Novel Ring Systems. Pyrazolo[1,5-*c*][1,3,5]benzotriazocin-5(4*H*)one and Pyrazolo[1,5-*c*][1,2,3,5]benzotetrazocin-5(4*H*)one Derivatives

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Received July 10, 1974

In connection with a larger synthetic program involving new types of polycondensed heterocycles of potential biological activity and in order to synthesize novel compounds pyrazolo[1,5-*c*][1,3,5]benzotriazocin-5(4*H*)one and pyrazolo[1,5-*c*][1,2,3,5]benzotetrazocin-5(4*H*)one derivatives, we decided to investigate the reactions of *N*-(3,4-R,R′-pyrazol-5-yl)-*o*-aminobenzamides (IVa,b,c) with triethyl orthoformate and nitrous acid.

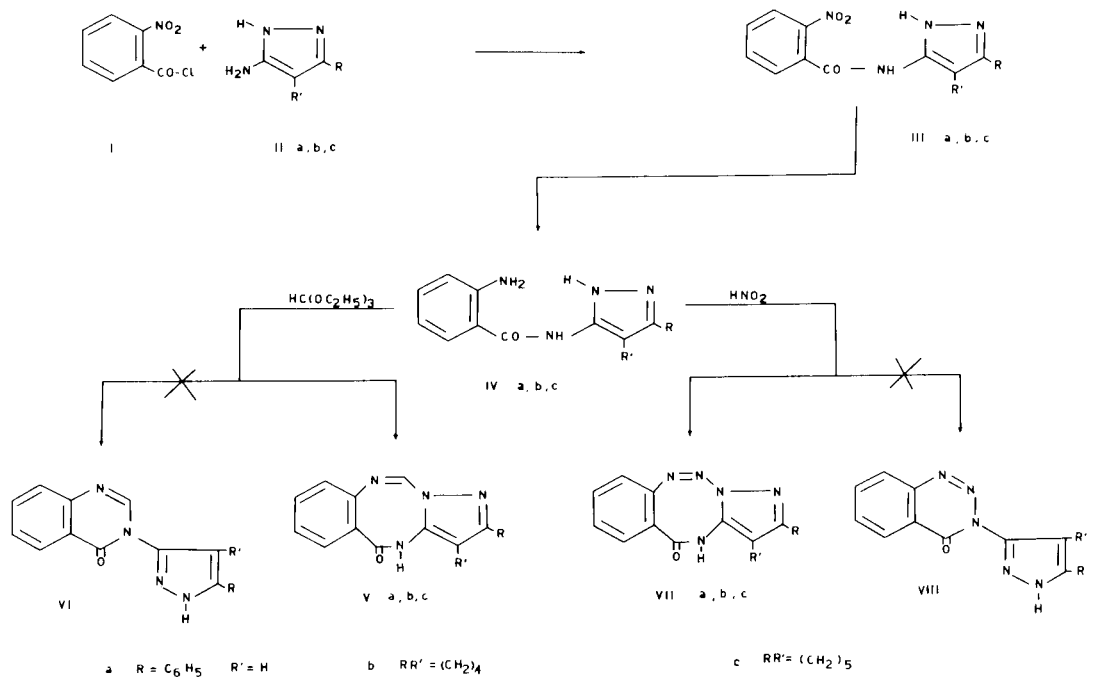
The compounds IVa,b,c, which are promising intermediates for the synthesis of these heterocyclic systems, were readily prepared by condensation of aminopyrazoles (IIa, b,c) with *o*-nitrobenzoyl chloride (I) followed by catalytic reduction on palladium on charcoal.

In the *N*-(3,4-R,R′-pyrazol-5-yl)-*o*-aminobenzamides, the amide and pyrazole NH groups, because of their different nature, possess different nucleophilic potential. Condensation of IVa,b,c with orthoformate and diazotisation may occur in two possible ways; 1) by reaction of the amino group and pyrazole NH to lead to eight member ring formation V and VII respectively; 2) reaction of the amino group and amide NH to form 3-substituted-*N*-quinazolinylpyrazoles of type VI and 3-substituted-*N*-benzo-1,2,3-triazinylpyrazoles of type VIII (Scheme I).

The elemental analysis of the obtained compounds were consistent with cyclic structures V and VII. Ir spectra (Nujol) showed absorption bands at 3100-3200 cm^{-1} (NH) and a strong band at 1680 cm^{-1} (CO), the presence in the nmr spectra (DMSO-d_6) of a singlet at 12.64-13.70 δ (1H) showed the presence of a mobile proton attributable to the NH of a cyclic amide structure. Moreover, these compounds exhibited acidic character. They were dissolved by dilute alkali and were precipitated unchanged by adding satured aqueous ammonium chloride.

