12. Approaches to the Synthesis of Cytochalasans. Part 2. Pyrrolinone Derivatives as Basic Units[1][2])

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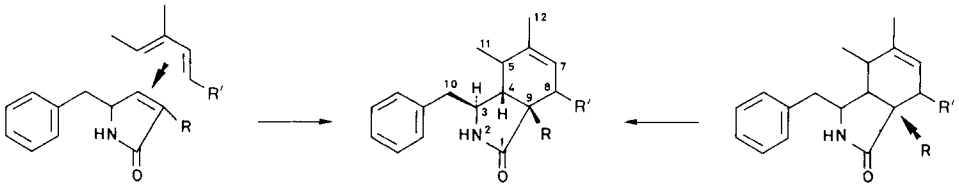
Summary

Several attempts to prepare 3-acetyl-5-benzyl-3-pyrrolin-2-one (**7**) from phenylalanine are described. This goal was only reached formally, because compound **7** exists in the tautomeric form of (*Z*)-5-benzyl-3-(1′-hydroxyethylidene)-4-pyrrolin-2-one (**17**) according to the spectral data. The problem of tautomerism in pyrrolinone systems is discussed.

The formation of an appropriate pyrrolinone system represents a major task in any synthetic approach toward cytochalasans [2]. Several studies have been carried out for the construction of this part of the molecule which should serve as a basic unit for the annelation of the cyclohexane ring. Because a *cis* ring-fusion is required for the resulting octahydroisoindolone system, a *Diels-Alder* reaction was used for its formation. Some difficulties arose, however, with respect to the intro-

Scheme 1



duction of the functionality R which should allow an easy completion of the macrocyclic system. The substituent R may either be present already in the dienophile, or may be inserted after the elaboration of the condensed ring system *(Scheme 1)*. The first approach has been used in early attempts by several authors [1] [3–5] and was recently realized by *Stork et al.* [6] in the synthesis of a relay compound which was convertible to cytochalasin B (Phomin). The second concept

[1]) Part 1: [1].

[2]) Part of the Ph.D. Thesis of *T. Schmidlin*, Basel 1979.

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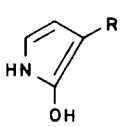
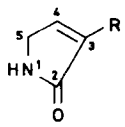
was adopted as a consequence of symmetry in the initial steps [7-10]. However, the introduction of a suitable functionality R with correct stereochemistry has so far failed [9] [10].

The present paper deals with two synthetic approaches to the construction of the pyrrolinone system **7** carrying an acetyl group at C(3). This functionality is readily convertible into a variety of other potentially useful groups, and was thought to be equally suitable for the synthesis of both the macrocarbocyclic and the macrolidic cytochalasans. In the latter case the acetyl group has to be transformed at a later stage into the acetoxy group by a *Baeyer-Villiger* reaction.

From the literature one might conclude that 2-hydroxy-pyrroles (**1**) do not exist [11] [12]. The pyrrolinone structures **2** or **3** are clearly favoured (^{1}H-NMR.) [13]; moreover, one could assume that the presence of a C(3)-carbonyl function in a pyrrolinone like **7** (see *Scheme 2*) would stabilize the C(3), C(4)-double bond [12].



1



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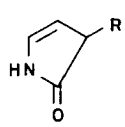


