Anal. Calcd for $C_{19}H_{18}ClN_3O_4S$: C, 54.34; H, 4.32; N, 10.01; S, 7.63. Found: C, 54.46; H, 4.22; N, 9.83; S, 7.94.

Registry No.—**6**, 30855-63-1; **7**, 30855-64-2; **8**, 30855-65-3; **9**, 30855-66-4; **10**, 30855-67-5; **11**, 30855-68-6; **12**, 30855-69-7; **13**, 30855-70-0; **14**, 30855-71-1; **15a**, 30855-72-2; **15b**, 30855-73-3; **16**, 30855-74-4; **17**, 30855-75-5; **18**, 30855-76-6; **19**, 30855-77-7; **20**, 30855-78-8.

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Pyrazolotriazines from Condensation of Nitro with Amino Groups

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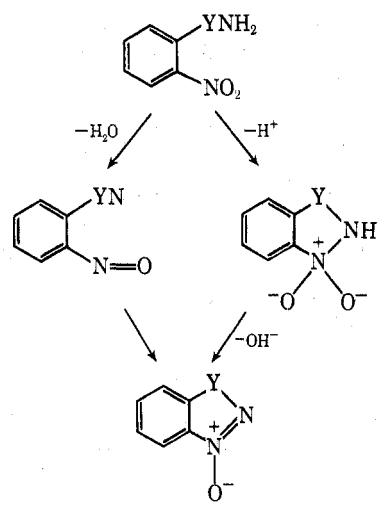
The *o*-nitrophenylhydrazones and 2,4-dinitrophenylhydrazones of α-cyanophenylacetaldehyde and its *p*-chloro and *p*-methoxy derivatives were isomerized to the corresponding 1-*o*-nitroaryl-5-aminopyrazoles. These were converted to 3-arylpyrazolo[5,1-*c*]benzo-1,2,4-triazine 5-oxides with potassium hydroxide. The expected interference if a nitroso nitrene intermediate were involved could not be detected. The 3-phenyl and 3-*p*-methoxyphenyl analogs were deoxygenated to the corresponding 3-arylpyrazolobenzotriazines by catalytic hydrogenation. 3-Phenylpyrazolo[5,1-*c*]benzo-1,2,4-triazine was also prepared by cyclization of the diazonium salt of 5-amino-1,4-diphenylpyrazole.

Various heterocyclic structures having a cyclic azoxy group can be prepared by base-catalyzed reaction of nitro and primary amino groups in the same molecule.[3] The mechanism has been assumed to be nucleophilic attack by the amino group on the nitro nitrogen, analogous to the aldol condensation,[3,4] but the assumption has never been questioned and the mechanism has never been investigated. A plausible alternative mechanism is internal oxidation of the amino group by the nitro group, with expulsion of water and formation of a nitroso nitrene as an intermediate (eq 1). Oxidation of



(1)

Y = bridge of 1 or 2 atoms

amino groups to give products that might have arisen from a nitrene has been reported,[5] and there is precedent for reaction of a nitrene with a nitroso group in the recent report that *o*-azido-*o'*-nitrosobiphenyl is converted to benzocinnoline oxide by heat.[6] The fact that this product is also formed by the base-catalyzed cyclization of *o*-nitro-*o'*-aminobiphenyl[7] is suggestive (eq 1, Y = *o*-C_6H_4).

We had in our hands a way to test whether the cyclization of nitro and amino groups to form an azoxy function involves a nitrene intermediate. The test is based on the fact that reactions that should produce 5-nitrenopyrazoles in fact produce the isomeric fragmentation products, azoacrylonitriles.[8] A 1-*o*-nitrophenyl-5-aminopyrazole, therefore, should produce some fragmentation product when exposed to cyclizing conditions, if it passes through a nitrene stage (Scheme I). This would be a significant limitation on the synthetic use of this cyclization.

