

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE<sup>1</sup>]

## Resolution and Rearrangement of $\alpha$ -Methylhydrocinnamic Acid and of Its 3,4-Dimethoxy Derivative

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(-)- $\alpha$ -Methylhydrocinnamic acid (I), prepared by resolution with (+)- $\alpha$ -methylbenzylamine, was converted to optically pure (-)- $\alpha$ -methylphenethylamine (II). An analogous series of reactions was carried out with the 3,4-dimethoxy derivative.

(+)- $\alpha$ -Methylhydrocinnamic acid, obtained by resolving the racemate with quinine<sup>2</sup> or menthylamine,<sup>3</sup> has been used extensively, especially by Wallis and his school, in studying the steric course of saturated nucleophilic rearrangements.<sup>4</sup> Thus the Curtius,<sup>5</sup> Hofmann,<sup>6</sup> Lossen,<sup>7</sup> Schmidt,<sup>8</sup> and Wolff<sup>9</sup> rearrangements were shown to proceed with retention of configuration.

It seems surprising that no method for preparing the optical isomer, (-)-I,<sup>10</sup> of this acid has been reported. Indeed, references to the *levo* isomer mention only partly racemic material, recovered from the mother liquors of the quinine salt of (+)-I.<sup>5,9b</sup>

The use of (-)- and (+)- $\alpha$ -methylbenzylamine ( $\alpha$ -phenylethylamine) (III) in the resolution of

atrolactic and mandelic acid<sup>18</sup> suggested its application to the resolution of I into both antipodes.

Treatment of racemic I with (-)-III and fractional crystallization of the diastereoisomeric salts from ethyl acetate provided, in 50% yield, (+)-I-(-)-III, from which (+)-I,  $[\alpha]_D^{25} +23.5^\circ$  (undiluted) was obtained. Resolving the impure *levo* acid from the mother liquors (or racemic I) with (+)-III similarly afforded (-)-I,  $[\alpha]_D^{25} -24.6^\circ$ . It may be mentioned that (+)-I, as obtained by resolution with quinine or menthylamine, had specific rotations not higher than  $22.6^\circ$ ,<sup>2,3</sup> and in most reported instances considerably lower.<sup>5,6,7,9</sup>

Both the Curtius and the Schmidt rearrangement of (-)-I provided (-)- $\alpha$ -methylphenethylamine (*levo*-amphetamine) (II),<sup>10</sup> the hydrochloride of which in water had  $[\alpha]_D^{25} -25.6^\circ$  (*c* 4.8) (identical values in both rearrangements) and  $-24.6^\circ$  (*c* 9.0). The latter value agrees with that reported by Leithe<sup>17</sup> for pure (+)-II hydrochloride<sup>18</sup> obtained by resolving racemic II. Essentially complete retention of asymmetry was to be expected, since the Curtius<sup>19</sup> and Schmidt<sup>20</sup> rearrangements of hydropyridic acid also proceed with over 99% retention. The reported<sup>5,8</sup> rotations of (+)-II hydrochloride formed in the same rearrangements from (+)-I were, on the other hand, considerably lower,<sup>18</sup> a fact which can be explained only partly by the optical impurity of the acid used as the starting material.<sup>5</sup>



Arylaliphatic acid azides generally have been prepared from the acid chlorides with sodium azide in anhydrous solvents ("dry method"<sup>21</sup>); this pro-

(1) The National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

(2) F. S. Kipping and A. E. Hunter, *J. Chem. Soc.*, **83**, 1005 (1903).

(3) R. H. Pickard and J. Yates, *J. Chem. Soc.*, **95**, 1011 (1909).

(4) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press, Ithaca, N. Y., 1953, p. 500.

(5) L. W. Jones and E. S. Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926).

(6) E. S. Wallis and S. C. Nagel, *J. Am. Chem. Soc.*, **53**, 2787 (1931).

(7) E. S. Wallis and R. D. Dripps, *J. Am. Chem. Soc.*, **55**, 1701 (1933).

(8) J. v. Braun and E. Friehmelt, *Ber.*, **66**, 684 (1933).

