1,2,4-Triazoles. XX. Pyrolytic Decomposition of Ketone Hydrazones Derived from Pyrid-2-ylhydrazine and Related Bases. Some Further Examples of the *s*-Triazolo[4,3-*a*]pyrazine and *s*-Triazolo[4,3-*a*]quinoxaline Series (1)

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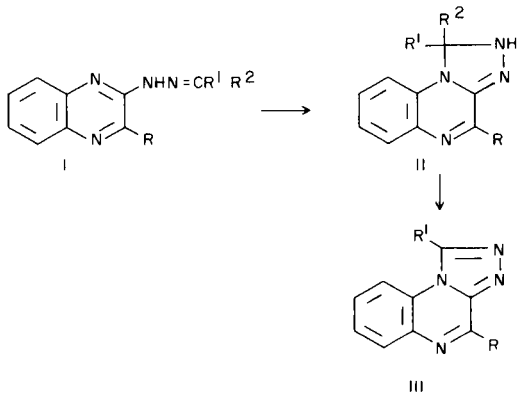
Pyrolytic decomposition of ketone 2-heterylhydrazones has been shown to be unsatisfactory for the preparation of fused *s*-triazole derivatives. The introduction of more diversified substituents into the *s*-triazolo[4,3-*a*]pyrazine and *s*-triazolo[4,3-*a*]quinoxaline systems has been accomplished and some reactions and spectral characteristics of these ring systems are reported. Isomerization of the *s*-triazolo[4,3-*a*]pyrazine system to the *s*-triazolo[1,5-*a*]pyrazine system is described.

A report (2) of the ready synthesis of *s*-triazolo[4,3-*a*]-quinoxaline derivatives (III) by thermal rearrangement of ketone hydrazones of 3-alkyl(aryl)-2-quinoxalines (I) made it of interest to investigate this reaction as a means of synthesis of other ring-fused *s*-triazole systems. This ring closure was envisaged (2) as occurring through an intermediate such as II. Identification of the evolved hydrocarbon fragment was reported to give results analogous to those obtained (3) in the thermal degradation of Schiffs bases derived from *o*-phenylenediamine and ketones, a route to substituted benzimidazoles.



Ketones analogous to those used in the earlier work (2,3) and which would also yield several alkyl- and aryl-*s*-triazolo[4,3-*a*]pyridines available as reference compounds (4) were chosen for this study. The ketone 2-heteryl-hydrazones were obtained by standard procedures and the properties of the hydrazones prepared are described in Table I and in the Experimental Section. The exceptionally poor yields obtained in the quinoline series seem to be a result of the instability of quinol-2-ylhydrazine.

Pyrolytic decomposition of the above hydrazones was attempted at various reaction temperatures and under various reaction conditions and in no instance was any of the fused *s*-triazole system isolated. Upon refluxing the pyrid-2-ylhydrazones in anhydrous benzene for several days, quantitative recovery of the starting material resulted; in boiling tetralin, the hydrazone, 2-aminopyridine, and a large amount of unidentified tarry material were isolated. At the hydrocarbon evolution temperatures (200-280°) reported to be most effective by the earlier workers (2,3), the same products obtained when tetralin was used as a diluent were isolated, though in different proportions.

Decomposition was more extensive and, at temperatures higher than 280° over longer reaction periods, decomposition of the pyrid-2-ylhydrazones was complete. On heating the quinol-2-ylhydrazones and pyrazin-2-ylhydrazones at the stated hydrocarbon evolution temperatures (3) for several hours in the absence of a solvent, purification of the resulting tarry residues yielded the starting hydrazones in near quantitative amounts. Higher temperatures (up to 300°) were employed for several of the quinol-2-ylhydrazones without significant change in the results and the thermal stability of the quinol-2-ylhydrazones paralleled that of the pyrid-2-ylhydrazones. On the other hand, temperatures above 230° led to complete decomposition of the pyrazin-2-ylhydrazones with no evidence of the presence of the original hydrazone, the fused system, or 2-aminopyrazine.

In the quinoxaline series, several hydrazones which had previously been reported to undergo this thermal cycliza-

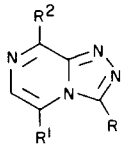
TABLE I

Some Heter-2-ylhydrazones

Ketone Substituents		Yield %	B.P. °C./0.1 mm.	M.P. °C	Formula	Analyses Calcd % C	H	N	Found % C	H	N
				Pyrid-2-ylhydrazones							
C_6H_5	CH_3 (a)	70	-	86-88	$C_{13}H_{13}N_3$	73.9	6.2	19.9	74.1	6.2	19.6
C_3H_7	CH_3 (b)	55	95	-	$C_{10}H_{15}N_3$	67.8	8.5	23.7	67.8	8.6	23.7
C_4H_9	C_2H_5 (b)	57	114	-	$C_{12}H_{19}N_3$	70.2	9.3	20.5	70.0	9.3	20.65
i-C_4H_9	CH_3 (b)	55	114	-	$C_{11}H_{17}N_3$	69.1	9.0	22.0	69.0	9.0	21.9
C_6H_5	C_6H_5 (a)	56	-	103-105	$C_{18}H_{15}N_3$	79.1	5.5	15.4	78.6	5.6	15.3
i-C_3H_7	CH_3 (b)	65	88-93	-	$C_{10}H_{15}N_3$	67.8	8.5	23.7	67.2	8.7	23.45
C_5H_{11}	CH_3 (b)	71	114	-	$C_{12}H_{19}N_3$	70.2	9.3	20.5	70.1	9.4	20.1
C_2H_5	CH_3 (b)	69	104-106	-	$C_9H_{13}N_3$	66.2	8.0	25.75	65.9	8.1	26.1
CH_3	CH_3 (a)	60	-	69-70	$C_8H_{11}N_3$	64.4	7.4	28.2	64.3	7.3	28.0
				Quinol-2-ylhydrazones							
C_6H_5	CH_3 (c)	37	-	116-118	$C_{17}H_{15}N_3$	78.1	5.8	16.1	78.0	6.0	16.1
C_4H_9	C_2H_5 (d)	37	-	76-78	$C_{16}H_{21}N_3$	75.3	8.3	16.5	75.5	8.25	16.2
C_6H_5	C_6H_5 (e)	31	-	150-152	$C_{22}H_{17}N_3$	81.7	5.3	13.0	81.7	5.3	13.05
i-C_4H_9	CH_3 (a)	31	-	88-89	$C_{15}H_{19}N_3$	74.7	8.0	17.4	74.7	8.0	17.2

