216. Intramolecular Carbenoid Reactions of Pyrrole Derivatives. A Total Synthesis of (±)-Ipalbidine

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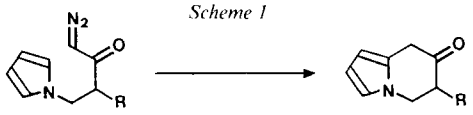
(I.X.86)

A new method for alkaloid synthesis is described. The rhodium(II)-acetate-catalyzed decomposition of 3-(4-acetoxyphenyl)-1-diazo-4-(pyrrol-1-yl)-2-butanone (**5d**) gave 6-(4-acetoxyphenyl)-5,6-dihydro-7(8*H*)-indolizinone (**6d**) in 82% yield *via* an intramolecular carbenoid reaction. The latter compound was converted in four steps in 13% overall yield to (±)-ipalbidine (**1b**).

Introduction. – Alkaloids containing the indolizidine ring system are found in several plant species and have attracted much attention as synthetic targets [1]. Various methods have been devised for making the indolizidine skeleton. Most are 1,2-annelations of pyrrolidine or piperidine rings which exploit iminium ions [2], acyliminium ions [3], and enamines [4], or entail aldol [5], *Claisen* [6], and *Dieckmann* [7] condensations. Other methods involve the intramolecular *N*-alkylation of pyrrolidine [8], piperidine [8a] [9], pyridones and dihydropyridones [10], and the cycloadditions of *N*-acylpiperidines [11] and α-aminoacyl radicals [12]. The simultaneous construction of both rings by the intramolecular bis-alkylation of an amine [13] and imino *Diels-Alder* reactions [14] has also been reported.

Although pyrrole has been widely used as the starting point for building pyrrolizidine rings [15], its use for the synthesis of indolizidines has been restricted to the formation of the pyrrolidine part which was subsequently annelated by one of the above-mentioned methods [6] [8a]. Similarly, carbenes have been used for making intermediates [6] [16], but rarely for the critical step [15a] [17]. We recently demonstrated that the decomposition of

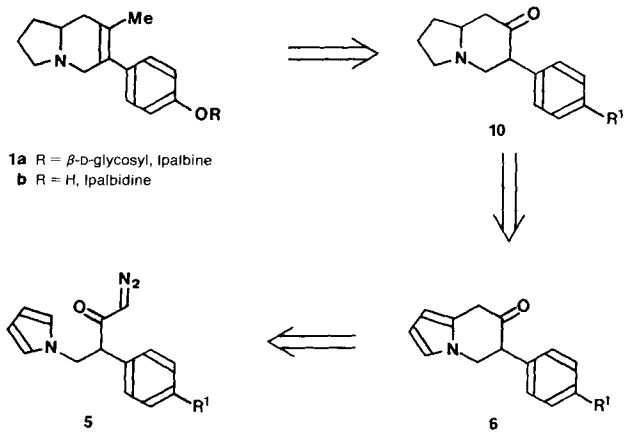
Scheme 1



a (pyrrol-1-yl) diazo ketone afforded dihydropyrrolizines and indolizines in high yields [18] *(Scheme 1)*. We now describe how this cyclization can be applied to the total synthesis of (±)-ipalbidine (**1b**), the aglycone of ipalbine (**1a**) isolated from *Ipomea alba* L. [19].

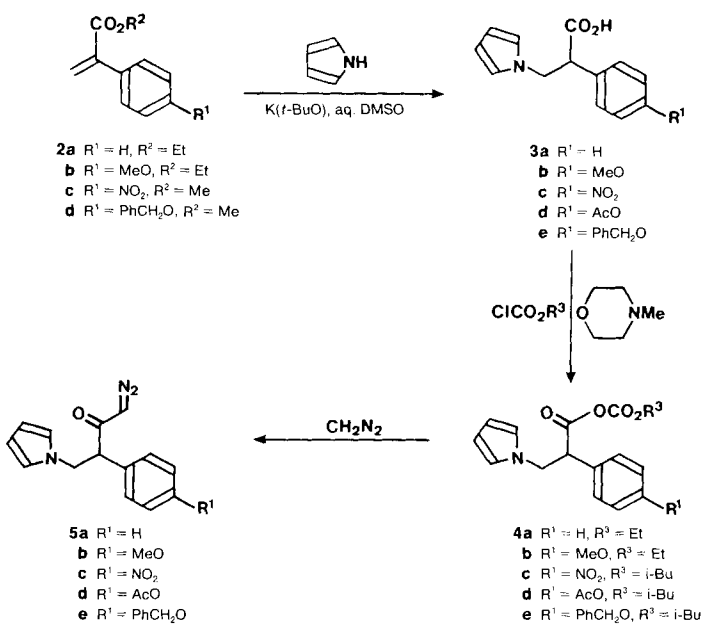
Results and Discussion. – Our strategy is based on the retrosynthesis in which the bicyclic ketone **10** constitutes the key relay *(Scheme 2)*. The 4-methoxy derivative **10**

Scheme 2



(R^1 = MeO) has been previously prepared [2b] [4b] [5c] [7] and converted [2b] [7] into ipalbidine. However, **10** and its derivatives should be equally accessible by hydrogenation of the indolizinone **6**, which itself could be constructed by selective intramolecular C-atom insertion at the α-position of the pyrrole precursor **5**. Before embarking on the synthesis, we wanted to ascertain the influence of the aryl group on the crucial act of cyclization (**5**→**6**). In the diazo ketone **5** the nascent carbene can compete in principle for the pyrrole and benzene rings. In the first instance, cyclization would give the required

Scheme 3



dihydroindolizinone **6**, while attack by the benzene ring would lead to the unwanted formation of an indanone. Since the transition-metal-catalyzed decomposition of diazo ketones undoubtedly involves a metal-carbenoid intermediate, the ring closure of **5** is best considered as nucleophilic attack by the appropriate ring on an electrophilic carbenoid center. Therefore, the chances are inherently good for cyclization in the desired sense because of the pronounced nucleophilic character of pyrrole. Nevertheless, in order to minimize any possible involvement of the benzene ring, its C(4)-substituent must be carefully chosen. The ideal substituent should render the benzene ring less nucleophilic and at the same time be convertible to the relay. We, therefore, prepared five aryl-diazobutanones possessing different C(4)-substituents (see **5a–e**, *Scheme 3*).

Preparation of Diazobutanones **5**. The starting materials, the arylpropenoates **2**, were readily prepared [4b] [20] from their corresponding arylacetic acids in high yields.

Few examples of the *Michael* addition of pyrrole have been reported [15c] [21]. Moreover, employment of the standard (benzyltriethylammonium chloride/CH_2Cl_2/NaOH) or the solid-liquid (NaOH/CH_3CN) [21b] phase-transfer conditions proved to be ineffective for the addition of pyrrole to the propenoates **2**. As the *N*-alkylation of pyrrole is favored in polar solvents when weakly coordinating metal cations are present [22], we decided to use 1-potassiopyrrole in dimethylsulfoxide (DMSO) solution. Unfortunately, *Michael* addition to **2** was inefficient owing to polymerization of the propenoate. Changing the solvent to tetrahydrofuran (THF) [15c] or using K(*t*-BuO) was also without much effect. Moreover, using K(*t*-BuO) in catalytic quantities or adding equimolar Bu_4NI [22] was not satisfactory as *C*-alkylation at the pyrrole α-position occurred as well. We concluded that the lack of success was due to the p*K* values of K(*t*-BuO), pyrrole, and the *Michael* adduct which being similar meant that addition was reversible and, therefore, allowed the propenoate to polymerize. These difficulties were overcome by adding a small amount of H_2O (5–10%) to a solution of K(*t*-BuO) in DMSO. Under these conditions, not only was the anion efficiently quenched, but the ester group of **2** was saponified as well, thereby giving the propanoic acids **3** in high yields[1]). As an exception, the 4-nitrophenyl analogue **2** led to the methyl ester which was hydrolysed subsequently to the acid **3c**. Presumably, the nitro group stabilizes the intermediate anion preventing hydrolysis of the ester group.

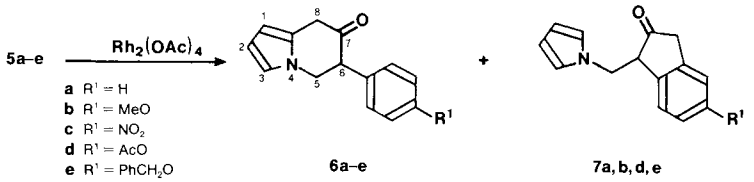
Since the acetoxy function would not be stable to the conditions of the *Michael* reaction **2**→**3**, we prepared the 4-acetoxy derivative **3d** by debenzylation of **3e** (H_2, Pd/C) followed by acetylation (64% overall yield).

The conventional procedure for the conversion of acids into α-diazoketones *via* their acyl chlorides could not be applied to **3**→**5** owing to the nucleophilicity of the pyrrole ring. However, conversion of the acids **3** into their mixed carbonic anhydrides **4** [18] [23] gave, with excess diazomethane, the desired diazobutanones **5** in 44–76% yield *(Scheme 3)*.

Decomposition of Diazobutanones **5**. Although Cu powder in refluxing benzene is a good catalyst for the decomposition of diazobutanones *(Scheme 1)* [18a], rhodium(II) acetate is better [24]. Thus, 1–2 mol-% of $Rh(OAc)_2$ in CH_2Cl_2 at room temperature dramatically increased the rate of decomposition. The diazobutanones **5** reacted completely in 30 min, and the products **6/7** so obtained were easily purified by simple

[1]) In a control experiment it was shown that pyrrole does not add to the propenoic acids **2** (R^2 = H) under these reaction conditions.

Scheme 4



filtration through a column of *Florisil (Scheme 4)*. The results are summarized in the *Table*. The yields were uniformly high (75–89%), and as expected the pyrrole nucleus proved to be more nucleophilic than the benzene ring even when the latter carried an electron-donating group. When the benzene ring of the diazobutanone **5** carried an electron-withdrawing substituent, the yield of the unwanted indanone **7** fell sharply. Thus, the 4-nitrophenyl derivative **5c** gave solely the dihydroindolizinone **6c**, while its 4-acetoxy analogue **5d** gave less than 3% of the indanone **7d**.

Table. *Product Composition Obtained from the Rhodium(II)-Acetate Catalyzed Decomposition of the Diazobutanones* **5a–e**

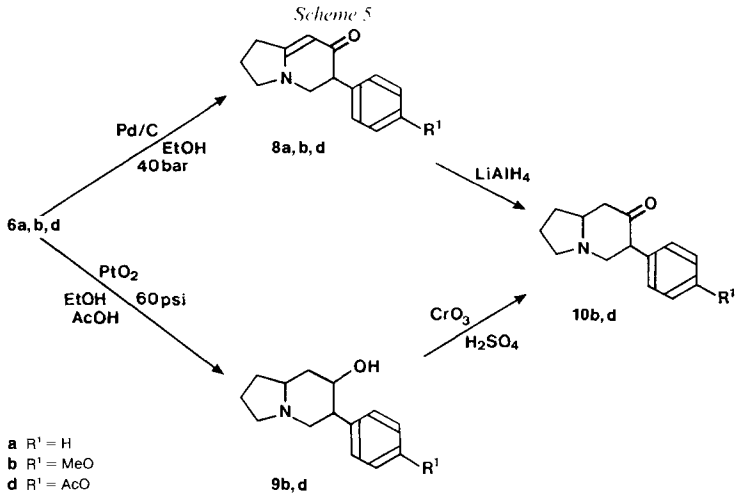
Substrate	Ratio **6**/**7**[a])	Yield of Products **6** + **7**[b]) [%]
5a	6:1	75 (51)
5b	7:2	89
5c	> 100:1[c])	76 (76)[c])
5d	36:1	89 (82)
5e	4:1	85

[a]) Determined by ^{1}H-NMR (360 MHz) of the purified reaction mixture in $CDCl_3$ solution.
[b]) Yield of isolated dihydroindolizinone **6** in parenthesis.
[c]) No **7c** was detected.

A Formal and a Total Synthesis of (±)-Ipalbidine (**1b**). Reduction of 5,6-dihydro-6-(4-methoxyphenyl)-7(8*H*)-indolizinone (**6b**) to the hexahydroindolizinone **10b** would constitute a formal synthesis of ipalbidine. Unfortunately, little is known in general about the relative efficiencies of hydrogenation catalysts for the reduction of bicyclic pyrrole systems. Certain pyrrolizidines have been successfully hydrogenated over Pd/C [11] [25], PtO_2 [8a] [26], and Rh/C or Rh/activated alumina [15f] [27]. We, therefore, hydrogenated the inseparable 7:2 mixture **6b**/**7b** over PtO_2 in abs. EtOH containing a slight excess of AcOH. A pair of epimeric alcohols **9b** was obtained in 44% yield based on **6b** *(Scheme 5)*. Alternatively, hydrogenation over Pd/C gave the known [4b] unstable vinylogous amide **8b** in 40% yield. Selective reduction of **8b** with $LiAlH_4$ afforded the target ketone **10b** in 61% yield (overall yield from **5b** 22%; *Scheme 5*). Since the hexahydroindolizinone **10b** has already been converted to (±)-ipalbidine [2a] [7] in three steps, our reaction sequence leading to **10b** constitutes a formal synthesis of (±)-ipalbidine (**1b**).

