Reactivity of 1-(2-Nitrophenyl)-5-Aminopyrazoles under Basic Conditions and Synthesis of New 3-, 7-, and 8-Substituted Pyrazolo[5,1-*c*][1,2,4]Benzotriazine 5-Oxides, as Benzodiazepine Receptor Ligands

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The reaction of 1-(2-nitrophenyl)-5-aminopyrazoles under basic conditions has been reinvestigated and the structures of the obtained pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxides confirmed by spectroscopic means. In particular the different aromatic nucleophilic attack on 8-chloro derivatives **4a** and **6a** and 7-nitro derivatives **11a** and **12a** was determined. From these latter compounds unexpected (phenyl-*ONN*-azoxy)pyrazoles were isolated.

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Recent papers have reported the affinity for the benzodiazepine receptor of various planar polycondensed heterocycles, whose structures are very different from those of the benzodiazepines. Particular interest has been aroused by tricyclic ring systems bearing a pyrazole moiety, which have shown high affinity for the BDZ receptor, with agonist, antagonist and inverse agonist activity [1-4]. Continuing our investigation on tricyclic heterocycles condensed with a pyrazole ring, with potential CNS activity [5,6], we synthesized pyrazolo [5,1-c][1,2,4] benzotriazine 5-oxide (**1a**) and some of its new derivatives bearing hydrophilic or lypophilic substituents at the 3-, 7- or 8-position in order to evaluate the influence of such substitutions on biological properties.

A survey of the literature revealed that the parent compound pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxide (**1a**) is unknown at present and the few cited derivatives of this system [7-10] are not the subject of pharmacological investigations.

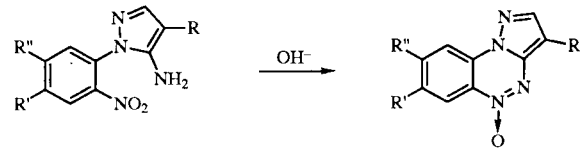
Chemistry.

The pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxide (**1a**) was synthesized from 1-(2-nitrophenyl)-5-aminopyrazole (**1**) (prepared according to a procedure described in one of our previous papers [6]) which cyclized to the triazine system in 10% sodium hydroxide at room temperature. The intramolecular cyclization between the nitro and the amino group under basic conditions is well known [11,12] and was utilized by some authors [8,9] to synthesize some 2-and/or 3-substituted pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxides.

Analogously, the new series of 3-, 7- and 8-substituted derivatives of **1a**, could be obtained from suitable 1- (2-nitrophenyl)-5-aminopyrazoles **2-12** under the same basic conditions.

The 1-(2-nitrophenyl)-5-aminopyrazoles **4**, **5**, **7**, **9** and **10** were prepared by reaction of 2-nitro-5-chlorophenylhydrazine [13], of 2-nitro-4-chlorophenylhydrazine [13] and of 2,4-dinitrophenylhydrazine with ethyl 2-cyano-3-ethoxypropeneate or 2-ethoxy-1,1-ethenedicarbonitrile, according to the procedure of Hayashy *et al* [14] which we employed in the synthesis of **2** and **3** in our previous paper [6].

Scheme 1



1-12 **1a-16a**

R = H	**1** [6]	R' = R" = H		R = H	**1a**
R = COOEt	**2** [6]			R = COOH	**2a**
R = CN	**3** [6]			R = CN	**3a**
				R = $CONH_2$	**3a'** [10]
R = COOEt	**4**	R' = H R" = Cl		R = COOH	**4a**
R = CN	**5**			R = CN	**5a**
				R = $CONH_2$	**5a'**
R = H	**6**			R = H	**6a**
R = COOEt	**7**	R' = Cl R" = H		R = COOH	**7a**
R = H	**8**			R = H	**8a**
R = COOEt	**9**	R' = NO_2 R" = H			
R = CN	**10**				
R = H	**11**			R = H	**11a**
R = $CONH_2$	**12**			R = $CONH_2$	**12a'**
				R = COOH	**12a**
		R' = H R" = OH		R = COOH	**13a**
				R = H	**15a**
		R' = H R" = OEt		R = COOH	**14a**
				R = H	**16a**

The treatment of the 1-(2-nitrophenyl)-5-aminopyrazoles **4**, **5**, **7** and **9** with orthophosporic acid at 180-200° or with concentrated hydrochloric acid under reflux, yielded the 4-unsubstituted aminopyrazoles **6**, **8** and **11**. The following condensation between the nitro and amino group of the aminopyrazoles **2-12** yielded interesting

results, depending on the different basic conditions or temperature used (see Scheme 1). Using 10% sodium hydroxide at room temperature the aminopyrazoles **6**, **8** and **11** cyclised similarly to **1**, to give the expected 8-chloro, 7-chloro and 7-nitropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxides **6a**, **8a** and **11a**. Under the same conditions the ethyl 1-(2-nitrophenyl)-5-aminopyrazole-4-carboxylates **2**, **4** and **7** condensed to the tricyclic system undergoing ester group hydrolysis, to give the acids **2a**, **4a** and **7a**, respectively. Treatment of 1-(2-nitrophenyl)-5-aminopyrazole-4-carbonitriles **3** and **5** with 10% sodium hydroxide afforded a mixture of 3-cyano and 3-carbamoylpyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxide **3a** and **3a'** [10] and **5a** and **5a'**, respectively, which were separated by chromatography.