(9) (a) J. F. Lane, J. Willenz, A. Weissberger, and E. S. Wallis, *J. Org. Chem.*, **5**, 276 (1940); (b) K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, **78**, 1640 (1956).

(10) The absolute *D*-configuration of (-)-I and (-)-II, shown in the formulas,<sup>11</sup> follows from Karrer and Ehrhardt's<sup>12</sup> conversion of *D*-phenylalanine to *L*-(+)-II.<sup>13</sup> The *D*-configuration of (-)-IV and (-)-V has been demonstrated<sup>14</sup> by an analogous conversion of *L*-3,4-dihydroxyphenylalanine to *N*-tosyl(-)-V, which was found to have the same negative rotation as the compound obtained by direct tosylation of (-)-V.

(11) Cf. W. Klyne, *Chemistry and Industry*, 1022 (1951).

(12) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

(13) The change from *D* to *L* in this conversion is due to the change in the chief function.

(14) A. W. Schrecker and J. L. Hartwell, to be published. This direct proof that (-)-I and (-)-IV belong to the same configurational series confirms the previously postulated<sup>15</sup> configuration of guaiaretic acid and related lignans.

(15) A. W. Schrecker and J. L. Hartwell, *J. Org. Chem.*, **21**, 381 (1956).

(16) L. Smith, *J. prakt. Chem.*, (2) **84**, 731 (1941).

(17) W. Leithe, *Ber.*, **65**, 660 (1932).

(18) The reported constants for (+)-II hydrochloride are: m.p.  $147^\circ$ ,<sup>5</sup>  $146^\circ$ ,<sup>8</sup>  $156^\circ$ ;<sup>17</sup>  $[\alpha]_D^{25}$  (in water)  $+16.6^\circ$  (*c* 4.80),<sup>5</sup>  $+16.1^\circ$  (*c* 4.163),<sup>8</sup>  $[\alpha]_D^{15} +24.8^\circ$  (*c* 9.00).<sup>17</sup>

(19) J. Kenyon and D. P. Young, *J. Chem. Soc.*, 263 (1941).

(20) A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).

(21) P. A. S. Smith, *Org. Reactions*, **3**, 373 (1946).

cedure was used in the Curtius rearrangements of (+)-I<sup>6</sup> and of hydratropic acid.<sup>19</sup> The "wet method"<sup>21</sup> has apparently not been employed for this class of compounds. However, its use in the present study yielded (without isolation of the various intermediates) over 90% of pure (-)-II hydrochloride.

Resolution of 3,4-dimethoxy- $\alpha$ -methylhydrocinnamic acid (IV), required for determining the absolute configuration of various lignans,<sup>15</sup> with quinine yielded (+)-IV,  $[\alpha]_D^{25} +27.5^\circ$  (chloroform). The impure (-)-IV, set free from the mother liquors, yielded a (-)-IV-(-)-III salt, slightly less soluble in ethyl acetate than its diastereoisomer (Table I),<sup>22</sup> from which (-)-IV,<sup>10</sup>  $[\alpha]_D^{25} -28.1^\circ$  (chloroform) was isolated. The Curtius rearrangement of the enantiomorphous acids yielded (+)- and (-)-3,4-dimethoxy- $\alpha$ -methylphenethylamine (V).<sup>10</sup>

TABLE I

PHYSICAL CONSTANTS OF  $\alpha$ -METHYLBENZYLAMINE SALTS

Salt	M.p., °C	$[\alpha]_D^{25}$	Solubility <sup>b</sup>
(+)-I-(+)-III <sup>c</sup>	120-121	+22.7°	2.64
(-)-I-(+)-III	127.3-129.5	+1.4°	1.00
(+)-I-(-)-III	127-129.5	-1.5°	—
(+)-IV-(+)-III <sup>c</sup>	107-109	+22.3°	1.39
(-)-IV-(+)-III <sup>c</sup>	113.5-114.5	-2.1°	1.47
(-)-IV-(-)-III	107-109	-22.0°	—
(+)-IV-(±)-III <sup>c,d</sup>	110.4-111.4	+12.8°	—

<sup>a</sup> 2% solution in chloroform. <sup>b</sup> Determined in ethyl acetate at 23° and expressed as grams/100 g. of solution. <sup>c</sup> Prepared from the two pure components and crystallized from ethyl acetate. <sup>d</sup> Racemic III was recovered from this salt.

