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CODONOCARPUS ALKALOIDS—III

THE STRUCTURE OF CODONOCARPINE†

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Abstract—The structures of two Lunaria-type alkaloids, codonocarpine and N-methylcodonocarpine, from *Codonocarpus australis* were established by a series of chemical transformations and spectral studies.

The bark of the Australian tree, *Codonocarpus australis* A. Cunn., (Fam. Phytolaccaceae) has yielded six crystalline alkaloids[1] of which two, codonocarpine (**1**) and its N-Me derivative **2** are the subject of this report. They are biogenetically related to the Lunaria-type alkaloids,[2] in that the building units are two phenylpropides and spermidine. Prior to this work, this class of alkaloids was reported only in the family Cruciferae.

Codonocarpine (**1**), a yellow crystalline solid, m.p. 187° (d) is optically inactive and gives a molecular ion in the mass spectrum corresponding to the formula $C_{26}H_{31}N_3O_5$. The UV spectrum indicated a conjugated benzenoid chromophore, and the bathochromic shift under strong alkaline conditions suggested the presence of a phenolic group. Strong acid hydrolysis yielded spermidine (**3**) which was characterized as the hydrochloride and picrate salts. This information and the presence of an IR band at 1650 cm^{-1} in the starting material indicated that amide functionality was present and a Lunaria-type[2] alkaloid was suspected. The NMR spectrum showed absorption in the aliphatic and aromatic regions, but the only readily interpretable peak was a three-proton singlet at δ 3·84 for a methoxy group.

Acetylation of codonocarpine produced a neutral diacetate **4** with two 3-proton singlets at δ 2·08 (NAc) and 2·40 (OAc) in the NMR spectrum. The starting material contains, therefore, two amide groups. Mild alkaline hydrolysis of the diacetate **4** cleaved one acetate function to generate the phenolic product **5**, which was readily methylated to O - methyl - N - acetyl - codonocarpine (**6**). The UV spectrum of codonocarpine was reminiscent of a *trans*-cinnamide[3] including the observation of a large bathochromic shift under strong acid conditions, when performed on derivative **6**. The *trans*-olefin protons are clearly observed in the NMR spectrum of codonocarpine diacetate (**4**) as two AB quartets each with a coupling constant of J = 15·5 Hz. Hydrogenation of the diacetate **4** to tetrahydrocodonocarpine diacetate **7** resulted in loss of the AB quartets and an increase of eight protons in the methylene region.

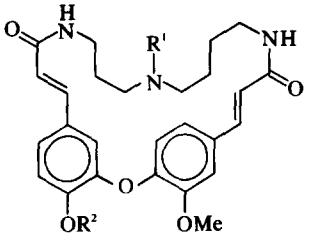
The ether nature of the third oxygen in codonocarpine was established by the isolation of a diphenyl ether dicarboxylic acid on potassium permanganate oxidation of permethylated codonocarpine. Of the possible diphenyl ethers suggested on biogenetic grounds, the two structures **8** or **9** seemed the most likely with the latter preferred on the basis of the complex NMR spectrum in the aromatic region (two overlapping ABX patterns) and of the melting points of the diacid and its dimethyl ester **10**. 2,2′ - Dimethoxy - 4,5′ - dicarboxydiphenyl ether (**9**) and its diester **10** were originally prepared by Proskurnina[4] utilizing the Ullmann condensation to form the diphenyl ether linkage. We prepared these compounds by utilizing the diaryliodonium salt method of Beringer[5] in which 2,2′ - dimethoxy - 5,5′ - diformyldiphenyliodonium sulfate was coupled with methyl vanillate to give 2,2′ - dimethoxy - 5′ - formyl - 4 - methoxycarbonyldiphenyl ether (**11**) which was not isolated but hydrolyzed to the monocarboxylic acid as an aid to purification and then oxidized to the dicarboxylic acid **9**. Diacid **9** and its dimethyl ester **10** were identical with the products obtained from codonocarpine, thus establishing for the alkaloid not only the mode of linkage of the aromatic units but also the oxygenation pattern and the location of the side chains.

To confirm the presence of the dimeric phenylpropide unit, tetrahydrocodonocarpine diacetate **7**

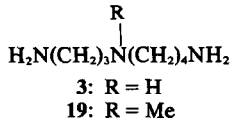
†A preliminary report and part I of this series is given in *Chem. Commun.*, 300 (1971). Part II is Ref 1.

was hydrolyzed by strong acid and the isolated phenolic diacid **12** was converted to the following derivatives: dimethyl ester **13** by use of diazomethane, diacid **14** from compound **13** by saponification and finally diamide **15**. Spermidine was also isolated as the trihydrochloride from the hydrolysis mixture, thus the two units forming codonocarpine were obtained without alteration of the carbon skeletons.

