[Contribution from the Research Division of Smith, Kline and French Laboratories]

# REARRANGEMENT OF 1-AMINO-1-(3-PHTHALIDYL)ALKANES. A NEW SYNTHESIS OF SUBSTITUTED ISOQUINOLONES

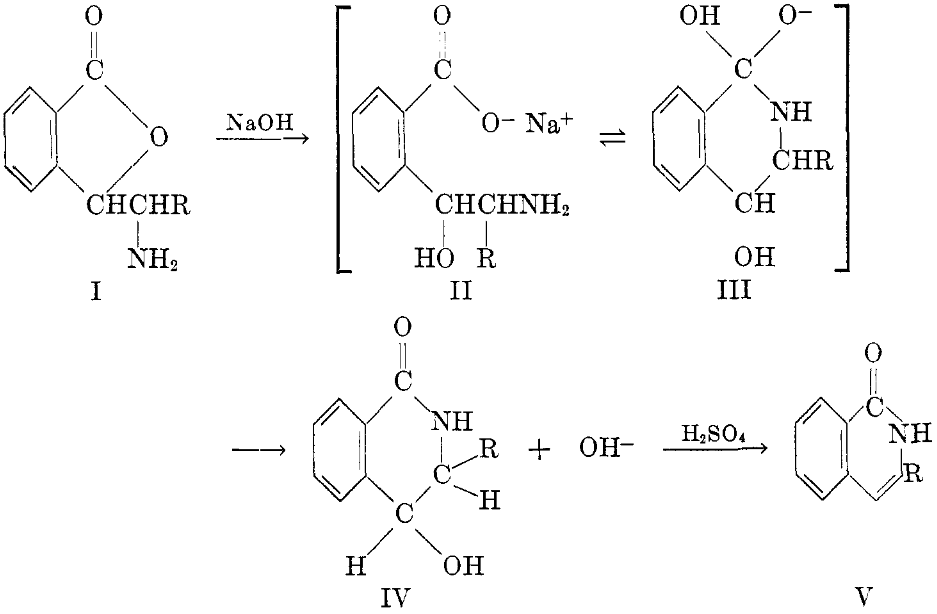
JAMES W. WILSON, III, ELVIN L. ANDERSON, and GLENN E. ULLYOT

*Received January 15, 1951*

In earlier papers (1) we have described the synthesis of a series of 1-amino-1-(3-phthalidyl)-alkanes (I) for testing as possible analgetic agents. In studying the properties of these compounds, it was found that they could be readily rearranged under neutral or alkaline conditions to give substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolones (IV). This rearrangement has been mentioned briefly in an earlier paper (1a).

Szeki (2) has also reported a single example of this reaction. He treated phthalidylmethylamine (I; R = H) hydrochloride with excess alkali and after acidification with acetic acid, isolated a product (m.p. 164–165°) to which he assigned the correct structure (IV; R = H). However, he did not rigorously establish the structure of his product and he made no attempt to determine the useful limits of the reaction.

In the present work we have extended the study of this rearrangement to a series of twelve (see Table I) aminophthalidylalkanes (I). In all but two cases the substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolones (IV) which resulted were isolated as crystalline solids. The structures of the products were verified by dehydration with sulfuric acid to the corresponding 1,2-dihydroisoquinolones (V). Six of the isoquinolones reported in Table II have been described earlier (see footnotes). In two cases (see footnotes) we have repeated the earlier work