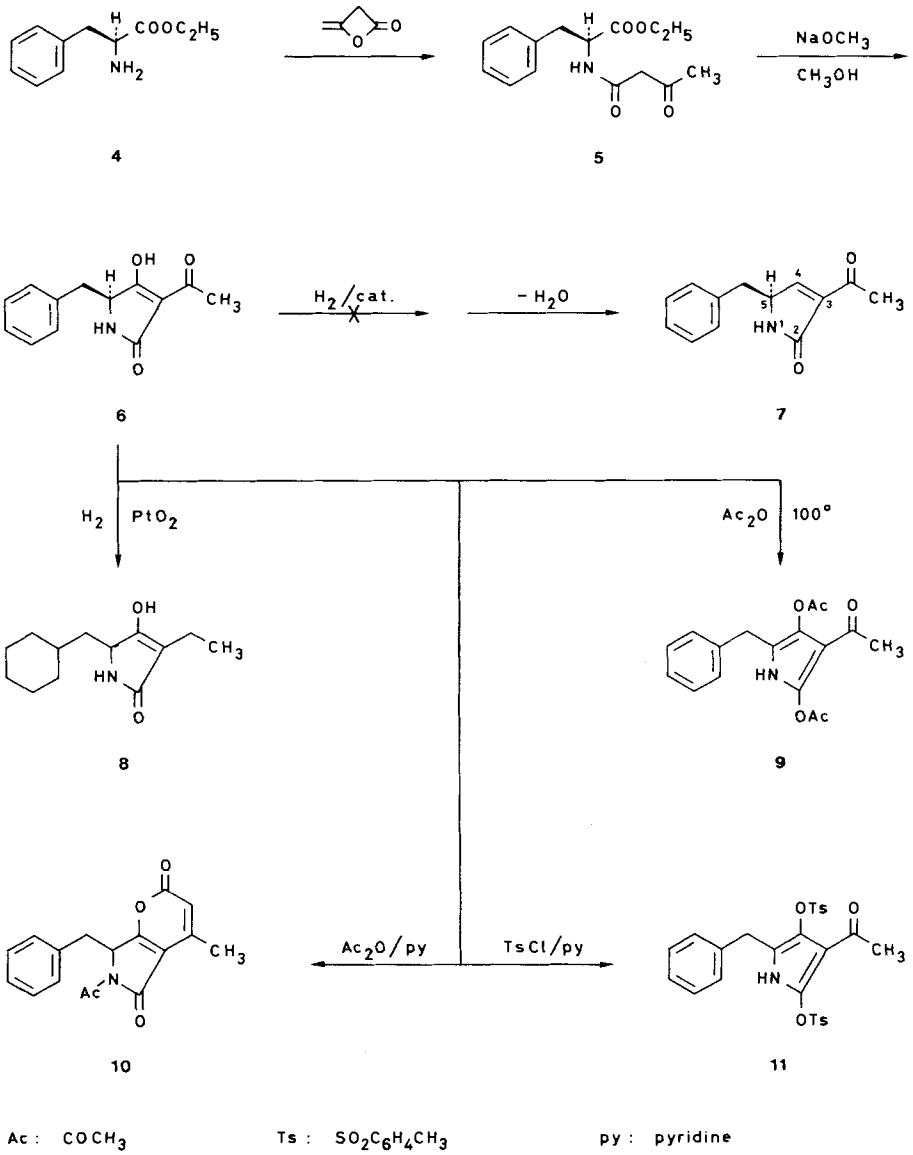
3

We first tried to obtain the desired pyrrolinone **7** using the readily available tetramic acid **6** [14], which already contains the desired 3-acetyl and 5-benzyl groups. Furthermore, if derived from (*S*)-phenylalanine, the resulting chiral **6** possesses the same configuration as, for instance, cytochalasin B. It should therefore be suitable for the stereospecific construction of the octahydroisoindolone moiety of the cytochalasans. When **6** was prepared from (*S*)-phenylalanine ethyl ester (**4**) according to [14], the reaction proceeded with racemization. Pure (*S*)-**6** exhibits a specific rotation of $-216°$ (ethanol). It can be prepared in high optical purity provided any excess of base during the condensation is strictly avoided.

For convenience, the investigations to be described have been conducted with the racemates. The conversion of **6** to **7** was expected to be easily achieved by selective catalytic hydrogenation of the enolic double bond followed by the elimination of water from the resulting hydroxy ketone. In spite of known analogies [15], the enolic double bond in **6** did not react with hydrogen in the presence of Pd-black, Pd/C or *Raney*-Ni under a variety of conditions, but with *Adams*'s catalyst a slow uptake of five mol-equivalents occurred. Surprisingly, a strongly polar product with acidic properties was formed in high yield. Analytical and spectroscopic data agreed well with structure **8** resulting from a reduction of the side chain carbonyl group and saturation of the phenyl ring.

Since the enolic double bond was so inert, we turned our attention to indirect methods. Enolizable 1,3-diketones are converted into 1,3-diols or even allylic alcohols by complex hydrides [16]. However, sodium borohydride failed to react with **6** even in boiling propan-2-ol for several hours. Because extensive delocalization of π-electron density might be responsible for the inertness of the keto-enol

Scheme 2



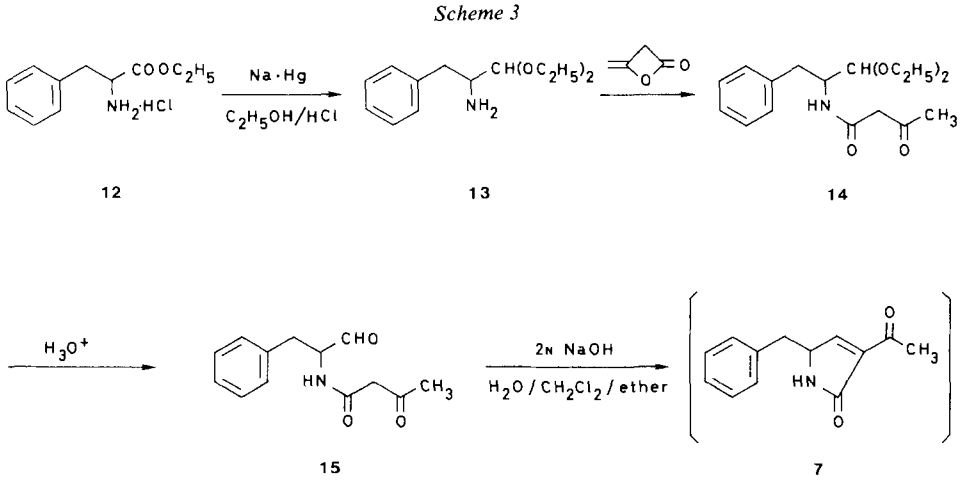
Ac : $COCH_3$ Ts : $SO_2C_6H_4CH_3$ py : pyridine

system, we tried to block selectively the enolic hydroxyl group. Treatment of **6** with acetic anhydride resulted, however, in the formation of the undesired di-*O*-acetyl derivative **9**[3]). With acetic anhydride in pyridine a mixture of products was

[3]) Compounds **9** and **11** are only tentatively formulated as pyrrole derivatives by analogy [17]. Tautomeric dienolic structures can not be ruled out, but this problem is irrelevant for this investigation.

obtained from which only compound **10** could be isolated in low yield[4]). The methoxymethyl ether could not be prepared, compound **6** and its sodium salt reacting neither with methoxymethylmethane sulfonate in tetrahydrofuran nor with methylal/phosphoric anhydride in chloroform. Attempts to convert the enolic hydroxyl group selectively into the corresponding tosylate for subsequent reductive elimination [19] were unsuccessful, only the di-*O*-tosylate **11**[3]) being obtained.

Scheme 3



12 13 14 15 7

Since the conversion of the tetramic acid **6** into the desired 3-acetyl-5-benzyl-3-pyrrolin-2-one (**7**) failed, a reaction sequence was studied in which the enolic hydroxyl group is not formed. 2-Amino-3-phenylpropanal diethyl acetal (**13**) [20], obtained by reduction of the ester **12**, was condensed with diketene to give the acetoacetic amide **14** in almost quantitative yield. Hydrolysis of the acetal group of **14** by 7% hydrochloric acid in aqueous tetrahydrofuran led to the free aldehyde **15** *(Scheme 3)*, easily recognizable by its strong reducing properties. Although the aldehyde **15** undergoes rapid alteration, presumably by polymerization, freshly prepared samples when treated with 2N aqueous sodium hydroxide solution in a dichloromethane/ether mixture at room temperature, underwent a clean intramolecular *Knoevenagel-Cope* condensation[5]) to give a new compound in 66% yield. According to elemental analysis and the molecular peak *m/z* 215 in the mass spectrum, the product possesses the formula $C_{13}H_{13}NO_2$. However, much to our surprise, the ^{1}H-NMR. spectrum did not exhibit an ABMX-spin-system which should give rise to an 8-line splitting pattern, highly characteristic for the C(5) proton of structure **7**. Furthermore, **7** was ruled out by the presence of two broad single proton signals at 8.65 and 11.3 ppm, which were assigned to an NH or OH group;

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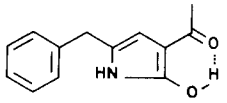
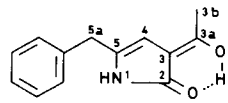
[4]) The formation of a pyran-2-one by intramolecular condensation represents a stereoelectronically favoured 6-*exo*-trig process [18].

