Cardiotonic Agents. 3. Synthesis and Biological Activity of Novel 6-(Substituted 1*H*-imidazol-4(5)-yl)-3(2*H*)-pyridazinones

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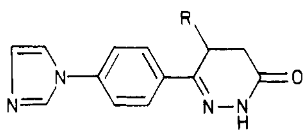
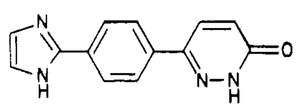
Several 6-(substituted 1*H*-imidazol-4(5)-yl)-3(2*H*)-pyridazinones were synthesized and evaluated for positive inotropic activity. The 1*H*-imidazol-4-yl regioisomers 4,5-dihydro-6-(1-methyl-2-phenyl-1*H*-imidazol-4-yl)-3(2*H*)-pyridazinone (**25a**) and 6-(1-methyl-2-phenyl-1*H*-imidazol-4-yl)-3(2*H*)-pyridazinone (**28a**) were potent positive inotropic agents. By contrast, the corresponding 1*H*-imidazol-5-yl regioisomers **25b** and **28b** were only weak positive inotropic agents. Compounds **25a** and **28a** were also potent inhibitors of cardiac phosphodiesterase fraction III.

As part of an ongoing project to identify novel compounds with cardiotonic activity for the treatment of congestive heart failure (CHF), we have recently discovered and reported a new class of potent positive inotropic agents, the 4,5-dihydro-6-[4-1*H*-imidazol-1-yl)phenyl]-3-(2*H*)-pyridazinones and 6-[4-(1*H*-imidazol-1-yl)phenyl]-3-(2*H*)-pyridazinones.[1,2] Two members of this class, **1a** (CI-914) and **1b** (CI-930), are presently under development for the treatment of CHF.



1a, R = H (CI-914)
1b, R = CH_3 (CI-930)

We have also discovered that the compound **2**, in which the phenylpyridazinone moiety is attached to the 2-position of the imidazole, is also a potent positive inotropic agent.[3]



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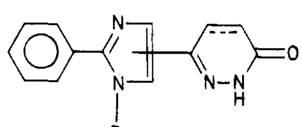
In order to further define the structural requirements for positive inotropic activity in this series, we synthesized some novel 3(2*H*)-pyridazinones having structure I in which the pyridazinone moiety is attached to the 4- or 5-position of the imidazole ring.



I

Some of the pyridazinones of structure I in which the pyridazinone moiety is attached to the 4-position of the imidazole ring (e.g., **25a** and **28a**) exhibited positive inotropic activity in the same range as **1a** when tested in the anesthetized dog model.[4] By contrast, the corresponding regioisomers **25b** and **28b** exhibited only weak positive inotropic activity. In this paper we report the synthesis of compounds related to structure I and discuss some of the structure–activity relationships including cardiac phosphodiesterase inhibitory activity.

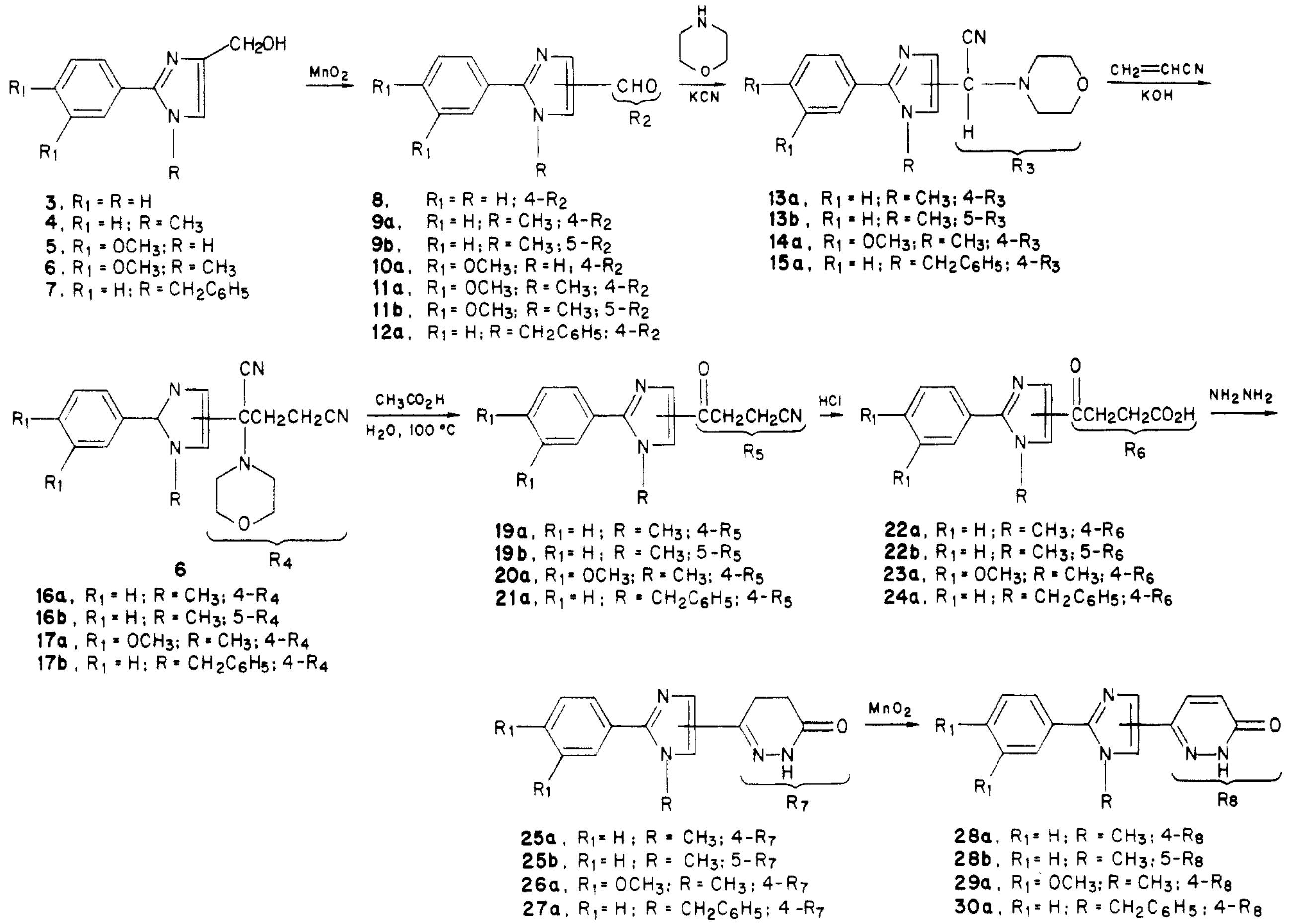
Chemistry. The 6-(substituted imidazol-4(5)-yl)-3-(2*H*)-pyridazinones listed in Table IV were prepared from 2-aryl-1*H*-imidazole-4-methanols following the sequences shown in Scheme I. The requisite 2-phenyl-1*H*-imidazole-4-methanols (**3**, **5**) were obtained from the appropriate benzonitrile via the imidate hydrochloride by a modification of the literature procedure[5] (Scheme II). The imidazolemethanol **3** was alkylated with iodomethane in presence of potassium hydroxide in *N*,*N*-dimethylformamide to give the corresponding 1-methylimidazole **4** as a single product in low to moderate yield. Manganese dioxide oxidation of **4** gave an aldehyde that was found to be identical with **9a**. In practice, it was found advantageous to oxidize **3** to the aldehyde **8** which was then alkylated with (i) dimethyl sulfate under phase-transfer conditions and (ii) iodomethane in the presence of potassium hydroxide to give a 3:2 mixture of 4- and 5-formyl derivatives (**9a** and **9b**), respectively, in 70% combined yield. The isomers were separated by column chromatography over silica gel and characterized. The ^1H NMR spectrum ($CDCl_3$) of **9a** (4-formyl) shows an *N*-methyl resonance at δ 3.75, an imidazole proton at δ 7.64, and the formyl proton (C*H*O) at δ 9.80. By contrast, the *N*-methyl group of **9b** (5-formyl) resonates at δ 3.95 and the formyl proton at δ 9.65. Thus the *N*-CH_3 of **9b** is deshielded by the anisotropic effect of the 5-formyl functionality relative to **9a**. Nuclear Overhauser studies (conducted at 360 MHZ in degassed Me_2SO-d_6 solution) further confirm the assignment of structures **9a** and **9b**, respectively. Irradiation of the *N*-methyl signal at δ 3.83 in **9a** caused a significant increase in the intensity of the imidazole singlet at δ 8.18, with no effect on the aldehyde singlet at δ 9.75. Conversely, irradiation of the *N*-methyl signal at δ 3.93 in **9b** had no effect on the singlet at δ 8.00 but caused a significant increse in the intensity of the aldehyde singlet at δ 9.76.

