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Synthesis of models related to taspine

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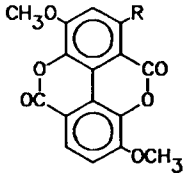
Abstract. The synthesis of diphenylic compounds related to the alkaloid taspine **1** is reported.

Taspine **1**[1] is an alkaloid with an unusual diphenylic skeleton, whose synthesis has never been reported.



	R
1	$(CH_2)_2-N(CH_3)_2$
2	CH_3
3	H

In view of the problems involved in its synthesis, i. e. the difficulties typical of the asymmetric diphenylic coupling, the introduction of four and five suitable substituents in the two moieties to join, the strong steric hindrance due to the presence of two substituents *ortho* to both the positions to couple, we

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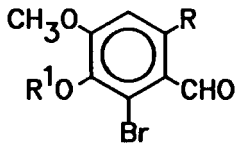
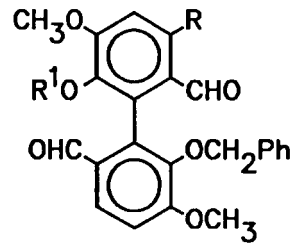
considered correct a preliminary approach through the synthesis of simplified models.

We wish to report here the synthesis of the compound **2**, that carries a methyl group instead of the 2-(N-dimethylamino)-ethyl group present in taspine **1** and of the symmetric lactone **3**[2], obtained as a by-product.

In a first attempt to obtain **2** we have synthetized the two bromoaldehydes, 2-bromo-4-methoxy-3-methoxycarbonyloxy-6-methylbenzaldehyde **5**[3] and 3-benzyloxy-2-bromo-4-methoxybenzaldehyde **6** with the aim to couple them through the Ullmann reaction[4]. The methoxycarbonyl as protecting group was preferred to the acetyl, since the debromination of the reagents - the usual side reaction in the Ullmann condensation - occurs only in very small extent, by using the former derivative.



	R	R^1
4	CH_3	H
5	CH_3	CO_2CH_3
6	H	CH_2Ph



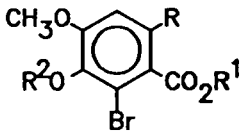
	R	R^1
7	CH_3	CO_2CH_3
7a	H	CH_2Ph

Test experiments of self condensation of the two units have shown that the less accessible moiety, i.e. the bromo-aldehyde **5** is sensibly more reactive than the other unit **6**. We suppose that this difference in reactivity may be caused by the greater steric requirement of the benzyl group in **6** as compared to the

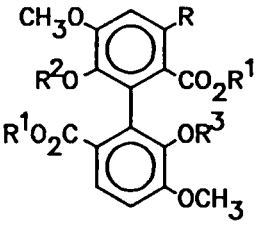
methoxycarbonyl group in **5**. Therefore, the Ullmann reaction was carried out with an excess of the reagent **6**.

The diphenylic derivative **7** was isolated from the complex reaction mixture in 56% yield, that can be considered satisfactorily, taking into account the high temperature of the reaction (180 °C), and the difficulties outlined above.

However, the formyl groups, also in the deprotected derivatives, proved



	R	R^1	R^2
8	CH_3	H	CO_2CH_3
9	H	H	CH_2Ph
10	CH_3	CH_3	CO_2CH_3
11	H	CH_3	CH_2Ph



	R	R^1	R^2	R^3
12	CH_3	CH_3	CO_2CH_3	CH_2Ph
13	CH_3	CH_3	CO_2CH_3	H
14	CH_3	H	H	H
15	H	CH_3	CH_2Ph	CH_2Ph

to be resistant to oxidation - probably for steric reasons - and the dilactone **2** was obtained only in poor yields.

Therefore, we decided to oxidize the formyl groups in the starting units, **5** and **6**. The acid **9** was easily obtained from **6**, whereas **5** appeared to be less reactive. It was necessary to use the Jone's reagent[5], under controlled conditions, in order to avoid the methoxycarbonyloxy group hydrolysis.

The acids **8** and **9** were subsequently converted into the o-bromo esters **10** and **11**. Their condensation, in spite of the high steric hindrance of the carboxyester groups - the reaction required a high temperature (220-240 °C) - afforded the diphenyl derivative **12** in 35% yield.

Benzyl group of **12** was removed by hydrogenolysis to give **13**. The hydrolysis of all the ester functions was carried out in alkaline medium, under nitrogen atmosphere. The hydroxy acid **14**, not isolated, was directly heated at 80 °C with 80 % sulphuric acid. The dilactone **2** was obtained in high yields, as a solid material, insoluble in all the usual solvents, only slightly soluble in boiling dimethylformamide, m.p. 300 °C, dec.