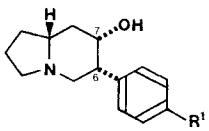
Having completed the formal synthesis of ipalbidine, we decided to improve our procedure and particularly the yield of the cyclization **5**→**6** *(Scheme 4)*. $Rh(OAc)_2$-catalyzed decomposition of 3-(4-acetoxyphenyl)-1-diazo-4-(pyrrol-1-yl)-2-butanone (**5d**)

Scheme 5

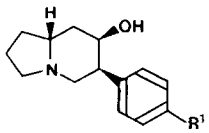


gave, after recrystallisation of the crude product, pure 6-(4-acetoxyphenyl)-5,6-dihydro-7(8*H*)-indolizinone **6d** in 82% yield.

Now, a different route to (±)-ipalbidine (**1b**) with a better overall yield was possible starting from the 4-acetoxyphenyl derivative **6d**. Hydrogenation of **6d** over Pd/C at 40 bar gave the vinylogous amide **8d** in low yield, but hydrogenation over PtO_2 gave a mixture of alcohols **9d** in 71% yield *(Scheme 5)*. The major alcohol was shown by ^{1}H-NMR to have the 6α,7α-configuration (see the *Figure*, R^1 = AcO) and the two minor alcohols the 6β,7β- and 6β,7α-configuration[2]). Reduction over Rh/activated alumina gave a mixture of the same alcohols **9d** in 60% yield contaminated with the vinylogous amide **8d** (13%) and the ketone **10d** (7%) *(Scheme 5)*.



9 6α,7α-configuration



9 6β,7β-configuration

Figure[2])

Identification of the isomeric alcohols **9d** was established from the ^{1}H-NMR pattern of H–C(7), which appears at 4.0–4.2 ppm as a narrow *m* (H_α) and at 3.7–3.9 ppm as a *dt* (H_β). The major isomer was identified by the strong deshielding of H–C(2') and H–C(6') of the axially disposed aryl ring by the contiguous N-lone pair. Furthermore the *trans*-fusion was revealed by the strong *Bohlmann* bands [28] in the IR spectrum near 2800 cm^{-1} and the size of the geminal coupling constant ^2J for CH_2(3) and CH_2(5) [29].

Jones oxidation [30] of the isomeric mixture of alcohols **9d** led to a single ketone **10d** in 62% yield (overall yield from **5d** 36%), in which the aryl ring adopted the equatorial position [5c] *(Scheme 5)*. Reaction of **10b** with excess MeLi gave the expected octahydro-7-hydroxy-7-methylindolizine **11** (R = H) in 62% yield accompanied by the hydroxyphenyl

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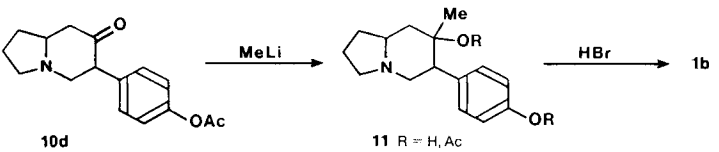
[2]) Compounds **9** are racemic. Consequently, the descriptors α and β designate, in this instance, relative configurations.

Scheme 6



10d **11** R = H, Ac

ketone **10** (R^1 = OH, 17%), while reaction of **10d** with MeLi followed by quenching with Ac_2O yielded the diacetate **11** (R = Ac; *Scheme 6*). Treatment of the latter with hot HBr/H_2O gave (±)-ipalbidine (**1b**) in 30% overall yield from the ketone **10d** (11% from diazobutanone **5d**).

Conclusion. – We have demonstrated that the intramolecular carbene cyclization of a pyrrolyl diazo ketone affords a practical route to (±)-ipalbidine (**1b**) and can, therefore, be added to the other methods for the synthesis of functionalized indolizines which are found in alkaloids. We are presently investigating the scope of this approach for the synthesis of other alkaloids, the results of which will be published elsewhere.

Experimental Part

General. All solvents were distilled prior to use, except DMSO, MeOH, and EtOH which were used as received (*AR* grade, *Merck*). Et_2O and THF were dried over $LiAlH_4$ or sodio/potassio-benzophenone and freshly distilled before use. CH_2Cl_2 was dried and distilled from P_2O_5. Pyrrole and *N*-methylmorpholine were distilled and stored over KOH pellets. Diazomethane was prepared from *N*-methyl-*N*-nitroso-4-toluenesulfonamide, using a minimum amount of H_2O and 2-ethoxyethanol as cosolvent, and was dried over KOH pellets at −20° before use. All other liquids were distilled and stored under N_2. TLC: silica gel *60* F_{254} *Merck*. Column chromatography (CC): silica gel *60* (230–400 mesh ASTM *Merck*) and *Florisil* (100–200 mesh, *Fluka*). M.p.: *Reichert*-hot-stage microscope (uncorrected). UV spectra: *Uvikon 860*. IR spectra: *Perkin Elmer 681* spectrometer. ^{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* spectrometer. MS: *Varian SM-1-B* and *Finnigan GC/MS 4023* using *INCOS* data system. Elemental analyses were performed by Dr. *H. Eder*, Service de Microchimie, Institut de Chimie Pharmaceutique, Université de Genève.

Propenoates 2. – *Ethyl 2-Phenylpropenoate* (**2a**). A soln. of diethyl oxalate (12.0 g, 82 mmol) in abs. EtOH (10 ml) was added dropwise to an ice-cold soln. of NaOEt (from 2.53 g (110 mmol) of Na) in abs. EtOH (60 ml). The mixture was then treated dropwise with a soln. of ethyl phenylacetate (13.5 g, 82 mmol) in abs. EtOH (20 ml). The ice-bath was removed, and the mixture was stirred vigorously for 48 h before evaporation of the solvent. The colorless waxy residue was taken up in H_2O (500 ml) and washed with Et_2O (2 × 100 ml). The aq. layer was cooled in an ice bath and carefully acidified with conc. HCl soln. The turbid soln. was extracted with CH_2Cl_2 (3 × 100 ml) and dried ($MgSO_4$). Evaporation of the solvent gave *diethyl 2-oxo-3-phenylsuccinate* (20.6 g, 95%) as a yellow oil. IR (film): 3440*m* (br.), 3065*w*, 3035*w*, 2985*m*, 2940*w*, 2910*w*, 2875*w*, 1735*vs* (br.), 1645*m*, 1615*m*, 1300*s*, 1270*s*, 1235*s*, 1195*s*, 1060*s*, 1025*s*, 720*m*, 700*m*. ^{1}H-NMR (60 MHz, CCl_4): *ca.* 3:2 mixture of keto and enol forms; 0.8–1.5 (3*t*, 2 $CO_2CH_2CH_3$); 3.8–4.5 (3*q*, 2 $CO_2CH_2CH_3$); 5.3 (*s*, 0.6 H, H–C(2)); 7.2–7.6 (2*m*, C_6H_5); 12.9 (br. *s*, 0.4 H, OH).

The oxosuccinate (20.4 g, 76 mmol) was suspended in H_2O (100 ml) and 30% aq. formaldehyde (12 ml, 120 mmol) added. To the vigorously stirred mixture was added dropwise over 30 min a soln. of K_2CO_3 (7.9 g, 57 mmol) in H_2O (50 ml). The mixture was stirred vigorously for 60 h and the org. layer separated. The aq. layer was extracted with Et_2O (3 × 100 ml) and the combined extract dried over $MgSO_4$ and evaporated. The residue was distilled to give **2a** as a colorless oil (15.15 g, 70%), b.p. 72–73°/0.45 Torr ([20a]: 114–116°/12 Torr). IR (film): 3060*w*, 3030*w*, 2980*m*, 2940*w*, 2905*w*, 1722*vs*, 1613*m*, 1492*m*, 1445*m*, 1368*m*, 1328*m*, 1305*m*, 1302*m*, 1194*s*, 1092*s*, 1028*s*, 772*m*, 700*s*. ^{1}H-NMR (60 MHz, CCl_4): 1.3 (*t*, ^3J = 7, $CO_2CH_2CH_3$); 4.3 (*q*, ^3J = 7, $CO_2CH_2CH_3$); 5.9 (*d*, ^2J = 2, H–C(3)); 6.2 (*d*, ^2J = 2, H–C(3)); 7.2–7.7 (*m*, C_6H_5).

Similarly were prepared the following propenoates:

Ethyl 2-(4'-Methoxyphenyl)propenoate (**2b**). Ethyl (4'-methoxyphenyl)acetate (12.8 g, 65 mmol) gave *diethyl 2-(4'-methoxyphenyl)-3-oxosuccinate* (16.2 g, 85%) as a yellow oil. IR (film): 3000 (br.), 2980*m*, 2935*w*, 2905*w*, 2815*w*, 1735*vs*, 1610*m*, 1512*s*, 1462*m*, 1442*m*, 1368*m*, 1250*s*, 1180*s*, 1060*m*, 1028*s*, 832*m*. ^{1}H-NMR (60 MHz, CCl_4): keto/enol form *ca.* 1:1; 0.9–1.6 (4*t*, 2 $CO_2CH_2CH_3$); 3.8 (*s*, MeO); 3.9–4.6 (4*q*, 2$CO_2CH_2CH_3$); 5.2 (*s*, 0.5 H, H–C(2)); 6.7–7.4 (*m*, arom.); 8.3 (br. *s*, 0.5 H, OH).

The oxosuccinate (15.4 g, 52 mmol) gave **2b** (6.4 g, 59%) as a colorless oil, b.p. 112–113°/0.01 Torr ([20b]: 132–136°/5 Torr). IR (film): 3040*w*, 2980*m*, 2960*w*, 2935*m*, 2900*m*, 2835*m*, 1720*s*, 1610*s*, 1512*s*, 1322*m*, 1288*s*, 1248*s*, 1194*s*, 1176*s*, 1087*s*, 1030*s*, 833*s*. ^{1}H-NMR (200 MHz): 1.34 (*t*, ^3J = 7, $CO_2CH_2CH_3$); 4.30 (*q*, ^3J = 7, $CO_2CH_2CH_3$); 5.82 (*d*, ^2J = 1.5, H–C(3)); 6.27 (*d*, ^2J = 1.5, H–C(3)); 6.90 (*A* of *AB*, ^3J = 9, H–C(3'), H–C(5')); 7.29 (*B*, ^3J = 9, H–C(2'), H–C(6')).

Methyl 2-(4'-Benzyloxyphenyl)propenoate (**2e**). Methyl (4'-benzyloxyphenyl)acetate (25.6 g, 0.1 mol) gave [4b] *dimethyl 2-(4'-benzyloxyphenyl)-3-oxosuccinate* (27.5 g, 80%) as colorless microplatelets, m.p. (Et_2O) 76–78°. IR (KBr): 3460*m* (br.), 3035*w*, 3015*w*, 2962*w*, 2938*w*, 2920*w*, 2882*w*, 2850*w*, 1750*s*, 1733*s*, 1658*m*, 1611*m*, 1516*s*, 1455*s*, 1440*m*, 1280*s* (br.), 1244*s* (br.), 1378*s*, 1064*s*, 1013*s*, 843*m*, 770*w*, 748*m*, 696*m*. ^{1}H-NMR (200 MHz): keto/enol form 1:1; 3.59 (*s*, 1.5 H, CO_2Me); 3.76 (*s*, 1.5 H, CO_2Me); 3.78 (*s*, 1.5 H, CO_2Me); 3.85 (*s*, 1.5 H, CO_2Me); 5.05 (*s*, CH_2O); 5.33 (*s*, 0.5 H, H–C(2)); 6.9–7.5 (*m*, 9 arom.); 12.35 (br. *s*, 0.5 H, OH).

A CH_2Cl_2 soln. of the oxosuccinate was treated as for **2a** to give, after CC (Et_2O/hexane 1:1) and recrystallization (hexane/Et_2O), **2e** (3.5 g, 66%) as colorless microplatelets, m.p. 36–38°. IR ($CHCl_3$): 3095*w*, 3070*w*, 2955*m*, 2875*w*, 1724*s*, 1610*s*, 1513*s*, 1455*m*, 1439*m*, 1288*m*, 1242*s*, 1174*s*, 1092*m*, 1024*m*, 1011*m*, 835*m*, 695*m*. ^{1}H-NMR (200 MHz): 3.82 (*s*, CO_2Me); 5.08 (*s*, CH_2O); 5.83 (*d*, ^2J = 1, H–C(3)); 6.27 (*d*, ^2J = 1, H–C(3)); 6.95 (*d*, ^3J = 8.5, H–C(3'), H–C(5')); 7.30–7.48 (*m*, H–C(2'), H–C(6'), C_6H_5).

