Synthesis and Spectra of Some Triazolo and Triazinophthalazines of Possible Hypotensive Activity

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Cyclization of hydralazine **1** with acid chlorides or ethyl cyanoacetate gave the appropriate *s*-triazolo derivatives, while with ketoesters or 1,2-dicyclohexanedione it afforded the *as*-triazino derivatives. Reaction of **1** with ketosteroids yielded hydrazones. Preliminary cardiovascular testing revealed possible hypotensive activity of some of these derivatives.

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Hydralazine is a potent antihypertensive agent, but it has been found to possess serious side-effects and care must be taken in case of prolonged administration especially with coronary patients [2]. In continuation of our previous work [3-8] some new phthalazine derivatives with triazolo or triazino residue were prepared for testing as possible hypotensives.

Condensation of the key intermediate 1-hydrazinoph-

Scheme I

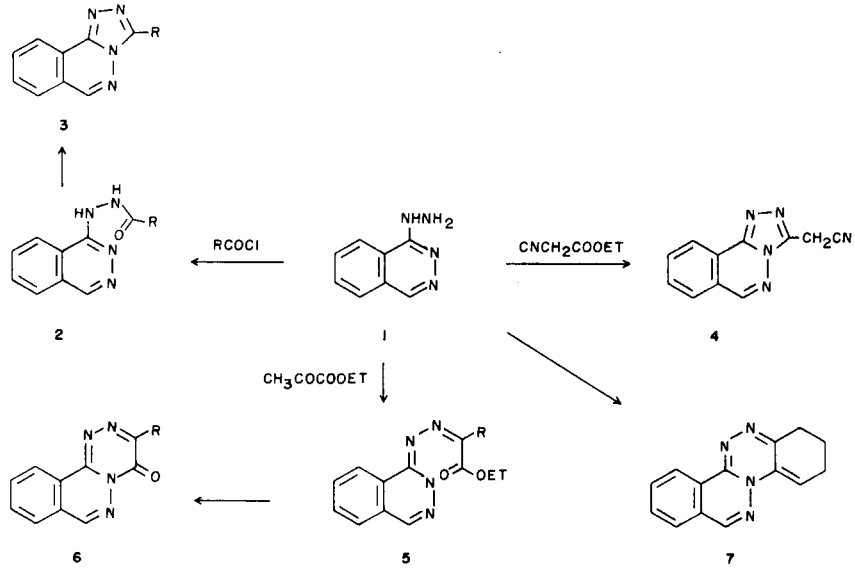


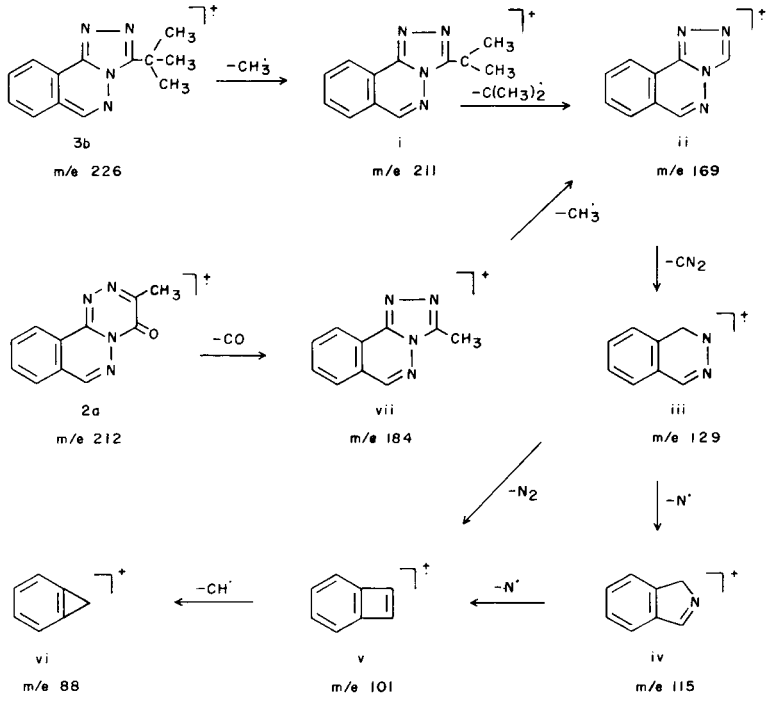
Table 1

Triazolo- and Triazinophthalazines

Compound No.	R	Yield %	Mp °C	Formula	Calcd. % C	H	N	Found % C	H	N
2b	$(CH_3)_3C$	90	252	$C_{13}H_{16}ClN_4O$	58.8	5.7	20.0	59.9	5.8	20.1
2c	C_6H_5	92	230	$C_{15}H_{12}ClN_4O$	60.1	4.0	18.7	60.0	4.1	18.6
2d	$4\text{-}CH_3C_6H_4$	94	242	$C_{16}H_{14}ClN_4O$	61.2	4.4	17.8	60.0	4.2	17.6
2e	$3\text{-}ClC_6H_4$	85	180	$C_{15}H_{11}Cl_2N_4O$	53.9	3.3	16.8	53.6	3.3	16.7
3a	CH_3	85	173 [a]	$C_{10}H_8N_4$	65.2	4.3	30.4	65.1	4.5	30.6
3b	$(CH_3)_3C$	84	190	$C_{13}H_{14}N_4$	69.0	6.2	24.3	69.2	6.3	24.9
3c	C_6H_5	70	214 [b]	$C_{15}H_{10}N_4$	73.2	4.1	22.7	73.4	4.2	22.6
3d	$4\text{-}CH_3C_6H_4$	80	213	$C_{16}H_{12}N_4$	73.8	4.6	21.5	73.8	4.7	21.7
3e	$3\text{-}ClC_6H_4$	82	230	$C_{15}H_9ClN_4$	64.2	3.2	19.9	64.4	3.4	20.0
4	CH_2CN	55	190	$C_{11}H_7N_5$	63.1	3.3	33.5	63.0	3.2	33.3
5	CH_3	88	125	$C_{13}H_{14}N_4O_2$	60.4	5.4	21.7	60.3	5.2	21.2
6a	CH_3	75	258 [c]	$C_{11}H_8N_4O$	62.3	3.8	26.4	62.4	3.7	26.6