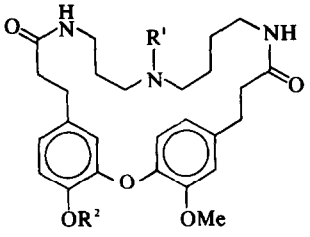
The unanswered questions about the structure of codonocarpine include, which of the oxygenate positions is phenolic and by which of the severa possible ways is spermidine attached to the diaci unit? A total of twelve isomers are possible. Of th two locations for the phenolic group, only one ha an unsubstituted *para* position. Application of th Gibbs' test[6] to N-acetyl tetrahydrocodonocarpin (**16**) gave a negative result indicating that th phenolic group did not possess an unsubstitute *para* position. The anomalous result obtained whe



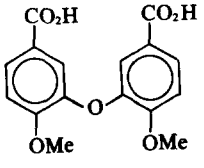
1: $R^1 = R^2 = H$
2: $R^1 = Me$, $R^2 = H$
4: $R^1 = R^2 = Ac$
5: $R^1 = Ac$, $R^2 = H$
6: $R^1 = Ac$, $R^2 = Me$
20: $R^1 = Me$, $R^2 = Ac$



3: R = H
19: R = Me



7: $R^1 = R^2 = Ac$
16: $R^1 = Ac$, $R^2 = H$
18: $R^1 = Me$, $R^2 = Ac$



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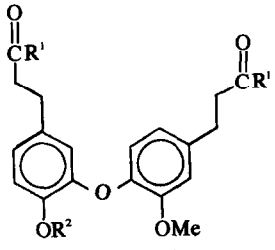
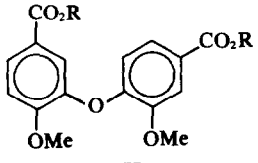
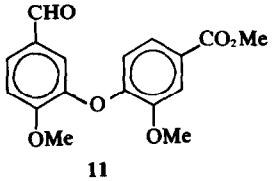


12: $R^1 = OH$, $R^2 = H$
13: $R^1 = OMe$, $R^2 = Me$
14: $R^1 = OH$, $R^2 = Me$
15: $R^1 = NH_2$, $R^2 = Me$



9: R = H
10: R = Me



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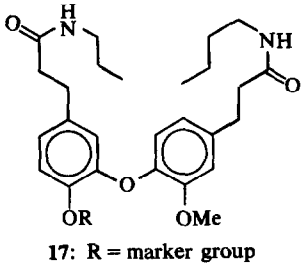
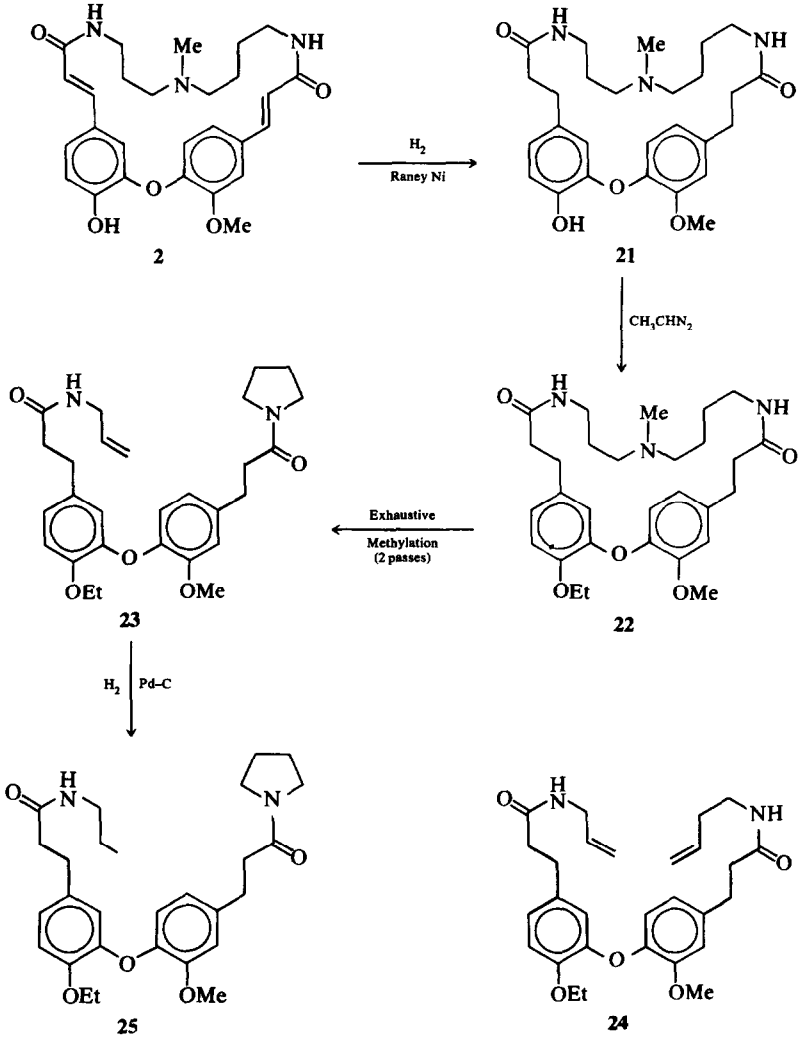


17: R = marker group

codonocarpine (1) was subjected to the test, was attributed to the α,β-unsaturated amide units.

To settle the arrangement of the spermidine (3) unit, it was planned to cleave codonocarpine (1) at the amine position by two exhaustive methylations to ultimately yield the product 17. However if spermidine is not attached via the two primary amino groups, then 17 would not be formed but instead exhaustive methylation and hydrogenation would give trimethylamine on the first cycle and a product that on hydrolysis would yield N - (3 - aminopropyl) - n - butylamine or N - (4 - aminobutyl) - n - propylamine. Lack of an adequate supply of codonocarpine at this stage of our investigation prevented its direct use in the degradation scheme, but the availability of a congener overcame this drawback.

