A SYNTHETIC APPROACH TO RESERPINE AND RELATED COMPOUNDS

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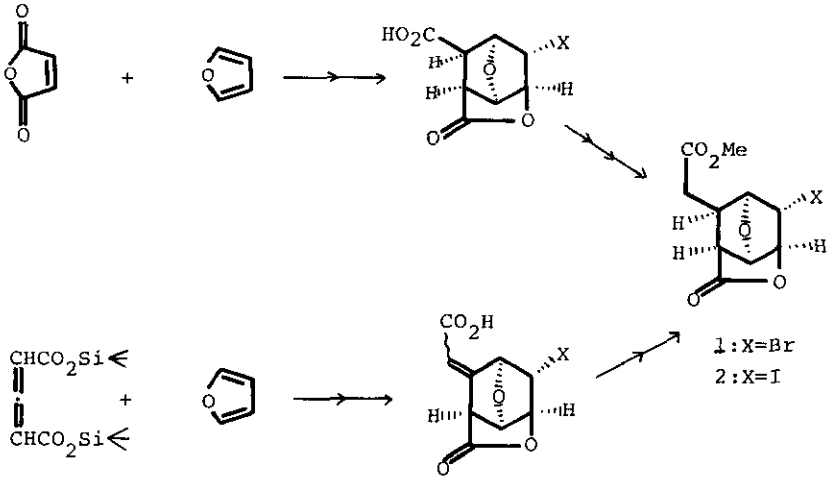
Abstract —— Key intermediates in the synthesis of the Rauwolfia alkaloids deserpidine (8) and reserpine (9) are compounds (6a), (6b), (16), and (17) whose stereoselective syntheses are described.

We[1] have recently reported a convenient route to 3,8-epoxy-7-keto-6-oxabicyclo[3.2.1]octane derivatives (1) and (2) from furan and maleic anhydride and bis(trimethylsilyl)allenedicarboxylate, as shown in Scheme 1.

Scheme 1

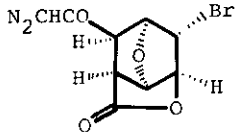


As an extension of this work, we examined further transformations toward the synthesis of Rauwolfia alkaloids through known diazoketone (3).[1]

Wolff rearrangement[2] of the diazoketone (3) with tryptamine or 6-methoxytryptamine in the presence of freshly made silver oxide afforded the corresponding amide (4)[3], mp 220 ∿ 222°; ir (KBr) 3380, 1780 and 1660 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 5.13 (1H, d, J = 5 Hz, C<u>H</u>-OCO); m/e 420 (M^+ + 2), 418 (M^+), and (5)[3], mp 233 ∿ 235°; ir ($CHCl_3$) 3460, 1780 and 1655 cm^{-1}; δ ($CDCl_3$) 3.80 (3H, s, OC<u>H</u>$_3$), 4.87 (1H, d, J = 5 Hz, C<u>H</u>-OCO), m/e 450 (M^+ + 2), 448 (M^+), respectively in good yields. On treatment of amide (4) with refluxing phosphorous oxychloride it was smoothly converted to the 3,4-dihydrocarboline hydrochloride. Without purification this salt was catalytically reduced to afford a seperable (silica gel column chromatography) mixture of compounds (6a), mp 199 ∿ 201°; ir ($CHCl_3$) 3450 and 1780 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 4.83 (1H, d, J = 5 Hz, C<u>H</u>-OCO); m/e 404 (M^+ + 2), 402 (M^+); and (6b), mp 199 ∿ 201°; ir ($CHCl_3$) 3450 and 1780 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 4.81 (1H, d, J = 5 Hz, C<u>H</u>-OCO); m/e 404 (M^+ + 2), 402 (M^+). These two compounds were produced in 65 % yield and in an approximately 1 : 1 ratio. Although it is obvious that these two compounds are diastereoisomeric at C, it is not possible to assign configurations to (6a) and (6b) at this stage. Acetylation products (7a) and (7b) were prepared and characterised.

Thus although we have succeeded in the preparation of key intermediates, the synthesis of Rauwaolfia alkaloids by this route is somewhat circuituous in that it is still necessary to introduce one more carbon (to C_3,) at some stage. An obviously more efficient approach to Rauwolfia alkaloids would be through the Diels-Alder adduct (11) derived from maleic anhydride and benzyl furfuryl ether (10).