The foregoing data does not permit a definite structural

SCHEME I



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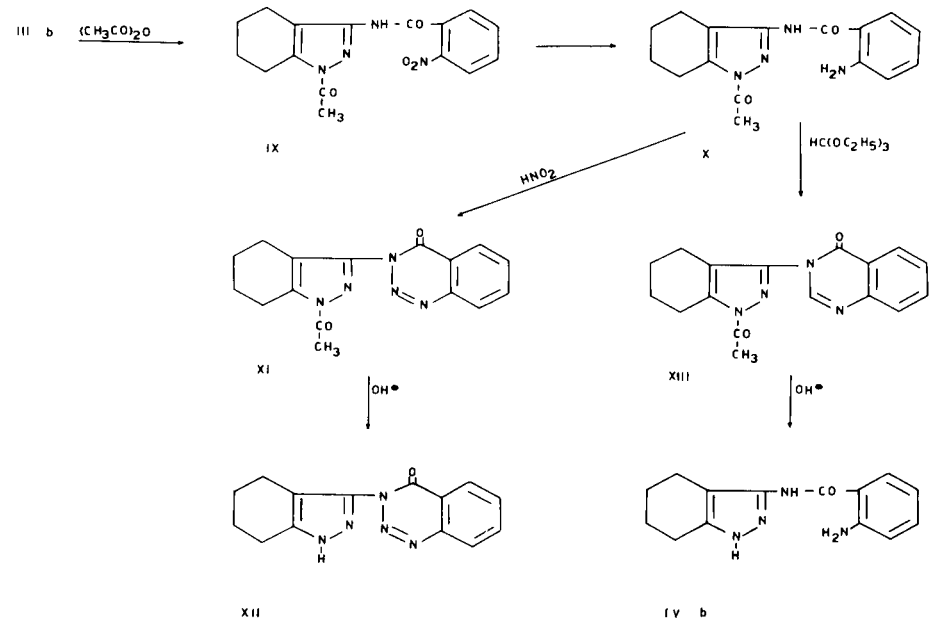


TABLE I

N-(3,4-R,R′-Pyrazol-5-yl)-*o*-nitrobenzamides and -*o*-aminobenzamides.

III IV

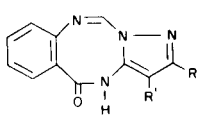
	R	R′	M.P., °C	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	C_6H_5	H	216-218°	$C_{16}H_{12}N_4O_3$ (a)	62.33	3.92	18.18	62.40	3.91	18.38
IIIb	$(CH_2)_4$		254-256°	$C_{14}H_{14}N_4O_3$ (b)	58.73	4.93	19.57	58.78	4.86	19.49
IIIc	$(CH_2)_5$		210-213°	$C_{15}H_{16}N_4O_3$ (c)	59.99	5.37	18.66	60.20	5.52	18.76
IVa	C_6H_5	H	248-250°	$C_{16}H_{15}ClN_4O$	61.04	4.45	17.80	61.31	4.67	17.87
IVb	$(CH_2)_4$		108-110°	$C_{14}H_{16}N_4O$ (d)	65.60	6.29	21.86	65.51	6.47	21.77
IVc	$(CH_2)_5$		150-152°	$C_{15}H_{18}N_4O$ (e)	66.66	6.71	20.73	66.85	6.78	20.58

(a) Ir: 3420-3200 cm^{-1} (broad) (2 x NH) 1680 cm^{-1} (CO); nmr: 7.10 δ (s, 1H, pyrazole CH) 7.30-8.40 δ (m, 9H, C_6H_5 and C_6H_4) 11.32 δ (s, 1H, NH) 13.10 (s, 1H, NH). (b) Ir: 3400-3200 cm^{-1} (broad) (2 x NH), 1680 cm^{-1} (CO); nmr: 1.30-2.80 δ (m, 8H, $(CH_2)_4$) 7.40-8.30 δ (m, 4H, C_6H_4) 10.30 (s, 1H, NH) 11.86 δ (s, 1H, NH). (c) Ir: 3400-3200 cm^{-1} (broad) (2 x NH) 1680 cm^{-1} (CO); nmr: 1.20-2.80 δ (m, 10H, $(CH_2)_5$) 7.60-8.00 δ (m, 4H, C_6H_4) 10.22 δ (s, 1H, NH) 12.02 (s, 1H, NH). (d) Ir: multiple bands in the 3 μ region and 1660 cm^{-1} (CO); nmr: 1.30-2.80 δ (m, 8H, $(CH_2)_4$) 6.36 δ (s, 2H, NH_2), 6.50-7.18 δ (m, 4H, C_6H_4), 9.60 δ (s, 1H, NH), 11.84 δ (s, 1H, NH). (e) Ir: multiple bands in the 3 μ region and 1660 cm^{-1} (CO); nmr: 1.20-2.80 δ (m, 10H, $(CH_2)_5$), 6.40 δ (s, 2H, NH_2), 9.52 δ (s, 1H, NH), 11.90 δ (s, 1H, NH).

