Synthesis and Antihypertensive Properties of a Novel Series of 3-Substituted Amino-*s*-triazolo[3,4-*a*]phthalazine Derivatives

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A novel series of 3-substituted amino-*s*-triazolo[3,4-*a*]phthalazine derivatives has been synthesized by the one-pot cyclodesulfurization reactions utilizing 1-hydrazinophthalazine, alkyl, aryl, or aralkylisothiocyanates and dicyclohexylcarbodiimide (DCCD) mixtures. The products did not exhibit any antihypertensive properties. Their pmr and mass spectral analysis is given.

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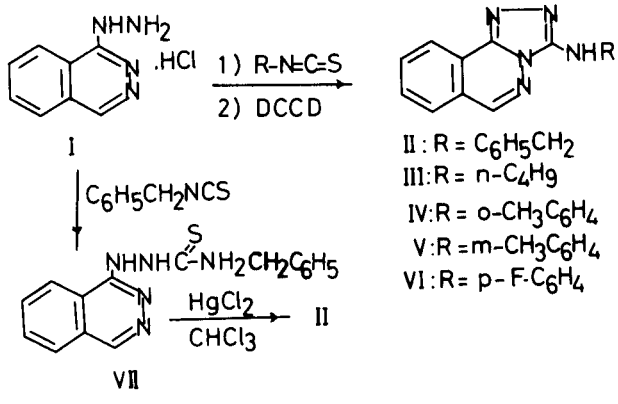
The synthetic studies of antihypertensive agents have shown that several structural modifications of 1-hydrazinophthalazine (I) (1), as substitution in the hydrazino function (2-4), in the ring (5,6), or cyclization into the *s*-triazolo[3,4-*a*]phthalazine system (6-8), proceed with retention of hypotensive activities. In addition, the introduction of a substituted amino function in the α-position of some heterocyclic rings was effective in inducing antihypertensive properties in the products (9). It was therefore of interest to study the preparation and antihypertensive effects of a new series of 3-substituted amino-*s*-triazolo-[3,4-*a*]phthalazines (Scheme I). The results are reported in this communication.



Scheme I

The synthesis of the designed compounds II-VI (Scheme I) was accomplished by application of the one-pot cyclodesulfurization method (10) recently established for the synthesis of various azoles (11) and benzotriazepinones (12) and extended to the preparation of some bridgehead nitrogen heterocyclics including imidazo[1,5-*a*]pyridine (13) and imidazo[1,5-*a*]benzimidazole derivatives (14). In the initial experiment, the mixture of 1-hydrazinophthalazine hydrochloride (I), sodium carbonate, and the equivalent amount of benzylisothiocyanate was heated briefly in ethanol, treated with 1.5 molar equivalent of DCCD and refluxed until completion of the reaction. The separation of 3-benzylamino-*s*-triazolo[3,4-*a*]phthalazine (II) was effected by evaporating the reaction mixture to dryness, heating the residue with excess dilute hydrochloric acid solution, extracting the insoluble part with benzene, and neutralizing the acid layer with sodium hydrogen carbonate. The reaction of butyl, *o*-tolyl, *m*-tolyl, or *p*-fluorophenylisothiocyanate, under the same conditions, with 1-hydrazinophthalazine (I) and DCCD gave the corresponding cyclized products III-VI in a rather poor yield (Table). The attempted use of cyclohexyl or *p*-chlorophenylisothiocyanate to prepare additional 3-substituted amino-*s*-triazolo[3,4-*a*]phthalazines was unsuccessful. The benzylamino derivative II could be also prepared through cyclodesulfurization of 4-benzyl-1-phthalazino-3-thiosemicarbazide (VII) (15) with mercuric chloride (16,17) but the yield was relatively lower than in the case of DCCD.

The cyclized products were isolated in the form of free bases, as hydrochlorides, or picric acid salts. Their structure was confirmed by elemental analysis, ir, pmr and mass spectra. In the pmr spectra, the N-H proton of the products appeared at various chemical shifts (Table) depending on the nature of substituent present. It resonated at 4.75 in the butyl III, at 4.07 in the benzyl II, at 7.68 in the hydrochloride salt of the *o*-tolyl IV, and at 9.42 ppm in the *p*-fluorophenyl VI hydrochloride derivative. The chemical shift of the C_6-H proton was also dependent on the nature of the product. It resonated at 8.34 in the benzyl and butyl derivatives II and III and at 8.86 ppm for the hydrochloride salts of the *o*-tolyl IV and the *p*-fluorophenyl VI derivatives.