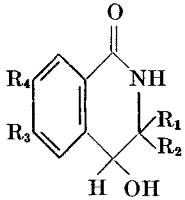


I II III

IV V

TABLE I

4-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLONES

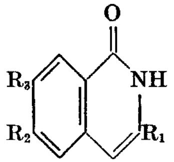


| R | $R_2$ | $R_3$ | $R_4$ | FORMULA | M.P., °C. | YIELD, % | ANALYSES | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calc'd | | | Found | | |
| | | | | | | | C | H | N | C | H | N |
| H | H | H | H | $C_9H_9NO_2$[a] | 163–164[b] | 91 | — | — | 8.52 | — | — | 8.64 |
| H | $CH_3$ | H | H | $C_{10}H_{11}NO_2$ | 166.5–167.5[c] | 64[d] | 67.78 | 6.27 | 7.91 | 67.29 | 6.40 | 7.95 |
| H | $C_2H_5$ | H | H | $C_{11}H_{13}NO_2$[e] | 184–185.5[f] | 95 | 69.09 | 6.85 | 7.32 | 69.00 | 6.93 | 7.38 |
| $CH_3$ | $CH_3$ | H | H | $C_{11}H_{13}NO_2$ | 164.5–165.5 | 68 | 69.09 | 6.85 | 7.32 | 69.18 | 7.01 | 7.22 |
| H | $n$-$C_3H_7$ | H | H | $C_{12}H_{15}NO_2$ | 129–130[g] | 89 | 70.20 | 7.37 | — | 70.23 | 7.26 | — |
| H | $n$-$C_4H_9$ | H | H | $C_{13}H_{17}NO_2$ | 118–118.5 | 92 | 71.20 | 7.81 | 6.39 | 71.17 | 7.79 | 6.40 |
| H | $CH_2CH(CH_3)_2$ | H | H | $C_{14}H_{19}NO_2$ | oil[h] | — | — | — | — | — | — | — |
| H | $n$-$C_5H_{11}$ | H | H | $C_{14}H_{19}NO_2$ | 112–112.5 | 78 | 72.07 | 8.21 | — | 72.06 | 7.61 | — |
| H | $n$-$C_6H_{13}$ | H | H | $C_{16}H_{21}NO_2$ | oil[h] | 78 | — | — | — | — | — | — |
| H | $C_6H_5$ | H | H | $C_{15}H_{13}NO_2$ | 172–173.5 | 77 | 75.29 | 5.48 | — | 75.59 | 5.44 | — |
| H | $C_2H_5$ | $CH_3$ | $CH_3$ | $C_{13}H_{17}NO_2$ | 198–199 | 62 | 71.20 | 7.81 | — | 71.28 | 7.56 | — |
| H | $C_2H_5$ | H | $NH_2$[i] | $C_{11}H_{14}N_2O_2$ | 216–217 | 40 | 64.06 | 6.84 | 13.58 | 63.89 | 6.89 | 13.51 |

[a] Szeki, *Ber. ungar. pharm. Ges.*, **13**, 680 (1937) [*Chem. Abstr.*, **31**, 6644 (1937)], has reported a compound, m.p. 164–165°, which most probably has this structure. [b] Another crystalline form, m.p. 150–151°, was also isolated. [c] A second racemic form, m.p. 161–163°, was also isolated. It markedly depressed the melting point of the other isomer. *Anal.* Found: C, 67.94; H, 6.18; N, 7.94. [d] Figures in this column refer to the total yield of rearranged material. [e] Ullyot, Stehle, Zirkle, Shriner, and Wolf, *J. Org. Chem.*, **10**, 429 (1945). [f] A racemic form, m.p. 128–130°, was also obtained. [g] Another crude racemate, m.p. 55–59° was also isolated. [h] This product was not characterized as such. The structure was established by dehydration to the corresponding isocarbostyril (see Table II). [i] The position of the amino group has not been absolutely established. See Wilson, Zirkle, Anderson, Stehle, and Ullyot, J. Org. Chem., **16**, preceding article.

