Ring Closure of 1-[4-(Imidazol-1-yl)phenyl]-3-phenyl-2-propen-1-one Derivatives to Potential Biologically Active Compounds

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1-[4-(Imidazol-1-yl)phenyl]-3-phenyl-2-propen-1-one **1** reacted with acetone cyanohydrin, ethyl phenylacetate and cyanoacetamide to give the adducts **2**, **8** and **10** respectively. Action of hydrazine hydrate on both the γ-ketonitrile **2** and the corresponding γ-ketoacid **4** led to pyridazine derivatives **3** and **5**. 4,5-Dihydropyridazinone **5** was dehydrogenated by the action of bromine in acetic acid to give pyridazinone **6**. Cyclization of acid **8** in acetic medium resulted in α-pyrone **9**. Cyanopentanamide **10** was converted with hydrochloric acid into δ-ketoacid **13** which led to α-pyrone **14** *via* an intramolecular dehydration. Refluxing **10** in the presence of acetic acid and ammonium acetate gave 3,4-dihydropyridone **11** which was dehydrogenated to produce pyridone **12**.

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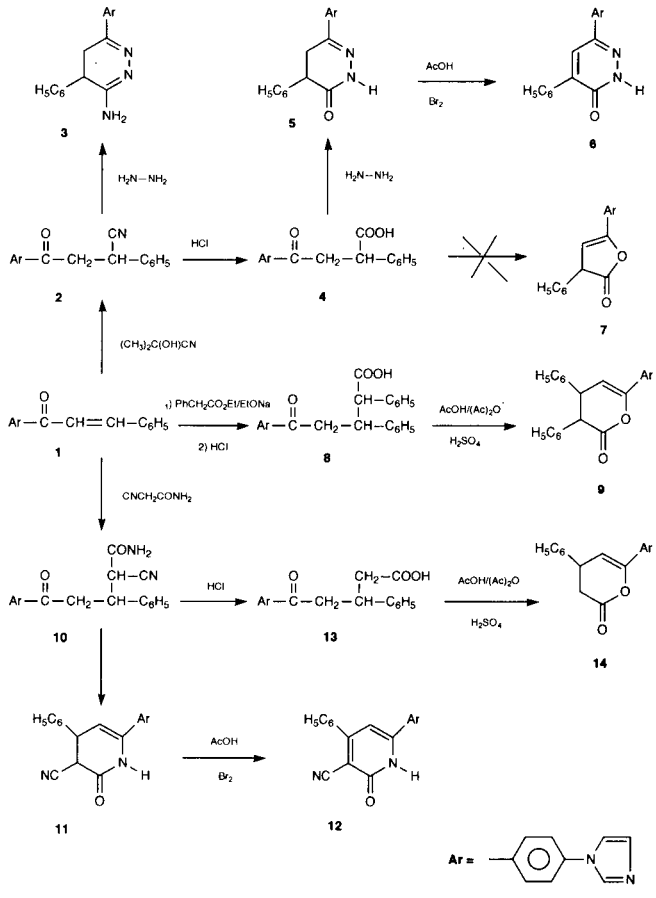
Much attention has been focused on the synthesis of imidazole derivatives because they have exhibited a great number of biological properties such as cholinergic [1], H_1 and H_2-receptor antagonist effects [2], antifungal [3], and antihypertensive activities [4,5]. In a previous paper [6] we described the synthesis of 6-[(4-imidazol-1-yl)phenyl]-4-phenyl-4,5-dihydro-2*H*-pyridazin-3-one **5** which showed an important inhibition of PAF-acether induced blood platelet aggregation *in vitro*. The results of this study prompted us to explore the reactivity of imidazolylchalcone derivatives in the construction of new potential biologically active heterocyclic compounds.