(a) Colorless plates; (b) pale yellow oils; (c) yellow needles; (d) yellow plates; (e) colorless needles.

TABLE II

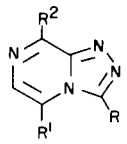


Some Substituted-*s*-triazolo[4,3-*a*]pyrazines

R	R^1	R^2	Yield %	M.P. (a) °C.	Purification Method (b)	Formula	Analyses Calcd % C	H	N	Found % C	H	N
H	H	CH_3	56	133-135	A,B,C	$C_{12}H_9N_7O_7$ (c)	-	-	27.05	-	-	26.9
H	CH_3	CH_3	80	171	A,B	$C_7H_8N_4$	56.7	5.4	37.8	57.1	5.6	37.4
CH_3	H	CH_3	42	204-206	A,B,C	$C_7H_8N_4$	56.7	5.4	37.8	56.6	5.9	37.4
CH_3	CH_3	CH_3	80	153-154 (d)	A,B	$C_8H_{10}N_4$	59.2	6.2	34.55	59.1	6.1	39.3
Et	H	CH_3	81	159-161 (d)	A,B	$C_8H_{10}N_4$	59.2	6.2	39.55	59.0	6.25	34.5
Et	CH_3	CH_3	68	128-130 (d)	A,B	$C_9H_{12}N_4$	69.6	5.4	25.0	69.8	5.6	24.9
Ph	CH_3	CH_3	48	188-190	C	$C_{13}H_{12}N_4$	61.4	6.8	31.8	61.1	6.8	31.6

(a) All crystallized as colorless plates except d which separated as colorless needles. (b) A = sublimation; B = benzene; C = benzene-petroleum ether. (c) Picrate.

TABLE III



Ultraviolet Absorption Spectral Data for Some Substituted-*s*-triazolo[4,3-*a*]pyrazines (a)

R	R^1	R^2	λ max. mμ (log ε)		
H	H	CH_3		276 (3.96)	270 (b) (3.95)
H	CH_3	CH_3	280 (b) (4.29)	272 (3.97)	264 (b) (4.28)
CH_3	H	CH_3	280 (3.83)	270 (3.83)	263 (b) (3.81)
CH_3	CH_3	CH_3	280 (b) (3.96)	272 (3.97)	265 (b) (3.93)
Et	H	CH_3	288 (4.00)	272 (b) (3.97)	265 (b) (3.90)
Et	CH_3	CH_3	290 (4.20)	275 (b) (4.98)	263 (b) (4.13)
Ph	CH_3	CH_3	280 (3.94)	270 (3.96)	263 (b) (3.94)

(a) Spectra determined in methanol. (b) Shoulder.

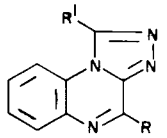
tion reaction (2) were subjected to conditions identical to those indicated for successful cyclization. After purification *via* alumina chromatography, only the original hydrazones were isolated and no cyclization to the fused *s*-triazole system had occurred. Higher reaction temperatures and prolonged reaction periods yielded only the hydrazones and a slight amount of undesirable decomposition products and this thermal stability of the quinoxalin-2-ylhydrazones was quite marked compared to the others studied.

There is no obvious explanation for the failure of the hydrazones described above to undergo thermal cyclization to the fused *s*-triazole systems as reported earlier (2). Acid or base catalysis did not effect cyclization and despite repeated attempts in our laboratory to dublicate the results reported by the earlier workers, we were not successful.

In connection with this thermal cyclization study, it was necessary to have available additional authentic samples of the fused *s*-triazole systems being studied. We now take the opportunity to describe additional members of the *s*-triazolo[4,3-*a*]pyrazine series (6) and also of the *s*-triazolo-[4,3-*a*]quinoxaline series (2), as well as some interesting characteristics of these ring systems.

The pyrazin-2-yl and quinoxalin-2-yl hydrazines were readily obtained by displacement of chlorine with hydrazine from the 2-chloro analogs in a modification of the methods used earlier (2,6). The ease of chlorine displacement in the pyrazine series is well documented (7) and, of the methods available for the synthesis of 2-chloropyrazines (8), the direct chlorination of pyrazines in carbon tetrachloride (9) was found to be most suitable in the present study. The structures of the isomeric chloropyrazines IV and V obtained from 2-methylpyrazine under these conditions were established by the n.m.r. chemical shifts of the methyl protons--7.34τ for IV and 7.44τ for V as compared to 7.43τ for the methyl protons of 2-methylpyrazine. By carefully controlled conditions, it was possible to separate these isomers by vacuum distillation even though their boiling points were 81°/35 mm and 83°/35 mm for IV and V, respectively. Both distilled as colorless, viscous liquids and required storage under nitrogen at less than zero degrees due to their instability in the presence of air and light. Fractional crystallization of the hydrazino derivatives of IV and V also provided a profitable means of separation.