6b	CH_2Br	60	235	$C_{11}H_7BrN_4O$	45.3	2.4	19.2	45.1	2.3	19.1

[a] Lit [11], 171-172°. [b] Lit [11], 208-209°. [c] Lit [9], 252.

Scheme II



thalazine **1** with different acid chlorides, afforded the corresponding acyl hydrazide hydrochlorides **2** which readily cyclized in hot pyridine to the 3-substituted *s*-triazolo-[3,4-*a*]phthalazines **3** (Scheme I).

Consistent with the assigned structure the ir spectra of the acyl hydrazides **2** exhibited a secondary amide carbonyl absorption at 1650-1665 cm^{-1}, which is lacking in the ir spectra of the cyclic derivatives **3**. The ^1H nmr spectra (Table 2) of the triazolo derivatives **3** showed two multiples in the regions δ 8.0-8.2 and 8.7-9.0 for the phthalazine residue. Their ^{13}C nmr spectra were recorded (Table 2) and agreed with the suggested structures. Further confirmation of the structure of the triazoles **3** is derived from their mass spectral data. The mass spectrum of **3b** showed the molecular ion peak at m/e 226. Other peaks are observed at m/e 211, 169, 129, 155, 101 and 88 which could be assigned to some of the fragments shown in Scheme II. The base peak at m/e 211 is formulated as the ion **i** formed by loss of CH_3 radical from the molecular ion. **i** on losing the radical $(CH_3)_2C$ yield the species **ii** at m/e 169. The ion radical **ii** loses CN_2 to give **iii** at m/e 129. Elimination of N atom from **iii** gave the cation **iv** at m/e 115, while loss of the N_2 molecule yield the species **v** at m/e 101, which on loss of CH radical gave the cation **vi** at m/e 88.

Condensation of hydralazine **1** with ethyl cyanoacetate afforded 3-cyanomethyl-*s*-triazolophthalazine **4**. In agreement with the suggested structure, the ir spectra of **4** exhibited a strong CN absorption at 2250 cm^{-1}. Its ^1H nmr spectrum showed a methylene singlet at δ 4.6 as well as the two multiplets of the phthalazine residue at δ 8.9 and 8.2. Its ^{13}C nmr spectrum exhibited the two signals of the CN and CH_2 at δ 109.6 and 14.5 respectively.

