Komplexe, $C_3H_5NiC_5H_5$ und $C_3H_5PdC_5H_5$, nach Geschwindigkeitsgesetzen unterschiedlicher Ordnung verlaufen, dürfte in erster Linie in sterischen Faktoren zu suchen sein.

Im Gang befindliche Arbeiten sollen weiteren Aufschluss über den Mechanismus der hier diskutierten Reaktionen, und zwar insbesondere über die Natur der einzelnen Zwischenverbindungen und die Struktur der organischen Reaktionsprodukte, erbringen.

Frau *Monika Mahrer* danken wir sehr herzlich für ihre geschickte experimentelle Mitarbeit. Der *Schweizerische Nationalfonds* unterstützte in grosszügiger Weise die vorliegenden Untersuchungen.

Experimentelles. Die kinetischen Untersuchungen müssen unter völligem Ausschluss von Luft durchgeführt werden. Die Darstellung der Ausgangskomplexe $C_3H_5NiC_5H_5$ [8] [9] und $C_3H_5PdC_5H_5$ [9] [10] erfolgte nach Literaturangaben. Die verwendeten Phosphite waren Handelsprodukte der Fa. *Fluka*; sie wurden durch sorgfältige Destillation unter N_2 nochmals gereinigt. Für genauere Angaben bezüglich der Durchführung der Geschwindigkeitsmessungen siehe [6].

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54. The Conversion of Isoindolobenzazepines into Dibenzazecines: A new Synthesis of α-Allocryptopine from Schöpf's Base VI

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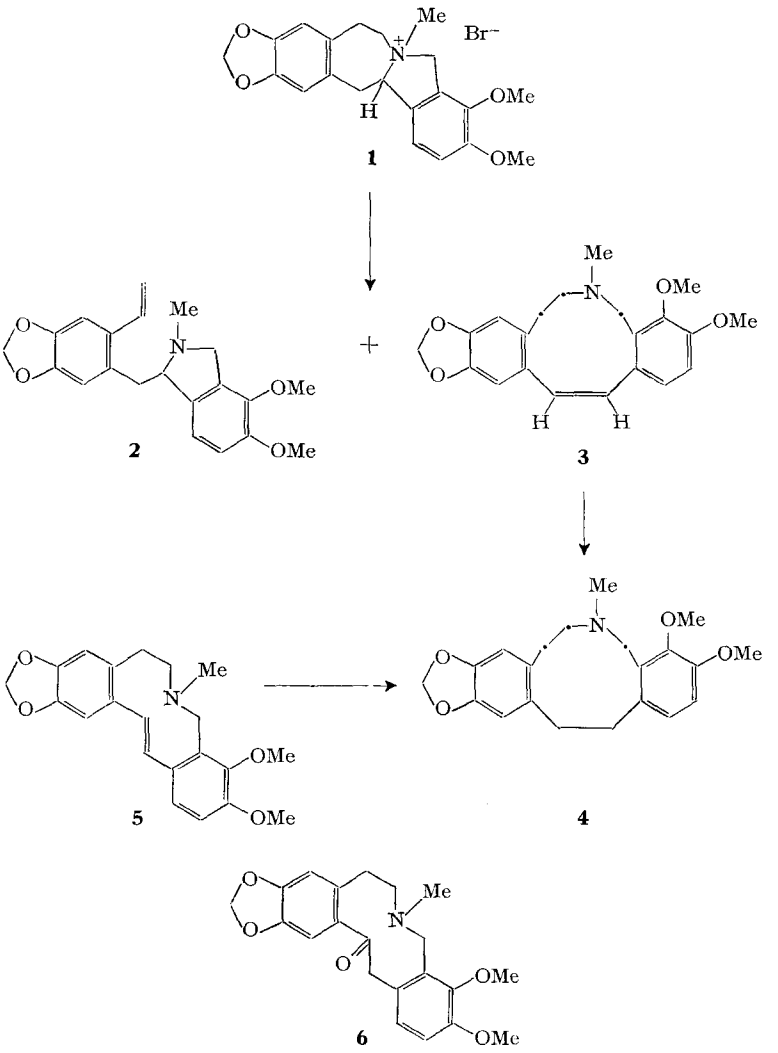
(27. XII. 72)

