239. 1-Aralkylated Tetrahydro-2-benzazepines[1]). Part I: Synthesis from Methoxylated Phenylpropionamides

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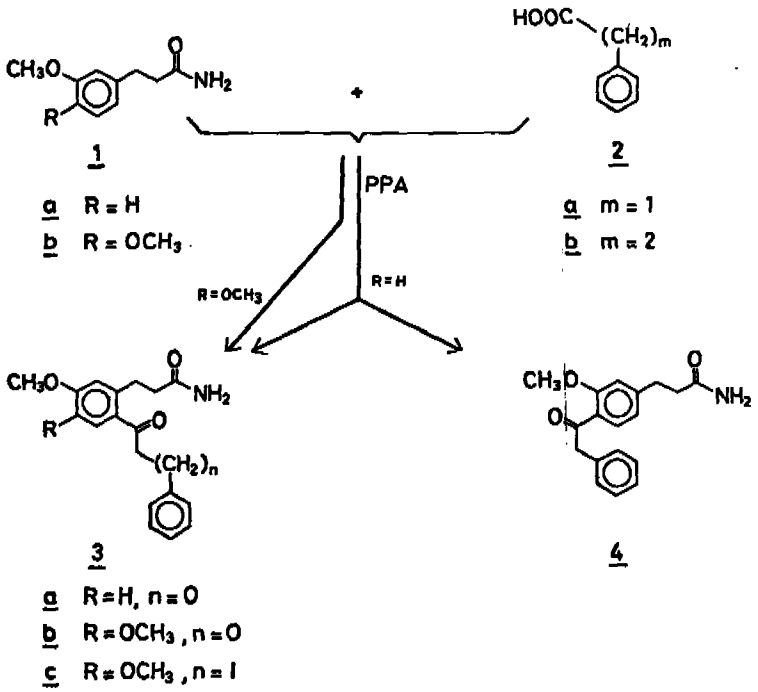
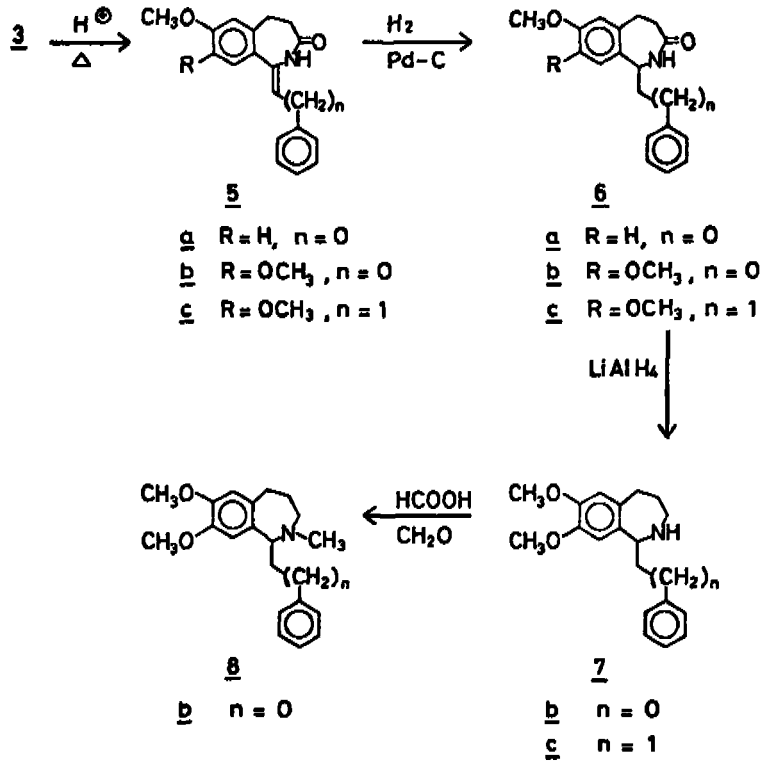
Summary. Phenylpropionamides acylated in the ortho position with aralkanecarboxylic acids were cyclised to give, after reduction, 1-aralkyl-tetrahydro-2-benzazepines.

Introduction. – Methoxylated phenylpropionamides were acylated at the ortho position to the propionamide chain with phenylacetic acid or phenylpropionic acid. The cyclo-dehydration of the resulting aromatic ketone gave methoxylated 1-benzylidene- or 1-benzylmethylidene-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-ones in moderate yields. These were reduced to the corresponding 1-benzyl or 1-phenethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines.

