carbon tetrachloride indicated only compounds **1b** and **2b** in a ratio of 1:4 by comparison with pmr spectra of authentic samples of **1b** and **2b** in the same solvent.

Reaction of 1b with Triethylcarbinylamine.—Triethylcarbinylamine (2 equiv) and **1b** (1 equiv) in *n*-hexane were stirred at room temperature for 4 days. A pmr spectrum of the hexane-soluble compounds in carbon tetrachloride indicated only compounds **1b** and **2f** by comparison with pmr spectra of authentic samples in the same solvent.

threo-**2-Benzoyl-1-piperidino-1-phenylpropane** (**4a**).—Piperidine (0.95 g, 0.011 mol) was added to 2.22 g (0.010 mol) of 2-benzoyl-1-phenylpropene and the mixture was allowed to react at room temperature for 7 days. The mixture solidified and was crystallized from 100 ml of a 1:1 ethyl ether–methanol mixture. The white solid which separated weighed 2.96 g (96%): mp 141–142°; λ_{max} (isooctane) 240 mμ (ε 13,900); $\nu_{C=O}$ (CCl_4) 1688 cm^{-1}; nmr peaks ($CDCl_3$) 435–480 (m, 5 H, benzoyl), 428 (s, 5 H, phenyl), 230–280 (m, J = 11, 6.5 Hz, 2 H, methines), 120–170 (m, 4 H α to N), 60–120 Hz (β and γ to N and methyl, J = 6.5 Hz).

Anal.[15a] Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.78; H, 8.29; N, 4.50.

threo-**2-Benzoyl-1-morpholino-1-phenylpropane** (**4b**).—To a 6.66-g (0.030 mol) sample of 2-benzoyl-1-phenylpropene (**7**) was added 2.61 g (0.030 mol) of morpholine and the mixture was allowed to stand at room temperature for 5 days. The mixture was analyzed by nmr spectrometry at various stages of conversion and only one configurational isomer was detected along with starting material. The mixture solidified upon standing and recrystallization of the solid from a 1:1 ethyl ether–methanol mixture yielded 7.24 g (80%) of white crystals: mp 149–150°; λ_{max} (isooctane) 240 mμ (ε 14,100); $\nu_{C=O}$ (CCl_4) 1688 cm^{-1}; nmr peaks 435–480 (m, 5 H, benzoyl), 431 (s, 5 H, phenyl), 230–280 (m, 2 H, J = 11, 6.5 Hz, methines), 210–230 (t, 4 H, J = 5 Hz, α to O), 120–170 (4 H, α to N), and 88 Hz (d, 3 H, J = 6.5 Hz, methyl).

Anal.[15a] Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.43; H, 7.49; N, 4.68.

Materials Used in Kinetic Studies.—β-Benzoyl-γ-phenylallyl bromide (**1a**) and the corresponding chloride (**1b**) were prepared as described previously.[4] Samples of **1a** which were used for kinetics were recrystallized from ether–hexane mixtures, mp 81° (corrected) and λ_{max} 285 mμ (ε 17,100) in *n*-hexane. The purity of **1b** was checked with data recorded previously.[4] Piperidine and cyclohexylamine were distilled from sodium through a 90-cm spinning band. Morpholine, *tert*-butylamine, triethylcarbinylamine, and *N*-methylcyclohexylamine were distilled from barium oxide and redistilled twice. All the compounds used in kinetic studies were purified immediately before use. Fisher Spectro-analyzed *n*-hexane was used as the solvent in the reactions which were monitored by uv spectroscopy. For other kinetic studies Phillip's *n*-hexane was freshly distilled from calcium hydride.

Kinetic Procedures.—The rates of formation of halide ion in the reactions of **1a** and **1b** with amines were obtained by an ampoule technique. The reactions were arrested by cooling to −80° and the contents of the ampoules were extracted into dilute nitric acid. The halide ion content of the aqueous layer was estimated by the Volhard method using a visual end point. The initial concentrations of the amine solutions were estimated by the addition of aliquots to a known excess of hydrochloric acid in methanol and back titration against a standard solution of morpholine in methanol using a pH meter.

The reactions of **1a** and of **1b** with cyclohexylamine and of **1a** with triethylcarbinylamine were also followed by a sampling technique. The rate of disappearance of the band in the 280-mμ region due to the cinnamoyl chromophore of **1a** or **1b** was measured. Absorption in this region due to the products **2b** or **2f** was slight and suitable corrections were made.

The rate constants were evaluated from the following expression, by the method of linear least squares

$$k_2 = \frac{1}{t(a - 2b)} \ln \frac{b(a - 2x)}{a(b - x)}$$

where a and b are the initial concentrations of the amine and allyl halide, respectively, x is the concentration of product, and t is the corresponding time.

Registry No.—**1a**, 14181-92-1; **1b**, 14181-99-8; **2a**, 31893-05-7; **4a**, 31893-06-8; **4b**, 31893-07-9; cyclohexylamine, 108-91-8; morpholine, 110-91-8; piperidine, 110-89-4; *N*-methylcyclohexylamine, 100-60-7; triethylcarbinylamine, 1571-51-3; *tert*-butylamine, 75-64-9.

Acknowledgment.—This work was supported in part by Grant No. 02931 from the National Cancer Institute of the U. S. Public Health Service.

1,2,4-Triazines. VI. Tautomerism in Substituted 2,3-Dihydro-3-oxo-1,2,4-triazines

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A series of 2,3-dihydro-3-oxo-1,2,4-triazines have been prepared. It has been established that **4c,e** is the major tautomer, where R_1 and/or R_2 = C_6H_5. When the substituent at C-5 is a methyl group, a methyl–methylene (**8b** ⇌ **9b**; **8d** ⇌ **9d**) tautomeric mixture exists. The equilibrium constants for these equilibria were determined.

