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Original paper

Cardiotonic agents. 10. Cardiovascular evaluation of dihydropyridazinone ring open analogues of imazodan

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Summary — Several series of 4,5-dihydropyridazinone ring (A-ring) open analogues of imazodan (CI-914) were prepared and evaluated for inotropic activity in an anesthetized dog model. Although the overall cardiovascular profile of the acylhydrazone series was similar to the corresponding cyclic analogues, the inotropic potency was significantly reduced. The guanylhydrazone series demonstrated enhanced inotropic potency that was comparable to 4,5-dihydropyridazinones (DHPZ). Although these acyclic analogues qualitatively fit a 5-point model developed for several cyclic inotropes, at least partly, the inotropic mechanism of the guanylhydrazones seems to be different from the corresponding acylhydrazones and cyclic 4,5-dihydropyridazinones.

Résumé — **Agents cardiotoniques. 10. Evaluation cardiovasculaire des analogues à noyau dihydropyridazinone.** *Plusieurs séries d'analogues de l'imazodan, ouverts au niveau du cycle dihydro-4,5 pyridazinone (cycle A), ont été préparés. Leur activité inotrope a été évaluée dans un modèle de chien anesthésié. Bien que, dans son ensemble, le profil cardiovasculaire de la série des acylhydrazones soit semblable à celui des analogues cycliques correspondants, l'activité inotrope est considérablement réduite. La série des guanylhydrazones démontre une activité inotrope accrue et comparable aux dihydro-4,5 pyridazinones (DPHZ).*

Ces analogues acycliques vérifient qualitativement un modèle à cinq points dérivé de l'étude de plusieurs inotropes cycliques; il apparaît cependant que le mécanisme inotrope des guanylhydrazones est, au moins en partie, distinct de celui des acylhydrazones correspondantes et des dihydro-4,5 pyridazinones cycliques.

imazodan (analogues) / dihydropyridazinone (derivatives) / acylhydrazones / guanylhydrazones / cardiovascular / cardiotonic / inotropic activity

Introduction

One traditional approach to the treatment of heart failure is the enhancement of myocardial contractility with the administration of inotropic drugs to improve depressed cardiac function. Recent advances in this area have revealed the importance of vasodilator therapy that reduces preload and impedance as an additional and / or adjunct therapy [1, 2, 3]. Examples of the first generation of newer non-glycoside, non-catecholamine cardiotonics with mixed inotropic / vasodilator activity are amrinone, milrinone, imazodan, CI-930, enoximone and piroximone (Chart 1). Although these new inotropic drugs can stimulate the failing ventricle and improve hemodynamics, their influence on the natural history of heart failure is not clear, and the impact of these agents on medical practice is unknown [4]. In order to develop novel cardiotonics, we analyzed these inotropes by both qualitative and quantitative structure–activity methods and molecular modeling techniques, and considered a variety of spatially and electronically similar entities. In this paper, the synthesis and pharmacological activities of several 4,5-dihydropyridazinone ring (DHPZ, A-ring) open analogues that emerged from these analyses are reported.

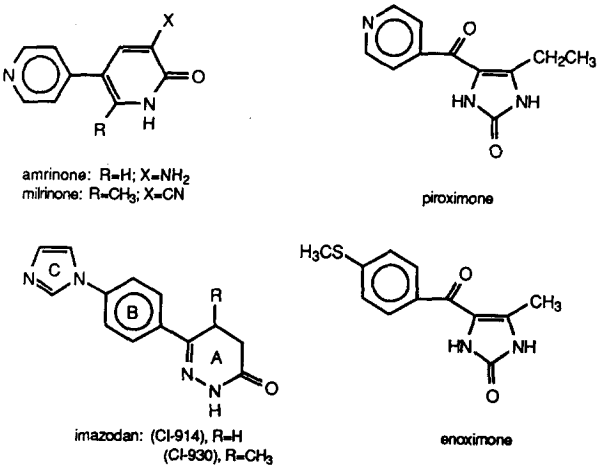


Chart I.

