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STUDIES ON THE SYNTHESIS OF BENZOLACTAM RINGS. II[1].
SYNTHESIS OF 1,4-DIHYDRO-3(2H)-ISOQUINOLINONE DERIVATIVES

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Abstract — A new synthesis of 1,4-dihydro-3(2H)-isoquinolinones by the amidomethylation with arylacetamide or arylacetonitrile and paraformaldehyde in some acid-catalysts is described.

In a series of study for synthesis of benzolactam compounds, we established the new route to 1,4-dihydro-3(2H)-isoquinolinones (5)[1] process of which includes an acid-catalyzed intramolecular amidomethylation on the aromatic carbon atom of N-hydroxymethylphenylacetamides (3)[2] prepared easily from phenylacetamides (1) and formaldehyde in alkaline medium.
Meanwhile, Deák and co-workers[3] explored extensively a method for synthesizing 1-aryl-substituted 1,4-dihydro-3(2H)-isoquinolinones from arylacetamides or arylacetonitriles and aromatic aldehydes under acid-catalyzed conditions.
In this paper, we wish to report an alternative method for the preparation of 1-unsubstituted 1,4-dihydro-3(2H)-isoquinolinones (six-member benzolactams) by the amidomethylation of arylacetamides (1) or arylacetonitriles (8) with paraformaldehyde (2) instead of aromatic aldehydes[3] as well as the formation of some by-products under various acid-catalyzed conditions.
A mixture of 0.01 M of phenylacetamide (1-a) or 4-chlorophenylacetamide (1-b) and 0.01 M of 2 was heated in pyrophosphoric acid ($H_4P_2O_7$) at 150-160° C for 1 h to afford 1,4-dihydro-3(2H)-isoquinolinone (5-a)[1,4] in 95% yield or 7-chloro derivative (5-b) in 61% yield. The same products were obtained in phosphoric acid (H_3PO_4) [yielding: 5-a 14%, 5-b 21%], in polyphosphoric acid (PPA) [yielding: 5-a 26%, 5-b 16% at 150-160° C] for 1 h, respectively.
Above result suggests that the carbonium ion (4) formed from the intermediate ($ArCH_2CONHCH_2O^+H_2$) by dehydration with acid-catalyst attacks the aromatic carbon atom, then normally intramolecular amidomethylation is resulted in the six-member

benzolactam (5-a or 5-b) as shown in Chart 1.

When a mixture of arylacetamide (1-a or 1-b) and 2 was allowed to stand at room temperature for 18 h in acidic condensing agent or refluxed in $CHCl_3$ with P_2O_5 for 1 h, the intermolecular amidomethylation occurred and a dimer, N,N'-methylenebisarylacetamide (6) was produced as follows: used acid (the yields of 6), $H_4P_2O_7$ (6-a[5] 43%, 6-b 55%), H_3PO_4 (6-a 78%, 6-b 34%), PPA (6-a 8%, 6-b 5%), conc-HCl (6-a 88 %, 6-b 40%), P_2O_5 in boiling $CHCl_3$ (6-a 49%, 6-b 27%).

At room temperature or refluxing in $CHCl_3$ with P_2O_5, the carbonium ion may attack to unshared electron pair on the nitrogen atom of another molecule of 1 to furnish the dimer (6) as shown in Chart 1.