Methyl 2-(4'-Nitrophenyl)propenoate (**2c**). (4'-Nitrophenyl)acetic acid (45.0 g, 0.25 mol) was converted into 2-(4'-nitrophenyl)-3-piperidinopropionic acid (69.0 g, 99%) [20d] which, on treatment with dil. HCl soln., gave after recrystallization from CH_2Cl_2/acetone, 2-(4'-nitrophenyl)propenoic acid (**2**, $R^1 = NO_2$, $R^2 = H$; 9.45 g, 21%) as pale yellow platelets, m.p. 174–175° ([20e]: 174–175°). The acid (5.85 g, 30 mmol) was esterified with MeOH/H_2SO_4 [20f] to give **2c** (5.8 g, 93%) as colorless needles, m.p. (Et_2O) 108–110° ([20f]: 110.5–111°). IR ($CHCl_3$): 3120*w*, 3090*w*, 3025*w*, 3010*w*, 2960*m*, 2895*w*, 1728*s*, 1603*m*, 1523*s*, 1440*m*, 1352*s*, 1318*m*, 1250*m*, 1215*s*, 1184*m*, 1091*s*, 860*s*. ^{1}H-NMR (360 MHz): 3.88 (*s*, MeO); 6.06 (*d*, ^2J = 1, H–C(3)); 6.57 (*d*, ^2J = 1, H–C(3)); 7.62 (*A* of *AB*, ^3J = 9, H–C(2'), H–C(6')); 8.24 (*B*, ^3J = 9, H–C(3'), H–C(5')).

***Michael* Adducts 3**. – *2-(4'-Methoxyphenyl)-3-(pyrrol-1''-yl)propionic Acid* (**3b**). Pyrrole (1.34 g, 20 mmol) was added to a soln. of K(*t*-BuO) (2.24 g, 20 mmol) in 8% aq. DMSO (45 ml). The golden yellow soln. was cooled to 20° and treated dropwise with a soln. of **2b** (2.06 g, 10 mmol) in DMSO (20 ml). The red-brown soln. was stirred 3 h at 20°, then poured into ice/H_2O (500 ml) and extracted with CH_2Cl_2 (4 × 100 ml). The aq. layer was cooled with ice, acidified with conc. HCl soln. and extracted with $CHCl_3$ (3 × 100 ml). The org. extracts were washed with brine (3 × 50 ml) and dried ($MgSO_4$). Evaporation gave a black oil which, after flash CC (SiO_2, Et_2O/hexane 5:1), gave **3b** (2.07 g, 84%) as a rapidly darkening colorless oil. IR ($CHCl_3$): 3015*w*, 3000*s* (v.br.), 2965*w*, 2940*w*, 2920*w*, 2845*m*, 1715*s*, 1615*s*, 1588*m*, 1513*s*, 1500*m*, 1465*m*, 1444*m*, 1413*m*, 1305*s*, 1286*s*, 1250*s* (br.), 1182*s*, 1090*m*, 1036*s*, 830*m*, 820*w*, 614*m*. ^{1}H-NMR (360 MHz): 3.82 (*s*, MeO); 3.96 (*dd*, ^3J = 8, 6.5, H–C(2)); 4.14 (*dd*, ^2J = 14, ^3J = 6.5, H–C(3)); 4.57 (*dd*, ^2J = 14, ^3J = 8, H–C(3)); 6.11 (*t*, ^3J = 2, H–C(3''), H–C(4'')); 6.58 (*t*, ^3J = 2, H–C(2''), H–C(5'')); 6.89 (*A* of *AB*, ^3J = 9.5, H–C(3'), H–C(5')); 7.20 (*B*, ^3J = 9.5, H–C(2'), H–C(6')); 9.55 (br. *s*, CO_2H).

Ethyl ester of **3b**; colorless oil, b.p. 168°/0.01 Torr. IR (film): 3136*w*, 3105*w*, 2984*m*, 2960*m*, 2940*w*, 2910*w*, 2840*m*, 1732*s*, 1613*s*, 1515*s*, 1498*m*, 1464*m*, 1443*m*, 1372*m*, 1304*m*, 1284*m*, 1250*s*, 1180*s*, 1162*m*, 1091*m*, 1034*m*, 832*m*, 725*s*. ^{1}H-NMR (360 MHz): 1.14 (*t*, ^3J = 7, $CO_2CH_2CH_3$); 3.76 (*s*, MeO); 3.88 (*dd*, ^3J = 8.5, 6, H–C(2)); 4.05–4.25 (*m*, $CO_2CH_2CH_3$, H–C(3)); 4.53 (*dd*, ^2J = 14, ^3J = 8.5, H–C(3)); 6.06 (*t*, ^3J = 2, H–C(3''), H–C(4'')); 6.54 (*t*, ^3J = 2, H–C(2''), H–C(5'')); 6.83 (*A* of *AB*, ^3J = 8.5, H–C(3'), H–C(5')); 7.17 (*B*, ^3J = 8.5 H–C(2'), H–C(6')). MS: 274 (7), 273 (32, $M^{+\cdot}$), 206 (31), 194 (16), 193 (22), 162 (13), 135 (57), 134 (29), 133 (63), 121 (100), 91 (18), 80 (62), 77 (27). Anal. calc. for $C_{19}H_{19}NO_3$ (273.33): C 70.31, H 7.01, N 5.12; found: C 70.08, H 6.77, N 5.04.

2-Phenyl-3-(pyrrol-1''-yl)propionic Acid (**3a**). As above (**2b**→**3b**), **2a** (3.86 g, 22 mmol) was converted to **3a**, a pale-brown oil (3.80 g, 73%). IR (CCl_4): 3086*w*, 3062*w*, 3034*w*, 3000*s* (br.), 2980*w*, 1710*s*, 1601*w*, 1494*s*, 1414*m*, 1284*s*, 1088*m*, 1069*m*, 719*s*, 693*s*. ^{1}H-NMR (360 MHz): 3.98 (*dd*, ^3J = 8.5, 6.5, H–C(2)); 4.15 (*dd*, ^2J = 14, ^3J = 6.5, H–C(3)); 4.57 (*dd*, ^2J = 14, ^3J = 8.5, H–C(3)); 6.07 (*t*, ^3J = 2, H–C(3''), H–C(4'')); 6.53 (*t*, ^3J = 2, H–C(2''), H–C(5'')); 7.15–7.45 (*m*, C_6H_5).

Ethyl ester of **3a**; colorless oil, b.p. 150°/0.02 Torr (Kugelrohr). IR (film): 3096*w*, 3062*w*, 3028*w*, 2978*w*, 2833*w*, 1729*s*, 1493*m*, 1451*m*, 1443*m*, 1368*m*, 1283*m*, 1212*m*, 1160*m* (br.), 1087*m*, 723*s*, 694*m*. ^{1}H-NMR (360 MHz): 1.16

(*t*, ^3J = 7.5, $CO_2CH_2CH_3$); 3.99 (*dd*, ^3J = 8.5, 6, H–C(2)); 4.05–4.25 (*m*, $CO_2CH_2CH_3$, H–C(3)); 4.50 (*dd*, ^2J = 14, ^3J = 8.5, H–C(3)); 6.08 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.55 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 7.25–7.45 (*m*, C_6H_5). MS: 244 (9), 243 (63, $M^{+\cdot}$), 103 (13), 81 (14), 80 (100). Anal. calc. for $C_{15}H_{17}NO_2$ (243.31): C 74.05, H 7.04, N 5.76; found: C 73.92, H 7.24, N 5.68.

2-(4′-Nitrophenyl)-3-(pyrrol-1″-yl)propionic Acid (**3c**). Treated as above (**2b**→**3b**), **2c** (1.31 g, 6 mmol) gave the *methyl ester of* **3c** as cream-colored microprisms, m.p. (CCl_4) 73–74°. IR (CCl_4): 3115*w*, 3085*w*, 3010*w*, 2960*m*, 2940*w*, 2870*w*, 1745*s*, 1611*m*, 1532*s*, 1498*m*, 1438*m*, 1350*s*, 1290*m*, 1165*m*, 1090*m*, 857*m*, 852*m*, 722*s*, 692*m*, 616*m*. ^{1}H-NMR (360 MHz): 3.73 (*s*, MeO); 4.12 (*t*, ^3J = 7, H–C(2)); 4.23 (*dd*, ^2J = 14, ^3J = 7, H–C(3)); 4.61 (*dd*, ^2J = 14, ^3J = 7, H–C(3)); 6.09 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.61 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 7.40 (*d*, ^3J = 9, H–C(2′), H–C(6′)); 8.18 (*d*, ^3J = 9, H–C(3′), H–C(5′)). MS: 274 (4, $M^{+\cdot}$), 168 (1), 167 (2), 119 (1), 103 (1), 102 (2), 80 (100). Anal. calc. for $C_{14}H_{14}N_2O_4$ (274.28): C 61.31, H 5.14, N 10.21; found: C 61.19, H 5.06, N 10.21.

The methyl ester was hydrolyzed in 20% aq. MeOH in 97% yield to give **3c** as colorless microplatelets, m.p. ($CHCl_3$/pentane) 146–147°. IR ($CHCl_3$): 3500 (br.), 3100 (v. br.), 3090*w*, 2960*w*, 2880*w*, 1755*m*, 1720*s*, 1612*w*, 1530*s*, 1500*m*, 1352*s*, 1289*m*, 1137*w*, 1092*m*, 1075*m*, 859*m*. IR (KBr): 3200 (br.), 1740*s*, 1700*m*, 1610*m*, 1602*m*, 1528*s*, 1349*s*, 728*s*. ^{1}H-NMR (360 MHz): 4.16 (*t*, ^3J = 7, H–C(2)); 4.26 (*dd*, ^2J = 14, ^3J = 7, H–C(3)); 4.62 (*dd*, ^2J = 14, ^3J = 7, H–C(3)); 6.09 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.51 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 7.41 (*d*, ^3J = 9, H–C(2′), H–C(6′)); *ca.* 7.5 (v. br., CO_2H); 8.20 (*d*, ^3J = 9, H–C(3′), H–C(5′)).

2-(4′-Benzyloxyphenyl)-3-(pyrrol-1″-yl)propionic Acid (**3e**). Treatment of **2e** (8.0 g, 30 mmol) as above (**2b**→**3b**) gave, after recrystallization from hexane/EtOAc, **3e** (6.76 g, 71%) as colorless needles, m.p. 99–101°. IR ($CHCl_3$): 3075*w*, 3010*m*, 3000*m* (br.), 2970*w*, 2835*w*, 2810*w*, 2780*w*, 1717*s*, 1612*m*, 1588*w*, 1513*s*, 1500*m*, 1286*m*, 1245*s*, 1180*m*, 1090*m*, 693*m*. ^{1}H-NMR (200 MHz): 3.92 (*dd*, ^3J = 8, 6, H–C(2)); 4.12 (*dd*, ^2J = 14, ^3J = 6, H–C(3)); 4.54 (*dd*, ^2J = 14, ^3J = 8, H–C(3)); 5.05 (*s*, CH_2O); 6.08 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.54 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 6.94 (*A* of *AB*, ^3J = 8, H–C(3′), H–C(5′)); 7.17 (*B*, ^3J = 8, H–C(2′), H–C(6′)); 7.3–7.5 (*m*, C_6H_5); *ca.* 7.8 (v. br., CO_2H). MS: 321 (22, $M^{+\cdot}$), 171 (6), 92 (8), 91 (100), 81 (7), 80 (93). Anal. calc. for $C_{20}H_{19}NO_3$ (321.38): C 74.75, H 5.96, N 4.36; found: C 74.55, H 5.94, N 4.17.