[5]) A variety of commonly applied reaction conditions, *e.g.* catalysis by triethylammonium benzoate in boiling xylene, piperidine in boiling pyridine or potassium carbonate in methanol at room temperature gave very unsatisfactory results.

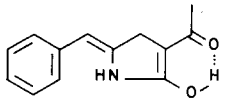
when deuteriochloroform was replaced by hexadeuterioacetone these signals collapsed to a broad two proton signal centered at 9.45 ppm[6]). The tautomeric structures **16–19** had to be considered for the reaction product.



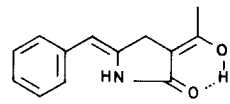
16



17



18

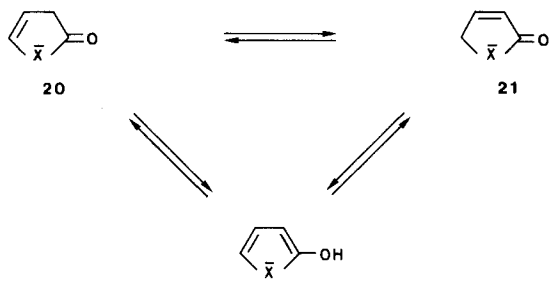


19

Although the ^{1}H-NMR. spectrum was compatible with an aromatic system such as **16**, the existence of a real hydroxypyrrole was doubtful[7]). For instance 2-hydroxypyrroles with a carboxyl group at position 3 [21] possess the pyrrolinone structure [22]. In the case of 3,4-dimethyl-3-pyrrolin-2-one the presence of the tautomeric 3,4-dimethyl-2-hydroxypyrrole was ruled out by spectral evidence [23]. The same conclusion was reached for the parent 3-pyrrolin-2-one (^{1}H-NMR.) [12]. Another derivative, originally believed to be 3,4-dimethyl-5-formyl-2-hydroxypyrrole [24], was later recognized to have the non-aromatic structure of 3,4-dimethyl-5-hydroxymethylene-3-pyrrolin-2-one (IR. and ^{1}H-NMR.) [25].

Semi-empirical SCF-MO-calculations [13] show that the gain in resonance energy associated with a change from the 3-pyrrolin-2-one to the tautomeric 2-hydroxypyrrole is far too small to provide the free energy required for the enolization of the lactam carbonyl group. Of the prototropic forms **20**, **21** and **22**, for both X=O and X=NH, these quantum mechanical calculations predict structure **21** to be thermodynamically favoured over **20** and **22**.

On the basis of the following arguments structure **17** can be assigned to the condensation product obtained from the aldehyde **15**. UV. absorption is observed at 207, 238 and 325 nm with extinction coefficients of 15,960, 10,280 and 5,700,



20 **21** **22**

6) The change of solvent caused only small shifts for the other resonances.

7) For heteroaromatic systems with potential hydroxyl or amino groups it may be often difficult to decide firmly whether one single form or a mixture of individual tautomers is present.

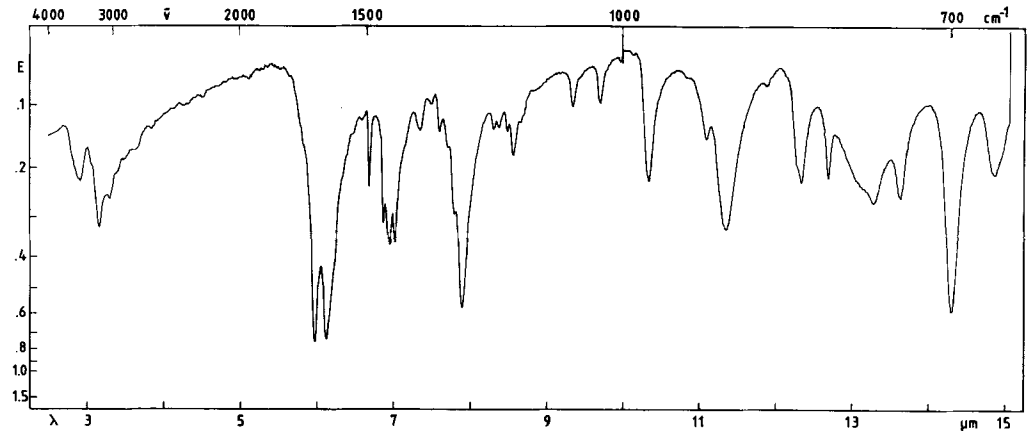


Fig. 1. *IR. spectrum of* **17** *in KBr*

respectively. By comparison with the tetramic acid **6**, which absorbs at 203 and 272 nm, and toluene [26], which absorbs at 206.5 nm, we assign the bands at 207 in **17** and at 203 nm in **6** to the benzyl group. For the benzylidene group in **18** or **19**, a strong absorption near 245 nm would have been expected in analogy to styrene [26].

Additional structural information resulted from a comparison of the double-bond absorption in the IR. spectrum with the corresponding bands in the *Raman* spectrum[8]) (*cf. Fig. 1* and *2*). The high IR. absorption at 1670 cm^{-1} appears as an extremely strong band at 1665 cm^{-1} in the *Raman* spectrum, whereas the IR. absorptions at 1635 cm^{-1} (strong) and 1605 cm^{-1} (weak) are found in the *Raman* spectrum at 1630 (medium) and 1603 cm^{-1} (medium). These facts are in agreement with common experience if one assumes that the band at highest frequency corresponds to the enolic double bond, the band at 1635/1630 cm^{-1} to the conjugated lactam carbonyl group and the low frequency absorption at 1605/1603 cm^{-1} to the conjugated ethylenic bond. The broad band in the hydroxylic region at 3200 cm^{-1} of the IR. spectrum is indicative of a strong hydrogen bond which gives rise to a broadened absorption band of the lactam carbonyl group at 1635 cm^{-1}.