## TABLE II

Isocarbostyrils



| $R_1$ | $R_2$ | $R_3$ | FORMULA | M.P., °C. | YIELD, % | ANALYSES |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | Calc'd |  |  | Found |  |  |
|  |  |  |  |  |  | C | H | N | C | H | N |
| H | H | H | $C_9H_7NO$[a] | 211–215 | 94 | — | — | 9.65 | — | — | 9.48 |
| $CH_3$ | H | H | $C_{10}H_9NO$[b] | 212–214[c] | 93 | — | — | 8.80 | — | — | 8.80 |
| $C_2H_5$ | H | H | $C_{11}H_{11}NO$[d] | 144–145[c] | 93 | 76.27 | 6.40 | 8.08 | 76.04 | 6.87 | 7.78 |
| $n$-$C_3H_7$ | H | H | $C_{12}H_{13}NO$[e] | 129–130[c] | 70 | 76.98 | 6.95 | 7.48 | 77.04 | 7.00 | 7.62 |
| $n$-$C_4H_9$ | H | H | $C_{13}H_{15}NO$ | 139.5–140.5 | 83 | 77.58 | 7.51 | 6.96 | 77.43 | 7.36 | 7.03 |
| $CH_2CH(CH_3)_2$ | H | H | $C_{13}H_{15}NO$[f] | 137–138 | 95 | — | — | — | — | — | — |
| $n$-$C_5H_{11}$ | H | H | $C_{14}H_{17}NO$ | 106.5–108 | 95 | 78.10 | 7.96 | — | 78.19 | 7.75 | — |
| $n$-$C_6H_{13}$ | H | H | $C_{15}H_{19}NO$ | 118–118.5 | 47 | 78.56 | 8.35 | — | 78.35 | 8.35 | — |
| $C_6H_5$ | H | H | $C_{15}H_{11}NO$[g] | 199.5–200 | 60 | — | — | — | — | — | — |
| $C_2H_5$ | $CH_3$ | $CH_3$ | $C_{13}H_{15}NO$ | 248–249 | 97 | 77.58 | 7.51 | — | 77.29 | 7.49 | — |
| $C_2H_5$ | H | $NH_2$ | $C_{11}H_{12}N_2O$ | 202–203 | 100 | 70.19 | 6.43 | 14.88 | 70.33 | 6.32 | 14.93 |

[a] Gabriel and Colman, *Ber.*, **33,** 985 (1900); Bamberger and Frew, *Ber.*, **27,** 208 (1894). [b] Gabriel and Colman, *Ber.*, **33,** 988 (1900). The synthesis of Gabriel and Colman was repeated. The product, m.p. 214–215°, did not depress the melting point of the material obtained *via* the rearrangement. [c] Only one product was obtained by the dehydration of the two racemic hydroxytetrahydroisoquinolones. [d] Gabriel and Michael, *Ber.*, **11,** 1683 (1878); Damerow, *Ber.*, **27,** 2235 (1894); Ullyot, Stehle, Zirkle, Shriner, and Wolf, *J. Org. Chem.*, **10,** 429 (1945). [e] Albahary, *Ber.*, **29,** 2394 (1896), reported m.p. 130–131° for this compound. [f] Lehmkuhl, *Ber.*, **30,** 896 (1897), reported m.p. 138–139° for this compound. [g] Gabriel, *Ber.*, **18,** 3471 (1885); Ulrich, *Ber.*, **37,** 1692 (1904). A sample of this compound prepared by Gabriel's procedure was identical with the product obtained *via* the rearrangement.

and proved beyond question the structures of the products obtained *via* the rearrangement and dehydration.

The methods described in the literature for the synthesis of substituted isoquinolones are not readily adapted to preparative work. We have, therefore, utilized the rearrangement and dehydration reactions as preparative methods for a series of substituted isoquinolone (3) intermediates.

*Discussion.* When an aqueous solution of 1-amino-1-phthalidylpropane (I; R = $C_2H_5$) hydrochloride was neutralized with one equivalent of aqueous sodium hydroxide, an oil separated from the solution. This mixture (*p*H approximately 8), when heated at reflux or just below reflux temperature, yielded, when cooled, a quantity of crystalline 3-ethyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolone-1 (IV; R = $C_2H_5$) which varied directly with the period of heating. When an aqueous solution of the same salt was carefully mixed with two equivalents of sodium hydroxide solution, an oil separated but quickly redissolved. When this solution of II (R = $C_2H_5$) was heated at reflux temperature for a relatively short period of time, the tetrahydroisoquinolone (IV; R = $C_2H_5$) separated from the hot alkaline solution as an oil which crystallized upon cooling. If the hydroxytetrahydroisoquinolone was removed from the cold reaction mixture, the filtrate on standing or after additional heating, slowly deposited an additional quantity of the crystalline rearrangement product.

In the absence of excess alkali, an almost quantitative yield of IV (R = $C_2H_5$) could be realized if the period of heating was sufficiently long (15–20 hours). After shorter heating periods, an appreciable quantity of starting amine could be recovered by acidification of the reaction mixture and evaporation to dryness.

When two equivalents, or more, of alkali were employed, the theoretical yield of IV (R = $C_2H_5$) could be realized after a considerably shorter period of heating (3–6 hours), if the rearrangement product was removed from the reaction mixture as it formed.

In each case the rate of the rearrangement reaction decreased very markedly with decreases in temperature.

