

37. The Synthesis of Some 7,8-Dimethoxy-5-phenyl-2H-3-benzazepin-2-one Derivatives¹⁾

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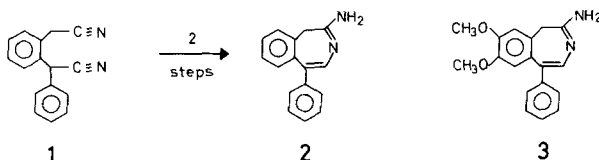
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Summary

The benzazepin-2-ones **7** and **9** were prepared from homoveratroyl chloride (**4**) and phenacylamine. Compounds **7** and **9** were used for the preparation of the benzazepin-2-amines **3**, **11**, **13** and **14**. A synthesis of the benzazepine-1,2-dione **17** and the benzazepine-2,4-dione **20** is also described.

Introduction. – A study, made by another group in these laboratories, led to the discovery of some pharmacologically active 5-phenyl-1H-3-benzazepin-2-amines [2]. Starting from dinitriles of type **1**, 1H-3-benzazepin-2-amines of type **2** were obtained in two steps (s. *Scheme 1*). We have extended these investigations in order to obtain derivatives such as **3**, substituted at positions 7 and 8 by methoxy groups.

Scheme 1



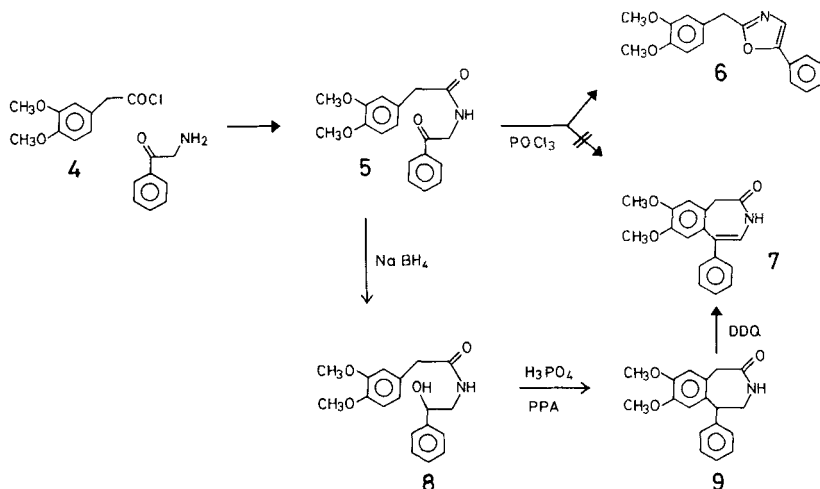
As these derivatives were not readily accessible by the original route, another synthetic approach was developed.

Two recent papers describing the synthesis of some substituted 5-phenyl-2H-3-benzazepines [3] prepared by somewhat similar routes have prompted us to publish our results.

Results. – In a first attempt to synthesize **3**, homoveratroyl chloride (**4**) was reacted with phenacylamine to give the keto-amide **5** (s. *Scheme 2*). On heating of **5**

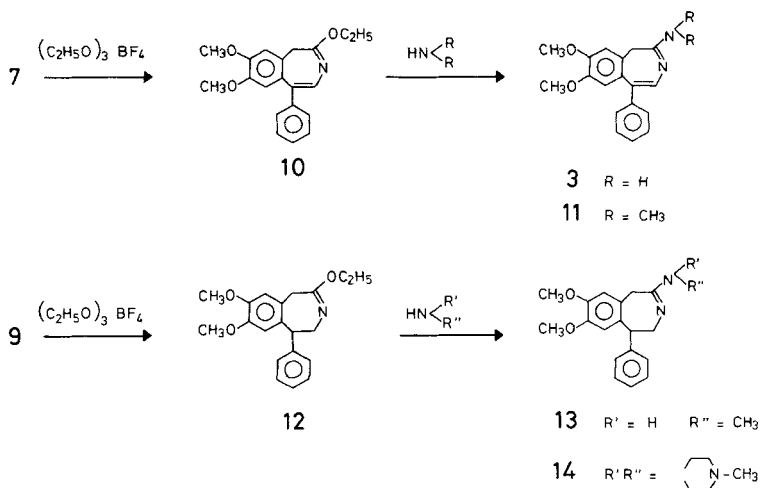
¹⁾ 27th Communication on sevenmembered heterocycles; 26th communication [1].

