Condensed Heterocyclic Lactams. I. Study on the Cyclization Methods Resulting in 4-Aryl-3,4-dihydroquinolin-2(1*H*)-ones

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Cyclization reactions with polyphosphoric acid of 3-aryl-3-hydroxypropionanilides carrying a *p*-nitro- **7a** or *p*-amino substituent **10** on the C-3 phenyl group were investigated. In the case of *p*-nitro substitution the preferred reaction is, instead of cyclization, the elimination of water to give the corresponding cinnamic acid derivative. On the other hand, reaction of the *p*-amino-substituted analogue gave the new compound 4-(4-aminophenyl)-3,4-dihydroquinolin-2(1*H*)-one (**2b**) in a good yield. The intermediate product of the cyclization was isolated and its structure established.

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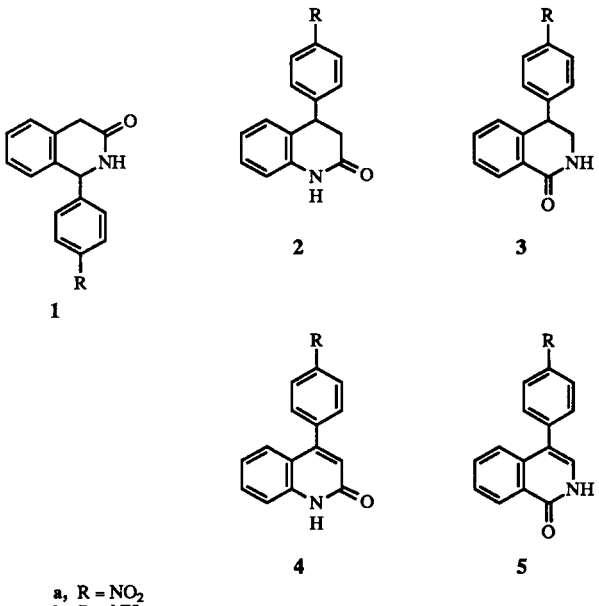
In several earlier publications [1] we have reported on the syntheses and biological properties of heterocyclic fused-ring lactams, such as numerous derivatives of 1-aryl-1,4-dihydroisoquinolin-3(2*H*)-ones of type **1** (Scheme 1). Of the compounds **1c**, 1-[4'-(ethylaminoacetyl)aminophenyl]-1,4-dihydroisoquinolin-3(2*H*)-one - owing to its highly significant anticonvulsive action [2] - will probably get into the stage of clinical tests in cooperation with the National Institute of Health [3], as a potential antiepileptic agent. In view of the fact that, besides the above mentioned products, the group of lactam-type quinoline and isoquinoline compounds also includes the 3,4-dihydro derivatives **2** and **3** of quinolin-2(1*H*)-ones and isoquinolin-1(2*H*)-ones, we considered worthwhile to synthesize similar derivatives of the latter compounds. A number of 4-aryl derivatives of type **2** and **3** (and of the unsaturated analogues, **4** and **5**) have been described in the literature; however, as it appears of the 4'-nitro- and 4'-amino compounds shown in Scheme 1 - which are the most important intermediates for our work - only **4a** 4-(4-nitrophenyl)quinolin-2(1*H*)-one is the sole cyclic lactam prepared so far [4]. (The synthesis and biological actions of the aminoquinolinones **4b** and those substituted with a basic side chain **4c**, prepared by us from **4a**, will be reported elsewhere [5]).