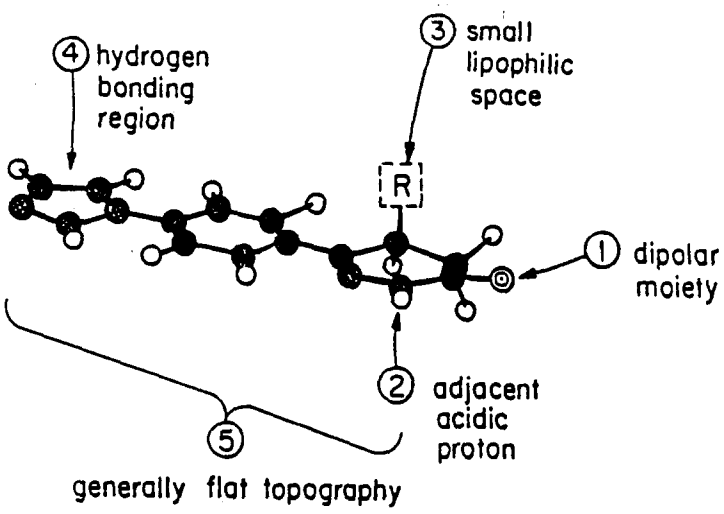
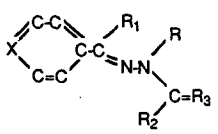


Fig. 1. Five-point model for positive inotropic activity.

A 5-point model that was developed for potent inotropic activity is shown in Figure 1. This qualitative model originally [5] suggested that the following characteristics may be important for cardiotonic activity mediated through PDE inhibition: (1) a dipolar moiety at one end of the molecule (C=0); (2) an adjacent acidic proton (NH); (3) a potential hydrogen bonding region at the other end of the molecule; (4) a generally flat topography of the molecule (excepting milrinone); and (5) a small lipophilic space in the mid-region between the dipole and the hydrogen bonding region. The model was later refined in terms of cAMP, the natural substrate for cAMP PDE [6].

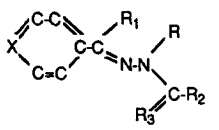
The A-ring open analogues (Tables I–III) fit the conformational, topographical, and electronic requirements of this model in a qualitative sense. Thus a series of these compounds was prepared and evaluated for positive inotropic activity.

It is noted that A-ring open analogues will have considerably greater flexibility relative to pyridazinone, pyridone, or imidazolone cardiotonics. The resulting differences in molecular geometry could, in principle, result in altered activity. In fact, preferred conformations of the A-ring open portion of the molecules described herein should prefer anti-syn or anti-anti orientations for the reasons described below.