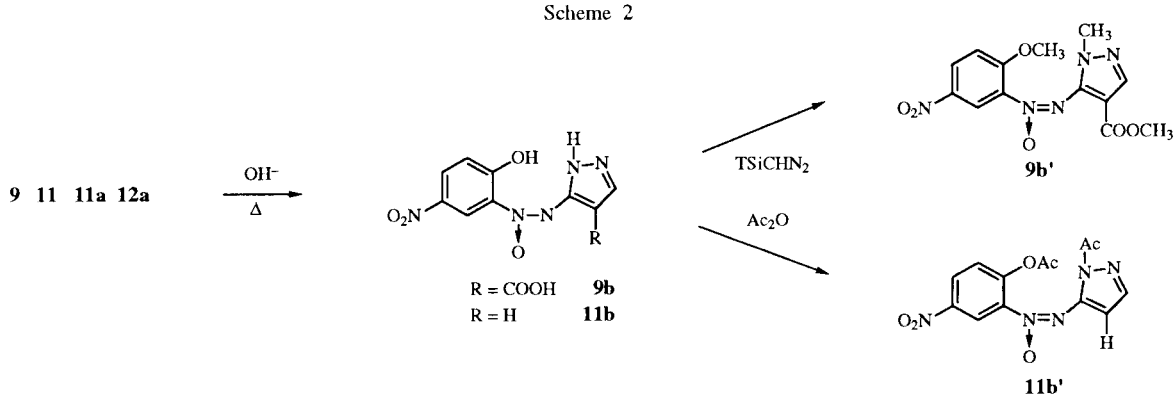
Inseparable solid mixtures were obtained by treatment of **9** and **10** under the same conditions. Instead, treatment of 1-(2,4-dinitrophenyl)-5-aminopyrazole-4-carboxyamide (**12**), with 10% sodium hydroxide, yielded the desired 5-oxide **12a'**. The acid **12a** was obtained in good yield from **12a'** by treatment with sodium nitrite and sulphuric acid; on the other hand **12a** could not be prepared by acid hydrolysis of the carboxyamides **12** or **12a'**, which under these conditions decarboxylated easily, to give **11** and **11a**, respectively. When the condensation was carried out under 40% sodium hydroxide and 40% sodium hydroxide in ethanol, with heating, the 1-(2-nitro-5-chlorophenyl)-5-aminopyrazoles **4** or **6** cyclized, but also underwent nucleophilic aromatic substitution, to give the 8-hydroxy and 8-ethoxy derivatives **13a**, **14a**, **15a** and **16a**. Under the same conditions, the 1-(2-nitro-4-chlorophenyl)-5-aminopyrazoles **7** and **8** cyclized only to the triazine system to give **7a** and **8a**. Moreover, it was observed that under the above conditions aromatic nucleophilic substitution occurs only when the leaving group is at the 8-position of the pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxides. Only the 8-chloro derivatives **4a** and **6a** yielded the 8-ethoxy derivatives **14a** and **16a**, by reaction with sodium ethoxide in ethanol. The same reaction of the 7-chloroderivativcs **7a** and **8a** and the 7-nitro derivatives **11a** and **12a** was unsuccessful.

Interesting results were obtained by refluxing 1-(2,4-dinitrophenyl)-5-aminopyrazoles **9** and **11** in 40% sodium hydroxide. Under these conditions, in addition to the expected condensation between the adjacent nitro and amino groups, nucleophilic attack at the aromatic C-1 activated by a second nitro group at the 4 position occurs. This produces a cleavage of Ar-N (pyrazole) bond, to yield the 5(3)-(3-nitro-6-hydroxyphenyl-*ONN*-azoxy)-pyrazoles **9b** and **11b**. Compounds **9b** and **11b** were obtained also by **12a** and **11a** respectively, under the same basic conditions to confirm the proposed mechanism, (see Scheme 2). Moreover, the isolation of the 1-methoxy-2,4-dinitrobenzene [15], by treatment of **9** with sodium methoxide in methanol, confirmed the easy cleavage of Ar-N (pyrazole) bond, after nucleophilic attack at aromatic activated carbon by a *para* nitro group.

The structures of **9b** and **11b** have been proven by chemical and spectroscopic means. The presence of phenolic OH and pyrazolic NH groups, was confirmed by synthesis of the dimethyl derivative of the methyl ester **9b'**, by reaction of **9b** with trimethylsilyldiazomethane [16], and by synthesis of the diacetyl derivative **11b'**. The ^{13}C-nmr data of **9b'** appear to be in agreement with the structure methyl 5-(3-nitro-6-methoxyphenyl-*ONN*-azoxy)-1-methylpyrazole-4-carboxylate. In fact, the signal at 141.0 ppm, attributable to the pyrazole CH, appears as a doublet (^1J C3-H3 = 192.5 Hz); no long range coupling is noticed, confirming that the methyl group is on the pyrazole nitrogen near the azoxy group. Our previous experiences have demonstrated that this long range coupling is diagnostic data for assignment of a methyl group on the pyrazole nitrogen [17]. The 7-nitropyrazolo [5,1-*c*][1,2,4]benzotriazine-5-oxide (**11a**), was again obtained by vacuum sublimation of **11b**.

Finally, the acids **2a**, **4a**, **7a**, **12a**, **13a** and **14a** were converted into the methyl or ethyl ester derivatives, to

Scheme 2



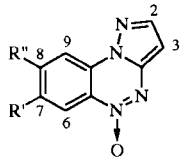
preserve the ester group at the 3-position, useful in the structure-activity relationship study. To the same purpose, the 3-bromo derivatives **1d**, **11d** and **16d** were also prepared treating the pyrazole[5,1-*c*][1,2,4]benzotriazine 5-oxides **1a**, **11a** and **16a** with a solution of bromine in chloroform [9].

The structures of the synthesized compounds were confirmed by ir and ^{1}H-nmr data (see Experimental). The pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxide (**1a**), parent compound of this class of tricyclic compounds, **6a**, **8a** and **11a**, chosen as example of 7- and 8-substituted derivatives, and **9b'** were also characterized by a ^{13}C-nmr study (see Table 1).

A biological investigation is now in progress to evaluate the affinity for BDZ receptor and the vivo CNS activity of the pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxides whose syntheses are reported in this paper.

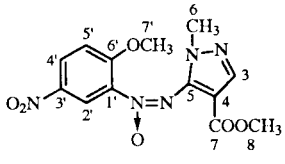
Table I

^{13}C NMR Data



δ (deuteriochloroform)

Compound No.	C2	C3	C6	C7	C8	C9
1a	144.8	99.8	123.5	127.4	136.0	115.8
6a	145.3	100.2	125.1	128.0		115.8
8a	145.1	100.2	123.1		136.4	117.4
11a	146.7	101.4	130.2		120.5	117.5



9b' [a] δ (deuteriochloroform)

C3	141.0 d	^{1}J C3-H3 = 192.2 Hz	
C4	106.7 d	^{2}JC4-H3 = 9.1 Hz	
C5	137.8 m		
C1'	140.6 m		
C2'	128.2 dd	^{1}J C2-H2 = 175.7 Hz	^{3}J C2'-H4' = 5.3 Hz
C3'	142.3 m		
C4'	122.3 dd	^{1}J C4'-H4' = 178.8 Hz	^{3}J C4'-H2' = 5.4 Hz
C5'	113.4 d	^{1}J C5'-H5' = 165.8 Hz	
C6'	156.6 m		
C7'	57.8 q	^{1}J = 146.7 Hz	
C6	37.0 q	^{1}J = 141.5 Hz	
C7	162.2 m		
C8	52.1 q	^{1}J = 132.1 Hz	

[a] Varian VXR-300 instrument.

