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RESOLUTION DURING TOTAL SYNTHESIS OF RESERPINE

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IN their brilliant total synthesis, Woodward *et al.*[1] carried out the resolution in the final stage by means of (+)-camphor-10-sulfonic acid and obtained (-)-reserpine, identical with the natural product. With respect to technical preparation, placing the resolution at the end of a long synthesis is unfavourable. Therefore, the work of Velluz *et al.*,[2] who performed the resolution in the stage of *cis*-5-hydroxy-8-oxo-1,4,5,8,9,10-hexahydro-1-naphthoic acid - using the first Woodward's variant [3] of the synthesis in the opening phases, is a considerable improvement. This method, however, is impracticable in the very advantageous second Woodward's variant.[4]

In order to achieve the resolution at the stage of the hydroxy lactone Ia,[1,5] we prepared its acid phthalate Ib (m.p. 215°; found : C, 67,08;

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[1] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).

[2] L. Velluz, G. Muller, R. Joly, G. Nominé, J. Mathieu, A. Allais, J. Warnant, J. Valls, J. Bucourt and J. Jolly, *Bull. Soc. Chim. Fr.* 673 (1958).

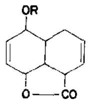
[3] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *J. Amer. Chem. Soc.* **78**, 2023 (1956).

[4] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *J. Amer. Chem. Soc.* **78**, 2657 (1956).

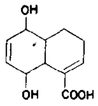
[5] E. Adlerová, L. Bláha, M. Borovička, I. Ernest, J. O. Jílek, B. Kakáč, L. Novák, M. Rajšner and M. Protiva, *Coll. Czech. Chem. Comm.* **24**, In press (1959).

H, 4,88; COOH, 13,62. $C_{19}H_{16}O_6$ requires C, 67,05; H, 4,75; COOH, 13,22) and acid succinate Ic (m.p. 142°; found: C, 61,91; H, 5,81; COOH, 15,40. $C_{15}H_{16}O_6$ requires C, 61,64; H, 5,52; COOH, 15,39) and by way of the brucine salt of the former (m.p. 218-222°; $[\alpha]_D^{20}$ + 5° in $CHCl_3$; found: C, 68,92; H, 6,01; N, 3.93. $C_{42}H_{42}N_2O_{10}$ requires C, 68,65; H, 5.76; N, 3,81) we obtained the (+)-acid phthalate Ib (m.p. 190-193°; $[\alpha]_D^{20}$ + 57° in $CHCl_3$; found: C, 67,15; H, 4,92; COOH, 13,16. $C_{19}H_{19}O_6$ requires C, 67,05; H, 4,75; COOH, 13,22). Also by crystallisation of the (-)-menthoxyacetate Ib it was possible to achieve the resolution and to obtain one diastereoisomer in pure form (m.p. 128-129°; $[\alpha]_D^{20}$ -36° in $CHCl_3$; found C, 71,39; H, 8,44. $C_{23}H_{32}O_5$ requires C, 71,10; H, 8.30). Attempts to transform these substances (Ib, Id) back to the hydroxy lactone Ia by hydrolysis led, however, to complicated and non-crystallising mixtures.

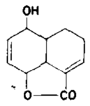
By alkaline hydrolysis of the hydroxy lactone Ia we aquired the new dihydroxy acid $C_{11}H_{14}O_4$, m.p. 175°, also resolvable in the form of its



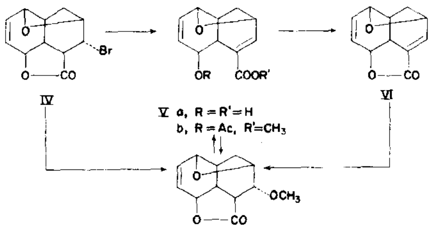
I a, R=H
b, R=o-COC_6H_4COOH
c, R=$COCH_2CH_2COOH$
d, R=$COCH_2OC_{10}H_{19}$