C=N-N-C anti
R-N-C=R$_3$ syn

anti-syn



C=N-N-C anti
R-N-C=R$_3$ anti

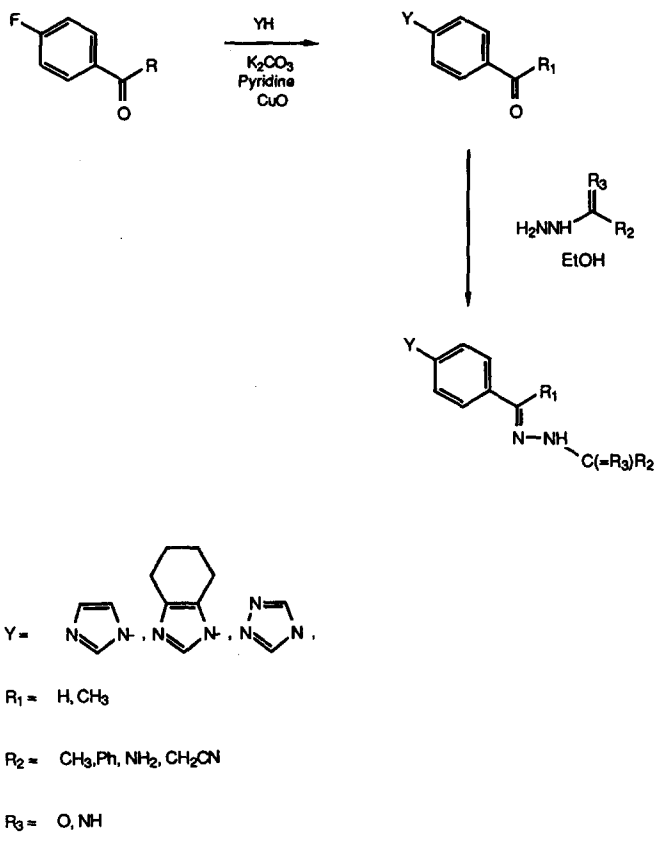
anti-anti

A search of the Cambridge Crystallographic Database (59,263 entries) uncovered 20 unique cases with coordinates containing the acyclic substructure C=N-N-C=O. These compounds were about equally split between anti-syn and anti-anti. Anti-syn and anti-anti orientations displayed X...R_3 distances of 8.6 and 7.2 angströms, respectively. Eight compounds with the acyclic substructure C=N-N-C=N were found, all with anti C=N-N-C geometry. The R-N-C=R_3 geometry was ambiguous. Anti-syn and anti-anti orientations displayed X...R_3 distances of 8.8 and 7.3 angströms, respectively.

For comparison, cardiotonics of the pyridazinone, pyridone, and imidazolone classes have X...R_3 distances of 8.2 [6a], 8.3 [7], and 8.7 [8] angströms, respectively, based on X-ray crystallographic data. It is suggested, based on these data, that the cardiotonic activity of A-ring open compounds in this article may result more from the anti-syn than the anti-anti orientation.

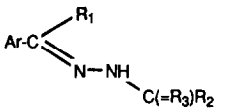
Chemistry and biological Discussion

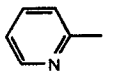
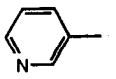
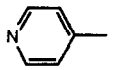
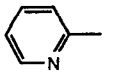
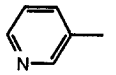
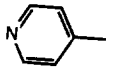
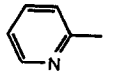
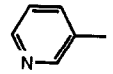
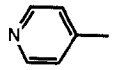
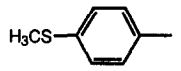
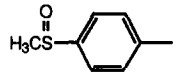
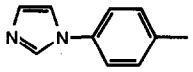
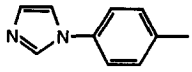
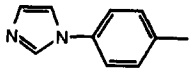
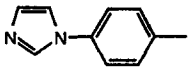
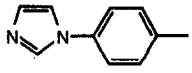
The A-ring open analogues (Tables I and II) were prepared by reaction of the requisite carbonyl compounds with the corresponding side chains, such as semicarbazide hydrochloride, acylhydrazines, and aminoguanidine acid salts, preferably in the presence of mild base. Yields of the products varied from 25–92% (Scheme 1).



Scheme 1.

Table I. A-ring open analogues of 4,5-dihydropyridazinones – acylhydrazone derivatives.