EXPERIMENTAL

Melting points were determinated with a Gallenkamp apparatus and are uncorrected. The ir spectra were recorded in Nujol mulls using a Perkin-Elmer 681 spectrophotometer. The ^{1}H- and ^{13}C-spectra were measurated on a Varian Gemini-200 or Varian VXR-300 instrument, and chemical shifts are expressed in δ (ppm), using DMSO-d_6 or deuteriochloroform as the solvent. Multiplicity is indicated by s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, bs, broad singlet with exchange with deuterium oxide. Purity of the sample was determinated by tlc, which was performed using Macherey-Nagel Duren, Alugram silica gel plates UV 254. Microanalysis were performed by Laboratories of Dipartimento Farmaco Chimico Tecnologico of University of Siena, Italy, with a Perkin-Elmer Model 240 C Elemental Analyzer and results are within ±0.4% of theoretical values. The mass spectra were carried out at the "Mass Spectrometry Center" of Faculty of Medicine, University of Firenze, Italy, and were obtained with a VG 70-70 EQ instrument (VG Analytical Manchester, U.K.) in D.E.I. (Direct Eletro Impact) at M/DM=1500 mass resolution (10% valley definition) and a run speed of 2 s per decade. The data was processed on a Digital PDP8/A computer system.

General Procedure for Synthesis of **4**, **5**, **7**, **9** and **10**.

A solution of equimolar amounts (0.036 mole) of a suitable 2-nitrophenylhydrazine and ethyl 2-cyano-3-ethoxypropeneate or 2-ethoxy-1,1-ethenedicarbonitrile in 60 ml of 95% ethanol with acetic acid in catalytic amount, was refluxed for 24-48 hours, following the reaction by tlc (chloroform:methanol 10:1 as eluent). After evaporation of the solvent, *in vacuo*, the residue was treated with a little amount of water, then was purified by recrystallization.

Ethyl 1-(2-Nitro-5-chlorophenyl)-5-aminopyrazole-4-carboxylate (**4**).

From 2-nitro-5-chlorophenylhydrazine and ethyl 2-cyano-3-ethoxypropeneate, yellow crystals were obtained from ethanol/water (yield 67%), mp 135-136°; ir: cm^{-1} 3460, 3320, 1680; pmr (deuteriodimethyl sulfoxide): 8.20 (1H, d, aromatic proton H-3'), 7.90 (1H, d, aromatic proton H-6'), 7.80 (1H, dd, aromatic proton H-4'), 7.70 (1H, s, 1H pyrazole H-3), 6.70 (2H, bs, NH_2 exchangeable), 4.20 (2H, q, CH_2), 1.30 (3H, t, CH_3) ppm.

Anal. Calcd. for $C_{12}H_{11}N_4O_4Cl$: C, 46.38; H, 3.56; N, 18.03. Found: C, 46.40; H, 3.62; N, 17.82.

1-(2-Nitro-5-chlorophenyl)-5-aminopyrazole-4-carbonitrile (**5**).

From 2-nitro-5-chlorophenylhydrazine and 2-ethoxy-1,1-ethenedicarbonitrile, yellow crystals were obtained from isopropyl alcohol (yield 46%), mp 180-181°; ir: cm^{-1} 3340, 3200, 2240; pmr (deuteriodimethyl sulfoxide): 8.20 (1H, d, aromatic proton H-3'), 7.90 (1H, d, aromatic proton H-6'), 7.80 (2H, m, aromatic proton H-4', pyrazole H-3), 7.10 (2H, bs, NH_2 exchangeable) ppm.

Anal. Calcd. for $C_{10}H_6N_5O_2Cl$: C, 45.55; H, 2.29; N, 26.56. Found: C, 45.79; H, 2.10; N, 26.23.

Ethyl 1-(2-Nitro-4-chlorophenyl)-5-aminopyrazole-4-carboxylate (**7**).

From 2-nitro-4-chlorophenylhydrazine and ethyl 2-cyano-3-ethoxypropeneate, yellow crystals were obtained from isopropyl

alcohol (yield 55%), mp 156-157°; ir: cm^{-1} 3420, 3380, 1680; pmr (deuteriochloroform): 8.05 (1H, d, aromatic proton H-3'), 7.80 (1H, s, 1H pyrazole H-3), 7.75 (1H, dd, aromatic proton H-5'), 7.56 (1H, d, aromatic proton H-6'), 5.22 (2H, bs, NH_2 exchangeable), 4.30 (2H, q, CH_2), 1.38 (3H, t, CH_3) ppm.

Anal. Calcd. for $C_{12}H_{11}N_4O_4Cl$: C, 46.38; H, 3.56; N, 18.03. Found: C, 46.68; H, 3.86; N, 17.82.

Ethyl 1-(2,4-Dinitrophenyl)-5-aminopyrazole-4-carboxylate (**9**).

From 2,4-dinitrophenylhydrazine and ethyl 2-cyano-3-ethoxypropeneate, yellow crystals were obtained from ethanol (yield 75%), mp 142-143°; ir: cm^{-1} 3480, 3340, 1700; pmr (deuteriodimethyl sulfoxide): 9.10 (1H, d, aromatic proton H-3'), 8.90 (1H, dd, aromatic proton H-5'), 8.30 (1H, d, aromatic proton H-6'), 8.00 (1H, s, 1H pyrazole H-3), 7.00 (2H, bs, NH_2 exchangeable), 4.40 (2H, q, CH_2), 1.50 (3H, t, CH_3) ppm.

Anal. Calcd. for $C_{13}H_9N_5O_6$: C, 47.13; H, 2.73; N, 21.14. Found: C, 47.50; H, 2.46; N, 20.85.