Results. – When (3-methoxyphenyl)-propionamide [2] (**1**) was heated with phenylacetic acid (**2a**) in polyphosphoric acid (PPA) the two acylation products **3a** and **4**



1) 18th Communication on seven-membered heterocycles; 17th Communication: [1].



were obtained in equal amounts; they could be separated by fractional crystallisation. Compound **3a** was cyclised to the tetrahydro-2-benzazepin-3-one **5a** by boiling in toluene in the presence of *p*-toluenesulfonic acid (*p*-TsOH).

Heating of 3,4-dimethoxyphenylpropionamide [3] (**1b**) with **2a** and PPA gave product **3b** in good yield, which was then cyclised to **5b**[2]).

Similarly the amide **1b** was reacted with phenylpropionic acid **2b** and the resulting aromatic ketone **3c** was cyclised to **5c**.

The three benzylidene- and benzylmethylidene-tetrahydrobenzazepinones **5a**, **5b** and **5c**, were hydrogenated to the benzyl and phenethyl-tetrahydro-benzazepinones, **6a**, **6b** and **6c**. Lactame **6b** and **6c** were reduced with $LiAlH_4$ to give the corresponding amines **7b** and **7c**. Compound **7b** was methylated by the *Clarke-Eschweiler* method to **8**.

3,4-Dimethoxyphenylpropionamide (**1b**), PPA and cinnamic acid (**9**) were heated together to give the indanone **10** which was cyclized to the tetrahydro-cyclopenta-[*j*,*k*][2]-benzazepin-4-one **11**. Product **11** was hydrogenated to **12**, reduced with $LiAlH_4$ giving **13a** and then methylated at the nitrogen yielding the hexahydro-cyclopenta[*j*,*k*][2]-benzazepine **13b**.

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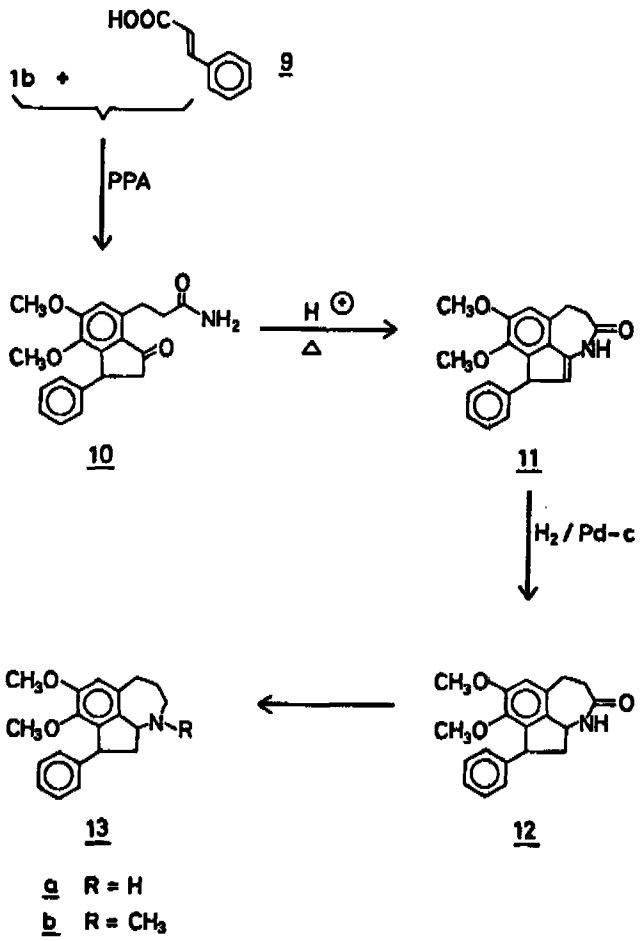
[2]) Similar results were obtained when *p*-chlorophenyl-acetic acid was used instead of **2a** but the corresponding product of type **5** could not be hydrogenated without loss of the chlorine atom. Acylation of the amide **1b** with 3,4-dimethoxyphenylacetic acid in PPA was unsuccessful. In order to overcome these difficulties another method for preparing 1-benzylated-tetrahydro-2-benzazepines was developed and will be described in part II of this study.



Experimental Part

General. NMR. spectra were taken at 60 MHz in $CDCl_3$ with TMS as an internal standard, using a *Varian* T-60 high resolution NMR. spectrometer. In the case of salts, a sample of the free base was prepared and used in $CDCl_3$. Abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, br. = broad; chemical shift in δ-values (ppm) coupling constants in Hz. – Analytical results obtained for the indicated elements were within ± 0.4% of the theoretical values.