Since the separation of isomers **9a** and **9b** was inconvenient, the mixture was used for further transformations. Reaction of the mixture of **9a** and **9b** with morpholine and KCN in the presence of *p*-toluenesulfonic acid gave the morpholineacetonitrile derivatives **13a** and **13b**, which underwent Michael addition to 2-propenenitrile[6] in the presence of base to afford **16a** and **16b**, respectively. Use of methyl acrylate instead of 2-propenenitrile failed to give the esters corresponding to **16a** and **16b**. Attempted addition of 2-butenenitrile to **13** to obtain the methyl homologue of **16** was also unsuccessful. Treatment of **16a** and **16b** with aqueous acetic acid at 100 °C gave a mixture of crystalline γ-oxo nitrile derivatives **19a** and **19b**. Hydrolysis of **19a** and **19b** with 6 N HCl gave a mixture of

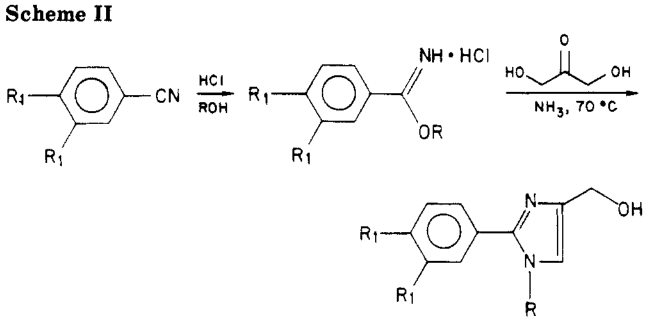
(1) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* **1984**, *27*, 1099.
(2) Sircar, I.; Duell, B.; Bobowski, G.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1985**, *28*, 1405.
(3) Sircar, I.; Bristol, J. A. DD 208615.
(4) Evans, D. B.; Weishaar, R. E.; Kaplan, H. R. *Pharmacol. Ther.* **1982**, *16*, 303.
(5) Dziuron, P.; Schunack, W. *Arch. Pharm. (Weinheim, Ger.)* **1973**, *306*, 349.
(6) Albright, J. B.; McEvoy, F. J.; Moran, B. *J. Heterocycl. Chem.* **1978**, *15*, 881.

0022-2623/86/1829-0261$01.50/0

Scheme I



Scheme II



γ-oxo acids **22a** and **22b**. This upon treatment with hydrazine in refluxing ethanol resulted in a mixture of 4,5-dihydropyridazinones **25a** and **25b**, which was separated by fractional crystallization. Manganese dioxide oxidation of pure isomers **25a** and **25b** gave pyridazinone derivatives **28a** and **28b**, respectively.

The reaction of **3** with benzyl bromide gave a single isomer which was assigned the structure **7** based on the analogy discussed earlier. Compound **7** was oxidized by MnO_2 to give an aldehyde **12**. Following the previous reaction sequences, **12** was subsequently converted to the 4,5-dihydropyridazinone **27a**, which was oxidized to the pyridazinone **30a**.

The dimethoxy analogue **5** was converted to the corresponding aldehyde **10a**, which on alkylation with iodomethane gave a 3:2 mixture of **11a** and **11b**. These were easily separated by fractional crystallization. Compound **11a** was converted to the 4,5-dihydropyridazinone **26a** and the pyridazinone **29a** by following the same reaction sequence as discussed earlier. Compound **11b** formed the corresponding morpholineacetonitrile derivative, which failed to undergo Michael addition to 2-propenenitrile.

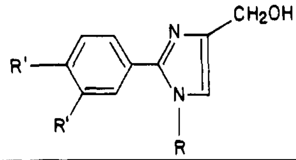
Biological Results

The pyridazinones in Tables III and IV were evaluated intravenously in an acutely instrumented anesthetized dog model for positive inotropic activity as described briefly in the Experimental Section.[4] Heart rate, myocardial contractility (derived by measuring dP/dt_{max} of left ventricular pressure), and aortic blood pressure were recorded. Dose–response curves were determined with at least four doses of each compound.