1-(2,4-Dinitrophenyl)-5-aminopyrazole-4-carbonitrile (**10**).

From 2,4-dinitrophenylhydrazine and 2-ethoxy-1,1-ethenedicarbonitrile, yellow crystals were obtained from water (yield 45%), mp 220-224°; ir: cm^{-1} 3480, 3400, 2220; pmr (deuteriodimethyl sulfoxide): 8.90 (1H, d, aromatic proton H-3'), 8.70 (1H, dd, aromatic proton H-5'), 8.10 (1H, d, aromatic proton H-6'), 7.90 (1H, s, 1H pyrazole H-3), 7.20 (2H, bs, NH_2 exchangeable) ppm.

Anal. Calcd. for $C_{10}H_6N_6O_4$: C, 43.80; H, 2.20; N, 30.65. Found: C, 43.95; H, 2.56; N, 30.30.

General Procedure for Obtaining **6**, **8**, and **11**.

Method A.

Five mmoles of **4**, **7**, or **9** were treated with 40 mmoles (3.98 g) of 99% orthophosphoric acid and kept in an oil bath at 160°-180° for 3 hours, up to complete carbon dioxide evolution. After cooling the mixture was treated with water/ice, and neutralized with concentrated ammonia. The solid obtained was filtered and recrystallized from a suitable solvent.

Method B.

A suspension of **4**, **7**, or **9** (1.00 g) in 15 ml of concentrated hydrochloric acid was refluxed for 12 hours. After cooling at room temperature, the respective hydrochloridres were filtered. Upon solution in water and neutralization with concentrated ammonia, the 5-aminopyrazoles **6**, **8**, or **11** obtained were filtered and recrystallized.

1-(2-Nitro-5-chlorophenyl)-5-aminopyrazole (**6**).

From **4** according to the general procedures, yellow crystals were obtained from water (method A, yield 70%; method B, yield 85%), mp 122-124°; ir: cm^{-1} 3320, 3180; pmr (deuteriodimethyl sulfoxide): 8.10 (1H, d, aromatic proton H-3'), 7.80 (1H, d, aromatic proton H-6'), 7.70 (1H, dd, aromatic proton H-4'), 7.30 (1H, d, 1H pyrazole H-3), 5.60 (2H, bs, NH_2 exchangeable), 5.40 (1H, d, 1H pyrazole H-4) ppm.

Anal. Calcd. for $C_9H_7N_4O_2Cl$: C, 45.29; H, 2.95; N, 23.48. Found: C, 45.60; H, 3.27; N, 23.13.

1-(2-Nitro-4-chlorophenyl)-5-aminopyrazole (**8**).

From **7** according to the general procedures, yellow crystals were obtained from ethanol (method A, yield 50%; method B, yield 80%), mp 102-103°; ir: cm^{-1} 3340, 3180; pmr (deuteriochloroform): 7.96 (1H, d, aromatic proton H-3'), 7.72 (1H, dd, aromatic proton H-5'), 7.62 (1H, d, aromatic proton H-6'), 7.48 (1H, d, 1H pyrazole H-3), 5.70 (1H, d, 1H pyrazole H-4), 3.62 (2H, bs, NH_2 exchangeable) ppm.

Anal. Calcd. for $C_9H_7N_4O_2Cl$: C, 45.29; H, 2.95; N, 23.48. Found: C, 45.55; H, 3.30; N, 23.24.

1-(2,4-Dinitrophenyl)-5-aminopyrazole (**11**).

From **10** according to the general procedures yellow crystals were obtained from isopropyl alcohol (method A, yield 65%; method B, yield 90%), mp 147-148°; ir: cm^{-1} 3400, 3320; pmr (deuteriochloroform): 8.80 (1H, d, aromatic proton H-3'), 8.60 (1H, dd, aromatic proton H-5'), 7.90 (1H, d, aromatic proton H-6'), 7.50 (1H, d, 1H pyrazole H-3), 5.70 (1H, d, 1H pyrazole H-4), 3.70 (2H, bs, NH_2 exchangeable) ppm.

Anal. Calcd. for $C_9H_7N_5O_4$: C, 43.37; H, 2.83; N, 28.10. Found: C, 43.67; H, 2.54; N, 27.85.

1-(2,4-Dinitrophenyl)-5-aminopyrazole-4-carboxamide (**12**).

A solution of 1.00 g of **10** in 4 ml of concentrated sulphuric acid was heated at 70-80° with stirring for 1 hour. After cooling the solution was treated with water/ice and neutralized with concentrated ammonia. The solid was filtered and recrystallized from water (yield 85%), yellow crystals, mp 231-235° dec; ir: cm^{-1} 3500, 3380, 3340, 3180, 1670; pmr (deuteriodimethyl sulfoxide): 8.86 (1H, d, aromatic proton H-3'), 8.64 (1H, dd, aromatic proton H-5'), 8.05 (1H, d, aromatic proton H-6'), 7.97 (1H, s, 1H pyrazole H-3), 7.46 (1H, bs, NH amide exchangeable), 6.96 (1H, bs, NH amide exchangeable), 6.73 (2H, bs, NH_2 exchangeable) ppm.

Anal. Calcd. for $C_{10}H_8N_6O_5$: C, 41.10; H, 2.75; N, 28.76. Found: C, 41.35; H, 2.56; N, 28.52.

General Procedure for Synthesis of **1a, 2a, 3a, 3a', 4a, 5a, 5a', 6a, 7a, 8a, 11a** and **12a'.**

A suspension of 4 mmoles of a suitable 5-aminopyrazole in 40 ml of 10% aqueous sodium hydroxide was kept at room temperature for 24 hours. The precipitate was filtered and purified by crystallization or by column chromatography.

Pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**1a**).

This compound was obtained from **1**, yellow crystals from isopropyl alcohol (yield 70%), mp 146°; ir: cm^{-1} 1560; pmr (deuteriochloroform): 8.56 (1H, d, H-9), 8.40 (1H, d, H-6), 8.09 (1H, d, H-2), 7.96 (1H, t, H-8), 7.63 (1H, t, H-7), 6.75 (1H, d, H-3) ppm; ms (m/z) 186 (M^+, 100).

Anal. Calcd. for $C_9H_6N_4O$: C, 58.04; H, 3.26; N, 30.09. Found: C, 58.20; H, 3.26; N, 29.79.