Scheme 1



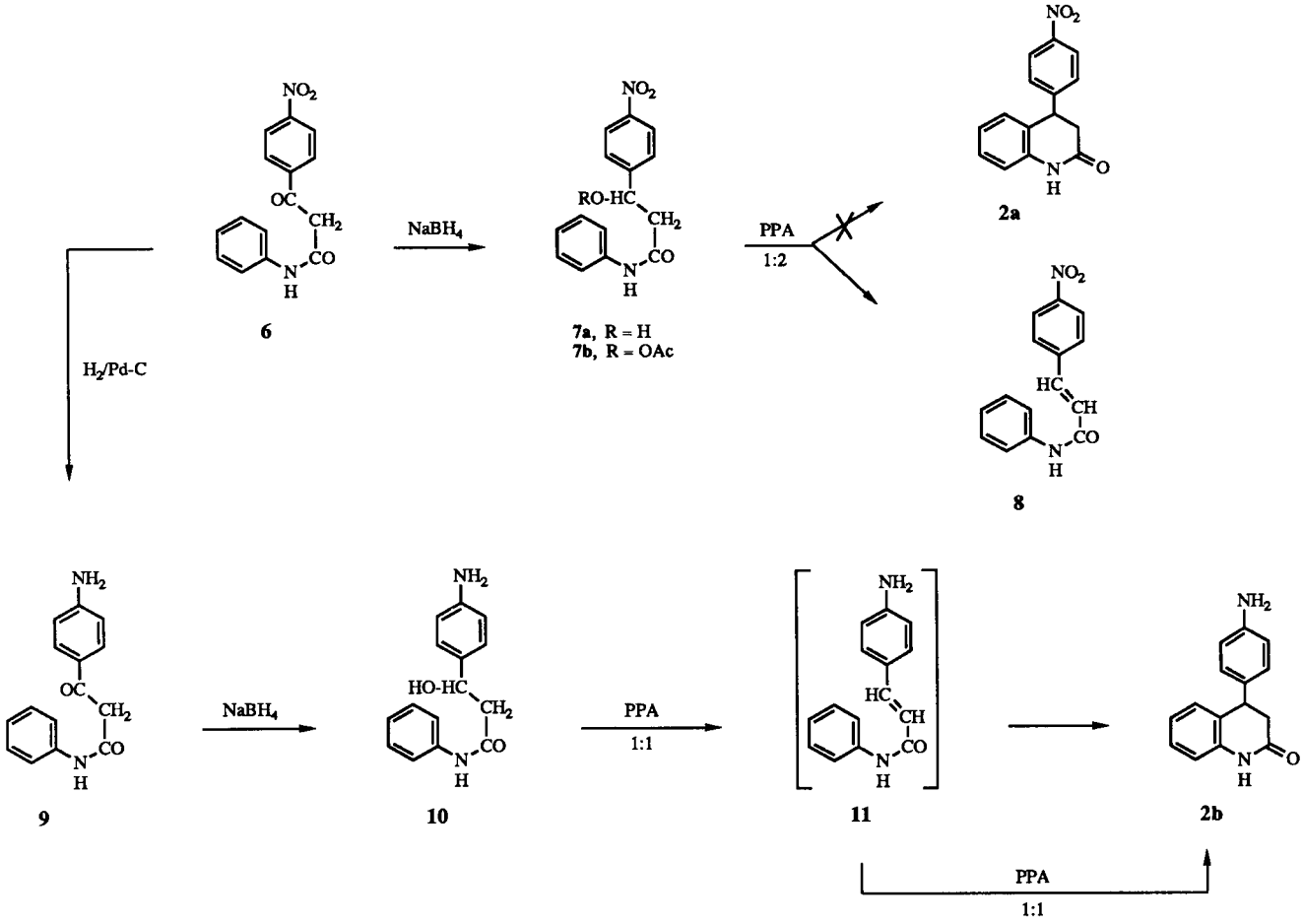
a, R = NO_2
b, R = NH_2
c, R = alkylaminoacylamino side chain

In addition to the pharmacological interest attached, the elaboration of synthetic methods to prepare heterocycles of type **2**, **3** and **5** has organic chemical importance; of our researches in this field, the results obtained in the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones of type **2** by cyclization are reported in this paper.