3-(5-Methoxy-2-phenylacetyl-phenyl)-propionamide (**3a**) *and 3-(3-methoxy-4-phenylacetyl-phenyl)-propionamide* (**4**). 3-(3-Methoxyphenyl)-propionamide (17.9 g, 0.1 mol), phenylacetic acid (17.7 g, 0.13 mol) and PPA (350 g) were mixed and heated for 1.5 h at 80°. The hot reddish reaction mixture was poured slowly into water (3000 ml) with stirring; the solution was cooled by the addition of ice and was then extracted with $CHCl_3$. The organic layer was dried and evaporated to dryness. The two products were separated by fractional crystallisation from $CHCl_3$/ether. 10.5 g (35%) of **3a** (m.p 130–133°) and 8 g (27%) of **4** (m.p 124–126°). – NMR. of **3a**: 2.3 (*t*, 2 H, $ArCH_2$); 2.5 (*t*, 2 H, CH_2CON); 3.95 (*s*, 3 H, OCH_3); 4.3 (*s*, 2 H, $PhCH_2CO$); 5.5 (br., 2 H, NH_2); 7.7 (*d*, 1 H, arom). –NMR. of **4**: 2.15 (*t*, 2 H, $ArCH_2$); 2.5 (*t*, 2H, CH_2CON); 3.85 (*s*, 3 H, OCH_3); 4.25 (*s*, 2 H, $PhCH_2CO$); 5.9 (br., 2 H, NH_2); 7.9 (*d*, 1 H, arom). – For both products; $C_{18}H_{19}NO_3$: C, H, N.

3-(3,4-Dimethoxy-2-phenylacetyl-phenyl)-propionamide (**3b**). 3-(3,4-Dimethoxyphenyl)-propionamide (104.6 g, 0.5 mol), phenylacetic acid (88.5 g, 0.65 mol) and PPA (1000 g) were mixed and heated to 70–80° for 1 h 45. Work-up as for **3a** yielded 107 g (65%) of **3b**, m.p. 127–128°. – $C_{19}H_{21}NO_4$: C, H, N.

3-[4,5-Dimethoxy-2-(3-phenylpropionyl)-phenyl]-propionamide (**3c**). PPA (800 g), 3-[(3,4-dimethoxy)phenyl]-propionamide (21 g, 0.1 mol), 3-phenylpropionic acid (60 g, 0.4 mol) were mixed together and heated to 90° for 1 h and then kept over-night at room temp. As 3-phenylpropionic acid partly cyclised to 1-indanone, a large excess of this acid was needed. After standard working-up and recrystallization from $CHCl_3$/ether, 26 g (76%) of **3c** were obtained, m.p. 123–124°. – $C_{20}H_{23}NO_4$: C, H, N.

*1-Benzylidene-7-methoxy-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one* (**5a**). Ketone **3a** (20.8 g, 0.07 mol) was suspended in toluene (800 ml) and *p*-toluenesulfonic acid (TsOH) (0.2 g) was added; the mixture was allowed to reflux for 20 h, the water formed being removed by a *Dean-Stark* water-trap. The hot solution was treated with charcoal, filtered and evaporated to dryness. The residue was recrystallized from $CHCl_3$/ether yielding 9.7 g (49.5%) of **5a**, m.p 137–142°. – NMR.: 2.95 (*m*, 4H, $ArCH_2CH_2CON$); 3.9 (*s*, 3H, OCH_3); 6.1 (*s*, 1H, olefinic); 6.8 (*s*, 1H, ArH). – $C_{18}H_{17}NO_2$: C, H, N.

*1-Benzylidene-7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one* (**5b**). Compound **3b** (107 g, 0.33 mol) was suspended in dry toluene (1000 ml) and TsOH (1 g) was added. The mixture was vigorously refluxed for 3 h, the water formed being removed by a *Dean-Stark* trap. The hot solution was filtered through charcoal then cooled to 0° where compound **5b** crystallized. Yield 92.4 g (91.5%), m.p. 180–182°. – NMR.: 3.15 (*m*, 4H, $ArCH_2CH_2CON$); 4.0 (*s*, 3H, OCH_3); 4.05 (*s*, 3H, OCH_3); 6.2 (*s*, 1H, olefinic); 6.8 (*s*, 1H, ArH); 7.1 (*s*, 1H, ArH). – $C_{19}H_{19}NO_3$: C, H, N.