A group of 1-(*o*-nitrophenyl)-5-aminopyrazoles were prepared by treating arylcyanoacetaldehydes (I) with 2-nitro- or 2,4-dinitrophenylhydrazine. When carried out in benzene without any added catalyst but with continuous removal of water, the reaction generally yielded the corresponding hydrazones II, which were readily cyclized by exposure to acid to form the isomeric 5-aminopyrazoles (Table I). The uncyclized hydrazones more or less readily assumed a red tint on long exposure in solution to air. The parent compound, α-cyanophenylacetaldehyde phenylhydrazone, eventually produced small amounts of α-phenyl-β-phenylazoacrylonitrile; deliberate oxidation with permanganate gave this product in 95.4% yield.

The 1-(*o*-nitrophenyl)-5-aminopyrazoles were warmed with potassium hydroxide in aqueous pyridine and were thereby converted to orange-red, crystalline products. No infrared absorption could be detected in the region for C≡N stretching, although their color while somewhat light was not inconsistent with the highly conjugated arylazoacrylonitrile structure. These substances, which were obtained pure in very high yields

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(3) J. D. London and G. Tennant, *Quart. Rev., Chem. Soc.*, **18**, 389 (1964).

(4) A. Wohl, W. Aue, and O. Ahlert, *Ber.*, **36**, 4135 (1906); A. Wohl and W. Aue, *ibid.*, **34**, 2442 (1901); P. Jacobson, W. Lischke, and P. Askenazy, *Justus Liebigs Ann. Chem.*, **303**, 367 (1898).

(5) P. A. S. Smith, "Nitrenes," W. Lwowski, Ed., Interscience–Wiley, New York, N. Y., 1970, Chapter 4.

(6) L. A. Neiman, W. I. Maimind, and M. M. Shemyakin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1357 (1964).

(7) C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wotring, and E. A. Pacofsky, *J. Org. Chem.*, **25**, 736 (1960).

(8) P. A. S. Smith, G. J. W. Breen, M. K. Hajek, and D. V. C. Awang, *ibid.*, **35**, 2215 (1970).

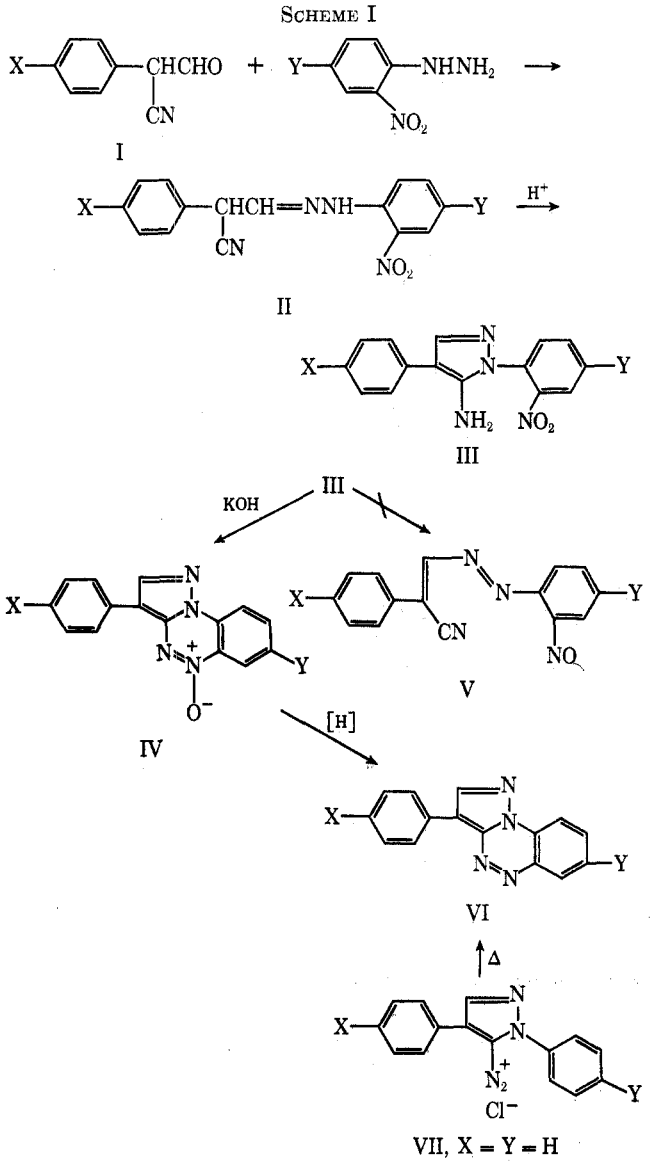
TABLE I

ARYL-α-CYANOACETALDEHYDE o-NITROPHENYLHYDRAZONES (II), 1,4-DIARYL-5-AMINOPYRAZOLES (III), AND 3-ARYLPYRAZOLO[5,1-c]BENZO-1,2,4-TRIAZINE 5-OXIDES (IV)[a]

