hydrochloric acid was added to the oily mixture and stirred well. The flocculent white precipitate was added to the oily mixture and stirred well. The flocculent white precipitate was filtered, air-dried, and then recrystallized from 60% ethanol–water containing 2 drops of concentrated hydrochloric acid. The precipitate was then washed with a small amount of water and dried; yield 0.80 g. (59.2%) of 2-chloro-4,7-dibenzylaminoimidazo[4,5-*d*]pyridazine hydrochloride, m.p. 180–182° dec.

Anal. Calcd. for $C_{19}H_{17}N_6Cl{\cdot}HCl$: C, 56.8; H, 4.51; N, 20.9. Found: C, 56.5; H, 4.58; N, 20.9.

4,7-Dibenzylaminoimidazo[4,5-*d*]pyridazine Hydrochloride.—2 - Chloro - 4,7 - dibenzylaminoimidazo[4,5 - *d*]-pyridazine hydrochloride (0.5 g., 1.25×10^{-3} mole) was suspended in 40 ml. of liquid ammonia. This suspension was prepared in a three-neck flask equipped with a mechanical stirrer and a drying tube. With vigorous stirring, small pieces of sodium were added to the liquid ammonia suspension until a permanent blue color was visible. This operation required about 0.22 g. (8.3×10^{-3} mole) of ammonium chloride. The solution was allowed to stir for another hour and then evaporated to dryness and the residue air-dried. The inorganic salts were extracted with 10 ml. of warm water which was then decanted from the very gummy free base as reported by Carbon.[11] This residue was dissolved in 5 ml. of 3 *N* sodium hydroxide, a red tar removed by filtration, and the filtrate made strongly acid with concentrated hydrochloric acid. The colorless crystals were removed by filtration, washed with a small amount of water, and dried. The product was recrystallized from *n*-propyl alcohol; yield 0.19 g. (42.5%) of colorless needles, m.p. 200–202° dec.

Anal. Calcd. for $C_{19}H_{18}N_6{\cdot}HCl$: C, 62.2; H, 5.18; N, 22.9. Found: C, 61.6; H, 5.30; N, 22.8.

Dichloro-(2 or 4 or 7)-hydroxyimidazo[4,5-*d*]pyridazine.—2,4,7-Trichloroimidazo[4,5-*d*]pyridazine (0.5 g.) was dissolved in concentrated sulfuric acid and the resultant solution then cooled in an ice bath. Four milliliters of fuming nitric acid (sp. gr. 1.5) was added to the cold solution; there was no visible reaction. The temperature of the solution was then raised to 90° and maintained there for 10 min. During this period there was some gas evolution with the solution turning to a brown color. The solution was thereupon cooled and poured into 50 ml. of crushed ice. The white precipitate which formed was removed by filtration and dried. The material was recrystallized from 30 ml. of 1 *N* hydrochloric acid; yield 0.32 g. (69.5%) of fine white crystals which did not melt below 300°.

Anal. Calcd. for $C_5H_2N_4OCl_2$: C, 29.2; H, 0.98; N, 27.3. Found: C, 29.1; H, 1.20; N, 27.1.

Adjacent Nitro and Guanidino Groups. III. Preparation and Rearrangement of Some Pyrido[2,3-*e*]-*as*-triazine 1-Oxides[1]

JOHN A. CARBON AND SHIRLEY H. TABATA

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

Received February 9, 1962

A series of 2-guanidino-3-nitro-5-substituted pyridines (II) has been prepared by treatment of the corresponding 2-chloro compounds (I) with guanidine in *t*-butyl alcohol. These compounds (II) undergo a rapid base-catalyzed cyclization to form 3-aminopyrido[2,3-*e*]-*as*-triazine 1-oxides (III). The cyclized compound (IIIa) rearranges in hot alkaline solution to form triazolo[4,5-*b*]pyridine 3-carboxamide (IV) and triazolo[4,5-*b*]pyridine (V). The 3-amino derivatives (III) were converted to the corresponding 3-hydroxy compounds (VI) with nitrous acid, and then to the 3-chloro compounds (VII) with phosphorus oxychloride. Displacement reactions on the 3-chloro compounds (VII) gave a series of pyrido[2,3-*e*]-*as*-triazine 1-oxides with various groups in the 3-position (VIII). The *N*-oxide function in compound IIIa was best removed by treatment with sodium dithionite at room temperature to form the 1,2-dihydro compound (X), followed by aromatization with potassium ferricyanide to form XI.

As a continuation of our work on the extension of the Arndt benzotriazine 1-oxide ring closure[2] to heterocyclic systems, we have now prepared some pyridine compounds containing adjacent nitro and guanidino groups and have studied their behavior in hot aqueous alkali. The formation of both the normal ring closed products, *e.g.*, 3-aminopyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIa), and rearranged products, *e.g.*, triazolo[4,5-*b*]pyridine (IVa), was observed. The base-catalyzed rearrangement of fused ring triazine *N*-oxides, recently discovered in our laboratory, therefore occurs in the pyrido[2,3-*e*]-*as*-triazine 1-oxide series as well as in the 1,2,4-benzotriazine 1-oxide series described earlier.[1b]

Attempts to prepare 2-guanidino-3-nitropyridine (IIa) by the treatment of 2-chloro-3-nitropyridine (Ia) with a solution of guanidine in ethanol resulted predominantly in ether formation, the main product being 2-ethoxy-3-nitropyridine. A small quantity (4.6%) of the desired product (IIa) could be isolated and characterized, however. The use of guanidine in acetone solution also gave low yields with much tar formation.