3-Carboxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**2a**).

This compound was obtained from **2** after acidification with 6*N* hydrochloric acid, yellow crystals from ethanol (yield 80%) mp 315-316° dec; ir: cm^{-1} 2800, 1680, 1580; pmr (deuteriodimethyl sulfoxide): 12.50 (1H, bs, OH, exchangeable), 8.29 (1H, s, H-2), 8.15 (2H, m, H-6, H-9), 7.85 (1H, t, H-8), 7.50 (1H, t, H-7) ppm.

Anal. Calcd. for $C_{10}H_6N_4O_3$: C, 52.17; H, 2.61; N, 24.34. Found: C, 51.99; H, 2.74; N, 24.67.

3-Cyanopyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**3a**).

This compound was obtained from **3** after purification on a silica gel column (chloroform:methanol, 10:1, faster running band), yellow crystals from isopropyl alcohol (yield 30%,) mp

221-223°; ir: cm^{-1} 2240, 1580; pmr (deuteriodimethyl sulfoxide): 8.86 (1H, s, H-2), 8.50 (2H, m, H-6, H-9), 8.22 (1H, t, H-8), 7.88 (1H, t, H-7) ppm.

Anal. Calcd. for $C_{10}H_5N_5O$: C, 56.87; H, 2.38; N, 33.16. Found: C, 57.12; H, 2.65; N, 32.98.

3-Carbamoylpyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**3a'**)[10].

This compound was obtained from **3** after purification on a silica gel column (chloroform:methanol, 10:1, second running band), yellow crystals (yield 10%), mp 303-304° (according to lit); ir: cm^{-1} 3480, 3300, 1700, 1570; pmr (deuteriodimethyl sulfoxide): 8.68 (1H, s, H-2), 8.48 (2H, m, H-6, H-9), 8.10 (1H, t, H-8), 7.80 (1H, t, H-7), 7.58 (1H, bs, NH exchangeable), 7.15 (1 H, bs, NH exchangeable) ppm.

Anal. Calcd. for $C_{10}H_7N_5O_2$: C, 52.40; H, 3.07; N, 30.55. Found: C, 52.68; H, 3.35; N, 30.28.

3-Carboxy-8-chloropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**4a**).

This compound was obtained from **4** after acidification with 6*N* hydrochloric acid, yellow crystals from isopropyl alcohol (yield 85%), mp 281-282°; ir: cm^{-1} 2900, 1680, 1570; pmr (deuteriochloroform): 13.00 (1H, bs, OH, exchangeable), 8.62 (1H, s, H-2), 8.46 (1H, d, H-6), 8.44 (1H, d, H-9), 7.84 (1H, dd, H-7) ppm.

Anal. Calcd. for $C_{10}H_5N_4O_3Cl$: C, 45.38; H, 1.90; N, 21.17. Found: C, 45.01; H, 2.03; N, 20.98.

3-Cyano-8-chloropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**5a**).

This compound was obtained from **5** after purification on a silica gel column (chloroform:acetonitrile, 10:1, faster running band), yellow crystals (yield 43%), mp 242-243°; ir: cm^{-1} 2240; pmr (deuteriodimethyl sulfoxide): 8.86 (1H, s, H-2), 8.46 (1H, d, H-6), 8.48 (1H, d, H-9), 7.86 (1H, dd, H-7) ppm.

Anal. Calcd. for $C_{10}H_4N_5OCl$: C, 48.89; H, 1.64; N, 28.51; Found: C, 48.85; H, 1.64; N, 28.53.

3-Carbamoyl-8-chloropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**5a'**).

This compound was obtained from **5** after purification on a silica gel column (chloroform:acetonitrile, 10:1, second running band), yellow crystals (yield 10%), mp 285-287°; ir: cm^{-1} 3480, 3340, 1680; pmr (deuteriodimethyl sulfoxide): 8.62 (1H, s, H-2), 8.48 (1H, d, H-6), 8.44 (1H, d, H-9), 7.84 (1H, dd, H-7), 7.62 (1H, bs, NH amide exchangeable), 7.20 (1H, bs, NH amide exchangeable) ppm.

Anal. Calcd. for $C_{10}H_6N_5O_2Cl$: C, 45.55; H, 2.29; N, 26.56. Found: C, 45.86; H, 2.58; N, 26.34.

8-Chloropyrazolo [5,1-*c*][1,2,4]benzotriazine 5-Oxide (**6a**).

This compound was obtained from **6**, yellow crystals from ethanol (yield 55%), mp 218-220°; ir: cm^{-1} 1570; pmr (deuteriochloroform): 8.50 (1H, d, H-6), 8.40 (1H, d, H-9), 8.15 (1H, d, H-2), 7.58 (1H, dd, H-7), 6.75 (1H, d, H-3) ppm.

Anal. Calcd. for $C_9H_5N_4OCl$: C, 48.99; H, 2.28; N, 25.39. Found: C, 48.59; H, 2.42; N, 25.22.

3-Carboxy-7-chloropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**7a**).

This compound was obtained from **7** after acidification with 6*N* hydrochloric acid, yellow crystals from methoxyethanol (yield 85%,) mp 297°; ir: cm^{-1} 2700, 1690, 1570; pmr (deuteriodimethyl sulfoxide): 13.00 (1H, bs, OH, exchangeable), 8.62 (1H, s, H-2), 8.50 (1H, d, H-6), 8.46 (1H, d, H-9), 8.20 (1H, dd, H-8) ppm.

Anal. Calcd. for $C_{10}H_5N_4O_3Cl$: C, 45.38; H, 1.90; N, 21.17. Found: C, 44.90; H, 2.23; N, 20.95.

7-Chloropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**8a**).

This compound was obtained from **8**, yellow crystals from ethanol (yield 80%), mp 201-202°; ir: cm^{-1} 1550; pmr (deuteriochloroform): 8.56 (1H, d, H-6), 8.36 (1H, d, H-9), 8.10 (1H, d, H-2), 7.90 (1H, dd, H-8), 6.81 (1H, d, H-3) ppm.

Anal. Calcd. for $C_9H_5N_4OCl$: C, 48.99; H, 2.28; N, 25.39. Found: C, 48.86; H, 2.23; N, 25.29.