Thus, three series were synthesized: pyridazines, cyclic esters and pyridone derivatives (Scheme 1). The γ-ketonitrile **2** reacted with hydrazine hydrate in ethanol to give 3-aminopyridazine **3**. The previously described dihydropyridazinone **5** was dehydrogenated by bromination and dehydrobromination in acetic acid to produce pyridazinone **6**.

Pyrone **9** was obtained by cyclization of δ-ketoacid **8** in acetic anhydride and acetic acid with catalytic amounts of sulphuric acid. When γ-ketoacid **4** was similarly heated in acetic medium, cyclization did not occur and furanone **7** was not isolated. Synthesis of acid **8** was achieved using literature procedure [7]. When chalcone **1** was allowed to react with ethyl phenylacetate at room temperature for 24 hours in presence of sodium ethoxide, followed by heating with additional quantity of sodium ethoxide, it gave rise to the expected acid **8**. Refluxing chalcone **1** with cyanoacetamide in the presence of sodium ethoxide and piperidine, as described in literature [8], led to cyanopentanamide **10**. Hydrolysis and partial decarboxylation of **10** in 10*N* hydrochloric acid furnished δ-ketoacid **13** which gave rise to pyrone **14** *via* an intramolecular dehydratation. Furthermore it was possible to prepare 2-pyridones from compound **10**. Thus, 3,4-dihydropyridone **11** was synthesized by refluxing **10** in acetic acid with a large excess of ammonium acetate. Dehydrogenation of derivative **11** was obtained by action of bromine in acetic acid and led to pyridone **12**.

Scheme 1



The structures of the products were established both by spectral data and elemental analyses.

EXPERIMENTAL

Melting points were determined on a Reichert apparatus and were uncorrected. Infrared spectra were taken in potassium bromide pellets on a Beckman 4240 spectrophotometer. The ^1H nmr spectra were recorded in deuteriodimethylsulfoxide as the solvent on a Varian EM 360A spectrometer with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million and signals are quoted as s (singlet), br s (broad singlet), d (doublet), m (multiplet). Elemental analyses were carried out at the Service Central d'Analyses, Centre National de la Recherche Scientifique 69390 Vernaison France.

Preparation of compounds **1**, **2**, **4**, **5** were reported in a previous paper [6].

3-Amino-4-phenyl-4,5-dihydro-6-[(4-imidazol-1-yl)phenyl]pyridazine Hemihydrate (**3**).

To a stirred mixture of nitrile **2** (1.8 g, 0.0064 mole) in ethanol (20 ml) and acetic acid (1 ml) was added hydrazine hydrate (0.32 g, 0.0064 mole). The mixture was heated at reflux for 12 hours. After cooling, the resulting precipitate was filtered off and washed with water. Recrystallization from dimethyl sulfoxide-water (80:20) afforded 0.73 g (35%) of yellow crystals, mp 269-270°; ir: ν (cm^{-1}) 3300-2600 (NH, OH), 1600, 1590, 1500, 1470 (C=N, C=C); ^1H nmr: δ 3.4 (m, 3H, CH_2 + 0.5 H_2O), 3.7 (m, 1H, C*H*CH_2), 6.5-8.5 (m, 12H, C_6H_5 + C_6H_4 + 3CH= imid), 10.3 (br s, 2H, NH_2).

Anal. Calcd. for $C_{19}H_{17}N_5 \cdot 0.5H_2O$: C, 70.37; H, 5.55; N, 21.60. Found: C, 70.30; H, 5.51; N, 21.66.

4-Phenyl-6-[(4-imidazol-1-yl)phenyl]-(2*H*)-pyridazin-3-one Hemihydrate (**6**).