2-(4′-Acetoxyphenyl)-3-(pyrrol-1″-yl)propionic Acid (**3d**). A soln. of **3e** (6.15 g, 19 mmol) in abs. EtOH (250 ml) was hydrogenated at r.t. over 5% Pd/C (900 mg). After 21 h, the mixture was filtered through *Celite*, the solvent evaporated and the residue extracted with Et_2O. Filtration and evaporation gave *2-(4′-hydroxyphenyl)-3-(pyrrol-1″-yl)propionic acid* (**3**, R^1 = OH; 3.29 g, 74%) as colorless microneedles, m.p. 129–134°, used without further purification (a sample recrystallized from Et_2O/pentane had m.p. 138–139°). IR (KBr): 3480 (br.), 3180 (br.), 3100*w*, 3033*w*, 2938*w*, 1742*m*, 1700*s* (br.), 1613*m*, 1600*m*, 1516*s*, 1500*s*, 1438*m*, 1281*s*, 1222*m* (br.), 1176*m*, 1099*m*, 820*m*, 728*s*. ^{1}H-NMR (5% DMSO/$CDCl_3$, 200 MHz): 3.82 (*dd*, ^3J = 8.5, 6, H–C(2)); 4.06 (*dd*, ^2J = 14, ^3J = 6, H–C(3)); 4.52 (*dd*, ^2J = 14, ^3J = 8.5, H–C(3)); 6.01 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.58 (*t*, ^3J = 2, H–C(2″), H–C(5″)); *ca.* 6.6 (br., OH); 6.78 (*A* of *AB*, ^3J = 8, H–C3′), H–C(5′)); 7.10 (*B*, ^3J = 8, H–C(2′), H–C(6′)); *ca.* 8.4 (br., CO_2H).

N-Methylmorpholine (3.44 g, 3.75 ml, 34 mmol) was added to a suspension of **3** (R^1 = OH; 3.29 g, 14 mmol) in CH_2Cl_2 (100 ml) cooled to 0° (ice bath). The clear soln. was then treated dropwise with acetyl chloride (3.03 g, 2.74 ml, 38 mmol). After 1 h at 0° and 30 min at r.t., H_2O (20 ml) was added and the CH_2Cl_2 removed by distillation *in vacuo*. Pyridine (40 ml) was then added and the mixture stirred 2.5 h before pouring into ice/H_2O (300 ml) containing conc. HCl (46 ml). The soln. was extracted with EtOAc (2 × 200 ml) and the combined extract washed with brine (3 × 100 ml), dried (Na_2SO_4), and evaporated. The residue was recrystallized from $CHCl_3$ to give **3d** (3.35 g, 86%) as colorless needles, m.p. 174–175° (sublimes above 150°). IR (KBr): 3265*s* (br.), 3138*w*, 3108*w*, 3062*w*, 2958*m*, 2938*w*, 1745*s*, 1732*s*, 1603*w*, 1506*m*, 1502*m*, 1440*m*, 1372*m*, 1285*m*, 1250*s*, 1210*m*, 1198*m*, 1170*m*, 1160*m*, 1098*w*, 1078*w*, 1019*w*, 950*w*, 928*w*, 850*w*, 728*m* (br.). ^{1}H-NMR (5% DMSO/$CHCl_3$, 200 MHz): 2.30 (*s*, OCOMe); 3.94 (*dd*, ^3J = 8, 6.5, H–C(2)); 4.11 (*dd*, ^2J = 14, ^3J = 6.5, H–C(3)); 4.57 (*dd*, ^2J = 14, ^3J = 8, H–C(3)); 6.04 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.58 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 7.04 (*A* of *AB*, ^3J = 8, H–C(3′), H–C(5′)); 7.30 (*B*, ^3J = 8, H–C(2′), H–C(6′)); *ca.* 8.0 (br., CO_2H). MS: 273 (5, $M^{+\cdot}$), 184 (1), 120 (2), 107 (1), 91 (3), 81 (5), 80 (100). Anal calc. for $C_{15}H_{15}NO_4$ (273.29): C 65.92, H 5.53, N 5.13; found: C 65.84, H 5.46, N 5.02.

Diazobutanones 5. – *3-(4′-Acetoxyphenyl)-1-diazo-4-(pyrrol-1″-yl)-2-butanone* (**5d**). An ice-cold suspension of **3d** (1.37 g, 5 mmol) in Et_2O (230 ml) was treated successively with isobutyl chloroformate (0.78 g, 0.75 ml, 5.7 mmol) and *N*-methylmorpholine (0.55 g, 0.6 ml, 5.4 mmol). A white precipitate was formed and the mixture stirred 40 min at 0°, then 50 min at r.t. The mixture was filtered through *Celite* and the filtrate treated at 0° with an Et_2O soln. of diazomethane from 10.71 g (50 mmol) of *N*-methyl-*N*-nitroso-4-toluenesulfonamide. The mixture was allowed to warm to r.t. over 16 h and the solvent carefully evaporated. The residue was dissolved in EtOAc (150 ml), the soln. washed with brine (25 ml), dried (Na_2SO_4), and evaporated. The residue was purified by flash CC (SiO_2, Et_2O/hexane 1:1) to give, after recrystallization from CCl_4, **5d** (1.09 g, 73%) as pale-yellow cubes, m.p.

115–117°. IR ($CHCl_3$): 3130*m*, 3008*m*, 2955*w*, 2932*w*, 2115*s*, 1760*s*, 1645*s*, 1508*m*, 1499*m*, 1372*s*, 1286*m*, 1197*s*, 1170*m*, 1140*m*, 1089*m*, 1018*m*, 913*w*, 847*w*, 618*w*. ^{1}H-NMR (200 MHz): 2.30 (*s*, OCOMe); 3.80 (br. *t*, H–C(3)); 4.08 (*dd*, ^2J = 14, ^3J = 6, H–C(4)); 4.69 (*dd*, ^2J = 14, ^3J = 8, H–C(4)); 5.10 (*s*, H–C(1)); 6.08 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.53 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 7.05 (*A* of *AB*, ^3J = 8, H–C(3′), H–C(5′)); 7.21 (*B*, ^3J = 8, H–C(2′), H–C(6′)). MS: 269 (12, $M^{+\cdot} - N_2$), 162 (7), 147 (30), 120 (100), 119 (23), 108 (10), 107 (53), 91 (27), 80 (90), 79 (23), 78 (11), 77 (10). Anal. calc. for $C_{16}H_{15}N_3O_3$ (297.31): C 64.54, H 5.09, N 14.13; found: C 64.63, H 5.13, N 14.19.

1-Diazo-3-phenyl-4-(pyrrol-1″-yl)-2-butanone (**5a**). With ethyl chloroformate, **3a** (2.50 g, 11.6 mmol) was converted into the mixed anhydride **4a**. Treatment with CH_2N_2 (from 17.2 g (80 mmol) of *N*-methyl-*N*-nitroso-4-toluenesulfonamide) gave **5a** which was purified by flash CC (SiO_2, EtOAc/hexane 1:4) and recrystallized from CCl_4 to give pure **5a** (1.60 g, 58%) as pale yellow platelets, m.p. 71–72°. IR (CCl_4): 3125*w*, 3075*w*, 3040*w*, 2975*w*, 2120*s*, 1655*s*, 1500*m*, 1365*s*, 1288*m*, 1262*s*, 1158*m*, 1070*m*, 1035*m*, 722*s*. ^{1}H-NMR (360 MHz): 3.81 (*m*, H–C(3)); 4.10 (*dd*, ^2J = 13.5, ^3J = 6, H–C(4)); 4.73 (*dd*, ^2J = 13.5, ^3J = 8, H–C(4)); 5.09 (*s*, H–C(1)); 6.07 (*t*, ^3J = 1.8, H–C(3″), H–C(4″)); 6.56 (*t*, ^3J = 1.8, H–C(2″), H–C(5″)); 7.10–7.45 (*m*, C_6H_5). MS: 211 (22, $M^{+\cdot} - N_2$), 115 (16), 107 (63), 104 (52), 103 (56), 91 (19), 80 (100), 79 (83), 77 (43). Anal. calc. for $C_{14}H_{13}N_3O$ (239.28): C 70.27, H 5.48, N 17.56; found: C 69.00, H 5.58, N 16.67.

1-Diazo-3-(4′-methoxyphenyl)-4-(pyrrol-1″-yl)-2-butanone (**5b**). With ethyl chloroformate, **3b** (2.0 g, 8 mmol) was converted into the mixed anhydride **4b** which, on treatment with CH_2N_2 (from 9.05 g (42 mmol) of *N*-methyl-*N*-nitroso-4-toluenesulfonamide), gave crude **5b** which was flash chromatographed (SiO_2, Et_2O/hexane 1:1) and recrystallized from CCl_4 to give pure **5b** (0.97 g, 44%) as colorless needles, m.p. 70° (dec.). IR (CCl_4): 3100*w*, 3000*w*, 2960*w*, 2935*w*, 2838*w*, 2105*s*, 1637s, 1610*m*, 1512*s*, 1496*m*, 1363*s*, 1252*s*, 726*m*. ^{1}H-NMR (360 MHz): 3.81 (*s*, MeO); 3.77 (*dd*, ^3J = 8, 6, H–C(3)); 4.09 (*dd*, ^2J = 14, ^3J = 6, H–C(4)); 4.69 (*dd*, ^2J = 14, ^3J = 8, H–C(4)); 5.08 (*s*, H–C(1)); 6.07 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.54 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 6.87 (*A* of *AB*, ^3J = 9, H–C(3′), H–C(5′)); 7.13 (*B*, ^3J = 9, H–C(2′), H–C(6′)). MS: 242 (5), 241 (26, $M^{+\cdot} - N_2$), 213 (7), 161 (18), 136 (11), 134 (100), 133 (16), 119 (16), 107 (16), 105 (13), 91 (22), 80 (32), 79 (10), 77 (10). Anal. calc. for $C_{15}H_{15}N_3O_2$ (269.30): C 66.90, H 5.61, N 15.60; found: C 67.06, H 5.70, N 15.23.

1-Diazo-3-(4′-nitrophenyl)-4-(pyrrol-1″-yl)-2-butanone (**5c**). With isobutyl chloroformate, **3c** (1.30 g, 5 mmol) was converted into its mixed anhydride **4c** which on reaction with CH_2N_2 (from 10.71 g (50 mmol) of *N*-methyl-*N*-nitroso-4-toluenesulfonamide) gave, after flash CC (SiO_2, Et_2O/hexane 1:1) **5c** (1.08 g, 76%) as pale yellow platelets, m.p. (Et_2O/hexane) 122.5–124° (dec.). IR ($CHCl_3$): 3122*w*, 3090*w*, 2985*w*, 2955*w*, 2935*w*, 2865*w*, 2120*s*, 1645*m*, 1611*m*, 1605*w*, 1528*s*, 1498*m*, 1368*s*, 1351*s*, 1288*m*, 1140*m*, 1092*m*, 857*m*, 618*w*. ^{1}H-NMR (360 MHz): 3.96 (br. *t*, H–C(3)); 4.20 (*dd*, ^2J = 14, ^3J = 7, H–C(4)); 4.70 (*dd*, ^2J = 14, ^3J = 7.5, H–C(4)); 5.15 (*s*, H–C(1)); 6.09 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.51 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 7.41 (*d*, ^3J = 8.5, H–C(2′), H–C(6′)); 8.20 (*d*, ^3J = 8.5, H–C(3′), H–C(5′)). MS: 256 (1, $M^{+\cdot} - N_2$), 228 (8), 149 (5), 119 (8), 115 (14), 107 (30), 103 (9), 102 (15), 91 (10), 89 (11), 80 (100), 79 (63), 78 (22), 77 (22), 76 (12). Anal. calc for $C_{14}H_{12}N_4O_3$ (284.27): C 59.15, H 4.25, N 19.71; found: C 59.03, H 4.27, N 19.04.

3-(4′-Benzyloxyphenyl)-1-diazo-4-(pyrrol-1″-yl)-2-butanone (**5e**). With isobutyl chloroformate, **3e** (215 mg, 0.67 mmol) was converted into its mixed anhydride **4e** which, on reaction with excess CH_2N_2 (from 7.28 g (34 mmol) of *N*-methyl-*N*-nitroso-4-toluenesulfonamide), gave, after flash CC (SiO_2, EtOAc/hexane 1:4) **5e** (128 mg, 55%) as a pale yellow amorphous powder, m.p. (hexane/Et_2O) 75.5–76.5° (dec.). IR (CCl_4): 3118*w*, 3068*w*, 3035*w*, 2948*w*, 2932*w*, 2868*w*, 2108*s*, 1650*s*, 1611*s*, 1511*s*, 1497*m*, 1360*s*, 1284*m*, 1246*s*, 1177*m*, 1140*m*, 1106*w*, 1088*m*, 1066*w*, 1020*w*, 906*m*, 720*s*, 693*m*, 660*m*. ^{1}H-NMR (200 MHz): 3.75 (br. *t*, H–C(3)); 4.07 (*dd*, ^2J = 14, ^3J = 6, H–C(4)); 4.67 (*dd*, ^2J = 14, ^3J = 8, H–C(4)); 5.04 (*s*, CH_2O); 5.08 (*s*, H–C(1)); 6.06 (*t*, ^3J = 2, H–C(3″), H–C(4″)); 6.52 (*t*, ^3J = 2, H–C(2″), H–C(5″)); 6.93 (*A* of *AB*, ^3J = 8.6, H–C(3′), H–C(5′)); 7.10 (*B*, ^3J = 8.6, H–C(2′), H–C(6′)); 7.28–7.46 (*m*, C_6H_5). MS: 317 (1, $M^{+\cdot} - N_2$), 210 (6), 167 (1), 149 (3), 119 (1), 105 (1), 92 (7), 91 (100), 80 (15), 69 (6), 65 (11), 57 (8). Anal. calc for $C_{21}H_{19}N_3O_2$ (345.40): C 73.02, H 5.54, N 12.16; found: C 72.94, H 5.56, N 12.00.

