HETEROCYCLES, Vol. 11, 1978

SYNTHESIS, STRUCTURE AND PROPERTIES OF METHYL-AZULENO[1,8-cd]-PYRIDAZINES[+]

Klaus Hafner[+], Hans Jörg Lindner and Werner Wassem†

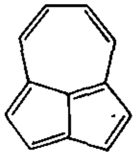
Institut für Organische Chemie der Technischen Hochschule
Petersenstrasse 22, D-6100 Darmstadt, Germany

N-Substituted 2H-cyclopenta[d]pyridazines (6) possessing methyl groups in 1- and/or 4-positions are easily deprotonated by strong bases to anions of type (7) which react with derivatives of β-dicarbonyl compounds to the substitution products (11) and (17). Cyclization of these in the presence of acids afford 1,3,5-trimethyl- and 1,3-dimethyl-azuleno[1.8-cd]pyridazine (12) and (18). The structure of the novel heterocyclic azulenes was determined by spectroscopic methods as well as by an X-ray analysis of (12).

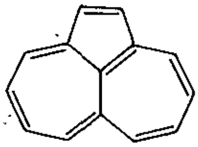
Detailed information about the influence of heteroatoms in the perimeter on bonding character and reactivity of nonbenzenoid π-electron systems are desirable for experimental support of quantum chemical predictions as well as for the synthesis of new heterocycles with interesting properties[1].

[+] Dedicated with best wishes to Professor Tetsuo Nozoe at the occasion of his 77th birthday.

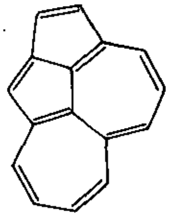
In analogy to the synthesis of numerous nonbenzenoid polycyclic conjugated hydrocarbons as e.g. cyclopent[cd]azulene (1), aceheptylene (2), pentaleno[6.1.2-def]heptalene (3) or azuleno[8.1.2-def]heptalene (4)[2] by peri-anellation of one or two 5- or 7-membered rings to azulene, aza-analogues of these π-electron systems should be accessible by similar synthetic routes, starting from 2H-cyclopenta[d]pyridazine (6) (R=H) which resembles azulene in its reactivity.



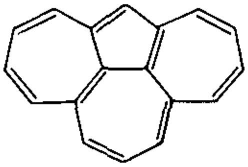
1



2

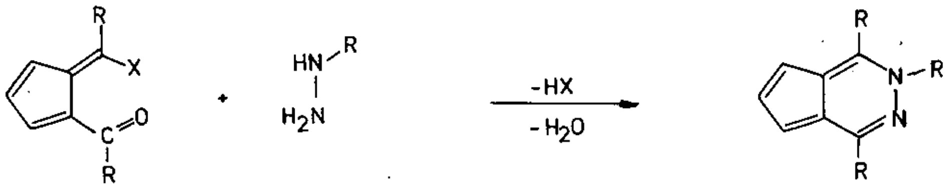


3



4

(6) (R=H) and several of its derivatives are easily synthesized by condensation of 1-acyl-6-dialkylamino- or 1-acyl-6-hydroxyfulvenes (5)[3] with hydrazine or its monoalkyl- or monoaryl derivatives or by N-alkylation of the corresponding 2H-cyclopenta[d]pyridazines in the presence of base[4].