The conversion of **2** into taspine **1** could be performed by conversion of the methyl group of **2** into the dimethylamino-ethyl moiety of **1** through a literature method[6,7]. However this way appears not feasible, owing to the extreme insolubility of **2**.

During the chromatografic isolation of **12** we obtained, as the major product of the Ullmann reaction, the autoadduct **15** of the benzylether **11**. After removal of the protective groups and heating with 80% sulphuric acid, the symmetric dilactone **3** was obtained in high yield. It showed the same insolubility as **2**. Properties of **3** resulted different from those reported by Murari *et al.* [2] for a compound with the same structure, obtained in poor yields by oxidation of quercetin.

Experimental Section

^{1}H-NMR spectra were determined with a Varian XL 300 instrument in $CDCl_3$ with chemical shifts recorded in ppm downfield from internal TMS and coupling constants in Hz. All mps are uncorrected.

2-Bromo-6-methylisovanillin **4** *and its 3-methoxycarbonylester,* **5**

To a solution of 6-methylisovanillin[3] (800 mg, 4,81 mmol) in 15 ml of acetic acid, 770 mg of Br_2 (4.81 mmol) in 5 ml of the same solvent were added dropwise in 30 min at room temp. After 90 min, 20 ml of water were added and the mixture was allowed to stand at 0-5 °C overnight. After filtration, 670 mg of **4** were obtained, as pale yellow solid. Extraction with benzene of the mother liquor, and crystallisation from water of the solid residue gave additional 350 mg of **4**, pure by TLC. m.p. 151-153 °C, overall yield 86%. ^{1}H-nmr: δ 10.35 (CHO, s), 8.40 (OH, bs), 7.05 (H-5, s), 3.85 (OCH_3, s), 2.60 (CH_3, s).

The methoxycarbonyl derivative **5** was obtained in 90% yield by reaction of **4** with methyl chloroformate in anhydrous dioxane/pyridin. Compound **5** crystallizes from MeOH/H_2O 1:1, m.p. 124-127 °C. ^{1}H-nmr: δ 10.20 (CHO, s), 6.60 (H-5, s), 3.85 (6H, CH_3OCO_2, CH_3O), 2.55 (CH_3, s). (Found: C 43.45, H 3.75%. $C_{11}H_{11}O_5Br$ requires: C 43.58, H 3.66%.)

2-Bromo-3-benzylisovanillin, **6**

A solution of 2-bromoisovanillin[8] (10 g, 43.3 mmol) in 30 ml of distilled dimethylformamide is treated with benzylbromide (8.05 g, 47.0 mmol), stirring in the presence of 15 g of anhydrous K_2CO_3 for 14 hrs. The reaction was worked up and the solution of the product in benzene was washed with 2N NaOH , and finally with water. The solution, dried over anhydrous sodium sulfate, was evaporated *in vacuo* at 90 °C till constant weight. The viscous oil residue, (12 g) pure by TLC, yield 87%, crystallized from EtOH, m.p. 77-9 °C. ^{1}H-nmr: δ 10.10 (CHO, s), 7.55 (H-6, d, $J_{orto} = 9.5$), 6.75 (H-5, d, $J_{orto} = 9.5$), 7.0-7.4 (5H, Ph), 4.90 ($\underline{CH_2}$-Ph, s), 3.80 (CH_3O, s). (Found: C 55.95, H 4.12%. $C_{15}H_{13}O_3Br$ requires: C 56.09, H 4.08%.)

Coupling of **5** *and* **6** *by the Ullmann reaction. Diphenylic dialdehydes* **7** *and* **7a**

The reaction was carried out as described for 12, on 270 mg of **5** and 570 mg of **6** at 180 °C, with 850 mg of recently activated copper bronze[4b]. After chromatografic purification, 230 mg of **7** were obtained, as amorphous solid. Yield 56%, calculated on the component **5**. ^{1}H-nmr: δ 9.60 (CHO, s), 9.50 (CHO, s), 7.80 (H-5', d, J_{orto} = 9.0), 6.75 (H-4', d, J_{orto} = 9.0), 6.9-7.3 (5H, Ph), 6.85 (H-4, s), 4.95 and 4.80 ($\underline{CH_2}$-Ph, AB system, J_{AB} = 11.0), 3.95 (CH_3O, s), 3.90 (CH_3O, s), 3.65 (CH_3OCO_2, s), 2.60 (CH_3, s). (Found: C 68.72, H 5.10%. $C_{26}H_{24}O_8$ requires: C 68.84, H 4.95%.)

The symmetric dimer **7a** was also obtained (150 mg). It crystallizes from MeOH/H_2O 9:1, m.p. 123-5 °C. ^{1}H-nmr: δ 9.30 (2H, 2xCHO, s), 7.60 (H-5, H-5', d, J_{orto} = 8.0), 7.2-6.6 (12H, H-4, H-4', 2xPh), 4.65 (4H, 2x$\underline{CH_2}$-Ph), 3.88 (6H, 2xCH_3O, s). (Found: C 74.55, H 5.60%. $C_{30}H_{26}O_6$ requires: C 74.67, H 5.43%.)

