REFERENCES

[1] *M. Dobler*, Helv. *55*, 1371 (1972).
[2] *M. Dobler, J. D. Dunitz & B. T. Kilbourn*, Helv. *52*, 2573 (1969).
[3] *M. Dobler & R. P. Phizackerley*, Helv. *57*, 664 (1974).
[4] *G. Szabo, G. Eisenman, R. Laprade, S. M. Ciani & S. Krasne*, Membranes, Vol. 2, p. 179 (1973).
[5] *P. Main, M. M. Woolfson & G. Germain*, Multan 74, University of York, England (1974).
[6] *Y. Nawata, T. Sakamaki & Y. Iitaka*, Chem. Letters (Japan) *1975*, 151.

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63. 1-Aralkylated Tetrahydro-2-benzazepines[1]). Part II: Synthesis from 3-(3,4-Dimethoxyphenyl)-propylamine

by **Daniel Berney** and **Theodor Jauner**

Research Institute *Wander* Ltd., a *Sandoz* Research Unit, Berne, Switzerland.

(7. I. 76)

Summary. 3-(3,4-Dimethoxyphenyl)-propylamine was N-acylated with aralkanecarboxylic acid chlorides. The resulting amides were subjected to *Bischler-Napieralski* ring closure to give the corresponding 1-aralkyl-dihydro-2-benzazepines. These were reduced to the title compounds.

Introduction. – In Part I of this study, the synthesis of some 1-aralkyl-tetrahydro-2-benzazepines from methoxylated phenylpropionamides was described [1]. The method reported in the previous paper was found to be unsuccessful for the preparation of 2-benzazepines where the 1-aralkyl group had methoxy- or chloro-substituents in the aromatic nucleus. The difficulties encountered in the synthesis of these compounds were avoided by the use of the route here described, which involves a *Bischler-Napieralski* ring closure.

Results. – 3-(3,4-Dimethoxyphenyl)-propylamine **1** was allowed to react with the phenylacetyl chlorides **2a**, **b** and **c**, giving the amides **3a**, **b** and **c**. These amides did not cyclize when heated with $POCl_3$ alone; one mol of anhydrous $AlCl_3$ had to be added for each mol of amide to effect ring closure. The imines **4a**, **b** and **c** were used as crude oils in the reduction with $NaBH_4$, giving the corresponding amines **5a**, **b** and **c**. Compound **5a** was identical with the product obtained by the route previously described [1]. The amine **5b** was treated with formaldehyde, and the adduct was reduced with $NaBH_4$, giving the methylated compound **6b**. The amine **5c** was methylated by the *Clarke-Eschweiler* method to give **6c**. The 'homoxylopine' **7** was obtained by treating **5b** with formaldehyde and HCl.

Similarly the phenylpropylamine **1** was allowed to react with the phenylpropionyl chlorides **2d** and **2e** to give the amides **3d** and **3e**, respectively. These amides were cyclized to **4d** and **4e** which were then reduced to **5d** and **5e**. Product **5d** was identical with the benzazepine previously reported [1]. The amines **5d** and **5e** were methylated to **6d** and **6e** by the *Clarke-Eschweiler* method.

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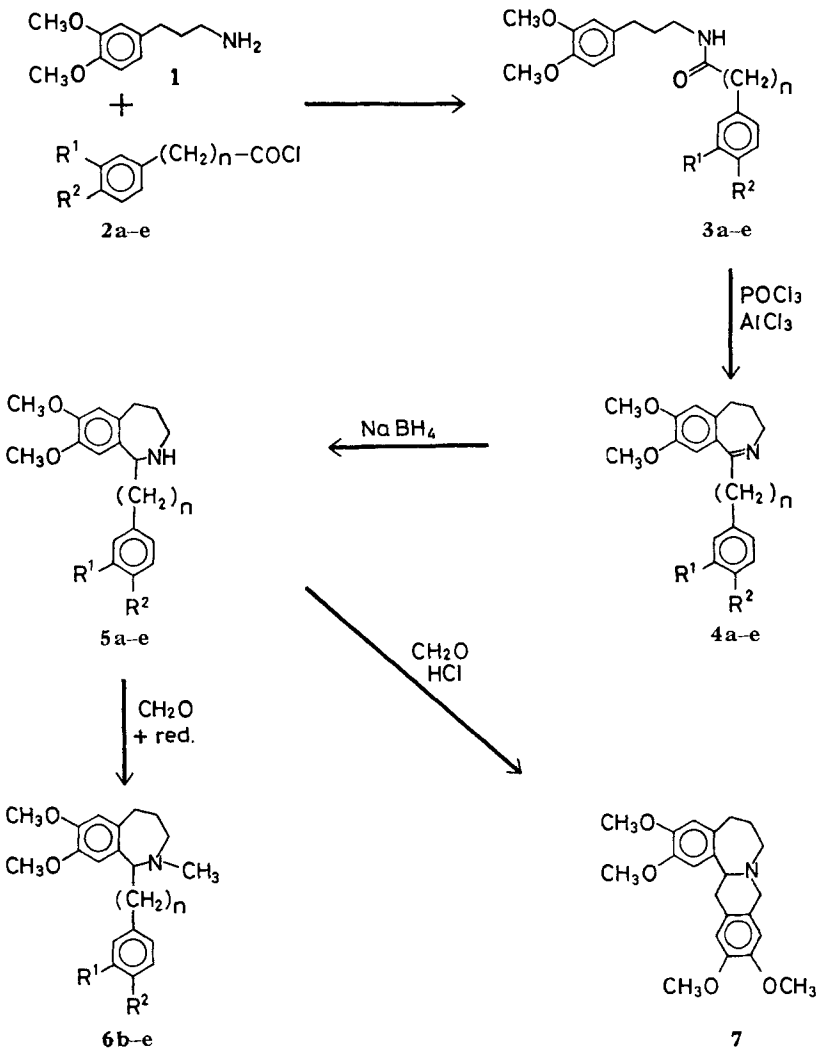
[1]) 19th Communication on seven-membered heterocycles; 18th Communication: [1].