Scheme 2



in POCl_3 or polyphosphoric acid (PPA) the oxazole **6** was obtained in quantitative yield instead of the desired intermediate **7**. Consequently, compound **5** was reduced with NaBH_4 to the alcohol **8** which was successfully cyclized in PPA to the tetrahydro-2H-3-benzazepin-2-one (**9**²). Compound **9** was then oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give **7**. In order to obtain the amidine **3**, compound **7** was reacted with triethyloxonium fluoroborate to give the imino-ether **10**, which, with ammonia, yielded the desired product **3** (s. Scheme 3). Similarly, the 1H-3-benzazepin-2-amine **11** was prepared by reacting **10** with dimethylamine.

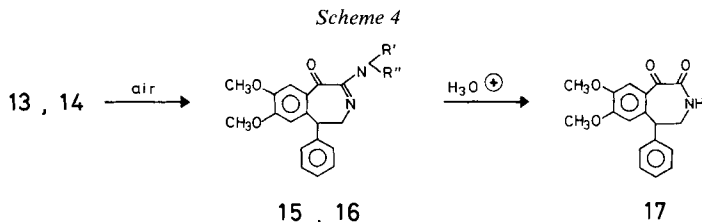
Scheme 3



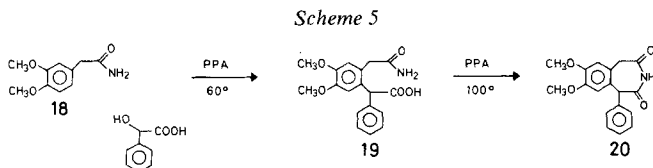
²) For proof of structure, both **9** and **20** were reduced with B_2H_6 to the known 7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine [4].

In analogy to these reactions, the imino-ether **12** was prepared from **9**, and on further treatment with methylamine or *N*-methylpiperazine, **12** gave compounds **13** and **14**, respectively.

Unexpectedly, the bases **13** and **14**, in ethyl acetate solution, were slowly oxidized by air to the 4,5-dihydro-1*H*-3-benzazepin-1-ones **15** and **16**³⁾, respectively (s. Scheme 4). This spontaneous oxidation was accelerated by bubbling air through the solutions. The keto-amidine **16** was readily hydrolyzed in 1*N* HCl to give the keto-lactam **17**. No such oxidation took place with the benzazepines **3** and **11** when treated under similar conditions.



A third approach for the synthesis of **3** was considered (s. Scheme 5): The amide **18** and mandelic acid, when heated in PPA at 60° for 2 h, gave the condensation product **19**. However, when the reaction mixture was heated for 30 min at 60° and for a further 45 min at 100°, the 1*H*-3-benzazepine-2,4(3*H*,5*H*)dione **20**²⁾ was isolated, but only in yields up to 15%. This approach was therefore not pursued further.

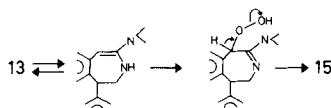


Experimental Part

General remarks. - ¹H-NMR. spectra were taken at 60 MHz in CDCl₃ unless otherwise stated, with TMS as an internal standard and using a Varian T-60 spectrometer. In the case of salts, a sample of the free base was prepared and used in CDCl₃. Abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, br. = broad signal; chemical shift in δ-values (ppm), coupling constants *J* in Hz.