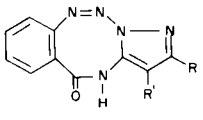
assignment for the products obtained. To remove any doubt concerning the structures V and VII, we synthesized the compound IX with the pyrazole nitrogen carrying an acetyl group (1). On reduction of compound IX the amino derivative X was obtained which was not characterized but directly converted to XI and XIII by treatment with nitrous acid and triethyl orthoformate, respectively. The structural assignment of XI and XIII rested on the analytical and spectroscopic data (nmr and ir). By action of alkali aqueous on XI, XII was obtained which showed nmr, ir

TABLE II

Pyrazolo[1,5-c][1,3,5]benzotriazocin-5(4*H*)one and Pyrazolo[1,5-c][1,2,3,5]benzotetrazocin-5(4*H*)one Derivatives.



V



VII

	R	R'	M.P., °C	Formula	Analysis Caled. C	Caled. H	Caled. N	Found C	Found H	Found N
Va	C_6H_5	H	275-278°	$C_{17}H_{12}N_4O$ (a)	70.82	4.20	19.44	70.63	4.19	19.59
Vb	$(CH_2)_4$		245-248°	$C_{15}H_{14}N_4O$ (b)	67.65	5.30	21.04	67.78	5.41	20.90
Vc	$(CH_2)_5$		225-227°	$C_{16}H_{16}N_4O$ (c)	68.55	5.75	19.99	68.72	5.81	19.87
VIIa	C_6H_5	H	268-272°	$C_{16}H_{11}N_5O$ (d)	66.42	3.83	24.21	66.66	3.89	24.53
VIIb	$(CH_2)_4$		226-228°	$C_{14}H_{13}N_5O$ (e)	62.91	4.90	26.20	63.02	5.01	26.36
VIIc	$(CH_2)_5$		234-236°	$C_{15}H_{15}N_5O$ (f)	64.04	5.37	24.90	64.12	5.46	24.90

(a) Uv λ max nm log ε 312 (4.33) 262 sh (4.10) 232 (4.18); ir: 3200-3100 cm^{-1} (multiple bands) (NH), 1680 cm^{-1} (CO); nmr: 7.10 δ (s, 1H, pyrazole CH), 7.40-8.40 δ (m, 9H, C_6H_5 and C_6H_4), 8.62 δ (s, 1H, triazocine CH), 13.60 δ (s, 1H, NH). (b) Uv: λ max nm log ε 315 sh (3.46) 305 (3.67) 276 (3.83) 266 (3.92) 252 (3.94) 228 (4.53); ir: 3200-3100 cm^{-1} (multiple bands) (NH), 1680 cm^{-1} (CO); nmr: 1.50-2.80 δ (m, 8H, $(CH_2)_4$) 7.40-8.10 (m, 4H, C_6H_4) 8.28 δ (s, 1H, triazocine CH), 12.64 δ (s, 1H, NH). (c) Uv: λ max nm log ε 316 sh (3.50) 304 (3.60) 276 (3.89) 266 (3.96) 254 (3.95) 228 (4.58); Ir: 3200-3100 cm^{-1} (multiple bands) (NH) 1680 cm^{-1} (CO); nmr: 1.20-2.80 δ (m, 10H, $(CH_2)_5$, 7.30-8.10 (m, 4H, C_6H_4), 8.24 (s, 1H, triazocine CH) 12.64 (s, 1H, NH). (d) Uv: λ max nm log ε 312 sh (3.94) 250 sh (4.43) 230 (4.48); ir: 3200 cm^{-1} (NH) 1680 cm^{-1} (CO); nmr: 7.10 δ (s, 1H, pyrazole CH), 7.40-8.60 δ (m, 9H, C_6H_5 and C_6H_4), 13.70 δ (s, 1H, NH). (e) Uv: λ max nm log ε 315 sh (3.60) 290 (3.73) 258 (3.72) 250 (3.81) 248 (3.85) 228 (4.42); Ir: 3200 cm^{-1} (NH) 1680 cm^{-1} (CO); nmr: 1.50-2.80 δ (m, 8H, $(CH_2)_4$), 7.70-8.50 δ (m, 4H, C_6H_4), 12.68 (s, 1H, NH). (f) Uv: λ max nm log ε 315 sh (3.60) 288 (3.80) 266 (3.74) 250 (3.80) 248 (3.88) 226 (4.47); ir: 3200 cm^{-1} (NH), 1680 cm^{-1} (CO) nmr: 1.20-2.80 δ (m, 10H, $(CH_2)_5$), 7.70-8.50 δ (m, 4H, C_6H_4), 12.70 δ (s, 1H, NH).

spectra and melting point quite different from VIb. This fact confirmed the assigned structures VIa,b,c to be correct (Scheme II).