Corroborating evidence for structure **17** emerged from a ^{13}C-NMR. study *(Fig. 3)*. The signal at 19.9 ppm (quartet in the off-resonance spectrum) is obviously caused by a methyl group adjacent to an enolized keto group as in **17** or **19**. In acetylacetone [27a] and ethyl acetoacetate [27b] the resonance of the methyl group in the enolic form appears at 24.3 and 21.1 ppm, respectively, and is shifted approximately by 6 and 9 ppm to higher field with respect to the ketonic forms. Apart from structure **16**, the occurrence of a signal at 34.5 ppm belonging to a methylene C-atom is only compatible with a benzylic methylene group as in structure **17** for which a chemical shift of 37.5 ppm is estimated according to additivity rules [28a], and not for a bi-allylic methylene group within the ring as, for example, in structure **18**, for

[8]) We thank Dr. *H. Hürzeler* and Mr *S. Moss* from the *Gruppe für Optische Spektroskopie der Ciba-Geigy AG*, Basel, for the performance and the interpretation of these spectra.

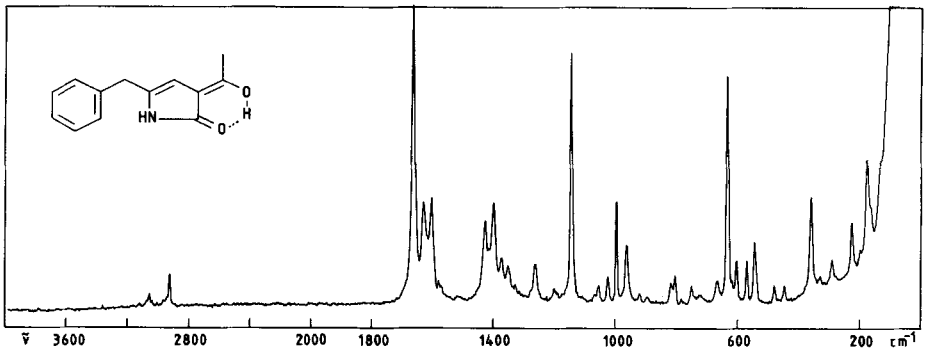


Fig. 2. Raman *spectrum of* **17**

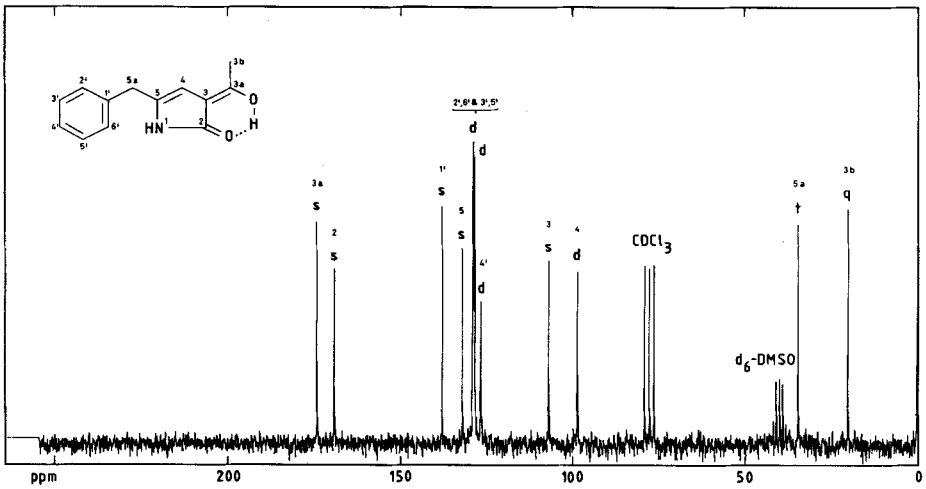


Fig. 3. *Broad band decoupled 22.63 MHz-*^{13}*C-FT-NMR. spectrum of* **17** *in* $CDCl_3/(D_6)DMSO$ (200 mg in 0.6 ml); pulse angle 15°; pulse width 1,5 µs; 20,000 scans; 16 K/8 K points.

which a value of 24.1 ppm is calculated. The resonance of a vinylic C-atom bearing only one H-atom is located at 98.7 ppm and must be assigned to C(4) in **17** or C(5a) in **19**. No distinction within the originally considered structure **7** and the tautomers **16**–**19** is possible with respect to the resonance of the quaternary C(3) appearing at 106.8 ppm[9]). The chemical shifts observed for the aromatic C-atoms are in good agreement with those of toluene [27c] and *N*-acetyl-phenylalanine methyl ester [27d], but differ considerably from those of styrene [28b] precluding structures **18** and **19**. C-atom 5 bonded to nitrogen must be correlated with the resonance at 131.8 ppm, because the corresponding C-atom in *N*-vinyl-2-pyrrolidone [27e] is found at 129.8 ppm. The resonance at 169.3 ppm is attributed to C(2) in **17** (lactam carbonyl C-atom), shifted by some ppm to higher field owing to conjugation with an ethylenic double bond. It corresponds well to 2-pyrrolidone

[9]) A similar position is found in the spectrum of acetylacetone [27a].

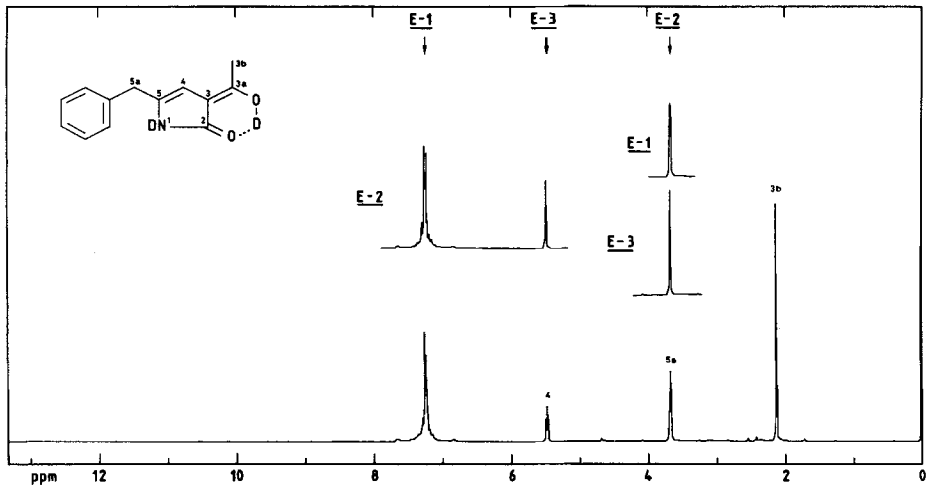


Fig. 4. *Irradiation experiments in the 90-MHz-^{1}H-FT-NMR. spectrum of* **17** *after deuterium exchange*

[27f] and *N*-vinyl-2-pyrrolidone [27e], where the carbonyl C-atom appears at 179.4 and 172.9 ppm, respectively. The resonance of C(3a) at 174.2 ppm is shifted to higher field in the cross-conjugated system of **17** compared with the corresponding C-atoms in the enolic forms of acetylacetone (191.4) [27a] and dibenzoylmethane (185.5) [27g].