Good yields of 2-guanidino-3-nitropyridine (IIa) were finally obtained by the slow addition of a solution of guanidine in *t*-butyl alcohol to a refluxing solution of 2-chloro-3-nitropyridine (Ia) in the same solvent. The reverse procedure, addition of the chloro compound to the guanidine solution, was much less satisfactory. Solutions of guanidine in *t*-butyl alcohol were conveniently prepared by adding an equivalent of guanidine hydrochloride to a suspension of sodium *t*-butoxide (prepared from sodium hydride) in *t*-butyl alcohol, heating for a

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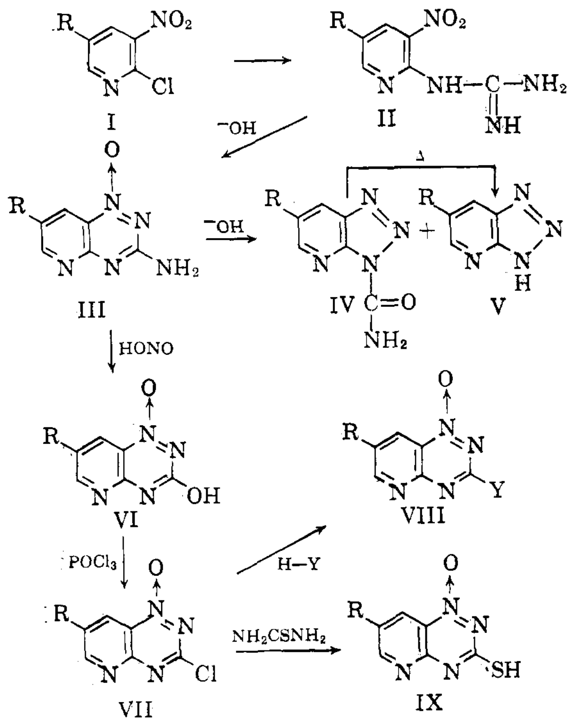
(1) For preceding papers in this series, see (a) J. A. Carbon, *J. Org. Chem.*, **26**, 455 (1961); (b) J. A. Carbon, *ibid.*, **27**, 185 (1962).

(2) F. Arndt, *Ber.*, **46**, 3522 (1913). See ref. 1 for a detailed discussion and leading references.



Series a: R = H
Series b: R = CH_3
Series c: R = Cl

short time at 50° to complete the reaction, and filtering to remove the sodium chloride.

The 2-guanidino-3-nitropyridines (II) prepared in this work were bright yellow-orange crystalline solids, soluble in hot water, but fairly insoluble in cold water. They have the property of forming monohydrochloride salts which were quite insoluble in cold water, a characteristic very useful in their purification.

Preliminary studies on the base-catalyzed ring closure of 2-guanidino-3-nitropyridine (IIa) using 1 *N* sodium hydroxide at 100° showed that the desired 3-aminopyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIa) was formed very rapidly, the reaction being complete in three to five minutes. The ring-closed product (IIIa) was isolated as a bright yellow, beautifully crystalline solid from the cooled reaction mixture. Although the yield in the 5-methyl series (IIb→IIIb) was good (75%), we were unable to raise the yield above 40% in the desmethyl series (IIa→IIIa) when aqueous sodium hydroxide was used as the base. A yield study, using various concentrations of alkali, revealed that the yield of product (IIIa) at base concentrations between 1–5% is fairly constant at 35–40%. Base concentrations below 1% seemed to be inadequate to bring about the cyclization, while at concentrations of alkali above 5% very little product was obtained because of conversion to base-soluble compounds, subsequently identified as IVa and Va. It was found, however, that the use of a strong potassium carbonate solution at 100° for the ring closure gave much higher yields of the desired triazine 1-oxide (IIIa). The rearrangement of IIIa to IVa is minimized under these conditions.

An examination of the mother liquors from the sodium hydroxide-catalyzed cyclization of IIa revealed the presence of a labile, acidic compound which separated from the acidified reaction mixture. Air-dried samples of this compound exhibited a strong carbonyl absorption in the infrared at 5.7 μ. However, drying at 100° *in vacuo* or recrystallization from water resulted in the formation of a different compound which was transparent in the carbonyl region. The latter compound gave satisfactory elemental analyses for $C_5H_5N_4$ and gave an infrared spectrum identical in all respects with that of an authentic sample of triazolo[4,5-*b*]pyridine (Va),[3] prepared by the treatment of 2,3-diaminopyridine (IXa) with nitrous acid.