Alkaloid IV,[1] possesses formula $C_{27}H_{33}N_3O_5$, or one methylene group (14 daltons) larger than codonocarpine (1), shows a bathochromic shift in the UV region, and exhibits a three-proton singlet in the NMR spectrum at δ 2·26. After strong acid hydrolysis of the acetyl tetrahydro derivative 18, a triamine was obtained that showed a parent ion in the mass spectrum at *m/e* 159 corresponding to $C_8H_{21}N_3$; or one CH_2 greater than spermidine. It gave a crystalline picrate and was characterized as N^2-methylspermidine (19) on the following basis. Since Alkaloid IV forms a basic monoacetate 20, the 14 mass units must be as a methyl group at N^2 of the spermidine and not as a carbon linked methylene or methyl, nor as N-methyl on an amide nitrogen. Recently, N^2-methylspermidine (19) was synthesized[7] and the reported properties corres-



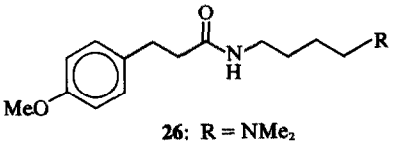
SCHEME 1

pond with our material. Furthermore, codonocarpine (**1**) was N-methylated by the Japanese modification[8] of the Eschweiler–Clarke alkylation to Alkaloid IV; thus Alkaloid IV is N-methylcodonocarpine (**2**).

Utilization of N-methylcodonocarpine in the sequence of reactions shown in Scheme 1 settled the remaining question about the structure of codonocarpine (**1**). Hydrogenation of N-methylcodonocarpine (**2**) with Raney nickel as catalyst gave in good yield the tetrahydro compound **21**, which was ethylated with diazoethane to the ethyl ether **22**, to mark the position of the phenolic group. An exhaustive methylation, performed twice, converted the ethyl ether **22** to the Hofmann bismethine **23** rather than the expected product **24**. The molecular ion at *m/e* 480 of the bis-methine was consistent with **24** yet hydrogenation to **25** in which all the olefinic protons were lost (as indicated by the NMR spectrum) resulted in the uptake of only one mole of hydrogen. Product **23** has only one vinyl group, for the NMR spectrum shows one 3-proton ABC pattern (δ 4·9–6·1), and looses only one proton on deuterium oxide exchange in agreement with formation of a cyclized product involving a nitrogen. The mass spectrum supported the assignment of a pyrrolidinyl amide (peaks at *m/e* 70, 98 and 112) both in the Hofmann methine **23** and the hydrogenated product **25**. The genesis of pyrrolidine formation was established from model studies.

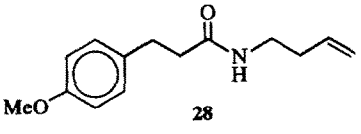
N - (4 - Dimethylaminobutyl) 3 - (p - methoxyphenyl)propionamide (**26**) was converted to th methohydroxide **27** and subjected to the Hofman pyrolysis conditions. The products of the reactio were N - but - 3 - enyl 3 - (*p* - methoxy phenyl)propionamide (**28**) the normal Hofman methine, and N-[3-(*p*-methoxyphenyl)propionyl pyrrolidine (**29**) in a ratio of about 1:3 For confirmation the latter product was also pre pared from pyrrolidine and 3 - (*p* - methoxy phenyl)propionic acid. The cyclization reaction re quires base since heating of the methochloride sa of **26** under similar conditions resulted in recover of starting material.

The high resolution mass spectrum of diphen ether diamide **25** showed four peaks that allowe the assignment of the propyl amide unit to th phenyl ring bearing the ethoxy group and th pyrrolidinyl amide unit to the other phenyl rin The peaks at *m/e* 251 (2%) and 250 (0·5%) corre pond to fragment ions **30a** and **30b**, respectivel while those at *m/e* 249 (2%) and 248 (1%) corre pond to ions **31a** and **31b**. The largest ion of eac group results from a proton transfer du ing fragmentation. No peaks were present at *m* 220, 236 or 237 nor at 246, 262 or 263 whic would be required if the amide units were re versed. Consequently, structure **25** is supporte by the MS data and in addition was confirme by unambiguous chemical synthesis as describe in the following paper. Codonocarpine mus therefore, be formulated as **1** and its N-Me ana logue as **2**.



26: R = NMe_2

27: R = $\overset{+}{N}Me_3OH^-$



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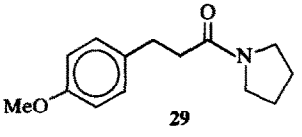

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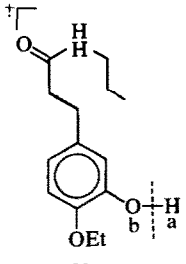

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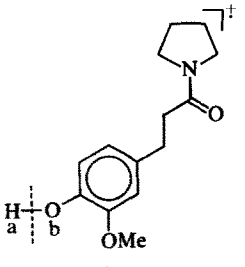

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EXPERIMENTAL

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 recording spectrophotometer in the stated solvent. NMR spectra were determined on a Varian A-60A instrument in the solvent recorded with TMS as internal standard and chemical shifts are reported in δ (ppm) units. Abbreviations for spin patterns are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Optical rotations were taken on a Zeiss polarimeter. Mass spectra were obtained on an AEI MS-902 double-focusing mass spectrometer or on a DuPont model 21-491 instrument via the direct inlet mode at 70 eV.

Codonocarpine (**1**). Isolation of this alkaloid was reported[1] and its physical properties are given in part I of this series (see footnote on title page).

Hydrolysis of codonocarpine (**1**). A soln of 50 mg codonocarpine in 10 ml 6N HCl was heated in a sealed tube at 110° (oil bath) for 20 h. The gelatinous ppt that formed on cooling was removed by filtration and did not yield any pure constituents. The filtrate was evaporated to dryness, dissolved in a minimum quantity of water and treated with an aqueous soln of picric acid. The yellow ppt that formed was recrystallized from water to give 12 mg of **3**-picrate identical (m.m.p., TLC and IR) with an authentic sample.