EXPERIMENTAL<sup>23</sup>

*$\alpha$ -Methylcinnamic acid.* A vigorously stirred suspension of 9.1 g. of sodium hydride in 125 ml. of methyl propionate was cooled in ice and treated with 0.45 ml. of absolute ethanol, then with 31.84 g. of benzaldehyde in 50 ml. of methyl propionate during 10 min. The ice bath was removed after one hour, replaced as soon as the vigorous reaction started, then removed again, and stirring was continued for another 2 hr. The organic layer was separated, after cautious addition of 28 ml. of acetic acid, then of 100 ml. of water, and the aqueous phase extracted with ethyl acetate. The combined ester solutions were washed with *N* hydrochloric acid and with sodium chloride solution, dried with sodium sulfate, and evaporated *in vacuo*. The residual ester was refluxed with 33.6 g. of potassium hydroxide in 60 ml. of water and 240 ml. of methanol for one hour. The solution was concentrated, diluted with water to ca. 500 ml., acidified with 6 *N* hydrochloric acid, chilled overnight, and the collected solid was washed with ice water; yield 35.67 g.

(22) The small difference in solubilities would appear to make a direct resolution of racemic IV with III impractical. However, such a direct resolution could nevertheless be accomplished, apparently because the (-)-IV-(-)-III salt (and its antipode) crystallizes more rapidly than the diastereoisomeric salt. It is noteworthy that the solubility relationship is reversed in the case of the I-III salts.

(23) Melting points are corrected and were determined with the Hershberg apparatus. Boiling points are uncorrected.

(73%), m.p. 75-81°. The acid crystallized from hexane in colorless prisms, m.p. 80.5-81.0° (lit.<sup>24</sup> m.p. 81-82°).

*3,4-Dimethoxy- $\alpha$ -methylcinnamic acid.* The combined ester solutions, obtained from 18.53 g. of sodium hydride, 101.7 g. of veratraldehyde, and 356 ml. of methyl propionate, were washed with *N* hydrochloric acid, extracted with aqueous potassium carbonate, dried over potassium carbonate, concentrated, and passed through an alumina column which was then washed with chloroform. Evaporation of the eluates and crystallization from ether-hexane yielded 115.0 g. (80%) of the methyl ester as colorless prisms, m.p. 62.5-64.5° (lit.<sup>25</sup> m.p. 65-67°). The free acid was obtained in 99% yield by saponifying this ester with 2 molar equivalents of potassium hydroxide. It formed colorless needles, m.p. 142.8-143.8° (lit. m.p. 142-143°, 144°<sup>26</sup>). Additional acid, isolated by acidifying the potassium carbonate extract and by saponifying the evaporated mother liquors of the recrystallized ester, was purified by crystallization from ethanol, raising the total yield from veratraldehyde to 86%.

*DL- $\alpha$ -Methylhydrocinnamic acid (I)* was prepared in 95% yield by treating 30 g. of  $\alpha$ -methylcinnamic acid and 99.8 g. of sodium hydroxide in 900 ml. of water with 90 g. of Raney nickel-aluminum alloy at 90°. The cooled filtrate and washings were stirred into 720 ml. of concd. hydrochloric acid and about 700 g. of ice and extracted with ether (600 + 300 + 300 ml.). The ether extracts were washed with 2 *N* hydrochloric acid and with sodium chloride solution, dried, and evaporated. The distilled acid (b.p. 148-149°/9 mm., 116.5°/0.5 mm.) solidified on chilling; m.p. 36-37°; yield 28.9 g. (95%). A sample crystallized from pentane in colorless prisms, m.p. 36.6-37.5° (lit.<sup>28</sup> m.p. 37°).

*DL-3,4-Dimethoxy- $\alpha$ -methylhydrocinnamic acid (IV)* was obtained in 94% yield as colorless hexagonal plates, m.p. 61.5-62.8° (lit.<sup>29</sup> m.p. 58-59°), after evaporating the ether extracts and recrystallizing the residue from ether-pentane.