The mass spectra of the compounds (Table) often showed the molecular ion peak as the base peak. A fragmentation pattern for all the compounds was found to be in agreement with that proposed for all 3-benzylamino-*s*-triazolo[3,4-*a*]phthalazine (II), Chart I. Compound II either eliminated HCN to give ion B at m/e 248 or suc-

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Table

Physical, Analytical, Pmr and Mass Spectral Data of 3-Substituted Amino-*s*-triazolo[3,4-*a*]phthalazines II-VI

Compound No.	State	M.p. °C (Crystallization Solvent)	Yield %	Formula	Analyses: Calcd./Found % C	H	N	Pmr (δ) ppm	Mass Spectra, m/e (Relative Intensities %)
II	free base	159-161 (ethanol)	62	$C_{16}H_{13}N_5$	69.80 69.89	4.76 5.10	25.40 25.60	4.85 (d, 2H, J = 6 Hz, -CH_2-, becoming singlet at 4.82 on deuteration), 5.07 (m, 1H, disappearing on deuteration, N-H), 7.43 (m, 5H, C_6H_5), 7.80 (m, 3H), C_7, C_8 and C_9-H), 8.34 (s, 1H, C_6-H), 8.54 (2d, 1H, J = 8 Hz, C_{10}-H)	M^+ at 275 (100), 274 (75), 260 (8), 249 (8), 248 (19), 232 (5), 198 (19), 184 (7), 171 (9), 156 (5), 146 (5), 145 (16), 132 (5), 131 (12), 130 (12), 129 (43), 128 (5), 117 (5), 116 (4), 115 (6), 106 (6), 104 (6), 103 (12), 102 (25), 92 (6), 91 (64), 90 (5), 89 (8), 77 (5), 76 (6), 75 (5), 65 (18), 51 (9), 50 (4)
II	picrate	201-202 (ethanol)		$C_{22}H_{16}N_8O_7$	52.38 52.30	3.20 3.60	22.22 22.16		
III	free base	120-121 (benzene/light petroleum ether)	51	$C_{13}H_{15}N_5$	64.71 64.54	6.27 6.12	29.03 29.40	1.02 (t, 3H, J = 6 Hz, CH_3-), 3.65 (q, 2H, J = 6 Hz, and 12 Hz, -CH_2CH_3), 4.75 (m, 1H, disappearing on deuteration, N-H), 7.77 (m, 3H, C_7, C_8 and C_9-H), 8.36 (s, 1H, C_6-H), 8.48 (2d, 1H, J = 8 Hz, C_{10}-H)	M^+ at 241 (43), 222 (10), 212 (17), 211 (12), 199 (30), 198 (81), 186 (26), 185 (100), 184 (12), 172 (12), 171 (19), 130 (41), 129 (53), 115 (12), 103 (76), 102 (57), 89 (15), 88 (13), 76 (21), 75 (20), 55 (20), 51 (15), 41 (36), 39 (16), 28 (19), 26 (19)
IV	free base	241-243 (ethanol)	30	$C_{16}H_{13}N_5$			25.44 25.70		
IV	hydrochloride	263-265 (ethanol)		$C_{16}H_{14}ClN_5$	61.60 61.98	4.54 4.42	22.40 22.60	2.42 (s, 1H, Ar-CH_3), 7.06 and 7.30 (2m, 4H, Tolyl-H), 7.68 (s, 1H, disappearing on deuteration, N-H), 8.02 (m, 3H, C_7, C_8, and C_9-H), 8.52 (2d, 1H, J = 6 Hz, C_{10}-H), 8.86 (s, 1H, C_6-H)	M^+ at 275 (100), 274 (35), 260 (8), 259 (9), 247 (9), 246 (9), 220 (9), 193 (7), 146 (48), 145 (23), 132 (18), 131 (61), 129 (26), 128 (57), 119 (26), 118 (76), 117 (22), 105 (24), 104 (70), 103 (45), 91 (39), 90 (35), 89 (41), 88 (17), 78 (16), 77 (24), 76 (28), 75 (24), 65 (46), 63 (25), 41 (30), 39 (30)
V	picrate	209-210 (ethanol)	30	$C_{22}H_{16}N_8O_7$	52.38 52.51	3.20 3.44	22.22 22.24		
VI	hydrochloride	231-233 (ethanol)	52	$C_{15}H_{11}ClFN_5$	57.10 56.92	3.52 3.20	22.10 22.31	7.1 and 7.57 (2m, 7H, Ar-H), 8.49 (d, 1H, J = 8 Hz, C_{10}-H), 8.85 (s, 1H, C_6-H), 9.42 (s, 1H, disappearing on deuteration N-H)	M^+ at 279 (100), 278 (25), 251 (15), 250 (10), 238 (10), 230 (21), 229 (39), 222 (17), 221 (25), 103 (81), 102 (29), 95 (36), 76 (19), 75 (42)

