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A NEW SYNTHESIS OF 1,4-DIHYDRO-3(2H)-ISOQUINOLINONES BY THE CYCLIZATION OF N-HYDROXYMETHYLARYLACETAMIDES[1]

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Abstract — A new and facile synthesis of 1,4-dihydro-3(2H)-isoquinolinones by the intramolecular amidomethylation with pyrophosphoric acid is described.

Carbonium-immonium ion intermediates, $[\mathrm{RCONH\overset{+}{C}H_2} \longleftrightarrow \mathrm{RCO\overset{+}{N}H{=}CH_2}]$ formed by the acid-catalyzed dehydroxylation of the corresponding N-hydroxymethylamides are effective electrophiles in the intermolecular condensation[2], and the introduction of the amidomethyl group into aromatic rings in the presence of sulfuric acid (H_2SO_4) is known widely as the Tscherniac-Einhorn reaction[2].

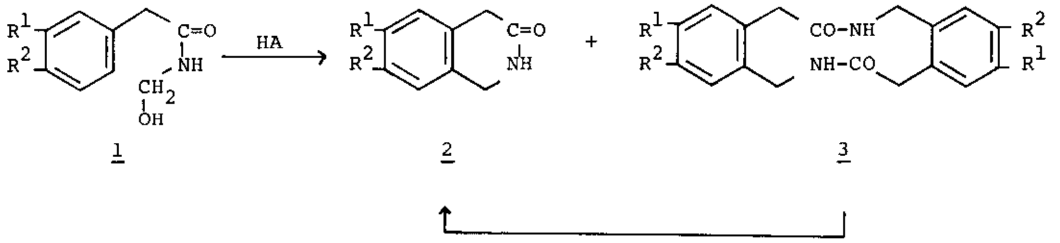
Although 1,4-dihydro-3(2H)-isoquinolinone (2a) and its substituted derivatives (2b and 2c) were obtained by various methods[3], there is no example prepared by the intramolecular amidomethylation of the corresponding N-hydroxymethylamides.

We now wish to report a new and facile synthesis of 1,4-dihydro-3(2H)-isoquinolinones (2) by the intramolecular condensation of N-hydroxymethylarylacetamides (1)[4a, b] with some acid catalysts and a conversion of the dimers (3) produced in this reaction into the monomers (2).

A mixture of N-hydroxymethylphenylacetamide (1a) (one part) and pyrophosphoric acid ($H_4P_2O_7$) (ten parts) was heated at 140-160° for 1 h and the reaction product was treated with water to give 1,4-dihydro-3(2H)-isoquinolinone (2a) (in 76.5% yield). The same condensation also occurred in using other phosphoric acids as follows: used acid (temp., reaction time) and yield of (2a); polyphosphoric acid (PPA) (140-160°, 1 h) 56.7%, 85% phosphoric acid (H_3PO_4) (140-160°, 1 h) 27.7%, phosphorus pentoxide (P_2O_5) (in refluxing $CHCl_3$, 1 h) 3.3%, and (in refluxing $C_2H_2Cl_4$, 1 h) 14.4%.

When (1a) was allowed to stand with $H_4P_2O_7$ or PPA at room temp. for 14 h, the reaction product was not (2a), but an unseparable mixture of gummy polymers.

Treatment of 1a with sulfuric acid, which was applied mostly as an amidomethylating catalyst in the Tscherniac-Einhorn reaction[2], also leads to a mixture of polymers. A mixture of disubstituted amide, *viz*. 3,4-dimethoxy- or 3,4-methylenedioxy-N-hydroxymethylphenylacetamide (1b or 1c)[4b] and $H_4P_2O_7$ was heated at 100° for 1 h, followed by treating with water to deposit crystals of the new dimer (3b in 15.5% yield or 3c in 29.8% yield) of which structural elucidation is shown in the Notes[5]. When each filtrate was shaken firstly with CH_2Cl_2 and with $AcOC_2H_5$ finally, so isolable second crop from the combined solution was the expected 1,4-dihydro-3(2H)-isoquinolinone (2b in 12.9% yield or 2c trace)[3b].



conc. HCl, refluxing 1 h, or
$H_4P_2O_7$, 120° 1 h, or
300 —306°/ 20 torr

a: $R^1=R^2=H$ b: $R^1=R^2=OCH_3$ c: R^1, $R^2=OCH_2O$

Changing the reaction conditions in using $H_4P_2O_7$, the yields of 2 and 3 varied as follows: the yields of 2 and 3, (temp., reaction time); 2b, 4.0% and 3b, 93.3% (room temp., 14 h); 2c, trace and 3c, 92.7% (room temp., 14 h); 2b, 7.2% and 3b, 67.8% (60°, 1 h); 2c, trace and 3c, 60.0% (60°, 1 h).