*1-Benzylmethylidene-7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one* (**5c**). Compound **3c** (9.2 g, 0.027 mol); toluene (400 ml) and TsOH (0.6 g) were refluxed for 2 h (conditions as for **5a**), yield 3.1 g (35.5%), m.p. 180–184°. – NMR.: 2.8 (*m*, 4H, $ArCH_2CH_2CON$); 3.55 (*d*, $J = 8$, 2H, allylic); 3.85 (two close together *s*, 6H, 2 OCH_3); 5.4 (*t*, $J = 8$, 1H, olefinic); 6.6 (*s*, 1H, ArH); 6.9 (*s*, 1H, ArH); 7.2 (*s*, 5H, phenyl); 8.2 (br., 1H, NH). – $C_{20}H_{21}NO_3$: C, H, N.

*1-Benzyl-7-methoxy-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one* (**6a**). Compound **5a** (4.7 g, 0.017 mol) was disolved in glacial acetic acid (100 ml) and hydrogenated at 40° at normal pressure using Pd/C (5.4%, 2 g) as catalyst. After filtration the solution was evaporated to a small bulk, treated with 1 N NaOH and extracted with $CHCl_3$. The organic layer was dried and evaporated to dryness; the residue was recrystallized from $CHCl_3$/ether, yielding 3.5 g (74%) of **6a**, m.p. 156–157°. – $C_{18}H_{19}NO_2$: C, H, N.

*1-Benzyl-7,8-dimethoxy-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one* (**6b**). Compound **5b** (5.2 g, 16 mmol) was dissolved in glacial acetic acid (75 ml) and Pd/C (5.4%, 1 g) was added. The compound was then hydrogenated at normal pressure and at room-temp. for 4 h. After filtration the solution was evaporated to dryness and the residue was crystallized from methanol, yielding 3.6 g (69%) of **6b**, change in the crystalline form, 163–165°, m.p. 175–176°. – NMR.: 3.8 (*s*, 3H, OCH_3); 3.9 (*s*, 3H, OCH_3); 4.8 (br., collapse to a $d \times d$ after deuterium exchange, 1H, ArCHN); 6.65 (*s*, 1H, ArH); 6.75 (*s*, 1H, ArH). – $C_{19}H_{21}NO_3$: C, H, N.

*7,8-Dimethoxy-1-(2-phenethyl)-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one* (**6c**). Compound **5c** (5.2 g, 0.016 mol), glacial acetic acid (75 ml) and Pd/C (5.4%, 1.5 g) were shaken under hydrogen atmosphere at normal pressure and room temp. After standard working-up and recrystallization from $CDCl_3$/ether 3.5 g (67%) of **6c** were obtained, m.p. 135–137°. – NMR.: 4.5 (*m* which collapses to a *t* after deuterium exchange, 1H, ArCHN). – $C_{20}H_{23}NO_3$: C, H, N.

*1-Benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**7b**) *hydrogen maleate.* Compound **6b** (10 g, 0.032 mol) was suspended in THF (tetrahydrofuran) (100 ml) and $LiAlH_4$ (3.1 g, 0.081 mol) was added. The reaction mixture was then refluxed for 3 h. After cooling, water was cautiously added and the resulting suspension was filtered and the filtrate was evaporated to dryness. The oily product was converted to its hydrogen maleate by dissolving it in a small amount of ethanol and adding a solution of maleic acid (3.7 g, 0.031 mol) in ethanol. Ether was added to the ethanolic solution and the salt was allowed to crystallize in the cold giving 10.5 g (78%) of **7b** hydrogen maleate, m.p. 156–158°. – NMR.: 3.75 (*s*, 3H, OCH_3); 3.85 (*s*, 3H, OCH_3); 4.15 ($d \times d$, 1H, ArCHN); 6.7 (2*s*, very close together, 2H, ArH); 7.2 (*s*, 5H, phenyl). – $C_{23}H_{27}NO_6$: C, H, N.

*7,8-Dimethoxy-1-(2-phenethyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine* (**7c**) *naphthalene-1,5-disulfonate.* Compound **6c** (3.8 g, 0.012 mol), THF (50 ml) and $LiAlH_4$ (1 g, 0.026 mol) were refluxed

for 1 h and worked-up, condition as for the reduction of **6b**. The residue was converted to its naphthalene-1,5-disulfonate by dissolving the oil in a small amount of ethanol and by adding naphthalene-1,5-disulphonic acid [4] (1.8 g, 0.006 mol) in ethanol. Ether was then added and the compound allowed to crystallize. Yield 3.9 g (75%), m.p. 287–290°. – $C_{25}H_{29}NO_6S$: C, H, N.