An analytically pure sample of the unknown carbonyl-containing compound (IVa) was finally obtained by dissolution in dilute aqueous alkali, filtering, and precipitation with acetic acid. After drying *in vacuo* at room temperature this material gave satisfactory analyses for $C_6H_5N_5O$, but was converted to Va when dried *in vacuo* at 100°. The structure of this carbonyl-containing compound is undoubtedly triazolo[3,4-*b*]pyridine-3-carboxamide (IVa), a compound which would be expected to lose the carboxamide group readily as cyanic acid.[4]

3-Aminopyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIa) undergoes the base-catalyzed rearrangement to form IVa much more readily than does 3-amino-1,2,4-benzotriazine-1-oxide. For example, compound IIIa is completely destroyed by 5% sodium hydroxide at 100° in less than twenty-five minutes, while 3-amino-1,2,4-benzotriazine 1-oxide requires three hours at 100° in 10% alkali to complete the rearrangement.[1b] This is readily explainable on the basis of the increased electron-withdrawing power of the pyridine ring over that of the benzene ring, which renders the 3-position of the triazine more susceptible to attack by the hydroxide ion.[5]

3-Amino-7-methylpyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIb) did not appear to rearrange as easily as the corresponding desmethyl compound (IIIa) and could be produced in good yield by the treatment of IIb with hot aqueous sodium hydroxide. The corresponding 7-chloro compound (IIIc) was more alkali-sensitive, and the use of potassium carbonate was required to give good yields of this compound.

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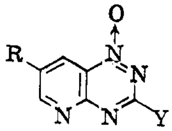
(3) A. E. Tschitschibabin and A. W. Kirsanow, *Ber.*, **60**, 766 (1927); J. R. Vaughan, Jr., J. Krapcho, and J. P. English, *J. Am. Chem. Soc.*, **71**, 1885 (1949).

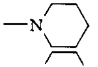
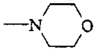
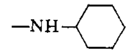
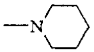
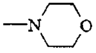
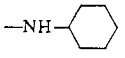
(4) The structure of IVa also follows from analogy with the base-catalyzed rearrangement of 3-amino-1,2,4-benzotriazine 1-oxide, which we have previously shown leads to benzotriazole-1-carboxamide and benzotriazole (see ref. 1b). In that case the structure of the carboxamide was proven unequivocally by synthesis from benzotriazole and cyanic acid. However, we have not been able to bring about a reaction of triazolo[3,4-*b*]pyridine (Va) with cyanic acid to form IVa.

(5) For a discussion of the probable mechanism of this rearrangement reaction, see ref. 1b.

TABLE I



3-SUBSTITUTED PYRIDO[2,3-*e*]-*as*-TRIAZINE 1-OXIDES

Y	R	M.p., °C.	Yield, %	Re-cryst. sol-vent[a]	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$—N(C_2H_5)_2$	H	124.5–125.0	88	B	$C_{10}H_{13}N_5O$	54.79	5.98	31.95	54.99	5.97	32.06
	H	116.5–117.5	65	B	$C_{11}H_{13}N_5O$	57.12	5.67	30.28	57.03	5.99	30.17
	H	169.0–169.5	86	A	$C_{10}H_{11}N_5O_2$	51.50	4.76	30.03	51.71	4.82	29.88
	H	190.5–191.0	59	A	$C_{12}H_{15}N_5O$	58.75	6.16	28.55	58.69	5.91	28.41
$—NHCH_2CH_2C_6H_5$	H	174.5–175.0	83	A	$C_{14}H_{13}N_5O$	62.90	4.90	26.20	62.89	4.99	26.07
$—NH—n\text{-}C_4H_9$	H	174.5–175.0	91	A	$C_{10}H_{13}N_5O$	54.79	5.98	31.95	54.80	5.99	32.15
$—NH(CH_2)_2N(CH_3)_2$	H	250–251 dec.[c]	99	A	$C_{11}H_{17}ClN_6O$	46.38	6.01	29.51	46.36	6.26	29.48
$—NHNH_2$	H	252–253 dec.	77	C	$C_6H_6N_6O$	40.44	3.40	47.17	40.64	3.38	47.42
$—OCH_3$	H	149.0–149.5 dec.[b]	69	A	$C_7H_6N_4O_2$	47.18	3.40	31.44	46.85	3.28	31.45
$—O—n\text{-}C_4H_9$	H	99.5–100.5	17	B	$C_{10}H_{12}N_4O_2$	54.54	5.49	25.45	54.25	5.70	25.60
—SH	H	197–198 dec.	70	D	$C_6H_4N_4OS$	39.99	2.24	31.11	38.46	2.32	31.04[d]
$—N(C_2H_5)_2$	CH_3	102–103	93	B	$C_{11}H_{15}N_5O$	56.63	6.48	30.02	56.86	6.53	30.03
	CH_3	137.5–138.5	88	B	$C_{12}H_{15}N_5O$	58.75	6.16	28.55	58.56	5.90	28.36
	CH_3	242–243	96	B	$C_{11}H_{13}N_5O_2$	53.42	5.30	28.32	53.40	5.54	28.16
	CH_3	219.5–220.0	49	A	$C_{13}H_{17}N_5O$	60.21	6.61	27.01	60.48	6.78	27.17
$—NHNH_2$	CH_3	245–246 dec.	82	C	$C_7H_8N_6O$	43.74	4.20	43.73	43.78	4.09	43.54

[a] Recrystallization solvents: A, ethanol; B, dilute ethanol; C, dissolved in hydrochloric acid, precipitated with alkali; D, dissolved in sodium hydroxide, precipitated with acid. [b] When placed on the block at 135°. [c] Monohydrochloride salt. [d] Calcd.: S, 17.79; O, 8.97. Found: S, 18.14; O, 8.87. No halogen or ash present. This compound was difficult to analyze reproducibly.