N,O-*Diacetylcodonocarpine* (**4**). Codonocarpine (**1**, 120 mg) was stirred with 7 ml Ac_2O and 1 ml pyridine for 12 h. The white ppt that formed was collected, washed with toluene and then recrystallized twice from acetone to give 97 mg of **4**, m.p. 169–171°; IR (KBr) 3300 (br, NH), 1770 (C=O, ArOAc), 1660 (C=O, sec amides) and 1630 cm^{-1} (C=O, tert amide); UV (MeOH) λ_{max} 305 (sh) nm (log ϵ 4·24), 274 (4·53) and 218 (4·51); NMR ($CDCl_3$–CD_3OD, 5:1) δ 2·08 (3H, s, NAc), 2·40 (3H, s, OAc), 3·82 (3H, s, OMe), and 5·91, 6·52, 7·41 and 7·57 (1H each, d, J = 15·5 Hz, two AB quartets for CH=CH—C=O); MS *m/e* 549·2458 (19%, M^+, $C_{30}H_{35}N_3O_7$ requires 549·2475), 507 (41, M—CH_2CO) and 464 (25, M—CH_2CO—CH_3CO).

N-*Acetylcodonocarpine* (**5**). Diacetylcodonocarpine (**4**, 50 mg) was dissolved in 3 ml of conc ammonium hydroxide. After 16 h, the solvent was evaporated and the residue dissolved in MeOH and taken to dryness. Crystallization twice from MeOH gave colorless rosettes (37 mg), m.p. 186–187°; IR (KBr) 3630 (OH), 3270 (NH), 1655 (C=O, amide) and 1620 (C=O, amide); UV (MeOH) λ_{max} 310 nm (log ϵ 4·11), 282 (4·26), 229 sh (4·23) and 217 (4·30); (0·02 N NaOH in MeOH) 355 (4·01), 308 (4·20) and 292 (4·22); MS *m/e* 507·2339 (77%, M^+, $C_{28}H_{33}N_3O_6$ requires 507·2369) and 464 (40, M—CH_2CO).

O - *Methyl* - N - *acetylcodonocarpine* (**6**). N - Acetylcodonocarpine (**5**, 100 mg) was dissolved in 5 ml of 5% NaOH aq and stirred with 0·3 ml Me_2SO_4. Additional NaOH aq and Me_2SO_4 was added until the initial yellow color disappeared and a white ppt formed. Then 25 ml water was added and the mixture exhaustively extracted with chloroform. The dried ($NaSO_4$) chloroform extract was evaporated to dryness and the residue (90 mg) crystallized from MeOH or acetone as fine needles, m.p. 169–171°; IR (Nujol) 1660 and 1620 cm^{-1} (C=O amides); UV (MeOH) λ_{max} 311 nm (log ϵ 4·46), 282 (4·56) and 217 (4·53), no change in 0·02 N methanolic NaOH except 217 nm peak is lost due to high end absorption, (70% $HClO_4$) 325 (4·58) and 234 (4·41); NMR ($CDCl_3$) δ 2·03 (3H, s, OAc), 3·77 (3H, s, OMe), 3·99 (3H, s, OMe), 5·55 (1H, br m, NH) and 5·8 (1H, br m, NH); MS *m/e* 521·2535 (100%, M^+, $C_{29}H_{35}N_3O_6$ requires 521·2526) and 336,0980 (27, $C_{20}H_{16}O_5$, the ion formed on loss of N-acetylspermidine requires 336·0998).

Methylation and oxidation of codonocarpine (**1**). Codonocarpine (**1**, 100 mg) was dissolved in 10 ml of 4% NaOH aq and stirred with 0·5 ml Me_2SO_4 for 2 h during which time the soln became clear. The mixture was diluted with water, heated on the steam bath and treated portionwise with 400 mg $KMnO_4$ till a pink color persisted. After cooling and acidifying with dil H_2SO_4. The mixture was heated for 15 min on the steam bath. The MnO_2 was removed by treatment with $NaHSO_3$ and the colorless soln extracted with diethyl ether. The ether residue crystallized from MeOH to give 12 mg of **9**, m.p. 272–273°; IR (Nujol) 3300–2400 (OH) and 1685 cm^{-1} (COOH).

The ester **10** of the acid **9** was prepared with diazomethane and crystallized from MeOH as needles, m.p. 96°; IR ($CHCl_3$) 1710 cm^{-1} (C=O ester); UV (MeOH) λ_{max} 287 nm (log ϵ 3·95) and 253 (4·37); NMR ($CDCl_3$) δ 3·85, 3·88, 3·90 and 3·95 (each 3H, s, OMe of ethers and esters); MS *m/e* 346 (100%, M^+, $C_{18}H_{18}O_7$ requires 346). The compound was found to be identical (m.m.p., TLC, IR and NMR) with an authentic sample.

2,2′ - *Dimethoxy* - 5,5′ - *diformyldiphenyliodonium sulfate.* Iodyl sulfate was prepared by adding 10·2 g of I_2 to 25·6 g of KIO_3 in 100 ml conc H_2SO_4 while stirring for 18 h. The yellow ppt was collected, washed with AcOH and then suspended in 50 ml AcOH. A mixture of 60 g *p*-anisaldehyde in 30 ml of acetic anhyride was added while stirring during 1 h at which the temp was kept between 10-20°. After stirring 24 h, the mixture was poured on crushed ice and stirred 1 h. The aqueous supernatant was decanted from the oily bottom layer and washed with diethyl ether. To the clear aqueous phase, 30 g KBr was added and a bright yellow sticky ppt formed which was repeatedly washed with water till it solidified. After filtration and successive acetone and ether washing, the iodonium bromide was obtained (9·5 g), m.p. 189–191°. The bromide was suspended in 200 ml of 10% aqueous EtOH and 3·3 g of finely powdered silver sulfate was added while stirring. After 2 h the AgBr was collected by filtration and the filtrate was evaporated to yield 8·5 g of 2,2′ - dimethoxy - 5,5′ - diformyldiphenyliodonium sulfate as a white powder.