Compound **25a** and its oxidized product **28a** produced dose-related increases in dP/dt_{max} comparable to **1a** when tested in anesthetized dogs (Table V). These effects were associated with small increases in heart rate and small decreases in blood pressure. The decreases in mean arterial blood pressure seen with these agents (**25a** and **28a**) at their inotropic ED_{50} were of the same magnitude as seen with **1a**. The corresponding regioisomers **25b** and **28b** were significantly less potent. Changing the *N*-alkyl substitution from methyl to benzyl, **27a** and **30a**, resulted in significant loss of activity. Compounds **26a** and **29a** in which the phenyl group is substituted with 3,4-dimethoxy groups were also inactive.

Since selective inhibition of a specific molecular form (type III) of cardiac phosphodiesterase (PDE) represents the principal component of the positive inotropic action of 1 (**a** and **b**),[1] both isomers **25a** and **25b** as well as their analogues were evaluated for their inhibitory effects of cardiac PDE III and the results are shown in Table VI. These data provide an explanation for the significantly different relative cardiotonic potencies of two isomes **25a** and **25b**. Both **25a** and **28a**, the 4-yl regioisomers, were potent inhibitors of cardiac PDE III (IC_{50} = 12.1 and 5.0

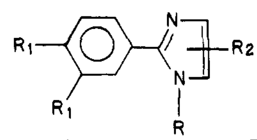
Table I. 2-Aryl-4-1*H*-imidazole-4-methanols



compd	R	R′	formula	yield, %	mp, °C	crystn solvent	UV, λ_{max} (ϵ)	^{1}H NMR, δ
4	CH_3	H	$C_{11}H_{12}N_2O$	45	129–130	Et_2O/EtOAc	260 (11085)	3.65 (s, 3 H, NCH_3), 4.20 (br, 1 H, OH), 4.60 (s, 2 H, CH_2OH), 6.85 (s, 1 H, H-5), 7.22–7.65 (m, 5 H, aromatic)[a]
5	H	OCH_3	$C_{12}H_{14}N_2O_3$	76	177–178	CH_3CN	278 (18060)	3.73 [s, 3 H, (3′-OCH_3)], 3.77 [s, 3 H, 4′-(OCH_3)], 4.38 (s, 2 H, CH_2OH), 4.90 (s, 1 H, CH_2OH), 6.90–7.05 (m, 2 H, H-5 and H-5′), 7.38–7.60 (m, 2 H, H-2′ and H-6′), 12.20 (1 H, NH)
6	CH_3	OCH_3	$C_{13}H_{16}N_2O_3$	44	162–163	EtOAc	264 (13630)	3.67 (s, 3 H, NCH_3), 3.80 [s, 6 H, Ar $(OCH_3)_2$], 4.35 (d, J = 5.5 Hz, 2 H, CH_2OH), 4.83 (t, J = 5.5 Hz, 1 H, OH), 6.95–7.20 (m, 4 H, H-5 and 3 H, aromatic)
7	$CH_2C_6H_5$	H	$C_{17}H_{16}N_2O$	60	178–179	EtOAc	258 (9030)	4.40 (d, J = 6.0 Hz, 2 H, CH_2OH), 4.86 (t, J = 6.0 Hz, 1 H, OH), 5.28 (s, 2 H, NCH_2), 6.95–7.60 (m, 10 H, aromatic)

[a] ^{1}H NMR spectra were recorded in $CDCl_3$.

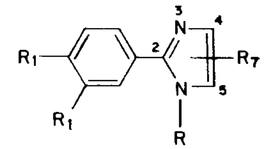
Table II. 2-Aryl-1*H*-imidazole-4(or 5)-carboxaldehydes

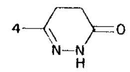
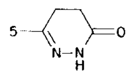
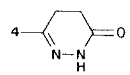
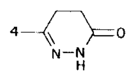


compd	R	R_1	R_2	formula	mp, °C	crystn solvent	UV, λ_{max} (ϵ)	IR (cm^{-1}), $\nu_{C=O}$	^{1}H NMR, δ
8	H	H	4-CHO	$C_{10}H_8N_2O$	169–170	CH_3CN/THF	286 (19180)	1660	7.30–7.55 (m, 3 H, H-5 and 2 H, aromatic), 7.95–8.10 (m, 3 H, aromatic), 9.70 (s, 1 H, CHO), 13.30 (NH)
9a	CH_3	H	4-CHO	$C_{11}H_{10}N_2O$	109–110	EtOAc/cyclohexane	266 (15130)	1690	3.75 (s, 3 H, NCH_3), 7.35–7.60 (m, 5 H, aromatic), 7.64 (s, 1 H, H-5), 9.82 (s, 1 H, CHO)[a] 3.82 (s, 3 H, NCH_3), 7.52 (m, 3 H, aromatic), 7.75 (m, 2 H, aromatic), 8.18 (s, 1 H, H-5), 9.75 (s, 1 H, CHO)
9b	CH_3	H	5-CHO	$C_{11}H_{10}N_2O$	94–95	$[(CH_3)_2CHO]_2O$	265 (15110)	1692	3.95 (s, 3 H, NCH_3), 7.35–7.70 (m, 5 H, aromatic), 7.80 (s, 1 H, H-4), 9.68 (s, 1 H, CHO)[a] 3.93 (s, 3 H, NCH_3), 7.63 (m, 3 H, aromatic), 7.74 (m, 2 H, aromatic), 8.00 (s, 1 H, H-4), 9.76 (s, 1 H, CHO)
10a	H	OCH_3	4-CHO	$C_{12}H_{12}N_2O_3$	203–204	THF	307 (18020), 253 (10635)	1660	3.78 [s, 6 H, $(OCH_3)_2$], 6.98 (d, J = 8.0 Hz, 1 H, H-5′), 7.68 (m, 2 H, H-2′ and H-6′), 7.95 (s, 1 H, H-5′), 9.63 (S, 1 H, CHO), 13.20 (NH)
11a	CH_3	OCH_3	4-CHO	$C_{13}H_{14}N_2O_3$	137–138	$(CH_3)_2CHOH$	262 (15600)	1678	3.76 [s, 9 H, $(CH_3)_3$], 6.92–7.28 (m, 3 H, aromatic), 8.03 (s, 1 H, H-5), 9.64 (s, 1 H, CHO)
11b	CH_3	OCH_3	5-CHO	$C_{13}H_{14}N_2O_3$	109–110	EtOAc/cyclohexane	262 (15650)	1668	3.83 [s, 6 H, $(OCH_3)_2$], 3.92 (s, 3 H, NCH_3), 6.82–7.22 (m, 3 H, aromatic), 7.75 (s, 1 H, H-4), 9.66 (s, 1 H, CHO)[a]
12a	$CH_2C_6H_5$	H	4-CHO	$C_{17}H_{14}N_2O$	97–98	$(CH_3)_2CHOH/CH_3CN$	263 (15030)	1685, 16 53	5.23 (s, 2 H, $ArNCH_2$), 6.95–7.55 (m, 10 H, aromatic), 7.60 (s, 1 H, H-5), 9.88 (s, 1 H, CHO)[a]

[a] ^{1}H NMR spectra were recorded in $CDCl_3$.