2-Bromo-3-methoxycarbonyl-6-methylisovanillic acid **8**, *methylester* **10**

A solution of **5** (1,56 g, 5 mmol) in 30 ml of acetone, distilled over $KMnO_4$, was treated at 0-5 °C with 5.1 ml of the Jone's reagent (10 mmol), added during 4 hrs. After 24 hrs at the same temp., the reaction mixture was treated with crushed ice and the excess CrO_3 reduced with a 4% solution of $Na_2S_2O_3$. The resultant solution was extracted with ether and the acid **8** was separeted with an ice cooled sat. solution of $NaHCO_3$. The alcaline solution was acidificated at 0 °C, extracted with ether and the organic layer was dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The resultant solid was washed by filtration with small amounts of benzene and crystallized from benzene/exane 1:1, m.p. 130-132 °C (1.04 g, yield 63%). ^{1}H-nmr: δ 11.40 (COOH, bs), 6.85 (H-5, s), 4.00 (CH_3OCO_2, s), 3.90 (CH_3O, s), 2.45 (CH_3, s).

Acid **8** was converted into methyl ester **10** with diazomethane. **10** crystallizes from exane, m.p. 81-82 °C. ^{1}H-nmr: δ 6.80 (H-5, s), 4.00 (6H, CH_3OCO_2, CH_3OCO), 3.90 (CH_3O, s), 2.40 (CH_3, s). (Found: C 43.135, H 4.05%. $C_{12}H_{13}O_6Br$ requires: C 43.26, H 3.93%.)

2-Bromo-3-benzylisovanillic acid **9** *and methyl ester* **11**

To a solution of 14 g (43 mmol) of **6** in 30 ml of acetone, distilled over $KMnO_4$, a solution of 22.3 ml of Jone's reagent, diluted with 50 ml of acetone, was added during 4 hrs at room temp.. After 24 hrs the reaction was worked up as described for **8**. The acid **9** was filtered, washed with water and dried: 12.45 g , yield 84%, of **9** which crystallizes from MeOH/H_2O 8:2, m.p. 165-6 °C. ^{1}H-nmr: δ 11.30 (COOH, s), 7.50 (H-6, d, J_{orto} = 9.0), 6.70 (H-5, d, J_{orto} = 9.0), 7.0-7.4 (5H, Ph), 4.80 ($\underline{CH_2}$-Ph, s), 3.85 (CH_3O, s).

The ester **11** was obtained from the acid **9** (12.4 g, 36.8 mmol), by reaction with MeOH/5% H_2SO_4. Viscous oil, pure at TLC and GLC, 11.2 g, yield 86%. ^{1}H-nmr: δ 7.45 (H-6, d, J_{orto} = 9.0), 6.75 (H-5, d, J_{orto} = 9.0), 7.0-7.4 (5H, Ph), 4.85 ($\underline{CH_2}$-Ph, s), 3.80 (6H, CH_3OCO, CH_3O, s). (Found: C 54.55, H 4.37%. $C_{16}H_{15}O_4Br$ requires: C 54.72, H 4.30%.)

Ullmann coupling of **10** *and* **11**. *Diphenylic diesters* **12** *and* **15**.

A mixture of 1 g of **10** (3 mmol) and 3.2 g of **11** (9 mmol) was treated under nitrogen atmosphere at 220/240 °C in a test tube, with 5 g of copper-bronze, as soon as activated[4b]. The copper powder was added in small portions in 20 min, stirring with a glass rod. After further heating (30 min) at the same temperature, the ester **10** had completely reacted. After cooling at room temperature, the reaction mixture was treated with acetone (60 ml), the insoluble components were centrifugated and exaustively washed with acetone.

The combined solutions were evaporated *in vacuo* and the residue was chromatographed on silica gel (benzene/diethyl ether 9:1), giving **12**, 0.62 g, 39% yield (calculated on the component **10**), as a crystalline powder, pure by TLC. **12** crystallizes from benzene, m.p.132-3 °C, . ^{1}H-nmr: δ 7.80 (H-5', d, J_{orto} = 8.5), 6.95 (H-4', d, J_{orto} = 8.5), 7.0-7.3 (5H, Ph), 6.80 (H-4, s), 4.80 ($\underline{CH_2}$-Ph, s), 3.90, 3.85 (6H, 2xCH_3OCO, s), 3.65, 3.60, 3.50 (9H, 2xCH_3O, CH_3OCO_2, s), 2.40 (CH_3, s). MS: *m/z* 524 (M^+). (Found: C 64.02, H 5.47%. $C_{28}H_{28}O_{10}$ requires: C 64.11, H 5.38%.).