2,2′ - *Dimethoxy* - 4,5′ - *dimethoxycarbonyldiphenyl ether* (**10**). A mixture of methyl vanillate (0·91 g), 2,2′ - dimethoxy - 5,5′ - diformyldiphenyliodonium sulfate (2·23 g) and 1 ml of triethylamine in 20 ml abs EtOH was stirred for 24 h and then warmed for 15 min on the steam bath. The insolubles were removed by filtration and the filtrate evaporated to leave 2·0 g of a low melting solid which after stirring 12 h in 1N NaOH in 50% aqueous MeOH left the by-product 3-iodoanisaldehyde as a crystalline ppt. The filtrate after evaporation and acidification with dil H_2SO_4 was extracted with chloroform, and removal of the solvent gave a yellow residue of the acid of **11** which was not characterized but oxidized, overnight, in 40 ml of 1% K_2CO_3 aq with 500 mg $KMnO_4$ at ambient temp. Acidification (H_2SO_4) and decolorization ($NaHSO_3$) left an aqueous soln that was extracted with ether and yielded 350 mg of **9** which crystallized from MeOH, m.p. 272–273° [lit[4] value m.p. 273–274°].

Treatment of acid **9** in MeOH with diazomethane gave **10** as needles, m.p. 96° [lit[4] value m.p. 95–96°] from

MeOH. It was identical with the product obtained from **1** after methylation.

N,O - *Diacetyltetrahydrocodonocarpine* (**7**). Compound **4**, (55 mg) in 25 ml of abs EtOH was shaken with H_2 at atmospheric pressure and ambient temp over pre-reduced PtO_2. When H_2 uptake ceased, the catalyst was removed and the filtrate evaporated to dryness to leave a white amorphous foam that could not be crystallized; IR ($CHCl_3$) 3440 and 3300 (OH), 1760 (C=O, ester), 1655 (C=O, sec amide) and 1625 cm^{-1} (C=O, tert amide); UV (MeOH) λ_{max} 273 nm (log ϵ 3·63) and 276 (3·63); NMR ($CDCl_3$) δ 1·98 (3H, s, Ac), 2·05 (3H, s, Ac) 3·82 (3H, s, OMe), 5·83 (1H, t, NH, lost in D_2O), 6·40 (1H, t, NH, lost in D_2O) and loss of the four olefinic protons in aromatic region with gain of four each at $\delta \sim 2{\cdot}5$ and $\sim 3{\cdot}0$; MS *m/e* 553·2791 (44%, M^+, $C_{30}H_{39}N_3O_7$ requires 553·2788), 511 (57, M—CH_2CO) and 468 (100, M—CH_2CO—CH_3CO).

Hydrolysis of N,O-*diacetyltetrahydrocodocarpine* (**7**). A 100 mg sample of **7** was heated in 5 ml of 4N HCl in a sealed tube at 105–110° for 12 h. The hydrolysis mixture was extracted exhaustively with chloroform and the extract washed with water, dried (Na_2SO_4) and evaporated to leave an oily residue (55 mg), which showed an NMR spectrum consistent with **12** [$\delta \sim 2{\cdot}7$ (8H, m, CH_2CH_2), 3·78 (3H, s, OMe), $\sim 6{\cdot}8$ (6H, m, ArH) and 8·8 (3H, br, OH and lost in D_2O)].

The aqueous acid soln after chloroform extraction left on evaporation a gummy residue that crystallized from abs EtOH, m.p. 256–258°; MS *m/e* 145 (2% M^+ for spermidine $C_7H_{19}N_3$). The product was identical with authentic 3-trihydrochloride.

The diacid **12** was treated with diazomethane to give the diester **13** as an oil; IR ($CHCl_3$) 1735 cm^{-1} (C=O, ester); NMR ($CDCl_3$) δ 2·74 (8H, m, CH_2CH_2), 3·62, 3·68, 3·82 and 3·84 (3H each, s, OMe), and 6·6–6·9 (6H, m, ArH); MS *m/e* 402 (100%, M^+, $C_{22}H_{26}O_7$), 371 (9%, M_e—OMe) and 329 (60%, M—$CH_2CO_2CH_3$).

Hydrolysis of 40 mg of **13** in 1N KOH in 50% aqueous MeOH for 16 h at ambient temp gave a residue on evaporation that after treatment with dilute mineral acid and ether extraction gave **14** as an oil (35 mg); NMR ($CHCl_3$) δ 3·81 and 3·85 (3H each, s, OMe).

The diacid **14** (35 mg) was treated with 0·1 ml $SOCl_2$ and warmed on the steam bath for 10 min. After removal of excess reagent at reduced pressure, the residue was mixed carefully with conc NH_4OH and after 5 min diluted with water and extracted with chloroform. The chloroform extract yielded on evaporation a foamy residue of **15** that would not crystallize; IR ($CHCl_3$) 3540–3100 cm^{-1} (NH) and 1680 (C=O); NMR ($CDCl_3$) δ 2·3–3·0 (8H, CH_2CH_2), 3·78 (3H, s, OMe), 3·82 (3H, s, OMe), 5·83 (4H, br s, NH_2) and 6·5 – 7·0 (6H, m, ArH); MS *m/e* 372·1687 (100% M^+, $C_{20}H_{24}N_2O_5$ requires 372·1685).