7-Nitropyrazolo [5,1-*c*][1,2,4]benzotriazine 5-Oxide (**11a**).

A). This compound was obtained from **11,** yellow crystals from ethanol (yield 84%), mp 215-216°; ir: cm^{-1} 1570, 1530, 1340; pmr (deuteriochloroform): 9.42 (1H, d, H-6), 8.78 (1H, dd, H-8), 8.55 (1H, d, H-9), 8.20 (1H, d, H-2), 6.85 (1H, d, H-3) ppm.

Anal. Calcd. for $C_9H_5N_5O_3$: C, 46.75; H, 2.18; N, 30.29. Found: C, 46.58; H, 2.28; N, 29.90.

B). This compound was obtained as the minor product from **11b** which was melted at 200-205°, in a sublimation equipment *in vacuo* and identified by tlc (toluene:ethyl acetate 8:2 as eluent) and by ^{1}H-nmr spectroscopy, in the sublimed mixture with the starting material.

3-Carbamoyl-7-nitropyrazolo[5,1-*c*][1,2,4] benzotriazine 5-Oxide (**12a'**).

This compound was obtained from **12,** yellow crystals from methoxyethanol (yield 78%), mp >300°; ir: cm^{-1} 3460, 3180, 1680, 1580, 1550, 1360; pmr (deuteriodimethyl sulfoxide): 9.08 (1H, d, H-6), 8.86 (1H, dd, H-8), 8.71 (1H, s, H-2), 8.58 (1H, d, H-9), 7.66 (1H, bs, NH exchangeable), 7.28 (1H, bs, NH exchangeable) ppm.

Anal. Calcd. for $C_{10}H_6N_6O_4$: C, 43.80; H, 2.20; N, 30.64. Found: C, 43.63; H, 2.23; N, 30.25.

3-Carboxy-7-nitropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**12a**).

A suspension of **12a'** (0.36 mmoles) in 10 ml of concentrated sulphuric acid was rapidly cooled to 0° and treated with sodium nitrite (250 mg in 5 ml water) with stirring. The solution was kept at room temperature and the precipitate was filtered and washed with water, yellow crystalswere obtained from acetic acid, (yield 80%), mp 317-318° dec; ir: cm^{-1} 2700-2600, 1700, 1580, 1540, 1360; pmr (deuteriodimethyl sulfoxide): 13.00 (1H, bs, OH, exchangeable), 9.05 (1H, d, H-6), 8.85 (1H, dd, H-8), 8.70 (1H, s, H-2), 8.60 (1H, d, H-9) ppm,

Anal. Calcd. for $C_{10}H_5N_5O_5$: C, 43.60; H, 1.83; N, 25.45. Found: C, 43.89; H, 1.82; N, 25.75.

General Procedure for Synthesis of **13a, 14a, 15a,** and **16a.**

A suspension of 4 mmoles of **4**, **4a**, **6** and **6a** in 40 ml of aqueous sodium hydroxide or in 60 ml of a solution of 40% solution of sodium hydroxide in ethanol (40% sodium hydroxide: ethanol 1:2), was refluxed for long time, following the reaction by tlc (eluent toluene:ethyl acetate 8:2). After acidification with concentrated hydrochloric acid the precipitate was filtered and purified by crystallization or extraction with ethyl acetate.

3-Carboxy-8-hydroxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**13a**).

This compound was obtained from **4** or **4a** by treatment with a 40% solution of sodium hydroxide and acidification with concentrated hydrochloric acid brown crystals from ethoxyethanol (yield 40% from **4**, yield 89% from **4a**), mp 235-237°; ir: cm^{-1} 3300, 2600, 1680, 1570; pmr (deuteriodimethyl sulfoxide): 12.00-12.50 (2H, bs, OH, COO*H* exchangeable), 8.58 (1H, s, H-2), 8.35 (1H, d, H-6), 7.58 (1H, d, H-9), 7.20 (1H, dd, H-7) ppm.

Anal. Calcd. for $C_{10}H_6N_4O_4$: C, 48.79; H, 2.46; N, 22.76. Found: C, 49.09; H, 2.71; N, 22.54.

3-Carboxy-8-ethoxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**14a**).

This compound was obtained from **4** or **4a** by treatment with a solution of 40% sodium hydroxide in ethanol and acidification with concentrated hydrochloric acid, yellow crystals from ethanol (yield 45% from **4**, yield 85% from **4a**), mp 280-282°; ir: cm^{-1} 2700, 1680, 1570; pmr (deuteriodimethyl sulfoxide): 12.80 (1H, bs, OH, exchangeable), 8.58 (1H, s, H-2), 8.38 (1H, d, H-6), 7.68 (1H, d, H-9), 7.34 (1H, dd, H-7), 4.38 (2H, q, CH_2), 1.42 (3H, t, CH_3) ppm.

This compound was also obtained from **4a** (0.50 mmole) by reaction with sodium ethoxide (100 mg sodium in 30 ml of absolute ethanol), for 1 hour, followed by dilution and acidification with 6*N* hydrochloric acid.

Anal. Calcd. for $C_{12}H_{10}N_4O_4$: C, 52.56; H, 3.68; N, 20.43. Found: C, 52.82; H, 3.83; N, 20.28.

8-Hydroxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**15a**).

This compound was obtained from **6** or **6a** by treatment with a 40% solution of sodium hydroxide and acidification with concentrated hydrochloric acid, yellow crystals from ethanol-water (yield 65% from **6**, yield 90% from **6a**) mp 253-255°; ir: cm^{-1} 3100, 2700, 1550; pmr (deuteriodimethyl sulfoxide): 11.75 (1H, bs, OH, exchangeable), 8.25 (1H, d, H-2), 8.30 (1H, d, H-6), 7.55 (1H, d, H-9), 7.15 (1H, dd, H-7), 6.82 (1H, d, H-3) ppm.

Anal. Calcd. for $C_9H_6N_4O_2$: C, 53.46; H, 2.99; N, 27.70. Found: C, 53.12; H, 3.40; N, 27.43.

8-Ethoxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**16a**).