Synthesis of 3,4-dimethoxy-N-phenacyl-benzeneacetamide (5). Homoveratric acid (57 g, 0.291 mol) was suspended in ether (250 ml) and SOCl₂ (38 g, 0.319 mol) was added dropwise. The mixture was then heated under reflux for 30 min. This solution, containing veratroyl chloride, was very slowly added to a cooled (0–5°) suspension of a finely powdered mixture of sodium acetate (95 g, 1.16 mol) and phenacylamine hydrochloride (50 g, 0.291 mol) in THF (450 ml). The mixture was then kept overnight at RT. Toluene (250 ml) was added, and the mixture was washed with H₂O followed by 1*N* NaOH. The organic phase was evaporated, and the residue crystallized from ether in the cold, giving 62.5 g (69%) of crude **5**, m.p. 105–108°. - ¹H-NMR.: 8.0–7.2 (*m*, C₆H₅); 6.8 (*s*, C₆H₃); 6.7 (br., HN); 4.7 (*d*, collapsed to *s* after D₂O exchange, CH₂N); 3.85 (2*s*, 2 CH₃O); 3.6 (*s*, ArCH₂).

³⁾ The oxidation may proceed according to the following scheme:



Synthesis of 2-(3,4-dimethoxybenzyl)-5-phenyloxazole (6). Compound **5** (3.13 g, 0.01 mol) was heated under reflux for 1 h in POCl₃ (15.3 g, 0.1 mol). Excess of POCl₃ was allowed to evaporate under reduced pressure, and the residue was treated with 2N KHCO₃, extracted with CH₂Cl₂, and the extract was dried and evaporated. The residue was recrystallized from ethanol in the cold, giving 2.55 g (86%) of **6**, m.p. 102–104°. – ¹H-NMR.: 7.75–7.15 (*m*, C₆H₅, and H–C(4)); 6.85 (*s*, C₆H₃); 4.1 (*s*, ArCH₂); 3.85 (2*s*, 2 CH₃O).

C₁₈H₁₇NO₃ (295.3) Calc. C 73.2 H 5.8 N 4.7% Found C 73.2 H 6.0 N 4.7%

Synthesis of 3,4-dimethoxy-N-(2-hydroxy-2-phenylethyl)benzeneacetamide (8). Compound **5** (47 g, 0.15 mol) was dissolved in methanol (750 ml), cooled to 0–5°, and NaBH₄ (2 g, 0.053 mol) added in small portions. After standard work-up 44.5 g (94%) of crude **8** were obtained, m.p. 105–107° (ether). – ¹H-NMR.: 7.15 (*s*, C₆H₅); 6.6 (*s*, C₆H₃); 6.15 (*br. t*, HN); 4.65 (*m*, collapsed to *d* × *d* after D₂O exchange, C₆H₅CH–O); 4.1 (*d*, HO); 3.8 (2*s*, 2 CH₃O); 3.4 (*m*, ArCH₂ and CH₂N).

Synthesis of 7,8-dimethoxy-5-phenyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (9). Compound **8** (171 g, 0.542 mol) was added to a mixture of PPA (2200 g) and 85% H₃PO₄ solution (1400 g). After heating for 1.5 h at 100°, the mixture was poured onto ice/H₂O and extracted with CH₂Cl₂. The organic layer was dried and evaporated, and the residue was recrystallized from ether, giving 66 g (41%) of **9**, m.p. 197–199°. – ¹H-NMR.: 7.1 (*m*, C₆H₅ and HN); 6.6 and 6.3 (2*s*, H–C(6), and H–C(9)); 4.25 (*d* × *d*, H–C(5)); 3.9–3.5 (*m*, 2 H–C(1), 2 H–C(4)); 3.8 and 3.55 (2*s*, 2 CH₃O).