N-*Acetyltetrahydrocodonocarpine* (**16**). Compound **7** (10 mg) was stirred with 10 ml of 1N methanolic NaOH for 2 h. The solvent was removed by evaporation and the residue acidified with dil H_2SO_4 and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated leaving an amorphous **16**; UV (MeOH) λ_{max} 282 nm (log ϵ 3·60) and 278 (3·59); (0·02N NaOH in MeOH) 298 (3·55) and 286 (3·54); MS *m/e* 511·2690 (M^+, $C_{28}H_{37}N_3O_6$ requires 511·2682). The Gibbs' test[6] on compound **16** showed no absorption between 500–700 nm, whereas codonocarpine shows a peak a 685 nm, a false positive, likely, due to the vinylogou carbonyl at the *para* position.

N-Methylation[8] *of codonocarpine.* Codonocarpin (35 mg) was suspended in 10 ml MeOH and 1·0 ml of 37% formaldehyde soln and stirred for 45 min in which time th alkaloid dissolved. $NaBH_4$ (200 mg) was added portion wise, and after stirring 45 min, the solution was acidifie with 2N HCl, diluted with water and evaporated to remov the MeOH. The remaining soln was basified with di NH_4OH and extracted with 25 ml (4 times) o $CHCl_3$–EtOH (9:1). The combined chloroform extract wa dried (Na_2SO_4) and after removal of solvent the residu was triturated with MeOH and the insoluble materia discarded. Crystallization of the MeOH-soluble materia was from MeOH–$CHCl_3$–water to give 31 mg of N-methyl codoncarpine, m.p. 167–171°; NMR (CD_3OD) δ 2·25 (3H, s NMe) and 3·97 (3H, s, OMe); IR spectrum superimposabl with that of alkaloid IV isolated from *C. australis* an m.m.p. was not depressed.

Hydrolysis of O - *acetyl* - N - *methyltetrahydrocodono carpine* (**18**). Compound **20** (60 mg) was mixed with 7 m 6N HCl and heated in a sealed tube at 110° for 18 h. Th cooled mixture was exhaustively extracted wit chloroform. The aqueous acid soln was evaporated t dryness, taken up in water, filtered, and mixed while ho with aqueous picric acid soln. On cooling a crystallin picrate (53 mg) of N^2-methylspermidine formed as yello plates, m.p. 202–203°. [lit[7] value m.p. 205°] The hydro chloride salt was prepared from the picrate (30 mg) b dissolving in 15 ml 6N HCl and extracting exhaustivel with diethyl ether. The aqueous acid soln was evaporate at reduced pressure and the residue triturated with MeOH Removal of MeOH left the trihydrochloride salt of N^2 methylspermidine (7 mg). MS *m/e* 159 (5%, M^+, $C_8H_{21}N$ requires 159), 115 (19, M—$CH_2CH_2NH_2$), 101 (3 M—$(CH_2)_3NH_2$), 72 (58, $(CH_2)_4NH_2$), 58 (100, $(CH_2)_3NH$ and 43 (30, CH_2NCH_3); 101 → 58, loss of CH_2NCH_3 unit i supported by *m** 33·3.

O - *Acetyl* - N - *methylcodonocarpine* (**20**). N - methyl codonocarpine (500 mg) was suspended in 14 ml Ac_2O an 2 ml pyridine and stirred at room temp. After 12 h yellowish soln formed. The solvent was evaporated a reduced pressure with aid of toluene. About 25 ml aceton was added to the residue and after cooling in the re frigerator the solid (562 mg, m.p. 176–179°) was collecte by filtration and dried. Recrystallization was from abou 30 ml acetone to give 489 mg of **20**,* m.p. 177–179°; I (Nujol) 1760 cm^{-1} (OAc); NMR ($CDCl_3$) δ 2·38 (3H, OAc), 2·47 (3H, s, NMe), 3·82 (3H, s, OMe); MS *m* 521·2551 (37%, M^+ $C_{29}H_{35}N_3O_6$ requires 521·2526) an 479·2421 (40, M—CH_2CO requires 479·2420).

N-*Methyltetrahydrocodonocarpine* (**21**). To Raney N W-2 (~ 100 mg) in 5 ml MeOH, presaturated with H_2 fo 24 h, was added 100 mg of **2** in 5 ml MeOH. After uptake c two equivs of H_2 in less than 1 h, the reaction was stoppe and the product [R_f 0·46, TLC on silica gel C MeOH–n-BuOH–H_2O–conc NH_4OH (20:20:19:1 iodoplatinic acid spray, starting material showed R_f 0·6 was crystallized from diethyl ether–isopropanol to giv 96 mg of **21**, m.p. 202–205°; IR ($CHCl_3$) 3660 (OH), 354 (NH), 3450–3100 (bonded OH and NH) and 1650 cm (C=O amide); NMR (CD_3OD) δ 2·16 (3H, s, NMe) an 3·82 (3H, s, OMe); MS *m/e* 483·2738 (0·5%, M $C_{27}H_{37}N_3O_5$ requires 483·2733).

O - *Ethyl* - N - *methyltetrahydrocodonocarpine* (22 Compound **21** (405 mg) was dissolved in 60 ml MeOH an

*Compound **20** crystallizes with acetone, but the solvent can be removed by extensive drying under high vacuum at 110°. The N-methyl peak is then found at δ 2·17.

