122. Acid-Catalyzed Rearrangements for a Diastereoselective Entry into a New Fused Hexacyclic Heterocycle: (5*RS*,7a*RS*,12*RS*,14a*RS*)-4,5,7,7a,11,12,14,14a-Octahydro-5,12-dimethyldiindolo[1,7-*bc*:1′,7′-*gh*][2,6]naphthyridine

by **Christos Papageorgiou*** and **Xaver Borer**

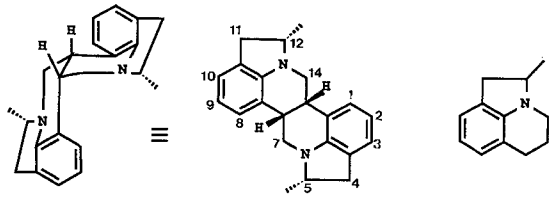
Präklinische Forschung, *Sandoz AG*, 4002–Basel

Dedicated to Prof. *Ch. Tamm* on the occasion of his 65th birthday

(6.IV.88)

The title compound **1** was obtained in 10.3% overall yield *via* two acid-catalyzed rearrangements and pyrrolidine formation. Thus, bi-oxindole **6** afforded exclusively the thermodynamically stable *cis*-diazachrysene **7** which, after allylation, followed by aza-*Claisen* rearrangement gave alcohol **2**. Pyrolytic ring closure of the latter yielded **1** in highly diastereoselective fashion.

In connection with our exploratory work towards the synthesis of new dimeric heterocycles, we have recently reported the preparation of *cis*-4b,5,6,10b,11,12-hexahydro-5,12-diazachrysene [1]. We now report an efficient entry into a new class of hexacyclic *cis*-fused compounds namely the diindolo[2,6]naphthyridines **1**. Although tetrahydropyrroloquinoline **1a** has been synthesized starting from tetrahydroquinoline [2], it was



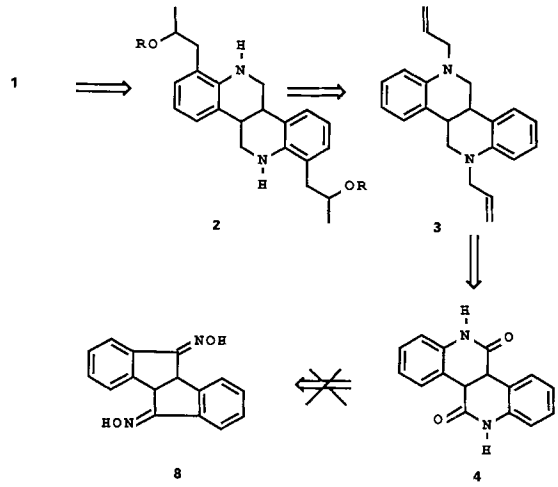
1 **1a**

quite clear to us that a different approach was needed to obtain compound **1**, a retrosynthetic analysis of which is outlined in *Scheme 1* (⇒**2**⇒**3**⇒**4**).

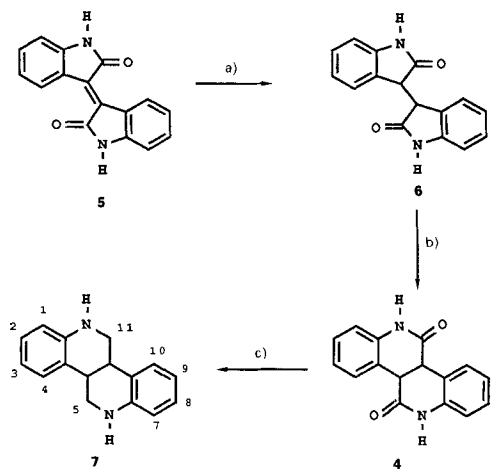
Therefore, our attention was focused on the synthesis of dilactam **4**. Our previous results [1] indicated that a double *Beckmann* rearrangement of dioxime **8** would not lead to the desired intermediate. In view of **4** being isomeric with a bioxindole, the possibility of rearranging **6** into a diazachrysene was investigated *(Scheme 2)*. Such rearrangement could proceed *via* hydrolysis of the amide bonds followed by ring closure to give the δ-lactams. An analogous reaction has been reported to occur in the course of an attempted synthesis of calycanthiacae alkaloids [3].

For our purpose, the double bond in isoindigo (**5**) was reduced with Zn in AcOH affording **6** as a 1:1 mixture of the *meso* and racemic form. Refluxing the latter in 5N HCl

Scheme 1



Scheme 2



a) Zn/AcOH. *b*) 5N HCl reflux. *c*) $LiAlH_4$.

gave a *diastereoisomerically pure* δ-lactam which was treated with $LiAlH_4$ to yield the corresponding hexahydro-diazachrysene **7** in 62% overall yield. When the reaction sequence was attempted with substituted isoindigos (7,7′-dimethyl and 5,5′-dimethyl), the yield decreased substantially.