The treatment of either 3-aminopyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIa) or the corresponding 7-methyl compound (IIIb) with nitrous acid resulted in conversion to the corresponding 3-hydroxy compounds (VIa and b).[6] As might be expected, VIa and b are acidic and are soluble in dilute aqueous alkali to form red solutions from which the original compounds may be obtained unchanged upon acidification.

The 3-hydroxy compounds (VI) were readily converted to the corresponding 3-chloro derivatives (VII) by hot phosphorus oxychloride. Low yields and highly colored by-products were encountered in these reactions until it was discovered that the refluxing should not be continued after the starting material had all dissolved and the resulting solution should be worked up without undue delay. Prolonged refluxing or allowing the reaction mixture to stand overnight invariably resulted in low yields and highly colored reaction mixtures.

These 3-chloro derivatives (VII) were quite reactive and would react rapidly with a variety of nucleophiles in chloroform or acetone solution at 0° to form the corresponding 3-substituted derivatives. Because of the high reactivity of VIIa and its sensitivity to bases, it was necessary to run displacement reactions at low temperature and to add the base slowly to avoid a local excess. The compounds produced in this manner are shown in Table I. Similarly, the treatment of VIIa with solutions of sodium methoxide in methanol and sodium *n*-butoxide in *n*-butyl alcohol resulted in the formation of the 3-methoxy (VIIIa, Y = OCH_3) and 3-*n*-butoxy (VIIIa, Y = OC_4H_9) derivatives, respectively. The action of thiourea in boiling ethanol on VIIa gave the 3-mercapto (or 3-thione) compound (IXa) as a dark red solid. This latter material was freely soluble in aqueous alkali as would be predicted for a heterocyclic mercapto derivative of this type.

The reduction of 3-aminopyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIa) was investigated with the intent of removing the *N*-oxide function. The treatment of IIIa with zinc dust in acetic acid[1b] or in aqueous ammonium chloride[7] gave only deep purple reaction mixtures from which no pure compounds could be obtained. Catalytic reduction of IIIa gave what was apparently a dihydro compound (X) since the desired 3-aminopyrido[2,3-*e*]-*as*-triazine (XI) could be produced from it by mild oxidation with potassium ferricyanide.[8] The best

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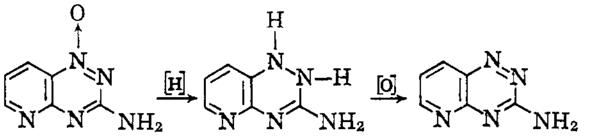
[6] These compounds probably exist in the keto form in the solid state since they give a strong carbonyl absorption at 5.9 μ (Nujol mull). However for convenience they are shown in the tautomeric 3-hydroxy form.

[7] J. Jiu and G. P. Mueller, *J. Org. Chem.*, **24**, 813 (1959).

[8] The reduction of the analogous benzo compound, 3-amino-1,2,4-benzotriazine 1-oxide, is known to give a 1,2-dihydro compound which is easily oxidized to 3-amino-1,2,4-benzotriazine by aqueous potassium ferricyanide (see ref. 2 and 7).

conditions for the reduction of IIIa were found to be aqueous sodium dithionite at room temperature, which very rapidly reduced compound IIIa to the dihydro derivative (X). This material was obtained as a cream-colored solid which was rapidly oxidized when exposed to the air. Compound X was best converted to the aromatic compound XI by oxidation with alkaline potassium ferricyanide.



IIIa X XI

Further work is in progress on the chemistry of adjacent nitro and guanidino groups in other heterocyclic systems and will be reported at a later date.

Experimental[9]

2-Guanidino-3-nitropyridine (IIa). A. Using Guanidine in Ethanol.—To a solution of sodium ethoxide, prepared by adding 2.42 g. (0.105 g.-atom) of sodium to 200 ml. of absolute ethanol, was added 10.0 g. (0.105 mole) of guanidine hydrochloride, and the resulting mixture was stirred for 15 min. at 50–60°. 2-Chloro-3-nitropyridine (Ia)[10] (7.93 g., 0.050 mole) was added portionwise and the mixture was refluxed with stirring for 2.5 hr. The sodium chloride was removed by suction filtration and the dark brown filtrate evaporated to dryness *in vacuo* to leave an oil, which was treated with 75 ml. of water and extracted into three portions of ether. The combined extracts were dried and evaporated, and the resulting yellow oil treated with 100 ml. of petroleum ether (b.p. 40–60°). Filtration and recrystallization of the yellow solid from water gave 0.42 g. (4.6%) of yellow-orange needles of IIa, m.p. 143–144°.

Anal. Calcd. for $C_6H_7N_5O_2$: C, 39.77; H, 3.90; N, 38.66. Found: C, 39.96; H, 3.71; N, 38.55.