Final proof for structure **17** arose from selective decoupling-experiments in the 90-MHz-^{1}H-NMR. spectrum *(cf. Fig. 4)* after exchange with deuterium oxide[10]). On irradiation near 7.25 ppm, the unresolved multiplet at 3.7 ppm arising from the benzylic protons changed to a doublet, whereas the other signals were unaffected. Irradiation in the region of 3.7 ppm led to an alteration of the splitting pattern of the aromatic protons and caused the triplet at 5.5 ppm of the vinylic proton to become a singlet. On irradiation of the triplet at 5.5 ppm, only the multiplet of the benzylic protons at 3.7 ppm was transformed to a *pseudo*-singlet[11]). These observations are consistent only with structure **17** and preclude structure **19** as well as **16** and **18**.

The support of this investigation by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* (Projects No. 2.435.0.75, 2.629.0.76 and 2.158.0.78) is gratefully acknowledged.

Experimental Part

General remarks. The melting points (m.p.) were determined on a *Kofler* block and are corrected; boiling points (b.p.) are uncorrected. IR. (cm^{-1}), UV. (λ_{max} nm ($\log\varepsilon$)) and optical rotations were measured with a *Perkin-Elmer* model 125 grating spectrometer, a *Beckman* D.K.2 spectrophotometer and a *Perkin-Elmer* model 141 polarimeter, respectively. The 90-MHz-^{1}H-NMR. and 22.63-MHz-^{13}C-NMR. spectra were recorded on a *Bruker* WH-90 spectrometer with *Fourier* transform in our spectral laboratory by Mr *K. Aegerter*. The following abbreviations are used: *s* singlet, *d* doublet, *t* triplet, *qa* quadruplet, br. broad and *J* coupling constant in Hz. The mass spectra (MS., *m/z*) of the compounds **8**, **9**, **10** and **11** were determined on an *A. E. I.* MS-30 instrument in the spectral laboratories of *Sandoz AG.*, Basel (Dr. *H. Lichti*). The remaining MS. were run in the Institute for Physical

[10]) Allylic coupling between the H–N and H–C(4) is thereby abolished.

[11]) Coupling with the *ortho* protons of the phenyl ring may be too small to be observed.

Chemistry, University of Basel, on a *Hitachi-Perkin-Elmer* model RMU 7 instrument *(A. Raas).* Elemental analyses were carried out in our laboratory for microanalysis by Mr *E. Thommen.* For column chromatography silica gel 60 (0.063–0.200 mm) purchased from *Merck AG.*, Darmstadt, was used. Extracts were dried with Na_2SO_4 and the solvents removed under adequately reduced pressure. Abbreviations: i.V. = *in vacuo*, RT. = room temperature.

(S)-N-Acetoacetyl-phenylalanine ethyl ester ((S)-**5**). To a solution of 22.97 g (100 mmol) of (*S*)-phenylalanine ethyl ester in 120 ml of ethanol were added 105 ml of 0.82M sodium ethoxide in ethanol. After cooling to 0°, 10 ml (120 mmol) of freshly distilled diketene were added dropwise over 2 h. The reaction mixture was then allowed to warm to RT., filtered and evaporated i.V. to yield 30.60 g of a yellow oil which was dissolved in 300 ml of CH_2Cl_2. After consecutive washing with 60 ml of water, 50 ml of 0.1N HCl and water (5 × 25 ml), 26.10 g of crude (*S*)-**5** were obtained. A sample of 2.76 g was purified by column chromatography on 110 g of silica gel. Six fractions of 40 ml with the following solvents were collected: $CHCl_3$ and $CHCl_3$/methanol 99:1, 97.5:2.5 and 95:5. The fractions 7 to 13 yielded together 1.753 g of pure (*S*)-**5** as a colourless oil. – IR. (KBr): 3430, 3350, 2980, 2940, 1735 (C=O, ester), 1715 (C=O, methyl ketone), 1675 (C=O, amide), 1605, 1520, 1375, 1350, 1215, 1200, 1160, 1030.

(5S)-3-Acetyl-5-benzyl-4-hydroxy-3-pyrroline-2-one ((S)-**6**). To a stirred solution of 238 mg (0.86 mmol) of dry (*S*)-**5** in 8.75 ml of methanol, 1.25 ml of 0.82M sodium methoxide in methanol were added and stirring continued for 30 h. For work-up the reaction mixture was cooled to 0°, acidified to pH 3 with 0.5N HCl and extracted with CH_2Cl_2/ether 1:4. Evaporation of the solvent i.V. left 184 mg of a crystalline residue. Recrystallization from methanol gave the following fractions: **A** 54.0 mg, m.p. 133–134°, $[\alpha]_D^{23} = -214° \pm 2°$ ($c = 1.0$, ethanol); **B** 33.0 mg, m.p. 132–134°, $[\alpha]_D^{23} = -210° \pm 2°$ ($c = 1.0$, ethanol); **C** 19.2 mg, m.p. 131–133°, $[\alpha]_D^{23} = -216° \pm 2°$ ($c = 1.0$, ethanol); and a mother liquor of 72.0 mg, $[\alpha]_D^{23} = -166° \pm 2°$ ($c = 1.0$, ethanol). – UV. (ethanol): 272 (4.14), (sh. 203 (4.11). – IR. (CH_2Cl_2): 3420 (N–H; O–H); 1705 (C=O, conj. lactam); 1655 (conj. $COCH_3$); 1610 (conj. C=C(O)). – ^{1}H-NMR. ($CDCl_3$): 13.2 (br., 1H, enol); 7.25 (*m*, 5H, phenyl); 6.10 (br., 1H, H–N); 4.02 (*d* × *d*, part *X* of the *ABX*-System, $J_{A,5} = 10$, $J_{B,5} = 4$, 1H, H–C(5)); 3.30 (*d* × *d*, part *B*, $J_{gem} = 14$, $J_{B,5} = 4$, 1H, benzylic); 2.71 (*m*, part *A*, $J_{gem} = 14$, $J_{A,5} = 10$, 1H, benzylic); 2.47 (*s*, 3H, acetyl).