The dimer (3b or 3c) was pyrolyzed in a glass tube at 300-306°/ 20 torr to provide 2b (80.0% yield) or 2c (40.0% yield).

From above experimental result coupled with the spectral and analytical data[5], these dimers seem reasonable to have the structures 3b and 3c formed by the bimolecular condensation of the same N-hydroxymethylamide.

Substitution with electron-donating groups at 3 and 4 positions on the aromatic ring in 1 is especially in favor of the twofold intermolecular condensation against the intramolecular one.

References and Notes

1. Presented in part at the ACS/CSJ Chemical Congress, Honolulu, Hawaii, April 2, 1979, Abstracts of papers, part 2, ORGN 111.
2. H. E. Zaugg and W. B. Martin, "*Organic Reactions*", ed. by R. Adams, John Wiley & Sons, Inc., New York, 1965, **14**, pp. 52-267.
3. Of a number of preparations of 1,4-dihydro-3(2H)-isoquinolinone (2a) and its substituted derivatives, cited herein only the literatures concerning our present paper.
   a) By the Beckmann rearrangement, R. E. Lyle and D. A. Walsh, *Org. Prep. Proced.*, 1973, **5**, 299.
   b) By the reduction of the corresponding 3-isoquinolinones, N. J. McCorkindale and A. W. McCulloch, *Tetrahedron*, 1971, **27**, 4653.
   c) By the treatment of a mixture of arylacetonitrile or arylacetamide and aromatic aldehyde with PPA or TFA, J. Finkelstein and A. Brossi, *J. Heterocyclic Chem.*, 1967, **4**, 315; Z. Csűrös, G. Deák, I. Hoffmann, and A. Török-Kalmár, *Acta Chim. Acad. Sci. Hung.*, 1969, **59**, 119; *ibid.*, 1969, **60**, 177; *ibid.*, 1976, **88**, 87; E. Koltai, D. Bánfi, L. Hazai, and G. Deák, *J. Label Comp. and Radiopharm.*, 1978, **15**, 331.
   d) By the condensation of the adduct of α,α-dimethylphenylacetamide and glyoxylic acid with methanesulfonic acid (MSA), and the cyclization of N-benzyl-bis(methoxycarbonylamino)acetamides with MSA, D. Ben-Ishai, N. Peled, and I. Sataty, *Tetrahedron Letters*, 1980, **21**, 569.
4. a) R. D. Haworth, R. MacGillivray, and D. H. Peacock, *J. Chem. Soc.*, 1950, 1493.
   b) N-Hydroxymethyl-3,4-methylenedioxyphenylacetamide (1c) is the new compound ; mp 128-129°; IR (nujol) cm^{-1}, ν_{max} 3270 (NH), 1630 (C=O); MS *m/e*, 209 (M^+); *Anal.* C, H, N (calcd.) % 57.23(57.41), 5.73 (5.30), 6.60(6.70).
5. The 1,4-dihydro-3(2H)-isoquinolinones (2b and 2c) were identical with the authentic samples by the alternative preparation according to the method of the literatures[3b]. The structures of these new dimers (3b and 3c) were elucidated as follows: 3b, mp>300°; IR (nujol) cm^{-1}, ν_{max} 3270 (NH), 1630 (C=O); MS *m/e*, M^+ 414.1801 ($C_{22}H_{26}N_2O_6$=414.1790). 3c, mp>300°; IR (nujol) cm^{-1}, ν_{max} 3270 (NH), 1645 (C=O); MS *m/e*, M^+ 382.1107 ($C_{20}H_{18}N_2O_6$=382.1164). Hydrolysis of 3b and 3c with boiling conc. HCl gave the lactamized products (2b and 2c).

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