With only two exceptions the aminophthalidylalkanes (I) which we studied possessed two asymmetric centers and thus existed in two different racemic forms. In three of the compounds studied (I; R = $CH_3$, $C_2H_5$, and *n*-$C_3H_7$), both of the racemic isomers have been obtained in essentially pure form (1a). The higher-melting racemic form has in each case been designated "isomer A" and the lower-melting racemic form "isomer B".

The corresponding hydroxytetrahydroisoquinolones (IV; R = $CH_3$, $C_2H_5$, and *n*-$C_3H_7$) can also exist in two racemic forms since they, too, possess two asymmetric centers. In this case, too, the higher-melting racemic form has been designated "isomer A" and the lower-melting "isomer B."

In each of the three cases (R = $CH_3$, $C_2H_5$, and *n*-$C_3H_7$), rearrangement of isomer A of the aminophthalidylalkane gave isomer B of the hydroxytetrahydroisoquinolone and the B isomer of the amine yielded the A isomer of the isoquinolone. In each of the three cases, the B isomer of the aminophthalidylalkane rearranged at a considerably faster rate than the corresponding A isomer. By taking advantage of this differential rate, aminophthalidylalkanes considerably richer in isomer A could be recovered from the partial rearrangement of a mixture of isomers A and B.

In the other cases where two racemic forms were possible, the racemic aminophthalidylalkane mixture (A and B) was used.

Both centers of asymmetry are removed by the dehydration with sulfuric acid. Thus any one pair of A and B isomers of IV gave only a single dihydroisoquinolone (V).

*Conclusions.* The rearrangement reaction is apparently a base-catalyzed one, and proceeds through the intermediate sodium salt of the carboxylic acid (II) formed when the phthalide ring is opened. The separation of the hydroxytetrahydroisoquinolone from a strongly alkaline solution suggests that the driving force for the reaction is the formation of a stable six-membered ring. This probably occurs through the intermediate III, in equilibrium with II, by the loss of hydroxyl ion. This formation of an amide, under conditions (strong alkali) which usually favor the hydrolysis of amides, is presumably due to the steric factors involved and to the stability of the rearranged product.

## EXPERIMENTAL

*Rearrangement of 1-amino-1-phthalidylalkanes* (I). An aqueous solution of the amine hydrochloride was treated with two equivalents of 40% sodium hydroxide solution. The resulting solution was heated at 92–100° for a period of three to six hours. For the most part the substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolones crystallized directly from the cold alkaline reaction mixture. Additional crystalline product was obtained by concentrating the filtrate on a steam-bath. The products were purified by crystallization from aqueous alcohol. The non-crystalline products were separated by extraction into benzene or chloroform. After removal of the solvent they were used as such. The results are summarized in Table I.

*Dehydration of substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolones* (IV). The carbinol was added with stirring to concentrated sulfuric acid at such a rate that the temperature did not exceed 95°. The resulting solution was then heated at 85–95° for three hours, cooled, and poured onto cracked ice. The product was isolated by filtration and purified by crystallization from alcohol. The melting point of those isocarbostyrils which were not new agreed with the previously reported values. In two cases the syntheses already described were repeated and the identity of the rearranged products was established by mixture melting points. The data are summarized in Table II.

### RACEMIC ISOMERS OF SUBSTITUTED 4-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLONES

*Isomer A.* A solution of 1.0 g. (0.0044 mole) of 1-amino-1-phthalidylpropane hydrochloride (isomer B) in 10 ml. of water containing 1.1 g. (0.0275 mole) of sodium hydroxide was heated to reflux and allowed to stand for five days. The crystalline product weighed 0.7 g. (83%); m.p. 183–185.5°.

*Isomer B.* A solution of 1.0 g. (0.0044 mole) of 1-amino-1-phthalidylpropane hydrochloride (essentially isomer A) in 10 ml. of water containing 1.1 g. (0.0275 mole) of sodium hydroxide was heated to reflux and allowed to stand for five days. After heating at 85–100° for an additional ten hours and standing for three days the solution was evaporated to a small volume and acidified with concentrated hydrochloric acid. The crystalline product (0.7 g.) was refluxed with alcohol and the inorganic material removed. Concentration of the alcohol solution and dilution with water yielded 0.45 g. (53%) of isomer B; m.p. 127–129°.