$C_{13}H_{13}NO_3$ (231.25) Calc. C 67.52 H 5.67 N 6.06% Found C 67.41 H 5.79 N 6.15%

rac-*3-Ethyl-5-cyclohexylmethyl-4-hydroxy-3-pyrroline-2-one* (**8**). A solution of 231.5 mg (1.00 mmol) of the racemic tetramic acid **6** [14] in 12.5 ml of 95% ethanol was shaken at 23° and 743 Torr in H_2 in the presence of 23.0 mg of PtO_2 for 64 h. An uptake of 139 ml of H_2 was observed. The catalyst was filtered off and the filtrate evaporated i.V. to yield 152.2 mg of crude **8**. An additional 59.4 mg of almost pure **8** were obtained by washing the catalyst with 95% ethanol. Recrystallization of the second crop from 95% ethanol gave 47.7 mg of pure **8**, plates, m.p. 171–173°. – IR. (KBr): 3220 (O–H, enol), 2920, 1675 (C=O, conj. lactam); 1605 (conj. C=C(O)), 1440, 1390, 1360, 1280, 1200, 1095, 845, 755. – ^{1}H-NMR. ($(CD_3)_2CO$): 10.2 (*s*, 1H, enol); 7.35 (br., 1H, H–N); 3.91–3.64 (*m*, 1H, H–C(5)); 2.03 (*qa*, $J = 7$, 2H, ethyl); 1.9–1.0 (*m*, 13H, cyclohexylmethyl); 0.91 (*t*, $J = 7$, 3H, ethyl). – MS.: 223 (M^+), 195 ($M^+ - 28$ (CO)), 180 ($M^+ - 43$ (NHCO)).

$C_{13}H_{21}NO_2$ (223.32) Calc. C 69.92 H 9.48 N 6.27% Found C 69.81 H 9.31 N 6.22%

2,4-Diacetoxy-3-acetyl-5-benzylpyrrole (**9**). A solution of 578.2 mg (2.5 mmol) of *rac*-**6** in 5.0 ml of acetic acid anhydride was heated to 100° for 9 h under exclusion of moisture. For work-up the reaction mixture was evaporated i.V. several times after addition of toluene/benzene 4:1, followed by CH_2Cl_2 and ether. The crude, crystalline material (735 mg) was purified by column chromatography on 20 g of silica gel deactivated with 10% water. Elution with CH_2Cl_2 and CH_2Cl_2/ether 95:5, 85:15, 70:30 and 50:50 (3 × 10 ml each) afforded 387.6 mg of product contained in fractions 8 to 10. Decolourization with charcoal in ether and concentration of the solution yielded 233.7 mg of pyrrole **9**, colourless prisms, m.p. 169–170°. – UV. (ethanol): 281.5 (3.62), sh. 235 (4.08) and 205 (4.31). – IR. (KBr): 3140, 3060, 2900, 1780 ($OCOCH_3$), 1750 ($OCOCH_3$), 1625 ($COCH_3$), 1610 (conj. C=C(O)), 1530, 1475, 1425, 1365, 1210, 1175 (C–O–C), 1080, 1010, 905, 840, 720, 705. – ^{1}H-NMR. ($CDCl_3$): 8.70 (br., 1H, H–N); 7.4–7.1 (*m*, 5H, phenyl); 3.79 (*s*, 2H, benzylic); 2.34 (*s*, 3H, CH_3CO–C(3)); 2.31 (*s*, 3H, $OCOCH_3$); 2.29 (*s*, 3H, $OCOCH_3$). – MS.: 315 (M^+), 273 ($M^+ - 42$ (CH_2CO)), 231 (273–42 (CH_2CO)), 91 (C_7H_7).

$C_{17}H_{17}NO_5$ (315.32) Calc. C 64.75 H 5.43 N 4.44% Found C 64.74 H 5.63 N 4.47%

rac-*8-Acetoxy-9-benzyl-5-methyl-8-aza-2-oxabicyclo[4.3.0]nona-1(6),4(5)-diene-3,7-dione* (**10**). To a stirred solution of 232.5 mg (1.00 mmol) of *rac*-**6** in 2.0 ml of dry pyridine were added 2.0 ml of acetic acid anhydride. After standing for 4 days at RT. the reaction mixture was evaporated i.V. repeatedly after adding 8 ml of toluene/benzene 1:1, followed by CH_2Cl_2 and ether to give 250 mg of crude acetylation product. Column chromatography on 25 g of silica gel, deactivated by 10% of water, was performed by elution with CH_2Cl_2/acetone 95:5, 90:10 and 85:15 (4× 12.5 ml each). Fractions 6 to 8 yielded a total of 35.9 mg of pure **10**, delicate needles, m.p. 164–165°. – IR. (KBr): 1755 (C=O, conj. lactone), 1735 (C=O, conj. lactam), 1690 (conj. C=C(O)), 1665 (C=O, N-acetyl), 1630 (conj. C=C), 1460, 1450, 1435, 1390, 1370, 1350, 1290, 1205, 735, 700. – ^{1}H-NMR. ($CDCl_3$): 7.3–6.75 (*m*, 5 H, phenyl); 6.14 (*qa*, J=1, 1H, H–C(4)); 5.22 (*d*× *d*, part *X*, $J_{A,9}$=3, $J_{B,9}$=6, 1H, H–C(9)); 3.60 (*d*× *d*, part *B*, J_{gem}=14, $J_{B,9}$=6, 1 H, benzylic); 3.36 (*d*× *d*, part *A*, J_{gem}=14, $J_{A,9}$=3, 1 H, benzylic); 2.59 (*s*, 3 H, $OCOCH_3$); 2.39 (*d*, J=1, 3 H, CH_3). – MS.: 297 (M^+), 282 (M^+-15 (CH_3)), 255 (M^+-42 (CH_2CO)), 254 (M^+-43 (CH_3CO)), 239 (282–43 (CH_3CO)), 164 (255–91 (C_7H_7)), 91 (C_7H_7).