Since the catalytic reduction of both **4a** and **4b**, attempted under different reaction conditions, failed in giving the 3,4-dihydro derivative **2b** [5], a direct cyclization method was sought for the synthesis of **2a** and **2b**.

First, possible pathways of preparing the nitro compound **2a** were examined (Scheme 2). The intermediary carbonyl compound 4-nitrobenzoylacetanilide **6**, required

Scheme 2



for the synthesis of the unsaturated lactam **4a**, was reduced with sodium borohydride to give the alcohol **7a**. The reactions of **7a** and of its acetyl derivative **7b** in various acidic media did not give **2a**. Finally, a homogeneous and identifiable product was obtained on treatment of **7a** in polyphosphoric acid (PPA) at a ratio of 1:2. However, instead of expected cyclization, the elimination of water took place, and the product was 4-nitrocinnamanilide (**8**). Though the preparation of 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones from the corresponding cinnamanilides by treatment with polyphosphoric acid is a known method [6], in the case of nitro substitution only the *meta* nitro derivatives can thus be prepared [7]; *p*-nitro substitution hinders the cyclization to quinolinone [8]. In our case, probably owing to the electron-withdrawing character of the *p*-nitro group, water elimination is the preferred route of the reaction and the resulting isolated cinnamanilide **8** is incapable of cyclization.

Since our plan would have been to prepare the 4′-aminophenyl derivative **2b** from the nitro compound **2a**, now it became necessary to elaborate a synthesis of **2b** by direct cyclization (Scheme 2). The carbonyl compound **6** was first reduced by catalytic hydrogenation to give the amino derivative **9**, and the keto group of the latter was successfully reduced with sodium borohydride to yield the corresponding alcohol **10**. This compound was then suitable for cyclization; in polyphosphoric acid (1:1) it furnished the desired 4-(4-aminophenyl)-3,4-dihydroquinolin-2(1*H*)-one (**2b**) in a good yield.

Following the course of the reaction by thin-layer chromatography revealed that before and during the formation of the end-product a new spot was present, which gradually disappeared with the increase of the amount of the final product **2b**. The reaction was therefore interrupted after a suitable period, and the products were separated by column chromatography. In this way the intermediate of the cyclization reaction could be isolated. Spectroscopic examination showed that it was *N*-phenyl-4-aminocinnamamide (**11**). Treatment in polyphosphoric acid of the isolated pure compound **11** under the conditions of the cyclization gave, naturally, **2b**.

According to those described above, the amino group, being present in the acidic reaction mixture in the protonated form, does not hinder cyclization occurring

through the unsaturated intermediate. Ring closure is preceded also here by the elimination of water, and finally the cyclized product results from the reaction of the carbon-carbon double bond, *i.e.* by the electrophilic substitution of the aromatic ring.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli melting point determining apparatus and are uncorrected. Infrared spectra were run in potassium bromide pellets on a Bruker IFS-113v FT-spectrometer and on a Perkin Elmer 457 spectrometer. The ^{1}H nmr spectra were recorded in dimethyl sulphoxide-d_6 solution on a Bruker AC-250 and on a Bruker WM-250 FT-spectrometer. The ^{13}C nmr spectra were run in dimethyl sulphoxide-d_6 solution on a Bruker WP-80-SY (**8**) or WM-250 FT-spectrometer (**2b**, **7a**,**b**, **10** and **11**). Mass spectra were obtained with an AEI-902 spectrometer (70 eV, direct insertion).

N-Phenyl-3-hydroxy-3-(4-nitrophenyl)propionamide (**7a**).