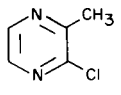
TABLE IV



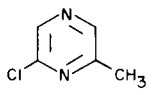
Ultraviolet Absorption Spectral Data for Some *s*-Triazolo[4,3-*a*]quinoxalines (a)

R^1	R	λ max. mμ (log ε)					
H	H	320 (b) (3.56)	308 (b) (3.75)	290 (b) (3.94)	284 (3.95)		
H	CH_3	320 (b) (3.65)	308 (b) (3.95)	293 (b) (3.98)	282 (4.01)		232 (4.30)
H	Ph	330 (b) (4.23)	302 (4.23)		277 (b) (4.16)	257 (4.29)	
		318 (4.25)				250 (b) (4.27)	
CH_3	H	322 (b) (3.63)	312 (3.88)	298 (3.95)	288 (b) (3.93)	240 (b) (4.14)	
					280 (b) (3.85)		
CH_3	CH_3	320 (b) (3.73)	305 (3.95)	292 (4.03)	283 (b) (4.02)	240 (b) (4.15)	
CH_3	Ph	330 (b) (4.21)	308 (b) (4.21)		280 (4.18)	253 (4.28)	230 (4.54)
		320 (4.23)				250 (b) (4.27)	
Et	H	330 (b) (3.30)	310 (b) (3.81)	297 (3.87)	287 (b) (3.84)	241 (b) (4.17)	
		322 (b) (3.60)					
Et	CH_3	330 (b) (4.20)	308 (b) (4.20)		278 (4.12)	256 (4.28)	226 (4.54)
		319 (4.23)				248 (4.27)	
Et	Ph	334 (b) (4.27)			286 (b) (4.17)	252 (b) (4.32)	227 (4.56)
		318 (4.30)				260 (4.34)	
Ph	CH_3	320 (b) (4.08)	308 (b) (4.26)	295 (4.34)		241 (4.71)	
Ph	Ph	318 (b) (4.03)			285 (b) (4.79)	272 (4.88)	258 (b) (4.85)
					280 (b) (4.85)		
OH	H	310 (3.65)		290 (3.65)		256 (b) (4.16)	247 (4.28)
OH	CH_3	305 (3.68)	293 (3.68)			250 (b) (4.29)	244 (4.29)
OH	Ph	330 (3.75)	285 (b) (4.21)			262 (b) (4.32)	233 (4.17)
						253 (4.26)	

(a) Spectra determined in methanol. (b) Shoulder.



IV



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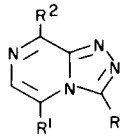
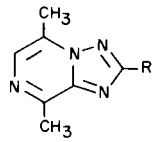


VI



VII

The 2-chloroquinoxalines were prepared from the corresponding 2-hydroxy compounds (10) by heating under reflux with freshly distilled phosphorous oxychloride and optimum conditions, superior to those described (2) earlier, are noted in the Experimental Section.

3-Alkyl-*s*-triazolo[4,3-*a*]pyrazines (VI) and 1-Alkyl-*s*-triazolo[4,3-*a*]quinoxalines (III).

The only method that was successful for the preparation of the *s*-triazolo[4,3-*a*]pyrazine derivatives of type VI (R=H, CH_3, Et) was the ring closure of the pyrazin-2-ylhydrazines with orthoesters, and the products obtained are described in Table II. In confirmation of earlier results (6), the pyrazin-2-ylhydrazines failed to undergo ring closure in the presence of carboxylic acids, acid anhydrides or their esters, yielding only 10% of the respective VI along with the uncyclized acyl intermediate. These latter reactions have been reported to occur with extreme ease in the pyridine (4) and pyrimidine (12) series and it is interesting that the presence of electron donating groups in the pyrazine nucleus has no effect on the ease of cyclization.

The cyclization of the quinoxalin-2-ylhydrazines to the 1-alkyl-*s*-triazolo[4,3-*a*]quinoxalines (III; R^1 = alkyl) occurred very readily with acids and esters, in contrast to the pyrazine series, as well as with orthoesters leading to very little contamination by uncyclized intermediates.

3-Phenyl-*s*-triazolo[4,3-*a*]pyrazine and 1-Phenyl-*s*-triazolo-[4,3-*a*]quinoxalines.

The only satisfactory procedure for the synthesis of these derivatives in the pyrazine series was the cyclization of the corresponding benzoyl compounds with phosphorous oxychloride. Using the Schotten-Baumann procedure the pyrazin-2-ylhydrazines produced benzoyl derivatives that invariable incorporated solvent of crystallization; these products are described in the Experimental Section. It is interesting to note that 3,6-dimethyl-pyrazin-2-ylhydrazine gave a monobenzoyl derivative, while 3-methyl pyrazin-2-ylhydrazine formed a dibenzoyl derivative. The latter hydrazine also formed a dihydrochloride and a dipicrate. The possibility of this resulting from any steric hindrance effect is eliminated by consideration of models of these compounds and is most likely the result of different solubilities of the various derivatives. The dibenzoyl compound did not undergo cyclization to the corresponding fused 3-phenyl compound. Under similar conditions the quinoxalin-2-ylhydrazines formed mono- or dibenzoyl derivatives without retaining solvent of crystallization. As in the 3-alkyl-*s*-triazolo[4,3-*a*]pyrazines, the pyrazin-2-ylhydrazines failed to cyclize in any substantial amount (less than 10%) to the desired 3-phenyl products by fusion with benzoic acid or its esters.