It has been reported that hydralazine reacts with pyru-

Scheme III

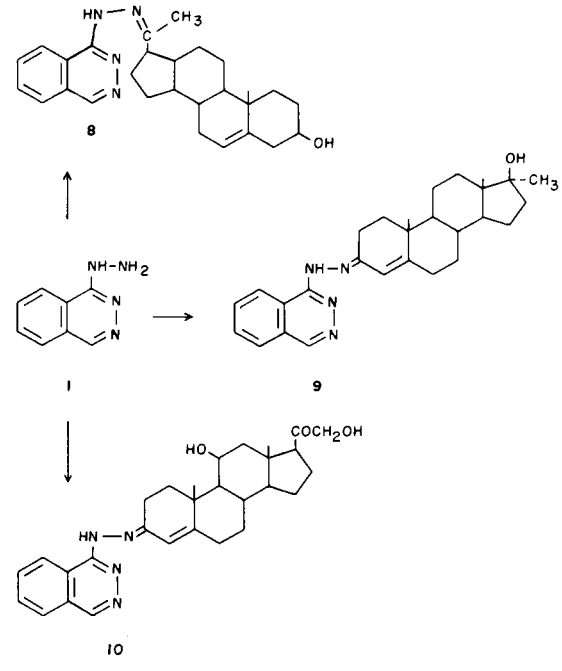


Table 2

NMR Spectra [a] of Phthalazine Derivatives

Compound No.	R	^{1}H NMR Phthalazines and Aromatic H [b]	Others	^{13}C NMR Phthalazines and Aromatic C	Others
1				122.0, 126.3, 131.2, 131.6, 140.3, 153.8	
3b	$(CH_3)_3C$	8.0, 8.7	1.7 (s, $3CH_3$)	122.5, 122.6, 127.5, 130.2, 133.2, 146.0, 155.0	32.6 ≡C, 27.3 $(CH_3)_3$
3c	C_6H_5	7.5, 8.2, 8.8		100.2, 111.6, 121.2, 123.0, 126.3, 131.4, 131.7, 134.4, 136.8, 137.9, 154.6	
3d	4-$CH_3C_6H_4$	7.4, 8.2, 9.0	2.4 (s, CH_3)	119.8, 120.4, 123.6, 124.3, 128.5, 128.9, 129.7, 133.4, 135.4, 143.0, 150.2	21.5 (CH_3)
3e	3-ClC_6H_4	7.6, 8.15, 8.7		118.8, 120.3, 121.4, 123.0, 124.8, 127.5, 127.8, 129.6, 132.4, 135.4, 135.3, 136.2, 140.2, 154.0	
4		8.2, 8.9	4.6 (s, CH_2)	121.1, 122.5, 123.4, 129.4, 131.6, 134.7, 142.9, 149.2	109.6 (CN), 14.5 (CH_2)
5 [c]	CH_3	7.7, 8.0, 8.6	1.3 (t, CH_3, J = 3 Hz), 2.3 (s, CH_3), 4.3 (q, CH_2, J = 3	124.9, 126.0, 127.5, 131.7, 132.6, 139.0, 148.4, 149.8, 151.7	13.3 (CH_3), 14.2 (CH_3), 61.2 (CH_2), 165.6 (CO)
6a	CH_3	8.0, 8.9	2.8 (s, CH_3)	124.6, 125.2, 125.7, 128.1, 134.8, 135.1, 149.5, 149.9, 156.8	17.5 (CH_3), 163 (CO)
6b	CH_2Br	8.15, 9.2	4.8 (s, CH_2)		
7		8.2, 8.7, 9.0	6.6 (t, CH=, J = 3 Hz), 2.0, 2.6 (m, cyclohexyl H)	122.2, 126.4, 130.3, 136.4, 136.8, 138.4, 148.2, 151.4	20.3, 25.6, 31.9, 99.2, 110.6, 118.9 (cyclohexyl C)

[a] Solutions in DMSO-d_6, δ in ppm. [b] Non-resolved multiplets. [c] Solutions in deuteriochloroform.

Table 3

Phthalazine Hydrazones

Compound No.	Yield %	Mp °C	Formula	Calcd. % C	H	N	Found % C	H	N	IR cm^{-1} OH	C=O	C=N
8	85	185	$C_{29}H_{35}N_4O_3$	71.4	7.2	11.5	71.1	7.0	11.3	3440	1700	1605
9	86	128	$C_{29}H_{38}N_4O$	76.0	8.3	12.2	75.8	8.3	12.1	3400		1610
10	80	240	$C_{28}H_{36}N_4O$	75.7	8.1	12.6	75.6	8.0	12.5	3420		1602