3-Acetyl-5-benzyl-2,4-ditosyloxypyrrole (**11**). A solution (5.0 ml) of 800 mg (4.2 mmol) of tosyl chloride and 0.45 ml of dry pyridine in 9.5 ml of abs. benzene was added to 230.4 mg (1.00 mmol) of **6**. The mixture was stirred at RT. for 24 h. Then 0.5 ml of methanol and 0.2 ml of pyridine were added to the reaction mixture which was then diluted with 25 ml of CH_2Cl_2/ether 1:4. The organic phase was washed with 2N HCl (4× 3 ml), 2N Na_2CO_3 (3× 3 ml) and water (6× 5 ml). The crude product (103 mg) was purified by column chromatography on 15 g of silica gel deactivated with 10% water. Elution was achieved by CH_2Cl_2 and CH_2Cl_2/acetone 99:1, 97.5:2.5 and 95:5 (4× 12.5 ml each time). Fractions 4 to 8 afforded 49.7 mg of crude tosylate **10**. Crystallization from acetone/ether gave 43.8 mg of pure **10**, m.p. 140° (dec.). – IR. (KBr): 3220, 3160, 3050, 1655 (C=O), 1595 (conj. C=C(O)), 1525, 1460, 1430, 1390, 1380, 1370, 1195, 1190, 1175, 890, 810, 730. – ^{1}H-NMR. ($CDCl_3$): 8.0 (br., 1H, H–N); 7.9–7.0 (*m*, 13 H, 3 phenyl); 3.83 (*s*, 2 H, benzylic); 2.43 (*s*, 6 H, 2 CH_3); 1.85 (*s*, 3 H, $COCH_3$). – MS.: 384 (M^+-155 ($CH_3C_6H_4SO_2$)), 368 (M^+-171 ($CH_3C_6H_4SO_3$)), 229 (384–155 ($CH_3C_6H_4SO_2$)), 91 (C_7H_7).

$C_{27}H_{25}NO_7S_2$ (539.62) Calc. C 60.09 H 4.67 S 11.88% Found C 60.37 H 4.90 S 11.84%

rac-*2-Amino-3-phenylpropanal diethyl acetal* (**13**). The acetal **13** was prepared according to [20], replacing water by dry ethanol as solvent. A solution of hydrochloric acid in dry ethanol was used to maintain the pH of the reaction mixture between 5 to 7. Starting from *rac*-phenylalanine ethyl ester hydrochloride pure **13** was obtained in 22% yield, b.p. 93–94°/0.30–0.22 Torr ([20]: 103–105°/0.25 Torr). – IR. (film): 3540 (N–H, asym.), 3390 (N–H, sym.), 3090, 3070, 3030, 2980, 2900, 1600, 1580, 1490, 1450, 1440, 1340 (C–H, acetal), 1120, 1060, 1020, 745, 700. – ^{1}H-NMR. ($CDCl_3$): 7.24 (*s*, 5 H, phenyl); 4.22 (*d*, J=5, 1H, H–C(1)); 4.0–3.4 (*m*, 4 H, 2 OCH_2); 3.25–2.85 (*m*, 2 H, H–C(2) and H–C(3)); 2.7–2.3 (*m*, 1H, H–C(3)); 1.24 (*t*, J=7, 8 H, 2 CH_3 and NH_2). – MS.: 224 (M^++1), 178 (M^+-45 (CH_3CH_2O)), 132 (M^+-91 (C_7H_7)), 120 (M^+-103 ($CH(OCH_2CH_3)_2$)), 91 (C_7H_7).

rac-*2-Acetoacetylamino-3-phenylpropanal diethyl acetal* (**14**). Diketene, purified by distillation i.V. (1.212 g, 13 mmol) was added dropwise to a solution of 2.237 g of **13** in 10.0 ml of dry ethanol at 0° under argon. After 2 h at 0° 80 ml of ether was added and the solvent evaporated under reduced pressure to yield 3.23 g of crude product. Column chromatography was performed on 120 g silica gel by elution with $CHCl_3$ and $CHCl_3$/ethanol 99:1 and 97.5:2.5 (8× 40 ml each). Fractions 17 to 23 afforded 3.060 g of pure **14** as a colourless oil, which upon cooling crystallized in needles, m.p. 24.0–24.5°. – IR. (CH_2Cl_2): 3425, 3350 (both N–H, amide), 2980, 2940, 2890, 1710 (C=O, $COCH_3$), 1670 (C=O, amide), 1515, 1130, 1060 (C–O–C, acetal). – ^{1}H-NMR. ($CDCl_3$): 7.25 (*s*, 5 H, phenyl); 6.76 (br. *d*, 1H, H–N); 4.6–4.2 (*m*, 2 H, H–C(1) and H–C(2)); 3.9–3.3 (*m*, 4 H, 2 OCH_2); 3.30 (*s*, 2 H, $COCH_2CO$); 3.15–2.6 (*m*, 2 H, 2 H–C(3)); 2.15 (*s*, 3 H, $COCH_3$); 1.24 (*t*, J=7, 3 H, CH_3); 1.19 (*t*, J=7, 3 H, CH_3).

rac-*2-Acetoacetylamino-3-phenylpropanal* (**15**). A solution (27 ml) of 2N HCl in 20% aqueous tetrahydrofuran was added to 992.6 mg (3.23 mmol) of **14** at 0°. The mixture was stirred at 0° for 2 h, then neutralized to pH 6.5 by addition of 65 ml of 1N $NaHCO_3$ and the tetrahydrofuran removed i.V. by azeotropic distillation with water. The residue was extracted with CH_2Cl_2/ether 3:1 to yield 733 mg of crude aldehyde **15** as a colourless oil, used in the next step without purification. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 9.7 (*s*, 1H, CHO); 7.3 (*s*, 5 H, phenyl); 4.6–4.1 (*m*, 1H, H–C(2)); 3.9–2.7 (*m*, 4 H, $COCH_2CO$ and 2 H–C(3)); 2.15 (*s*, 3 H, $COCH_3$).