a n = 1, $R^1 = R^2 = H$
b n = 1, $R^1 = H$, $R^2 = Cl$
c n = 1, $R^1 = R^2 = OCH_3$
d n = 2, $R^1 = R^2 = H$
e n = 2, $R^1 = H = R^2 = Cl$

Experimental Part

General. For general remarks on NMR. spectra and microanalysis see Part I [1].

N-[3-(3,4-Dimethoxyphenyl)-propyl]-phenylacetamide (**3a**). 3-(3,4-Dimethoxyphenyl)propylamine [2] (19.5 g, 0.1 mol) was dissolved in a stirred solution of dry CH_2Cl_2 (600 ml) and pyridine (8.7 g, 1.1 mol) which was cooled with ice/water. Phenylacetyl chloride (*Fluka*) (15.4 g, 0.1 mol) in CH_2Cl_2 (150 ml) was added dropwise. The ice-bath was then removed and the reaction mixture was stirred for a further 45 min. The solution was extracted twice with 1N HCl and once with water. The organic layer was dried and evaporated to dryness. The residue was recrystallized from $CHCl_3$/ether, yielding 23.4 g (75%) of the amide **3a**, m.p. 97–99°. – NMR.: 1.8 (*q*, 2H,

CH_2); 2.5 (*t*, 2H, $ArCH_2$); 3.2 (*q*, 2H, CH_2NHCO); 3.5 (*s*, 2H, $PhCH_2CO$); 3.8 (*s*, 6H, $2OCH_3$). – $C_{19}H_{23}NO_3$: C, H, N.

N-[3-(3,4-Dimethoxyphenyl)-propyl]-(4-chlorophenyl)-acetamide (**3b**). Conditions as described for **3a**. *p*-Chlorophenylacetyl chloride [3] (18.9 g, 0.1 mol) in CH_2Cl_2 were added to a solution of the phenylpropylamine **1** (23.4 g, 0.12 mol) and pyridine (10.3 g, 0.13 mol) in CH_2Cl_2 (600 ml). After working-up and recrystallization 26 g (75%) of **3b** were obtained, m.p. 120–121°.

N-[3-(3,4-Dimethoxyphenyl)-propyl]-(3,4-dimethoxyphenyl)-acetamide (**3c**). Conditions as described for **3a**; (3,4-dimethoxyphenyl)-acetyl chloride [4] (21.4 g, 0.1 mol) in CH_2Cl_2 were added to a solution of the amine **1** (23.4 g, 0.12 mol) and pyridine (10.3 g, 0.13 mol) in CH_2Cl_2 (600 ml). After working-up and recrystallization 24.2 g (65%) of the amide **3c** were collected, m.p. 107–109°.

N-[3-(3,4-Dimethoxyphenyl)propyl]-3-phenylpropionamide (**3d**). Conditions as described for **3a**; 3-phenylpropionyl chloride (*Fluka*) (16.7 g, 0.1 mol) in CH_2Cl_2, was added to a solution of the amine **1** (23.4 g, 0.12 mol) and pyridine (10.3 g, 0.13 mol) in CH_2Cl_2 (600 ml). After working-up and recrystallization 23 g (70%) of **3d** were obtained, m.p. 77–79°. – $C_{20}H_{25}NO_3$: C, H, N.