Decomposition of Diazobutanones 5. – *6-(4′-Acetoxyphenyl)-5,6-dihydro-7(8H)-indolizinone* (**6d**). A soln. of **5d** (1.59 g, 5.3 mmol) in CH_2Cl_2 (450 ml) was treated with $Rh(OAc)_2$ (10 mg) in the dark at r.t. After 90 min, the green soln. was evaporated and purified by CC (*Florisil*, CH_2Cl_2) to give 1.28 g (89%) of a 36:1 mixture **6d/7d**. Recrystallization from EtOAc/hexane gave **6d** (1.18 g, 82%) as colorless microprisms, m.p. 90–91°. IR ($CHCl_3$): 3110*w*, 3006*m*, 2925*w*, 2880*w*, 1762*s*, 1730*s*, 1510*s*, 1492*m*, 1371*m*, 1313*m*, 1196*s*, 1170*s*, 1018*m*, 1012*w*, 912*m*, 842*w*, 699*m*. ^{1}H-NMR (200 MHz): 2.29 (*s*, OCOMe); 3.78 (*dd*, ^2J = 21.5, ^4J = 1, H–C(8)); 3.82 (*dd*, ^2J = 21.5, ^4J = 1, H–C(8)); 3.91 (*dd*, ^3J = 8, 6, H–C(6)); 4.37 (*dd*, ^2J = 13, ^3J = 8, H–C(5)); 4.47 (*dd*, ^2J = 13, ^3J = 6, H–C(5)); 6.03 (*m*, H–C(1)); 6.18 (*dd*, ^3J = 3.5, 3, H–C(2)); 6.68 (*dd*, ^3J = 3, ^4J = 1.8, H–C(3)); 7.06 (*s*, H–C(2′), H–C(3′), H–C(5′), H–C(6′)). MS: 270 (7), 269 (32, $M^{+\cdot}$), 241 (8), 121 (10), 120 (100), 118 (11), 91 (12), 80 (40). Anal. calc. for $C_{16}H_{15}NO_3$ (269.31): C 71.36, H 5.61, N 5.20; found: C 71.30, H 5.62, N 5.14.

The mother liquors contained **6d**/5-acetoxy-1-[(pyrrol-1′-yl)methyl]-2-indanone (**7d**) in the ratio of 1.5:1. **7d**: ^{1}H-NMR (200 MHz): 2.29 (*s*, OCOMe); 3.35 (br. *d*, ^2J = 23, H–C(3)); 3.51 (br. *d*, ^2J = 23, H–C(3)); *ca.* 3.8 (*m*, H–C(1)); 4.18 (*dd*, ^2J = 14, ^3J = 7.5, 1H, CH_2N); 4.46 (*dd*, ^2J = 14, ^3J = 4.5, 1H, CH_2N); 6.07 (*t*, ^3J = 2, H–C(3′), H–C(4′)); 6.47 (*t*, ^3J = 2, H–C(2′), H–C(5′)); 6.76 (br. *d*, ^3J = 8, H–C(7)); 6.9–7.05 (*m*, H–C(4), H–C(6)).

*5,6-Dihydro-6-phenyl-7(8*H*)-indolizinone* (**6a**). Diazoketone **5a** (491 mg, 2 mmol) was decomposed with $Rh(OAc)_2$ (5 mg) to give 325 mg (75%) of a 6:1 (by ^{1}H-NMR) mixture **6a**/**7a**. On standing at −20°, **6a** crystallized and was recrystallized from hexane/Et_2O to give pure **6a** (220 mg, 51%) as colorless needles, m.p. 84–85°. IR (CCl_4): 3090*w*, 3068*w*, 3035*w*, 2975*w*, 2925*w*, 2880*w*, 1732*s*, 1492*m*, 1315*m*, 1072*w*, 696*s*. ^{1}H-NMR (360 MHz): 3.73 (*dd*, ^2J = 20.5, ^4J = 1, H–C(8)); 3.85 (*dd*, ^2J = 20.5, ^4J = 1, H–C(8)); 3.92 (*dd*, ^3J = 8.5, 6, H–C(6)); 4.41 (*dd*, ^2J = 13, ^3J = 8.5, H–C(5)); 4.43 (*dd*, ^2J = 13, ^3J = 6, H–C(5)); 6.00 (*m*, H–C(1)); 6.18 (*dd*, ^3J = 3.25, 2.5, H–C(2)); 6.65 (*dd*, ^3J = 2.5, ^4J = 1.75, H–C(3)); 7.06 (*dd*, ^3J = 7.5, ^4J = 2, H–C(2′), H–C(6′)); 7.31 (*m*, H–C(3′), H–C(4′), H–C(5′)). MS: 212 (4), 211 (30, $M^{+\cdot}$), 183 (11), 105 (10), 104 (100), 103 (16), 80 (37), 78 (21), 77 (13). Anal. calc. for $C_{14}H_{13}NO$ (211.26): C 79.59, H 6.20, N 6.63; found: C 79.79, H 6.46, N 6.81.

The mother liquors contained **6a**/1-[(pyrrol-1′-yl)methyl]-2-indanone (**7a**) in the ratio of 2:1. **7a**: IR (CCl_4): 1765*s* (C=O). ^{1}H-NMR (360 MHz): 3.33 (*d*, ^2J = 23, H–C(3)); 3.53 (*d*, ^2J = 23, H–C(3)); *ca.* 3.8 (*m*, H–C(1)); 4.29 (*dd*, ^2J = 14, ^3J = 7, 1H, CH_2N); 4.51 (*dd*, ^2J = 14, ^3J = 4, 1H, CH_2N); 6.08 (*t*, ^3J = 2, H–C(3′), H–C(4′)); 6.50 (*t*, ^3J = 2, H–C(2′), H–C(5′)); 6.92 (br. *d*, ^3J = 7, H–C(7)); 7.29 (*m*, H–C(4), H–C(5), H–C(6)).

*5,6-Dihydro-6-(4′-methoxyphenyl)-7(8*H*)-indolizinone* (**6b**). $Rh(OAc)_2$-catalyzed decomposition of the diazoketone **5b** (256.5 mg, 0.95 mmol) gave an inseparable 7:2 mixture **6b**/*5-methoxy-1-[(pyrrol-1′-yl)methyl]-2-indanone* (**7b**; 205 mg, 89%) as colorless oil. IR (film): 1750*s* (C=O, **7b**), 1725*s* (C=O, **6b**), 832 (arom., **6b**), 725 and 710 (arom., **7b**). ^{1}H-NMR (360 MHz; **6b**): 3.76 (*dd*, ^2J = 20.5, ^4J = 1, H–C(8)); 3.77 (*s*, MeO); 3.84 (*dd*, ^2J = 20.5, ^4J = 1, H–C(8)); 3.87 (*dd*, ^3J = 8.5, 5.5, H–C(6)); 4.37 (*dd*, ^2J = 13, ^3J = 8.5, H–C(5)); 4.46 (*dd*, ^2J = 13, ^3J = 5.5, H–C(5)); 6.02 (*m*, H–C(1)); 6.21 (*dd*, ^3J = 3.5, 2.7, H–C(2)); 6.69 (*dd*, ^3J = 2.7, ^4J = 1.5, H–C(3)); 6.89 (*A* of *AB*, ^3J = 8.5, H–C(3′), H–C(5′)); 6.99 (*B*, ^3J = 8.5, H–C(2′), H–C(6′)). ^{1}H-NMR (360 MHz; **7b**): 3.29 (*d*, ^2J = 23, H–C(3)); 3.48 (*d*, ^2J = 23, H–C(3)); 3.80 (*s*, MeO); 3.85 (*dd*, ^3J = 7.5, 4, H–C(1)); 4.22 (*dd*, ^2J = 14, ^3J = 7.5, 1H, CH_2N); 4.43 (*dd*, ^2J = 14, ^3J = 4, 1H, CH_2N); 6.07 (*t*, ^3J = 2, H–C(3′), H–C(4′)); 6.48 (*t*, ^3J = 2, H–C(2′), H–C(5′)); 6.76 (br. *d*, ^3J = 8, H–C(6)); 6.80 (br. *s*, H–C(4)); 6.83 (br. *d*, ^3J = 8, H–C(7)).

*5,6-Dihydro-6-(4′-nitrophenyl)-7(8*H*)-indolizinone* (**6c**). $Rh(OAc)_2$-catalyzed decomposition of **5c** (508 mg, 1.8 mmol) gave **6c** as yellow microplatelets which were recrystallized from CCl_4 to give pure **6c** (350 mg, 76%) as colorless microplatelets, m.p. 133–134°. IR (CCl_4): 3120*w*, 3090*w*, 2965*m*, 2933*m*, 2880*m*, 1736*s*, 1610*m*, 1531*s*, 1452*m*, 1361*m*, 1318*m*, 853*m*, 702*s*. ^{1}H-NMR (360 MHz): 3.82 (*dd*, ^2J = 21, ^4J = 1, H–C(8)); 3.91 (*dd*, ^2J = 21, ^4J = 1, H–C(8)); 4.07 (*dd*, ^3J = 8.5, 5.5, H–C(6)); 4.45 (*dd*, ^2J = 13, ^3J = 8.5, H–C(5)); 4.56 (*dd*, ^2J = 13, ^3J = 5.5, H–C(5)); 6.06 (*m*, H–C(1)); 6.24 (*dd*, ^3J = 3.8, 2.8, H–C(2)); 6.71 (*dd*, ^3J = 2.8, ^4J = 1.8, H–C(3)); 7.25 (*A* of *AB*, ^3J = 8.5, H–C (2′), H–C(6′)); 8.19 (*B*, ^3J = 8.5, H–C(3′), H–C(5′)). MS: 257 (11), 256 (83, $M^{+\cdot}$), 228 (100), 227 (17), 182 (11), 150 (10), 149 (86), 133 (14), 119 (37), 106 (10), 103 (42), 102 (14), 92 (21), 91 (26), 80 (22), 79 (24), 77 (55). Anal. calc for $C_{14}H_{12}N_2O_3$ (256.26): C 65.62, H 4.12, N 10.93; found: C 65.85, H 4.55, N 10.79.

*6-(4′-Benzyloxyphenyl)-5,6-dihydro-7(8*H*)-indolizinone* (**6e**). Diazoketone **5e** (32 mg, 0.09 mmol) was decomposed with $Rh(OAc)_2$ (2 mg) to give a 4:1 mixture **6e**/*5-benzyloxy-1-[(pyrrol-1′-yl)methyl]-2-indanone* (**7e**; 23.5 mg, 85%). IR (CCl_4): 1756*s* (C=O, **7e**), 1732*s* (C=O, **6e**), 828 (arom., **6e**), 721 and 698 (arom., **7e**). ^{1}H-NMR (360 MHz; **6e**): 3.77 (*dd*, ^2J = 21, ^4J = 1, H–C(8)); 3.83 (*dd*, ^2J = 21, ^4J = 1, H–C(8)); 3.87 (*dd*, ^3J = 8.3, 6,H–C(6)); 4.38 (*dd*, ^2J = 13, ^3J = 8.3, H–C(5)); 4.47 (*dd*, ^2J = 13, ^3J = 6, H–C(5)); 5.16 (*s*, CH_2O); 6.01 (*m*, H–C(1)); 6.20 (*dd*, ^3J = 3.5, 2.2, H–C(2)); 6.68 (*dd*, ^4J = 1.6, ^3J = 2.2, H–C(3)); 6.95 (*AA′* of *AA′BB′*, $J \approx 9$, H–C(3′), H–C(5′)); 7.01 (*BB′*, $J \approx 9$, H–C(2′), H–C(6′)); 7.32–7.48 (*m*, C_6H_5). ^{1}H-NMR (360 MHz; **7e**): 3.28 (*d*, ^2J = 23, H–C(3)); 3.45 (*d*, ^2J = 23, H–C(3)); *ca.* 3.75 (*m*, H–C(1)); 4.22 (*dd*, ^2J = 14, ^3J = 7.2, 1H, CH_2N); 4.44 (*dd*, ^2J = 14, ^3J = 4, 1H, CH_2N); 5.17 (*s*, CH_2O); 6.07 (*t*, ^3J = 2.2, H–C(3′), H–C(4′)); 6.48 (*t*, ^3J = 2.2, H–C(2′), H–C(5′)); 6.75 (*d*, ^3J = 9, H–C(6)); 6.88 (br. *s*, H–C(4)); 7.32–7.48 (*m*, H–C(7), C_6H_5).