(Z)-5-Benzyl-3-(1'-hydroxyethylidene)-4-pyrrolin-2-one (**17**). A solution of 733 mg (3.14 mmol) of crude **15** in 15 ml of CH_2Cl_2/ether 1:3 was shaken with 1.5 ml of 2N NaOH for 3 min. Then some ice was added, followed by 1.5 ml of 2N HCl for neutralization. After the mixture had been shaken again, the upper layer was separated and the aqueous phase was extracted with $CHCl_3$ (2 × 50 ml). The organic phases were washed with 2.5M NaCl (2 × 10 ml) and yielded 576 mg of yellowish crystals. Recrystallization from mixtures of CH_2Cl_2, ether and light petroleum gave 336.4 mg of pure **16**, colourless needles, m.p. 139–141°. – UV. (ethanol): 325 (3.76), 238 (4.01), sh. 207 (4.20). – IR. (KBr): see *Figure 1.* – *Raman:* see *Figure 2.* – ^{1}H-NMR. ($CDCl_3$): 11.35 (br., 1H, OH); 8.70 (br., 1H, H–N); 7.45–7.1 (*m*, 5H, phenyl); 5.50–5.45 (*m*, 1H, H–C(4)); 3.70 (br. *s*, 2H, 2H–C(5a)); 2.13 (*s*, 3H, 3H–C(3b)); see also *Figure 4.* – ^{13}C-NMR. ($CDCl_3$/$(CD_3)_2SO$): see *Figure 3.* – MS.: 215 (M^+), 197 ($M^+ - 18$ (H_2O)), 172 ($M^+ - 43$ (CH_3CO)), 91 (C_7H_7).

$C_{13}H_{13}NO_2$ (215.25) Calc. C 72.54 H 6.09 N 6.51% Found C 72.38 H 6.06 N 6.48%

REFERENCES

[1] *T. Schmidlin & Ch. Tamm,* Helv. *61*, 2096 (1978).

[2] *Cf. M. Binder & Ch. Tamm,* Angew. Chemie *85*, 369 (1973); Angew. Chemie Internat. Edit. *12*, 370 (1973); *Ch. Tamm* in S.W. Tanenbaum (Ed.), 'Cytochalasins – Biochemical and Cell Biological Aspects', Elsevier/North-Holland Biochemical Press, Amsterdam, New York, Oxford 1978, pp. 15–51.

[3] *D. Scherling,* Ph. D. Thesis, Basel 1974.

[4] *J. Auerbach & S.M. Weinreb,* J. org. Chemistry *40*, 3311 (1975).

[5] *S.J. Bailey, E.J. Thomas, W.B. Turner & J.A.J. Jarvis,* Chem. Commun. *1978*, 474.

[6] *G. Stork, Y. Nakahara, Y. Nakahara & W.J. Greenlee,* J. Amer. chem. Soc. *100*, 7775 (1978).

[7] *R. Brettle & D.P. Cummings,* J. chem. Soc. Perkin I *1977*, 2385.

[8] *E. Vedejs & R.C. Gadwood,* J. org. Chemistry *43*, 376 (1978).

[9] *C. Owens & R.A. Raphael,* J. chem. Soc. Perkin I *1978*, 1504.

[10] *M.Y. Kim & S.M. Weinreb,* Tetrahedron Letters *1979*, 579.

[11] *J. Elguero, C. Marzin, A.R. Katritzky & P. Linda,* 'Advances in Heterocyclic Chemistry – The Tautomerism of Heterocycles', Academic Press, New York, San Francisco, London 1976, p. 222.

[12] *V. Bocchi, L. Chierici, G.P. Gardini & R. Mondelli,* Tetrahedron *26*, 4073 (1970).

[13] *N. Bodor, M.J.S. Dewar & A.J. Harget,* J. Amer. chem. Soc. *92*, 2929 (1970).

[14] *H. Yuki, Y. Tohira, B. Aoki, T. Kano, S. Takama & T. Yamazaki,* Chem. pharm. Bull. *15*, 1107 (1967).

[15] *P.N. Rylander & S. Starrick,* Engelhard Ind. tech. Bull. *7*, 106 (1966).

[16] *H.O. House,* 'Modern Synthetic Reactions', 2nd Edition, W.A. Benjamin Inc., Menlo Park California, Reading Massachusetts, London, Amsterdam, Don Mills Ontario, Sydney 1972, pp. 82–84.

[17] *G. Rio & D. Masure,* Bull. Soc. chim. France *1972*, 4598.

[18] *J.E. Baldwin,* Chem. Commun. *1976*, 734.

[19] *W.J. Musliner & J.W. Gates jr.,* J. Amer. chem. Soc. *88*, 4271 (1966); *E. Vowinkel & C. Wolff,* Chem. Ber. *107*, 907 (1974); *W. Lonsky, H. Traitler & K. Kratzl,* J. chem. Soc. Perkin I *1975*, 169.

[20] *E. Fischer & T. Kametaka,* Liebigs Ann. Chem. *365*, 7 (1909).

[21] *W.O. Emery,* Liebigs Ann. Chem. *260*, 137 (1890).

[22] *C.A. Grob & P. Ankli,* Helv. *32*, 2010 (1949).

[23] *H. Plieninger & M. Decker,* Liebigs Ann. Chem. *598*, 198 (1956).

[24] *H. Plieninger, H. Bauer, A.R. Katritzky & U. Lerch,* Liebigs Ann. Chem. *654*, 165 (1962).

[25] *J.H. Atkinson, R.S. Atkinson & A.W. Johnson,* J. chem. Soc. C *1966*, 40.

[26] *D.H. Williams & I. Fleming,* «Spektroskopische Methoden in der organischen Chemie», G. Thieme Verlag, Stuttgart 1971, p. 30.

[27] a) *L.R.F. Johnson & W.C. Jankowski,* 'Carbon-13-NMR. Spectra', J. Wiley & Sons, Inc., New York, London, Sydney, Toronto, 1972, Spectrum No. 115; b) No. 181; c) No. 243; d) No. 435; e) No. 173; f) No. 67; g) No. 463.

[28] a) *J.T. Clerc, E. Pretsch & S. Sternhell,* «^{13}C-Kernresonanzspektroskopie», Akademische Verlagsgesellschaft, Frankfurt am Main 1973, p. 88; b) *ibid.*, p. 94.