4-Aroyl-1,3-dihydro-2*H*-imidazol-2-ones: A New Class of Cardiotonic Agents. 2. Effect of 4-Pyridoyl Substituents and Related Compounds[1]

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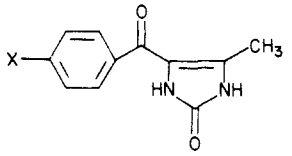
A group of 4-pyridoyl-1,3-dihydro-2*H*-imidazol-2-ones was prepared and tested for inotropic activity in the anesthetized dog. Positive inotropic effects as well as increases in heart rate and decreases in blood pressure were noted for most of these compounds. One of the compounds (8) is currently undergoing clinical trials for the treatment of congestive heart failure.

Recent reports, from this laboratory, have described the cardiovascular activity of the 4-aroyl-1,3-dihydro-2*H*-imidazol-2-ones.[2,3] Marked positive inotropic activity accompanied by minor positive chronotropic and hypotensive effects were found for a large number of these compounds. The combination of positive inotropic activity and after-load reduction suggested that these compounds may have beneficial effects in the treatment of congestive heart failure.[4]

Most of these previously reported compounds contained electron-donating substituents such as methoxy, hydroxy, or methylthio on the aroyl portion. The greatest cardiotonic activity resided with the methoxy- (1) and methylthio- (2) substituted compounds. In order to further define



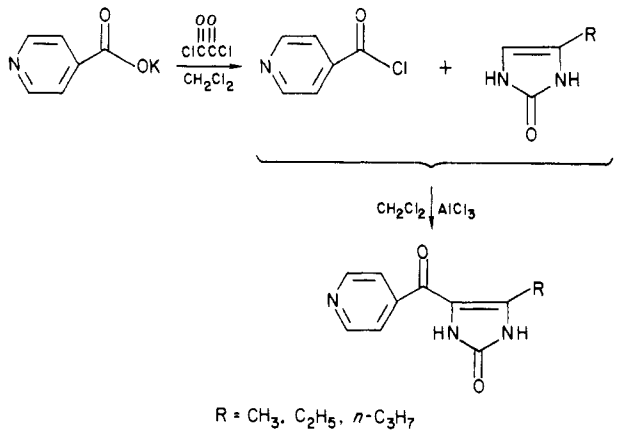
1, X = OCH_3
2, X = SCH_3

the cardiovascular effects of this series, compounds with electron-withdrawing functions such as pyridoyl and substituted pyridoyl compounds were prepared and evaluated. This paper describes the synthesis and pharmacology of compounds of this type.

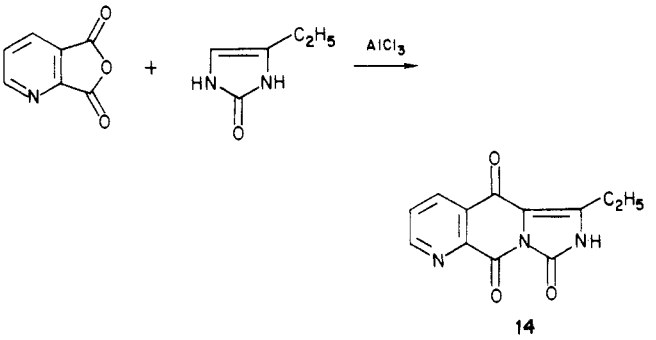
Chemistry

Friedel–Crafts acylation of the respective imidazolones with the pyridine acid chlorides provided the desired ketones as shown in Scheme I. The acid chlorides were synthesized from the potassium salts of the pyridinecarboxylic acids and oxalyl chloride in methylene chloride according to the method of Wingfield et al.[5] The *N*-oxide (13) was prepared by hydrogen peroxide oxidation of compound 8. The cyclized compound 14 was synthesized by acylation of 1,3-dihydro-4-ethyl-2*H*-imidazol-2-one with quinolinic anhydride in the presence of aluminum chloride as shown in Scheme II. The indicated isomer 14 is formulated by analogy with numerous literature examples whereby quinolinic anhydride gave only the 3-ketones under Friedel–Crafts conditions and no 2-ketones.[6-8]

Scheme I



Scheme II



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Results and Discussion

Compounds 3–14 were evaluated intravenously in anesthetized dogs with a Walton–Brodie strain gauge arch sutured to the left ventricle of the heart to record contractile force and needle electrodes inserted subcutaneously to record a lead II electrocardiogram and heart rate. Additionally, systemic blood pressure was recorded from a cannula inserted into the abdominal aorta via the femoral artery. Dose–response curves were determined with at least three doses of each compound. The dose of each compound to increase cardiac contractile force by 30%, to increase heart rate by 15%, and to decrease mean blood pressure by 20% was estimated and is shown in Table I. Most of the compounds produced significant increases in cardiac contractile force with lesser effects on heart rate and blood pressure.

