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CODONOCARPUS ALKALOIDS—IV[1]

SYNTHESIS OF 2-METHOXY-2′-ETHOXY-4-[2-(TETRAMETHYLENECARBAMOYL)ETHYL]-5′-[2-(PROPYLCARBAMOYL)ETHYL]DIPHENYL ETHER[a]

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Abstract—Synthesis of the title compound was accomplished by coupling the iodonium bromide (3) of 4-ethoxybenzaldehyde with methyl hydroferulate (4) to 2-methoxy-2′-ethoxy-4-(methyl β-propionate)-5′-formyldiphenyl ether (5) which was converted to the pyrrolidinyl amide 6, and then the aryl aldehyde group was extended to a n-propyl β-propionamide unit via the Knoevenagel malonic acid reaction through the *trans*-cinnamic acid 7 followed by hydrogenation and amide formation with n-propylamine.

THE location of the phenolic group and the positioning of the unsymmetrical triamine, spermidine, in codonocarpine **1** was supported by mass spectral fragmentation of the derived substance, 2-methoxy - 2′ - ethoxy - 4 - [2 - (tetramethylene - carbamoyl)ethyl] - 5′ - [2 - (propylcarbamoyl)ethyl] diphenyl ether (**2**).[1] Fragments resulting from cleavage of the diphenyl ether bond were obtained, however, in low yield and consequently a synthesis of compound **2** was necessary to confirm the structural assignment.

Initially, the plan was to synthesize two components containing the phenyl rings with appropriate amide side-chains which could be joined to form the diphenyl ether linkage (generally, the lowest yielding reaction) in the final step, via the iodonium salt procedure.[2] However, it was not possible to prepare in good yields, or at all, the appropriate iodonium salts bearing an amide function. Likewise, phenylation by simple iodonium salts of phenols bearing amide groups was obtained in poor yield. As a result, a simpler diaryl ether was synthesized early in the sequence and the amide groups added later. The synthetic steps are shown in Scheme 1.

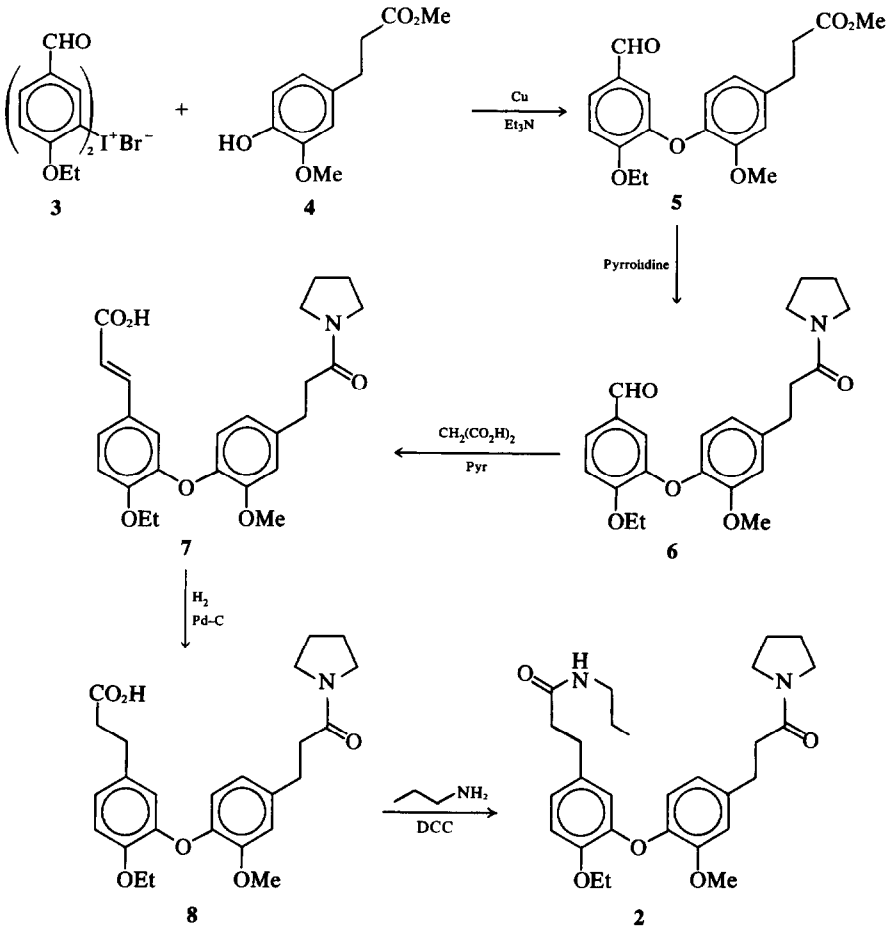
The iodonium bromide **3** prepared from 4-ethoxybenzaldehyde was coupled with methyl hydroferulate (**4**) in the presence of copper to give 2 - methoxy - 2′ - ethoxy - 4 - (methyl β - propionate) - 5′ - formyl diphenyl ether (**5**). Refluxing diaryl ether **5** in pyrrolidine yielded the pyrrolidinyl amide **6** which was subjected to the Knoevenagel malonic acid reaction to form the diaryl cinnamic acid **7**. The vinylic protons as an AB quartet at δ 6·17 and 7·63 show a large coupling constant, $J = 15{\cdot}4$ Hz, requiring that the olefin be *trans* substituted.[4] After hydrogenation of the olefinic group with palladium on carbon as catalyst, the dihydro compound **8** was converted to the final product, 2 - methoxy - 2′ - ethoxy - 4 - [2-(tetramethylenecarbamoyl)ethyl]-5′-[2-(propylcarbamoyl)ethyl]diphenyl ether **2**, with propylamine and dicyclohexylcarbodiimide. A direct comparison (IR, UV, NMR and TLC) of product **2** with that obtained from codonocarpine showed the two to be identical. Structure **1** for codonocarpine which was initially supported only by mass spectral data has now been confirmed by chemical synthesis to a common product.