Unfortunately, for the compound XIII the deacetylation reaction failed to give the corresponding tetrahydroindazolquinazolinone, but a product was obtained which was identical to IVb (m.p. and mixed m.p. ir, nmr). This fact clearly indicated that compound IVb was generated through initial addition of water across the 1,2-double bond in the quinazoline ring of XIII and further ring opening reaction followed by loss of formic and acetic acid catalyzed by hydroxyl ions, according to the mechanism suggested by Morley and Simpson (2).

Some of these compounds were tested for their pharmacological properties by Bristol Laboratories Syracuse N.Y., but no activity was observed.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Ir spectra were determined in nujol mull with a Perkin-Elmer infracord 137 spectrophotometer; uv spectra were determined in ethanol solution with a Beckmann DB recording spectrophotometer. The nmr spectra (DMSO-d_6) were obtained with a Jeol C-60H spectrometer (TMS as internal reference).

General Procedure for the *N*-(3,4-R,R'-pyrazol-5-yl)-*o*-nitrobenzamides.

A solution of 10 mmoles of IIa (3), b (4), c (5) in dry pyridine (100 ml.) was treated with 10 mmoles of 2-nitrobenzoylchloride (1). After stirring at room temperature for 24 hours the solution was evaporated under vacuum, the syrup mixed with aqueous sodium hydroxide 40% (100 ml.) was shaken at room temperature for 3 hours. To the filtered solution ammonium chloride was added. The precipitate was filtered, washed throughly with water, air dried and recrystallized from ethanol, yield 86-88%. The products are listed in Table I.

General Procedure for the *N*-(3,4-R,R'-pyrazol-5-yl)-*o*-aminobenzamides.

A mixture of 3 mmoles of IIIa,b,c, 350 ml. of ethanol and 500 mg. of 10% palladium on charcoal was hydrogenated in a Parr apparatus at 45-50 psi for 8 hours. After removal of catalyst, the solution was evaporated under vacuum to dryness and the residue was recrystallized from ethanol, yield 70-75%. The product IVa was characterized as hydrocloride derivative. The products are listed in Table I.

General Procedure for the Pyrazolo[1,5-c][1,3,5]benzotriazocin-5(4*H*)one Derivatives.

Compounds IVa,b,c (20 mmoles) and triethyl orthoformate (40 mmoles) were heated under reflux in ethanol (20 ml.) for 5 hours. On cooling, the precipitate was filtered off and washed

throughly with ethanol. Evaporation of the mother liquors gave further quantitaties of the required products, yield 68-72%. The products were recrystallized from ethanol and are listed in Table II.

General Procedure for the Pyrazolo[1,5-c][1,2,3,5]benzotetrazocin-5(4*H*)one Derivatives.

Compounds IVa,b,c (10 mmoles) were dissolved in acetic acid (70 ml.). Sodium nitrite (20 mmoles) in water (5 ml.) was added dropwise to the stirred solution at 0-5°. Stirring was continued for 1 hour at 0-5° and then the solution was allowed to warm to room temperature overnight. The precipitate obtained from the addition of water (100 ml.) to the solution was filtered off, washed with water and recrystallized from benzene, yield 67-70%. The products are listed in Table II.

N-(4,5,6,7-Tetrahydro-1-acetylindazol-3-yl)-*o*-nitrobenzamide (IX).

A mixture of IIIb (1 g.) and acetic anhydride (15 ml.) was stirred at room temperature for 24 hours. After the addition of water and solid sodium bicarbonate, the acetyl derivative was obtained, m.p. 210-212° (benzene-petroleum ether): ir: 3200 cm^{-1} (NH) 1700 and 1730 cm^{-1} (2 x CO); nmr: 1.30-3.00 δ (m, 11H, $(CH_2)_4$ and CH_3), 7.40-8.10 δ (m, 4H, C_6H_4) 10.90 δ (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.68; H, 5.06; N, 16.99.