The effect on contractile force of the pyridine isomers is clearly shown if compounds 3, 5, and 7 are compared. The isonicotinoyl isomer (7) was most active while the nicotinoyl (5) and picolinoyl (3) were less active. A similar trend, although not as dramatic was observed with 4, 6, and 8. The influence of the size of 5-alkyl substitution on the inotropic activity was seen with compounds 7–9 (iso-

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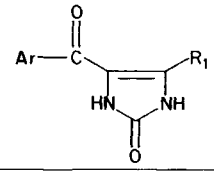
Table I. 4-Aroyl-1,3-dihydro-2*H*-imidazol-2-ones: Effect on Cardiac Contractile Force, Heart Rate, and Blood Pressure in Anesthetized Dogs



no.	Ar	R_1	yield, %	formula	mp, °C (recrystn solvent)[a]	anal.	equieffective dose,[b] mg/kg iv: contractile force, +30%	equieffective dose,[b] mg/kg iv: heart rate, +15%	equieffective dose,[b] mg/kg iv: blood pressure, −20%	no. of dogs
3	2-C_5H_4N	CH_3	18	$C_{10}H_9N_3O_2$	230–231 dec (A)	C, H, N	1.57 (0.04, 61.24)	3.29 (0.05, 232.76)	1.91 (0.43, 8.54)	2[d]
4	2-C_5H_4N	C_2H_5	27	$C_{11}H_{11}N_3O_2$	242–244 dec (A)	C, H, N	0.20 (0.06, 0.67)	0.83 (0.17, 4.03)	>3.00	4
5	3-C_5H_4N	CH_3	60	$C_{10}H_9N_3O_2$	>305 dec (B)	C, H, N	0.64 (0.16, 2.47)	>3.0	>3.0	3
6	3-C_5H_4N	C_2H_5	49	$C_{11}H_{11}N_3O_2$	220–222 dec (A)	C, H, N	0.22	>3.0	>3.0	9
7	4-C_5H_4N	CH_3	47	$C_{10}H_9N_3O_2$	298–299 dec (A)	C, H, N	0.13 (0.08, 0.17)	3.37 (1.24, 99.53)	2.58 (0.91, 512)	16
8	4-C_5H_4N	C_2H_5	48	$C_{11}H_{11}N_3O_2$	264–266 dec (C)	C, H, N	0.07 (0.02, 0.13)	0.42	1.70 (0.91, 7.00)	15
9	4-C_5H_4N	*n*-C_3H_7	33	$C_{12}H_{13}N_3O_2$	270–272 dec (A)	C, H, N	1.70 (0.54 5.38)	3.38 (0.36, 31.78)	>3.0	3
10	3-C_5H_3N-2-Cl	CH_3	46	$C_{10}H_8ClN_3O_2$	315–317 dec (A)	C, H, N	0.47 (0.28, 0.78)	5.10 (3.24, 8.03)	>10.0	6
11	3-C_5H_3N-2-Cl	C_2H_5	41	$C_{11}H_{10}ClN_3O_2$	273–275 dec (A)	C, H, N	0.31 (0.11, 0.85)	>3.0	>3.0	4
12	3-C_5H_3N-4-Cl	C_2H_5	36	$C_{11}H_{10}ClN_3O_2$	298–299 dec (A)	C, H, N	0.56 (0.41, 0.77)	11.80 (1.54, 90.32)	7.03 (1.99, 24.82)	5
13	4-C_5H_4N-1-oxide	C_2H_5	3	$C_{11}H_{11}N_3O_3$	274–275 dec (A)	C, H, N	>1.0[c]	>1.0	>1.0	1[d]

[a] A = EtOH; B = EtOH/H_2O; C = *i*-PrCH/H_2O. [b] Equieffective doses were obtained by extrapolation from a dose–response curve obtained with iv injections of at least three doses of each compound. Shown are means with 95% confidence intervals. [c] No effects were seen at doses up to 1 mg/kg. [d] Sample size precluded additional tests.

nicotinoyl). Optimum activity was found with **8**, which contained an ethyl substituent at this position, whereas somewhat less activity was seen with methyl and significantly less with propyl substitution. A similar pattern is seen with the nicotinoyl (**5**, **6**) and the picolinoyl compounds (**3**, **4**). Introduction of a halogen group does not markedly alter the potency (**10**–**12**); however, the cyclic compound **14** was inactive at doses up to 3 mg/kg (data not shown in table). The *N*-oxide **13** was also inactive (1 mg/kg).

The structure–activity relationship of this series shows that the 4-pyridoyl (isonicotinoyl) is the optimal ring isomer of pyridine for maximum contractile force effects while ethyl substitution at the 5-position is the optimal alkyl group. Thus, compound **8** of the series was picked for further development because of its greater relative potency and desirable cardiovascular profile.