Diels-Alder reaction between maleic anhydride and benzyl furfuryl ether (10) in water in the presence of catalytic amount of hydroquinone at room temperature for 7 days, followed by halolactonization without isolation of the adduct, according to the method of J. A. Berson et al.[4], afforded the desired bromolactonic acid (12)[3], mp 199 ∿ 200°; ir (KBr) 1785 and 1725 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 5.35 (1H, t, J = 5 Hz, O-C<u>H</u>), 5.05 (H, d, J = 5 Hz, C<u>H</u>-OCO), 4.87[5] (1H, s, C<u>H</u>-Br); and its isomer (13)[3], mp 178 ∿ 180°; ir (KBr) 1785 and 1705 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 4.77 (1H, d, J = 5 Hz, OC<u>H</u>), 4.82 and 4.65 (each 1H, s, C<u>H</u>-OCO and C<u>H</u>-Br). The ratio of isomers (12) and (13) was approximately 2 : 1 and it is suggested taht steric hindrance of the benzyl ether group at C_3 during the halolactonisation is responsible for this predominance of the required isomer (12). Further transformation of this acid (12) by the Arndt-Eistert reaction[2] was carried out in the usual manner. Treatment of the lactonic acid (12) with oxalyl



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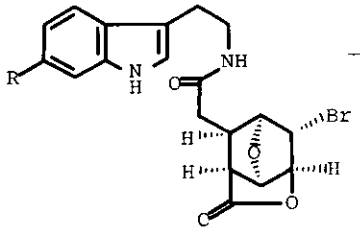
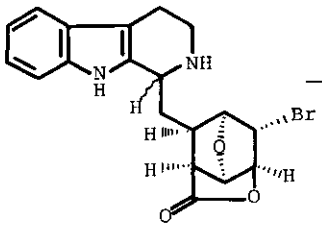
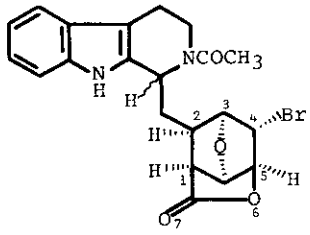


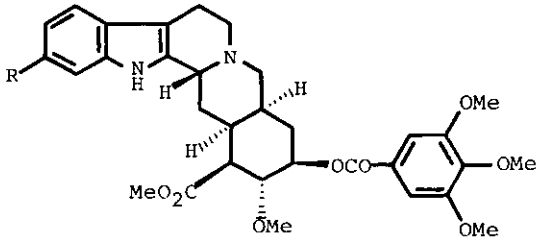
4 R=H
5 R=OMe



6a, 6b



7a, 7b



8 R=H
9 R=OMe

chloride in refluxing dry benzene gave the acid chloride (14) which on reaction with diazomethane in ether provided the diazoketone (15), mp 147 ∿ 149°; ir (KBr) 2140 and 1795 cm^{-1}, in almost quntitative yield. Refluxing of this compound (15) with tryptamine or 6-methoxytryptamine in dioxane in the presence of freshly made silver oxide afforded the amides (16)[3], mp 167 ∿ 168°; ir ($CHCl_3$) 3470, 1795 and 1670 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 5.19 (1H, t, J = 5 Hz, O-C<u>H</u>), 4.93 (1H, d, J = 5 Hz, C<u>H</u>-OCO); m/e 540 (M^+ + 2), 538 (M^+), in 98 % yield, and (17)[3], mp 107 ∿ 110°; ir ($CHCl_3$) 3450, 1790 and 1660 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 5.17 (1H, t, J = 5 Hz, O-C<u>H</u>), 4.87 (1H, d, J = 5 Hz, C<u>H</u>-OCO), 3.80 (3H, s, $OC\underline{H}_3$); m/e 570 (M^+ + 2), 568 (M^+), in 65 % yield respectively. Turning to cyclisation of these derivatives, it was observed that cyclisation under various conditions resulted in formation of an unexpected compound. Thus, Bischler-Napieralski cyclisation of amide (16) followed by sodium borohydride reduction (MeOH, r.t., 5 min) of the product afforded that lactam (19), ir ($CHCl_3$) 3450, 3400 ∿ 3200 (br) and 1620 cm^{-1}, as a single product in 94 % overall yield after purification. Acetylation produced the compound (20)[6], ir ($CHCl_3$) 3450, 1750 and 1630 cm^{-1}; δ ($CDCl_3$) 2.01 (3H, s, $OCOCH_3$); m/e 566 (M^+ + 2), 564 (M^+).

Formation of the lactam (19) can be attributed to a preference of the intermediate to adopt the (18b) conformation over the (18a) conformation presumably as a result of steric hindrance of the benzyl ether group.

Thus we have achieved stereoselective syntheses of the key intermediates (6a), (6b), (16) and (17) which should lead to efficient stereoselective syntheses of <u>Rauwolfia</u> alkaloids. The total synthesis of deserpidine (8), reserpine (9) and other indole alkaloids according to this method is in progress in these laboratories.