3-(4,5,6,7-Tetrahydro-1-acetylindazol-3-yl)benzo-1,2,3-triazin-4(3*H*)one (XI).

Crude *N*-4,5,6,7-tetrahydro-1-acetyl-3-yl-*o*-aminobenzamide (X) (10 mmoles) prepared by the hydrogenation general procedure was dissolved in acetic acid (70 ml.). Sodium nitrite (20 mmoles) in water (5 ml.) was added dropwise to the stirred solution at 0-5°. Stirring was continued for 1 hour at 0-5° and then the solution was allowed to warm to room temperature. The precipitate obtained was filtered off, washed with water and recrystallized from ethanol, yield 68%. The product melted at 208-210°; uv: λ max nm log ε 285 sh (3.80) 232 (4.33); ir: 1700 and 1730 cm^{-1} (2 x CO); nmr: 1.42-3.20 δ (m, 11H, $(CH_2)_4$ and CH_3), 7.80-8.40 δ (m, 4H, C_6H_4).

Anal. Calcd. for $C_{16}H_{15}N_5O_2$: C, 62.12; H, 4.89; N, 22.64. Found: C, 62.26; H, 5.09; N, 22.51.

Hydrolysis of XI.

3-(4,5,6,7-Tetrahydroindazol-3-yl)benzo-1,2,3-triazin-4(3*H*)one (XII).

A suspension of 3 mmoles of XI in aqueous sodium hydroxide 10% (30 ml.) was stirred for 24 hours at room temperature. The solid which separated quantitatively was filtered and recrystallized from ethanol, m.p. 185-188°; uv: λ max nm log ε 230 (3.52) ir 3200 cm^{-1} (NH) and 1700 cm^{-1} (CO); nmr: 1.30-2.80 δ (m, 8H, $(CH_2)_4$, 6.80-8.10 δ (m, 4H, C_6H_4), 12.30 δ (broad, 1H, NH).

Anal. Calcd. for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 63.09; H, 5.11; N, 26.16.

3-(4,5,6,7-Tetrahydro-1-acetylindazol-3-yl)quinazolin-4(3*H*)one (XIII).

Crude X (20 mmoles) and triethyl orthoformate (10 ml.) was heated under reflux for 8 hours. On cooling, the precipitate was filtered off and recrystallized from ethanol, m.p. 198-200°; uv: λ max nm log ε 305 (3.81) 256 sh (4.44) 232 (4.70); ir: 1700 and 1730 cm^{-1} 2 x CO; nmr: 1.40-2.10 δ (m, 11H, $(CH_2)_4$ and CH_3), 7.50-8.20 δ (m, 4H, C_6H_4), 8.32 δ (s, 1H, quinazoline CH).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.18; H, 5.50; N, 18.13.

Hydrolysis of XIII.

N-(4,5,6,7-Tetrahydro-2*H*-indazol-3-yl)-*o*-aminobenzamide (IVb).

A suspension of 3 mmoles of XIII in aqueous sodium hydroxide 10% (30 ml.) was stirred for 24 hours at room temperature. The solid which separated quantitatively was collected and recrystallized from ethanol m.p. 108-110°. The product was identical with IVb obtained by the above method (mixed m.p., ir, nmr).

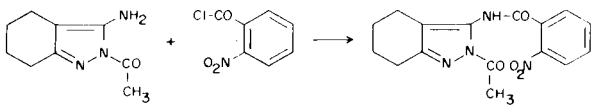
N-(4,5,6,7-Tetrahydro-2-acethylindazol-3-yl)-*o*-nitrobenzamide (XV).

Compound XIV (6) (3 mmoles) was dissolved in 30 ml. of chloroform and 3 mmoles of *o*-nitrobenzoyl chloride was added. Triethylamine (3 mmoles) was added in one portion and the mixture was then refluxed for 3 hours. The solution was evaporated under vacuum and the resulting crude solid was recrystallized from methanol, m.p. 192-194°; ir: 3200 cm^{-1} (NH) 1680 and 1720 cm^{-1} (2 x CO); nmr: 1.50-2.80 δ (m, 11H, $(CH_2)_4$ and CH_3), 7.60-8.30 δ (m, 4H, C_6H_4), 10.64 δ (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.58; H, 5.09; N, 17.20.

REFERENCES

(1) Acylation of IIIb with acetic anhydride at room temperature gave the corresponding acetylated product, which was assigned structure IX by the fact that it was different from the isomeric acetyl derivative XV synthesized by an unambigous route.



XIV I XV

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(4) Prepared by analogy with the method described by C. Iwanoff, *Chem. Ber.*, **87**, 1600 (1954).

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