C₁₈H₁₉NO₃ (297.4) Calc. C 72.7 H 6.4 N 4.7% Found C 72.6 H 6.7 N 4.7%

Synthesis of 7,8-dimethoxy-5-phenyl-1,3-dihydro-2H-3-benzazepin-2-one (7). Compound **9** (49.5 g, 0.166 mol) was suspended in benzene (1000 ml), 98% DDQ (44.7 g, 0.193 mol) was added, and the suspension was heated under reflux for 17 h under N₂. After cooling the dark solution was diluted with CHCl₃ (2000 ml), washed with 1N NaOH followed by H₂O (1000 ml), dried and evaporated to dryness. The residue was dissolved in CH₂Cl₂ (800 ml) and ether (300 ml), boiled with charcoal and filtered. More ether was added (250 ml) and the product was allowed to crystallize in the cold. The product was recrystallized from methanol, giving 25.3 g (52%) of **7**, m.p. 238–240°. – ¹H-NMR.: 8.6 (*br. d*, HN); 7.3 (*s*, C₆H₅); 6.8 and 6.45 (2*s*, H–C(6), and H–C(9)); 6.45 (*d*, collapsed to *s* after D₂O exchange, H–C(4)); 3.9 and 3.6 (2*s*, 2 CH₃O); 3.5 (*s*, 2 H–C(1)).

C₁₈H₁₇NO₃ (295.3) Calc. C 73.2 H 5.8 N 4.7% Found C 72.8 H 6.1 N 4.8%

Synthesis of 2-ethoxy-7,8-dimethoxy-5-phenyl-1H-3-benzazepine (10). Compound **7** (11.8 g, 0.04 mol) was added at RT. with stirring to a solution of triethyloxonium fluoroborate (9.9 g, 0.052 mol) in CH₂Cl₂ (100 ml) and left overnight. A solution of K₂CO₃ (4.2 g, 0.03 mol) in H₂O (4.2 ml) was added dropwise with efficient stirring. The mixture was then filtered through Kieselgur and evaporated to dryness. The residue was treated with abs. ethanol and allowed to crystallize, giving 7.5 g (58%) of crude **10**, m.p. 138–148°.

Synthesis of 7,8-dimethoxy-5-phenyl-1H-3-benzazepin-2-amine (3). A mixture of 3.7N ethanolic NH₃-solution (52 ml) and **10** (5.2 g, 0.016 mol) was heated in a pressure bomb for 3 h at 100°, and then evaporated to dryness. The residue was dissolved in 2N CH₃COOH, and the solution was filtered over Kieselgur to remove insoluble material. The filtrate was made alkaline with 30% NaOH-solution, extracted with CH₂Cl₂, and the extract was dried and evaporated. The residue was recrystallized from ethyl acetate, giving 3.4 g (72%) of **3**, m.p. 173–176°. – ¹H-NMR.: 7.25 (*s*, C₆H₅); 7.05, 6.58, and 6.55 (3*s*, H–C(4), H–C(6), and H–C(9)); 5.0 (*br.*, H₂N); 3.8 and 3.6 (2*s*, 2 CH₃O); 3.2 (*s*, H₂C(1)).

C₁₈H₁₈N₂O₂ (294.4) Calc. C 73.4 H 6.2 N 9.5% Found C 73.0 H 6.1 N 9.6%

Synthesis of 7,8-dimethoxy-N,N-dimethyl-5-phenyl-1H-3-benzazepin-2-amine (11). Compound **10** (6.5 g, 0.02 mol) was suspended in a 33% ethanolic solution of dimethylamine (50 ml, 0.36 mol), and the mixture was heated under reflux for 1.5 h, and then evaporated to dryness. The residue was dissolved in ethanol (50 ml), 1,5-naphthalenedisulfonic acid (NDS; 2.5 g, 0.009 mol) in ethanol (15 ml) was added, and the product was allowed to crystallize, giving 7.4 g (79%) of **11** NDS salt, m.p. > 300°. The base was liberated with 2N NaOH and extracted with CH₂Cl₂, m.p. 148–151°. – ¹H-NMR.: 7.3 (narrow *m*, C₆H₅); 4.4–2.6 (very *br.*, 2 H–C(1)); 3.85, and 3.6 (2*s*, 2 CH₃O); 3.15 (*s*, (CH₃)₂N).