Zusammenfassung. Der *Hofmann*'sche Abbau des Brommethylates **1** der «*Schöpf*-Base VI» gibt zwei ungesättigte Basen, für welche die Strukturen **2** und **3** abgeleitet wurden. Das 10gliedrige *cis*-Dibenzazecin **3** konnte in schlechter Ausbeute in das Protopinalkaloid α-Allocryptopin **6** übergeführt werden.

The tetracyclic benzazepino-isoindole known as *Schöpf*'s base VI can be prepared readily from commercially available β-hydrastine [1] and is, therefore, a convenient

intermediate for further chemical transformations. In this paper we report our studies of the *Hofmann* elimination of its methobromide **1**. The latter was obtained in almost quantitative yield[1]) from *Schöpf*'s base VI by treatment with methyl bromide in acetone solution. The conversion of methobromide **1** into its quaternary base was accomplished by passing an aqueous solution of **1** through an ion-exchange column pretreated with sodium hydroxide [2]. The pooled aqueous eluates were degraded as described by *Pyman* [3] to give two isomeric bases ($C_{21}H_{23}NO_4$) as major degradation products which were readily separated by chromatography on silica gel. The early



[1]) The almost quantitative yield of a methobromide and the analysis of its NMR. spectrum suggest that the stereochemistry of the methyl group and the adjacent hydrogen atom at the tertiary carbon atom is very probably *cis*.

ethyl acetate eluates afforded a crystaline base, m.p. 79°, for which the iso-indoline structure **2** could be assigned on the basis of its UV. spectrum and a detailed NMR. analysis (see Experimental). The presence of a vinyl group in compound **2** is due to the abstraction of a proton from the benzylic 8-position and rupture of the C(7)-N(6)-bond. After further chromatography the base (m.p. 121–122°) isolated was shown to be isomeric with **2**, suggesting that it had the ten-membered tetrahydro-dibenzazecine structure **3** with a *cis*-configuration at the ethylene bridge between the two substituted aromatic moieties. The NMR. data reported in the experimental section account for all the protons present in this molecule and the *cis*-configuration is strongly supported by the vinylic protons present at δ 6.60 and 6.70. Whereas isomeric *trans*-fused dibenzazecines have been obtained from berberine alkaloids [4] [5], this is the first time that a *cis*-substituted isomer of this type has been isolated. Chemical proof for the assigned ten-membered *cis*-structure of **3** was obtained by identifying its dihydro product **4** obtained by catalytic reduction, with the reduction product of *Russell*'s *trans*-compound **5** [2].

The difference in behavior of the N-oxides of the *cis*-dibenzazecine **3** and *Russell*'s *trans*-dibenzazecine **5** is noteworthy. The latter has been reported by *Haworth et al.* [6] to be converted in good yield into the protopine alkaloid α-allocryptopine (**6**) by acid catalysis involving a *trans*-annular reaction. The low-yield conversion of the N-oxide of the *cis*-isomer **3** into α-allocryptopine (**6**) by acid catalysis herein reported involves side reactions. The initial step in this conversion might involve isomerization of the *cis*-N-oxide into its isomeric *trans*-N-oxide followed by a *trans*-annular shift of the oxygen function, suggested by the fact that after short exposure of the *cis*-isomer to acid, TLC. analysis indicates the presence of material very probably identical with the isomeric *trans*-N-oxide.

Experimental. – All melting points (uncorrected) were taken on a *Kofler* microscope hot stage. The UV. spectra were measured with a *Carey* recording spectrophotometer Model 14M and the NMR. spectra were obtained with a *Varian* Model HA-100 spectrophotometer using tetramethylsilane as internal reference unless otherwise noted. Chemical shifts are reported in δ with the following abbreviations: (*s*) singlet, (*m*) multiplet, (*t*) triplet, (*q*) quartet, (b) broad. Extracts of the products in organic solvents were washed with water and dried over anhydrous sodium sulfate prior to evaporation.

