192. A Short, Simple Synthesis of (±)-Monomorine

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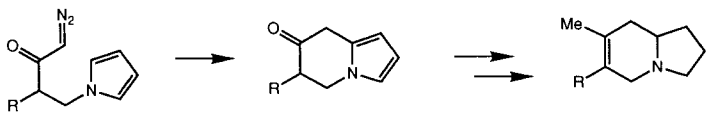
(2.X.89)

Racemic monomorine (**12**) is prepared in six steps in 26% overall yield from 2-butyl-1*H*-pyrrole and ethyl (*E*)-but-2-enoate by exploiting the rhodium(II)-acetate-catalyzed decomposition of (4*RS*)-4-(2′-butyl-1′*H*-pyrrol-1′-yl)-1-diazopentan-2-one (**7**).

Introduction. – Indolizidine alkaloids are found in several plant species and offer attractive targets for synthesis. Consequently, methods of great diversity have been devised for preparing them. We recently reported that the decomposition of 1-diazo-4-(1*H*-pyrrol-1-yl)butan-2-one derivatives **1** using rhodium(II) acetate as catalyst provides an economical means for constructing the dihydroindolizine ring **2** *(Scheme 1)*. The synthesis of ipalbidine (**3**) has demonstrated the high propensity for intramolecular insertion at the C(2) position of the pyrrole nucleus [1]. We now show that this methodology permits the easy assembly of disubstituted octahydroindolizine alkaloids. As an illustration, we have selected racemic monomorine (**12**) which is a trail pheromone of the pharaoh ant *(Monomorium pharaonis* L.). Because of its unusual biological properties, many syntheses of racemic **12** [2] [3] and of its pure enantiomers [4] have been undertaken. However, several of them entail multi-step sequences lacking in regioselectivity. In contrast, the synthesis described here has the advantage of conciseness and simplicity.



Results and Discussion. – The starting materials are commercial ethyl (*E*)-but-2-enoate (**4**) and the readily available 2-butyl-1*H*-pyrrole (**5**) [5]. *Michael* reaction gave the pyrrolylbutanoic acid **6** in 69% yield, but was incomplete as *ca.* 20% of **5** was recovered *(Scheme 2)*. The key intermediate, the diazoketone **7**, was prepared from its mixed isobutyl carbonic anhydride by reaction with diazomethane [1]. Unreacted butanoic acid **6** was removed by flash chromatography, thereby affording pure **7** in 86% yield. Decomposition of **7** was effected in CH_2Cl_2 at 25° in the presence of rhodium(II) acetate. A single product, the 6,8-dihydroindolizin-7(5*H*)-one **9**, was obtained in 88% yield after filtration through *Florisil*. Clearly, the transient α-keto carbenoid intermediate arising from **7**, being strongly electrophilic, has inserted preferentially at the least-substituted C(5),

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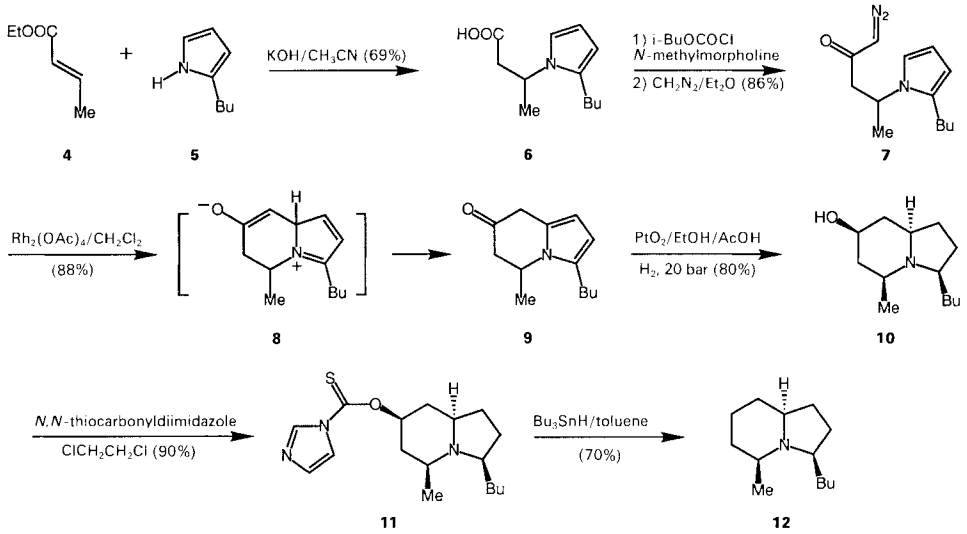

position of the attached pyrrole ring. The resulting dipolar species **8**, by proton transfer, accounts for the observed product **9**. Attack at the alternative C(2) position is probably prevented by the Bu substituent which would deny cancellation of the charges in the dipolar intermediate analogous to **8**.