15 ml diethyl ether and treated with an ether soln of diazoethane at 0° prepared from 2·0 gm N - ethyl - N' - nitro - N - nitrosoguanidine. Additional quantities of diazoethane were added over a period of 2 days until the TLC examination [silica gel, n-BuOH–n-PrOH–NH_4OH–H_2O (2:2:0·1:1·9)] showed one spot, R_f 0·5. The solvent was evaporated and the residue crystallized several times from acetone to give colorless needles of **22**, m.p. 157–159°; (Found: C, 67·48; H, 8·04; N, 8·13. $C_{29}H_{41}N_3O_5$ requires: C, 68·08; H, 8·08; N, 8·21. $C_{29}H_{41}N_3O_5 \cdot 1/2\ Me_2CO$ requires: C, 67·75; H, 8·20; N, 7·77%); IR (Nujol) 3310 (NH) and 1640 cm^{-1} (C=O); UV (MeOH) 280 nm (log ϵ 3·75) not altered by alkali; NMR ($CDCl_3$) δ 1·37 (3H, t, $J = 7$, CH_3CH_2), 2·09 (3H, s, NMe), 3·78 (3H, s, OMe) and 4·11 (2H, q, $J = 7$, CH_3CH_2).

Exhaustive methylation of O - *ethyl* - N - *methyltetrahydrocodonocarpine* (**22**). A 100 mg sample of **22** was mixed with 4 ml benzene and 2 ml MeI at ambient temp. After 45 min the white solid (methiodide) that precipitated was collected by filtration, washed with benzene, dried under N_2 and dissolved in 2 ml water. The soln was passed through a column (1 × 20 cm) of IRA-400 (OH^-) and the column washed with 60 ml water. The effluent was evaporated to dryness and the residue was heated under high vacuum (10^{-8} torr.) for 2·5 h at 110° (oil bath). The product* [R_f 0·48 on silica gel with BuOH–PrOH–NH_4OH–H_2O (2:2:0·1:1·9)] was dissolved in 3·5 ml benzene, 3·5 ml acetone and 1·5 ml MeI and after 2 h the solvent was evaporated and the residue dissolved in 2 ml water and passed through an IRA-400 (OH^-) column. The effluent residue was heated under high vacuum at 110° for 1·5 h. The mixture was chromatographed on a 20 g Merck silica gel column (1·5 × 26 cm) with elution by chloroform and $CHCl_3$–MeOH mixtures of increasing polarity. The effluent residue (TLC R_f 0·75), **23**, was amorphous and weighed 37 mg; NMR ($CDCl_3$) δ 1·32 (3H, t, $J = 7$, CH_3CH_2), 3·93 (3H, s, OMe), 4·9–6·1 (3H, complex ABC pattern, $CH{=}CH_2$), 5·9 (1H, br m, NH) lost in D_2O and 6·7 – 7·0 (6H, two br d, Ar-H); MS *m/e* 480·2615 (17%, M^+, $C_{28}H_{36}N_2O_5$ requires 480·2624), 396 (7, M—C_4H_6NO), 112 (27, $C_6H_{10}NO$), 98 (25, C_5H_8NO) and 70 (69, C_3H_5N).

Hydrogenation of **23**. A 25 mg sample of **23** from the exhaustive methylation procedure was hydrogenated at atmospheric pressure and ambient temp with Raney Ni W-2 (~25 mg) in 10 ml of MeOH. Removal of solvent by evaporation at reduced pressure left a residue (25 mg) that was chromatographed on a column of 10 g of silica gel G and elution with 2% MeOH in chloroform. Compound **25** was obtained in 23 mg yield as an amorphous solid with R_f 0·2 on TLC with silica gel G and 2% MeOH in $CHCl_3$; NMR ($CDCl_3$) δ 0·85 (3H, t, $J = 7$, $CH_3CH_2CH_2$), 1·30 (3H, t, $J = 7$, CH_3CH_2O), 3·84 (3H, s, OMe), 4·07 (2H, q, CH_3CH_2O) and 5·5 (1H, br m, NH) lost in D_2O; IR ($CHCl_3$) 3460 (NH) and 1660, 1630 cm^{-1} (amide C=O); MS *m/e* 482·2805 (100%, M^+, $C_{28}H_{38}N_2O_5$ requires 482·2781), 396·2206 (8, M—$CON(CH_2)_2CH_3$, $C_{24}H_{30}NO_4$ requires 396·2175), 384·2171 (3, M—$CON(CH_2)_3CH_2$, $C_{23}H_{30}NO_4$ requires 384·2175), 251·1540 (2, fragment **30a**, $C_{14}H_{21}NO_3$ requires 251·1521), 250·1443 (0·5, fragment **30b**, $C_{14}H_{20}NO_3$ requires 250·1443), 249·1363 (2, fragment **31a**, $C_{14}H_{19}NO_3$ requires 249·1365), 248·1306 (1, fragment **31b**, $C_{14}H_{18}NO_3$ requires 248·1287), 112·0761 (14, $CH_2CON(CH_2)_3CH_2$ requires 112·0762), 98·0606 (11, $CON(CH_2)_3CH_2$ requires 98·0606), 86·0619 (1, $CON(CH_2)_2CH_3$ requires 86·0606) and 70·0653 (24, $N(CH_2)_3CH_2$ requires 70·0657).