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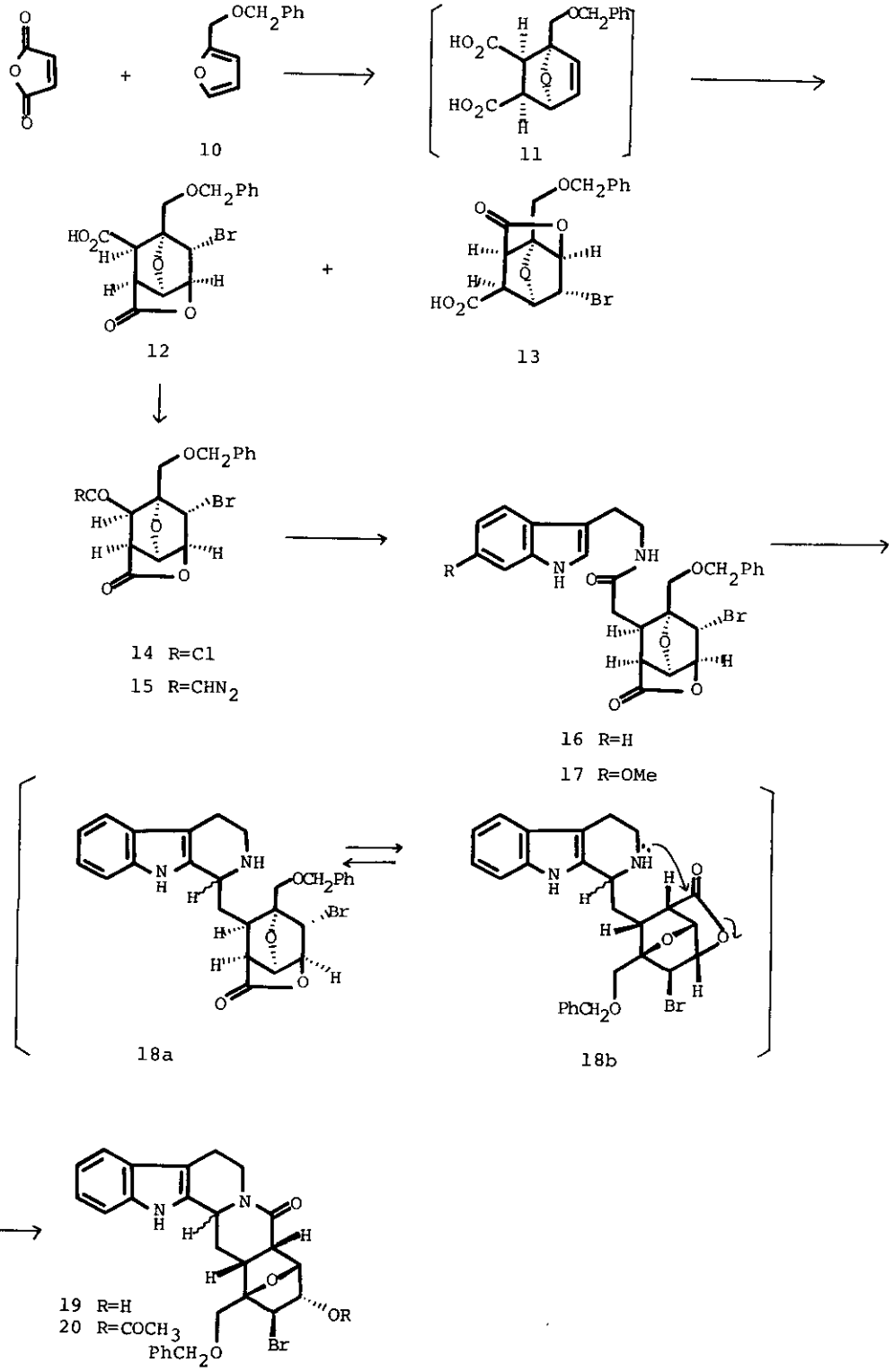
10
11
12
13
14 R=Cl
15 R=CHN2
16 R=H
17 R=OMe
18a
18b
19 R=H
20 R=COCH3

REFERENCES AND NOTES

1. T. Suzuki, S. Kagaya, A. Tomino, K. Unno and T. Kametani, Heterocycles, 1978, 9, 1749.

2. W. E. Backmann and W. S. Struve, Org. Reactions, 1942, 1, 38; T. Suzuki, A. Tomino, S. Kagaya, K. Unno and T. Kametani, Heterocycles, 1978, 9, 1263; idem, Heterocycles, 1978, 9, 1759.

3. Satisfactory elemental analysis has been obtained for this compound.

4. J. A. Berson and R. Swidler, J. Amer. Chem. Soc., 1953, 75, 1721 and references cited therein.

5. The methine proton at C_4 resonates downfield, at 4.87 ppm, due to an effect by the carboxyl group at C_2, which suggests the relative configuration of the carboxylic acid and bromine to be a trans relationship.

6. High resolution mass spectrum: m/e (M^+) requires 566.1239 and 564.1259; found 566.1209 and 564.1248.

7. In one experiment the desired compound (18a) was obtained but its attempted purification by silica gel chromatography, or its standing at room temperature, led to the isolation of cyclised derivative (19).

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