Tetrahedron Letters, No. 11, pp. 12-15, 1959. Pergamon Press Ltd. Printed in Great Britain.

TWO NOTES ON THE LAST STAGES OF A DL RESERPINE SYNTHESIS

M. Protiva, J. O. Jílek, I. Ernest and L. Novák

Pharmaceutical and Biochemical Research Institute, Prague

(Received 5 June 1959; in revised form 18 July 1959)

WEISENBORN and Diassi[1] have already noted that a combination of the principle of Woodward's total synthesis of reserpine[2] with their reduction method[1] "would form the basis for an alternative path to reserpine". We now wish to report our results in the realization of this idea, reached independently of the suggestion of the above authors.[1]

dl Methyl O-acetyldehydroreserpate perchlorate: m.p. 208°; (Found: C, 54.18; H, 5.71; N, 5.08. $C_{25}H_{31}ClN_2O_{10}$ requires C, 54.10; H, 5.63; N, 5.05), obtained from dl methyl O-acetyl-3-oxo-2,3-secoreserpate[2] by the action of phosphorus oxychloride and then sodium perchlorate, was reduced with zinc and perchloric acid in acetone-tetrahydrofuran-water[3] and the product (m.p. 243-245°) was deacetylated by hot methanolic sodium methoxide to a mixture - separated by chromatography on alumina - of 3 parts dl methyl reserpate:[2] m.p. 240-242°; (Found: C, 67.00; H, 7.40; N, 6.80; OCH_3, 22.68.

---

[1] F. L. Weisenborn and P. A. Diassi, J. Amer. Chem. Soc. 78, 2022 (1956).

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

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

$C_{23}H_{30}N_2O_5$ requires C, 66.64; H, 7.30; N, 6.76; OCH_3, 22.46. I.R. ($CHCl_3$) 1630, 1732, 2830, 3475 cm^{-1}) and 1 part dl methyl isoreserpate: m.p. 266–267°; (Found: C, 66.37; H, 7.18; N, 6.80; OCH_3, 22.72. $C_{23}H_{30}N_2O_5$ requires C, 66.64; H, 7.30; N, 6.76; OCH_3, 22.46. I.R. ($CHCl_3$): 1632, 1732, 2760, 2800, 2830, 3475 cm^{-1}). The former was compared with l methyl reserpate[4] by means of infra-red spectroscopy and paper chromatography; no difference was found. With acetic anhydride at 100° it gave dl methyl O-acetylreserpate: m.p. 275–276°; (Found: C, 65.92; H, 7.34; N, 6.15; OCH_3, 20.54. $C_{25}H_{32}N_2O_6$ requires C, 65.77; H, 7.07; N, 6.14; OCH_3, 20.40). The conversion of dl methyl reserpate into dl reserpine: m.p. 256–257°; (Found: C, 65.29; H, 6.59. $C_{33}H_{40}N_2O_9$ requires C, 65.11; H, 6.62) by reaction with 3,4,5-trimethoxybenzoyl chloride in pyridine[2] could largely be improved by the use of shorter reaction time (20 hr), by decreasing the excess of the acid chloride to 50 per cent only, and by using very pure pyridine (purified by way of the crystalline perchlorate): a yield of 72 per cent of the theoretical could thus be obtained.

An analogous approach was used in the deserpidine series: dl Methyl O-acetyl-3-oxo-2, 3-secodeserpidate (m.p. 215°)[5] was converted to dl methyl O-acetyldehydrodeserpidate perchlorate: m.p. 175°; (Found: C, 53.01; H, 5.43; N, 5.25. $C_{24}H_{29}ClN_2O_9.H_2O$ requires C, 53.09; H, 5.75; N, 5.16) and further to dl methyl deserpidate: m.p. 140°; (Found: C, 65.73; H, 7.10;

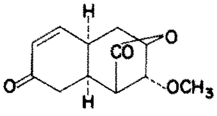
---

[4] L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André, Helv. Chim. Acta 37, 59 (1954).

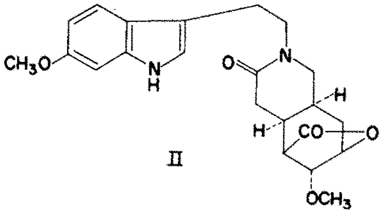
[5] L. Bláha, J. Weichet, J. Žváček, S. Šmolík and B. Kakáč, Coll. Czech. Chem. Comm. 24, In press (1959).

N, 7.15; OCH_3, 15.92. $C_{22}H_{28}N_2O_4.H_2O$ requires C, 65.65; H, 7.51; N, 6.96; OCH_3, 15.42. I.R. ($CHCl_3$): 1730, 2850, 3480 cm^{-1}), which can be transformed into dl deserpidine.[5]

In another series of experiments Woodward's 2-methoxy-3-hydroxy-7-oxo-Δ^5-cis-octalin-1-carboxylic acid[2] was converted into the lactone I (m.p. 179-181°)[6], which by ozonization and further by reaction with 6-methoxytryptamine followed by sodium borohydride reduction gave dl 3-oxo-2,3-secoreserpic acid lactone: II, m.p. 184.5-185.5°; (Found: C, 66.48; H, 6.42; OCH_3, 15.81. $C_{22}H_{26}N_2O_5$ requires C, 66.31; H, 6.58; OCH_3, 15.58. I.R. ($CHCl_3$): 1633, 1787, 2840 cm^{-1}). This could be cyclized by phosphorus oxychloride to dl dehydroreserpic acid lactone: perchlorate, m.p. 309-311°; (Found: C, 54.51; H, 5.36; N, 5.79; OCH_3, 12.73. $C_{22}H_{25}ClN_2O_8$ requires C, 54.95; H, 5.24; N, 5.83; OCH_3, 12.90. I.R. (Nujol): 1623, 1774 cm^{-1}).



I



II

---

[6] E. Adlerova, L. Blaha, M. Borovicka, I. Ernest, J. O. Jilek, B. Kakac, L. Novak, M. Rajsner and M. Protiva, Coll. Czech. Chem. Comm. 24, In press (1959).

The conversion of dehydroreserpic acid lactone into reserpic acid lactone and hence into reserpine has already been described by Muller[7] and Woodward.[2]

The authors are indebted to Dr. B. Kakáč for recording and interpretating the spectra, to Dr. K. Macek for paper chromatographic analyses and to all members of the staff of the Analytical Laboratory of our Institute for their helpful assistance.

---

[7] G. Muller, Fr. Pat. 1,164.747.