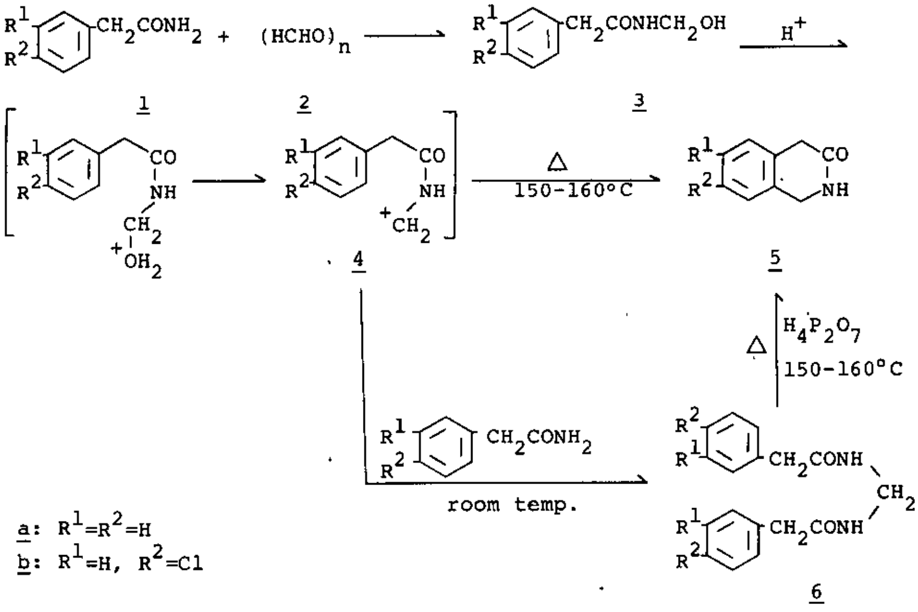


Chart 1

N,N'-Methylenebisarylacetamide (6) so obtained was heated at 150-160° C with $H_4P_2O_7$ to generate the six-member lactam in 85% yield of 5-a and in 87% yield of 5-b (Chart 1).

On the other hand, arylacetamide having electron-donating group on the aromatic ring such as 3,4-dimethoxy (1-c) or 3,4-methylenedioxyphenylacetamide (1-d) was allowed to react with 2 in $H_4P_2O_7$ at room temperature for 18 h or even at elevated temperature for 1 h to give the corresponding 2-hydroxymethylphenylacetic acid lactone (7-c[6] in 95% yield or 7-d[6] in 54% yield) as the sole product (Chart 2).

Changing the reaction conditions varied with the yield of 7 as follows: used acid (temperature, reaction time) and yield of the lactone; $H_4P_2O_7$ (60-70° C , 1 h) 7-c 85 %, 7-d 16%; $H_4P_2O_7$ (150-160° C, 1 h) 7-c 27%, 7-d 0%; H_3PO_4 (room temperature, 18 h) 7-c 60 %, 7-d 53%; PPA (room temperature, 18 h) 7-c 64%, 7-d 21%; conc-HCl (room temperature, 18 h) 7-c 49%, 7-d 40%.

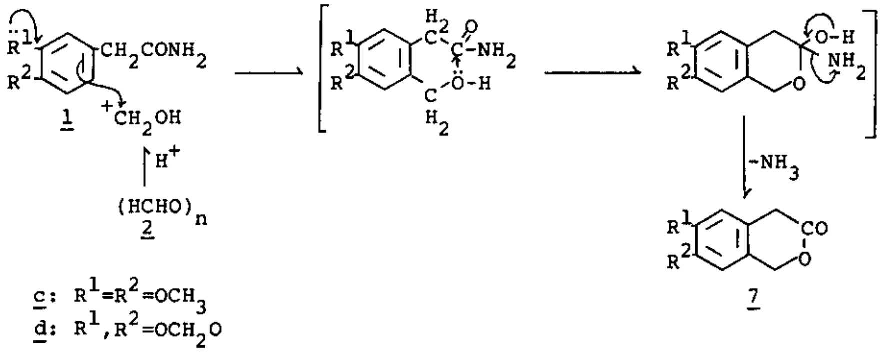


Chart 2

Next we dealed in an analogous procedure with arylacetonitriles (8) instead of arylacetamides (1). Phenylacetonitrile (8-a) or its 4-chloro derivative (8-b) on treatment with 2 in $H_4P_2O_7$ at elevated temperature converted to 5-a or 5-b besides a small amount of the corresponding phenylacetic acid or phenylacetamide after pouring the reaction mixture into cold water. The yields of 5 under various conditions are shown as follows: acid-catalyst, temperature, (yield of 5) for 1 h in every case; $H_4P_2O_7$, 200° C (5-a 36%, 5-b 40%); $H_4P_2O_7$, 130° C (5-a 29%, 5-b 11%); PPA, 200° C (5-a 30%, 5-b 35%); 85% H_3PO_4,160°C (5-a 26%, 5-b 0%); 98% H_3PO_4 in refluxing AcOH (5-a 23%, 5-b 0%).

As described above, when a mixture of 4-chloro-substituted nitrile (8-b) and 2 was heated at 160° C with 85% H_3PO_4 or with 98% H_3PO_4 in refluxing AcOH for 1 h, the product was not a benzolactam (7-chloro-1,4-dihydro-3(2H)-isoquinolinone), but a hydrolyzed compound (4-chlorophenylacetic acid) under the former condition, or a water-added compound (4-chlorophenylacetamide) under the latter condition in almost quantitative yield. A mixture of 8-a or 8-b and 2 was set aside with $H_4P_2O_7$ at room temperature for 12 h to give a bis-compound (6-a in 96% yield, 6-b in 90% yield), respectively.