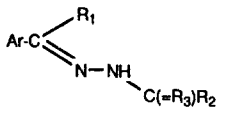


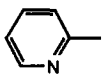
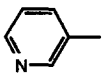
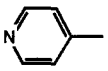
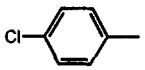
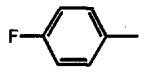
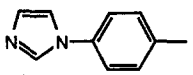
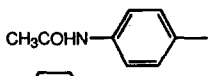
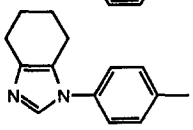
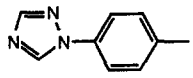
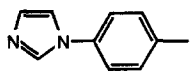
Cmpd. No.	Ar	R_1	R_2	R_3	Yield,[a] %	Mol Formula	mp, °C[b]	Dose (mg/kg) to cause 50% increase in LV dP/dt_{max}
1		H	CH_3	0	75	$C_8H_9N_3O$	127.5-128.5	>3.1
2		H	CH_3	0	70	$C_8H_9N_3O$	154-155	>3.1
3		H	CH_3	0	68	$C_8H_9N_3O$	163-164	>3.1
4		CH_3	CH_3	0	60	$C_9H_{11}N_3O$	162-163	0.31
5		CH_3	CH_3	0	62	$C_9H_{11}N_3O$	132-133	0.50
6		CH_3	CH_3	0	65	$C_9H_{11}N_3O$	176-177	0.31
7		CH_3	C_6H_5	0	60	$C_{14}H_{13}N_3O$	147.5-149	>3.1
8		CH_3	C_6H_5	0	58	$C_{14}H_{13}N_3O$	160.5-162	>3.1
9		CH_3	C_6H_5	0	62	$C_{14}H_{13}N_3O$	172.5-173.5	>3.1
10[d]		CH_3	CH_3	0	68	$C_{11}H_{14}N_2OS$	173-174	-
11[d]		CH_3	CH_3	0	85	$C_{11}H_{14}N_2O_2S$	176-178	-
12		CH_3	CH_3	0	78	$C_{13}H_{14}N_4O$	209-210	2.0
13[d]		CH_3	CH_2CN	0	68	$C_{14}H_{13}N_5O$	216-217 (dec)	-
14[d]		H	CH_2CN	0	56	$C_{13}H_{11}N_5O$	209-209 (dec)	-
15		H	NH_2	0	70	$C_{11}H_{11}N_5O$	232-233 (dec)	>3.1
16		CH_3	NH_2	0	70	$C_{12}H_{13}N_5O$	240-241	>3.1

[a]Yields were not optimized. [b]Compounds were recrystallized from ethanol. [c]Data shown are arithmetic mean of two determinations obtained from a dose–response curve. [d]Data could not be obtained due to poor solubility.

Selected compounds from Tables I and II were evaluated for inotropic activity in an anesthetized dog model [9]. The dose of each compound required to increase myocardial contractility (derived by measuring dP/dt_{max}) by 50% (ED_{50}) was recorded from a dose–response curve (Tables I and II). The inotropic activities of the cyclic compounds are included in Table III for comparison. Table I lists compounds that are true A-ring open analogues of the 4,5-dihydropyridazin-3(2*H*)-ones (DHPZ). The pyridyl series appears to be more potent than the (imidazol-1-yl) phenyl series. For example, compare the ED_{50} value of **12** (2.0) *vs.* **6** (0.31) and **5** (0.5). The potencies of the acyclic compounds are comparable to respective cyclic analogues, [10] and **6** (ED_{50} = 0.31) is almost as potent as **27** (ED_{50} = 0.5). By contrast, A-ring open (imidazol-1-yl)phenyl analogues are substantially less potent than the corresponding DHPZ. Compounds **2** and **3** (desmethyl analogues of **5** and **6**) showed very weak activity, as expected. The structure–activity relationships (SAR) did not follow the trend observed in other classes of cyclic inotropes. This dis-

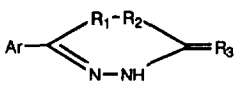
Table II. A-ring open analogues of 4,5-dihydropyridazinones - guanylhydrazone derivatives (continued).

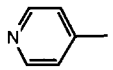
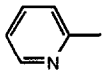
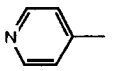
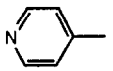
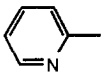
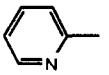
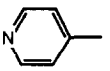
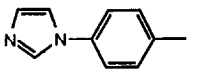
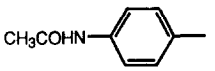
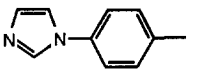


