optically inactive.

**Deuterated Raney Nickel and Ethylbenzene.**—Deuterio-ethanol (35 ml.), ethylbenzene (6.00 g.) and deuterated Raney nickel (*ca.* 15 g.) were heated under reflux for 6 hr. The product was isolated as described above, then distilled. The distillate was dried over phosphoric anhydride and redistilled into three fractions: (1) b.p. 129–132.5°,  $n^{21D}$  1.4722, 0.48 g.; (2) b.p. 132.5–133.5°,  $n^{21D}$  1.4860, 0.52 g., and (3) b.p. 133.5°,  $n^{21D}$  1.4904, 1.33 g. A sample of the third fraction was oxidized to benzoic acid. The latter was purified by sublimation and burned. Its combustion water was found mass spectrometrically to contain 26.8% deuterium oxide, corresponding to about 1.5 gram atoms of deuterium per mole of benzoic acid.

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(4) Performed by Dr. Harold Eding at the Stanford Research Institute.