*Anal.* Calc'd for C<sub>12</sub>H<sub>16</sub>O<sub>4</sub>: C, 64.27; H, 7.19. Found: C, 64.39; H, 7.44.

*L-(+)- $\alpha$ -Methylhydrocinnamic acid.*<sup>10</sup> A cold solution of 41.0 g. of racemic I in 350 ml. of ethyl acetate was treated with 30.25 g. of (-)- $\alpha$ -methylbenzylamine (III),<sup>30</sup> heated to dissolve the precipitate, and allowed to cool slowly. The solid was recrystallized six times from ethyl acetate to yield 16.1 g. of the (+)-I-(-)-III salt as long colorless needles, m.p. 127-129.5°,  $[\alpha]_D^{25} -1.48^\circ$  (*c* 2.00, chloroform). Systematic recrystallization of the second crops gave another 1.8 g. of pure salt, bringing the total yield to 50%.

*Anal.* Calc'd for C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.69; H, 8.08; N, 4.90.

The free acid was obtained in 95% yield by shaking the salt with ether and excess 2 *N* sulfuric acid and extracting the aqueous phase<sup>31</sup> with additional ether. The extracts were washed four times each with 2 *N* sulfuric acid and with sodium chloride solution, dried, and evaporated. Distillation gave (+)-I, b.p. 112°/0.25 mm., *d*<sub>4</sub><sup>20</sup> 1.0654,  $[\alpha]_D^{25} +23.51^\circ$  (l 1, undiluted) (lit.<sup>3</sup> +22.65°).

*D-(-)- $\alpha$ -Methylhydrocinnamic acid.*<sup>10</sup> The impure (-)-I,

(24) R. Stoermer and G. Voht, *Ann.*, **409**, 36 (1915).

(25) A. Müller, M. Mészáros, K. Körmeny, and A. Kuszman, *J. Org. Chem.*, **17**, 787 (1952).

(26) W. S. Ide and J. S. Buck, *J. Am. Chem. Soc.*, **62**, 425 (1940).

(27) E. Schwenk, D. Papa, B. Whitman, and H. F. Ginsberg, *J. Org. Chem.*, **9**, 175 (1944).

(28) M. Conrad and C. A. Bischoff, *Ann.*, **204**, 177 (1880).

(29) R. D. Haworth, C. R. Mavin, and G. Sheldrick, *J. Chem. Soc.*, 1423 (1934).

(30) A. W. Ingersoll, *Org. Syntheses, Coll. Vol. 2*, 506 (1943); W. Theilacker and H. G. Winkler, *Ber.*, **87**, 690 (1954). Both methods appear equally satisfactory.

(31) Pure (-)-III is recovered from the aqueous solution by treatment with alkali, ether extraction, and distillation.

recovered from the mother liquors of the (+)-I(-)-III salt and treated with (+)-III,<sup>30</sup> yielded 51% of the (-)-I-(+)-III salt, m.p. 127.3–129.5°,  $[\alpha]_D^{20} +1.36^\circ$  (c 2.00, chloroform), which was also prepared from racemic I (after 10 recrystallizations: m.p. 128–130°,  $[\alpha]_D^{20} +1.13^\circ$ ). The free acid had b.p. 111°/0.22 mm.,  $n_D^{20}$  1.5145,  $d_4^{22}$  1.065,  $[\alpha]_D^{22} -24.56^\circ$  (l 1, undiluted).

L-(+)-3,4-Dimethoxy- $\alpha$ -methylhydrocinnamic acid.<sup>10</sup> The quinine salt was prepared from 96.7 g. of racemic IV and 140 g. of quinine in about 1800 ml. of ethanol and recrystallized thrice from the same solvent. It formed electrified needles, m.p. 163.7–164.3°,  $[\alpha]_D^{20} -84.5^\circ$  (c 1.98, chloroform). The yield, including pure material isolated from the mother liquors, was 90%.

Anal. Calc'd for  $C_{12}H_{16}O_4 \cdot C_{20}H_{24}N_2O_2$ : C, 70.05; H, 7.35; N, 5.11. Found: C, 69.71; H, 7.15; N, 5.00.