Reduction of Dihydroindolizinones 6. – *2,3,5,6-Tetrahydro-6-phenyl-7(1*H*)-indolizinone* (**8a**). A soln. of **6a** (40.5 mg, 0.19 mmol) in abs. EtOH (25 ml) was hydrogenated over 10% Pd/C (35 mg) at r.t. and at an initial pressure of 35 bar. After 17 h, the mixture was filtered through *Celite* and the solvent evaporated to give a green-brown oil. Purification by flash CC (SiO_2, MeOH/$CHCl_3$ 1:9) gave **8a** (22 mg, 54%) as a colorless oil rapidly turning green. IR ($CHCl_3$): 3100*w*, 3080*w*, 3045*w*, 2970*m*, 2945*m*, 2870*m* (br.), 1630*s*, 1590*s*, 1576*s*, 1503*m*, 1448*m*, 1368*m*, 1241*s*, 1204*s*, 1192*w*, 1158*s*, 1100*m*, 863*w*. ^{1}H-NMR (360 MHz): 2.07 (*quint.*, ^3J = 7.5, 2H–C(2)); 2.73 (*t*, ^3J = 7.5, 2H–C(1)); 3.42 (*m*, 2H–C(3)); 3.54 (*dd*, ^2J = 12, ^3J = 8, H–C(5)); 3.61 (*m*, H–C(6)); 3.71 (*dd*, ^2J = 12, ^3J = 6, H–C(5)); 5.15 (*s*, H–C(8)); 7.28 (*m*, C_6H_5).

*2,3,5,6-Tetrahydro-6-(4′-methoxyphenyl)-7-(1*H*)-indolizinone* (**8b**). Hydrogenation of **6b**/**7b** (7:2, 205 mg) over 10% Pd/C (150 mg) as for **8a** gave, after flash CC (SiO_2, MeOH/$CHCl_3$ 1:19), **8b** (64 mg, 40%) as a colorless

oil which crystallized on standing, m.p. 91–93° ([4b]: m.p. 125–138°). UV (abs. EtOH): 223 (10800), 278 (sh, 3000), 285 (sh, 3900), 318 (13300). IR (CH_2Cl_2): 3040*w*, 2965*m* (br.), 2940*m*, 2860*w*, 2842*m*, 1660*s*, 1615*s*, 1585*vs*, 1515*s*, 1363*m*, 1308*m*, 1240*s*, 1200*m*, 1180*s*, 1152*s*, 1098*m*, 1036*s*, 853*w*, 832*m*, 808*w*, 793*m*. ^{1}H-NMR (360 MHz): 2.01 (*quint.*, ^3J = 7, 2H–C(2)); 2.77 (*t*, ^3J = 7, 2H–C(1)); 3.44 (*m*, 2H–C(3)); 3.55 (*dd*, ^2J = 11, ^3J = 8, H–C(5)); 3.61 (*m*, H–C(6)); 3.71 (*dd*, ^2J = 11, ^3J = 6, H–C(5)); 5.23 (*s*, H–C(8)); 6.87 (*AA'* of *AA'BB'*, *J* ≈ 8.5, H–C(3'), H–C(5')); 7.20 (*BB'*, *J* ≈ 8.5, H–C(2'), H–C(6')).

6-(4'-Acetoxyphenyl)-2,3,5,6-tetrahydro-7(1H)-indolizinone (**8d**). Hydrogenation of **6d** (62 mg, 0.23 mmol) over 10% Pd/C (60 mg) as for **8a** gave, after flash CC (MeOH/$CHCl_3$ 1:19), **8d** (15.5 mg, 25%) as a rapidly darkening colorless oil which crystallized on standing, m.p. 128–130°. UV (abs. EtOH): 210 (10200), 265 (sh, 800), 272 (sh, 1150), 317 (13150). IR ($CHCl_3$): 2860*w* (br.), 1760*s*, 1628*s*, 1580*vs*, 1506*s*, 1371*m*, 1198*m*, 1169*m*, 1152*w*, 1098*w*, 1018*m*, 1012*w*, 943*w*, 914*m*, 845*w*. ^{1}H-NMR (200 MHz): 1.98–2.18 (*m*, 2H–C(2)); 2.28 (*s*, $COCH_3$); 2.74 (br. *t*, ^3J = 8, 2H–C(1)); 3.30–3.70 (*m*, 2H–C(3)); 3.52 (*dd*, ^2J = 10, ^3J = 7, H–C(5)); 3.61 (*m*, H–C(6)); 3.71 (*dd*, ^2J = 10, ^3J = 5, H–C(5)); 5.12 (*t*, ^3J = 1, H–C(8)); 7.02 (*AA'* of *AA'BB'*, *J* ≈ 8.5, H–C(3'), H–C(5')); 7.26 (*BB'*, *J* ≈ 8.5, H–C(2'), H–C(6')). MS: 272 (2), 271 (10, $M^{+\cdot}$), 229 (2), 162 (6), 121 (11), 120 (100), 119 (8), 110 (25), 91 (8), 81 (5), 65 (4).

1,2,3,5,6,7,8,8a-Octahydro-6-(4'-methoxyphenyl)indolizin-7-ol (**9b**). A mixture **6b**/**7b** (7:2, 390 mg) in abs. EtOH (50 ml) containing AcOH (0.5 ml) was hydrogenated over pre-reduced PtO_2 (100 mg) at 50° and at an initial pressure of 26 psi. After 15 h, the pale-green mixture was filtered through *Celite*, the solvents were evaporated, and the residual pale-green oil was dissolved in CH_2Cl_2 (100 ml). This soln. was washed with sat. aq. $NaHCO_3$ soln. (50 ml), dried ($MgSO_4$), and evaporated. The golden yellow oil was purified by flash CC (SiO_2, MeOH/hexane 1:4) to give the 6*β*, 7*β*- and 6*β*, 7*α*-isomer of **9b** in 105 and 35 mg yield respectively (44%). The 6*β*, 7*β*-isomer of **9b** crystallized from CCl_4/hexane to give colorless platelets, m.p. 130–131° (sublimation above 120°). IR (CCl_4): 3600*w*, 3350 (v.br.), 2965*m*, 2940*m*, 2920*w*, 2880*w*, 2840*w*, 2810*m* (br.), 1615*m*, 1518*s*, 1464*m*, 1443*w*, 1250*s*, 1180*m*, 1162*w*, 1138*w*, 1109*w*, 1106*w*, 1042*s*, 910*s*. ^{1}H-NMR (360 MHz): 1.40 (*dq*, ^2J = 12, ^3J = 12, 12, 7, H_β–C(1)); 1.59 (*ddd*, ^2J = 13, ^3J = 12,3, H_α–C(8)); 1.65–1.95 (*m*, 2H–C(2), H_α–C(1)); 2.11 (*dt*, ^2J = 13, ^3J = 3,3, H_β–C(8)); 2.25 (*q*, ^2J = ^3J = 9, H_β–C(3)); 2.33 (*m*, H_β–C(8a)); 2.71 (*dd*, ^2J = 11, ^3J = 10, H_β–C(5)); 2.90–3.15 (*m*, H_α–C(5), H_α–C(6), H_α–C(3)); 3.77 (*s*, CH_3O); 4.05 (*m*, H_α–C(7)); 6.86 (*d*, ^3J = 9, H–C(3'), H–C(5')); 7.18 (*d*, ^3J = 9, H–C(2'), H–C(6')). MS: 248 (3), 247 (26, $M^{+\cdot}$), 246 (21), 139 (12), 135 (15), 134 (100), 122 (13), 121 (15), 119 (11), 100 (26), 96 (13), 91 (17), 84 (38), 77 (11). HR-MS: 247.1564 ($C_{15}H_{21}NO_2$, calc. 247.1572).

6β, 7α-Isomer of **9b**: colorless oil. ^{1}H-NMR (360 MHz): 1.42 (br. *q*, ^2J = ^3J = 12, H_α–C(8)); 1.55–2.00 (*m*, 2H–C(1), 2H–C(2)); 2.06 (*m*, H_β–C(8a)); 2.13 (*q*, ^2J = ^3J = 9, H_α–C(3)); 2.18 (*t*, ^2J = ^3J = 11, H_β–C(5)); 2.26 (*ddd*, ^2J = 12, ^3J = 4, 2, H_β–C(8)); 2.77 (br. *dt*, ^3J = 11, 11, 4, H_α–C(6)); 3.05 (*dt*, ^2J = 9, ^3J = 9, 2, H_α–C(3)); 3.12 (*dd*, ^2J = 11, ^3J = 4, H_α–C(5)); *ca.* 3.75 (*m*, H_β–C(7)); 3.79 (*s*, CH_3O); 6.83 (*d*, ^3J = 9, H–C(3'), H–C(5')); 7.20 (*d*, ^3J = 9, H–C(2'), H–C(6')).

6-(4'-Acetoxyphenyl)-1,2,3,5,6,7,8,8a-octahydroindolizin-7-ol (**9d**). *a*) Dihydroindolizinone **6d** (77 mg, 0.285 mmol) was hydrogenated over PtO_2 (70 mg) as for **9b** to give, after flash CC (SiO_2, MeOH/CH_2Cl_2 1:3) 3 isomers of **9d** (56 mg, 71%; relative yields 51:28:21). The major low-R_f 6*α*, 7*α*-isomer was recrystallized from EtOAc to give needles, m.p. 133–135° (sublimation above 120°), the two higher-R_f 6*β*, 7*α*- and 6*β*, 7*β*-isomers were obtained as colorless oils. *6α, 7α-Isomer of* **9d**: IR ($CHCl_3$): 3580*m*, 2972*m*, 2940*m*, 2925*m*, 2796*m*, 1765*s*, 1505*s*, 1370*s*, 1222*s*, 1200*s*, 1168*s*, 1112*w*, 1089*m*, 1059*m*, 1018*m*, 1012*m*. ^{1}H-NMR (360 MHz): 1.46 (br. *q*, ^2J = ^3J = 11, H_α–C(8)); 1.60–1.84 (*m*, 2H–C(1)); 1.84–2.02 (*m*, 2H–C(2), H_β–C(8a)); 2.15–2.40 (*m*, H_α–C(3), H_β–C(8)); 2.30 (*s*, $COCH_3$); 2.57 (*m*, H_β–C(5)); 3.05 (*dt*, ^2J = 9, ^3J = 9, 2, H_α–C(3)); 3.18 (*m*, H_β–C(6)); 3.31 (*dd*, ^2J = 11.5, ^3J = 4, H_α–C(5)); 3.91 (*dt*, ^3J = 10, 5, 5, H_β–C(7)); 7.02 (*d*, ^3J = 8.5, H–C(3'), H–C(5')); 7.69 (br. *d*, ^3J = 8.5, H–C(2'), H–C(6')). MS: 275 (32), 274 (31), 258 (4), 162 (28), 120 (100), 107 (10), 100 (17), 96 (20), 91 (13), 84 (52), 70 (29), 69 (27). Anal. calc. for $C_{16}H_{21}NO_3$ (275.35): C 69.79, H 7.69, N 5.09; found: C 69.82, H 7.66, N 5.12.

6β, 7α-Isomer of **9d**: IR ($CHCl_3$): 3695*m*, 3600*m*, 2978*m*, 2922*m*, 2870*w* (br.), 2800*m*, 1757*s*, 1606*w*, 1506*m*, 1372*s*, 1222*s*, 1200*s*, 1168*m*, 1108*m*, 1073*m*, 1050*w*, 1016*w*, 1005*m*. ^{1}H-NMR (360 MHz): 1.48 (br. *q*, ^2J = ^3J = 11.5, H_α–C(8)); 1.51–1.65 (*m*, 2H–C(1)); 1.68–2.30 (*m*, 2H–C(2), H_β–C(3), H_β–C(5), H_β–C(8), H_β–C(8a)); 2.31 (*s*, $COCH_3$); 2.89 (*m*, H_α–C(6)); 3.11 (*dt*, ^2J = 9, ^3J = 9, 2.5, H_α–C(3)); 3.19 (*dd*, ^2J = 11.5, ^3J = 4, H_α–C(5)); 3.80 (*dt*, ^3J = 10.5, 10.5, 4.5, H_β–C(7)); 7.07 (*d*, ^3J = 8.5, H–C(3'), H–C(5')); 7.30 (*d*, ^3J = 8.5, H–C(2'), H–C(6')). *6β, 7β-Isomer of* **9d**: IR ($CHCl_3$): 3700*w* (br.), 3610*m*, 2995*m*, 2920*m*, 2810*w*, 1760*s*, 1605*m*, 1508*m*, 1457*w*, 1369*m*, 1225*s*, 1202*s*, 1169*m*, 1132*w*, 1102*w*, 1042*m*, 1017*m*. ^{1}H-NMR (360 MHz): 1.63–2.11 (*m*, 2H–C(1), 2H–C(2), H_α–C(8)); 2.19 (*dt*, ^2J = 14, ^3J = 3, 3, H_β–C(8)); 2.31 (*s*, $COCH_3$); 2.49 (*q*, ^3J = ^2J = 9, H_β–C(3)); 2.82 (*m*, H_β–C(8a)); 3.01 (br. *t*, ^2J = ^3J = 10.5, H_β–C(5)); 3.25 (*dd*, ^2J = 10.5, ^3J = 4, H_α–C(5)); 3.32–3.45 (*m*, H_α–C(3), H_α–C(6)); 4.13 (*q*, ^3J = 2.5, H_α–C(7)); 7.08 (*d*, ^3J = 8.5, H–C(3'), H–C(5')); 7.25 (*d*, ^3J = 8.5, H–C(2'), H–C(6')).

b) A soln. of **6d** (400 mg, 1.49 mmol) in abs. EtOH (130 ml) was hydrogenated at 50° and at an initial pressure of 60 psi over Rh/activated alumina (200 mg). After 5 h, the mixture was filtered, evaporated, and purified by CC on silica gel. Elution with $MeOH/CH_2Cl_2$ 1:19 afforded **10d** (28 mg, 7%), then **8d** (53 mg, 13%), elution was continued with $MeOH/CH_2Cl_2$ 1:3 to give **9d**. Recrystallization from EtOAc gave the 6α, 7α-isomer of **9d** (103 mg, 25%) as colorless needles and a *ca.* 1:1 mixture of the 6β, 7α- and 6β, 7β-isomers of **9d** (145 mg, 35%).