EXPERIMENTAL

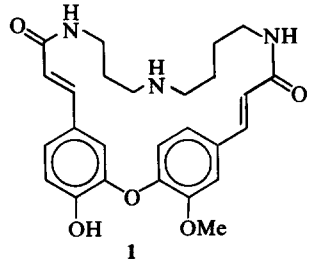
M.ps were taken on a Kofler hot stage. IR spectra were taken on a Perkin-Elmer 257 IR spectrophotometer under conditions given. UV spectra were obtained on a Cary model 15 spectrophotometer in the stated solvent. NMR spectra were determined on a Varian A-60A instrument in the given solvent with TMS as internal standard with chemical shifts recorded in δ(ppm) units. Abbreviations for spin patterns are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Mass spectra were obtained on a DuPont model 21-491 instrument via the direct inlet probe.

2.2′ - *Diethoxy* - 5,5′ - *diformyldiphenyliodonium bromide* (**3**). Iodyl sulfate was prepared by adding 1·02 g I_2 to 2·57 g potassium periodate in 12 ml conc H_2SO_4 while stirring. After 24 hr the suspension of the yellow reagent, cooled in an ice-bath, was treated while stirring with 5·4 g 4 - ethoxybenzaldehyde[5] and 0·4 g A_2O. After 3 hr at 0°

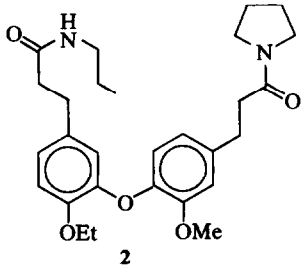
[a] According to Chemical Abstracts nomenclature, the name of this compound is 3 - [4 - ethoxy - 3 - [2 - methoxy - 4 - [2 - (1 - pyrrolidinylcarbonyl) ethyl] phenoxy] phenyl] - N - propyl propionamide.



SCHEME 1



1



2

the mixture was stirred at ambient temp for 16 hr and th poured over 50 g ice, diluted with 100 ml water a filtered. The ppt was suspended in 100 ml water on steam bath and filtered hot. Both filtrates were combin and washed with 50 ml diethyl ether, 3 times, and th treated with 5 gm KBr. The ppt of **3** after drying weigh 8·5 gm and on recrystallization from 90% formic ac melted at 191–192°, (Found: C, 39·99; H, 4·3 $C_{18}H_{18}O_4IBr \cdot 2H_2O$ requires: C, 39·95; H, 4·10%).