Table 4

NMR Spectral Data [1] of Phthalazine Hydrazones

Compound No.	^{1}H NMR Phthalazine H [b]	Steroid H [b]	Others	Phthalazine C	^{13}C NMR Steroid C	Others
8	7.8, 8.5	2.0	1.0 (CH_3), 1.4 (CH_3)	122.9, 125.0, 126.0, 130.3, 136.2, 157.7, 159.9	20.4, 22.9, 30.7, 32.7, 32.8, 33.7, 46.2, 51.1, 55.3, 66.8, 68.5, 87.8, 111.2, 119.5, 160.7	11.9 (CH_3), 16.3 (CH_3), 198.0 (CO)
9	7.6, 8.4	1.6	0.7 (CH_3), 1.0 (CH_3), 2.1 (CH_3)	123.9, 125.8, 127.4, 127.5, 131.4, 137.3, 140.7, 146.2	21.1, 23.7, 24.3, 32.0, 32.6, 36.5, 37.2, 38.9, 42.2, 43.9, 50.1, 56.7, 59.4, 71.6, 121.4, 165.2	13.4 (CH_3), 18.7 (CH_3), 19.4 (CH_3), 199.6 (CO)
10	7.7, 8.5	1.7	0.9 (CH_3), 1.2 (CH_3), 1.3 (CH_3)	123.9, 125.8, 127.6, 127.8, 132.4, 138.3, 143.7, 146.8	19.4, 21.1, 23.7, 24.3, 30.9, 32.1, 36.5, 37.2, 38.9, 42.2, 43.9, 50.1, 56.7, 59.4, 71.6, 121.4, 165.2	13.4 (CH_3), 18.8 (CH_3), 199.6 (CO)

[a] Solutions in deuteriochloroform in ppm, δ. [b] Non-resolved multiplets.

vic acid to yield the hydrazone acid which on heating cyclises to the corresponding triazolo derivative [9]. In the present work, we found that ethyl pyruvate reacts with **1** to give the corresponding hydrazone ester **5** or the *as*- triazino derivative **6a**, depending on the reaction conditions. However, the hydrazone **5** has been readily cyclized on heating to **6a**. With ethyl bromopyruvate the only product observed was the *as*-triazino derivative **6b**. The ir spectrum of the hydrazone **5** showed a strong ester carbonyl absorption at 1710 cm^{-1} as well as a weak NH band at 3335 cm^{-1}. On the other hand, the ir spectra of **6** exhibited a cyclic carbonyl absorption at 1685-1690 cm^{-1}. The ^1H nmr spectra of the hydrazone **5** showed the presence of an ethyl ester signals which is lacked in the spectra of the cyclic compounds **6**. Further evidence concerning the structure of the triazino derivative **6a** has been derived from its mass spectral data which gave the same pattern of fragmentation (Scheme II) as **3b** except of the first step which lead to ion **vii**. It gave a strong molecular ion peak at m/e 212, while the base peak is the m/e 115.

Reaction of hydralazine with 1,2-cyclohexanedione gave the *as*-triazino derivative **7**. Its structure was confirmed by ^1H and ^{13}C nmr spectra (Table 2).

On the other hand, condensation of **1** with pregenolone, 17-methyltestosterone or hydrocortisone gave the corresponding phthalazine hydrazones (Scheme III). The ir spectra of these hydrazones showed an NH absorption at 3335-3350 cm^{-1} as well as a CN absorption at 1602-1610 cm^{-1}. Their ^1H and ^{13}C nmr are recorded in Table 4.

Table 5

Comparative Study of the Effect of Similar Molar Concentration [a] of Some Tested Compounds With Hydralazine

Compound	Mean Reduction of Response [b], % ± SE
1	56.5 ± 1.3
2b	65.0 ± 1.2
3b	66.2 ± 1.5
4	65.1 ± 1.2
5	68.1 ± 1.4
6a	55.3 ± 1.1
7	67.4 ± 1.3

[a] The concentration used was 3×10^{-5} mole/ml. Aqueous solutions were used. [b] Average of three experiments.

EXPERIMENTAL

The ^1H nmr spectra were recorded with a Varian EM 360L spectrometer using TMS as internal standard. The ^{13}C nmr spectra were recorded on Jeol JNM-FX 100 NMR Spectrometer. The ir spectra were obtained using sodium chloride plates on a Perkin-Elmer 297 spectrophotometer as a solution in bromoform. Mass spectra were recorded on a Kratos MS 30. Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected.

3-Substituted *s*-Triazolo[3,4-*a*]phthalazine (**3**) (Table 1).