At this stage, the stereochemical outcome of the rearrangement **6**→**4** was investigated by ^{1}H-NMR since two diastereoisomeric structures were compatible with **4** *(Figure)*. The *trans*-isomer possesses a center of symmetry and, therefore, is achiral. The *cis*-isomer has a C_2 axis and is expected to give diastereoisomers when reacted with an optically pure

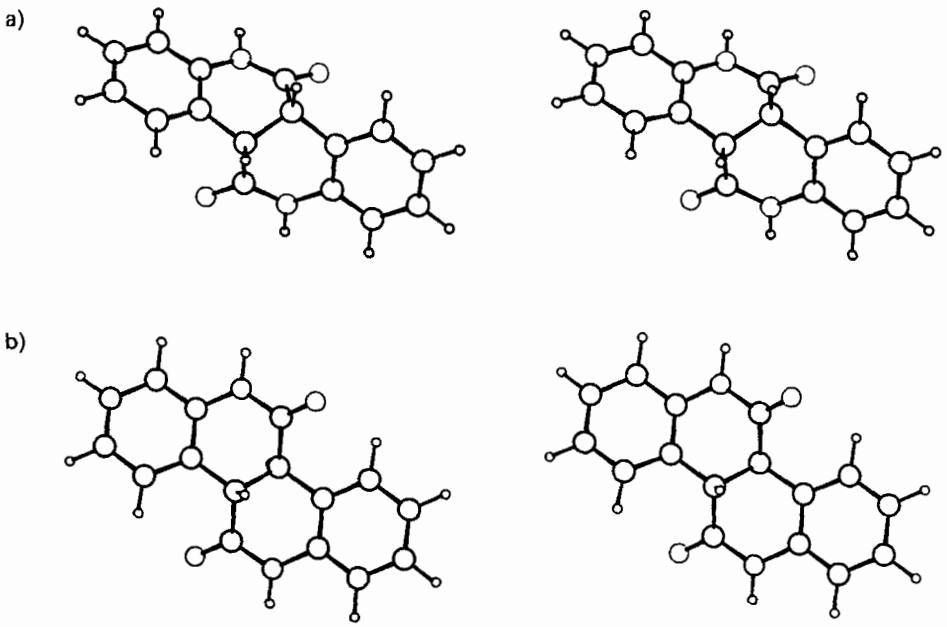


Figure. *Stereoscopic projections of the minimum energy conformations of* a) cis-*configurated and* b) trans-*configurated* **4**

compound. In the ^{1}H-NMR spectrum ($CDCl_3$) of **4** the methine protons appeared as a *s*, but in presence of a chiral solvent[1]) it was split into 2 *s* indicating clearly that the ring junction in **4** is *cis*. An energy difference of *ca.* 42 kJ · mol^{-1} was calculated for the two diastereoisomers[2]). The minimum-energy conformation of the *cis*-isomer was −9.5 kJ-mol^{-1} and that of the *trans*-isomer +33.0 kJ · mol^{-1}. In addition, a strong NOE between H−C(11)/H−C(5) and H−C(10)/H−C(4) in **7** confirmed our previous assignment.

The synthesis was accomplished as expected from the retrosynthetic analysis. The diallyl compound **3**, obtained in 93% yield from amine **7**, underwent azonia-*Claisen* rearrangement in diluted H_2SO_4 solution [4] to give 25% of alcohol **2** (R=H), along with 32% of half-rearranged compound, a product where only one allyl moiety had migrated and which could not be further transformed, even after prolonged heating. The ^{1}H-NMR spectrum showed that **2** was a 60:40 diastereoisomeric mixture[3]). Activation of the secondary alcohols was troublesome; tosylation, mesylation, or halogenation only affording the corresponding derivatives in low yields. We then investigated dehydrating agents with the hope that the N-atoms would be sufficiently nucleophilic to attack the activated OH groups prior to elimination. Indeed, thermolysis of **2** in hexamethylphosphorous triamide (HMPT) [5] at 235° led to 72% of a chromatographically separable 95:5 diastereoiso-

---

[1]) (−)-(*R*)-1-(9-Anthryl)-2,2,2-trifluoroethanol.

[2]) Calculations were made with a *Sandoz* internal computer program (PIF) which uses the same energy function as the multi-option simplex minimizer of the 'SYBIL Molecular Modeling System': *Tripos Associates, Inc.*, St. Louis, Missouri, 63117.