A vigorously stirred solution of compound **5** (3.25 g, 0.01 mole) in glacial acetic acid (40 ml) was heated to 70° and then treated portionwise with bromine (1.92 g, 0.012 mole) for 15 minutes. The mixture was stirred further for 3 hours and poured into ice water. The obtained solution was slowly brought to *p*H = 10 with concentrated ammonia. The resulting precipitate was filtered off, washed subsequently with water and recrystallized from ethanol to give 3.18 g (98%) of compound **6**, mp 224-225°; ir: ν (cm^{-1}) 3300-2600 (NH, OH), 1650 (CO), 1600, 1580, 1520, 1490 (C=N, C=C); ^1H nmr: δ 3.4 (br s, 1H, 0.5 H_2O), 7.1-8.6 (m, 13H, C_6H_5 + C_6H_4 + CH= + 3CH= imid), 12.9 (br s, 1H, NH).

Anal. Calcd. for $C_{19}H_{14}N_4O \cdot 0.5H_2O$: C, 70.59; H, 4.64; N, 17.34. Found: C, 70.34; H, 4.59; N, 17.16.

2,3-Diphenyl-5-oxo-5-[(4-imidazol-1-yl)phenyl]pentanoïc Acid Hemihydrate (**8**).

Ethyl phenylacetate (1.64 g, 0.01 mole) and chalcone **1** (2.83 g, 0.01 mole) were added successively to an ethanolic solution (30 ml) of sodium (0.23 g). The mixture was stirred at room temperature for 24 hours, then an additional ethanolic solution (30 ml) of sodium (0.46 g) was added and the resulting mixture was refluxed for 4 hours. After evaporation of the solvent, the residue was dissolved in 10% hydrochloric acid and concentrated ammonia was added dropwise until *p*H = 6. The precipitate which separated was collected by filtration, washed with water and dried to give 2.80 g (66%) of the expected acid **8**, which was used without further purification. An analytical sample was recrystallized in ethanol to give colorless needles, mp 135°; ir: ν (cm^{-1}) 3400-2500 (OH), 1720 (CO), 1680 (CO ketone), 1600, 1580, 1510, 1490, 1450 (C=N, C=C); ^1H nmr: δ 3.5 (br s, 1H, 0.5 H_2O), 4.0 (m, 2H, CH_2), 5.5 (m, 2H, 2CH), 6.7-8.5 (m, 18H, $2C_6H_5$ + C_6H_4 + 3CH= imid + COOH).

Anal. Calcd. for $C_{26}H_{22}N_2O_3 \cdot 0.5H_2O$: C, 74.46; H, 5.49; N, 6.68. Found: C, 74.59; H, 5.40; N, 6.69.

3,4-Diphenyl-3,4-dihydro-6-[(4-imidazol-1-yl)phenyl]pyran-2-one Hemihydrate (**9**).

To a suspension of acid **8** (1.7 g, 0.004 mole) in anhydride acetic (7 ml) and acetic acid (13.5 ml), ten drops of sulphuric acid were added. The mixture was heated at 110° for 8 hours. After cooling and dilution with water (100 ml), the resulting solution was brought to *p*H = 4.5-5.0 by addition of sodium hydrogenocarbonate. The solid which separated was collected by filtration and chromatographed on a silica gel column (SDS silica, 70-230 mesh) to furnish the pyrone **9** in 37% yield (0.6 g), mp 260°; ir: ν (cm^{-1}) 3400 (OH), 1770 (CO), 1650, 1600, 1520, 1490, 1450 (C=N, C=C); ^1H nmr: δ 4.5 (m, 2H, 2CH), 4.7 (br s, 1H, 0.5 H_2O), 6.4 (s, 1H, CH= pyran), 7.3 (m, 10H, $2C_6H_5$), 7.6 (s, 1H, CH= imid), 8.2 (s, 1H, CH= imid), 8.0 (m, 4H, C_6H_4), 9.1 (s, 1H, N-CH=N).

Anal. Calcd. for $C_{26}H_{20}N_2O_2 \cdot 0.5H_2O$: C, 77.80; H, 5.24; N, 6.98. Found: C, 77.85; H, 5.16; N, 7.01.

2-Cyano-3-phenyl-5-oxo-5-[(4-imidazol-1-yl)phenyl]pentanamide Hemihydrate (**10**).