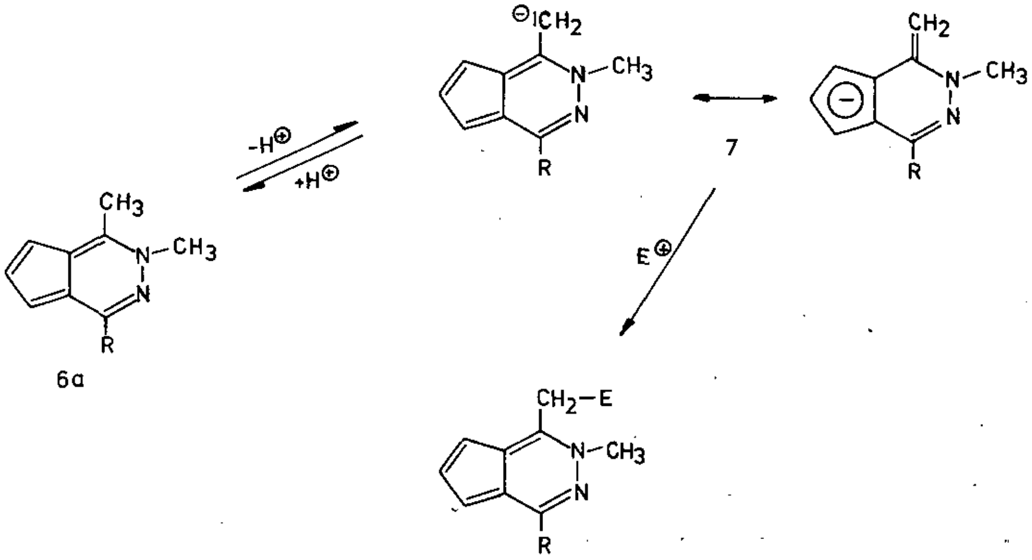


5

6

X : R_2N, OH ; R : H, alkyl, aryl

Like azulenes[5] also (6) is substituted by electrophilic reagents in the 5-membered ring, mainly in 5- and/or 7-positions[6]. Furthermore, methyl groups in the electron deficient 1- and 4-positions of (6), similar to those in 4-, 6- and 8-positions of azulene[5], are easily and reversibly deprotonated by base under formation of resonance stabilized anions, e.g. (7), which react with electrophiles