The preparation of various 1-phenyl-4-substituted-*s*-triazolo[4,3-*a*]quinoxalines was accomplished quite readily using both the phosphorous oxychloride and benzoic acid methods described above; however, a longer reflux period for a benzoyl derivative with phosphorous oxychloride was found to be necessary in this series. In the benzoic acid fusion with the quinoxalin-2-ylhydrazines the fusion temperature was critical. Below 220° only the benzoyl derivative was isolated; above 290° for several hours, the cyclized product was formed. Fusion of the benzoyl derivatives also resulted in cyclization. The yields by these two methods were competitive with those obtained from heating benzoyl chloride solutions of the hydrazine described earlier (2) and the relatively drastic reaction conditions are not unexpected in view of the molecular overcrowding present in these 1-phenyl products.

3-Amino-*s*-triazolo[4,3-*a*]pyrazine (VI; R = NH_2) and 1-Amino-*s*-triazolo[4,3-*a*]quinoxaline (III; R^1 = NH_2).

Using the cyanogen bromide cyclization procedures described for the synthesis of other 3-amino ring fused-*s*-triazole systems (4), facile cyclization to the above amino compounds occurred in quantitative yields (see Experimental Section).

s-Triazolo[4,3-*a*]pyrazin-3-ol (VI; R = OH) and 4-Substituted-*s*-triazolo[4,3-*a*]quinoxalin-1-ol (III; R^1 = OH).

These compounds were readily obtained from the appropriate hydrazine by fusion with urea at 180-200° until ammonia evolution had ceased and are described in the Experimental Section. Shiho and Tatami (2) prepared the quinoxalin-1-ols from the hydrazines and ethyl chloroformate, and the urea fusion employed here is more convenient. By replacing ethyl chloroformate with ethyl allophanate, a reaction that gave excellent results in the pyridine series (4), the hydroxy compounds were obtained in only 35% yields.

It should be pointed out that the infrared spectra of these compounds showed an amide II band as well as an

hydroxyl absorption, indicating the presence of some keto-enol tautomerism.

s-Triazolo[4,3-*a*]pyrazine-3-thiol (VI; R = SH) and 4-Substituted *s*-triazolo[4,3-*a*]quinoxaline-1-thiol (III; R^1 = SH).

Carbon disulfide (13), thiophosgene (14) and potassium trithiocarbonate (15) have all been shown to be effective reagents for the cyclization of pyrid-2-ylhydrazines (4) to the corresponding fused-ring 3-thiol. In both the pyrazine and quinoxaline series, carbon disulfide in chloroform was found to produce the best yields as well as being the most convenient method. Upon addition of an equal molar amount of the pyrazin-2-ylhydrazine to a solution of carbon disulfide in chloroform, the intermediate dithiocarbamic acid precipitated immediately; on heating it redissolved in the chloroform with subsequent precipitation of the cyclized product. However, in the quinoxaline series, the intermediate dithiocarbamic acid precipitated after several hours of reflux and a much shorter reflux period was required for cyclization to occur.

Potts and Nelson (6) were unable to accomplish this carbon disulfide ring closure with 5,6-diphenylpyrazin-2-ylhydrazine, apparently as a result of the phenyl substituents decreasing the basicity of the system. In the present case, however, the methyl groups appear to enhance the basicity of the nitrogen atom for this type of cyclization. However, this apparently is not sufficient for cyclization with aliphatic acids to occur (see above).

The infrared data for the *s*-triazolo[4,3-*a*]pyrazine-3-thiol indicate that in the solid state the thiol is a tautomeric mixture of the thiol form (ν_{SH}2600 cm^{-1}) and of the thione form ($\nu_{C=S}$1450 and 1270 cm^{-1}) and is analogous to the corresponding hydroxy compounds. In the presence of base and methyl iodide, ready formation of the 3-methylthio-*s*-triazolo[4,3-*a*]pyrazine derivative (VI; R = SCH_3) occurred. It was not possible to form the corresponding *O*- or *N*-methyl derivative from an *s*-triazolo-[4,3-*a*]pyrazin-3-ol under these mild conditions.

The infrared spectrum of the *s*-triazolo[4,3-*a*]quinoxaline-1-thiol (III; R^1 = SH) indicates only the presence of the thione tautomer ($\nu_{C=S}$1440 to 1425 cm^{-1} and 1375 to 1340 cm^{-1}). This is further borne out by the inability of this thiol to react with methyl iodide in the presence of base to form the methylthio compound. This is clearly the result of steric overcrowding at the 1-position of the fused nucleus.

Rearrangement of 5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazine to 5,8-Dimethyl-*s*-triazolo[1,5-*a*]pyrazine.

When 5,8-dimethyl-*s*-triazolo[4,3-*a*]pyrazine was refluxed with 10% sodium hydroxide solution for *ca.* 60 hours, the product isolated was found to have the same molecular formula as the starting material. However, the melting point, solubility characteristics and ultraviolet spectral data were sufficiently different to eliminate the possibility of the product being starting material and the change in the ultraviolet absorption spectrum was of the order expected (6) for the isomeric 5,8-dimethyl-*s*-triazolo-[1,5-*a*]pyrazine (VII).

Similar isomerizations in dilute acid, base, or merely application of heat, have been observed in the *s*-triazolo-[4,3-*a*]pyridine (16) and *s*-triazolo[4,3-*c*]- (17) and [4,3-*a*]pyrimidine (18) series. It was found in this present work that rearrangement of VII only occurred in a hot 10% sodium hydroxide solution over a longer period of time with respect to the analogous pyridine compound. When VII was refluxed in 10% hydrochloric acid solution or heated above its melting point, a quantitative amount of the starting material was recovered.