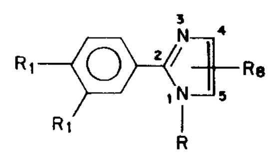
Table III. 4,5-Dihydro-6-(1-alkyl-2-aryl-1*H*-imidazol-4(or 5)-yl)-3(2*H*)pyridazinones

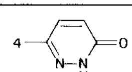
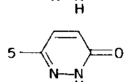
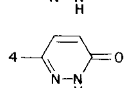
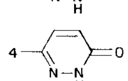


compd	R	R_1	R_7	formula	yield, %	mp,[b] °C	crystn solvent	UV, λ_{max} (ϵ)	IR (cm^{-1}) $\nu_{C=O}$	^1H NMR, δ
25a	CH_3	H		$C_{14}H_{14}N_4O$	30	271–272	C_2H_5OH	303 (26 000)	1672	2.40 (t, J = 7.0 Hz, CH_2-5′), 2.88 (t, J = 7.0 Hz, CH_2-4′), 3.80 (s, NCH_3), 10.80 (s, NH)
25b	CH_3	H		$C_{14}H_{14}N_4O$	23	214–215	EtOAc	290 (22 000)	1675	2.40 (t, J = 7.0 Hz, CH_2-5′), 2.95 (t, J = 7.0 Hz, CH_2-4′), 3.77 (s, NCH_3), 10.78 (s, NH)
26a	CH_3	OCH_3		$C_{16}H_{18}N_4O_3$	81	180–182	C_2H_5OH	238 (11 100), 298 (24 000)	1668	2.32 (t, J = 7.5 Hz, CH_2-5′), 2.88 (t, J = 7.5 Hz, CH_2-4′), 3.75 (s, NCH_3), 3.82 [s, 6 H, $(OCH_3)_2$], 10.75 (NH)
27a	$CH_2C_6H_5$	H		$C_{20}H_{18}N_4O{\cdot}HCl$	60	241–242	C_2H_5OH	292 (21 800)	1680	2.50 (t, J = 8.0 Hz, CH_2-5′), 3.00 (t, J = 8.0 Hz, CH_2-4′), 5.45 (s, 2 H, NCH_2), 8.35 (s, 1 H, H-5), 11.15 (s, 1 H, NH^+)

[a] Combined yield of **25a** and **25b** is 53%. [b] Melts with decomposition.

Table IV. 6-(1-Alkyl-2-aryl-1*H*-imidazol-4(or 5)-yl)-3(2*H*)-pyridazinones



compd	R	R_1	R_8	formula	yield, %	mp,[a] °C	crystn solvent	UV, λ_{max} (ϵ)	IR (cm^{-1}) $\nu_{C=O}$	^1H NMR, δ
28a	CH_3	H		$C_{14}H_{12}N_4O$	45	291–292	dioxane	277 (27 600)	1668, 1658	3.80, (s, NCH_3), 7.40 (d, J = 9.5 Hz, H-5′), 7.82 (d, J = 9.5 Hz, H-4′), 13.00 (s, NH)
28b	CH_3	H		$C_{14}H_{12}N_4O$	60	288–290	CH_3OH	269 (27 200)	1678, 1652	3.75 (s, NCH_3), 6.86 (d, J = 9.5 Hz, H-5′), 7.88 (d, J = 9.5 Hz, H-4′), 12.80 (s, NH)
29a	CH_3	OCH_3		$C_{16}H_{16}N_4O_3$	61	264–265	C_2H_5OH	208 (33 000), 271 (27 300)	1678, 1655	3.73, (s, NCH_3), 3.78 [s, 6 H, $(OCH_3)_2$], 3.80 (d, J = 9.5 Hz, H-5′), 7.80 (d, J = 9.0 Hz, H-4′), 12.72 (NH)
30a	$CH_2C_6H_5$	H		$C_{20}H_{16}N_4O$	45	239–240	C_2H_5OH	266 (27 800)	1678, 1655	5.32 (s, 2 H, NCH_2), 6.66 (d, J = 9.0 Hz, H-5′), 7.88 (d, J = 9.0 z, H-4′), 12.80 (s, NH)

[a] Melts with decomposition.