2 - *Methoxy* - 2′ - *ethoxy* - 4 - (*methyl β* - propionate 5′ - formyldiphenyl ether (**5**). To a soln of **3** (3·96 g) a methyl hydroferulate[3] (0·84 g) dissolved in 30 ml MeC was added 1·2 g Cu powder[6] and 2·12 g triethylamine, a the mixture was stirred for 20 hr. The mixture was filter and evaporated to leave a solid residue that was dissolv in chloroform and extracted successively with 1N HCl, $NaHCO_3$ aq and water. The dried (Na_2SO_4) chlorofo soln yielded 3·7 gm of a crystalline residue that af chromatography on 70 g silicic acid (Mallinkrodt) wi chloroform as solvent and monitored by TLC [silica gel MeOH–$CHCl_3$ (1:20), 2,4 - dinitrophenyl hydrazine re ent, R_f 0·41] gave 0·40 gm of **5** that was crystallized fr benzene–chloroform, m.p. 88–90°, (Found: C, 67·21; 6·21 $C_{20}H_{22}O_6$ requires: C, 67·02; H, 6·19%); IR (CHC 1735 (C=O, ester) and 1690 cm^{-1} (C=O, aldehyde); NM

($CDCl_3$) δ 1·42 (3H, t, $J = 6·8$, OCH_2CH_3), 4·21 (2H, q, $J = 6·8$, OCH_2CH_3), 3·68 (3H, s, CO_2Me), 3·81 (3H, s, OMe) and 9·78 (1H, s, CHO); and MS *m/e* 358 (100%, M^+) and 285 (58%, M-$CH_2CO_2CH_3$).

2 - *Methoxy* - 2' - *ethoxy* - 4 - [2 - (*tetramethylene* - *carbamoyl*)*ethyl*] - 5' - *formyldiphenyl ether* (**6**). Diaryl ether **5** (500 mg) was refluxed for 20 hr in 20 ml pyrrolidine. The mixture was distilled with addition of fresh pyrrolidine to remove 20 ml of distillate, and then refluxed 2 hr more. Removal of solvent by evaporation at reduced pressure left 526 mg of residue that was chromatographed on 80 g of silica gel G (Merck) with chloroform as eluent. The effluent residue (458 mg) with R_f 0·33 [TLC, silica gel G, MeOH–$CHCl_3$ (1:20)] was crystallized from chloroform–light petroleum or diethyl ether–MeOH to give **6**, m.p. 133–134°; (Found: C, 68·81; H, 6·91; N, 3·40. $C_{23}H_{27}N0_5$ requires: C, 69·50; H, 6·85; N, 3·52%, $C_{23}H_{27}NO_5 \cdot 1/4\ CH_3OH$ requires: C, 68·87; H, 6·96; N, 3·45%); IR ($CHCl_3$) 1690 (C=O, aldehyde) and 1630 cm^{-1} (C=O, amide); NMR ($CDCl_3$) δ 1·44 (3H, t, $J = 6·8$, OCH_2CH_3), 4·23 (2H, q, $J = 6·8$, OCH_2CH_3), 3·80 (3H, s, OMe) and 8·96 (1H, s, CHO); and MS *m/e* 397 (3%, M^+) and 149 (100%, EtOPhCHO).

2 - *Methoxy* - 2' - *ethoxy* - 4 - [2 - (*tetramethylene* - *carbamoyl*)*ethyl*] - 5' - (*β - acrylic acid*)*diphenyl ether* (**7**). Amide **6** (160 mg) in 10 ml freshly distilled pyridine was treated with 0·5 ml pyrrolidine and 84 mg malonic acid and heated under anhydrous conditions (condenser and drying tube) for 1 hr on the steam bath and then under reflux for 1 hr. The mixture was poured on 50 g ice and 20 ml conc HCl. The ppt that formed was quickly collected by filtration, washed with water and dried under vacuum to give 150 mg of **7** that crystallized from benzene as colorless needles, m.p. 163–164°; (Found: C, 67·97; H, 6·66; N, 3·19 · $C_{25}H_{29}NO_6$ requires C, 68·32; H, 6·65; N, 3·19%); IR ($CHCl_3$) 1690 (C=O, unsat acid) and 1630 cm^{-1} (C=O, amide); NMR ($CDCl_3$) δ 1·38 (3H, t, $J = 6·8$; OCH_2CH_3), 4·16 (2H, q, $J = 6·8$, OCH_2CH_3), 3·83 (3H, s, OMe), 6·17 and 7·63 (AB quartet, $J = 15·4$, *trans* CH=CH) and 9·37 (1H, br s, CO_2H); and MS *m/e* 439 (100%, M^+), 327 (17%, M-$CH_2CON(CH_2)_3CH_2$), 112 (51%, $CH_2CON(CH_2)_3CH_2$), 98 (56%, $CON(CH_2)_3CH_2$) and 70 (95%, $N(CH_2)_3CH_2$).