On the basis of Hückel Molecular Orbital Calculations, the 5-position of the *s*-triazolo[4,3-*a*]pyrazine nucleus has associated with it a greater π-electron density than do the corresponding positions in the *s*-triazolo[4,3-*a*]pyrimidine, *s*-triazolo[4,3-*a*]pyridine and the *s*-triazolo[4,3-*c*]pyrimidine nuclei. This could possibly explain the difficulty in effecting this rearrangement as well as the poor yields (20%) of the rearranged isomer, particularly if it involves an initial hydroxyl ion attack at the 5-position as proposed in the mechanismfor the pyridine series (16).

On refluxing a 3-hydroxy or a 3-mercapto-*s*-triazolo-[4,3-*a*]pyrazine in a 10% sodium hydroxide solution, there was a slight evolution of ammonia, possibly due to hydrolysis of the triazole nucleus. No rearranged product was isolated and these results parallel those obtained in the triazolopyridine series. Various members of the *s*-triazolo[4,3-*a*]quinoxaline series were treated under the above reaction conditions and resulted in a quantitative recovery of the starting material. This would be expected since the 5-position of the pyrazine nucleus is now part of the fused benzene ring.

Several other incidental observations relating to the *s*-triazolo[4,3-*a*]pyrazine system are reported here. The nucleus is relatively stable to hot potassium permanganate oxidation and, under extreme conditions, fragmentation of the nucleus occurs. A 3-amino substituent does not readily undergo the diazonium reaction and replacement of the 3-hydroxyl group with a chloro substituent cannot be readily effected with phosphorous oxychloride. Treatment of 5,8-dimethyl-*s*-triazolo[4,3-*a*]pyrazine with bromine in acetic acid gave the corresponding 3-bromo product which separated as the hydrobromide, a result consistent with those obtained in related ring systems.

ULTRAVIOLET DATA

The ultraviolet absorption spectral data for the fused *s*-triazoles discussed above are presented in Tables III and IV. Several interesting features are apparent. As expected,

the quinoxaline series had a much more complex series of spectra as a result of the fused benzene ring and the presence of extended conjugation. In the pyrazine series, there are two principle bands (265-275 mμ and 280-290 mμ) with no red or blue end absorption; the quinoxaline series shows a more spread out pattern with both red and blue end absorptions. There is only one principle band (280-300 mμ) in the same general region as the two which occur in the pyrazine series. These two principle bands in the pyrazine series have undergone a bathochromic shift to those associated with an aromatic system, particularly since there is no indication of absorption in the 240 mμ region. The majority of the bands are most likely the result of $\pi \rightarrow \pi^*$ transitions within the molecule and those at longer wavelength the $n \rightarrow \pi^*$ transitions.

An interesting substituent effect appears when the *s*-triazole ring bears a phenyl substituent. In the quinoxaline series an increase in the extinction coefficient can be attributed to the phenyl group being essentially co-planar with the nucleus. However, in the pyrazine series, steric interaction between the 5-methyl and 3-phenyl substituents prevents the phenyl group from being co-planar with the nucleus. Confirmation of this interaction was obtained from the up-field shift of the 5-CH_3 protons from 7.35τ in the unsubstituted product to 7.84τ in 5,8-dimethyl-3-phenyl-*s*-triazolo[4,3-*a*]pyrazine.

EXPERIMENTAL (16)

Preparation of 3-Methyl- and 6-Methyl-2-chloropyrazine.

Chlorine was bubbled into a solution of 2-methylpyrazine (0.8 mole) in carbon tetrachloride (2000 ml.) at a slow, steady rate with cooling and stirring of the reaction mixture. The hydrochloride commenced to precipitate after 45 minutes and chlorine was allowed to pass into the solution for an additional 75 minutes. After all the excess chlorine had escaped from the solution, the hydrochloride was filtered and washed with carbon tetrachloride (2 x 300 ml.) and petroleum ether (2 x 300 ml.). The hydrochloride (100%) was dissolved in water (600 ml.) and an orange oil separated. The aqueous solution was extracted with ether (3 x 200 ml.), the ether extracts were combined and added to the separated oil, the combined extracts dried (magnesium sulfate), and concentrated, leaving a red residue which was distilled *in vacuo*. Two colorless liquid fractions were obtained, b.p. 81°/35 mm. (3-methyl) and b.p. 83°/35 mm. (6-methyl); n.m.r. (deuteriochloroform), 3-methyl: τ 1.64 (5H, 6H), 7.34 (CH_3); 6-methyl: τ 1.83 (3H, 5H), 7.44 (CH_3).

Preparation of Pyrazin-2-ylhydrazines.

General Method.

A solution of the appropriate 2-chloropyrazine (0.1 mole), 98% hydrazine (16 ml., 0.5 mole), and absolute ethanol (50 ml.) was refluxed for 7 hours. The ethanol was removed under reduced pressure on a steam bath and the resulting crystalline product was recrystallized from benzene (Norit).

(3-Methylpyrazin-2-yl)hydrazine (7.3 g., 59%) was obtained as cream-colored needles, m.p. 140°; λ max (methanol) (log ε) 258 (3.88), 263 sh(3.85), 329 mμ (3.56); infrared (chloroform), 3.00 3.11, 6.20, 6.80 μ.

Anal. Calcd. for $C_5H_8N_4$: C, 48.4; H, 6.5; N, 45.1. Found: C, 48.3; H, 6.6; N, 45.1.