The anilide **6** (2 g, 7 mmoles) [9] was allowed to react with sodium borohydride (0.3 g, 7 mmoles) in methanol (150 ml), at room temperature, with stirring. After stirring for 1.5 hours, the reaction mixture was evaporated to dryness. The residue was boiled with water (75 ml). After cooling, the solid product was filtered off, washed with water and dried to obtain 1.35 g (67%) of **7a**, mp 172-173° (from ethanol); ir (potassium bromide): ν C=O 1660, NO_2 1515, 1350 cm^{-1}; ^{1}H nmr (dimethyl sulphoxide-d_6): δ 9.95 (br, 1H, NH), 5.84 (d, 1H, OH, J = 4.7 Hz), 2.70 (d, 2H, CH_2, J = 8 Hz), 5.25 (qa, 1H, CH), ArH (monosubstituted phenyl), 7.04 (t, 1H, H-4'), 7.30 (t, 2H, H-3',5'), 7.60 (d, 2H, H-2',6'), ArH (*p*-disubstituted phenyl), 7.68 (d, 2H, H-2,6), 8.22 (d, 2H, H-3,5); ^{13}C nmr (dimethyl sulphoxide-d_6): δ C=O 170.2, CH_2 48.2, CH 70.8, monosubstituted phenyl; C-1' 140.0, C-2',6' 121.0, C-3',5' 128.7, C-4' 124.9, *p*-disubstituted phenyl, C-1 148.3, C-2,6 130.3, C-3,5 125.0, C-4 154.8.

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 62.55; H, 4.70; N, 9.40.

N-Phenyl-3-acetoxy-3-(4-nitrophenyl)propionamide (**7b**).

The alcohol **7a** (2 g, 7 mmoles) was allowed to react with acetic anhydride (0.7 g, 7 mmoles) in pyridine (30 ml), with stirring at room temperature for 6 hours. The reaction mixture was poured into water (300 ml). The solid product was filtered off, washed with water and dried to give 1.55 g (67%) of **7b**, mp 142-143° (from methanol); ir (potassium bromide): ν NH 3320, C=O 1740, 1650, NO_2 1515, 1345 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.45 (br, 1H, NH), 2.81 (dd, 1H) and 2.99 (dd, 1H) (CH_2) (AB-part of an ABX spin system, J(A,B) = 15.0 Hz, J(A,X) = 5.5 Hz, J(B,X) = 8.0 Hz), 6.31 (dd, 1H, CH), 2.11 (s, 3H, CH_3), ArH (monosubstituted phenyl), 7.44 (d, 2H, H-2',6'), 7.32 (t, 2H, H-3',5'), 7.15 (t, 1H, H-4'), ArH (*p*-disubstituted phenyl), 7.55 (d, 2H, H-2,6, J = 8.8 Hz), 8.20 (d, 2H, H-3,5); ^{13}C nmr (dimethyl sulphoxide-d_6): δ C=O (amide) 168.6, CH_2 44.5, CH 73.2, C=O (ester) 171.1, CH_3 22.5, monosubstituted phenyl, C-1' 140.5, C-2',6' 121.0, C-3',5' 130.4, C-4' 125.1, *p*-disubstituted phenyl, C-1 149.2, C-2,6 129.2, C-3,5 125.4, C-4 148.9; ms: ($C_{17}H_{16}N_2O_5$, 328.33) m/z (I%) 329 (5.2), 328 (26.5, M), 285 (3.7, M-43), 268 (11.7, M-60), 176 (25.8, M-152, 268-92), 146 (6.1, M-182), 130 (5.5, M-198), 119 (18.5, M-209), 102 (5.5), 93 (100.0), 43 (33.6).

Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.28; H, 5.02; N, 8.30.

N-Phenyl-4-nitrocinnamamide (**8**).