A mixture of cyanoacetamide (0.84 g, 0.01 mole) and of chalcone **1** (2.83 g, 0.01 mole) in ethanol (100 ml) was heated on a boiling water bath, in the presence of piperidine (0.8 ml), for 1 hour. The reaction mixture was evaporated *in vacuo* to dryness and the residue was triturated with diethylether until solidification. Recrystallization from ethanol-diethyl ether (40:60) gave 1.5 g (41%) of compound **10**, mp 194-195°; ir: ν (cm^{-1}) 3600-2600 (NH_2, OH), 2250 (CN), 1670 (2CO); ^1H nmr: δ 2.4 (m, 2H, CH_2), 3.7-4.7 (m, 3H, 2CH + 0.5 H_2O), 6.9 (br s, 2H, NH_2), 7.2-8.0 (m, 10H, C_6H_5 + C_6H_4 + CH= imid), 8.3 (s, 1H, CH= imid), 9.0 (s, 1H, N-CH= N).

Anal. Calcd. for $C_{21}H_{18}N_4O_2 \cdot 0.5H_2O$: C, 68.66; H, 5.18; N, 15.26. Found: C, 68.31; H, 5.22; N, 15.47.

3-Cyano-3,4-dihydro-4-phenyl-6-[(4-imidazol-1-yl)phenyl]-2(1*H*)-pyridone Hydrate (**11**).

A mixture of amide **10** (1.47 g, 0.004 mole) and ammonium acetate (3.08 g, 0.04 mole) in acetic acid (20 ml) was refluxed under stirring for 5 hours. The reaction product was poured into cold water and the resulting solution was neutralized with concentrated ammonia. The precipitate which separated, was filtered off and recrystallized from ethanol-water (50:50) to afford 1.07 g (75%) of pale brown needles, mp 155-156°; ir: ν (cm^{-1}) 3600 (OH), 3220 (NH), 2220 (CN), 1690 (CO), 1640, 1600, 1520, 1470, 1450 (C=N, C=C); ^1H nmr: δ 3.5 (br s, 2H, H_2O), 3.8-4.6 (m, 2H, 2CH), 5.5 (m, 1H, CH= pyridone), 7.0-8.2 (m, 11H, C_6H_5 + C_6H_4 + 2CH= imid), 8.5 (s, 1H, N-CH=N), 10.3 (br s, 1H, NH).

Anal. Calcd. for $C_{21}H_{16}N_4O \cdot H_2O$: C, 70.39; H, 5.03; N, 15.64. Found: C, 70.01; H, 5.22; N, 15.83.

3-Cyano-4-phenyl-6-[(4-imidazol-1-yl)phenyl]-2(1*H*)-pyridone Dihydrate (**12**).

From **11** (1 g, 0.0029 mole), bromine (0.48 g, 0.003 mole) and

25 ml of acetic acid according to **6**, the yield was 0.5 g (49%), mp 280°; ir: ν (cm^{-1}) 3300-2400 (NH, OH), 2200 (CN), 1750 (CO), 1600, 1500, 1450 (C=N, C=C); ^1H nmr: δ 4.5 (br s, 4H, $2H_2O$), 6.8 (s, 1H, CH= pyridone), 7.3-8.4 (m, 13H, C_6H_5 + C_6H_4 + 3CH= imid + NH).

Anal. Calcd. for $C_{21}H_{14}N_4O \cdot 2H_2O$: C, 67.38; H, 4.81; N, 14.97. Found: C, 67.11; H, 4.55; N, 14.56.

3-Phenyl-5-oxo-5-[(4-imidazol-1-yl)phenyl]pentanoïc Acid (**13**).