The petroleum ether filtrate from IIa was evaporated and the oil distilled under vacuum to give **2-ethoxy-3-nitropyridine** as a pale yellow oil, b.p. 125–128° at 14 mm., n^{25}_D 1.5370. The yield was 4.8 g. (57%).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 49.98; H, 4.79; N, 16.66. Found: C, 50.07; H, 4.69; N, 16.86.

B. Using Guanidine in *t*-Butyl Alcohol.—A suspension of sodium *t*-butoxide in *t*-butyl alcohol was prepared by the cautious addition of 60.8 g. (1.43 moles) of sodium hydride (56.5% suspension in mineral oil) to 2400 ml. of dry *t*-butyl alcohol. The resulting mixture was allowed to stand at room temperature until reaction was complete (about 1 hr.). Guanidine hydrochloride (150 g., 1.5 moles) was added in one portion, and the mixture warmed on the steam bath with frequent stirring for about 0.5 hr. The resulting white suspension was filtered with suction and the filter cake (sodium chloride) washed with fresh *t*-butyl alcohol. The combined filtrates were slowly added over a period of 5 hr. to a rapidly stirred and refluxing solution of 112 g. (0.71 mole) of 2-chloro-3-nitropyridine (Ia) in 400 ml. of *t*-butyl alcohol. The resulting solution was refluxed an additional 3 hr.

The clear, dark yellow solution was cooled slightly, then 125 ml. of concentrated hydrochloric acid was slowly added with stirring. The resulting precipitate of **2-guanidino-3-nitropyridine hydrochloride** was collected and washed with ethanol to give 124.7 g. (82%), m.p. 258–260° dec. For analysis, this compound was recrystallized from water to obtain pale yellow needles of a monohydrate, m.p. 262–264° dec. Anhydrous samples could be obtained by drying *in vacuo* at 100°.

Anal. Calcd. for $C_6H_8ClN_5O_2$: C, 33.12; H, 3.71; Cl, 16.29. Found: C, 33.42; H, 3.89; Cl, 16.44.

The **free base** (IIa) was obtained as orange needles, m.p. 143–144°, by neutralization of an aqueous solution of the hydrochloride. The material thus obtained was identical in all respects to that produced by method A.

2-Guanidino-5-methyl-3-nitropyridine (IIb).—The reaction of 2-chloro-5-methyl-3-nitropyridine (Ib)[11] (17.3 g., 0.10 mole) with guanidine (0.21 mole) in *t*-butyl alcohol, using a procedure exactly analogous to that given above (method B) gave 2-guanidino-5-methyl-3-nitropyridine hydrochloride (11.0 g., 48%) as pale yellow leaflets from aqueous ethanol, decomposing slowly above 260°.

Anal. Calcd. for $C_7H_{10}ClN_5O_2$: C, 36.29; H, 4.35; Cl, 15.30. Found: C, 36.48; H, 4.36; Cl, 15.35.

The **free base** (IIb) was obtained as hydrated orange needles by neutralization of an aqueous solution of the hydrochloride salt. This material, apparently a monohydrate (Calcd. for $C_7H_9N_5O_2 \cdot H_2O$: H_2O, 8.45. Found: H_2O, 8.91), melted at 60–65°, resolidified, and finally melted at 145–147°. The anhydrous material, dried at 75° *in vacuo* overnight, had m.p. 145–147°.

Anal. Calcd. for $C_7H_9N_5O_2$: C, 43.07; H, 4.65; N, 35.88. Found: C, 42.86; H, 4.76; N, 35.99.

5-Chloro-2-guanidino-3-nitropyridine (IIc).—A similar application of method B to the reaction of guanidine (0.21 mole) in *t*-butyl alcohol with 2-bromo-5-chloro-3-nitropyridine[12] (23.8 g., 0.10 mole) gave a dark-colored reaction mixture, from which the hydrochloride salt of IIc could be precipitated by the addition of hydrochloric acid as a dark brown solid. This material was treated with 150 ml. of boiling water, filtered hot to remove a small quantity of insoluble material, and the resulting solution decolorized with Norit. The addition of concentrated ammonium hydroxide to pH 9 gave 7.8 g. (36%) of product (IIc) as orange needles, m.p. 127–133°.

An analytical sample was obtained as orange needles from water, m.p. 134.5–135.5°. This material was the **hemihydrate** (Calcd. for $C_6H_6ClN_5O_2 \cdot 1/2H_2O$: H_2O, 4.01. Found: H_2O, 4.18), but could be rendered anhydrous by drying overnight at 75° *in vacuo.*

Anal. Calcd. for $C_6H_6ClN_5O_2$: C, 33.42; H, 2.80; Cl, 16.45; N, 32.49. Found: C, 33.60; H, 2.88; Cl, 16.58; N, 32.53.

The **hydrochloride salt** of IIc was obtained as pale yellow plates by the addition of concentrated hydrochloric acid to a solution of IIc in ethanol, followed by recrystallization from water. This compound did not possess a definite melting point, but decomposed slowly above 220°.

Anal. Calcd. for $C_6H_7Cl_2N_5O_2$: C, 28.59; H, 2.80; Cl, 28.13; N, 27.78. Found: C, 28.39; H, 2.97; Cl, 27.84; N, 27.95.