1-Benzyl-7,8-dimethoxy-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (**8**) *hydrogen maleate.* Compound **7b** (19 g, 0.064 mol) was refluxed for 30 min with formic acid (30 ml) and 35% aqueous formaldehyde (20 ml). The reaction 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 was converted to its hydrogen maleate as for **7b**. Yield 22.5 g (83%), m.p. 144–146°. – NMR.: 2.25 (*s*, 3H, NCH_3); 4.5 (*t*, 1H, ArCHN). – $C_{24}H_{29}NO_6$: C, H, N.

4,5-Dimethoxy-1-oxo-3-phenyl-7-indanpropionamide (**10**). The amide **1b** (44 g, 0.21 mol), cinnamic acid (**9**) (62,4 g, 0.42 mol) and PPA (450 g), were thoroughly stirred at 70° for 6 h (condition as for **3a**). After work-up the compound was recrystallized from ethanol, yielding 38.5 g (54%), m.p. 194–200°. – NMR.: 3.3 (*s*, 3H, OCH_3); 3.9 (*s*, 3H, OCH_3); 4.6 (*d* × *d*, 1H, ArCHPh), 5.85 and 6.3 (2 br. signals, 2H, NH_2). – $C_{20}H_{21}NO_4$: C, H, N.

8,9-Dimethoxy-1-phenyl-1,3,5,6-tetrahydro-cyclopenta[j,k][2] benzazepin-4-one (**11**). The indanone **10** (15.8 g, 0.047 mol), toluene (500 ml) and TsOH (1 g) were refluxed for 6 h (conditions as for the cyclization of **3a**). After working-up, the compound was crystallized from methanol, yielding 4.5 g (30%), m.p. 203–205° (dec.) – NMR.: 3.3 (*s*, 3H, OCH_3); 3.8 (*s*, 3H, OCH_3); 4.7 (*d*, $J = 2$, 1H, ArCHPh); 5.7 (*d*, $J = 2$, 1H, olefinic). – $C_{20}H_{19}NO_3$: C, H, N.

8,9-Dimethoxy-1-phenyl-1,2,2a,3,5,6-hexahydro-cyclopenta[j,k][2]-benzazepin-4-one (**12**). Compound **11** (47 g, 0.14 mol) glacial acetic acid (1500 ml) and Pd/C (5.4%, 10 g) were hydrogenated for 5 h at normal pressure and room temp. (the same conditions as for **5a**). After work-up the residue crystallized from methanol yielding 23 g (49%) of **12**, m.p 215–220°. – NMR.: 3.1 (*s*, 3H, OCH_3); 3.8 (*s*, 3H, OCH_3); 4.3 (*d* × *d*, 1H, ArCHPh); 5.1 (indistinct *m*, 1H, ArCHN). – $C_{20}H_{21}NO_3$: C, H, N.

8,9-Dimethoxy-1-phenyl-1,2,3,4,5,6-hexahydro-cyclopenta[j,k][2]-benzazepine (**13a**) *hydrochloride.* Compound **12** (30 g, 0.093 mol), THF (1000 ml) and $LiAlH_4$ (8.5 g 0.22 mol) were refluxed for 2 h (the same conditions as for **6b**). After work-up the oily residue was dissolved in a small amount of ethanol and converted to the hydrochloride by treatment with an etheral solution of HCl. The product was recrystallized from methanol/ether yielding 20.7 g (64%) of **13a**. HCl, m.p. 267–270° (dec.), m.p. of free base 110–112°. – NMR.: 3.15 (*s*, 3H, OCH_3); 3.8 (s, 3H, OCH_3), 4.3 (2 superimposed *t*, 2H, ArCHN and ArCHPh). – $C_{20}H_{24}ClNO_2$: C, H, N.

8,9-Dimethoxy-3-methyl-1-phenyl-1,2,3,4,5,6-hexahydro-cyclopenta[j,k][2]-benzazepine (**13b**) *naphthalene-1,5-disulfonate.* The amine **12a** (10 g, 0.032 mol) was treated with formic acid (15 ml) and 35% formaldehyde solution (10 ml) (conditions as for **7b**). After work-up the oil was converted to its naphthalene-1,5-disulfonate as for **7c**. Yield 5.49 (36%) of **13b** salt, m.p. 261–263°. – $C_{26}H_{29}NO_5S$: C, H, N.

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