The dihydroindolizinone **9** proved to be unstable. Prompt catalytic reduction with PtO_2 under H_2 pressure gave the octahydroindolizinol **10** in which the Bu, OH, and Me substituents are all disposed *cis* to each other as a consequence of the unidirectional transfer of H-atoms from the surface of the catalyst. The relative configurations at C(3), C(5), and C(7) were deduced from the NMR spectrum [1]. The yield of **10** was 80%, after chromatographic separation from the trace of an isomeric alcohol.

Deoxygenation of **10** to give monomorine (**12**) proved not to be a trivial affair. As the preferred conformation of **10** places the OH group in the equatorial position, all conventional methods for reduction were unsuccessful. Fortunately, this difficulty was overcome by recourse to *Barton*'s procedure [6]. The alcohol **10** was initially converted to its imidazolecarbothioate **11** in 90% yield. Thereafter, reduction by tributylstannane in refluxing toluene afforded **12** in 70% isolated yield, although some 17% of alcohol **10** was recovered. The synthetic monomorine so obtained had identical spectral data (360-MHz ^{1}H- and ^{13}C-NMR and mass spectra) with those reported for racemic monomorine [3].

Conclusion. – The present synthesis delivers racemic monomorine (**12**) in just six steps in an overall yield of 26% from commercially available starting materials by means of a simple, non-tedious procedure. The key features are the regiospecific one-step assembly of the dihydroindolizine ring from a suitably substituted pyrrole skeleton and its subsequent reduction to the all-*cis*-substituted penultimate octahydroindolizine intermediate. By an appropriate choice of starting materials derived from chiral α-amino acids, a range of related alkaloids should be accessible with equal ease in an enantiomerically pure state. Such experiments are under way, and the results will be reported in due course.

Experimental Part

General. All solvents were distilled prior to use. Et_2O was dried over sodio-benzophenone and freshly distilled before use. *N*-Methylmorpholine was distilled and stored over CaH_2. Diazomethane was prepared from *N*-methyl-*N*-nitroso-4-toluenesulfonamide, using a minimum amount of H_2O and EtOH as solvent, and dried over KOH pellets at –20° before use. TLC: silica gel *60* F_{254} *Merck* or aluminium oxide F_{254} *Fluka*. Column chromatography [6]: silica gel *60* (230–400 mesh ASTM *Merck*), *Florisil* (100–200 mesh, *Fluka)*, and aluminium oxide (neutral, 70–230 mesh ASTM, *Merck*). ^{1}H-NMR spectra: $CDCl_3$ soln. unless stated otherwise; chemical shifts in ppm relative to internal TMS (= 0 ppm), coupling constants *J* in Hz; *Varian T-60, XL-200*, or *Bruker WH-360* spectrometers. ^{13}C-NMR spectra: $CDCl_3$ soln., *XL-200* spectrometer. MS: *Varian SM-1-B* and *Finnigan GC/MS 4023* using INCOS data system. IR spectra: CCl_4 soln.; in cm^{-1}, *Perkin-Elmer-681* spectrometer. Elemental analyses were performed by Dr. *H. Eder*, Service de Microchimie, Institut de Chimie Pharmaceutique, Université de Genève.