*3,4-Dimethoxy-10,11-methylenedioxy-7,8,13,13a-tetrahydro-5*H*-benzo[4,5]azepino[2,1-*a*]isoindole methobromide hemihydrate* (**1**). To a solution of 5.0 g (0.0147 mol) of *Schöpf*'s Base VI in 700 ml of acetone was added 13.9 g (0.147 mol) of methyl bromide in 25 ml of acetone. After standing at room temperature 24 h, the white crystals were filtered off, washed with 200 ml of acetone and dried to give 5.9 g (95%) of **1**, m.p. 223–225° (dec.); NMR. ($(CD_3)_2SO$) δ 2.07 (*s*, 3H, CH_3N), 3.78 (*s*, 6H, $2CH_3O$), 5.03 (*s*, 2H, $ArCH_2N$), 5.18 (*t*, 1H, J = 4 Hz, CHN), 5.92 (*s*, 2H, OCH_2O), 6.64, 7.06 (*s*, 2H, aromatic), 6.96, 7.04 (*AB*, 2H, J_{ortho} = 8 Hz, aromatic).

$C_{21}H_{23}BrNO_4, 0.5\ H_2O$	Calc.	C 56.90	H 5.46 N 3.16%
(443.30)	Fd.	,, 56.75	,, 5.45 ,, 3.12%

4,5-Dimethoxy-2-methyl-1-[(3,4-methylenedioxy)-6-vinyl-benzyl]-isoindoline (**2**) *and* cis-*3,4-dimethoxy-6-methyl-10,11-methylenedioxy-5,6,7,8-tetrahydro-dibenzo*[c,g]*azecine* (**3**). A solution of 2.0 g (0.0045 mol) of (**1**) in 100 ml of distilled water was run through a column of 14.0 g of IRA-400 resin (which had been previously treated with 280 ml of 10% sodium hydroxide and washed with 280 ml of distilled water). The solution was collected under nitrogen, and the column was then washed with 50 ml of distilled water. The original solution and washings were evaporated under

reduced pressure as described by *Russell* [2] to give 1.6 g of crude product, which was chromatographed on silica gel using ethyl acetate as eluant. The early fractions gave 0.38 g (24%) of **2**: m.p. 79°. UV. λ_{max}^{EtOH} (ε): 264 (10,500), 306 nm (5000). NMR. ($CDCl_3$): δ 2.38 (*s*, 3H, CH_3N), 2.97 (*d*, 2H, J = 6.5 Hz, CH_2CH), 3.59, 4.36 (*AB*, 2H, J = 14 Hz, CH_2N), 4.82 (*m*, 1H, CH_2CH), 3.77 (*s*, 3H, CH_3O), 3.79 (*s*, 3H, CH_3O), 5.14, 5.47, 6.98 (*AMX*, 3H, J_{am} *gem* 1.5 Hz, J_{ax} *cis* 11 Hz, J_{mx} *trans* 17.5 Hz, $CH_x = CH_aH_m$), 5.90 (*s*, 2H, OCH_2O), 6.49, 6.67 (*AB*, 2H, J_{ortho} = 8.5 Hz, aromatic), 6.71, 6.98 (*s*, 2H, aromatic).

$C_{21}H_{23}NO_4$ (353.42) Calc. C 71.37 H 6.56 N 3.96% Found C 71.19 H 6.69 N 3.82%

The later fractions afforded 0.63 g (39%) of **3**: m.p. 121–122°. UV. $\lambda_{max}^{cyclohexane}$ (ε): 295 nm (6360), λ_{max}^{EtOH} (ε): 294 nm (7000). NMR. ($CDCl_3$): δ 2.34 (*s*, 3H, CH_3N), 3.48 (*s*, 2H, CH_2), 3.62, 3.64 (*s*, 6H, CH_3O), 5.80 (*s*, 2H, OCH_2O), 6.42, 6.48 (*s*, 2H, aromatic), 6.67 (*s*, 2H, aromatic), 6.60, 6.70 (*AB*, 2H, J_{cis} = 12 Hz, CH=CH).