In order to rationalized the formation of the final products 5 and 6 in above result, we propose the following reaction path: the additions of C^+H_2OH (formed from 2 and the acid-catalyst representable as HOP) and of HOP to the cyano moiety of the nitrile (8) produce the phosphorylated N-hydroxymethylimine from which the carbonium ion having a phosphorylated imino group (9) is formed after protonation and dehydration. Then attack of this ion (9) to remaining nitrile (8) produces the second intermediate, N,N'-methylenebis(phosphorylated imine).

Treatment of this intermediate with HOP at higher temperature to afford 5, and at room temperature to give the bis-compound (6) (Chart 3).

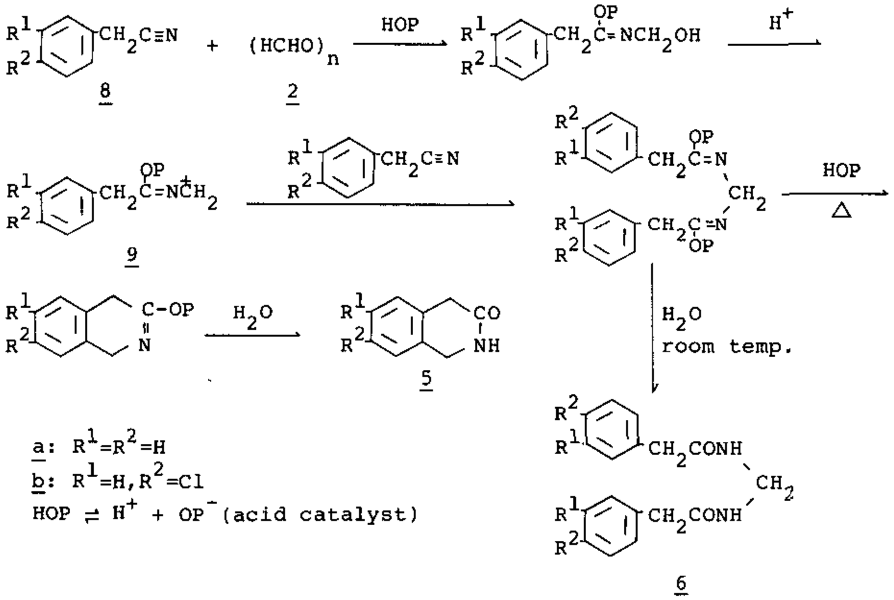


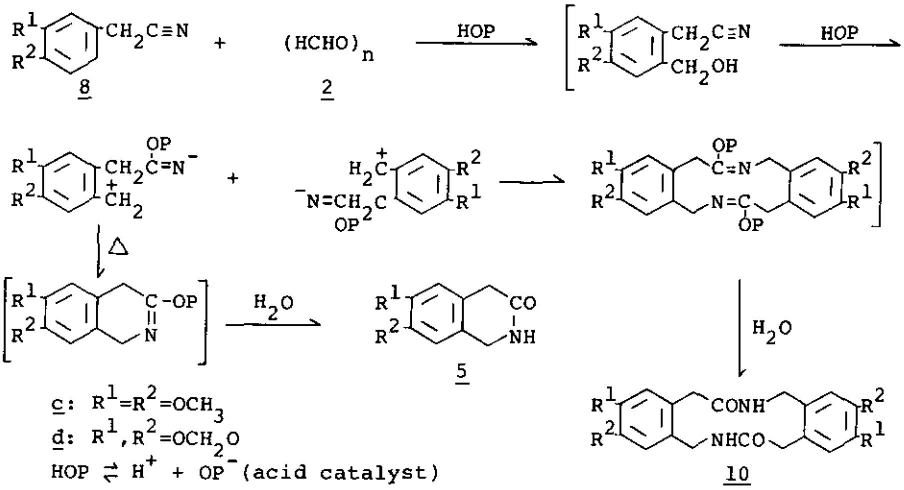
Chart 3

Treatment of 3,4-dimethoxyphenylacetonitrile (8-c) with 2 in $H_4P_2O_7$ at 130° C for 1 h produced 6,7-dimethoxy-1,4-dihydro-3(2H)-isoquinolinone (5-c) as a main product besides a small amount of the corresponding lactone (7-c). The former (5-c) has never been obtained by the action of the phenylacetamide (1-c) on 2 under any acidic conditions. Same procedure on another nitrile (8-d) at 130° C gained neither 6,7-methylenedioxy-1,4-dihydro-3(2H)-isoquinolinone (5-d) nor the corresponding lactone (7-d), but an intractable polymer.