[3]) The presence of 4 chiral C-atoms in **2** and **1** should afford 2^3 diastereoisomers. In fact, only 2 are obtained because of the presence of the C_2 axis of symmetry and the exclusive *cis* ring junction.

meric mixture of dimethyl-diindolo[2,6]naphthyridine **1**. The Me groups of the major isomer showed a strong NOE with their axial H-neighbours and should, therefore, be in the α-position. The ^{1}H-NMR resonance of the Me groups of the minor isomer occurred 0.4 ppm upfield due to the ring-current effect of the opposite benzene moieties. So the latter compound must be the epimer with the Me groups in β-position.

The preferred formation of one diastereoisomer from **2** can easily be explained by the mechanism of the pyrrolidine-ring formation. Assuming a S_N2 mechanism, only a suitably oriented tetrahedral intermediate can further cyclize to give **1**.

Thus, based on two parallel acid-catalyzed oxindole/diazachrysene and azonia-*Claisen* rearrangements followed by the unusual pyrolidine-ring formation, compound **1**, the first member of a new class of *cis*-fused hexacyclic heterocycles, has been synthesized in six steps with 10.3% overall yield.

Experimental Part

General. The reactions were routinely carried out under dry Ar. Chromatographic purifications: *Merck* silica gel (230–400 mesh). M.p.: *Büchi SMP-20* apparatus; not corrected. NMR spectra: *Bruker Spectrospin WH-360* (360 MHz) spectrometer. Mass spectra: for all the compounds consistent with the proposed structures.

cis-*4b,10b-Dihydrodibenzo[*c,h*][2,6]naphthyridine-5(6*H*),11(12*H*)-dione* (**4**). A suspension of oxindole (= 2,3-dihydro-1*H*-indol-2-one; 150.0 g, 1.1 mol) and isatine (= 1*H*-indole-2,3-dione; 165.0 g, 1.1 mol) in AcOH (2.2 l) conc. HCl soln. (12 ml) was heated under reflux overnight. The mixture was allowed to cool and filtered. The solid material was washed with AcOEt and dried to give *isoindigo* (= *3-(2,3-dihydro-2-oxo-1*H*-indol-3-ylidene)-2,3-dihydro-1*H*-indol-2-one*; **5**; 118.0 g, 100%).

Zn dust (48.0 g, 740 mmol) was added portionwise to a cooled (0°) suspension of **5** (84.0 g, 320 mmol) in AcOH (840 ml) and conc. HCl soln. (3.5 ml). The mixture was stirred at r.t. overnight and filtered. The filtrate was concentrated to a heavy oil and extracted with 10% Na_2CO_3 soln. The crystals obtained were filtered and washed several times with H_2O under suction. An anal. sample of *[3,3'-bi-1*H*-indole]-2(3*H*),2'(3*H*)-dione* (**6**) melted at 260–265° (dec.). ^{1}H-NMR ((D_6)DMSO): 4.03 (*s*, 1 H); 4.18 (*s*, 1 H); 6.7–7.2 (*m*, 8 H); 9.70 (*s*, NH); 10.21 (*s*, NH).

Crude **6** was refluxed in 4N HCl (850 ml) for 10 h (4.5-l flask because of foaming). The mixture was cooled, filtered, and the solid washed with H_2O and dried to afford **4** (72.5 g, 85% overall). M.p. > 300°. ^{1}H-NMR ((D_6)DMSO): 4.12 (*s*, 2 H); 6.8–7.3 (*m*, 8 H); 10.45 (*s*, NH). Anal. calc. for $C_{16}H_{12}N_2O_2$: C 78.04, H 4.88, N 11.38; found: C 78.00, H 4.83, N 11.41.

cis-*4b,5,6,10b,11,12-Hexahydrodibenzo[*c,h*][2,6]naphthyridine* (**7**). Portionwise, **4** (15.8 g, 60 mmol) was added to a stirred suspension of $LiAlH_4$ (11.3 g, 300 mmol) in dry THF (500 ml). The mixture was refluxed for 4 h, then cooled to 0° and quenched by careful addition of a sat. aq. Na_2SO_4 soln. The solid material was removed by filtration and the cake washed with AcOEt. The filtrate was concentrated to afford crystalline material which was recrystallized (MeOH) to give pure **7** (10.9 g, 78%). M.p. 188°–189°. ^{1}H-NMR ($CDCl_3$): 3.1–3.4 (*m*, 6 H); 4.00 (*s*, 2 NH); 6.5–6.8 (*m*, 4 H); 7.0–7.2 (*m*, 4 H). Anal. calc. for $C_{16}H_{16}N_2$: C 81.35, H 6.78, N 11.86; found: C 81.30, H 6.81, N 11.83.