1-Hydrazinophthalazine (0.4 g, 0.001 mole) was heated on a water bath with the appropriate acid chloride (0.0015 mole) for one hour. The acyl hydrazides that separated out in the form of the hydrochlorides were recrystallized from methanol in needles (Table 1). Cyclization to 3-substituted *s*-triazolophthalazine was performed by refluxing these acylhydrazides (0.001 mole) in dry pyridine (8 ml) for 1-2 hours. The reaction mixture was then poured into 10% sodium carbonate solution and the solid which separated was recrystallized from methanol in needles; ms: m/e (relative intensity) (compound **3b**) M^+ 226 (43), 225 (16), 212 (15), 211 (100), 169 (5), 129 (10), 117 (5), 115 (8), 114 (2), 102 (5), 101 (2), 89 (8), 88 (5), 83 (7), 77 (2), 44 (19), 28 (76), 27 (10).

Reaction of Hydralazine with Ethyl Pyruvate (Table 1).

(a) Phthalazine Hydrazone Ester (**5**).

A solution of **1** (0.4 g, 0.001 mole) in ethanol (15 ml) was refluxed with ethyl pyruvate (0.15 g, 0.0015 mole) for one hour. The reaction mixture was then concentrated to yield a yellow solid of the hydrazone which recrystallized from ethanol in yellow needles; ir (bromoform): 1710 cm^{-1} (CO), 3335 (NH).

(b) 3-Methyl-4-oxo-*as*-triazino[3,4-*a*]phthalazine (**6a**).

A solution of **1** (0.4 g, 0.001 mole) in ethanol (15 ml) was refluxed with ethyl pyruvate (0.15 g, 0.0015 mole) for 6 hours. The reaction mixture was then concentrated to yield white solid which recrystallized from benzene in needles; ir (bromoform): 1690 cm^{-1} (CO); ms: m/e (relative intensity) M^+ 212 (96), 184 (43), 170 (10), 169 (14), 156 (9), 129 (34), 128 (19), 116 (12), 115 (100), 114 (23), 102 (22), 101 (9), 88 (26), 77 (5), 28 (39), 27 (27).

The same compound **6a** was also prepared (45%) when **5** was heated at 105° in nitrogen atmosphere for 4 hours. After cooling the residue treated with methanol to give the desired compound.

3-Bromomethyl-4-oxo-*as*-triazino[3,4-*a*]phthalazine (**6b**).

A solution of **1** (0.4 g, 0.001 mole) in ethanol (15 ml) was refluxed with ethyl bromopyruvate (0.2 g, 0.001 mole), for 3 hours. The reaction mixture on concentration yielded an orange red solid of the cyclized compound **6b**. This crude product was recrystallized from benzene to give orange needles; ir (bromoform): 1685 cm^{-1} (CO).

3-Cyanomethyl-*s*-triazolo[3,4-*a*]phthalazine (**4**) (Table 1).

A solution of **1** (0.4 g, 0.001 mole) in ethanol (20 ml) was refluxed with ethyl cyanoacetate (2.0 ml) for 8 hours. The reaction mixture was then poured into ice-cold water, when a yellow solid separated out. It was recrystallized from ethanol in yellow needles; ir (bromoform): 2250 cm^{-1} (CN).

Reaction of Hydralazine with 1,2-Cyclohexanedione (**7**).

A solution of **1** (0.4 g, 0.001 mole) in ethanol (10 ml) was refluxed with 1,2-cyclohexanedione (0.15 g, 0.0015 mole) for 24 hours. The reaction ws then poured into water and the solid separated out was recrystallized (0.13 g, 22%) from ethanol as needles, mp 210°.

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.2; H, 5.1; N, 23.7. Found: C, 71.2; H, 5.0; N, 23.4.

Phthalazine Hydrazones (Table 3).

A solution of **1** (0.4 g, 0.001 mole) in ethanol (15 ml) was refluxed with the ketosteroids (0.001 mole) for 2 hours. The reaction mixture on concentration afforded yellow solids, which were purified by recrystallization from ethanol to yield yellow needles of the corresponding hydrazones.

Biological Testing.

The cardiovascular activity of **2b, 3b, 4, 5, 6a** and **7** was examined using the blood pressure response of chloroalose-urethane anesthetized cats. The compounds were injected into the femoral vein and the blood pressure was recorded from the carotid artery. The experiments revealed a marked hypotensive activity for all tested compounds. The most pro-

nounced effect was produced by **6a**. This effect could not be blocked by atropine indicating that it was not mediated through cholinergic nerve fibres but might have been due to a direct vasodilating effect on smooth muscles, an effect similar to that known for **1** [10].

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