6-(4'-Acetoxyphenyl)-2,3,5,6,8,8a-hexahydro-7(1H)-indolizinone (**10d**). To an ice-cold soln. of a mixture of **9d** (280 mg, 1.04 mmol) in acetone (20 ml) was added H_2SO_4 (96%, 0.08 ml), then *Jones* reagent (0.2 ml) [30]. The mixture was stirred 65 min at 0°, then quenched with i-PrOH (0.5 ml), diluted with EtOAc (50 ml), and neutralized with 5% aq. $NaHCO_3$ soln. with vigorous stirring. The resulting suspension was filtered through *Celite* and the org. layer separated, washed with H_2O (3 × 20 ml), dried (Na_2SO_4), and evaporated. Purification of the residue by flash CC (SiO_2, EtOAc) gave, after recrystallization from Et_2O/hexane, **10d** (176 mg, 62%) as colorless needles, m.p. 93–95°. IR ($CHCl_3$): 2975*m*, 2940*m*, 2880*w*, 2706*m*, 1756*s*, 1720*s*, 1509*s*, 1372*s*, 1193*s*, 1168*m*, 1018*m*, 1011*w*, 913*m*. ^{1}H-NMR (360 MHz): 1.60 (*m*, H–C(1)); 1.86 (*m*, H–C(2)); 1.95–2.15 (*m*, H–C(1), H–C(2)); 2.28 (*s*, $COCH_3$); 2.28 (*q*, $^3J = {}^2J = 9$, H_β–C(3)); 2.40–2.54 (*m*, H_β–C(8a), H_α–C(8)); 2.58 (br. *t*, $^2J = {}^3J = 11.5$, H_β–C(5)); 2.68 (*m*, H_β–C(8)); 3.18 (*dt*, $^2J = 9$, $^3J = 9, 2$, H_α–C(3)); 3.47 (*dd*, $^2J = 11.5$, $^3J = 6.5$, H_α–C(5)); 3.85 (*dd*, $^3J = 11.5, 6.5$, H_α–C(6)); 7.07 (*AA'* of *AA'BB'*, $^3J \approx 8.5$, H–C(3'), H–C(5')); 7.16 (*BB'*, $^3J \approx 8.5$, H–C(2'), H–C(6')); ^{1}H-NMR (C_6D_6, 360 MHz): 1.35 (*m*, H–C(1)); 1.55 (*m*, H–C(2)); 1.68 (*m*, H–C(1)); 1.82 (*m*, H–C(2)); 1.90 (*s*, $COCH_3$); 1.98 (*q*, $^3J = {}^2J = 8.5$, H_β–C(3)); 2.13 (*m*, H_β–C(8a)); 2.25 (*dd*, $^2J = 13$, $^3J = 11.5$, H_α–C(8)); 2.33 (*dd*, $^2J = 11$, $^3J = 12$, H_β–C(5)); 2.60 (*dd*, $^2J = 13$, $^3J = 3$, H_β–C(8)); 2.93 (*dt*, $^2J = 8.5$, $^3J = 8.5, 2.5$, H_α–C(3)); 3.15 (*dd*, $^2J = 11$, $^3J = 6$, H_α–C(5)); 3.70 (*dd*, $^3J = 12, 6$, H_α–C(6)); 7.12, 7.23 (*AA'BB'*, $^3J \approx 8.5$, arom. H). MS: 273 (42, $M^{+\cdot}$), 272 (10), 230 (6), 166 (22), 134 (15), 133 (8), 121 (9), 120 (100), 112 (8), 97 (16), 96 (25), 91 (7), 84 (8), 83 (7), 82 (8), 70 (20), 68 (8). Anal. calc. for $C_{16}H_{19}NO_3$ (273.33); C 70.31, H 7.01, N 5.13; found: C 70.23, H 6.97, N 5.12.

2,3,5,6,8,8a-Hexahydro-6-(4'-methoxyphenyl)-7(1H)-indolizinone (**10b**). $LiAlH_4$ (6.5 mg, 0.17 mmol) was added to a soln. of **8b** (43 mg, 0.17 mmol) in dry THF (10 ml). The mixture was stirred 10 min, quenched with H_2O (0.5 ml), and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was purified by flash CC (SiO_2, $MeOH/CHCl_3$ 1:19) to give **10b** (26 mg, 61%) as colorless needles, m.p. 109–110° ([7]: 105–106°; [4b] [5c]: 109–110°). IR (CH_2Cl_2): 3040*w*, 3010*w*, 2970*m*, 2945*m*, 2885*w*, 2845*w*, 2810*m*, 1718*s*, 1618*m*, 1518*s*, 1464*m*, 1243*m*, 1218*m*, 1181*s*, 1232*w*, 1213*w*, 1201*w*, 1036*m*, 910*s*, 833*m*. ^{1}H-NMR (360 MHz): 1.65 (*m*, H–C(1)); 1.89 (*m*, H–C(2)); 1.96–2.13 (*m*, H–C(1), H–C(2)); 2.31 (*q*, $^2J = {}^3J = 9$, H_β–C(3)); 2.40–2.57 (*m*, H_α–C(8), H_β–C(8a)); 2.58 (*dd*, $^2J = 11$, $^3J = 11.5$, H_β–C(5)); 2.69 (*m*, H_β–C(8)); 3.22 (*dt*, $^2J = 9$, $^3J = 9, 2$, H_α–C(3)); 3.51 (*dd*, $^2J = 11$, $^3J = 6.5$, H_α–C(5)); 3.82 (*s*, CH_3O); 3.83 (*dd*, $^3J = 11.5, 6.5$, H_α–C(6)); 6.93 (*AA'* of *AA'BB'*, $^3J \approx 8.5$, H–C(3'), H–C(5')); 7.09 (*BB'*, $^3J \approx 8.5$, H–C(2'), H–C(6')). MS: 247 (7), 245 (39, $M^{+\cdot}$), 244 (8), 148 (11), 135 (12), 134 (100), 120 (10), 97 (19), 96 (18), 91 (10). Anal. calc. for $C_{15}H_{19}NO_2$ (245.32): C 73.44, H 7.81, N 5.71; found: C 73.52, H 7.99, N 5.68.

1,2,3,5,6,7,8,8a-Octahydro-6β-(4'-hydroxyphenyl)-7α-methylindolizin-7β-ol (**11**, R=H). A soln. of **10d** (62 mg, 0.23 mmol) in dry THF (7 ml) was added dropwise over 25 min to a soln. of MeLi (1.35M in Et_2O; 6 ml, 8 mmol) in dry THF (23 ml). After stirring at r.t. for 18 h, the mixture was quenched with 10% aq. HCl soln. (5 ml), and Et_2O (50 ml) was added. The aq. layer was separated, its pH adjusted to 10 with conc. aq. NH_3 soln., and extracted with CH_2Cl_2 (4 × 50 ml). The org. layers were washed with brine (50 ml), dried ($MgSO_4$) and evaporated. The oily solid was purified by flash CC (SiO_2). Elution with acetone yielded **10** (R^1 = OH; 9 mg, 17%) and elution with acetone/MeOH 1:1 **11** (R = H; 35 mg, 62%) as a colorless oil which on trituration with Et_2O gave an amorphous powder, m.p. 136–138°.

2,3,5,6,8,8a-Hexahydro-6-(4'-hydroxyphenyl)-7(1H)-indolizinone (**10**; R^1 = OH): IR (CH_2Cl_2): 3695*m*, 3605*m*, 2955*s*, 2800*m*, 1712*s*, 1612*w*, 1600*m*, 1516*s*, 1260*s*, 1248*s*, 1216*w*, 1172*m*, 862*s*. ^{1}H-NMR (200 MHz): 1.5–1.75 (*m*, H–C(1), H–C(2)); 1.8–2.1 (*m*, H–C(1), H–C(2), H_α–C(8)); 2.29 (*q*, $^2J = {}^3J = 9$, H_β–C(3)); 2.4–2.7 (*m*, H_β–C(5), H_β–C(8), H_β–C(8a)); 3.20 (br. *t*, $^2J = {}^3J = 9$, H_α–C(3)); 3.46 (*dd*, $^2J = 11$, $^3J = 6$, H_α–C(5)); 3.8 (*dd*, $^3J = 12, 6$, H_α–C(6)); 6.79 (*AA'* of *BB'*, $^3J \approx 8.5$, H–C(3'), H–C(5')); 6.99 (*BB'*, $^3J \approx 8.5$, H–C(2'), H–C(6')).

11 (R = H): IR (CH_2Cl_2): 3700*m*, 3605*m*, 3300 (v.br.), 2972*s*, 2935*s*, 2880*w*, 2820*m*, 1618*m*, 1518*s*, 1455*m* (br.), 1378*m*, 1260*s*, 1173*s*, 1106*m*, 1068*w*, 1040*w*, 1013*m*, 836*m*. ^{1}H-NMR (200 MHz): 1.02 (*s*, CH_3); 1.47 (*dq*, $^2J = 11$, $^3J = 11, 11, 7$, H_α–C(1)); 1.53 (*dd*, $^2J = 13.5$, $^3J = 12$, H_α–C(8)); 1.70–1.92 (*m*, H_β–C(1), 2H–C(2)); 1.96 (*dd*, $^2J = 13.5$, $^3J = 3$, H_β–C(8)); 2.27 (*q*, $^2J = {}^3J = 9$, H_β–C(3)); 2.49 (*m*, H_β–C(8a)); 2.70 (*dd*, $^2J = 12$, $^3J = 10$, H_β–C(5)); 2.82 (*dd*, $^2J = 12$, $^3J = 3$, H_α–C(5)); 2.98 (*dd*, $^3J = 9.5, 3$, H_β–C(6)); 3.13 (*dt*, $^2J = 9$, $^3J = 9, 2$, H_α–C(3)); 4.10 (v.br., 2 OH); 6.76 (*d*, $^3J = 8.5$, H–C(3'), H–C(5')); 7.05 (*d*, $^3J = 8.5$, H–C(2'), H–C(6')). MS: 247 (22, $M^{+\cdot}$), 246 (15), 230 (4), 188 (8), 128 (22), 120 (36), 107 (10), 100 (10), 97 (10), 96 (12), 70 (100). HR-MS: 247.1571 ($C_{15}H_{21}NO_2$, calc. 247.1572).