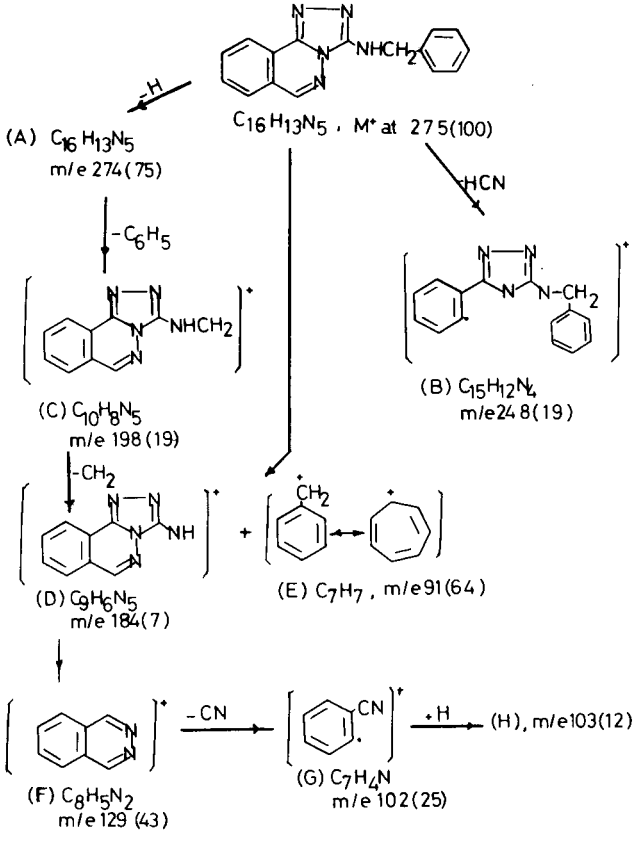

Chart I

cessively loses a phenyl and a methylene group giving ions C and D at m/e 198 and 184. The one-step elimination of the benzyl function from compound II was evidenced by the appearance of the tropylium ion E at m/e 91. Further fragmentation of the ion D produces the phthalazine ion F at m/e 129 and the phenylcyanide ion H at m/e 103. The compounds were tested for antihypertensive activity at 10 mg./kg. PO in conscious spontaneously hypertensive rats. None of them exhibited any activity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The pmr spectra were recorded on a Perkin-Elmer R-32 Spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) from TMS as the internal reference. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. The mass spectra were measured on an AEI Ms-50.

3-Substituted Amino-*s*-triazolo[3,4-*a*]phthalazines (II-VI) from the One-Pot Cyclodesulfurization of the Mixtures of 1-Hydrazinophthalazine Hydrochloride (I), Alkyl, Aryl, or Aralkylisothiocyanate and DCCD. General Procedure.

The mixture of 1-hydrazinophthalazine hydrochloride (I) (0.4 g., 0.002 mole), sodium carbonate (0.4 g., 0.003 mole) and the selected isothiocyanate derivative (0.002 mole) was heated under reflux in ethanol for 30 minutes. DCCD (0.62 g., 0.003 mole) was added and the mixture heated under reflux for 10 hours. Ethanol was evaporated and the residue boiled with excess 10% aqueous hydrochloric acid solution (50-70 ml.). After cooling, it was extracted with benzene, and the solvent evaporated to

afford dicyclohexylthiourea. In some experiments, the material remaining insoluble in both benzene and hydrochloric acid solution was filtered, crystallized from ethanol and identified as the hydrochloric salt of the product. The acidic layer was made distinctly alkaline with sodium hydrogen carbonate to separate the free bases of the products. They were crystallized from the proper solvents and identified by elemental analysis, pmr and mass spectra (Table); ir (Nujol): ν max 3400-3240 (NH) and 1635-1550 cm^{-1} (C=N and C=C).

3-Benzylamino-*s*-triazolo[3,4-*a*]phthalazine (II) through Cyclodesulfurization of 4-Benzyl-1-hydrazino-3-thiosemicarbazide (VII) with Mercuric Chloride.

The mixture of compound VII (0.3 g., 0.001 mole) and three molar equivalents of mercuric chloride in dry chloroform (50 ml.) was heated under reflux, while stirring, for 24 hours. Chloroform was evaporated, and the residue boiled with ethanol (20 ml.) containing 10% aqueous hydrochloric acid solution (30 ml.) and saturated with hydrogen sulfide gas. The mercuric sulfide formed was filtered, and the filtrate evaporated until all alcohol was removed. After cooling, it was extracted with benzene, the benzene was then removed to give the uncyclized products. The acidic layer was made distinctly alkaline with sodium hydrogen carbonate to separate compound II (50%) which was identified as mentioned in the above experiment.

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