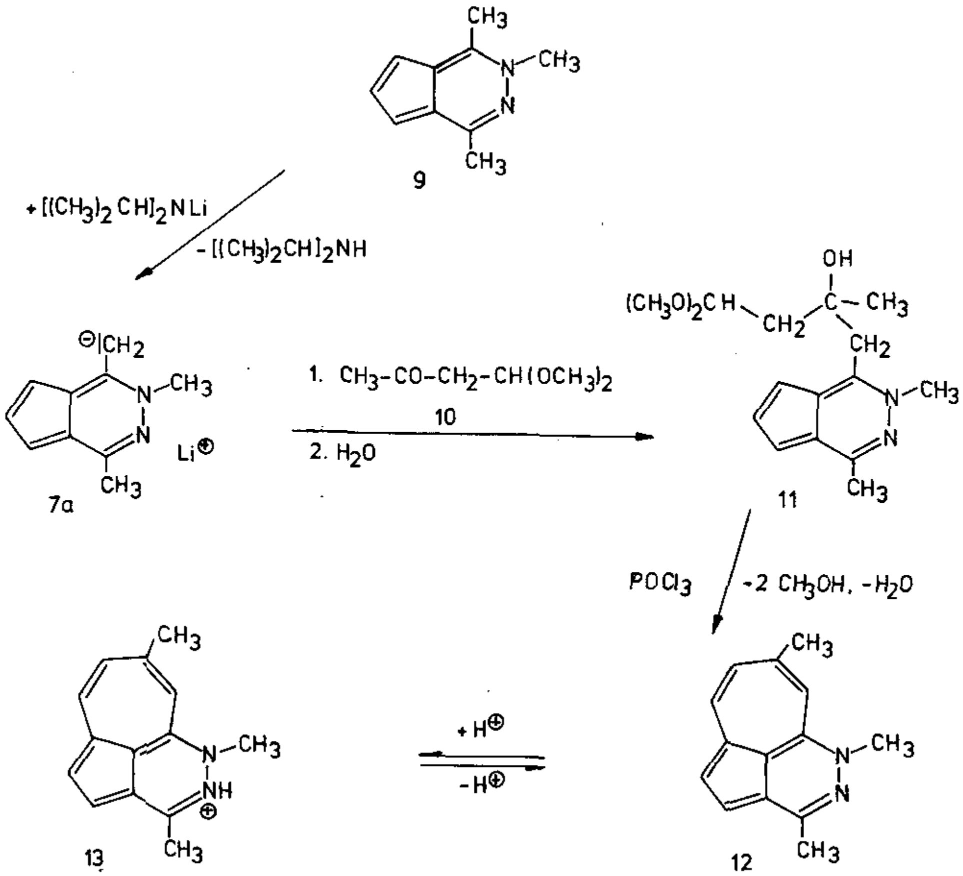


6a

7

8

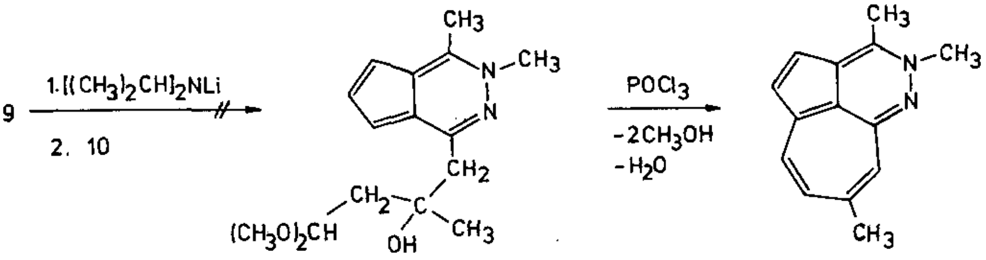
to substitution products of type (8)[6a]. In agreement with these findings the 1,2,4-trimethyl-2H-cyclopenta[d]pyridazine (9)[6a] (obtained by condensation of 1-acetyl-6-hydroxy-6-methyl-fulvene[7] with hydrazine in ethanol and N-methylation of the first formed



1,4-dimethyl-2H-pyridazine with methyl iodide in the presence of base) after deprotonation with lithium diisopropylamide in ether (2h, 25°C) to the anion (7a) (pale yellow needles) reacted with 1,1-dimethoxybutane-3-one (10) in tetrahydrofuran (4h, 25°C) to the yellow acetal (11). The intramolecular condensation of (11) with phosphoryl chloride (in ether at 28°C, 1h) afforded

65 % of the thermodynamically stable 1,3,5-trimethylazuleno[1,8-cd]pyridazine (12) (deep blue needles, m.p. 120 °C (ethyl acetate); uv (n-hexane), λ_{max}(log ε): 229(4.53), 250(4.56), 282(4.13), 349 (4.01), 362(4.05), 366(4.05), 404(2.87), 578(sh 2.66), 618(2.81), 677(2.81), 753nm(2.51)).

The structure of (12) was confirmed by a single crystal X-ray analysis, which excludes the alternative constitution (15) with an azulenoquinone structure, which should result from a condensation of (9) with the β-ketoacetal (10) at the methyl group in