The pharmacological properties of compound **8** have been reported in detail elsewhere.[9-11] Briefly, the cardiovascular effects of compound **8** were found to be mediated directly and did not involve stimulation of α- or β-adrenergic receptors or histamine receptors.[9,10] Furthermore, biochemical studies indicated that compound **8** did not directly alter calcium uptake or release from sarcoplasmic reticulum vesicles isolated from dog heart or Na^+,K^+-ATPase activity at reasonable concentrations.[11] However, inotropic amounts of compound **8** selectively inhibited the low K_m cAMP-phosphodiesterase (F III) from dog heart (IC_{50} = 7.2 M at 0.25 M cAMP)[11] and increased the level of cyclic AMP in the cat papillary muscle, in vitro.[12] Thus, it is likely that selective cAMP-phosphodiesterase inhibition is an important aspect of the positive inotropic mechanism of this compound.

In summary, 1,3-dihydro-4-isonicotinoyl-5-ethyl-2*H*-imidazol-2-one (**8**, piroximone) is a potent positive inotropic agent in dogs with moderate blood pressure lowering activity. Because of this desirable profile, it was chosen for further studies in man to determine its possible utility in the treatment of congestive heart failure.[13]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR and NMR spectra were obtained for all compounds and were consistent with assigned structures. IR spectra were recorded with a Perkin-Elmer 521 instrument. NMR spectra were recorded with a Varian Associates A60-A instrument with tetramethylsilane as the internal standard. Elemental analyses were within 0.4% of theoretical values when indicated by symbols of the elements.

1,3-Dihydro-4-isonicotinoyl-5-ethyl-2*H*-imidazol-2-one (8, Table I). In 130 mL of dry methylene chloride was suspended 9.0 g (0.056 mol) of potassium isonicotinate. The mixture was cooled with an ice–water bath, and 7.45 g (0.058 mol) of oxalyl chloride was added dropwise over a 20-min period. The mixture was then refluxed 30 min, cooled, and filtered. The filtrate was set aside for use in the subsequent reaction below. 1,3-Dihydro-4-ethyl-2*H*-imidazol-2-one (4.7 g, 0.042 mol) was suspended in 50 mL of methylene chloride, and 16.7 g (0.125 mol) of anhydrous aluminum chloride was added at room temperature. To this mixture was slowly added the above filtrate over a 5-min period. The solution was heated with vigorous stirring, and the

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solvent was allowed to evaporate from the reaction flask. The residue was heated in an oil bath at 120 °C for 30 min, cooled, and treated with 150 mL of water to dissolve the residue. The solution was treated with 13.7 g (0.16 mol) of sodium bicarbonate and refrigerated 15 h. A solid separated that was collected and recrystallized from 60 mL of 2-propanol/water (2:1) to give 4.3 g (48%) of 8, mp 264–265 °C. Compunds 3–12 were prepared by this method.

1,3-Dihydro-4-isonicotinoyl-5-ethyl-2*H*-imidazol-2-one 1-Oxide (13, Table I). In 140 mL of acetic acid were dissolved 5.0 g (0.023 mol) of 1,3-dihydro-4-isonicotinoyl-5-ethyl-2*H*-imidazol-2-one (8) and 6.5 mL of 30% (0.057 mol) hydrogen peroxide. The solution was warmed on the steam bath for 30 min after which the solvent was evaporated to 50 mL and cooled. A solid separated that was collected and discarded. The filtrate was evaporated to dryness and the residue chromatographed over silica gel with chloroform/methanol (4:1) as eluent to give compound 13. The material was purified by recrystallization from ethanol to give 0.16 g (3%): mp 274–275 °C; MS, *m/e* 233 (M^+).

1-Ethylimidazo[7,6-*c*][1,7]-naphthyridine-3,5,10(2*H*)-trione (14). In 100 mL of methylene chloride were placed 5.0 g (0.051 mol) of 1,3-dihydro-4-ethyl-2*H*-imidazol-2-one and 20.4 g (0.15 mol) of anhydrous aluminum chloride followed by 7.60 g (0.051 mol) of quinolinic anhydride. The mixture was heated, and the methylene chloride was allowed to distill from the reaction mixture. The stirred residue was heated to 120 °C for 30 min, cooled, and quenched with 200 mL of water. On standing 15 h, a solid separated that was collected and recrystallized from absolute ethanol to give 0.4 g (2%) of a yellow solid: mp >300 °C; MS, *m/e* 243 (M^+). Anal. ($C_{12}H_9N_3O_3$) C, H, N.