C₂₀H₂₂N₂O₂ (322.4) Calc. C 74.5 H 6.9 N 8.7% Found C 74.3 H 6.9 N 8.8%

Synthesis of 2-ethoxy-7,8-dimethoxy-5-phenyl-4,5-dihydro-1H-3-benzazepine (12). Compound **9** (29.7 g, 0.1 mol), dissolved in CH_2Cl_2 (200 ml), was added at RT. to a stirred solution of triethyloxonium fluoroborate (24.6 g, 0.13 mol) in CH_2Cl_2 (50 ml). After stirring for 2 h, a solution of K_2CO_3 (10.5 g, 0.08 mol) in H_2O (10.5 ml) was added dropwise. The mixture was then filtered through Kieselgur, and partly evaporated to give 278 g of solution containing **12**, which was used without further purification for the preparation of the amidines **13** and **14**.

Synthesis of 7,8-dimethoxy-N-methyl-5-phenyl-4,5-dihydro-1H-3-benzazepin-2-amine (13). An 33% ethanolic solution of methylamine (100 ml, 1.0 mol) was added dropwise with stirring to the crude solution of **12** (139 g of sol., ~0.05 mol) cooled to -10° . The mixture was left for 2 h at RT., and was then heated under reflux for 1 h, and evaporated to dryness. Product **13** was isolated as NDS salt (11.2 g, 49% from **9**), m.p. 204–206°. The base **13** was liberated with 2N NaOH and crystallized from ether, m.p. 146–149°. A sample of **13** oxalate was prepared for analysis, m.p. 201–204°. – $^1\text{H-NMR.}$: 7.6 (m, C_6H_5); 6.55 and 6.3 (2s, H-C(6) and H-C(9)); 4.4–3.2 (m, 2 H-C(1) , 2 H-C(4) and H-C(5)); 3.85 and 3.6 (2s, 2 CH_3O); 2.7 (s, CH_3N).

$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_6$ (400.4) Calc. C 63.0 H 6.0 N 7.0% Found C 63.3 H 6.2 N 7.0%

Synthesis of 7,8-dimethoxy-2-(4-methyl-1-piperazinyl)-5-phenyl-4,5-dihydro-1H-3-benzazepine (14). A mixture of *N*-methylpiperazine (5 g, 0.05 mol) and toluene (50 ml) was added to the crude solution of **12** (92 g of sol., ~0.033 mol). After heating under reflux for 2 h, the mixture was worked up and the product isolated as hydrochloride. The salt was treated with 1N NaOH, giving 3.1 g (25%) of **14**, m.p. 139–142°.

$\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2$ (379.5) Calc. C 72.8 H 7.7 N 11.1% Found C 72.9 H 7.7 N 11.1%

Synthesis of 7,8-dimethoxy-2-methylamino-5-phenyl-4,5-dihydro-1H-3-benzazepin-1-one hydrochloride (15·HCl). Crude base **13** (3.05 g, 9.8 mmol) was dissolved in ethyl acetate (50 ml), and the solution was heated to 60° whilst a slow stream of air was bubbled through. After standing overnight at RT., the solution was evaporated to dryness, and the residue was treated with ethanol/ether/HCl, and **15·HCl** was allowed to crystallize (2.55 g, 72%), m.p. 215–216°. – $^1\text{H-NMR.}$: 7.5 (s, H-C(9)); 7.1 (m, C_6H_5); 6.5 (s, H-C(6)); 5.2 (br. s, HN); 4.4 (m, H-C(5)); 4.1–3.8 (m, 2 H-C(4)); 3.9 and 3.7 (2s, 2 CH_3O); 2.7 (s, CH_3N).