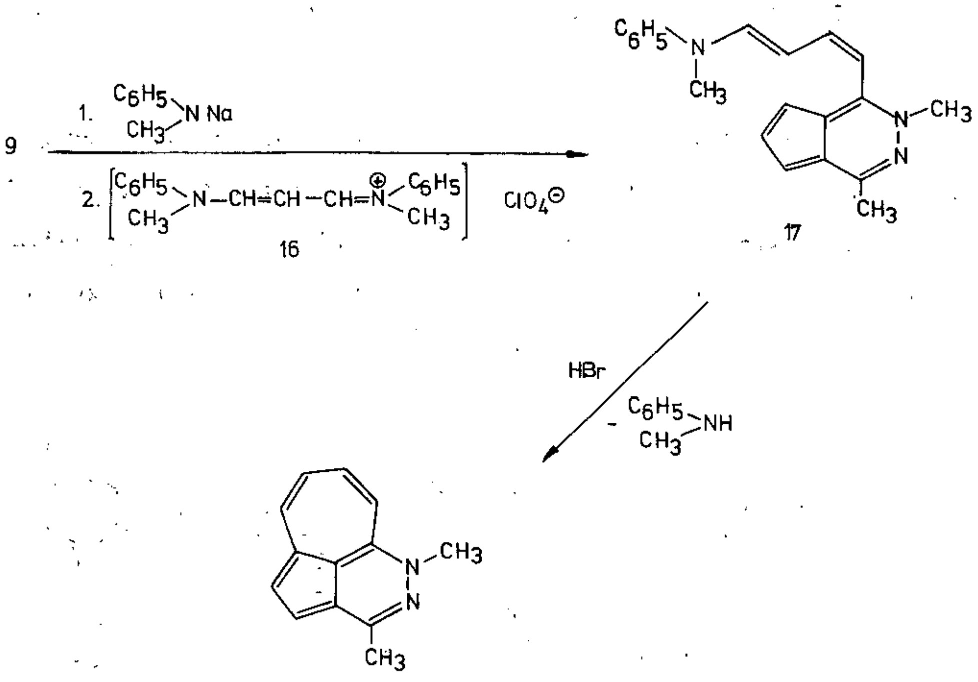


14

15

4-position to (14) and subsequent cyclization. In agreement with this the ^{1}H-NMR-spectrum of (12) ($CDCl_3$) exhibits signals at δ: 6.98(d, J=11Hz, 7-H), 6.83(d, J=4Hz, 9-H), 6.62(d, J=4Hz, 8-H), 5.63(s, 4-H), 5.40(q, J=11 and 1Hz, 6-H), 3.40(s, N-CH_3), 2.17 (s, 1-CH_3), 2.03(d, J=1Hz, 5-CH_3). In 2N H_2SO_4 (12) is reversibly protonated to the green conjugate acid (13).

In a similar reaction sequence as that leading to (12), (18) (blue crystals, m.p. 14o-141°C from ethyl acetate) could be obtained by deprotonation of (9) with sodium N-methylanilide (in ether, 1h,



25°C), condensation with the vinylogous amidinium perchlorate (16) (in tetrahydrofuran , 2 h, 25°C) to the yellow green dienamine (17) and subsequent cyclization with hydrogen bromide in acetic acid (15 min. at 4o°C). (18) corresponds in its ^{1}H-NMR-spectrum (δ: 7.18(d, J=1o.2Hz, 7-H), 6.88(d, J=3.9Hz, 9-H), 6.67(d, J= 3.9Hz, 8-H), 6.37(d,d,d, J=12.o, 8.7 and 1.1Hz, 5-H), 5.66(d, J= 12.oHz, 4-H), 5.46(d,d, J=1o.2 and 8.7Hz, 6-H), 3.25(s, $N-CH_3$), 2.o7(s, $1-CH_3$)) and its uv spectrum (n-hexane) (λ_{max}(logε): 241 (4.52), 281(4.oo), 347(4.o2), 362(4.o6), 387(2.93), 4o3(2.61), 41o(2.84), 587(2.69), 635(2.87), 7oo(2.89), 76o(2.46), 785nm (2.64)) to the trimethyl derivative (12).

The result of the single crystal X-ray analysis identifying (12) as 1,3,5-trimethylazuleno[1,8-cd]pyridazine is shown in fig. 1[8]. Bond lengths and bond angles calculated from the final parameters (last R value o.11) are compiled in fig. 2. Least-squares planes of the molecule and the deviations of the atomic positions from these planes are given in table 1.

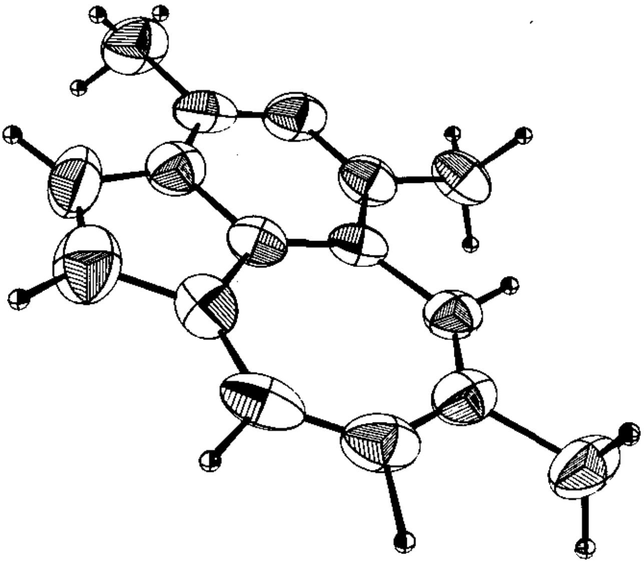
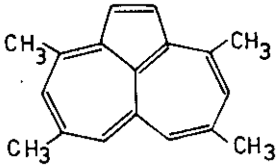


Fig. 1: Molecular structure of (12)

The planar molecule displays alternating bond lengths, with exception of the delocalized five-membered ring. This alternance is very similar to that of the isoelectronic 3,5,8,1o-tetramethylaceheptylene (19)[9].