This compound was obtained from **6** or **6a** by treatment with a solution of 40% sodium hydroxide in ethanol and acidification with concentrated hydrochloric acid, yellow crystals from ethanol (yield 53% from **6**, yield 80% from **6a**), mp 189-190°; ir: cm^{-1} 1550; pmr (deuteriodimethyl sulfoxide): 8.26 (1H, d, H-2), 8.34 (1H, d, H-6), 7.64 (1H, d, H-9), 7.26 (1H, dd, H-7), 6.86 (1H, d, H-3), 4.35 (2H, q, CH_2), 1.45 (3H, t, CH_3) ppm.

This compound was also obtained from **6a** (0.50 mmole) by reaction with sodium ethoxide (100 mg sodium in 30 ml absolute ethanol) for 1 hour.

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.37; N, 24.33. Found: C, 57.01; H, 4.57; N, 23.95.

General Procedure for Obtaining **9b** and **11b.**

A suspension of **9**, **11**, **11a** and **12a** in a 40% solution of sodium hydroxide was refluxed for 2 hours. The resulting solution was made acidic by addition of diluted hydrochloric acid. A precipitate was filtered and purified by recrystallization.

5(3)-(3-Nitro-6-hydroxyphenyl-*ONN*-azoxy)pyrazole-4-carboxylic Acid (**9b**).

From **9** or **12a** cream crystals were obtained from acetic acid (yield 66% from **9**, yield 75% from **12a**), mp 317° dec; ir: cm^{-1} 3240, 2700-2500, 1690; pmr (deuteriodimethyl sulfoxide): 13.00-12.50 (2H, bs, OH, COO*H* exchangeable), 8.80 (1H, d, H-2'), 8.35 (1H, dd, H-4'), 8.25 (1H, s, H-3), 7.40 (1H, d, H-5') ppm.

Anal. Calcd. for $C_{10}H_7N_5O_6$: C, 40.96; H, 2.40; N, 23.80. Found: C, 40.61; H, 2.30; N, 23.54.

5(3)-(3-Nitro-6-hydroxyphenyl-*ONN*-azoxy)pyrazole (**11b**).

From **11** or **11a** cream crystals were obtained from ethanol (yield 50% from **11**, yield 80% from **12a**), mp 208-210°; ir: cm^{-1} 3460; pmr (deuteriodimethyl sulfoxide): 13.50 (1H, bs, NH, exchangeable), 12.50 (1H, bs, OH, exchangeable), 8.65 (1H, d, H-2'), 8.32 (1H, dd, H-4'), 7.95 (1H, d, H-3), 7.30 (2H, m, H-4 and H-5') ppm.

Anal. Calcd. for $C_9H_7N_5O_4$: C, 43.37; H, 2.83; N, 28.10. Found: C, 43.10; H, 2.78; N, 27.75.

Methyl 5-(3-Nitro-6-methoxyphenyl-*ONN*-azoxy)-1-methylpyrazole-4-carboxylate (**9b'**).

In a solution of methanol (10 ml) and benzene (10 ml), 100 mg of **9b** was dissolved, and a 2*M* solution of trimethylsilyldiazomethane in cyclohexane (3.00 ml) (Aldrich) was added. The reaction mixture was kept at room temperature for 3 hours. The solvent was evaporated and the residue was recrystallized from ethanol, cream crystals (yield 50%), mp 191-192°; ir: cm^{-1} 1720; pmr (deuteriochloroform): 8.65 (1H, d, H-2'), 8.45 (1H, dd, H-4'), 7.94 (1H, s, H-3), 7.22 (1H, d, H-5'), 4.09 (3H, s, OCH_3), 3.85 (6H, s, NCH_3, $COOCH_3$) ppm.

Anal. Calcd. for $C_{13}H_{13}N_5O_6$: C, 46.57; H, 3.91; N, 20.80. Found: C, 46.67; H, 3.83; N, 20.71.

5-(3-Nitro-6-acethoxyphenyl-*ONN*-azoxy)-1-acetylpyrazole (**11b'**).

A suspension of **11b** (60 mg) in acetic anhydride (5 ml) and acetic acid (3 ml), was refluxed for 1 hour. The resulting solution was treated with water and a white precipitate was formed. After filtration the residue was purified by recrystallization from ethanol, white crystals (yield 45%), mp 138-139°; ir: cm^{-1} 1800, 1760; pmr (deuteriochloroform): 9.00 (1H, d, H-2'), 8.44 (1H, dd, H-4'), 8.34 (1H, d, H-3), 7.50 (1H, d, H-4), 7.46 (1H, d, H-5'), 2.80 (3H, s, $NCOCH_3$), 2.40 (3H, s, $OCOCH_3$) ppm.

Anal. Calcd. for $C_{13}H_{11}N_5O_6$: C, 46.86; H, 3.32; N, 21.02. Found: C, 47.02; H, 3.54; N, 20.95.

General Procedure for Synthesis of **2c, 4c, 7c, 12c, 13c** and **14c.**

A). A suspension of 0.36 mmole of acids **2a, 4a, 13a** or **14a** in 20 ml of anhydrous ethanol or metahnol, containing 5 ml of concentrated sulphuric acid, was refluxed two days, until starting material disappeared in tlc (toluene:ethyl acetate, 8:2 as eluent). After cooling a precipitate was filtered and purified by recrystallization from a suitable solvent.

B). A suspension of 0.38 mmole of **4a, 7a** or **12a** in 10 ml of diethylcarbonate and 2 ml of concentrated sulphuric acid, was refluxed for 5 hours. After evaporation of the solution, the residue was treated with a few ml of ethanol, filterd and crystallized from a suitable solvent.

3-Methoxycarbonylpyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**2c**).

From **2a** by method A, yellow crystals were obtained from ethanol (yield 80%), mp 213-214°; ir: cm^{-1} 1730, 1570; pmr (deuteriochloroform): 8.60 (1H, d, H-9), 8.58 (1H, s, H-2), 8.45

(1H, d, H-6), 8.05 (1H, t, H-8), 7.71 (1H, t, H-7), 3.90 (3H, s, CH_3) ppm.

Anal. Calcd. for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.30; N, 22.94. Found: C, 54.05; H, 3.27; N, 22.79.

3-Ethoxycarbonyl-8-chloropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**4c**).