From the same chromatographic column 1,6 g of **15** were obtained. **15** crystallizes from MeOH, m.p. 116-8 °C. ^{1}H-nmr: δ 7.70 (H-5,H-5', d, J_{orto} = 8.0), 7.2-6.6 (12H, H-4, H-4', 2xPh), 4.70 (4H, 2x$\underline{CH_2}$-Ph), 3.82 (6H, 2xCH_3OCO, s), 3.52 (6H, 2xCH_3O, s). MS: *m/z* 542 (M^+). (Found: C 70.65, H 5.70%. $C_{32}H_{30}O_8$ requires: C 70.83, H 5.57%.).

Debenzylation of **12**, *diphenilic diester* **13**

A solution of 510 mg of **12** in 30 ml of metanol/dioxane 1:1 was treated with H_2/C-Pd (10%, 55 mg) at room temp. and atmospheric pres.; after evaporation of organic solvents, 400 mg of debenzylated product **13**, pure by TLC, were obtained, yield 92%. **13** crystallizes from MeOH, m.p. 181-83 °C. ^{1}H-nmr: δ 7.60 (H-5', d, J_{orto} = 8.5), 6.90 (H-4', d, J_{orto} = 8.5), 6.80 (H-4, s), 5.60 (OH, s), 3.95, 3.90 (6H, 2xCH_3OCO, s), 3.70, 3.60, 3.45 (9H, 2xCH_3O, CH_3OCO_2, s), 2.45 (CH_3, s). MS: *m/z* 434 (M^+). (Found: C 57.90, H 5.22%. $C_{21}H_{22}O_{10}$ requires: C 58.06, H 5.11%.).

Dilacton **2**

A solution of 100 mg of **13** in 2 ml of methanol/dioxane 1:1 was treated with 0.6 ml of NaOH (2N) at room temp. for 12 hrs under nitrogen atmosphere.

The solution was neutralized with 6N HCl and concentrated *in vacuo* to small volume; 0.6 ml of H_2SO_4 (80%) were added and the solution of the not isolated acid **14** was kept 30 min at 80 °C. The white solid residue of **2**, 47 mg, yield 80%, was filtered off, washed with water and finally with methanol; the dilacton **2** is insoluble in the common solvents, partially soluble in boiling DMSO, from whom crystallizes, m.p. 277 °C (dec.). ^{1}H-nmr (CF_3COOD): δ 8.35 (H-5', d, J_{orto} = 8.7), 7.55 (H-4', d, J_{orto} = 8.7), 7.35 (H-4, s), 4.25 (6H, 2xCH_3O, s), 2.98 (CH_3, s). MS: *m/z* 312 (M^+). (Found: C 65.20, H 3.95%. $C_{17}H_{12}O_6$ requires: C 65.38, H 3.87%.).

Dilacton **3**

The symmetric dimer **15** (540 mg) was submitted to the hydrogenolysis and to subsequent alkaline hydrolysis in the conditions described for **12** and **13**. The dilactone **3** (250 mg) was recovered with an overall yield of 85 % as white solid residue. It is insoluble in the usual solvents and only soluble in boiling DMSO from whom it crystallizes. Dilactone **3** slowly sublimates at 320 °C, without melting. MS: *m/z* 298 (M^+).

References

1. T.P.Platanova, A.D.Kuzovkov, P.S.Massagetov, *Zhur. Obshchei Khim.*, **23**, 880 (1953); .....*C.A.*, **48**, 3987d (1954). R.Marini Bettolo, M.L.Scarpati, *Phytochemistry*, **18**, 520 (1979).

2. R.Murari, S.Rangaswami, T.R.Seshadri, *Indian J. Chem.*, **13**, 543 (1975).

3. M.L.Scarpati, A.Bianco, L.Mascitelli , P.Passacantilli, *Synthetic Comm.*, **20**, 2565 (1990)

4. a) P.E.Fanta, *Synthesis*, 9 (1974); b) R.C.Fuson, E.A.Cleveland, *Org. Synth. Coll. Vol. 3*, ...339; c) M.Sainsbury, *Tetrahedron*, **36**, 3327 (1980).

5. J.Meinwald, J.Croudall, W.E.Himans, *Org. Synth. Coll.Vol.5*, 866 (1973).

6. S.Kubota, T.Masui, E.Fujita, S.M.Kupchan, *J. Org. Chem.*, **31**, 516 (1966).

7. R.N.Icke, B.B.Wisegarner, *Org. Synth. Coll. Vol. 3*, 723.

8. T.A.Henry, T.M.Sharp, *J. Chem. Soc.*, 2279 (1930).

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