$C_{21}H_{23}NO_4$ (353.40) Calc. C 71.37 H 6.56 N 3.96% Found C 71.6 H 6.63 N 3.92%

3,4-Dimethoxy-6-methyl-10,11-methylenedioxy-5,6,7,8,14,15-hexahydro-dibenzo[c,g]*azecine* (**4**). A solution of 0.1 g (0.29 mmol) of **3** in 4.0 ml of 3 N HCl was hydrogenated in the presence of *Adam*'s catalyst. The catalyst was removed by filtration, and the filtrate was rendered alkaline with ammonium hydroxide and extracted with ether. The residue, after removal of the ether, was crystallized from ether/ligroin to give 0.06 g (60%) of **4**: m.p. 127–128° (lit. 129°). NMR. ($CDCl_3$) δ 2.07 (*s*, 3H, N—CH_3), 2.56–3.10 (*m*, 8H, CH_2CH_2), 3.74 (*s*, 3H, OCH_3), 3.81 (*s*, 3H, OCH_3), 3.85 (*s*, 2H, CH_2), 5.87 (*s*, 2H, O—CH_2—O), 6.13, 6.67 (*s*, 2H, aromatic), 6.79, 6.84 (*AB*, 2H, J_{ortho} = 9.0 Hz).

$C_{21}H_{25}NO_4$ (355.43) Calc. C 70.96 H 7.09 N 3.94% Found C 70.85 H 7.06 N 3.90%

This base is identical by mixed m.p. and TLC. with a sample prepared by catalytic reduction of the *trans* isomer **5** reported by *Russell* [2] and described below.

Trans-*3,4-dimethoxy-6-methyl-10,11-methylenedioxy-5,6,7,8-tetrahydro-dibenzo*[c,g]*azecine* (**5**). Compound **5** was prepared as described by *Russell* [2] and crystallized from ethyl acetate to give m.p. 134–135° (lit. 135°). UV. $\lambda_{max}^{cyclohexane}$ (ε) 281 nm (9500), λ_{max}^{EtOH} (ε): 233 nm (12,600). NMR. ($CDCl_3$) δ 2.2 (*s*, 3H, CH_3N), 2.72 (*s*, 4H, CH_2CH_2), 3.67 (*s*, 2H, CH_2), 3.78 (*s*, 3H, CH_3O), 3.84 (*s*, 3H, CH_3O), 5.87 (*s*, 2H, OCH_2O), 6.38, 7.09 (*AB*, 2H, J_{trans} = 16.5 Hz, CH=CH), 6.60, 6.68 (*s*, 2H, aromatic), 6.87 (*s*, 2H, aromatic).

Conversion of **5** into its N-oxide followed by acid catalyzed rearrangement by procedures reported by *Haworth & Perkin* [6] afforded α-allocryptopine (**6**), m.p. 158–159°, NMR. ($CDCl_3$) δ 1.89 (*s*, 3H, CH_3N), 2.3–3.2 (*m*, 4H, CH_2CH_2), 3.6–3.8 (*m*, 4H, CH_2), 3.77 (*s*, 3H, OCH_3), 3.85 (*s*, 3H, OCH_3), 5.92 (*s*, 2H, O—CH_2—O), 6.62, 6.94 (*s*, 2H, aromatic), 6.81, 6.84 (*AB*, 2H, aromatic).