*(3*RS*)-3-(2'-Butyl-1'*H*-pyrrol-1'-yl)butanoic Acid* (**6**). A soln. of 2-butyl-1*H*-pyrrole [5] (**5**; 16.14 g, 131 mmol) in CH_3CN (80 ml) was added dropwise to a suspension of finely powdered KOH (35 g, 625 mmol) in CH_3CN (400 ml). After 15 min, a soln. of ethyl (*E*)-but-2-enoate (**4**; 14.93 g, 131 mmol) in CH_3CN (130 ml) was added dropwise over 90 min at 0°. The mixture was stirred for 1 h at 25° and the orange-brown soln. poured into 1 l of ice/H_2O. The mixture was washed first with CH_2Cl_2 (3 × 300 ml), then the aq. layer was acidified with conc. aq. HCl soln. and extracted again with CH_2Cl_2 (4 × 300 ml). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated. The resulting brown oil was slowly bulb-to-bulb distilled at 80°/0.01 Torr to remove polymeric ethyl butenoate. Subsequent distillation at 110°/0.01 Torr gave **6** (18.8 g, 69%). IR: 3100*w*, 3000 (br.), 2960*s*, 2935*s*, 2870*m*, 1710*vs* (br.), 1482*m*, 1450*w* (br.), 1426*m*, 1415*w* (br.), 1378*w*, 1286*s*, 1230*w*, 1206*w*, 1120*w*, 1098*w*, 1028*w*, 1009*w*, 930*w* (br.), 887*w*, 770*w*, 696*s*, 618*w*. ^{1}H-NMR (360 MHz): 0.96 (*t*, *J* = 7.2, 3 H); 1.44 (*sext.*, *J* = 7.2, 2 H); 1.49 (*d*, *J* = 7, 3 H); 1.65 (*quint. J* = 7.2, 2 H); 2.61 (*t*, *J* = 7.2, 2 H); 2.77 (*ABd*, *J* = 16, 8, 1 H); 2.88 (*ABd*, *J* = 16, 6.5, 1 H); 4.68 (br. *sext.*, 1 H); 5.94 (*m*, 1 H); 6.22 (*t*, *J* = 3, 1 H); 6.72 (*dd*, *J* = 3, 2, 1 H); 10.3 (br. *s*, 1 H). MS: 209 (71, $M^{+\cdot}$), 180 (8), 167 (45), 166 (85), 150 (10), 136 (28), 120 (16), 106 (23), 94 (24), 80 (100), 53 (59). Anal. calc. for $C_{12}H_{19}NO_2$: C 68.87, H 9.15, N 6.69; found: C 68.67, H 9.02, N 6.48.

*(4*RS*)-4-(2'-Butyl-1'*H*-pyrrol-1'-yl)-1-diazopentan-2-one* (**7**). A mixture of **6** (3.14 g, 15 mmol), *N*-methylmorpholine (2.1 ml, 19 mmol), and freshly distilled isobutyl chloroformate (2.62 ml, 20 mmol) in Et_2O (200 ml) were allowed to react [1]. The resulting soln., after filtration through *Celite*, was treated at 0° with a dry (KOH) Et_2O soln. of diazomethane (prepared from 150 mmol of *N*-methyl-*N*-nitroso-4-toluenesulfonamide). A vigorous evolution of N_2 occurred, and the mixture was allowed to warm to 25° overnight. Removal of the solvent afforded an orange oil which was purified by flash chromatography [7] (SiO_2, AcOEt/hexane 1:4): **7** (3 g, 86%). IR: 3095*m* (br.), 2960*s*, 2935*s*, 2865*m*, 2103*vs*, 1640*vs* (br.), 1482*w*, 1452*w*, 1428*w*, 1370*vs* (br.), 1332*s*, 1286*s*, 1230*w*, 1145*m* (br.), 1128*m*, 1100*w*, 1016*w*, 888*w*, 699*m*. ^{1}H-NMR (360 MHz): 0.95 (*t*, *J* = 7.2, 3 H); 1.44 (*sext.*, *J* = 7.2, 2 H); 1.47 (*d*, *J* = 7, 3 H); 1.61 (*quint. J* = 7.2, 2 H); 2.57 (*t*, *J* = 7.2, 2 H); 2.58–2.68 (*m* 1 H); 2.70–2.80 (*m*, 1 H); 4.60–4.70 (*m*, 1 H); 4.98 (*s*, 1 H); 5.86 (*m*, 1 H); 6.16 (*t*, *J* = 3, 1 H); 6.66 (*dd*, *J* = 3, 2, 1 H). MS: 206 (5), 205 (33), 163 (18), 162 (100), 134 (14), 120 (10), 106 (11), 55 (7). Anal. calc. for $C_{13}H_{19}N_3O$: C 66.92, H 8.21, N 18.01; found: C 66.96, H 8.30, N 18.01.

*(5*RS*)-3-Butyl-6,8-dihydro-5-methylindolizin-7(5*H*)-one* (**9**). To a soln. of (244 mg, 1.05 mmol) in CH_2Cl_2 (40 ml), rhodium(II) acetate (2 mg) was added. A rapid evolution of N_2 was observed. After 30 min, the mixture was concentrated to 2 ml and filtered through *Florisil* with CH_2Cl_2: **9** (188 mg, 88%). IR: 3440*vw*, 3106*w*, 2982*vs*, 2932*vs*, 2876*s*, 2862*s*, 1730*vs*, 1638*m*, 1595*m*, 1506*m*, 1454*m*, 1434*s*, 1406*s*, 1380*s*, 1330*s*, 1301*s*, 1276*w*, 1265*m*, 1232*m*, 1210*w*, 1188*m* (br.), 1162*w*, 1102*w*, 1092*w*, 1078*w*, 1062*w*, 1030*w*, 1012*w*, 928*vw*, 908*vw*, 852*vw*. ^{1}H-NMR (360 MHz): 0.99 (*t*, *J* = 7.2, 3 H); 1.37 (*d*, *J* = 6.5, 3 H); 1.47 (*sext.*, *J* = 7.2, 2 H); 1.69 (*quint.*, *J* = 7.2, 2 H); 2.56–2.66 (*m*, 3 H); 2.93 (*ABd*, *J* = 16, 6, 1 H); 3.64 (*AB*, *J* = 22, 1 H); 3.76 (*AB*, *J* = 22, 1 H); 4.63 (*quint. d*, *J* = 6.5, 2, 1 H); 5.87–5.93 (*m*, 2 H). MS: 205 (43, $M^{+\cdot}$), 163 (15), 162 (100), 134 (39), 120 (36), 106 (8), 95 (8), 94 (12), 93 (14), 65 (10).