II



III



VII

brucine salt (m.p. 143-147°; $[\alpha]_D^{20}$ -71° in 90 % CH_3OH; found: C, 64,56; H, 7,12; N, 4,31. $C_{34}H_{40}N_2O_8.1\frac{1}{2}H_2O$ requires C, 64,65; H, 6,86; N, 4,44) and obtainable in the (-)-form (m.p. 185°; $[\alpha]_D^{20}$ -162° in 90 % CH_3OH; found: C, 63,19; H, 6,85. $C_{11}H_{14}O_4$ requires C, 62,84; H, 6,71). This dihydroxy acid gave by the action of N,N -dicyclohexylcarbodiimide the hydroxy lactone $C_{11}H_{12}O_3$ (found: C, 68,73; H, 6,43; requires C, 68,73; H, 6,29), melting at 123°, i.e. at exactly the same temperature as the starting lactone Ia, but showing a deep depression of the melting point when mixed with the latter (acetate of Ia, m.p. 97-98°;[5] acetate of III, m.p. 123-124°). The infra-red (1689 and 1753 cm^{-1}) and ultra-violet spectra (λ_{max} = 229 mμ, log ϵ= 3,74) of the new lactone clearly indicate the conjugation of the double bond with the carboxyl group, which suggests formulations II and III for the dihydroxy acid and the new lactone respectively. In the alkaline hydrolysis the double bond evidently shifts into conjugation.

By alkaline hydrolysis of the bromo lactone IV [1,5] we prepared the unsaturated acid Va (m.p. 183-184°; ultra-violet spectrum λ_{max} = 222 mμ, log ϵ= 3,56; found: C, 63,29; H, 5,72. $C_{11}H_{12}O_4$ requires C, 63,45; H, 5,81), resulting also from the methoxy lactone VII [1,5] by the same method. By crystallisation of the brucine salt of this acid both diastereoisomers (<u>A</u>, needles of m.p. 185°; $[\alpha]_D^{20}$ -17° in H_2O; found: C, 67,76; H, 6,45; N, 4,79. $C_{34}H_{38}N_2O_8$ requires C, 67,76; H, 6,36; N, 4,65; <u>B</u>, m.p. 147;150°, $[\alpha]_D^{20}$ -20° in H_2O; found: C, 65,71; H, 6,67; N, 4,59. $C_{34}H_{38}N_2O_8.H_2O$ requires C, 65,79; H, 6,50; N, 4,51) were obtainable and from the former the (-)-hydroxy acid Va (m.p. 165°; $[\alpha]_D^{20}$ -22° in CH_3OH; found: C, 63,21; H, 6,11; COOH, 21,18. $C_{11}H_{12}O_4$ requires C, 63,45; H, 5,81; COOH, 21,62). That this compound belongs to the reserpine series was proved in the following way: By the action of N,N -dicyclohexylcarbodiimide in dioxane (or of acetic anhydride in pyridine) we obtained the unsaturated lactone VI (m.p. 166°; $[\alpha]_D^{20}$ -16° in $CHCl_3$; found: C, 69,38; H, 5,30. $C_{11}H_{10}O_3$ requires C, 69,46; H, 5,30), which adds one molecule of methanol in the presence of a small quantity of sodium methoxide giving the (+)-methoxy lactone VII (m.p. 99°; $[\alpha]_D^{20}$ + 49° in C_2H_5OH; found: C, 64,71; H, 6,30; CH_3O, 13,61. $C_{12}H_{14}O_4$ requires C, 64,85; H, 6,35; CH_3O, 13,86). This compound can also be prepared by methanolysis of the methylester of the acetoxy acid Vb (m.p. 90°; found: C, 63,80; H, 6,34; CH_3O, 11,57. $C_{14}H_{16}O_5$ requires C, 63,62; H, 6,10; CH_3O, 11,73).

The (+)-methoxy lactone VII is evidently identical with the substance of Velluz et al.,[2] who give the m.p. of 102° and $[\alpha]_D^{20}$ + 48° in ethanol. Our contribution thus constitutes a new and practical method of resolution during the total synthesis of reserpine.