N-[3-(3,4-Dimethoxyphenyl)-propyl]-3-(4-chlorophenyl)-propionamide (**3e**). Conditions as described for **3a**; (p-chlorophenyl)-propionyl chloride [5] (20.3 g, 0.1 mol) in CH_2Cl_2 was added to a solution of the amine **1** (23.4 g, 0.12 mol) and pyridine (10.3 g, 0.13 mol) in CH_2Cl_2. After working-up and recrystallization 27 g (75%) of the amide **3e** were obtained, m.p. 111°.

*1-Benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**5a**) *hydrogen maleate.* The amide **3a** (6.3 g, 0.02 mol) was dissolved in $POCl_3$ (150 ml) and powdered anhydrous $AlCl_3$ (*Fluka*) (3.2 g, 0.024 mol) was added. The mixture was stirred and heated at 80° under nitrogen for 12 h. Phosphorus oxychloride was then evaporated off, and the residue was treated with 1 N NaOH and extracted 3× with $CHCl_3$. The organic layer was washed with brine, dried and evaporated to dryness. The brown crude imine **4a** was imediately reduced with $NaBH_4$ (2 g, 0.053 mol) in methanol (150 ml) between 0 and 5°. A large amount of water was added and the resulting suspension was extracted with $CHCl_3$. After drying and evaporation of the organic extract, the crude oily residue was converted to its hydrogen maleate, yielding 4 g (48%) of **5a** salt, m.p. 156–157°, identical with previously reported product [1]. – $C_{23}H_{27}NO_6$: C, H, N.

*1-(4-Chlorobenzyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**5b**) *naphthalene-1,5-disulfonate.* As for the preparation of **5a**. The amide **3b** (50 g, 0.144 mol), $POCl_3$ (1500 ml) and $AlCl_3$ (20 g, 0.15 mol) were heated at 120° for 24 h. After working-up, the oily product was reduced with $NaBH_4$ (10 g, 0.27 mol) in methanol at 0–5°, giving 32 g of crude amine. The naphthalene-,1,5-disulfonate was prepared by dissolving the amine in a small amount of ethanol and adding a warm solution of naphthalene-1,5-disulfonic acid [6] (20 g, 0.069 mol). Ether was added and the product allowed to crystallize, giving 28 g (41%) of **5b** salt, m.p. 280–282°. – $C_{24}H_{26}ClNO_5S$: C, H, N.

*1-(3,4-Dimethoxybenzyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**5c**) *naphthalene-1,5-disulfonate.* As for the preparation of **5a**. The amide **3c** (100 g, 0.27 mol), $POCl_3$ (2000 ml) and $AlCl_3$ (46 g, 0.35 mol) were heated to 80° for 20 h. After working-up, the residue was reduced with $NaBH_4$ (15 g, 0.39 mol) in methanol at 0–5°, yielding 40 g of crude oil. The compound was converted to its naphthalene-1,5-disulfonate as for **5b**, giving 41 g (31%) of **5c** salt, m.p. 262–266°, free base m.p. 98–100°. – $C_{26}H_{31}NO_7S$: C, H, N.

*7,8-Dimethoxy-1-(2-phenethyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**5d**) *naphthalene-1,5-disulfonate.* As for the preparation of **5a**. The amide **3d** (16.3 g, 0.05 mol), $POCl_3$ (300 ml) and $AlCl_3$ (6.5 g, 0.05 mol), were heated to 80° for 2 days. After working-up, the oily residue was reduced with $NaBH_4$ (3.5 g, 0.09 mol) in methanol at 0–5°, yielding 12.5 g of crude oil which was converted to its naphthalene-1,5-disulfonate as for **5b**, giving 10.7 g (47%) of **5d** salt, m.p. 288–290°, identical with previously reported product [1]. – $C_{25}H_{29}NO_5S$: C, H, N.

*1-[2-(4-Chlorophenyl)ethyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**5e**) *naphthalene-1,5-disulfonate.* As for the preparation of **5a**. The amide **3e** (36.2 g, 0.1 mol), $POCl_3$ (600 ml) and $AlCl_3$ (14.3 g, 0.11 mol) were heated 2 days at 80°. After working-up, the oily product was reduced with $NaBH_4$ (7 g, 0.19 mol) in methanol at 0–5°, yielding 18 g of crude amine. The naphthalene-5-disulfonate was prepared as for **5b** giving 16.5 g (34%) of **5e** salt, m.p. 257–260°. – $C_{25}H_{28}ClNO_5S$: C, H, N.