$\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}_3$ (360.8) Calc. C 63.2 H 5.9 Cl 9.8 N 7.8%
Found „ 63.4 „ 5.9 „ 10.0 „ 7.8%

Synthesis of bis(7,8-dimethoxy-2-(4-methyl-1-piperazinyl)-5-phenyl-4,5-dihydro-1H-3-benzazepin-1-one)maleate monohydrate (16·(C₄H₄O₄)₂·H₂O). A slow stream of air was bubbled through a solution of **14** (14.8 g, 0.039 mol) in ethyl acetate (500 ml) for 19 h. The solution was evaporated to dryness, the residue was dissolved in CH_2Cl_2 (50 ml) and diluted with ether (200 ml) in order to precipitate some oily impurities. The solution was decanted and filtered, then evaporated to dryness to give 10.8 g of crude **16**. Pure **16** was isolated as bis(hydrogen maleate) monohydrate (12.5 g, 51%), m.p. 179–183°. – $^1\text{H-NMR.}$: 7.4–6.9 (m, 6 arom. H); 6.45 (s, H-C(9)); 4.4 (t, $J=6$, H-C(5)); 3.95 and 3.7 (2s, 2 CH_3O); 3.8 (d, 2 H-C(4)); 3.3 and 2.35 (2t, 2 ($\text{CH}_2\text{-CH}_2$)); 2.3 (s, CH_3N).

$\text{C}_{31}\text{H}_{35}\text{N}_3\text{O}_{11}\cdot\text{H}_2\text{O}$ (643.6) Calc. C 57.8 H 5.5 N 6.5% Found C 57.8 H 5.7 N 6.7%

Synthesis of 7,8-dimethoxy-5-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-1,2-dione (17). Compound **16·(C₄H₄O₄)₂·H₂O** (313 mg, 0.5 mmol) was dissolved in 1N HCl (3 ml) and heated under reflux for 1 h. The mixture was cooled at RT., and the crystals which had formed were filtered off, washed with H_2O , and finally dried under vacuum, giving 110 mg of **17** (71%), m.p. 199–201°. – $^1\text{H-NMR.}$: 7.4–6.9 (m, 6 arom., HN); 6.45 (s, H-C(9)); 4.5 (d×d, $J=3$ and 6, H-C(5)); 3.9 and 3.75 (2s, 2 CH_3O); 3.9–3.5 (m, 2 H-C(4)).

$\text{C}_{18}\text{H}_{17}\text{NO}_4$ (311.3) Calc. C 69.4 H 5.5 N 4.5% Found C 69.4 H 5.5 N 4.2%

Synthesis of 4,5-dimethoxy-2-(carbamoylmethyl)-diphenyl-acetic acid (19). (3,4-Dimethoxyphenyl)-acetamide (**18**; 19.5 g, 0.1 mol) and mandelic acid (25.2 g, 0.16 mol) were heated in PPA (400 g) for 2 h at 60° . The mixture was then poured into ice/ H_2O , extracted with CH_2Cl_2 , and the extract was dried and evaporated. The residue was recrystallized from CH_2Cl_2 /ether, giving 4.3 g (12%) of **19**, m.p. 105–115°.

Synthesis of 7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-2,4-dione (20). (3,4-Dimethoxyphenyl)acetamide (**18**; 5.86 g, 0.03 mol) was thoroughly mixed with mandelic acid (5.48 g, 0.036 mol) and heated to 120° to form a clear melt. PPA (113 g) was added, and the mixture was stirred for 30 min at 60°, and for 45 min at 100–110°, and was then poured into ice/H₂O, extracted with CH₂Cl₂, and the extract was dried and evaporated. The residue was recrystallized from ethanol to give 1.1 g (12%) of **20**, m.p. 206–208°. – ¹H-NMR.: 8.2 (br. s, HN); 7.2 (m, C₆H₅); 6.8 and 6.7 (2 s, H–C(6) and H–C(9)); 5.25 (s, H–C(1)); 3.9 (s, 2 CH₃O); 3.55 (s, 2 H–C(5)).

C₁₈H₁₇NO₄ Calc. C 69.4 H 5.5 N 4.5% Found C 69.6 H 5.6 N 4.5%

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