Cmpd. No.	Ar	R_1	R_2	R_3	Yield,[a] %	Mol Formula	mp, °C[b]	Dose (mg/kg) to cause 50% increase in LV dP/dt_{max}
17		H	NH_2	NH	55	$C_7H_9N_5 \cdot HNO_3$ 0.3 H_2O	143-147 (dec)	1.0
18		H	NH_2	NH	50	$C_7H_9N_5 \cdot HNO_3$	239-240	>1.0
19		H	NH_2	NH	78	$C_7H_9N_5 \cdot HNO_3$	>235	1.0
20		H	NH_2	NH	63	$C_8H_9ClN_4 \cdot HNO_3$	211-214	>1.0
21		H	NH_2	NH	92	$C_8H_9FN_4 \cdot HNO_3$	206-207	>1.0
22		H	NH_2	NH	52	$C_{11}H_{12}N_6 \cdot CH_2O_3$	239-242	0.3
23		H	NH_2	NH	50	$C_{10}H_{13}N_5O \cdot HNO_3$	238-239	0.08
24		H	NH_2	NH	60	$C_{15}H_{18}N_6 \cdot HNO_3$	166-168	0.5
25		H	NH_2	NH	75	$C_{10}H_{11}N_7 \cdot HNO_3$	237-237.5 (dec)	1.0
26		CH_3	NH_2	NH	25	$C_{12}H_{14}N_6 \cdot HNO_3$	255-258 (dec)	0.1

a, b, c See Table I.

Table III. Cyclic analogues of 4,5-dihydropyridazinones (continued).



Cmpd. No.	Ar	R_1	R_2	R_3	Yield,[a] %	Mol Formula	mp, °c[b]	Dose (mg/kg) to cause 50% increase in LV dP/dt_{max}
27		CH_2	CH_2	O		$C_9H_9N_3O$	189-190	0.5
28		CH_2	CH_2	O		$C_9H_9N_3O$	182-183	>1.0
29		$(CH_3)CH$-	CH_2	O		$C_{10}H_{11}N_3O$	155-156.5	0.03
30		$(CH_3)CH$-	CH_2	NH		$C_{10}H_{12}N_4$	214-216	>3.1
31		$(CH_3)CH$-	CH_2	O		$C_{10}H_{11}N_3O$	122-123	0.2
32		$(CH_3)CH$-	CH_2	NH		$C_{10}H_{12}N_4$	190-192	>3.1
33		CH_2	$(C_6H_5)CH$	O		$C_{15}H_{13}N_3O$	223-224	3.1
34		CH_2	CH_2	O		$C_{13}H_{12}N_4O$	206-207	0.045
35		CH_2	CH_2	O		$C_{12}H_{13}N_3O_2$	249-251	0.01
36		$(CH_3)CH$-	CH_2	O		$C_{13}H_{15}N_3O_2$	237-238	0.013

[a, b, c] See Table I.

crepancy may be explained on the following basis: the optimum distance between the polar group (C=O) on one end and the hydrogen accepting moiety on the other end of the molecule was not achieved in the case of the acyclic imidazol-1-yl analogues [11].

However, other possibilities such as differing conformational flexibilities or altered molecular geometrics exist. Guanylhydrazone derivatives [12] prepared as a modification of the acylhydrazones are listed in Table II. These compounds are significantly more potent than the acylhydrazones, but still less potent than DHPZ analogues. Compounds **22** and **23** are 8 times less potent than the corresponding cyclic DHPZ **34** and **35** (see Table IV). The SAR of this series follows the same trend as imazodan and other series of analogues, with the acetamido analogue **23** being the most potent [13]. The importance of the methyl group was also evident in this series. Compound **26** is 3 times more potent than **23** and one-tenth as potent as **36**. The semicarbazone derivatives, **15** and **16** obtained by replacement of the imino group with oxygen in the guanylhydrazone series, demonstrated very weak inotropic activity. By contrast, cyclic series oxygen analogues were more potent thant the imino derivatives (compare **29** and **31** with **30** and **32**, respectively). This is the first report of cardio-

Table IV. Comparative effects of cyclic *versus* acyclic analogues on cardiovascular function in anesthetized dogs.