19

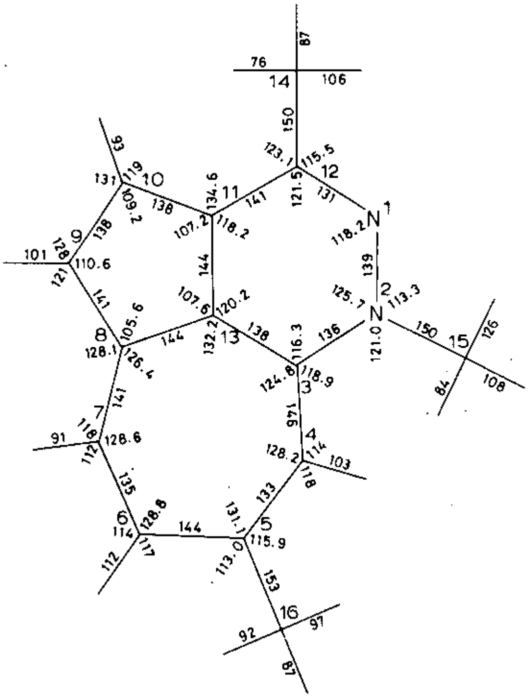


Fig. 2: Bond lengths and bond angles of (12) in pm and degrees

(σ_{XX}= 1pm, σ_{CH}= 9pm, σ_{XXX}= o.6°, σ_{XXH}= 4°, X = C,N)

Table 1: Least-squares planes of (12) in orthogonal pm space with deviations of the atomic positions from these planes in pm

Equations of the planes: $PX + QY + RZ = S$

	1	2	3	4
P	-0.0731	-0.0685	-0.0724	-0.0798
Q	0.3183	0.3222	0.3260	0.3124
R	0.9452	0.9442	0.9426	0.9466
S	307.9	310.0	311.5	305.5

Deviations of the atomic positions out of the planes

N(1)	-0.5			0.5
N(2)	-0.8			0.4
C(3)	-0.6	-1.4		-0.4
C(4)	1.4	0.5		
C(5)	1.2	0.7		
C(6)	-1.0	-0.5		
C(7)	-1.6	-0.6		
C(8)	-0.1	0.7	0.1	
C(9)	0.2		0.4	
C(10)	0.3		-0.6	
C(11)	2.3		0.6	1.2
C(12)	-1.2			-1.3
C(13)	0.5	0.6	-0.4	-0.4
C(14)	-3.8			
C(15)	0.1			
C(16)	-0.4			

Angles between the planes

1	3	0.3°
2	4	0.9°
3	4	0.9°

Bond lengths derived from the π-bond orders calculated by a π-SCF-method using standard relations[1o] and modified equations that take in account the observed bond shortening of about 1 %

$$r_{\mu\nu}^{CC} = 149.4 - 17.4\ p_{\mu\nu} \quad (pm)$$
$$r_{\mu\nu}^{CN} = 143.1 - 17.8\ p_{\mu\nu} \quad (pm)$$
$$r_{\mu\nu}^{NN} = 14o.o - 17.7\ p_{\mu\nu} \quad (pm)$$

are shown in fig. 3. The results of calculation and experiment agree fairly well. Only the alternance of the bond lengths in the 7-membered ring is underestimated in the calculations.

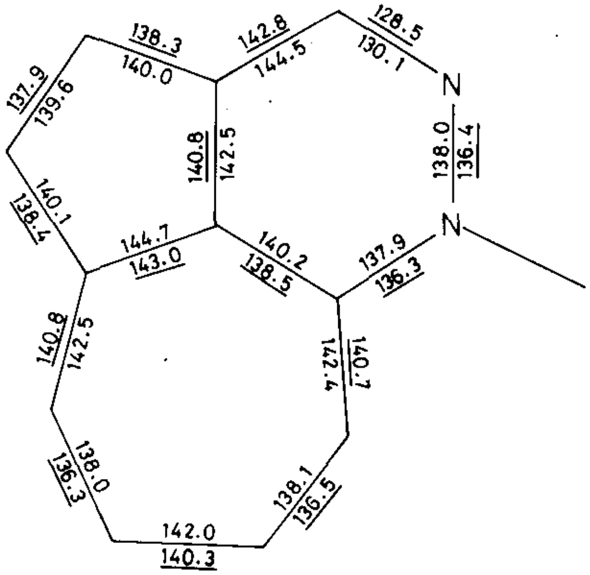


Fig. 3: Calculated bond lengths of (12) using standard relations[1o] and the relations given in this paper (underlined values)

Crystal data: dark blue needles, $C_{14}H_{14}N_2$, M = 21o.3, monoclinic, space group $P2_1/n$ with a = 1878(1), b = 836.3(5), c = 744.o(5) pm, $\beta = 1o3.5o(5)^{o}$, $V = 1136.5 x 1o^{6} pm^{3}$, Z = 4, $D_X = 1.229\ g\ cm^{-3}$.