The alcohol **7a** (1.0 g, 3.5 mmoles) was subjected to attempted cyclization in polyphosphoric acid (15 g) of 1:2 ratio [10] by stirring the mixture at 80° for 3 hours. The reaction mixture was poured into water (200 ml) and made alkaline with concentrated ammonium hydroxide. The solid was filtered off, washed with water and dried. After purification on a column of neutral aluminium oxide(Brockmann II), the solid was rubbed with chloroform to give 0.2 g (21%) of a product, which, however, was not the expected **2a**, but the cinnamic acid derivative **8**, mp 202-204° (from ethanol) (lit [8] mp 211° and lit [11] mp 208°); ir (potassium bromide): ν NH 3300, C=O 1655, C=C 1620, NO_2 1510, 1335 cm^{-1}; ^{1}H nmr (dimethyl sulphoxide-d_6): δ 10.35 (br, 1H, NH), 7.70 (dd, 1H, =CH, J = 7.2 Hz), 7.03 (d, 1H, CH=), ArH (monosubstituted phenyl), 7.72 (d, 2H, H-2',6'), 7.36 (t, 2H, H-3',5'), 7.10 (t, 1H, H-4'), ArH (*p*-disubstituted phenyl), 7.90 (d, 2H, H-2,6), 8.29 (d, 2H, H-3,5); ^{13}C nmr (dimethyl sulphoxide-d_6): δ C=O 164.6, =CH 128.4, CH= 139.3, monosubstituted phenyl, C-1' 140.7, C-2',6' 121.2, C-3',5' 130.5 [12], C-4' 125.3, *p*-disubstituted phenyl, C-1 143.1, C-2,6 130.4 [12], C-3,5 125.8, C-4 149.4.

α-(4-Aminobenzoyl)acetanilide (**9**).

The anilide **6** (4.0 g, 14 mmoles) was dissolved in dimethylformamide (140 ml) and hydrogenated in the presence of 10% palladium-on-charcoal (Engelhardt) catalyst at room temperature and atmospheric pressure until the absorption of hydrogen ceased. The catalyst was removed by filtration. The solvent was evaporated, and the residual oil was rubbed with water. The resulting solid was filtered off, thoroughly washed with water and dried, to give 2.1 g (59%) of **9**, mp 160-162° (from ethanol) (lit [9] mp 165-166°); ir (potassium bromide): ν NH_2 3400, 3320, C=O 1660, 1645 (shoulder) cm^{-1}.

N-Phenyl-3-(4-aminophenyl)-3-hydroxypropionamide (**10**).

The ketone **9** (2.1 g, 8.3 mmoles) was reduced with sodium borohydride, as described for the preparation of the alcohol **7a**. The product was 1.61 g (76%) of **10**, mp 162-164° (from ethanol); ir (potassium bromide): ν C=O 1657, NH_2 3370, 3270 cm^{-1}; ^{1}H nmr (dimethyl sulphoxide-d_6): δ 2.48 and 2.65 (2 x dd, 2 x 1H, CH_2, ^{2}J = 14.0, ^{3}J = 8.8 and 4.8 Hz), ~ 4.9 [13] (m, 1H, CH), 5.14 (d, 1H, OH, J = 4.2 Hz), ~ 4.93 [13] (broad s, 2H, NH_2), 9.83 (s, 1H, NH), *p*-disubstituted ring, 6.51 (~ d, 2H, H-3',5', J = 8.3 Hz), 7.03 [14] (d, 2H, H-2',6'), phenyl group, 7.00 [14] (t, 1H, H-4), 7.28 (~ t, 2H, H-3,5), 7.59 (~ d, 2H, H-2,6); ^{13}C nmr (dimethyl sulphoxide-d_6): δ C=O 171.3, CH_2 48.9, CH 71.6, *p*-disubstituted ring, C-1' 134.4, C-2',6' 128.4, C-3',5' 121.0, C-4' 149.4, phenyl group, C-1 141.2, C-2,6 115.4, C-3,5 130.6, C-4 124.9.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.95; H, 6.19; N, 10.75.

4-(4-Aminophenyl)-3,4-dihydroquinolin-2(1*H*)-one (**2b**).