$C_{21}H_{23}NO_5$ (369.40) Calc. C 68.28 H 6.28 N 3.79% Found C 68.02 H 6.29 N 3.62%

N-Oxide of **3**. A solution of 2.0 g (5.6 mmol) of **3** in 20 ml of chloroform was gradually added to a solution of 1.25 g (6.2 mmol) of 85% *m*-chloroperbenzoic acid in 100 ml of ether while the temperature was maintained below 5° by immersion in an ice bath. After remaining overnight in the refrigerator at 5°, the mixture was stirred with 24 ml of 10% sodium hydroxide at room temperature for 2 h, the resulting solid was collected, dried, and recrystallized from chloroform ether to give 1.8 g (90%) of N-oxide, m.p. 109–110°: NMR. ($CDCl_3$): δ 3.23 (*s*, 4H, CH_2CH_2), 3.47 (*s*, 3H, CH_3N), 3.86 (*s*, 6H, $2CH_3O$), 4.75 (*s*, 2H, CH_2), 5.92 (*s*, 2H, OCH_2O), 6.44, 6.74 (*s*, 2H, aromatic), 6.69, 6.85 (*AB*, 2H, J_{ortho} = 8.5 Hz), 6.79 (*s*, 2H, CH=CH).

$C_{21}H_{23}N_1O_5$ (369.40) Calc. C 68.28 H 6.28 N 3.79% Found C 67.98 H 6.32 N 3.54%

Conversion of **3** N-*oxide into* α-*allocryptopine* (**6**). A solution of 0.1 g (0.29 mmol) of **3** N-oxide in 1.5 ml of glacial acetic acid and 1.5 ml of concentrated hydrochloric acid was heated at 100° for 6 h. The pale yellow solution was diluted with water, made alkaline with potassium hydroxide, extracted with ether, washed and dried. The crude product was crystallized from ethyl acetate/ligroin to give 0.015 g (15%) of α-allocryptopine (**6**), m.p. 156–157°, identical by mixed m.p. and TLC. with a sample prepared from **5**.

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55. Méthylène-10,11- et méthyl-11-prostaglandine[1])

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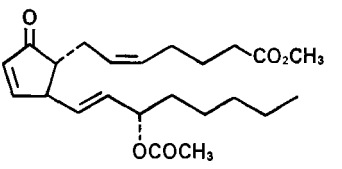
(10 I 73)

Summary. The title compounds **6** and **7** have been prepared from a natural occurring PG-A_2 derivative. The structure and configuration of these novel prostaglandins are deduced from their mode of preparation and from their spectroscopic properties.

Plusieurs dérivés des prostaglandines ont été préparés par synthèse totale [1], en faisant appel à la méthode développée à *Harvard* [2]. Une autre voie d'accès consiste à utiliser les dérivés de la PG-A_2, désormais disponibles en grandes quantités par extraction des gorgones de la famille *Plexaura homomalla*, originaires de la mer des Caraïbes [3]. Ces composés ont été utilisés comme produits de départ pour la préparation des prostaglandines naturelles PG-E_2 et PG-$F_{2\alpha}$ [4]. Le système cétonique

Schéma 1



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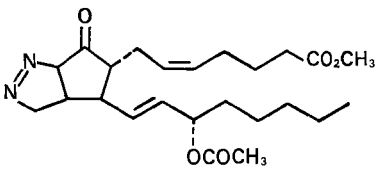

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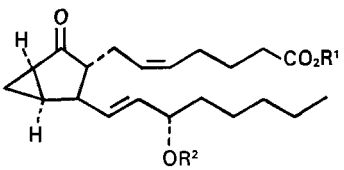
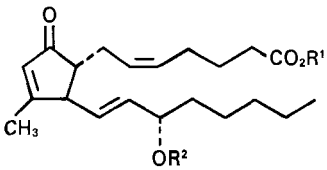


3: $R^1 = CH_3$; $R^2 = COCH_3$
5: $R^1 = CH_3$; $R^2 = H$
6: $R^1 = R^2 = H$



4: $R^1 = CH_3$; $R^2 = COCH_3$
7: $R^1 = R^2 = H$

[1]) Contribution No. 420 du Syntex Institute of Organic Chemistry. Study in Prostaglandins No. 22.

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