*1-(4-Chlorobenzyl)-7,8-dimethoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**6b**) *naphthalene-1,5-disulfonate.* The amine **5b** (6.6 g, 0.02 mol) was refluxed for 30 min with formic acid

(10 ml) and a 35% aqueous formaldehyde solution (7 ml). The mixture was poured into water, made alkaline with 5N NaOH and extracted with $CHCl_3$. The organic layer was dried, evaporated to dryness and the crude base converted to its naphthalene-1,5-disulfonate, yielding 6.8 g (69%) of **6b** salt, m.p. 250–252°. – $C_{25}H_{28}ClNO_5S$: C, H, N.

*7,8-Dimethoxy-2-methyl-1-(2-phenethyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**6d**) *naphthalene-1,5-disulfonate.* Compound **5d** was methylated to **6d**, which was converted to its naphthalene-1,5-disulfonate as described for **6b**, giving 79% of salt, m.p. 253–255°. – $C_{26}H_{31}NO_5S$: C, H, N.

*1-[2-(4-Chlorophenyl)ethyl]-7,8-dimethoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**6e**) *naphthalene-1,5-disulfonate.* Compound **5e** was methylated to **6e**, which was converted to its naphthalene-1,5-disulfonate as described for **6b**, giving 70% of salt, m.p. 233–236°. – $C_{26}H_{30}ClNO_5S$: C, H, N.

*1-(3,4-Dimethoxybenzyl)-7,8-dimethoxy-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**6c**) *naphthalene-1,5-disulfonate.* The amine **5c** (7.5 g, 21.0 mmol) was dissolved in 25 ml of ethanol, 40 ml of 35% aqueous solution of formaldehyde were added, and the solution was refluxed for 1.5 h. The reaction mixture was then cooled to 0–5° and $NaBH_4$ (7,5 g, 0.20 mol) was added in small portions. The mixture was allowed to warm up to RT. After addition of a large amount of water, the mixture was extracted with $CHCl_3$. The organic layer was dried, evaporated to dryness and the residual oil converted to its naphthalene-1,5-disulfonate as for **5b**, giving 8.4 g (78%) of **6c** salt, m.p. 233–235°. – $C_{27}H_{33}NO_7S$: C, H, N.

2,3,10,11-Tetramethoxy-5,6,7,7a,8,13-hexahydro-isoquinolo[3,2-a]-2-benzazepine (**7**). The amine **5c** (7.5 g, 21 mmol) was dissolved in 2N HCl (75 ml) and a 35% aqueous formaldehyde solution (40 ml) was added. The mixture was refluxed for 1.5 h, then cooled and made alkaline with 2N NaOH. The compound was extracted with $CHCl_3$. The organic extract was dried, evaporated to dryness and the residue recrystallized from $CHCl_3$/petroleum ether, giving 4.7 g (61%) of **7**, m.p. 163–165°. Naphthalene-1,5-disulfonate m.p. 223–235°. – NMR: 3.6 (*s*, 3H, OCH_3); 3.8 (3 close together *s*, 9H, $3OCH_3$); 4.3 (*t*, 1H, ArCHN); 6.5, 6.55, 6.7 and 6.73 (4*s*, 4H, 4ArH). – $C_{22}H_{27}NO_4$: C, H, N.

REFERENCES

[1] *D. Berney & K. Schuh*; Helv. *58*, 2228 (1975).
[2] *F. Benington, R. D. Morin & L. C. Clark, Jr.*, J. org. Chemistry *21*, 1545 (1956).
[3] *P. D. Bartlett & Ch. Rüchardt*, J. Amer. chem. Soc. *82*, 1756 (1960).
[4] *R. D. Haworth, W. H. Perkin & J. Rankin*, J. chem. Soc. *125*, 1694 (1924).
[5] *Ng. Ph. Buu-Hoï, Ng. Hoán & Ng. D. Xuong*, J. chem. Soc. *1951*, 3499.
[6] *H. Ed. Fierz-David & A. W. Haster*, Helv. *6*, 1133 (1923).

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64. Herstellung von Dihydro-, Tetrahydro- und Hexahydro-chelidamsäure-Derivaten[1])

von **Kurt Hermann**[2]) und **André S. Dreiding**
Organisch-Chemisches Institut der Universität Zürich, Rämistrasse 76, 8001 Zürich

Prof. *H. H. Inhoffen* zum 70. Geburtstag gewidmet

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Preparation of dihydro-, tetrahydro- and hexahydro-chelidamic-acid derivatives. – *Summary.* Three methods for the preparation of 4-oxo-2,6-piperidine-dicarboxylic acid (**3**) and derivatives, required as a synthon for betalaine pigments, were explored.

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[1]) Aus der Dissertation von *K. Hermann*, Universität Zürich, 1976.

[2]) Stipendiat des Fonds zur Unterstützung von Doktoranden auf dem Gebiet der Chemie. Gegenwärtige Adresse: Department of Organic Chemistry, University of Groningen, Zernikelaan, Groningen, The Netherlands.