Compound No.	Dose (mg / kg)	% Change from control[a]		
		Heart rate (HR)	Mean arterial blood pressure (MABP)	LV dP / dt_{max}
5	0.1	2.0	−1.0	9.0
	0.31	−2.0	−2.5	23.0
	1.0	−1.0	−4.0	78.0
	3.1	9.0	−9.0	137.0
6	0.1	7.0	−3.0	31.0
	0.31	9.0	−5.0	48.0
	1.0	12.0	−5.0	70.0
	3.1	8.0	−1.0	74.0
12	0.1	−1.0	−1.0	3.0
	0.31	2.0	−1.0	8.0
	1.0	1.0	−1.5	20.0
	3.1	7.0	−2.5	75.0
22	0.01	1.0	2.0	2.0
	0.03	−2.0	2.5	11.5
	0.1	−6.0	4.5	62.0
	0.31	−2.5	15.0	224.0
23	0.01	1.0	4.0	3.0
	0.03	5.0	8.0	18.0
	0.1	−3.0	4.0	16.0
	0.31	−7.0	13.5	56.0
	1.0	−47.0	66.0	111.0
26	0.01	0	1.5	5.0
	0.03	−1.0	−1.0	23.0
	0.1	−3.0	−1.0	59.0
	0.31	6.0	7.0	109.0
	1.0	21.0	16.0	121.0
27	0.1	−5.0	−3.5	12.5
	0.31	2.0	−4.5	36.5
	1.0	2.0	−10.0	60.0
	3.1	10.0	−29.0	153.5
34	0.01	0±1.2	−0.7±0.4	10.2±1.3
	0.03	5.6±3.4	−4.1±1.0	37.2±8.0
	0.1	6.2±5.8	−5.3±1.6	74.2±13.3
	0.31	19.2±9.1	−13.2±2.8	127.3±25.0
	1.0	33.8±17.0	−22.4±2.8	146.7±25.0
35	0.003	5±2	2±1	18±2
	0.01	7±2	−1±2	44±4
	0.03	19±5	−10±2	85±8
	0.1	33±6	−21±3	126±17
	0.3	52±15	−19±2	148±21
36	0.001	2.5±2.1	2.1±1.9	10.5±9.0
	0.003	5.6±3.6	1.0±2.1	24.6±4.2
	0.01	6.0±5.3	−1.7±1.1	50.6±11.2
	0.03	25.2±8.2	−7.4±1.3	124.0±29.4
	0.10	43.8±12.0	−19.0±1.3	148.5±22.5

[a]Values shown are the arithmetic mean of 2 separate experiments. For compounds **34**–**36**, values are expressed as the mean ± SEM ($n = 6$). Significant at $P<0.05$ compared to control.

vascular activity of the semicarbazone derivatives, although antitumor activity of 2-acetylpyridine thiosemicarbazones [14] has been claimed.

The cardiovascular profiles of several active compounds from the acylhydrazone and guanylhydrazone series are shown in Table V. The activity profile of the former series was similar to respective cyclic analogues. Compounds **5**, **6**, and **12** produced dose-related increases in myocardial contractility (dP/dt_{max}), associated with small increases in heart rate (HR) and slight decreases in mean arterial blood pressure (MAP). In contrast, guanylhydrazones **22**, **23** and **26** produced dose related increases in dP/dt_{max} associated with slight decreases in HR and slight increases in MAP.

The inotropic response to **23** was blocked in the presence of propranolol in anesthetized dogs (data not shown) in contrast to results obtained previously with imazodan and analogues, where inotropic responses were attenuated but not blocked in presence of propranolol [9]. These results suggest neurotransmitter release activity for **23** involving cardiac adrenergic receptors. Compound **23** demonstrated a weak ($IC_{50} > 1$ μM) inhibitory effect on crude PDE, isolated from guinea pig ventricle. Thus, it appears that the mechanism of inotropic action of guanylhydrazone **23** (and presumably other A-ring open analogues) is somewhat different from the cyclic DHPZ. A detailed study was not undertaken to define the mechanism of action of these agents, although from a structural similarity with guanabenz [15, 16], a central alpha$_2$ agonist profile seems reasonable for the inotropic activity.