cis-*6,12-Diallyl-4b,5,6,10b,11,12-hexahydrodibenzo[*c,h*][2,6]naphthyridine* (**3**). To a cooled (0°) and stirred soln. of **7** (7.4 g, 31 mmol) in dry DMF (75 ml), NaH (63 mmol, 2.0 g of an 80% suspension in oil) was added portionwise. The ice bath was removed and stirring continued for 1 h at r.t. Allyl bromide (1.80 ml, 310 mmol) was added dropwise and the mixture stirred for another 4 h. H_2O was carefully added and the soln. extracted with AcOEt (3 × 100 ml). The org. phase was collected, dried ($MgSO_4$), concentrated to a brown oil, and flash chromatographed (silica gel, hexane/AcOEt 4:1) to yield **3** as redish oil (9.4 g, 94%). ^{1}H-NMR ($CDCl_3$): 2.9–3.1 (*m*, 4 H); 4.67 (*d*, *J* = 11, 2 H); 5.71 (*dd*, *J* = 12, 8, 2 H); 6.4–6.6 (*m*, 4 H); 7.0–7.3 (*m*, 6 H); 7.4–7.6 (*m*, 2 H). Anal. calc. for $C_{22}H_{24}N_2$: C 83.54, H 7.59, N 8.86; found: C 83.31, H 7.61, N 8.90.

cis-*4b,5,6,10b,11,12-Hexahydro-α,α'-dimethyldibenzo[*c,h*][2,6]naphthyridine-1,7-diethanol* (**2**). For 3 days, **3** (5.0 g, 15.8 mmol) was refluxed in 2N H_2SO_4 (400 ml). The soln. was cooled (0°), made alkaline with conc. NaOH soln. and extracted with AcOEt. The org. phase was dried ($MgSO_4$), evaporated and flash chromatographed (silica gel, hexane/AcOEt 1:1) to yield **2** (2.9 g, 25%). M.p. 151°–153°. ^{1}H-NMR ($CDCl_3$): 1.26, 1.32 (2*d*, *J* = 6, 6 H);

2.5–2.7 (*m*, 4 H); 3.1–3.5 (*m*, 10 H, 4 among them exchangeable with D_2O); 4.1 (*m*, 2 H); 6.6–6.8 (*m*, 2 H); 6.9–7.1 (*m*, 4 H). Anal. calc. for $C_{22}H_{28}N_2$: C 75.00, H 7.95, N 7.95; found: C 75.11, H 8.00, N 8.01.

*(5*RS,*7a*RS,*12*RS,*14a*RS*)-4,5,7,7a,11,12,14,14a-Octahydro-5,12-dimethyldiindolo[1,7-*bc:*1′,7′-g*h*][2,6]-naphthyridine* (**1**). To preheated (235°) HMPT (10 ml) was added **2** (2.0 g, 5.7 mmol). After 25 min, the soln. was cooled to r.t., H_2O (75 ml) added, and the mixture extracted with AcOEt. The org. layer was dried ($MgSO_4$), evaporated and flash chromatographed (silica gel, hexane/AcOEt 4:1) to afford **1** (1.3 g, 70%). M.p. 249°–251°. ^{1}H-NMR ($CDCl_3$): 1.39 (*d*, $J = 6$, 2 CH_3); 2.4–2.7 (*m*, H_{ax}–C(7), H_{ax}–C(14), 1 H–C(4), 1 H–C(11)); 2.95, 3.05 (*dd*, $J = 12$, 11, H_{eq}–C(7), H_{eq}–C(14)); 3.3–3.5 (*m*, H–C(5), H–C(12), H–C(7a), H–C(14a), 1 H–C(4), 1 H–C(11)); 6.7 (*t*, $J = 8$, H–C(2), H–C(9)); 6.9–7.2 (*m*, H–C(1), H–C(3), H–C(8), H–C(10)). Anal. calc. for $C_{22}H_{24}N_2$: C 83.54, H 7.59, N 8.86; found: C 83.55, H 7.58, N 8.83.

We thank Mrs. *T. Zardin* for helpful comments concerning the NMR data and Dr. *R. Amstutz* for a critical discussion of the manuscript.

REFERENCES

[1] C. Papageorgiou, X. Borer, *J. Org. Chem.* **1987,** *52,* 4403.
[2] R.J. Bass, R.C. Koch, C.H. Richards, J.E. Thorpe, *J. Agric. Food Chem.* **1981,** *29,* 576.
[3] J.B. Hendrickson, R. Göscke, E. Rees, *Tetrahedron* **1964,** *20,* 565 and ref. cit. therein.
[4] S. Jolidon, H.-J. Hansen, *Helv. Chim. Acta* **1977,** *60,* 978; M. Schmid, H.-J. Hansen, H. Schmid, *ibid.* **1973,** *56,* 105.
[5] R.S. Monson, D.N. Priest, *J. Org. Chem.* **1971,** *36,* 3826.