Base-Catalyzed Cyclization and Rearrangement of 2-Guanidino-3-nitropyridine (IIa). A. In 1% Sodium Hydroxide.—Compound IIa (1.0 g., 5.5 mmoles) was suspended in 5.0 ml. of 1% sodium hydroxide and heated at 100° for 17 min. The starting material dissolved during this period to form a dark red solution from which **3-aminopyrido-[2,3-*e*]-as-triazine 1-oxide** (IIIa) quickly separated as yellow-brown needles. The mixture was cooled, filtered, the product washed with methanol to obtain 0.31 g. (35%) of IIIa, m.p. 254–255° dec. An analytical sample was prepared by recrystallization from water to obtain long yellow

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[9] The melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus.

[10] Purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin and recrystallized from petroleum ether (80–100°) before using.

[11] S. J. Childress and R. L. McKee, *J. Am. Chem. Soc.*, **73**, 3504 (1951).

[12] A. H. Berrie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 2042 (1952).

needles of unchanged melting point. It was necessary to dry this material at 140° at 0.2 mm. overnight to obtain completely anhydrous samples.

Anal. Calcd. for $C_6H_5N_5O$: C, 44.18; H, 3.09; N, 42.94. Found: C, 44.22; H, 2.93; N, 43.03.

The original alkaline filtrate from the above reaction was acidified by pH 4–5 with glacial acetic acid and chilled. Scratching the vessel wall induced crystallization of a cream-colored powder, subsequently identified as **triazolo[4,5-*b*]pyridine-3-carboxamide (IVa)**, m.p. 196–200° dec. This material could not be purified by conventional recrystallization from water because of ready conversion to triazolo[4,5-*b*]pyridine (V). An analytically pure sample was obtained by dissolution in cold aqueous sodium hydroxide, filtering, and neutralization to pH 4 with glacial acetic acid to obtain a colorless solid, m.p. 207–208° (converts to V on the block). This compound must be dried at room temperature *in vacuo,* since elevated temperatures result in transformation to compound V.

Anal. Calcd. for $C_6H_5N_5O$: C, 44.18; H, 3.09; N, 42.94. Found: C, 44.45; H, 3.21; N, 42.78.

This 3-carboxamide (IV) exhibits a strong carbonyl absorption in the infrared at 5.7 μ, while triazolo[4,5-*b*]pyridine (V) is transparent in this region.

Heating compound IV at 100° *in vacuo,* or recrystallization from hot water, gave **triazolo[4,5-*b*]pyridine** (V) as colorless needles, m.p. 207–208°, lit. m.p. 206–207°.[3] The infrared spectrum of this material was identical to that of an authentic sample, prepared by the method of Tschitschibabin.[3]

Anal. Calcd. for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.65. Found: C, 50.06; H, 3.45; N, 46.49.

B. Cyclization of IIa Using Aqueous Potassium Carbonate.—A mixture of 5.0 g. (0.021 mole) of IIa hydrochloride salt, 15 g. of potassium carbonate, and 50 ml. of water was vigorously stirred on the steam bath for 6.5 hr.[13] The resulting suspension was chilled to 5°, filtered, and the product washed with water and a little methanol to obtain 2.6 g. (74%) of IIIa as dark yellow needles, m.p. 254–255° dec. Recrystallization from water gave yellow needles of unchanged melting point, identical in all respects with the product produced by method A.

Rearrangement of 3-Aminopyrido[2,3-*e*]-*as*-triazine 1-Oxide (IIIa).—A suspension of 1.0 g. (6.1 mmoles) of IIIa in 7 ml. of 5% sodium hydroxide was heated at 100° in a water bath. After 10 min., the starting material had all dissolved and the pH had dropped to 8. An additional 1 ml. of 20% sodium hydroxide was added and the mixture heated at 100° for an additional 15 min. The pH was at least 10–11 at this point. The solution was cooled, filtered to clarify, and acidified to pH 4 with glacial acetic acid. The resulting pale yellow precipitate was collected and air-dried to give 0.77 g., m.p. 206–208° dec., which gave an infrared spectrum identical to that of **triazolo[3,4-*b*]pyridine-3-carboxamide (IV)** (see above). Heating a sample of this material overnight at 100° *in vacuo* gave **triazolo[4,5-*b*]-pyridine (V)**, identified by the infrared spectrum.

3-Amino-7-methylpyrido[2,3-*e*]*as*-triazine 1-Oxide (IIIb).—Twelve grams (0.056 mole) of IIb was mixed with 60 ml. of 1 *N* sodium hydroxide and heated to 80–85°. At this temperature an exothermic reaction occurred, and the heat source was removed. After the reaction had subsided an additional 50 ml. water was added, the mixture was cooled, and the product isolated by suction filtration to obtain 8.3 g. (83%) of yellow needles, m.p. 268–269° dec. The material was purified for analysis by recrystallization from methoxyethanol–water (7:3) and obtained as bright yellow needles of unchanged melting point.

Anal. Calcd. for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53. Found: C, 47.64; H, 4.16; N, 39.59.