		II		III			IV		
X	Y	Yield, %	Mp, °C	Yield, %	Mp, °C	Color[b]	Yield, %	Mp, °C	Color[b]
H	H	85	139–140	80	153–155	Y	92	213–214	BO
Cl	H	92	164–165	91	154–155	Y	94	236–237	BO
CH_3O	H	89	133–134	86	135.5–136.5	O	87	218–219	OR
H	NO_2	90	163–164	89	188–189	Y	91	262–263	DR
Cl	NO_2	93	180 dec	93	201–202	OBr	93	286–287	DR
CH_3O	NO_2	85	163–164	84	160–161	YO	73	257–258	DR

[a] Satisfactory analyses (±0.2% for C, H, and N) were obtained for all compounds reported here: Ed. [b] O = orange, R = red, Y = yellow, Br = brown, B = bright, D = dark.

SCHEME I



(Table I), appeared to be the isomeric pyrazolo[5,1-c]-benzo-1,2,4-triazine 5-oxides (IV), but infrared identification of the azoxy function was too ambiguous to be decisive.

The structures of two of them were confirmed by reduction in good yield to the corresponding pyrazolobenzotriazines (VI) with hydrazine and palladium (the other examples too easily suffered dehalogenation or reduction of a nitro group). The isomeric 3-[α-cyanobenzyl]benzo-1,2,4-triazine structure was ruled out by the lack of a C≡N stretching band in the infrared. The spectra of the deoxygenation products were also simpler than those of the 5-oxides in the 1200–1350-cm^{-1} region, where azoxy compounds generally absorb;[9] bands at 1222–1225 and 1337–1340 cm^{-1} were present in the spectra of IV (except that IVc lacked the latter) but not VI. Furthermore, simple deoxygenation, without concomitant addition of hydrogen, is a reaction only to be expected of an *N*-oxide function and not of the nitrosophenylazoacrylonitrile structure.

The only previously reported example of the pyrazolo[5,1-c]benzo-1,2,4-triazine system is the 2,3-dimethyl compound, which was prepared by cyclization of diazotized 5-amino-3,4-dimethyl-1-phenylpyrazole.[10] The structure of one of our deoxygenation products was confirmed by the analogous synthesis from 5-amino-1,4-diphenylpyrazole, which produced VIIa identical with that obtained by deoxygenation.

Our results thus uphold the putative aldol-type mechanism (although without strictly proving it) and demonstrate that synthesis of diazine *N*-oxide analogs can be accomplished without interference arising out of possible nitrene intermediates.

Experimental Section

α-Cyanoarylacetaldehyde Arylhydrazones (II).—These compounds were prepared from the α-cyanoarylacetaldehyde (11 mmol) and the arylhydrazine (10 mmol) by refluxing them in about 100 ml of benzene in an apparatus fitted with a Dean-Stark trap to remove water. The reactions appeared to be essentially complete in about 3 hr, but refluxing was continued for 16 hr, after which most of the solvent was removed *in vacuo*, and the products were precipitated in an essentially pure state by addition of ligroin. Analytical samples were obtained by recrystallization from ethyl acetate, alone or mixed with ligroin. The results are summarized in Table I. All samples showed consistent infrared spectra, including absorption at 2180–2200 cm^{-1} (C≡N stretching).

The unsubstituted compound, α-cyanophenylacetaldehyde phenylhydrazone, was isolated after only a 2-hr reflux period: yield 80%; white micro needles; mp 112–113°; infrared (Nujol) 3350 (w, NH), 2180 cm^{-1} (s, C≡N); nmr ($CDCl_3$) δ 6.06 (s, 1 H), 6.66–7.4 (m, 12 H). The nmr signal at δ 6.06 disappeared upon addition of D_2O.