Table 2: Structure parameters of (12)

anisotropic temperature factors in the form

$$T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$$

ATOM	X/A	Y/B	Z/C	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	0.0793(3)	0.1682(6)	0.4352(8)	0.0048(2)	0.0114(8)	0.0201(17)	0.0018(4)	0.0026(5)	0.0034(9)
N(2)	0.0225(3)	0.2697(6)	0.3521(8)	0.0038(2)	0.0113(8)	0.0191(16)	-0.0004(3)	0.0031(4)	0.0002(9)
C(3)	0.0301(3)	0.4229(6)	0.3003(8)	0.0034(2)	0.0104(9)	0.0110(17)	0.0000(4)	0.0021(5)	0.0002(9)
C(4)	0.9643(3)	0.5150(7)	0.2171(9)	0.0033(2)	0.0145(10)	0.0112(18)	0.0007(4)	0.0016(5)	-0.0006(10)
C(5)	0.9600(3)	0.6653(7)	0.1565(9)	0.0037(2)	0.0149(11)	0.0122(18)	0.0023(4)	0.0015(5)	-0.0013(11)
C(6)	0.0162(4)	0.7816(7)	0.1532(10)	0.0052(3)	0.0113(11)	0.0189(22)	0.0013(4)	0.0034(6)	0.0034(11)
C(7)	0.0894(4)	0.7670(7)	0.2149(10)	0.0053(3)	0.0104(9)	0.0172(20)	-0.0012(5)	0.0043(6)	0.0008(11)
C(8)	0.1299(3)	0.6337(7)	0.2990(10)	0.0032(2)	0.0137(10)	0.0181(20)	-0.0013(4)	0.0025(5)	-0.0027(11)
C(9)	0.2062(4)	0.6203(9)	0.3640(11)	0.0035(3)	0.0206(14)	0.0290(24)	-0.0021(5)	0.0012(6)	-0.0031(15)
C(10)	0.2247(3)	0.4703(9)	0.4353(11)	0.0023(2)	0.0256(16)	0.0251(23)	-0.0001(5)	0.0005(5)	-0.0041(15)
C(11)	0.1615(3)	0.3814(8)	0.4225(9)	0.0033(2)	0.0161(11)	0.0166(20)	0.0010(4)	0.0020(5)	-0.0014(11)
C(12)	0.1467(4)	0.2230(7)	0.4660(9)	0.0045(3)	0.0146(11)	0.0141(19)	0.0023(5)	0.0028(6)	0.0027(11)
C(13)	0.1007(3)	0.4814(6)	0.3348(9)	0.0034(2)	0.0108(8)	0.0125(18)	-0.0005(4)	0.0023(5)	-0.0020(9)
C(14)	0.7054(4)	0.3934(9)	0.0521(11)	0.0049(3)	0.0201(13)	0.0264(24)	-0.0045(5)	0.0020(7)	-0.0062(14)
C(15)	0.9483(3)	0.1941(7)	0.3242(10)	0.0041(3)	0.0125(10)	0.0219(22)	-0.0021(4)	0.0042(6)	0.0020(11)
C(16)	0.8830(4)	0.7271(9)	0.0709(10)	0.0044(3)	0.0204(14)	0.0198(20)	0.0040(5)	0.0015(6)	-0.0013(13)
H(4)	0.916(3)	0.456(7)	0.218(9)						
H(6)	0.501(3)	0.391(7)	0.434(9)						
H(7)	0.114(3)	0.850(8)	0.178(9)						
H(9)	0.240(3)	0.713(8)	0.354(9)						
H(10)	0.269(3)	0.429(7)	0.503(9)						
H(141)	0.738(3)	0.341(8)	0.134(10)						
H(142)	0.691(3)	0.468(8)	0.091(9)						
H(143)	0.238(3)	0.076(8)	0.458(10)						
H(151)	0.953(3)	0.107(8)	0.383(10)						
H(152)	0.925(3)	0.179(8)	0.178(10)						
H(153)	0.919(3)	0.270(8)	0.436(9)						
H(161)	0.874(3)	0.788(8)	0.174(10)						
H(162)	0.848(3)	0.656(8)	0.057(9)						
H(163)	0.879(3)	0.785(8)	-0.036(10)						

isotropic temperature factors for all hydrogen atoms: $B = 4.0 \times 10^4\,\mathrm{pm}^2$