The free acid was isolated in the same way as (+)-I; evaporation of the ethereal solution gave a viscous oil which, dried in a high vacuum, was used directly for further reactions. A sample was distilled in a bulb tube; b.p. 130° (bath temperature)/0.01 mm.,  $[\alpha]_D^{21} +27.5^\circ$  (c 4.01, chloroform).

Anal. Calc'd for  $C_{12}H_{16}O_4$ : C, 64.27; H, 7.19. Found: C, 63.84; H, 7.16.

The acid chloride, prepared from 1 g. of the acid with 1.15 ml. of oxalyl chloride in 97% yield, had b.p. 90° (bath temperature)/0.015 mm. and  $[\alpha]_D^{20} +20.5^\circ$  (c 5.73, benzene).

The amide was obtained from the acid chloride with concd. aqueous ammonia; it crystallized from water in colorless needles, m.p. 121.5–122.5°,  $[\alpha]_D^{21} +60.5^\circ$  (c 0.99, chloroform).

Anal. Calc'd for  $C_{12}H_{17}NO_2$ : C, 64.55; H, 7.68. Found: C, 64.44; H, 7.53.

D-(+)-3,4-Dimethoxy- $\alpha$ -methylhydrocinnamic acid.<sup>10</sup> Treating the impure (-)-IV, recovered from the quinine salt mother liquors, with (-)-III afforded the (-)-IV(-)-III salt in 77% yield, based on the racemic IV used originally. The major portion was obtained pure after three recrystallizations from ethyl acetate; m.p. 107–109.3°,  $[\alpha]_D^{20} -22.0^\circ$  (c 2.01, chloroform).

Anal. Calc'd for  $C_{12}H_{16}O_4 \cdot C_8H_{11}N$ : C, 69.54; H, 7.88; N, 4.06. Found: C, 69.46; H, 7.68; N, 3.86.

The free acid had b.p. 120° (bath temperature)/0.005 mm.,  $[\alpha]_D^{21} -28.1^\circ$  (c 4.16, chloroform).

Anal. Calc'd for  $C_{12}H_{16}O_4$ : C, 64.27; H, 7.19. Found: C, 63.80; H, 7.32.

The acid chloride had b.p. 95° (bath temperature)/0.01 mm.,  $[\alpha]_D^{21} -21.3^\circ$  (c 4.89, benzene).

Anal. Calc'd for  $C_{12}H_{15}ClO_3$ : Cl, 14.61. Found: Cl, 14.01.

D-(+)- $\alpha$ -Methylphenethylamine (II).<sup>10</sup> (a) By the Curtius rearrangement. (-)-I (5.35 g.) was refluxed with 8.4 ml. of oxalyl chloride for one hour, and the solution evaporated *in vacuo*<sup>32</sup> and re-evaporated twice after adding dry benzene. The acid chloride, dissolved in 22 ml. of dry acetone, was added rapidly at -10° to a magnetically stirred solution of 4.38 g. of sodium azide in 13 ml. of water. The mixture was stirred at 3° for 1 hr. and extracted twice with a total of 37 ml. of benzene; the extracts were washed with sodium chloride solution, dried rapidly with sodium sulfate, filtered, and the residue was washed with another 15 ml. of benzene. The filtrate was concentrated at room temperature *in vacuo*<sup>32</sup> to about 1/3 of its volume, brought to about its original volume with dry benzene, heated to 62° over 15 min. in the presence of a piece of Teflon (which seemed to promote nitrogen evolution), kept at this temperature for 1 hr., and evaporated *in vacuo*. The residue was warmed with 17.5

ml. of concd. hydrochloric acid at 45° for 5 min., diluted with water, and the solution extracted once with ether to remove a slight opalescence. It was then treated with excess 10 N sodium hydroxide and extracted twice with ether. The extracts were washed with 10 N sodium hydroxide, dried with powdered sodium hydroxide, filtered, treated with 8 ml. of 5 N ethanolic hydrogen chloride, and evaporated to dryness. The residual (-)-II hydrochloride was washed with ether and dried; yield 5.06 g. (90.5%), m.p. 155.7–156.7°,  $[\alpha]_D^{21} -25.62^\circ$  (c 4.80, water).<sup>18</sup> The neutral sulfate was obtained by treating the hydrochloride with 5 N sodium hydroxide, extracting the amine with benzene, and adding one equivalent of ethanolic sulfuric acid. It crystallized from water-ethanol-acetone in colorless leaflets,  $[\alpha]_D^{20} -22.34^\circ$  (c 8.00, water).<sup>33</sup>