The dipicrate crystallized from ethanol as green-yellow prisms, m.p. 143-145°. The analytical sample was dried at 100°/0.1 mm. for 4 hours.

Anal. Calcd. for $C_{17}H_{14}N_{10}O_{14}$: N, 24.1. Found: N, 24.25

The dihydrochlororide, prepared by addition of dry hydrogen chloride to a benzene solution of the hydrazine, crystallized from ethanol-ether as pale yellow plates, m.p. 210-212°. The analytical sample was dried at 140°/0.7 mm. for 72 hours to remove all traces of solvent of crystallization.

Anal. Calcd. for $C_5H_{10}Cl_2N_4$: N, 28.4. Found: N, 28.3.

(6-Methylpyrazin-2-yl)hydrazine (3.5 g., 45%) was isolated as colorless prisms, m.p. 86°.

Anal. Calcd. for $C_5H_8N_4$: C, 48.4; H, 6.5; N, 45.1. Found: C, 48.6; H, 6.6; N, 44.9.

(3,6-Dimethylpyrazin-2-yl)hydrazine (9.6 g., 70%) formed colorless needles, m.p. 121°; λ max (methanol) (log ε) 261 (4.23), 263 sh(4.22), 330 mμ (3.98); infrared (chloroform) 3.05, 6.20, 6.80 μ.

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.2; H, 7.3; N, 40.6. Found: C, 51.9; H, 7.1; N, 40.3.

The monopicrate crystallized from ethanol as yellow needles, m.p. 193-195° (dec.).

Anal. Calcd. for $C_{12}H_{13}N_7O_7$: N, 26.7. Found: N, 26.4.

Heter-2-ylhydrazones.

General Method of Preparation.

Equal molar amounts of the hydrazine and the ketone, along with several drops of dilute hydrochloric acid, were mixed and warmed on a steam bath for the time needed (about 2 hours) for the reaction to go to completion, indicated by the amount of water that was clearly visible on the sides of the reaction vessel. The reaction mixture was diluted with ether (50 ml.), the ether solution dried (sodium sulfate), and the ether evaporated. The resulting product either crystallized and was then recrystallized from a suitable solvent, or was distilled under reduced pressure as indicated in Table I. The pyrazin-2-yl- and quinoxalin-2-yl-hydrazones prepared were characterized as described below.

Benzophenone (3-Methylpyrazin-2-yl)hydrazone separated as yellow plates (73%), m.p. 133-135°; infrared (chloroform), 3.08 (NH), 6.10 μ (C=N); λ max (methanol) (log ε) 296 sh (4.25), 287 (4.28), 258 (4.24), 237 mμ (4.29).

Anal. Calcd. for $C_{18}H_{16}N_4$: C, 75.0; H, 5.6; N, 19.4. Found: C, 75.15; H, 5.7; N, 19.3.

Acetophenone (3,6-Dimethylpyrazin-2-yl)hydrazone was obtained as white needles (42%), m.p. 105-107°; infrared (chloroform), 3.15 (NH), 6.05 μ (C=N); λ max (methanol) (log ε) 297 sh (4.21), 266 mμ (4.41).

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 70.0; H, 6.7; N, 23.3. Found: C, 70.1; H, 6.6; H, 23.2.

Acetophenone (3-Methylquinoxalin-2-yl)hydrazone separated from aqueous methanol as yellow prisms (87%), m.p. 129°; infrared (chloroform), 3.15 (NH), 6.30 μ (C=N); λ max (methanol) (log ε) 300 sh (4.13), 272 sh (4.26), 267 (4.27), 262 (sh) mμ (4.27).

Anal. Calcd. for $C_{17}H_{16}N_4 \cdot H_2O$: C, 69.4; H, 6.2; N, 19.0. Found: C, 68.9; H, 6.5; N, 19.0.

Acetophenone Quinoxalin-2-ylhydrazone was obtained from methanol as orange needles (45%), m.p. 115-116°; infrared chloroform), 3.08 (NH), 6.20 μ (C=N); λ max (methanol) (log ε) 322 sh (3.84), 279 (4.59), 270 sh (4.58), 241 (sh) mμ (4.45).

Anal. Calcd. for $C_{16}H_{14}N_4 \cdot C_6H_6$: C, 77.6; H, 5.9; N, 16.5. Found: C, 77.2; H, 6.3; N, 16.45.

Acetone (3-Phenylquinoxalin-2-yl)hydrazone separated as yellow plates from aqueous methanol (68%), m.p. 141-142°; infrared (chloroform), 3.12 (NH), 6.20 μ (C=N); λ max (methanol) (log ε) 292 sh (4.48), 276 sh (4.53), 273 (4.54), 262 (sh) mμ (4.53).

Anal. Calcd. for $C_{17}H_{16}N_4$: C, 73.9; H, 5.8; N, 20.3. Found: C, 74.0; H, 5.9; N, 20.5.

Attempted Thermal Cyclization of Heter-2-ylhydrazones.

A sampling of the experimental procedures used is illustrated below for the pyrid-2-ylhydrazones. The hydrazone (0.2 g.) was refluxed in tetralin (25 ml., b.p. 207°) for 24 hours. The solution was concentrated under reduced pressure, and the residue was either distilled *in vacuo* or recrystallized from a suitable solvent, depending on the properties of the original hydrazone used. An alternate work-up procedure was to chromatograph the residue on neutral alumina. Investigation of the products and the residues using spectral methods (ir, uv) and TLC procedures gave no indication of cyclization having occurred.