Pharmacological Methods. Dogs of either sex, weighing 9–23 kg, were anesthetized with 35 mg/kg iv of sodium pentobarbital. The lungs were ventilated artificially with a Bird Mark 7 respirator following tracheal intubation. The left femoral vein was cannulated for the injection of drugs. The left femoral artery was cannulated, and the cannula was advanced into the thoracic aorta to measure systemic blood pressure. Blood pressure was recorded with a pressure transducer (Statham P23GC). The chest was opened at the left fifth intercostal space, and the pericardium was cut to expose the heart. A calibrated Walton–Brodie strain gauge arch was sutured to the left ventricle to record cardiac contractile force. Heart rate was recorded from the EKG (lead II) with a tachograph (Grass, 7D). The dogs were allowed to stabilize for at least 30 min following surgical preparation. Measurements of cardiac contractile force, heart rate, and blood pressure were made at 5- to 10-min intervals before and after drug administration.

Experimental compounds were given intravenously by injection. Sufficient time was allowed between doses for the variables to return completely to basal levels. Only one compound was administered to any one animal. Equieffective doses were obtained by extrapolation from dose–response curves.

All imidazolones were dissolved in normal saline or 1 N NaOH and normal saline, pH 12-13. Isoproterenol was dissolved in normal saline containing 0.01% ascorbic acid.

Registry No. 3, 100791-02-4; 4, 100791-03-5; 5, 100791-04-6; 6, 84490-13-1; 7, 82709-64-6; 8, 84490-12-0; 9, 100791-05-7; 10, 100791-06-8; 11, 100791-07-9; 12, 100791-08-0; 13, 100791-09-1; 14, 100791-10-4; 2-$C_5H_4NCO_2K$, 25108-36-5; 3-$C_5H_4NCO_2K$, 16518-17-5; 4-$C_5H_4NCO_2K$, 25108-37-6; 3-CsH_3N-2-$ClCO_2K$, 97510-86-6; 3-C_5H_3N-4-$ClCO_2K$, 100790-99-6; 2-CsH_4NCOCl, 29745-44-6; 3-C_5H_4NCOCl, 10400-19-8; 4-C_5H_4NCOCl, 14254-57-0; 3-C_5H_3N-2-ClCOCl, 49609-84-9; 3-C_5H_3N-4-ClCOCL, 100791-00-2; 1,3-dihydro-4-methyl-2*H*-imidazol-2-one, 1192-34-3; 1,3-dihydro-4-ethyl-2*H*-imidazol-2-one, 83962-06-5; 1,3-dihydro-4-propyl-2*H*-imidazol-2-one, 100791-01-3; quinolinic anhydride, 699-98-9.

Antineoplastic Activity of 3′-(Chloroethyl)nitrosourea Analogues of 2′-Deoxyuridine and 2′-Deoxy-5-fluorouridine[1]

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The (chloroethyl)nitrosourea analgoues of 2′-deoxyuridine and 2′-deoxy-5-fluorouridine, 3′-[3-(2-chloroethyl)-3-nitrosoureido]-2′,3′-dideoxyuridine (3′-CdUNU, 7) and 3′-[3-(2-chloroethyl)-3-nitrosoureido]-2′,3′-dideoxy-5-fluorouridine (3′-CFdUNU, 8), have been synthesized by treatment of the corresponding 3′-amino nucleosides with chloroethyl isocyanate, followed by nitrosation of the resulting ureas. Nucleoside nitrosoureas 7 and 8 exhibited marked anticancer activity against L1210 leukemia in tumor-bearing mice. At an optimum dosage level of 40 mg/kg, 7 and 8 produced 90% and 60% "cures" (>60-day survivors), respectively. The structure–activity relationships are discussed.

It has been shown by Wheeler et al.[4] that alteration of the carrier portion of nitrosoureas affects their physical and chemical properties and by Schein et al.[5,6] that bone marrow toxicity is reduced in nitrosourea derivatives containing a glucose carrier. Several nitrosourea analogues of thymidine have been synthesized earlier in our laboratory,[7] and the synthesis of other nucleoside nitrosoureas has also been reported.[8-10] Among these compounds, not only 3′-[3-(2-chloroethyl)-3-nitrosoureido]-3′-deoxythymidine (3′-CTNU) is threefold more potent than 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in the inhibition of L1210 leukemia cells in culture[7] but also more strikingly pyrimidine deoxyribonucleosides (thymidine, 2′-deoxyuridine, 2′-deoxycytidine) specifically prevent the inhibitory effects of this nitrosourea analogue of thymidine.[11]

(1) This paper has been presented in part; see: Lin, T. S.; Prusoff, W. H. In "Abstracts of Papers", 188th National Meeting of the American Chemical Society, Philadelphia, Pa, Aug 26–31, 1984; American Chemical Society: Washington, DC, 1984; Abstr CARB 2.
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