(b) By the Schmidt rearrangement. A well-stirred solution of 7.02 g. of (-)-I in 50 ml. of chloroform was treated with 13 ml. of concd. sulfuric acid, then at 45° with 3.62 g. of sodium azide over 0.5 hr.<sup>20</sup> Stirring at 45° was continued during 0.5 hr., and the mixture was worked up as under (a). The hydrochloride (yield 6.18 g., 84%) crystallized from ethanol-ether in colorless prisms, m.p. 153–155°,  $[\alpha]_D^{22} -25.62^\circ$  (c 4.78, water), -24.60° (c 9.02).<sup>18</sup> The neutral sulfate had m.p. 328–329° (decompn. and darkening),  $[\alpha]_D^{20} -24.57^\circ$  (c 2.00, water),  $[\alpha]_D^{21} -22.11^\circ$  (c 8.00).<sup>33</sup>

D-(+)-3,4-Dimethoxy- $\alpha$ -methylphenethylamine (V)<sup>10</sup> was obtained from (-)-IV by the Curtius rearrangement, following the procedure used for preparing (-)-II. The dried ethereal extract was evaporated, and the residue distilled (b.p. 96°/0.08 mm.). The viscous oil (83% yield) solidified in the receiver; m.p. 37–40°. A sample crystallized from pentane in long colorless needles, m.p. 39–40°,  $[\alpha]_D^{21} -31.9^\circ$  (c 3.80, ethanol) (-32.1°, c 4.00 in a second run), -30.9° (c 4.13, chloroform).

Anal. Calc'd for  $C_{11}H_{17}NO_2$ : C, 67.66; H, 8.78; N, 7.17. Found: C, 67.45; H, 8.63; N, 7.04.

The neutral sulfate was prepared in 91% yield with the exact amount of ethanolic sulfuric acid. It crystallized from dilute ethanol in colorless shiny leaflets, m.p. 313–315° (decompn. and darkening),  $[\alpha]_D^{21} -21.4^\circ$  (c 2.00, water).

Anal. Calc'd for  $2C_{11}H_{17}NO_2 \cdot H_2SO_4$ : S, 6.56. Found: S, 6.58.

The hydrochloride was too deliquescent to be obtained pure.

L-(+)-3,4-Dimethoxy- $\alpha$ -methylphenethylamine, yield 92%, had m.p. 37–40°,  $[\alpha]_D^{21} +32.1^\circ$  (c 3.98, ethanol), and formed a neutral sulfate, m.p. 313° (decompn.),  $[\alpha]_D^{20} +20.5^\circ$  (c 2.00, water).

Solubilities of  $\alpha$ -methylbenzylamine salts (Table I). The pure salts (1 g.) were stirred magnetically in a glass-stoppered Erlenmeyer flask at 35° for 18 hr., then at 23° for 1 hr., and the suspension was centrifuged. A 5-ml. aliquot of the supernatant was weighed in a stoppered weighing bottle and evaporated in an air current. The residue was weighed after drying in a vacuum desiccator.

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(33) Reported  $[\alpha]_D$  (in water) for (+)- and (-)-II sulfate (base resolved with tartaric acid): +24.3°, -26.2° (c 2)<sup>34</sup>; +21 to 22.7°, -22.70° (c 8).<sup>35</sup>

(34) F. M. Jaeger and J. A. van Dijk, *Proc. Acad. Sci. Amsterdam*, **44**, 26 (1941).

(35) Personal communication by G. E. Ulylyot.

(32) A rotating evaporator (Rinco Instrument Co., Greenville, Ill.) was used.