From **4a**, by method A (yield 80%) and B (yield 85%), yellow crystals were obtained from isopropyl alcohol, mp 192-193°; ir: cm^{-1} 1730, 1575; pmr (deuteriochloroform): 8.55 (1H, s, H-2), 8.50 (1H, d, H-6), 8.45 (1H, d, H-9), 7.65 (1H, dd, H-7), 4.45 (2H, q, CH_2), 1.45 (3H, t, CH_3) ppm.

Anal. Calcd. for $C_{12}H_9N_4O_3Cl$: C, 49.24; H, 3.09; N, 19.14. Found: C, 48.85; H, 3.24; N, 19.14.

3-Ethoxycarbonyl-7-chloropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**7c**).

From **7a** by method B (yield 70%), yellow crystals were obtained from ethanol, mp 205-207°; ir: cm^{-1} 1730, 1570; pmr (deuteriochloroform): 8.58 (1H, d, H-6), 8.52 (1H, s, H-2), 8.40 (1H, d, H-9), 7.96 (1H, dd, H-8), 4.45 (2H, q, CH_2), 1.40 (3H, t, CH_3) ppm.

Anal. Calcd. for $C_{12}H_9N_4O_3Cl$: C, 49.24; H, 3.09; N, 19.14. Found: C, 49.52; H, 3.07; N, 19.12.

3-Ethoxycarbonyl-7-nitropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**12c**).

From **12a**, by method B (yield 70%), yellow crystals were obtained from ethanol, mp 229-230°; ir: cm^{-1} 1730, 1570, 1540, 1340; pmr (deuteriochloroform): 9.42 (1H, d, H-6), 8.85 (1H, dd, H8), 8.65 (1H, d, H-9), 8.60 (1H, s, H-2), 4.45 (2H, q, CH_2), 1.40 (3H, t, CH_3) ppm.

Anal. Calcd. for $C_{12}H_9N_5O_5$: C, 47.52; H, 2.99; N, 23.09. Found: C, 47.45 H, 2.98; N, 22.91.

3-Methoxycarbonyl-8-hydroxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**13c**).

From **13a**, by method A (yield 70%), yellow crystals were obtained from ethanol, mp 281-282°; ir: cm^{-1} 3250, 1690, 1230; pmr (deuteriodimethyl sulfoxide): 11.90 (1H, bs, OH exchangeable), 8.60 (1H, s, H-2), 8.45 (1H, d, H-6), 7.55 (1H, d, H-9), 7.20 (1H, dd, H-7), 3.80 (3H, s, CH_3) ppm.

Anal. Calcd. for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.09; N, 21.53. Found: C, 50.43; H, 3.18; N, 21.15.

3-Ethoxycarbonyl-8-ethoxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**14c**).

From **14a**, by method A (yield 75%), yellow crystals were obtained from ethanol, mp 227-228°; ir: cm^{-1} 1740, 1570; pmr (deuteriochloroform): 8.52 (1H, s, H-2), 8.45 (1H, d, H-6), 7.70 (1H, d, H-9), 7.20 (1H, dd, H-7), 4.45 (2H, q, Ar-OCH_2), 4.30 (2H, q, CH_2), 1.54 (3H, t, CH_3), 1.42 (3H, t, Ar-OCH_2CH_3) ppm.

Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.66; N, 18.53. Found: C, 55.61; H, 4.64; N, 18.55.

General Procedure for Obtaining **1d, 11d** and **16d.**

A suitable pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-oxide **1a, 11a**, or **16a**, 0.60 mmole, was dissolved in 5 ml of chloroform and a equimolar amount of bromine in chloroform was slowly added. The reaction was monitored by tlc (toluene:ethyl acetate 8:2 as eluent); a solution or a precipitate was obtained and after the normal work up, the residue was recrystallized from a suitable solvent.

3-Bromopyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**1d**).

From **1a** by the general procedure, orange crystals were obtained from methoxyethanol (yield 77%), mp 248-250°; ir: cm^{-1} 1520; pmr (deuteriochloroform): 8.55 (1H, d, H-9), 8.35 (1H, d, H-6), 8.05 (1H, s, H-2), 7.95 (1H, t, H-8), 7.65 (1H, t, H-7) ppm.

Anal. Calcd. for $C_9H_5N_4OBr$: C, 40.79; H, 1.90; N, 21.14. Found: C, 40.66; H, 1.88; N, 20.91.

3-Bromo-7-nitropyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**11d**).

From **11a** according to the general procedure, orange crystals were obtained from isopropyl alcohol (yield 60%), mp 251-252°; ir: cm^{-1} 1520; pmr (deuteriochloroform): 9.40 (1H, d, H-6), 8.78 (1H, dd, H-8), 8.52 (1H, d, H-9), 8.18 (1H, s, H-2) ppm.

Anal. Calcd. for $C_9H_4N_5O_3Br$: C, 34.87; H, 1.30; N, 22.59. Found: C, 34.49; H, 1.30; N, 22.99.

3-Bromo-8-ethoxypyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxide (**16d**).

From **16a** by the general procedure, yellow crystals were obtained from ethanol (yield 50%), mp 210-211°; ir: cm^{-1} 1530; pmr (deuteriochloroform): 8.45 (1H, d, H-6), 8.05 (1H, s, H-2), 7.60 (1H, d, H-9), 7.15 (1H, dd, H-7), 4.38 (2H, q, -CH_2), 1.50 (3H, t, -CH_3) ppm.

Anal. Calcd. for $C_{11}H_9N_4O_2Br$: C, 42.75; H, 2.93; N, 18.13. Found: C, 42.98; H, 3.23; N, 17.89.

1-Methoxy-2,4-dinitrobenzene.

To a solution of sodium methoxide (100 mg sodium in 30 ml of methanol) was added 0.10 mmole of **9** at room temperature, with stirring, for 2 hours. After dilution a precipitate was filtered and recrystallized from water, colorless crystals (yield 70%), mp 90-91° (lit 94-95°/87-88° [15]); ir: cm^{-1} 1620, 1540, 1350, 1280; pmr (deuteriochloroform): 8.75 (1H, d, H-3), 8.48 (1H, dd, H-5), 7.23 (1H, d, H-6), 4.10 (3H, s, OCH_3) ppm.

Anal. Calcd. for $C_7H_6N_2O_5$: C, 42.43; H, 3.05; N, 14.10. Found: C, 42.01; H, 2.90; N, 13.75.

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