*3-Ethyl-1,2-dihydroisoquinolone-1 by the dehydration of isomers A and B.* A solution of 1.6 g. (0.0084 mole) of 3-ethyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolone-1 (isomer A; m.p. 180–183°) in 10 ml. of concentrated sulfuric acid was heated at 90° for three hours.

Cooling and the addition of cracked ice yielded 1.1 g. (79%) of crystalline product; m.p. 143–145° (softening at 128–130°).

In the same way 3.8 g. (0.02 mole) of isomer B (m.p. 128–130°) and 25 ml. of sulfuric acid yielded 2.7 g. (77%) of the same product; m.p. 143–145° (softening at 128–130°).

### EFFECT OF HEAT AND ALKALI ON THE REARRANGEMENT OF 1-AMINO-1-PHTHALIDYLPROPANE

*A. Under neutral or slightly alkaline conditions.* (1) *Three and one-half hours reflux.* To a solution of 22.8 g. (0.1 mole) of 1-amino-1-phthalidylpropane hydrochloride (a mixture of isomers A and B; m.p. 208–210°) in 100 ml. of water was added 7.0 ml. (0.1 mole) of 40% sodium hydroxide. The *p*H of the resulting mixture (an oil separated) was approximately 8. It was heated at reflux for 3.5 hours. After cooling, the solid was collected, washed with water, and dried; 12.4 g.; m.p. 148–160°. The filtrate was acidified with concentrated hydrochloric acid and evaporated to dryness. The organic material was separated from the sodium chloride by extraction with boiling alcohol. The alcohol solution was concentrated and diluted with acetone to yield 1.5 g. of starting material (water-soluble), m.p. 249–260° (essentially isomer A). Concentration of the mother liquor yielded an additional 1.0 g. of the starting amine, m.p. 212–230°, and 1.8 g. of water-insoluble rearranged product, m.p. 115–135°. The total yield of rearranged product (mixture of A and B isomers) was 14.2 g. (75%). The total yield of recovered starting material (richer in isomer A) was 2.5 g. (11%).

(2) *Two hours reflux.* The preceding experiment was repeated with the same mixture of isomers but the reflux time was reduced to two hours. A total of 9.2 g. (49%) of water-insoluble rearranged product, melting range 115–163°, was isolated. The recovered starting material (water-soluble fraction) weighed 8.7 g. (38%) and melted over the range 190–263°.

(3) *One hour reflux.* The same mixture of isomers was refluxed for one hour to give 5.8 g. (31%) of rearranged product, melting range 125–160°, and 13.3 g. (58%) of recovered starting material, melting range 215–266°.

*B. In the presence of one equivalent of sodium hydroxide.* A solution of 22.8 g. (0.1 mole) of essentially pure isomer B (m.p. 237–243°) in 100 cc. of water containing two equivalents of sodium hydroxide was heated at reflux for 1.5 hours. A total of 14.5 g. (80%) of rearranged product, m.p. 181–183.5°, was isolated directly from the reaction mixture. Acidification, evaporation, and extraction with alcohol yielded 3.7 g. (16%) of starting material; m.p. 238–241°.

## SUMMARY

1. A series of substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolones have been prepared by the alkaline rearrangement of aminophthalidylalkanes.

2. Dehydration of the hydroxytetrahydroisoquinolones has yielded the corresponding 1,2-dihydroisoquinolones.

3. The effect of heat and alkali on the rearrangement reaction has been studied qualitatively.

PHILADELPHIA, PENNSYLVANIA

## REFERENCES

(1) (a) ULLYOT, STEHLE, ZIRKLE, SHRINER, AND WOLF, *J. Org. Chem.*, **10**, 429 (1945); (b) ULLYOT, TAYLOR, AND DAWSON, *J. Am. Chem. Soc.*, **70**, 542 (1948); (c) WILSON, ZIRKLE, ANDERSON, STEHLE, AND ULLYOT, *J. Org. Chem.*, preceding article.

(2) SZÉKI, *Ber. ungar. pharm. Ges.*, **13**, 680 (1937) [*Chem. Abstr.*, **31**, 6643 (1937)].

(3) WILSON, DAWSON, BROOKS, AND ULLYOT, *J. Am. Chem. Soc.*, **71**, 937 (1949).