Various reaction conditions and the yields of products are shown as follows: acid-catalyst, temp. (yields of the products); $H_4P_2O_7$, 130° C (5-c 37%, 7-c 9%), (5-d 0%, 7-d 0%); $H_4P_2O_7$, 60° C (5-c 12%, 7-c 3%), (5-d trace, 7-d trace); PPA, 130°C (5-c 14%, 7-c 2%), (5-d trace, 7-d trace); 85% H_3PO_4 130° C (5-c 72%, 7-c 7%), (5-d 13%, 7-d 3%); 98% H_3PO_4 in refluxing AcOH (5-c 76%, 7-c 3%), (5-d 18%,7-d 2%). Thus the desired benzolactam (5-d) obtained as above could not also arise from the phenylacetamide(1-d).

The nitriles such as 8-c and 8-d with 2 on allowing to stand at room temperature for 12 h in $H_4P_2O_7$ changed into the dimeric amides (10-c^1 in 82% and 10-d^1 in 79% 10-d yield), the lactams (5-c in 10% and 5-d in 7% yield), and the lactones (7-c in 5% and 7-d in 2% yield) respectively.

Above reactions starting from the nitriles (8-c and 8-d) might be representable as Chart 4.



c: $R^1=R^2=OCH_3$
d: $R^1,R^2=OCH_2O$
HOP $\rightleftarrows$ H^+ + OP^-(acid catalyst)

Chart 4

EXPERIMENTAL

All melting point were uncorrected and measured on a Yanagimoto micro melting point apparatus. Infrared spectra were measured with a Nihon-Bunko Jasuko IRA-I spectrophotometer,and mass spectra with a Nihon-Denshi JMS-D100 spectrometer.

Preparation of 1,4-Dihydro-3(2H)-isoquinolinone(5-a), 7-Chloro-1,4-dihydro-3(2H)-isoquinolinone(5-b). *a.* A mixture of phenylacetamide(1-a)(0.01 M) or 4-chlorophenylacetamide(1-b)(0.01 M), paraformaldehyde(2)(0.011 M) and acid-catalysts ($H_4P_2O_7$ or PPA or H_3PO_4)(20 g) was heated at 50-160°C for 1 h. The reaction mixture was poured into ice-water, neutralized with k_2CO_3, and then extracted with AcOEt. The extract was washed with 10% k_2CO_3 and water, dried($MgSO_4$), filtered and evaporated to give a solid. Recrystallization gave the benzolactam as follows: (5-a); yellow needles; mp 145-8°C(from benzen); ir(nujol)$\nu_{max}$$cm^{-1}$ 3280

3190(NH) 1660(CO); fomula C_9H_9NO ms m/z 147(M^+), (5-b); new compound; pale yellow-green needles; mp 209-211°C(from AcOEt); ir(nujol)ν_{max}cm^{-1} 3240(NH) 1680 1624(CO); fomula C_9H_8ClNO; anal.C,H,N(calcd.)% 59.45(59.50) 4.27(4.40) 7.81 (7.71); ms m/z 181.5(M^+).

b. A mixture of phenylacetonitrile(8-a)(0.01 M) or 4-chlorophenylacetonitrile (8-b)(0.01 M), 2(0.011 M) and acid-catalysts(20 g) was heated at 200°C for 1 h, and then, treatment of the reaction mixture in the same manner as the preparation of *a* gave 5-a and 5-b.

c. *N,N'-methylenebisphenylacetamide*(6-a)(one part) or N,N'-methylenebis(4-chlorophenylacetamide)(6-b)(one part) and $H_4P_2O_7$(ten parts) was heated at 150-160°C for 1 h and the reaction mixture was treated by the same manner to *give* 5-a *and* 5-b.