N - (4 - *Dimethylaminobutyl*) 3 - (p - *methoxyphenyl*) *propionamide* (**26**). 3 - (*p* - Methoxyphenyl)-propionic acid (1·05 g) was refluxed 1 h in 25 ml benzene and 1·5 ml of $SOCl_2$. The mixture was evaporated under reduced pressure and the residue was dissolved in 15 ml benzene and added while stirring to a soln of 0·78 g 4-dimethylaminobutylamine and 0·66 g triethylamine in 25 ml benzene at ambient temp. A ppt formed. After 20 min, the benzene layer was extracted 4 times with 20 ml 1N HCl and the combined acid extract treated with 10% KOH aq and extracted with chloroform. The dried chloroform extract on evaporation gave 1·57 g of a crystalline residue that was recrystallized from diethyl ether–hexane to give 1·3 g of **26**, m.p. 47–48°, (Found: C, 69·02; H, 9·40; N, 9·95. $C_{16}H_{26}N_2O_2$ requires: C, 69·03; H, 9·41; N, 10·06%).

Methiodide of compound **26**. The amide **26** (1·3 g) was dissolved in 20 ml acetone and treated with 2·5 ml MeI. After 0·5 h the mixture was evaporated, and the crystalline residue was recrystallized from diethyl ether–MeOH to give white cubes (1·8 g) of the methiodide salt, m.p. 148–149°, (Found: C, 48·60; H, 7·02; N, 6·71. $C_{17}H_{29}N_2O_2I$ requires: C, 48·57; H, 6·98; N, 6·67%).

Hofmann degradation of methohydroxide **27**. The methiodide of **26** (1·8 g) was dissolved in 5 ml water and passed through a column (1·5 × 15 cm) of IRA-400 (OH^-). The 50 ml effluent was evaporated to dryness at reduced pressure and the residue (compd **27**) heated under vacuum (water aspirator) at 115–120° in an oil bath. Vigorous gas evolution was observed for 5 min and after 10 min in total, the cooled mixture was extracted with chloroform. The chloroform extract yielded 1·19 g of an oil that was chromatographed on a column (2·5 × 20 cm) of 50 g of silica gel G using 5% MeOH in EtOAc as eluant. After 80 ml effluent, a 17 mg fraction was eluted [R_f 0·50 on TLC, silica gel G, MeOH–EtOAc (1:20)] that crystallized from diethyl ether–hexane to give colorless needles of **28** (9 mg) m.p. 78–79°; IR ($CHCl_3$) 3460 (NH free), 3340 (NH bonded), 3080 (olefinic CH str), 1670 (C=O), 1620 (C=O) and 925 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3·79 (3H, s, OMe), 5·5 (1H, br m, NH), 4·8–6·0 (3H, ABC multiplet, $CH{=}CH_2$); MS *m/e* 233·1422 (33%, M^+, $C_{14}H_{19}NO_2$ requires 233·1416), 192·1023 (4, M—$CH_2CH{=}CH_2$, $C_{11}H_{14}NO_2$ requires 192·1024), 163·0766 (10, M—$NH(CH_2)_2CH{=}CH_2$, $C_{10}H_{11}O_2$ requires 163·0759), 135·0804 (7, M—$CONH(CH_2)_2CH{=}CH_2$, $C_9H_{11}O$ requires 135·0810) and 121·0650 (100, $CH_3OC_6H_4CH_2$ requires 121·0653).

Continuing elution of the adsorption column gave **29** (0·65 g), as a low melting solid, m.p. 42°, and showing R_f 0·35 in the TLC system; IR ($CHCl_3$) no N—H absorption, 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3·78 (3H, s, OMe), no peaks between 4·0–6·6; MS *m/e* 233·1433 (100%, M^+, $C_{14}H_{19}NO_2$ requires 233·1416), 163·0768 (2, M—$N(CH_2)_3CH_2$, $C_{10}H_{11}O_2$ requires 163·0759), 135·0798 (18, M—$CON(CH_2)_3CH_2$, $C_9H_{11}O$ requires 135·0810), 121·0664 (81, $MeOC_6H_4CH_2$ requires 121·0653), 112·0768 (50, $CH_2CON(CH_2)_3CH_2$ requires 112·0762), 98·0612 (13,

*NMR examination of the total reaction mixture showed very little absorption in the olefinic region (δ 4·5–6·5) where the ABC pattern for the vinyl group is found, thus the product is almost exclusively the N - pyrrolidinyl and N - (3 - dimethylaminopropyl) diamide. After the second Hofmann step, a small amount of material, that was isolated chromatographically before the major product **23**, had physical properties (NMR and MS) consistent with compound **24** but quantities were insufficient for complete characterization.

$\overline{CON(CH_2)_3CH_2}$ requires 98·0606) and 70·0655 (21, $\overline{N(CH_2)_3CH_2}$ requires 70·0657).

Heating of the methochloride salt of **26**, prepared by passing an aqueous soln of the methiodide through IRA-400 (Cl^-), at 115° for 0·5 h under vacuum resulted in recovery of starting material.

N - [3 - (*p* - methoxyphenyl)propionyl] - pyrrolidine (**29**). 3 - (*p* - Methoxyphenyl)propionic acid (5·0 g) was refluxed in 50 ml benzene containing 5 ml $SOCl_2$ for 1 h. The oil remaining after evaporation of the mixture at reduced pressure was dissolved in 50 ml benzene and added while stirring to a mixture of 50 ml benzene and 10 ml pyrrolidine at ambient temp. After 15 min the solution was extracted successively with water, 1N HCl and 1N $NaHCO_3$, and then dried (Na_2SO_4) and evaporated to dryness to yield an oil weighing 6·5 g. On cooling in the refrigerator crystals formed m.p. 43–45° which were identical (TLC, IR, NMR and m.p.) with the major product from the Hofmann degradation of **27**.

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