Compound **10** (1 g, 0.0027 mole) in 10*N* hydrochloric acid (15 ml) was stirred at room temperature for 3 hours, then refluxed for 12 hours. After evaporation *in vacuo* to dryness, the residue was dissolved in water (25 ml) and the resulting solution was slowly brought to *p*H = 6 with 1*N* aqueous solution of sodium carbonate. The precipitate which separated was collected by filtration, washed with water and dried to give 0.84 g (93%) of acid **13** which was used without further purification. An analytical sample was recrystallized in ethanol-water (35:65) to give colorless needles, mp 180°; ir: ν (cm^{-1}) 3200-2450 (OH), 1690 (CO), 1660 (CO ketone), 1590, 1500, 1440 (C=N, C=C); ^1H nmr: δ 2.7 (m, 2H, CH_2), 3.5 (m, 2H, CH_2COOH), 3.7 (m, 1H, CH), 7.0-8.6 (m, 12H, C_6H_5 + C_6H_4 + 3CH= imid), 8.8 (br s, 1H, OH).

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.86; H, 5.39; N, 8.38. Found: C, 71.64; H, 5.47; N, 8.29.

3,4-Dihydro-4-phenyl-6-[(4-imidazol-1-yl)phenyl]pyran-2-one (**14**).

To a suspension of acid **13** (1 g, 0.003 mole) in acetic anhydride (4 ml) and acetic acid (8 ml), six drops of sulphuric acid were added. The mixture was heated at 110° for 8 hours. After cooling and dilution with water (100 ml), the resulting solution was brought to *p*H = 4.5-5.0 by addition of sodium hydrogencarbonate and extracted with chloroform (3 x 100 ml). The organic extracts were collected, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a residue, which was chromatographed on a silica gel column (SDS silica, 70-230 mesh) to furnish the pyrone **14** as pale yellow needles (0.4 g, 42%), mp 154-155°; ir: ν (cm^{-1}) 1750 (CO), 1600, 1580, 1520, 1450 (C=N, C=C); ^1H nmr: δ 3.0 (m, 2H, CH_2), 4.1 (m, 1H, CH), 6.4 (d, 1H, CH= pyrone), 7.1-8.5 (m, 12H, C_6H_5 + C_6H_4 + 3CH= imid).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86. Found: C, 75.98; H, 5.04; N, 8.64.

REFERENCES AND NOTES

[1] M. W. Moon, C. G. Chidester, R. F. Heier, J. K. Morris, R. J. Collins, R. R. Russel, J. W. Francis, G. P. Sage and V. H. Sethy, *J. Med. Chem.*, **34**, 2314 (1991).

[2] T. H. Brown, R. C. Blakemore, P. Blurton, G. I. Durant, C. R. Ganellin, M. E. Parsons, A. C. Rasmussen, D. A. Rawlings and T. F. Walker, *Eur. J. Med. Chem.*, **24**, 65 (1989).

[3] G. C. Porretta, M. Biava, F. Cerreto, M. Scalzo, S. Panico, N. Simonetti and A. Villa, *Eur. J. Med. Chem.*, **23**, 311 (1988).

[4] D. J. Carini, J. V. Duncia, A. L. Johnson, A. T. Chiu, W. A. Price, P. C. Wong and P. B. M. W. Timmermans, *J. Med. Chem.*, **33**, 1330 (1990).

[5] D. J. Carini, J. V. Duncia, P. E. Aldrich, A. T. Chiu, A. L. Johnson, M. E. Pierce, W. A. Price, J. B. Santella III, G. J. Wells, R. R. Wexler, P. C. Wong, S. E. Yoo and P. B. M. W. Timmermans, *J. Med. Chem.*, **34**, 2525 (1991).

[6] P. Coudert, C. Rubat, J. Couquelet and P. Tronche, *J. Pharm. Belg.*, **45**, 191 (1990).

[7] Y. A. Al-Farkh, F. H. Al-Hajjar and H. S. Hamoud, *J. Heterocyclic Chem.*, **16**, 1 (1979).

[8] F. H. Al-Hajjar and A. A. Jarrar, *J. Heterocyclic Chem.*, **17**, 1521 (1980).