2 - *Methoxy* - 2' - *ethoxy* - 4 - [2 - (*tetramethylene* - *carbamoyl*)*ethyl*]-5'-(*β-propionic acid*)*diphenyl ether* (**8**). The acid **7** (65 mg) in 5 ml MeOH was hydrogenated over 50 mg of 5% Pd on C at ambient temp and pressure in about 30 min. Removal of catalyst and solvent left 65 mg of residue that crystallized from benzene to give **8**, m.p. 99–100°; (Found: C, 68·12; H, 7·02; N, 3·17. $C_{25}H_{31}NO_6$ requires: C, 68·01; H, 7·08; N, 3·17%); IR ($CHCl_3$) 1715 (C=O, acid) and 1625 cm^{-1} (C=O, amide); NMR ($CDCl_3$) δ 1·30 (3H, t, $J = 6·8$, OCH_2CH_3, 4·05 (2H, q, $J = 6·8$, OCH_2CH_3), 3·83 (3H, s, OMe and 8·72 (1H, br s, CO_2H); and MS *m/e* 441 (100%, M^+), 342 (31%, M-$COHN(CH_2)_3CH_2$), 329 (14%, M-$CH_2CON(CH_2)_3CH_2$) and 112 (42%, $CH_2CON(CH_2)_3CH_2$).

2 - *Methoxy* - 2' - *ethoxy* - 4 - [2 - (*tetramethylenecarba* - *moyl*)*ethyl*] - 5' - [2 - (*propylcarbamoyl*)*ethyl*]*diphenyl ether* (**2**). The acid **8** (50 mg) was dissolved in 4 ml acetonitrile–THF (1:1)[7] containing 35 mg dicyclohexylcarbodiimide, and 15 mg n-propylamine in 1 ml of the reaction solvent was added. After 48 hr at ambient temp the solvent was evaporated at reduced pressure and the residue was treated with 1 ml water and 2 drops AcOH. The ppt was collected, dried and chromatographed on 20 g of silica gel G (Merck) with chloroform as eluent. The diamide **2** was obtained as a colorless oil showing one spot on tlc examination [silica gel G, $KMnO_4$ spray, MeOH–$CHCl_3$ (1:50), R_f 0·20; n - BuOH–MeOH–H_2O–conc NH_4OH (20:20:19:1), R_f 0·60; n-BuOH–n-PrOH–H_2O–conc NH_4OH (20:20:19:1), R_f 0·46] and had the same IR, NMR and MS as the compound obtained from codonocarpine.[1]

REFERENCES

[1]Part III. R. W. Doskotch, A. B. Ray, W. Kubelka, E. H. Fairchild, C. D. Hufford and J. L. Beal, *Tetrahedron* **30**, 3229 (1974)

[2]F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler and C. C. Lumpkin, *J. Am. Chem. Soc.* **75**, 2708 (1953). T. Matsuura, A. Nishinaga, *J. Org. Chem.* **29**, 3168 (1964) and refs therein

[3]W. M. Whaley, M. Meadow, and W. L. Dean, *J. Org. Chem.* **19**, 1022 (1954)

[4]L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* pp. 301–302. Pergamon Press, New York (1969)

[5]H. H. Hodgson and E. W. Smith, *J. Soc. Chem. Ind. London, Trans. Commun.* **49**, 408T (1930)

[6]H. Ziegler and C. Marr, *J. Org. Chem.* **27**, 3335 (1962)

[7]G. Folsch, *Acta Chem. Scand.* **13**, 1407 (1959)