Table V. Cardiovascular Profile of Pyridazinones in Anesthetized Dogs

		% change		
compd (n)[a]	dose, mg/kg	dP/dt_{max}	heart rate	blood pressure
1a[b] (6)				
	0.01	10.2 ± 1.3	0 ± 1.2	−0.7 ± 0.4
	0.03	37.2 ± 8.0	5.6 ± 3.4	−4.1 ± 1.0
	0.10	74.2 ± 13.3	6.2 ± 5.8	−5.3 ± 1.6
	0.31	127.3 ± 25.0	19.2 ± 9.1	−13.2 ± 2.8
	1.0	146.7 ± 25.0	33.8 ± 17.0	−22.4 ± 2.8
2 (2)				
	0.01	35.0	1.5	−1.0
	0.03	82.5	12.5	−2.5
	0.10	119.5	31.5	−26.0
	0.31	111.5	30.5	−26.5
25a (2)				
	0.01	16.0	3.5	−1.2
	0.03	54.0	13.0	−5.0
	0.10	89.5	29.5	−11.8
	0.31	115.0	34.0	−23.2
	1.0	95.0	29.5	−31.8
25b (2)				
	0.01	7.0	3.0	1.75
	0.03	10.0	3.5	1.75
	0.10	11.0	4.5	1.50
	0.31	16.5	5.0	0.0
	1.0	30.5	5.5	−2.25
26a (2)				
	0.01	2	2.5	−1.0
	0.03	2.5	0.5	−1.25
	0.1	2.0	1.5	−0.25
	0.31	9.5	5.0	0
	1.0	0	8.5	1.5
27a (2)				
	0.01	2.5	2.0	1.0
	0.03	4.5	1.5	−0.5
	0.10	12.5	19.0	0
	0.31	10.5	18.5	−4.5
	1.0	3.0	8.0	−4.75
28a (2)				
	0.01	8.0	1.5	−1.5
	0.03	25.5	9.5	−0.25
	0.1	68.0	21.5	−6.5
	0.31	150.0	50.5	−15.75
	1.0	186.0	63.5	−31.25
28b (2)				
	0.01	2.0	−0.5	1.5
	0.03	5.0	−1.0	0.75
	0.1	8.0	−1.5	−1.75
	0.31	14.0	−3.0	−0.25
	1.0	17.0	−1.5	−2.5
29a (2)				
	0.01	3.5	1.5	0
	0.03	6.0	1.0	1.5
	0.1	4.5	−0.5	0
	0.31	5.0	−1.0	−1.0
	1.0	13.0	0.5	−4.5
30a (2)				
	0.1	21.0	3.0	8.5
	0.03	29.0	−1.0	6.5
	0.10	17.0	−1.0	8.0
	0.31	28.0	3.0	3.0
	1.0	55.0	8.0	2.0

[a] Values shown are the arithmetic mean of two separate experiments except for compound **1a**: n is the number of dogs. [b] Significant $p < 0.05$ compared to control.

μM, respectively). By contrast, compounds **25b** and **28b**, the 5-yl regioisomers, demonstrated only weak inhibitory effects.

In summary, structure–activity relationships of 6-(1H-imidazol-4(5)-yl)pyridazinones showed the potent positive inotropic activity resides in one regioisomer only, namely **25a** and **28a**, respectively. These compounds were not studied in depth because of their poor oral activity in conscious chronically instrumented dogs.

Table VI. IC_{50} Values on Type III of Guinea Pig Phosphodiesterase for 4,5-Dihydro-3(2H)-pyridazinones and 3(2H)-Pyridazinones

compd	IC_{50},[a] μM	compd	IC_{50},[a] μM
25a	12.1	**26a**	128.0
25b	38.0	**29a**	75.0
28a	8.0	**1a**	6.1
28b	160.0		

[a] IC_{50} values were determined by measuring the inhibiting effects of each agent over a concentration range of 1.0×10^{-7} to 1.0×10^{-4} M or 1.0×10^{-6} to 1.0×10^{-3} M for the less potent agents. Each value represents the mean of two to four experiments using different preparations of phosphodiesterases and were calculated from the dose–response curve.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded (Me_2SO-d_6 unless otherwise stated) on a Varian EM 390 and XL 200 spectrometer with Me_4Si as an internal standard. IR spectra were recorded on a Nicolet FT-IRMS-1 or FT-IR2 OSX spectrophotometer. Mass spectra were obtained on a Finnigan 1015 Quadrupole mass spectrometer. UV spectra were recorded in CH_3OH on a Cary 118 UV–visible recording spectrophotometer. TLC were performed on silica gel G (Stahl), and the plates were visualized with UV light and/or I_2 vapor. The elemental analyses (C, H, and N) for all new compounds were within ±0.4% of theory.

2-(3,4-Dimethoxyphenyl)-1*H*-imidazole-4-methanol (5, Table I). HCl gas was bubbled for 30 min into a cooled solution of 50.0 g (0.307 mol) of 3,4-dimethoxybenzonitrile in 550 mL of anhydrous methanol and the solution allowed to stand overnight at 23 °C. The resulting white crystals of methyl 3,4-dimethoxybenzenecarboximidate hydrochloride (24.9 g) were collected, mp 163–164 °C. On addition of 300 mL of ether to the mother liquor, a second crop of 18.3 g (total yield: 61%) was obtained, mp 163–164 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.03 [s, 3 H, Ar C(NH)OCH_3], 3.78 [s, 6 H, Ar (OCH_3)$_2$]. Anal. ($C_{10}H_{13}NO_3$·HCl) C, H, N.

A solution of 24.7 g (0.106 mol) of the above imidate and 9.31 g (0.11 mol) of 1,3-dihydroxyacetone in 90 g of anhydrous ammonia was heated at 68 °C for 4 h at 420 psi. After cooling, excess ammonia was removed, the solution was poured into 1 L of cold water, and the resulting solid was filtered to give 18.1 g (76%) of **5**, mp 176–177 °C dec. Crystallization from acetonitrile gave **5** as white crystals, mp 177–178 °C dec.

General Procedure for Alkylation of 2-Aryl-1*H*-imidazole-4-methanols (Table I). 1-Methyl-2-phenyl-1*H*-imidazole-4-methanol (4). To a stirred solution of 7.0 g (0.04 mol) of 2-phenyl-1H-imidazole-4-methanol (**3**)[3] and 11.2 g (0.2 mol) of finely powdered potassium hydroxide in 100 mL of anhydrous N,N-dimethylformamide was added 6.2 g (0.044 mol) of iodomethane and the mixture was heated at 55 °C for 5 h. The TLC (chloroform–methanol, 4:1) showed the absence of starting material (R_f 0.25), the new product appearing as a single spot of R_f 0.45. The solution was evaporated in vacuo, and the residue was dissolved in cold water and extracted twice with 250 mL of ethyl acetate. The combined extracts were washed, dried over Na_2SO_4, and evaporated. Chromatographic purification of the crude residue over 100 g of silica gel (using EtOAc–ether (1:1) as the eluent) afforded 3.4 g of pure single isomer **4**.

By use of an identical procedure, the dimethoxy analogue **5** was converted to the corresponding 1-methyl derivative **6**. The 1-(phenylmethyl) homologue **7** was also obtained from **5** and benzyl bromide by the above procedure.

General Procedure for Oxidation of 1*H*-Imidazole-4-methanols (3–7, Table II). 1-Methyl-2-phenyl-1*H*-imidazole-4-carboxaldehyde (9a). A rapidly stirred mixture of 0.7 g (0.04 mol) of **4** and 5.0 g (0.04 mol) of MnO_2 (Aldrich Chemical Co.) in 30 mL of dry tetrahydrofuran was heated under reflux for 1.5 h and subsequently allowed to stir overnight at 23 °C. The solid was filtered and washed with 75 mL of tetrahydrofuran. The filtrate was evaporated in vacuo and the residue crystallized to give 0.5 g (71%) of **9a**.