(±)-Ipalbidine (**1b**). A soln. of **10d** (43 mg, 0.16 mmol) in dry THF (8 ml) was added dropwise over 80 min to a soln. of MeLi (1.35M in Et_2O; 1.5 ml, 2.02 mmol) in dry THF (10 ml). The mixture was stirred 24 h at r.t. before quenching with Ac_2O (230 mg, 0.25 ml, 2.5 mmol). The yellow soln. was filtered to remove suspended solid and evaporated to give a yellow-orange solid. Et_2O (25 ml) was added and the soln. containing a fine solid was washed with sat. aq. $NaHCO_3$ soln. (10 ml), brine (10 ml), and dried ($MgSO_4$). Evaporation gave 50.5 mg (97%) of crude *6-(4'-acetoxyphenyl)-1,2,3,5,6,7,8,8a-octahydro-7-methylindolizin-7-yl acetate* (**11**, R = Ac). IR (CCl_4): 2970*m*, 2940*m*, 2875*w*, 2805*m*, 1770*s*, 1740*s*, 1609*w*, 1504*s*, 1368*s*, 1232*s*, 1212*s*, 1200*s*, 1158*m*, 1140*w*, 1120*w*, 1108*w*, 1068*w*, 1041*m*, 1018*s*, 940*w*, 910*m*, 840*w*. ^{1}H-NMR (200 MHz): 1.25–2.35 (*m*, 17H including 3*s* each of 3H at 1.32, 2.02, 2.27); 2.6–3.2 (*m*, H–C(3), 2H–C(5), H–C(6)); 6.95–7.35 (2*AB*, 4 arom. H). MS: 331 (13, $M^{+\cdot}$), 289 (14), 288 (13), 272 (54), 271 (56), 270 (20), 256 (16), 230 (13), 229 (10), 214 (8), 162 (24), 161 (31), 160 (18), 145 (13), 142 (20), 136 (14), 122 (16), 121 (16), 120 (100), 119 (13), 107 (18), 97 (15), 96 (20), 91 (19), 84 (14), 83 (42), 82 (19), 70 (55).

The crude **11** (R = Ac; 27 mg, 0.08 mmol) was dissolved in 48% aq. HBr soln. (10 ml) and heated to 80° for 1 h. The brown soln. was poured into sat. aq. $NaHCO_3$ soln. (40 ml) and extracted with $CHCl_3$ (4 × 30 ml). The org. layers were washed with brine (50 ml) and dried ($MgSO_4$). Evaporation gave a brown oil which was purified by flash CC (SiO_2, MeOH/$CHCl_3$ 1:9) to give **1b** (5.5 mg, 30%) as a colorless oil. UV (abs. EtOH): 238 (10150), 278 (1750). UV (abs. EtOH 1 drop of 10% NaOH): 161 (12400). IR ($CHCl_3$): 3605*m*, 2985*w*, 2915*w*, 2880*w*, 1611*m*, 1514*s*, 1256*m*, 832*m*. ^{1}H–NMR (360 MHz): 1.58 (br. *s*, CH_3); 1.60 (*m*, H–C(1)); 1.75–2.60 (*m*, H–C(1), 2H–C(2), H_β–C(3), 2H–C(8), H–C(8a)); 3.01 (br. *d*, ^2J = 15.5, H_β–C(5)); 3.31 (br. *t*, $^2J = {}^3J$ = 8.5, H_α–C(3)); 3.65 (br. *d*, ^2J = 15.5, H_α–C(5)); 6.77 (*AA'* of *AA'BB'*, $^3J \approx$ 8.5, H–C(3'), H–C(5')); 7.06 (*BB'*, $^3J \approx$ 8.5, H–C(2'), H–C(6')); MS: 229 (9, $M^{+\cdot}$), 214 (5), 160 (6), 149 (5), 145 (26), 115 (5), 107 (6), 71 (9), 70 (100), 57 (7).

REFERENCES

[1] a) J.E. Saxton, 'The Alkaloids', Specialist Periodical Report, The Royal Society of Chemistry, London, 1971–75, Vol. 1–5; b) J.A. Lamberton, *ibid.* 1976–83, Vol. 6–13; *Nat. Prod. Rep.* **1984,** *1,* 245; c) M.F. Grundon, *ibid.* **1985,** *2,* 235; d) S.R. Jones, J.A. Lamberton, 'The Alkaloids', Ed. R.H.F. Manske, Academic Press, London, 1973, Vol. 14, pp. 325–346; e) E. Gellert, *J. Nat. Prod.* **1982,** *45,* 50.

[2] a) R.V. Stevens, *Acc. Chem. Res.* **1977,** *10,* 193; b) R.V. Stevens, Y. Luh, *Tetrahedron Lett.* **1977,** 979; c) L.E. Overman, K.L. Bell, *J. Am. Chem. Soc.* **1983,** *103,* 1851.

[3] a) W.N. Speckamp, *Recl. Trav. Chim. Pays-Bas* **1981,** *100,* 345; b) D.J. Hart, T.-K. Yang, *Tetrahedron Lett.* **1982,** *23,* 2761; c) D.J. Hart, Y.-M. Tsai, *J. Org. Chem.* **1982,** *47,* 4403; d) A.R. Chamberlin, H.N. Nguyen, J.Y.L. Chung, *ibid.* **1984,** *49,* 1682; e) H. Hiemstra, M.H.A.M.O. Sno, R.J. Vijn, W.N. Speckamp, *ibid.* **1985,** *50,* 4014; f) J.-C. Gramain, R. Remuson, *Tetrahedron Lett.* **1985,** *26,* 327.

[4] a) S.H. Hedges, R.B. Herbert, *J. Chem. Res. (M)* **1979,** 410; b) A.S. Howard, G.C. Gerrans, J.P. Michael, *J. Org. Chem.* **1980,** *45,* 1713.

[5] a) A.E. Wick, P.A. Bartlett, D. Dolphin, *Helv. Chim. Acta* **1971,** *54,* 513; b) T. Shono, Y. Matsumura, K. Uchida, K. Tsubata, A. Makino, *J. Org. Chem.* **1984,** *49,* 300; c) H. Iida, Y. Watanabe, C. Kobayashi, *Chem. Lett.* **1983,** 1195; *J. Chem. Soc., Perkin Trans. 1* **1985,** 261.

[6] T. Tanaka, H. Iijima, *Tetrahedron* **1983,** *29,* 1285.

[7] a) T. Govindachari, A.R. Sidhaye, N. Viswanathan, *Tetrahedron* **1970,** *26,* 3829; b) Z.-J. Liu, R.-R. Lu, Q. Chen, H. Hong, *Acta Chim. Sinica* (English Edition) **1985,** 262.

[8] a) P.E. Sonnet, J.E. Oliver, *J. Heterocycl. Chem.* **1975,** *12,* 289; b) T.L. Macdonald, *J. Org. Chem.* **1980,** *45,* 193; c) T. Iwashita, T. Kusumi, H. Kakaisawa, *ibid.* **1982,** *47,* 231; d) H. Otomasu, N. Takatsu, T. Honda, T. Kametani, *Heterocycles* **1982,** *19,* 511; e) L.E. Overman, S.W. Goldstein, *J. Am. Chem. Soc.* **1984,** *106,* 5360.

[9] a) L.E. Overman, C. Fukaya, *J. Am. Chem. Soc.* **1980,** *102,* 1454; b) J. Royer, H.-P. Husson, *J. Org. Chem.* **1985,** *50,* 670.

[10] a) E.W. Thomas, *J. Org. Chem.* **1986,** *51,* 2184; b) A. Brandi, A. Guarna, A. Goti, F. De Sarlo, *J. Chem. Soc., Chem. Commun.* **1986,** 813.

[11] M.T. Pizzorno, S.M. Albonico, *J. Org. Chem.* **1974,** *39,* 731; *ibid.* **1977,** *42,* 909.

[12] a) D.J. Hart, Y.-M. Tsai, *J. Am. Chem. Soc.* **1982,** *104,* 1430; b) J.-K. Choi, D.J. Hart, Tetrahedron **1985,** *41,* 3959.

[13] a) S.R. Wilson, R.A. Sawicki, *J. Org. Chem.* **1979,** *44,* 330; b) T. Ohnuma, M. Tabe, K. Shijia, Y. Ban, T. Date, *Tetrahedron Lett.* **1983,** *24,* 4249; c) H. Setoi, H. Takeno, M. Hashimoto, *J. Org. Chem.* **1985,** *50,* 3950.

[14] a) N.A. Khatri, H.F. Schitthenner, J. Shringapure, S.M. Weinreb, *J. Am. Chem. Soc.* **1981,** *103,* 6387; b) Y.-S. Cheng, A.T. Lupo, F.W. Fowler, *ibid.* **1983,** *105,* 7696; c) S.D. Larsen, P.A. Grieco, *ibid.* **1985,** *107,* 1768; d) S.M. Weinreb, *Acc. Chem. Res.* **1985,** *18,* 16.

[15] a) D.J. Robins, *Adv. Heterocycl. Chem.* **1979,** *24,* 247; *Fortschr. Chem. Org. Naturstoffe* **1982,** *41,* 115; *Nat. Prod. Rep.* **1984,** *1,* 235; *ibid.* **1985,** *2,* 213; b) J.T. Wróbel, 'The Alkaloids', Ed. A. Brossi, Academic Press, London, 1985, Vol. 26, pp. 327–384; c) R. Neidlein, G. Jeromin, *J. Chem. Res. (M)* **1980,** 3078; *Chem. Ber.* **1982,** *115,* 714; d) W. Klose, K. Nickisch, F. Bohlmann, *ibid.* **1980,** *113,* 2694; e) E. Galeazzi, A. Guzmán, A. Pinedo, A. Salañada, D. Torre, J.M. Muchowski, *Can. J. Chem.* **1983,** *61,* 454; f) C. Ortiz, R. Greenhouse, *Tetrahedron Lett.* **1985,** *26,* 2831.

[16] S. Danishefsky, R. McKee, R.K. Singh, *J. Am. Chem. Soc.* **1972,** *99,* 4783.

[17] T. Kametani, H. Yukawa, T. Honda, *J. Chem. Soc., Chem. Commun.* **1986,** 651.

[18] C.W. Jefford, W. Johncock, *Helv. Chim. Acta* **1983,** *66,* 2666.

[19] a) Isolation: J.M. Gourley, R.A. Heacock, A.G. McInnes, B. Nikolin, D.G. Smith, *J. Chem. Soc., Chem. Commun.* **1969,** 709; b) synthesis: see [2b] [4a] [4b] [5a] [5c] [7].

[20] a) H. Schinz, M. Hinder, *Helv. Chim. Acta* **1947,** *30,* 1349; b) J. Dutta, R.N. Biswas, *J. Indian Chem. Soc.* **1963,** *40,* 629 (CA: **1963,** *59,* 13841c); c) G.M. Kasander, J.E. McMurry, M. Johnson, *J. Org. Chem.* **1977,** *42,* 1180; d) C. Mannich, L. Stern, *Ber. Dtsch. Chem. Ges.* **1925,** *58,* 2659; e) J.H. Schauble, E. Hertz, *J. Org. Chem.* **1970,** *35,* 2529; f) J.H. Schauble, E.H. Freed, M.D. Swerdloff, *ibid.* **1971,** *36,* 1302.

[21] a) K. Hartke, S. Radau, *Liebigs Ann. Chem.* **1974,** 2110; b) K. Matoba, T. Yamazaki, *Chem. Pharm. Bull.* **1982,** *30,* 2586, and ref. cit. therein.

[22] C.J. Hobbs, C.K. McMillin, E.P. Papadopoulos, C.A. Van der Werf, *J. Am. Chem. Soc.* **1962,** *84,* 43.

[23] a) D.S. Tarbell, J.A. Price, *J. Org. Chem.* **1957,** *22,* 245; b) B. Penke, J. Czombos, L. Baláspir, J. Petres, K. Kovács, *Helv. Chim. Acta* **1970,** *53,* 1057; c) B. Zwanenburg, L. Thijis, *Tetrahedron Lett.* **1974,** 2459.

[24] a) A.J. Anciaux, A.J. Herbert, A.F. Noels, N. Petiniot, P. Teyssie, *J. Org. Chem.* **1980,** *45,* 695; b) B.E. Maryanoff, *ibid.* **1982,** *47,* 3000; c) M.A. McKervey, S.M. Tuladhar, M.F. Twohig, *J. Chem. Soc., Chem. Commun.* **1984,** 120.

[25] D.J. Robins, S. Sakdarat, *J. Chem. Soc., Chem. Commun.* **1979,** 1181; *J. Chem. Soc., Perkin Trans. 1* **1979,** 1734.

[26] a) H. Visconti, M. Buzeck, *Helv. Chim. Acta* **1972,** *55,* 670; b) R.R. Renshaw, W.E. Cass, *J. Am. Chem. Soc.* **1939,** *61,* 1195.

[27] a) R. Adams, S. Miyano, D. Fles, *J. Am. Chem. Soc.* **1960,** *82,* 1466; b) E.E. Schweitzer, K.K. Light, *ibid.* **1964,** *86,* 2963.

[28] F. Bohlmann, *Chem. Ber.* **1958,** *91,* 2157.

[29] a) P.J. Chivers, T.A. Crabb, *Tetrahedron* **1970,** *26,* 3389; b) R. Cahill, T.A. Crabb, *Org. Magn. Reson.* **1972,** *4,* 259; c) B. Ringdahl, A.R. Pinder, W.E. Pereira, N.J. Oppenheimer, J.C. Craig, *J. Chem. Soc., Perkin Trans. 1* **1984,** 1.

[30] K. Bowden, I.M. Heilbron, E.R.H. Jones, B.C.L. Weedon *J. Chem. Soc.* **1946,** 39.