*(3*RS,5SR,7RS,9RS*)-3-Butyloctahydro-5-methylindolizin-7-ol* (**10**). A soln. of **9** (127.5 mg, 0.62 mmol) in EtOH (100 ml) containing glacial AcOH (1 ml) was hydrogenated over PtO_2 (120 mg) at an initial pressure of 20 bar for 16 h. The solvents were evaporated, and the residue was dissolved in CH_2Cl_2, washed with a sat. Na_2CO_3 soln. and brine, and dried ($MgSO_4$). Chromatography (Al_2O_3, Et_2O) gave **10** (105 mg, 80%). IR: 3606*m*, 3360*m* (br.), 2960*vs*, 2935*vs*, 2875*s*, 2862*s*, 1455*m* (br.), 1380*m*, 1342*w*, 1312*m*, 1208*m*, 1135*m*, 1109*w*, 1088*w*, 1022*s*, 962*w*, 951*w*, 924*w*, 902*w*. ^{1}H-NMR (360 MHz): 0.84 (*t*, *J* = 7, 3 H); 1.11 (*d*, *J* = 6.5, 3 H); 1.14–1.34 (*m*, 7 H); 1.38–1.52 (*m*, 2 H); 1.56–1.67 (*m*, 2 H); 1.78–1.94 (*m*, 2 H); 2.05 (*ddt*, *J* = 11.5, 5, 2, 1 H); 2.14 (*tdd*, *J* = 11, 5, 2, 1 H); 2.28

(*dqd*, J = 8.5, 6.5, 2.5, 1 H); 2.46 (*tt*, J = 9.5, 2.5, 14); 3.64 (*tt*, J = 11, 5, 1 H). MS: 211 (0.8, M^+), 210 (1), 196 (2), 155 (11), 154 (100), 68 (8), 55 (5).

*(3*RS,*5*SR,*9*SR*)-3-Butyloctahydro-5-methylindolizine* (**12**). To a soln. of **10** (90 mg, 0.427 mmol) in $ClCH_2CH_2Cl$ (10 ml) was added *N,N'*-(thiocarbonyl)diimidazole [6] (160 mg, 0.9 mmol). The mixture was stirred under reflux for 16 h. The solvent was evaporated. Chromatography (SiO_2, AcOEt/Et_2O 4:6) of the residue gave *O-[(3*RS,*5*SR,*7*RS,*9*RS*)-3-butyloctahydro-5-methylindolizin-7-yl] 1*H*-imidazole-1*H*-carbothioate* (**11**; 123 mg, 90%). ^{1}H-NMR (60 MHz): 0.6–2.7 (*m*, 23 H); 5.1–5.7 (*m*, 1 H); 6.9 (br. *s*, 1 H); 7.5 (br. *s*, 1 H); 8.2 (br. *s*, 1 H).

The soln. of **11** (90 mg, 0.28 mmol) in dried (Na) toluene (5 ml) was added dropwise to a soln. of Bu_3SnH (0.05 ml) in toluene (5 ml) which was boiling under reflux. After 2 h, more Bu_3SnH (0.05 ml) was added. The resulting mixture was stirred at reflux for 16 h, washed, dried ($MgSO_4$), and evaporated. Chromatography of the oil (Al_2O_3, Et_2O/hexane 1:9) gave **12** (38.4 mg, 70%). ^{1}H-NMR (360 MHz): 0.82 (*t*, J = 7, 3 H); 1.07 (*d*, J = 6.5, 3 H); 1.10–1.84 (*m*, 16 H); 1.96–2.06 (*m*, 1 H); 2.12–2.22 (*m*, 1 H); 2.38–2.48 (*m*, 1 H). ^{13}C-NMR (200 MHz): 14.12, 22.80, 22.84, 24.83, 29.36, 29.71, 30.28, 30.84, 35.75, 39.66, 60.19, 62.85, 67.09. MS: 195 (0.6, M^+), 194 (1), 139 (9), 138 (100).

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