General Procedure for Alkylation of 2-Aryl-1*H*-imidazole-4-carboxaldehydes (8 and 10, Table II). 1-Methyl-2-phenyl-1*H*-imidazole-4-carboxaldehyde (9a) and 1-Methyl-2-phenyl-1*H*-imidazole-5-carboxaldehyde (9b). Method A. To a stirred solution of 15.3 g (0.089 mol) of 8 and 5.3 g (0.098 mol) of sodium methoxide in 150 mL of anhydrous *N,N*-dimethylformamide was added 13.9 g (0.098 mol) of iodomethane dropwise at 23 °C over a period of 15 min and the solution allowed to stir for 6 h. After the solution was evaporated under reduced pressure, the residue was taken up in cold water and extracted twice with 150 mL of ethyl acetate. The combined extracts were dried over Na_2SO_4, concentrated, and filtered to give 8.7 g of a solid which was a mixture of both isomers (**9a** and **9b**), mp 95–101 °C. Passing the filtrate through silica gel gave 3.1 g (total yield: 71%) of additional products (**9a** and **9b**), mp 95–102 °C.

Method B. A solution of 100 mL of 30% aqueous potassium hydroxide was added to a vigorously stirred suspension of 5.2 g (0.03 mol) of 8 in 100 mL of dichloromethane, followed by dimethyl sulfate (4.1 g, 0.036 mol) and 0.5 g of Adogen 464 (Aldrich Chemical Co.). After 2 h at 23 °C, the two phases were separated, and the aqueous phase was extracted with 100 mL of dichloromethane. The combined extracts were dried (Na_2SO_4) and evaporated to give 4.1 g of a residue which solidified on standing. The TLC (chloroform–methanol–NH_3, 90:10:1) showed two spots, R_f 0.5 and 0.6, corresponding to two isomers **9a** and **9b**, respectively.

Separation and Characterization of Isomers 9a and 9b. A solution of 4.6 g of the above mixture of **9a** and **9b** in diethyl ether was passed through 100 g of silica gel and the column was eluted with ether–hexane (1:1). Crystallization of the combined evaporated residue from diisopropyl ether gave 0.6 g of the pure regioisomer 1-methyl-2-phenyl-1*H*-imidazole-5-carboxaldehyde (**9b**). The column was further eluted with ether–ethyl acetate (1:1) and the residue from the evaporated fractions was crystallized to give 1.1 g of pure 1-methyl-2-phenyl-1*H*-imidazole-4-carboxaldehyde (**9a**). This product was identical in all respects with the product obtained by oxidation of 4.

α-(1-Methyl-2-phenyl-1*H*-imidazol-4-yl)-4-morpholineacetonitrile (13a) and α-(1-Methyl-2-phenyl-1*H*-imidazol-5-yl)-4-morpholineacetonitrile (13b). A solution of 12.1 g (0.186 mol) of potassium cyanide in 12 mL of water was added to a stirred warm (40 °C) solution of 33.7 g (0.181 mol) of a mixture **9a** and **9b**, 34.5 g (0.181 mol) of *p*-toluenesulfonic acid monohydrate, and 31.2 g (0.362 mol) of morpholine in 200 mL of dry dioxane and the resulting mixture was heated under reflux for 1.5 h. After cooling to room temperature, the mixture was poured into 500 mL of 10% aqueous potassium carbonate solution and extracted twice with 500 mL of dichloromethane. The combined extracts were washed successively with saturated aqueous sodium bisulfite solution and water, dried (Na_2SO_4), and evaporated. The cakelike residue was crystallized from ether, giving 42.2 g (83%) of a mixture of **13a** and **13b**, mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 2.62 [m, 4 H, N(CH_2)$_2$], 3.70 [m, 9 H, O(CH_3)$_2$ and NCH_3], 4.74 (s, CHCN), 4.80 (s, CHCN), 7.10–7.65 (m, 6 H, 5 H, aromatic and H-4 and H-5); mass spectrum, *m/e* 282. Anal. ($C_{16}H_{18}N_4O$) C, H. N.

By following the procedure described above, two additional acetonitrile derivatives were obtained: **α-[2-(3,4-dimethoxyphenyl)-1-methyl-1*H*-imidazolyl-4-yl]-4-morpholineacetonitrile (14a)** [mp 111–112 °C; UV (CH_3OH) λ_{max} 261 nm (ε 14 750); ^{1}H NMR ($CDCl_3$) δ 4.78 (s, 1 H, C*H*CN), mass spectrum, *m/e* 342. Anal. ($C_{18}H_{22}N_4O_3$), C, H, N] and **α-[2-phenyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]-4-morpholineacetonitrile (15a)** [mp 143–144 °C; UV (CH_3OH) δ max 253 nm (ε 10 410); ^{1}H NMR ($CDCl_3$) δ 2.63 (t, *J* = 4.5 Hz, 4 H, N(CH_2)$_2$, 3.73 (t, *J* = 4.5 Hz, 4 H, O(CH_2)$_2$, 4.78 (s, 1 H, H-5), 5.13 (s, 2 H, NCH_2), 6.90–7.50 (m, 10 H, aromatic); mass spectrum, *m/e* 358. Anal. ($C_{22}H_{22}N_4O$) C, H, N].

2-(1-Methyl-2-phenyl-1*H*-imidazol-4-yl)-2-(4-morpholinyl)pentanedinitrile (16a) and 2-(1-Methyl-2-phenyl-1*H*-imidazol-5-yl)-2-(4-morpholinyl)pentanedinitrile (16b). 2-Propenenitrile, 6.0 g (0.113 mol) was added dropwise to a solution of 21.0 g (0.0745 mol) of a mixture of **13a** and **13b** in 175 mL of dry tetrahydrofuran containing 5 mL of 30% methanolic potassium hydroxide at 23 °C and the mixture was allowed to stir for 2 h. The ^{1}H NMR spectrum showed the absence of the protons at δ 4.74 and 4.80 (corresponding to the mixture of **13a** and **13b**) and IR showed two cyano functions at 2220 and 2228 cm^{-1}, indicating the formation of **16a** and **16b**. Since attempted crystallization failed, the above mixture was used in the next step.