3-Amino-7-chloropyrido[2,3-*e*]-*as*-triazine 1-Oxide (IIIc).—A mixture of 1.0 g. (4.6 mmoles) of IIc, 3.0 g. of potassium carbonate, and 10 ml. of water was heated at 100° for 6.5 hr. with stirring. After cooling, the product was isolated by filtration and washed with water. The crude product (0.84 g.), m.p. 194–198° dec., was purified by recrystallization from methoxyethanol with Norit, and obtained as 0.36 g. (39%) of yellow-orange leaflets, gradual decomposition above 260°.

Anal. Calcd. for $C_6H_4ClN_5O$: C, 36.47; H, 2.04; Cl, 17.95; N, 35.44. Found: C, 36.71; H, 2.06; Cl, 17.87; N, 35.49.

3-Hydroxypyrido[2,3-*e*]-*as*-triazine 1-Oxide (VIa).—Compound IIIa (50.1 g., 0.31 mole) was dissolved in a solution of 140 ml. of concentrated sulfuric acid in 560 ml. of water. The resulting solution was cooled to 20–25°, and a solution of 31.5 g. (0.46 mole) of sodium nitrite in 60 ml. of water slowly added with stirring over a 0.5-hr. period. After an additional hour at room temperature, the product was isolated by filtration and washed with water, m.p. 233–235° dec., 44.6 g. (88%). A sample was purified for analysis by dissolving in aqueous alkali, treating with Norit, and acidifying with acetic acid, to obtain pale yellow leaflets, m.p. 235–237° dec.

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.91; H, 2.46; N, 34.15; O, 19.00. Found: C, 44.12; H, 2.52; N, 34.03; O, 19.29.

3-Hydroxy-7-methylpyrido[2,3-*e*]-*as*-triazine 1-Oxide (VIb).—The treatment of compound IIIb (2.0 g., 0.011 mole) in 25 ml. of dilute sulfuric acid (20% v./v.) with 1.1 g. (0.016 mole) of sodium nitrite in 5 ml. of water, in a similar manner to that described for VIa, gave 1.57 g. (78%) of purified product, m.p. 230–231° dec. Purification is accomplished either by precipitation from aqueous alkali with acetic acid, or by recrystallization from methoxyethanol.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.18; H, 3.40; N, 31.44; O, 17.98. Found: C, 47.39; H, 3.53; N, 30.94; O, 18.00.

3-Chloropyrido[2,3-*e*]-*as*-triazine 1-Oxide (VIIa).—Twenty grams (0.12 mole) of the 3-hydroxy compound (VIa) was mixed with 200 ml. of phosphorus oxychloride and refluxed until a clear solution was obtained (about 1 hr.). The refluxing should not be prolonged past the point where solution occurs to avoid highly colored products. The excess phosphorus oxychloride was removed *in vacuo,* with bath temperatures below 55°, and the residue poured into ice water. After standing for 2 hr., the product was extracted into chloroform, the extracts were dried, and evaporated *in vacuo* to leave a light brown solid, 17.5 g. (79%), m.p. 130–135°. This material was used as much for the preparation of the compounds listed in Table I. For analyses, the product was obtained as pale yellow needles from methanol, m.p. 139.5–140.5°.

Anal. Calcd. for $C_6H_3ClN_4O$: C, 39.46; H, 1.65; Cl, 19.42; N, 30.69. Found: C, 39.71; H, 1.85; Cl, 19.57; N, 30.74.

This compound should be handled with care, since it is a powerful sternutator and skin irritant.

3-Chloro-7-methylpyrido[2,3-*e*]-*as*-triazine 1-Oxide (VIIb).—This compound was prepared in the same manner as described above for VIIa, using 5.0 g. (0.028 mole) of VIb in 50 ml. of phosphorus oxychloride. The crude product (5.0 g. 90%), m.p. 182–183°, was recrystallized from ethanol to obtain almost colorless crystals, m.p. 182.5–183.0°.

Anal. Calcd. for $C_7H_5ClN_4O$: C, 42.76; H, 2.56; Cl, 18.04; N, 28.50. Found: C, 42.55; H, 2.70; Cl, 18.21; N, 28.25.

3-Substituted Aminopyrido[2,3-*e*]-*as*-triazine 1-Oxides (VIII. Y = NR_2).—The amines of Table I were prepared by the following general method. Compound VIIa (0.10 mole) was dissolved in 300 ml. of chloroform and chilled to 0–5° in an ice bath. A solution of 0.21 mole of the de-

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[13] The yields are maximal at 6.5 hr. Longer reaction times give lower yields, presumably because of the rearrangement of the product, which occurs slowly in hot potassium carbonate.

sired amine in 120 ml. of chloroform was added in small portions keeping the temperature below 10°. After standing at 5° for 1 hr., the solution was poured into water, the product extracted with chloroform, and the extracts washed with water, dried, and evaporated. The crude products were purified by recrystallization from the appropriate solvent (see Table I).

Reactions using compound VIIb were run at room temperature instead of 0–5°. The 3-hydrazino compounds (VIII. Y = $NHNH_2$, R = H or CH_3) were prepared in ethanol solution at room temperature using a fivefold excess of hydrazine hydrate.