Conclusion

Given the modest size of this series of analogues, it is difficult to develop a detailed SAR, but some interesting trends have emerged. In the pyridyl series, inotropic activity is retained in A-ring opened analogues, and the potencies of these 2 series are comparable. In the imidazol-1-ylphenyl series, inotropic activity in ring opened analogues is significantly reduced. In the case of guanylhydrazones, the inotropic activity is enhanced in both the pyridyl and substituted phenyl series and the potencies are comparable with the cyclic pyridazinones. However, the mechanism of action of the guanylhydrazones seems to be somewhat different from the 4,5-dihydropyridazinones.

Experimental protocols

Melting points were uncorrected and were taken on a Thomas–Hoover capillary melting point apparatus. IR and ^{1}H NMR spectra of all new compounds were consistent with the proposed structures. Elemental analyses were within 0.4% of theory unless otherwise stated. The imidazol-1-yl carbonyl compounds were prepared from the corresponding fluoro analogues by following the literature procedure [9]. All other carbonyl compounds were obtained from commercial sources. 4,5-Dihydro-6-(pyridinyl)-3(2*H*)-pyridazinones (Table III) were prepared by following a patent procedure [10]. The syntheses of corresponding (imidazol-1-yl) phenylpyridazinones **34** and **36**, and acetylaminophenylpyridazinone **35** have been reported previously [9]. Molecular modeling (SYBYL) and Cambridge Crystallographic Database (CAMBRIDGE) work was performed as previously described [6a, 17].

General procedure for the synthesis of substituted hydrazones (Tables I–III).

*Example 1. Carbonohydrazonic diamide, N''-[[4-(4,5,6,7-tetrahydro-1H-benzimidazol-1-yl)phenyl]methylene]-, mononitrate (**24** Table II)*

A mixture of 3.4 g (15 mmol) of 4-(4,5,6,7-tetrahydro-1*H*-benzimidazol-1-yl)benzaldehyde and aminoguanidine nitrate (2 g, 15 mmol) in a mixture of EtOH / H_2O (30 / 10 ml) was heated at reflux for 12 h. The reaction mixture was cooled and the precipitate was filtered. The residue was washed successively with EtOH / H_2O mixture and ether, and air-dried to give 4.75 g of the crude product. This was recrystallized from 120 ml of methanol to give 3.0 g of the title compound.

IR (KBr); 1625, 1680 (C=NH) and 3180–3325 (NH_2) cm^{-1}. ^{1}H NMR (Me_2SO-d_6); ppm 1.8 (br, 4H) and 2.5 (br, 4H) (tetrahydrobenzimidazole), and 7.5–8.4 (m, 9H, aromatics and N*H*'s).

*Example 2. Acetamide, N-[4-[[(aminoiminomethyl)hydrazono]methyl]-phenyl]-, mononitrate (**23**, Table II)*

A solution of 84 g (0.613 mol) of aminoguanidine nitrate and 100 g (0.613 mol) of *p*-acetamidobenzaldehyde in a mixture of DMF / H_2O (500 / 1800 ml) was heated at 50–60°C for 1 h. The brown solution was filtered and allowed to cool. The brown crystals were filtered, washed with EtOH, and air-dried to provide 85.4 g of the desired product.

IR (KBr); 1630, 1670 (C=NH and $COCH_3$) and 3180–3325 (NH_2) cm^{-1}. ^{1} NMR (Me_2SO-d_6); ppm 2.0 (s, 3H, $NHCOCH_3$), 7.3–8.1 (m, 9H, aromatics and NH's), and 10.1 (s, 1H, N*H*$COCH_3$).

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