Similarly, **2-[2-(3,4-dimethoxyphenyl)-1-methyl-1*H*-imidazol-4-yl]-2-(4-morpholinyl)pentanedinitrile (17a) and 2-(4-morpholinyl)-2-[2-phenyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]pentanedinitrile (18a)** were obtained, starting from **14a** and **15a**, respectively.

1-Methyl-γ-oxo-2-phenyl-1*H*-imidazole-4-butanenitrile (19a) and 1-Methyl-γ-oxo-2-phenyl-1*H*-imidazole-5-butanenitrile (19b). A solution of the crude mixture of 17.5 g of **16a** and **16b** was heated with 75 mL of 80% aqueous acetic acid on a steam bath for 2 h and subsequently was evaporated in vacuo. The residue was taken up with cold aqueous potassium bicarbonate solution and extracted twice with 500 mL of dichloromethane. The combined organic extracts were washed, dried (Na_2SO_4), and evaporated to dryness. Crystallization of the residue from 2-propanol gave 6.1 g (68%) of a mixture of **19a** and **19b** as white crystals, mp 98–100 °C. Anal. ($C_{14}H_{13}N_3O$) C, H, N.

2-(3,4-Dimethoxyphenyl)-1-methyl-γ-oxo-1*H*-imidazole-4-butanenitrile (20a) was obtained from **17** in 71% yield: mp 163–164 °C; UV (CH_3OH) λ_{max} 263 nm (ε 11 950); IR (KBr) 2225 (CN), 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.72 (t, *J* = 6.5 Hz, 2 H, CH_2CN), 3.45 (t, *J* = 6.5 Hz, 2 H, CH_2C=O), 3.78 (s, 3 H, NCH_3), 3.94 [s, 6 H, (OCH_3)$_2$], 6.87–7.35 (m, 3 H, aromatic), 7.65 (s, 1 H, H-5); mass spectrum, *m/e* 229. Anal. ($C_{16}H_{17}N_3O_3$) C, H. N.

γ-Oxo-2-phenyl-1-(phenylmethyl)-1*H*-imidazole-4-butanenitrile (21a) was similarly obtained, mp 89–90 °C; UV (CH_3OH) λ_{max} 260 nm (ε 8200); IR (KBr) 2241 (CN), 1671 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.67 (t, *J* = 7.0 Hz, 2 H, CH_2CN), 3.40 (t, *J* = 7.0 Hz, 2 H, CH_2CO), 5.15 (s, 2 H, NCH_2), 6.90–7.50 (m, 10 H, aromatic), 7.5, (s, 1 H, H-5); mass spectrum, *m/e* 315. Anal. ($C_{20}H_{17}N_3O$) C, H, N.

1-Methyl-γ-oxo-2-phenyl-1*H*-imidazole-4-butanoic Acid (22a). A crude mixture of 17.5 g of the dinitriles **16a** and **16b** was heated with 40 mL of 20% hydrochloric acid at 100 °C for 6 h. After the solution was evaporated in vacuo, the residue was taken up in cold 20% sodium hydroxide to pH 10.0, and the nonacidic materials were extracted with ethyl acetate, and discarded. The alkaline solution was treated with glacial acetic acid at 0 °C to pH 5.5, causing partial precipitation of the solid. Recrystallization of the latter from ethyl acetate gave analytically pure **22a**, mp 191–192 °C; UV (CH_3OH) λ_{max} 275 nm (ε 20 000); IR (KBr) 1705 (CO_2H), 1668 (Ar C=O) cm^{-1}; ^{1}H NMR Me_2SO-d_6) δ 2.55 (t, *J* = 6.0 Hz, 2 H, CH_2CO_2H), 3.10 (t, *J* = 6.0 Hz, 2 H, Ar $COCH_2$), 3.80 (s, 3 H, NCH_3), 7.35–7.80 (m, 5 H, aromatic), 8.20 (s, 1 H, H-5), 12.00 (br, 1 H, CO_2H); mass spectrum, *m/e* 258. Anal. ($C_{14}H_{14}N_2O_3$), C, H, N.

The mother liquor and aqueous solution contained mixture of both isomers (**22a** and **22b**).

2-(3,4-Dimethoxyphenyl)-1-methyl-γ-oxo-1*H*-imidazole-4-butanoic Acid (23a). A solution of 2.1 g (0.007 mol) of **20a** in 40 mL of 20% hydrochloric acid and 25 mL of 1-propanol was heated under reflux for 5 h and subsequently evaporated to dryness in vacuo. The residue was taken up in cold water, adjusted to pH 6.5 with $NaHCO_3$, and filtered to give 1.8 g of crude **23a**, mp 196–198 °C dec. Recrystallization from ethyl acetate gave pure **23a** as white crystals, mp 200–201 °C dec; UV (CH_3OH) λ_{max} 246 nm (ε 12 000), 294 (18 330); IR (KBr) 1712 (CO_2H), 1665 (Ar C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 262 (t, *J* = 6.5 Hz, 2 H, CH_2CO_2H), 3.10 (t, *J* = 6.5 Hz, 2 H, Ar $COCH_2$), 3.82 (s, 9 H, (CH_3)$_3$), 6.85–7.18 (m, 3 H, aromatic), 7.82 (s, 1 H, H-5), 11.90 (br s, CO_2H). Anal. ($C_{16}H_{18}N_2O_5$) C, H, N.

4,5-Dihydro-6-(1-methyl-2-phenyl-1*H*-imidazol-4-yl)-3-(2*H*)-pyridazinone (25a) and 4,5-Dihydro-6-(1-methyl-2-phenyl-1*H*-imidazol-5-yl)-3(2*H*)-pyridazinone (25b; Table

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III). A crude mixture of 13.0 g (0.05 mol) of **22a** and **22b** in 150 mL of ethanol and 25 mL of glacial acetic acid was treated with 12 mL (0.22 mol) of 85% hydrazine hydrate at 85 °C for 6 h and then allowed to stand overnight at room temperature. The solid was collected and washed successively with water, cold ethanol, and ether, giving 4.2 g of **25a**. The filtrate was made slightly basic (pH 8.0) with ammonium hydroxide and extracted three times with 150 mL of ethyl acetate. The combined extracts were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated, giving 2.7 g of **25b**.