3-Alkoxypyrido[2,3-*e*]-*as*-triazine 1-Oxides (VIII. Y = OR).—The appropriate sodium alkoxide (0.21 mole) in 250 ml. of the corresponding dry alcohol was chilled to 5°, and a solution of 0.1 mole of VIIa in 100 ml. of the same alcohol added with stirring over a 0.5-hr. period. The product was filtered, washed with water to remove sodium chloride, and purified as shown in Table I.

3-Mercaptopyrido[2,3-*e*]-*as*-triazine 1-Oxide (IXa).—Six grams (0.033 mole) of VIIa was dissolved in ethanol containing 6.0 g. of thiourea. The solution was refluxed for 1 hr., cooled, and the dark red product isolated by suction filtration. The crude product was purified by dissolution in aqueous alkali and reprecipitation with acetic acid, to obtain 4.1 g. (69.5%) of a dark red solid, m.p. 197–198° dec. See Table I for the elemental analyses.

3-Aminopyrido[2,3-*e*]-*as*-triazine (XI). A. By Catalytic Hydrogenation of IIIa.—3-Aminopyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIa) (0.82 g., 5.0 mmoles) was dissolved in 100 ml. of glacial acetic acid containing 0.05 g. of 10% palladium on barium sulfate and hydrogenated at 2 atm. in a Parr shaker. Uptake of hydrogen was complete in 15 min. The catalyst was removed by filtration to give a clear yellow filtrate.[14] This solution was evaporated to dryness *in vacuo*, the residue taken up in 12 ml. of water and a solution of 2.5 g. of potassium ferricyanide in 10 ml. of water quickly added. The resulting solution was made basic with concentrated ammonium hydroxide, filtered to remove a black flocculent impurity, and chilled to 0° to precipitate the product as yellow needles, m.p. 246–250° dec., 0.4 g. (56%). Recrystallization from water with Norit gave bright yellow needles, m.p. 242–244° dec.

Anal. Calcd. for $C_6H_5N_5$: C, 48.97; H, 3.43; N, 47.60. Found: C, 49.11; H, 3.21; N, 47.57.

B. By Sodium Dithionite Reduction of IIIa.—Compound IIIa (4.9 g., 0.03 mole) was added to a solution of 10.6 g. (0.061 mole) of sodium dithionite (sodium hydrosulfite) in 75 ml. of water and stirred at room temperature for 1 hr. The bright yellow IIIa disappeared rapidly during this period and was replaced by a cream-colored precipitate of the 1,2-dihydro compound (X). This material (4.8 g.) was removed by suction filtration and converted to the aromatic compound (XI) by dissolving in 70 ml. water containing 22.5 g. of potassium ferricyanide and enough ammonium hydroxide to render the solution quite basic.[15] An immediate precipitation of XI occurred as a yellow solid. The mixture was chilled, filtered, with suction, and the product washed with cold water to give 2.5 g. (57%) of material, m.p. 235–240° dec. The infrared spectrum of this compound was identical to that of the compound prepared by method A.

Acknowledgment.—The authors are indebted to Mr. E. F. Shelberg and his staff for the microanalyses, Mr. W. Washburn and his staff for the infrared spectra, and to Mr. M. Freifelder for the catalytic hydrogenations.

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[14] This yellow solution quickly turns deep violet upon exposure to the air and should therefore be worked up without delay, preferably under a nitrogen atmosphere. Reduction using palladium on charcoal was also successful, however platinum on charcoal gave only deeply colored mixtures from which no product could be isolated.

[15] The dihydro compound (X) was quite unstable and quickly turned violet upon prolonged exposure to the air. It could not be purified for analysis because of this extreme instability.

The Reaction of Tertiary Amines with Halo-s-triazines and Halopyrimidines[1a]

EHRENFRIED KOBER[1b] AND RUDI RÄTZ[1b]

The Ohio State University Research Foundation, Columbus, Ohio

Received November 22, 1961

Trialkylamines, aryldialkylamines, and *N*-alkyl saturated nitrogen heterocycles, such as *N*-alkylpiperidines and *N*-alkyl morpholines, react with halo-*s*-triazines and halopyrimidines to form *s*-triazines and pyrimidines substituted by secondary amino groups.

The use of tertiary amines as acid scavengers is well known. In a great number of experiments, using tertiary amines as hydrochloride acceptors for the preparation of substituted *s*-triazines from the corresponding chloro-*s*-triazines, we observed the formation of by-products for which no well defined structures could be established. Analytical data and properties of these by-products did show that these compounds were not quaternary ammonium salts which—according to an Austrian patent[2]—are formed when tertiary amines are added to solutions of chloro-*s*-triazines in a nonpolar solvent.

A first hint on the nature of these products was obtained when we synthesized 2-chloro-4-*n*-butoxy-6-trichloromethyl-*s*-triazine by treating 2,4-dichloro-6-trichloromethyl-*s*-triazine (I)[3] with *n*-butyl alcohol in the presence of triethylamine. From this experiment, a by-product was isolated and identified as 2-*n*-butoxy-4-diethylamino-6-trichloromethyl-*s*-triazine (II). Apparently, in a side reaction a quaternary triethylammonium salt (III) had been formed as an intermediate

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[1] (a) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corp., New York, N. Y.; (b) Olin Mathieson Chemical Corp., New Haven, Conn.

[2] Austrian Patent 174,377.

[3] E. Kober and Ch. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959).