Preparation of 6,7-Dimethoxy-1,4-dihydro-3(2H)-isoquinolinone(5-c), 6,7-Methylenedioxy-1,4-dihydro-3(2H)-isoquinolinone(5-d). A mixture of 3,4-dimethoxyphenylacetonitrile(8-c)(0.01 M) or 3,4-methylenedioxyphenylacetonitorile(8-d)(0,01 M) and 2(0.011 M) was refluxed in AcOH 20 ml with 98%H_3PO_4(20 g) for 1 h and the reaction mixture was poured into ice-water, neutralized with K_2CO_3 and extracted with AcOEt. The organic layer was washed with 10% K_2CO_3 and water, dried($MgSO_4$) *and evaporated*. The residue was chromatographed on neutral alumina. Evaporation of the AcOEt eluent gave a yellowish crysral, which was recrystallized from MeOH to afford the benzolactm as follows: *(5-c); pale yellow-green plates;* mp 204-5°C (decomp); ir(nujo)ν_{max}cm^{-1} 3185(NH) 1682 1657(CO); fomula $C_{11}H_{13}NO_3$; ms m/z 207(M^+), (5-d); pale yellow-green plates; mp 228-230°C; ir(nujol)ν_{max}cm^{-1} 3180(NH) 1680 1658(CO); fomula $C_{10}H_9NO_3$; ms m/z 191(M^+).

Preparation of N,N'-Methylenebisphenylacetamide(6-a), N,N'-Methylenebis(4-chlorophenylacetamide)(6-b). A mixture of arylacetamide(1-a or 1-b)(0.01 M) or arylacetonitrile(8-a or 8-b)(0.01 M) and 2(0.011 M) was stirred and allowed to stand at room temperature *for* 12-18 h in acid-catalysts ($H_4P_2O_7$ or H_3PO_4 or PPA)(20 g) or refluxed in $CHCl_3$ with P_2O_5 for 1 h. The reaction mixture was poured into ice-water, and the precipitated product was filtered *off, washed with water,* dried and recrystallized from MeOH gave the N,N'-methylenebisamide as follows: (6-a); white needles; mp 210-213°C; ir(nujol)ν_{max}cm^{-1} 3290(NH) 1640(CO); fomula $C_{18}H_{18}N_2O_2$; ms m/z 282(M^+), (6-b); new compound; white needles; mp 239-240°C; ir(nujol)ν_{max} cm^{-1} 3280(NH) 1642(CO); fomula $C_{17}H_{16}Cl_2N_2O_2$; anal.C,H,N % 57.93(58.11) 4.42(4.55) 8.04(7.98); ms m/z 351(M^+).

Preparation of 4,5-Dimethoxy-2-aminomethylphenylacetic Acid Bisamide(10-c), 4,5-Methylenedioxy-2-aminomethylphenylacetic Acid Bisamide(10-d). A mixture of arylacetonitrile(8-c or 8-d)(0.01 M) and 2(0.011 M) was stirred and allowed to stand at room temperature for 12 h in $H_4P_2O_7$, and then, the reaction mixture was poured into ice-water, the solid was collected, washed with 10 % K_2CO_3 and water. The crude product was refluxed in AcOEt with stirring for several minutes, and filtered off, recrystallized from MeOH-AcOH gave the bisamide as follows: (10-c); white granules mp >300°C; ir(nujol)ν_{max}cm^{-1} 3270(NH) 1630(CO); fomula $C_{22}H_{26}N_2O_6$; ms m/z 414(M^+), (10-d); white granules; mp >300°C; ir(nujol)ν_{max}cm^{-1} 3270(NH) 1645(CO); fomula $C_{20}H_{18}N_2O_6$; ms m/z 382(M^+).

Reaction of 3,4-Dimethoxyphenylacetamide(1-c) or 3,4-Methylenedioxyphenylacetamide(1-d) and 2 in the Acid-catalysts. A mixture of 1-c(0.01 M) or 1-d(0.01M) and 2(0.011 M) was stirred and allowed to stand at room temperature for 12 h or heated at 60-70°C or 150-160°C for 1 h in acid-catalysts($H_4P_2O_7$ or H_3PO_4 or PPA or conc-HCl). The reaction mixture was poured into ice-water, neutralized with K_2CO_3 and extracted with AcOEt. The organic extract was washed 10% K_2CO_3 and water, dried($MgSO_4$), filtered and evaporated. Recrystallization from AcOEt gave the lactone as follows: (7-c); white needles; mp 107-9°C; ir(nujol) $_{max}$cm^{-1} 1728(CO); fomula $C_{11}H_{12}O_4$; ms m/z 208(M^+), (7-d); white needles; mp 127-131°C; ir(nujol)ν_{max}cm^{-1} 1728(CO); fomula $C_{10}H_8O_4$; ms m/z 192(M^+).

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