3-Alkyl-*s*-triazolo[4,3-*a*]pyrazines and 1-Alkyl-*s*-triazolo[4,3-*a*]-quinoxalines.

General Method of Preparation.

The hydrazine (0.1 mole) and the orthoester were refluxed together in anhydrous xylene (25 ml.) or anhydrous benzene (25 ml.) for 4.5 hours or 25 hours, respectively. The excess orthoester, alcohol, and solvent were removed under reduced pressure on a steam bath, and the residue recrystallized several times from the solvents listed in Table II.

Preparation of 1-Benzoyl-, 1,2-Dibenzoylpyrazin-2-yl and Quinoxalin-2-yl Hydrazines.

The hydrazine (0.04 mole) was dissolved in pyridine (100 ml.) and cooled in an ice bath for several minutes. Benzoyl chloride (4.3 ml., 0.04 mole) was added cautiously with constant stirring. The resulting solution was stirred at 0° for 5 minutes and at room temperature for 45 minutes and then heated on a steam bath for 1 hour. The warm reaction mixture was poured over ice, concentrated under reduced pressure on a steam bath, and allowed to stand for several hours. The crystalline products which separated are described below.

The dibenzoyl derivative of 3-methylpyrazin-2-ylhydrazine separated from aqueous methanol as white plates, m.p. 196° (dec.).

Anal. Calcd. for $C_{19}H_{16}N_4O_2 \cdot CH_3OH$: N, 15.4. Found: N, 15.45.

The monobenzoyl derivative of 3,6-dimethylprazin-2-ylhydrazine crystallized from aqueous ethanol as tan plates, m.p. 165-167°.

Anal. Calcd. for $C_{13}H_{14}N_4O \cdot H_2O$: C, 60.0; H, 6.2; N, 21.5. Found: C, 60.4; H, 6.1; N, 21.1.

The dibenzoyl derivative of quinoxalin-2-ylhydrazine separated from aqueous ethanol as tan needles, m.p. 197°.

Anal. Calcd. for $C_{22}H_{16}N_4O_2$: C, 71.7; H, 4.4; N, 15.2. Found: C, 71.8; H, 4.9; N, 15.0.

Cyclization of the Benzoyl Compound to the Corresponding 3-Phenyl-*s*-triazolo[4,3-*a*]pyrazine and 1-Phenyl-4-substituted-*s*-triazolo[4,3-*a*]quinoxaline with Phosphorous Oxychloride.

The benzoyl compound (0.02 mole) and phosphorous oxychloride (0.02 mole) were refluxed together in anhydrous toluene (50 ml.) until there was no longer any evolution of hydrogen chloride. As the cyclization product generally crystallized from the reaction mixture on standing, the toluene and any excess phosphorous oxychloride were decanted and the remaining residue placed under vacuum for several hours to remove any excess phosphorous oxychloride.

The products obtained in the pyrazine series were recrystallized from benzene-petroleum ether or methanol (Table II) and those of the quinoxaline series were in agreement with data reported in the literature (2).

Preparation of 1-Phenyl-4-substituted-*s*-triazolo[4,3-*a*]quinoxaline from the Quinoxalin-2-ylhydrazines and Benzoic Acid.

Equal molar amounts of the 3-substituted quinoxalin-2-ylhydrazine and benzoic acid were heated together at 210° for 1 hour. The melt crystallized on cooling and was recrystallized from benzene yielding colorless prisms, m.p. 292° (80%) of the benzoyl derivative, identical with the benzoyl derivative prepared from the hydrazine and benzoyl chloride. By heating the benzoyl derivative at 290° for several hours, 1-phenyl-4-substituted-*s*-triazolo[4,3-*a*]-quinoxaline crystallized from the melt. It was purified by chromatography on alumina with benzene as eluent and then recrystallized from the appropriate solvent described previously.

5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazin-3-ol.

Equal weights of 3,6-dimethylpyrazin-2-yl hydrazine and urea were heated at 150° until the melt solidified and the evolution of ammonia ceased. The solid material was recrystallized several times from methanol from which it separated as colorless needles (51%), m.p. 252°; λ max (methanol) (log ε) 265 sh(3.78), 272(3.80), 280 mμ (3.78); infrared (Nujol), 3.55, 5.90 μ.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.9; N, 34.1. Found: C, 51.4; H, 4.9; N, 33.95.

s-Triazolo[4,3-*a*]quinoxalin-1-ols.

Equal weights of the quinoxalin-2-ylhydrazine and urea were heated together until the evolution of ammonia ceased. The melt crystallized on cooling and was recrystallized several times from the solvents reported previously (4).

s-Triazolo[4,3-*a*]pyrazine-3-thiol and *s*-Triazolo[4,3-*a*]quinoxaline-1-thiol.

General Method of Preparation.

The hydrazine (0.1 mole) and carbon disulfide (0.4 mole) were refluxed for several days in chloroform until there was no longer any detectable evolution of hydrogen sulfide. The initial dithiocarbamic acid dissolved during the reflux period and the chloroform solution was concentrated under reduced pressure on a steam bath to give a residue which crystallized on standing.

5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazine-3-thiol was obtained from methanol as yellow needles (70%), m.p. 278°; λ max (methanol) (log ε) 231 (4.32), 263 sh(4.11), 320 (sh) mμ (3.56); infrared (Nujol) 4.58, 6.60 μ.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.6; H, 4.5; N, 31.1. Found: C, 46.4; H, 4.4; H, 30.9.

4-Methyl-*s*-triazolo[4,3-*a*]quinoxaline-1-thiol was isolated from acetic acid as orange prisms (90%), m.p. 267-269°.