The alcohol **10** (0.5 g, 2 mmoles) was stirred in 1:1 polyphosphoric acid (20 g) at 80° for 10 hours. The mixture was then poured into water (200 ml) and made alkaline with concentrated ammonium hydroxide. The resulting solid was filtered off, washed with water and dried to give 0.4 g (87%) of the cyclized product **2b**, mp 200-202° (from ethanol); ir (potassium bromide): ν C=O 1669, NH_2 3450, 3345 cm^{-1}; ^{1}H nmr (dimethyl sulphoxide-

d_6): δ 2.68 (m, 2H, CH_2-3), 4.10 (t, 1H, CH-4), 4.95 (broad s, 2H, NH_2), 10.15 (broad s, 1H, NH), 6.50 (~ d, 2H, H-3',5', *p*-disubstituted ring), 6.82 (~ d, 2H, H-2',6', *p*-disubstituted ring), ~ 6.9 (m, 3H, ArH-5,7,8), 7.14 (~ t, 1H, ArH-6; ^{13}C nmr (dimethyl sulphoxide-d_6): δ C=O 171.5, CH_2 40.1, CH 42.2, C-4a 129 [13], C-5,7 129.3 [13], C-6 124.1, C-8 117.2, C-8a 149.2, *p*-disubstituted ring, C-1' 131.2, C-2',6' 129.8, C-3',5' 116.0, C-4' 139.8; ms: ($C_{15}H_{14}N_2O$, 238.29) m/z (I%) 239 (24.1), 238 (100.0, M), 237 (64.5, M-H), 221 (3.5, M-17), 209 (19.9, M-29), 195 (35.3, M-43), 180 (3.6, M-58), 167 (4.2, M-71), 146 (8.6, M-92), 145 (3.5, M-93), 128 (3.4, M-110), 119 (10.3, M-119), 104 (4.3, M-134), 98 (7.0, M-140), 93 (7.3, M-145), 90 (3.9, M-148).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.94; H, 6.07; N, 11.98.

N-Phenyl-4-aminocinnamamide (**11**).

The alcohol **10** (1.0 g, 4 mmoles) was stirred in 1:1 polyphosphoric acid (40 g) at 80° for 30 minutes. The reaction mixture was worked up as described above for **2b**: the resulting material was then purified on a silica gel column to obtain 0.3 g (32%) of the product, mp 160-162° (from ethyl acetate); ir (potassium bromide): ν C=O 1665, C=C 1620, NH_2 3390, 3310 cm^{-1}; ^{1}H nmr (dimethyl sulphoxide-d_6): δ 5.68 (s, 2H, NH_2), 10.0 (s, 1H, NH), 6.52 (d, 1H, $=C_\alpha H$, J = 15.5 Hz), 7.46 (d, 1H, $=C_\beta H$), *p*-disubstituted ring, 6.62 (~ d, 2H, H-3',5', J = 8.2 Hz), 7.72 (~ d, 2H, H-2',6'), phenyl group, 7.04 (~ t, 1H, H-4), 7.3 (m, 4H, H-2,3,5,6); ^{13}C nmr (dimethyl sulphoxide-d_6): δ C=O 166.4, $=C_\alpha$ 124.0, $=C_\beta$ 141.6, *p*-disubstituted ring, C-1' 124.8, C-2',6' 131.3 [12], C-3',5' 121.0, C-4' 152.8, phenyl ring, C-1 143.1, C-2,6 115.7, C-3,5 130.6 [12], C-4 117.6; ms: ($C_{15}H_{14}N_2O$, 238.29) m/z (I%) 239 (3.7), 238 (23, M), 218 (0.1, M-18), 219 (0.2, M-19), 209 (0.6, M-29), 146 (100.0, M-92), 118 (12, M-120).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.46; H, 5.88; N, 11.82.

The intermediary product **11** was quantitatively converted into the cyclized compound **2b** when treated under the same reaction conditions as used for the preparation of the latter substance. The product was in every respect identical with **2b** made by the cyclization of the alcohol **10**.

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[12] Assignments are interchangeable.

[13] Overlapping signals.

[14] Overlapping signals.