D_o = 1.23(1) g cm^{-3}, μ = 5.8 cm^{-1}.

Structure determination and refinement: 1186 symmetry-independent reflections with $|F| \geqslant 3\sigma_F$, measured by use of $Cu_{K\alpha}$-radiation (λ = 154.18 pm), were used for structure determination by direct methods[11] and for the refinement by difference Fourier maps and least-squares calculations[12].

Anisotropic refinement for the carbon and nitrogen atoms and isotropic refinement of the hydrogen positions yielded an R-value of o.11. The final parameters are listed in table 2.

Acknowledgement: We gratefully acknowledge support of this research by the "Deutsche Forschungsgemeinschaft", the "Fonds der Chemischen Industrie" and the "Dr. Otto Röhm-Gedächtnisstiftung".

REFERENCES

1 K. Hafner, J. Heterocycl. Chem. 1975, 12 (Suppl. Vol. 3), S-33.

2 K. Hafner, Pure Appl. Chem., 1971, 28, 153.

3 K. Hafner, K.H. Vöpel, G. Ploß, and C. König, Liebigs Ann. Chem., 1963, 661, 52; A.G. Anderson, Jr. and D.M. Forkey, J. Am. Chem. Soc., 1969, 91, 924.

4 K. Hafner, K.H. Häfner, C. König, M. Kreuder, G. Ploß, G. Schulz, E. Sturm, and K.H. Vöpel, Angew. Chem., 1963, 75, 1; Angew. Chem. Int. Ed., 1963, 2, 123; K. Hafner, Pure Appl. Chem., 1971, Suppl. 2, 1.

5 T. Nozoe and S. Itô, in L. Zechmeister, Progr. Chem. Org. Nat. Prod., 1961, 19, 32.

6 a) K. Wagner, Dissertation Univ. München 1965; W. Wassem, Diplomarbeit TH Darmstadt 1973;

b) D. Lloyd and N.W. Preston, J. Chem. Soc. (C), 197o, 61o; H.L. Ammon, P.H. Watts, Jr., A.G. Anderson, Jr., D.M. Forkey, L.D. Grina, and Q. Johnson, Tetrahedron, 197o, 26, 57o7; A.G. Anderson, Jr., D.M. Forkey, and L.D. Grina, J. Org. Chem., 1972, 37, 3499; A.G. Anderson, Jr., D.M. Forkey, L.D. Grina, L.W. Hickernell, T. Tober, and M.T. Wills, J. Org. Chem., 1975, 4o, 2196.

7 W.J. Linn and W.H. Sharkey, J. Am. Chem. Soc., 1957, 79, 497o; H. Dohm, Dissertation Univ. Marburg/Lahn 1958.

8 C.K. Johnson, ORTEP, a FORTRAN Thermal-Ellipsoid Plot Program for Crystal Structure Illustration, ORNL-3794, National Laboratory Oak Ridge, Tennessee 1965.

9 E. Carstensen-Oeser and G. Habermehl, Angew. Chem., 1968, 8o, 564; Angew. Chem. Int. Ed., 1968, 7, 543; R. Quasba, F. Brandl, W. Hoppe, and R. Huber, Acta Cryst., 1969, B25, 1198.

1o M.J.S. Dewar and T. Morita, J. Am. Chem. Soc., 1969, 91, 796.

11 J. Karle and I.L. Karle, Acta Cryst., 1966, 21, 849; G. Germain and M.M. Woolfson, ibid., 1968, B24, 91.

12 W.R. Busing, K.O. Martin, and H.A. Levy, ORFLS, a FORTRAN Crystallographic Least-Squares Program ORNL-TM-3o5, National Laboratory Oak Ridge, Tennessee, 1962.

Received, 14th September, 1978