Anal. Calcd for $C_{15}H_{13}H_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.45; H, 5.52; N, 17.86.

Prolonged warming of the foregoing phenylhydrazone in ethanol converted it into the isomeric 5-amino-1,4-diphenylpyrazole, mp 138–140° (lit.[11] 140–141°). Repetition of the procedure of Rupe and Grünholz,[12] reported to produce the phenylhydrazone with mp 155–156°, in our hands produced only the foregoing pyrazole.

α-Phenyl-β-phenylazoacrylonitrile.—A solution of 235 mg of α-cyanophenylacetaldehyde phenylhydrazone in 50 ml of benzene

(9) B. W. Langley, B. Lythgoe, and L. S. Rayner, *J. Chem. Soc.*, 4191 (1952).
(10) E. Mohr, *J. Prakt. Chem.*, **90**, 509 (1914).
(11) C. Alberti, *Gazz. Chim. Ital.*, **89**, 1017 (1959).
(12) H. Rupe and J. Grünholz, *Helv. Chim. Acta*, **6**, 102 (1923).

was stirred vigorously at room temperature with 25 ml of a 1% solution of potassium permanganate in water for 3 hr. Evaporation of the dried benzene layer left 220 mg (94.4%) of dark red α-phenyl-β-phenylazoacrylonitrile, identical (infrared, mixture melting point) with the substance obtained[8] by thermolysis of 5-azido-1,4-diphenylpyrazole. The same product was formed in traces upon long exposure to the air of solutions of the phenylhydrazone in organic solvents and could be isolated by careful concentration, mp 95–96°.

5-Amino-1-(*o*-nitrophenyl)-4-arylpyrazoles (III).—The corresponding *o*-nitrophenylhydrazones (II) (generally 10 mmol) were boiled for 3 hr in 20 ml of glacial acetic acid containing 2 drops of concentrated sulfuric acid. The solvent was then removed *in vacuo*, the residue was triturated with ice water until it solidified, and a few drops of aqueous ammonia were added. The yellow solids so produced were washed with water, dried, and recrystallized from ethyl acetate. The results are collected in Table I. All of the substances so obtained were free of infrared absorption in the 2100–2300-cm^{-1} region, and all showed absorption at 3248–3300 and 3370–3410 cm^{-1} attributable to NH.

Some of the pyrazoles were also prepared directly from the aldehyde and arylhydrazine by refluxing them in ethanol solution for 48 hr, and in some cases ethanol was used as the recrystallizing solvent; yields were similar. When refluxing of the ethanolic reaction mixtures was discontinued as soon as clear solutions were obtained, the products were found to be the arylhydrazones contaminated with only small amounts of the isomeric pyrazoles.

Pyrazolo[5,1-*c*]benzo-1,2,4-triazine 5-Oxides (IV).—Solutions of the 5-aminopyrazoles (III, 5 mmol) in 10 ml of pyridine were mixed with 10 ml of 5% aqueous potassium hydroxide at room temperature; the mixtures soon became deep red. After heating on a steam bath for 3 hr, the mixtures were poured on ice slurried with enough dilute sulfuric acid to make the resulting mixture slightly acidic. The orange precipitates that separated were collected, washed with cold water, and dried. Analytical samples were obtained by recrystallization from ethyl acetate or dimethylformamide. The results are collected in Table I. None of the examples had infrared absorption above 3200 cm^{-1}, and all of them had a strong absorption peak at 1222–1226 cm^{-1}.

Pyrazolo[5,1-*c*]benzo-1,2,4-triazines (VI).—Compounds VIa and VIc were obtained by adding 1 ml of 90% hydrazine hydrate to a hot solution of 5 mmol of IVa or IVc in 200 ml of ethanol to which 100 mg of 5% palladium on charcoal had been added. After 16 hr of refluxing, the catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the residue was recrystallized from ethyl acetate. When the foregoing procedure was applied to IVb, the unsubstituted product VIa was obtained in 69% yield.

3-Phenylpyrazolo[5,1-*c*]benzo-1,2,4-triazine (VIa) was obtained in 73% yield, mp 166–167°, yellow-orange.