4,5-Dihydro-6-[2-phenyl-1-(phenylmethyl)-1*H*-imidazol-4-yl]-3(2*H*)-pyridazinone (27a). A solution of 3.1 g (0.01 mol) of **21a** in a mixture of 20 mL of 1-propanol and 30 mL of 20% aqueous HCl was refluxed for 4 h to give γ-oxo-2-phenyl-1-(phenylmethyl)-1*H*-imidazole-4-butanoic acid (**24a**). After the solution was concentrated to a volume of 15 mL, 3 mL (0.051 mol) of 85% hydrazine hydrate was added and the mixture was refluxed for 3 h. The reaction mixture was cooled and filtered to give 2.2 g of crude **27a**, which was recrystallized to give 1.7 g of analytically pure **27a**.

General Procedure for the Preparation of 3(2*H*)-Pyridazinones from the Corresponding 4,5-Dihydro-3-(2*H*)-pyridazinones (Table IV). 6-(1-Methyl-2-phenyl-1*H*-imidazol-4-yl)-3(2*H*)-pyridazinone (28a). A vigorously stirred mixture of 2.2 g (0.0085 mol) of **25a** and 12 g (0.142 mol) of MnO_2 (Aldrich Chemical Co.) in dioxane (175 mL) was heated at 70 °C for 22 h. Additional quantity of MnO_2 (8 g) was added and heating continued for an additional 5 h. The mixture was filtered and washed with hot dioxane and finally with warm tetrahydrofuran. The combined filtrate and washings were concentrated to yield 0.9 g of **28a** as off-white crystals.

Pharmacological Methods. Anesthetized Dog Model. Adult mongrel dogs of either sex were anesthetized with pentobarbital, 35 mg/kg, iv, and were subsequently maintained under anesthesia with a continuous infusion of pentobarbital, 5 mg kg^{-1} h^{-1}. A cannula was inserted into the femoral vein for administering test agents. A Millar catheter tip pressure transducer was inserted into the ascending aorta via the femoral artery for measuring aortic blood pressure. Another similar transducer was passed into the left ventricle via the left carotid artery for measuring left ventricular blood pressure. Needle electrodes were placed subcutaneously for recording a Lead II electrocardiogram (ECG). Heart rate, using a biotachometer triggered from the R wave of the ECG, and the first derivative of left ventricular blood pressure (dP/dt), obtained with a differentiator amplifier coupled to the corresponding pressure amplifier, were also recorded. A period of 30 min was utilized to obtain control data prior to administration of test agent. Depending on solubility of the agent, compounds were dissolved in 0.9% saline solution or in dilute HCl or NaOH (0.1 or 1.0 N) and were diluted to volume with normal saline. Each dose of the test agent was administrated in a volume of 0.1 ml/kg over a period of 1 min in a cumulative manner. Usually, half-log intervals were maintained between doses with typical dosing consisting of four to six doses (for example, 0.01, 0.03, 0.1, 0.3, 1.0 mg/kg) in order to establish any dose–response relationships. A 10–30-min interval was used between doses for the variables to reach a steady state. Only one compound was administered to any one animal. The inotropic activity of a compound was determined by measuring changes in dP/dt_{max} of left ventricular pressure from preceding base line. Data for only one compound is expressed as means ± SEM. All others are arithmatic means of two experiments. Statistical analysis of the data was performed with use of a Student's t test for paired or unpaired data. The probability value $p < 0.05$ was accepted as level of significance.

Isolation of Phosphodiesterases and Assay of Activity. The isolation of different forms of cardiac phosphodiesterase and their characterization was done by following the procedure of Thompson.[8] The three molecular forms of PDE (type I, type II, and type III) present in guinea pig left ventricular tissue were discretely eluted from a DEAE column using a sodium acetate gradient. Cross contamination was eliminated by chromatography of pooled fractions of each peak. Following complete separation, the combined phosphodiesterase fractions were concentrated to 14% of the original volume, diluted to 65% with ethylene glycol monoethyl ether, and stored at −20 °C (no significant change in hydrolytic activity was observed with storage of up to 6 weeks).

In evaluating the inhibiting effect of the different agents examined on type I, type II, and type III cardiac phosphodiesterases, the enzyme concentration in the assay was adjusted to ensure that reaction velocity was linear for 30 min at 30 °C, and that hydrolysis of substrate ([^{3}H]cyclic AMP or [^{3}H]cyclic GMP) did not exceed 10–20% of the available substrate in the absence of any inhibitor. The concentration of substrate was 1.0 μM for these studies. All agents examined were dissolved in dimethyl sulfoxide (Me_2SO). The final concentration of Me_2SO in the reactions medium was 2.5%. This concentration of Me_2SO inhibited enzyme activity by approximately 10%. IC_{50} values (the concentration that produces 50% inhibition of substrate hydrolysis) were determined from concentration–response curves that ranged from 10^{-7} to 10^{-4} M for the more potent inhibitors and from 10^{-5} to 10^{-3} M for the less potent inhibitors (half-log increments). Two to four such concentration–response curves were generated for each agent, typically using different enzyme preparations for each concentration–response curve.

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Registry No. 3, 43002-54-6; 4, 99280-78-1; 5, 53292-69-6; 6, 99280-79-2; 7, 99280-80-5; 8, 68282-47-3; **9a**, 94938-02-0; **9b**, 94938-03-1; **10a**, 99280-82-7; **11a**, 99280-83-8; **11b**, 99280-84-9; **12a**, 99280-85-0; **13a**, 94938-04-2; **13b**, 94938-05-3; **14a**, 99280-86-1; **15a**, 99280-87-2; **16a**, 99280-88-3; **16b**, 99280-89-4; **17a**, 99280-90-7; **18a**, 99280-91-8; **19a**, 94938-06-4; **19b**, 94938-07-5; **20a**, 99280-92-9; **21a**, 99280-93-0; **22a**, 94938-08-6; **22b**, 95402-88-3; **23a**, 99280-94-1; **24a**, 99280-96-3; **25a**, 94938-09-7; **25b**, 94937-82-3; **26a**, 99280-95-2; **27a**, 99280-97-4; **28a**, 94937-83-4; **28b**, 94937-84-5; **29a**, 99280-98-5; **30a**, 99280-99-6; 2-propenenitrile, 107-13-1; 3,4-dimethoxybenzonitrile, 2024-83-1; methyl 3,4-dimethoxybenzenecarboximidate hydrochloride, 99280-81-6; 1,3-dihydroxyacetone, 96-26-4.