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.6; H, 3.7; N, 25.9. Found: C, 55.4; H, 3.5; N, 26.0.

Preparation of 5,8-Dimethyl-3-methylthio-*s*-triazolo[4,3-*a*]pyrazine.

5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazine-3-thiol (0.01 mole) was dissolved in 1 *N* sodium hydroxide solution (20 ml.), a small amount of alcohol was needed for complete solution, and methyl iodide (2 ml., 0.025 mole) was added with constant stirring. The solution was shaken for 15 minutes and then stirred at room

temperature for 1.5 hour or until the pale yellow solution became colorless. The resulting basic solution was extracted with chloroform (6 x 50 ml.), the extracts were combined, dried (sodium sulfate), and the chloroform evaporated, leaving a residue which crystallized on standing. The material crystallized from benzene as pale-yellow needles (47%), m.p. 140°; infrared (chloroform), 3.20, 3.40, 6.22, 6.75, 7.00, 7.15, 7.38, 7.65, 9.15 μ; λ max (methanol) (log ε) 310 sh (3.72), 273 (3.89), 285 sh (3.85), 237 mμ (4.22); n.m.r. (deuteriochloroform), τ 2.70 (6-H), 7.14 (5-CH_3), 7.14 (8-CH_3), 7.14 (3-SCH_3).

Anal. Calcd. for $C_8H_{10}N_4S$: C, 49.5; H, 5.2; N, 28.8. Found: C, 49.7; H, 5.2; N, 28.3.

3-Amino-*s*-triazolo[4,3-*a*]pyrazine and 1-Amino-4-phenyl-*s*-triazolo-[4,3-*a*]quinoxaline.

General Method of Preparation.

The hydrazine (0.03 mole) was dissolved in methanol (50 ml.) and cooled during the addition of cyanogen bromide (0.03 mole). The resulting solution was refluxed for 5 hours and then concentrated under reduced pressure on a steam bath. The residue crystallized on standing and was recrystallized several times from ethanol-ether. The amino compounds were obtained in quantitative yields.

3-Amino-5,8-dimethyl-*s*-triazolo[4,3-*a*]pyrazine hydrobromide was obtained as orange prisms, m.p. 268° (dec.).

Anal. Calcd. for $C_7H_{10}BrN_5$: N, 28.7. Found: N, 28.7.

1-Amino-4-phenyl-*s*-triazolo[4,3-*a*]quinoxaline hydrobromide was isolated as yellow prisms, m.p. 297° (dec.).

Anal. Calcd. for $C_5H_{12}BrN_5$: N, 20.5. Found: N, 20.3.

The above hydrobromide salts were dissolved in the minimum amount of water and neutralized with sodium acetate. Upon basification to *p*H 10 and standing for several days, crystals separated from the solution and were collected. The products were recrystallized from ethanol.

3-Amino-5,8-dimethyl-*s*-triazolo[4,3-*a*]pyrazine was obtained as yellow needles (37%), m.p. 290-292°; infrared (Nujol), 3.10, 6.15 μ; λ max (methanol) (log ε) 320 sh (3.56), 263 sh (4.11), 231 mμ (4.32).

Anal. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.5; H, 5.7; N, 42.9.

1-Amino-4-phenyl-*s*-triazolo[4,3-*a*]quinoxaline was isolated as yellow plates (76%), m.p. 289° (dec.); infrared (Nujol), 3.15, 6.10 μ; λ max (methanol) (log ε) 304 sh (4.11), 290 (4.19), 268 sh (4.22), 264 (4.23), 262 (sh) mμ (4.22).

Anal. Calcd. for $C_{15}H_{11}N_5$: C, 69.0; H, 4.2; N, 26.8. Found: C, 68.8; H, 4.4; N, 26.7.

Rearrangement of 5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazine to 5,8-Dimethyl-*s*-triazolo[1,5-*a*]pyrazine.

5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazine (0.01 mole) was refluxed for 72 hours in 10% sodium hydroxide solution (50 ml.). The basic solution underwent a color change of yellow to orange to red. After the reflux period, it was extracted with chloroform in a continuous extractor for several days. The extract was dried over anhydrous sodium sulfate and concentrated, yielding a residue which crystallized on standing. The resulting crystals were recrystallized several times from petroleum ether and separated as pale yellow needles (20%), m.p. 77-78°; infrared (chloroform), 3.56, 6.30 μ; λ max (methanol) (log ε) 298 sh (3.56), 283 (3.86), 273 (sh) mμ (3.81).

Anal. Calcd. for $C_7H_8N_4$: C, 56.7; H, 5.4; N, 37.8. Found: C, 56.9; H, 5.6; N, 37.5.

On refluxing the above *s*-triazolo[4,3-*a*]pyrazine with 10% hydrochloric acid for 48-72 hours and using the same work-up procedure as above, the starting material was recovered. Similar results were obtained when the product was heated at 225-235° for 1-2 hours.

Bromination of 5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazine.

5,8-Dimethyl-*s*-triazolo[4,3-*a*]pyrazine (0.075 mole) was dissolved in acetic acid (10 ml.) and bromine (2 ml.) was added dropwise over a period of 15 minutes. The resultant solution was allowed to stand for 30 minutes, yielding crystals which were filtered off and recrystallized from ethanol-ether. These formed white prisms, m.p. 275-276° (dec.), of 3-bromo-5,8-dimethyl-*s*-triazolo[4,3-*a*]pyrazine hydrobromide (90%).

Anal. Calcd. for $C_7H_8Br_2N_4$: C, 27.3; H, 2.6; N, 18.2. Found: C, 27.2; H, 2.7; N, 18.0

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