Anal. Calcd for $C_{15}H_{10}N_4$: C, 73.15; H, 4.09; N, 22.75. Found: C, 73.22; H, 4.13; N, 22.86.

3-*p*-Methoxyphenylpyrazolo[5,1-*c*]benzo-1,2,4-triazine (VIc) was obtained in 76% yield, mp 152–153°, orange-red.

Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.53; H, 4.23; N, 20.32.

Preparation of VIa from VII.—A solution of 0.52 g (7.5 mmol) of sodium nitrite in 10 ml of water was added dropwise to a stirred and chilled solution of 1.18 g (5 mmol) of 5-amino-1,4-diphenylpyrazole (VII)[8] in 50 ml of 10% hydrochloric acid. After 15 min, 0.2 g of urea was added, and the mixture was allowed to stand in an ice bath for 3 hr and at room temperature overnight. The mixture was then brought to a boil, whereupon the flocculent, yellow precipitate coagulated to a brown mass. The product was filtered off, washed with cold water, and repeatedly recrystallized from ethanol with the aid of charcoal. A final recrystallization from ethyl acetate gave 0.40 g (32.5%) of yellow needles, mp 166–167°, identical in infrared spectrum and mixture melting point with VIa prepared from IVa.

Registry No.—IIa, 30953-09-4; IIb, 30885-17-7; IIc, 30885-18-8; IId, 30885-19-9; IIe, 30885-20-2; IIf, 30885-21-3; IIIa, 30885-22-4; IIIb, 30885-23-5; IIIc, 30885-24-6; IIId, 30885-25-7; IIIe, 30885-26-8; IIIf, 30885-27-9; IVa, 30885-28-0; IVb, 30885-29-1; IVc, 30885-30-4; IVd, 30885-31-5; IVe, 30885-32-6; IVf, 30885-33-7; VIa, 30885-34-8; VIc, 30885-35-9; α-cyanophenylacetaldehyde phenylhydrazone, 30885-36-0; α-phenyl-β-phenylazoacrylonitrile, 30885-37-1.

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Pyrimido[5,4-*e*]-*as*-triazines. V. The Preparation of Alkyl 6-Amino-*as*-triazine-5-carboxylates from Some 5-Chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazines[1]

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The reaction of 5-amino-4-chloro-6-hydrazinopyrimidine (**1**) with ethyl ortho(methoxy)acetate, ethyl ortho(chloromethyl)acetate, and ethyl ortho(ethoxycarbonyl)acetate gave, respectively, the corresponding 3-substituted 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazines (**3–5**). Oxidative 5-methoxydechlorination of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**2**), **3**, and **4** with silver oxide in MeOH gave the heteroaromatic 5-methoxy compounds **7–9**. The pyrimidine ring of **7** was opened with methanolic HCl to give methyl 6-amino-*as*-triazine-5-carboxylate (**17**). The formation of **17** and some 3-substituted derivatives was also effected by treatment of **2–5** with Br_2 in alcohol.

In previous papers, we described some replacement reactions of the chloro group of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**2**) with various nucleophiles.[2,3] We now report the preparation and conversion of this and related type compounds to the esters of 6-amino-*as*-triazine-5-carboxylate (*i.e.*, **17**). Previously, the preparation of derivatives of **17** from simple reactants was unsuccessful.[4]

The condensation of **1** with ethyl orthoformate in the presence of hydrochloric acid was shown to give **2**.[5] Similarly, the reaction of **1** with ethyl ortho(methoxy)-acetate,[6] ethyl ortho(chloromethyl)acetate,[7] and ethyl

(1) This investigation was supported by funds from the C. F. Kettering Foundation and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract NIH-71-2021.

(2) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **34**, 3161 (1969).

(3) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *ibid.*, **34**, 2102 (1969).

(4) R. N. Naylor, G. Shaw, D. V. Wilson, and D. N. Butler, *J. Chem. Soc.*, 4845 (1961).

(5) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **28**, 923 (1963).

(6) This ortho ester was prepared by the method of S. M. McElvain and P. M. Walters, *J. Amer. Chem. Soc.*, **64**, 1963 (1942).

(7) S. M. McElvain and J. W. Nelson, *ibid.*, **64**, 1825 (1942).