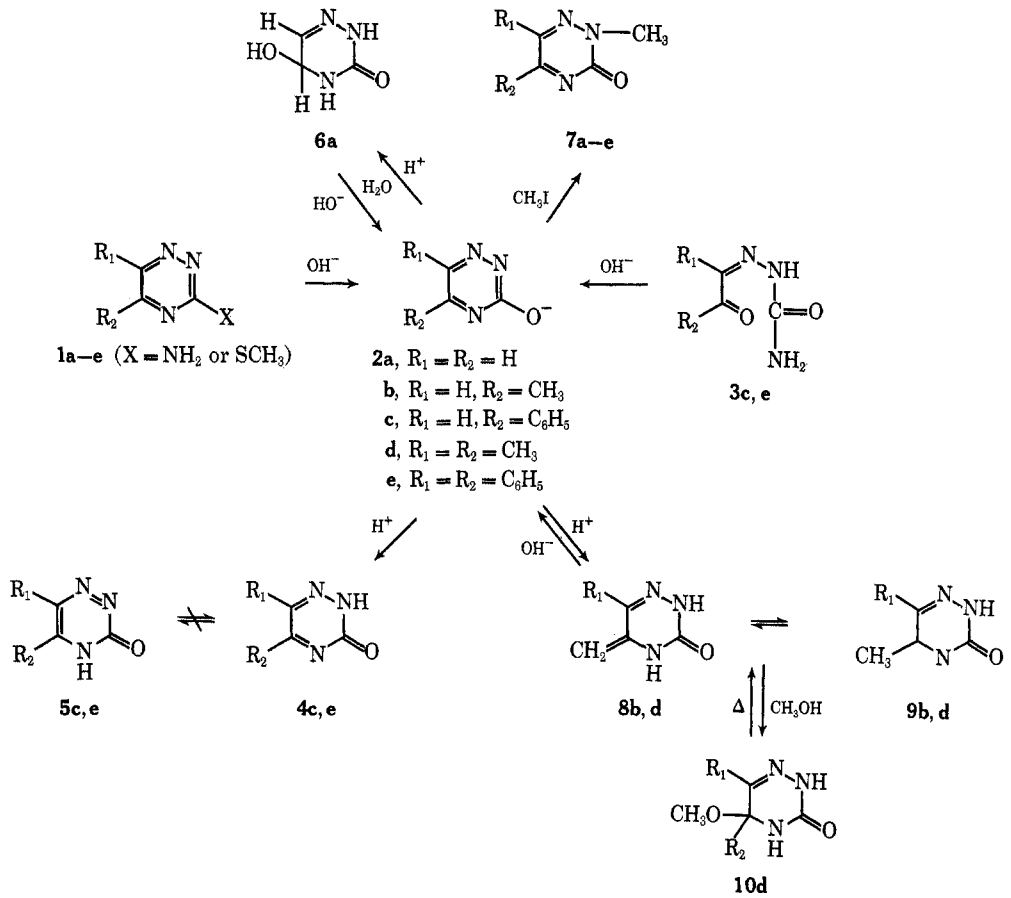
We have for some time[1-4] been interested in 1,2,4-triazines and now wish to describe a study of the tautomeric equilibria of some 2,3-dihydro-3-oxo-1,2,4-triazines. These compounds can in principle be prepared either by hydrolysis of 3-amino- (**1**, X = NH_2) or 3-methylthio (**1**, X = SCH_3) derivatives, or by cyclization of semicarbazone derivatives such as **3** (see Scheme I).

The conversions of compounds **3c–e** to compounds **2c–e**, respectively, have been described in the literature.[5,6] However, in our hands, using the described conditions, no product could be isolated from **3d**. This observation substantiates earlier reports to this effect.[7] Base hydrolysis of either 3-amino- or 3-methylthio-1,2,4-triazines (**1a–e**, X = NH_2 or SCH_3) gives the alkali metal salts of the corresponding 3-hydroxy-1,2,4-triazines (**2a–e**).[8]

Since the chemical shifts of the ring protons and the

(1) W. W. Paudler and J. M. Barton, *J. Org. Chem.*, **31**, 1720 (1966).
(2) W. W. Paudler and T. K. Chen, *J. Heterocycl. Chem.*, **7**, 767 (1970).
(3) W. W. Paudler and T. K. Chen, *J. Org. Chem.*, **36**, 787 (1971).
(4) W. W. Paudler and T. K. Chen, *J. Heterocycl. Chem.*, **4**, 224 (1967).
(5) W. Seibert, *Ber.*, **80**, 494 (1947).
(6) S. Rossi, *Rend. Ist. Lomb. Sci. Lett., Cl. Sci. Mat. Natur.*, **83**, 173 (1955); *Chem. Abstr.*, **50**, 10742h (1956).
(7) C. L. Pitzer, "The Chemistry of 1,2,4-Triazine and Some Related Compounds," Ph.D. Thesis, West Virginia University, 1967.
(8) The statement has been made[7] that basic hydrolysis of 3-amino-1,2,4-triazine (**1a**, X = NH_2) does not lead to identifiable products. This observation is now negated by our results.

SCHEME I



methyl protons in these alkali metal salts are very similar to the chemical shifts of the comparable protons in the 3-methylthio and 3-amino derivatives,[3] one can conclude that the negative charge resides largely on the oxygen atom, as shown in structure **2**. By analogy, the 5,6-diphenyl derivative (**2e**) is represented similarly.

On treatment of these salts with dilute acid, the expected oxo compounds (**4**) were obtained only in those instances where a phenyl substituent is present at C_5 (compounds **2c** and **e**).

The position of the tautomeric equilibrium **4** $\rightleftharpoons$ **5** can be established by comparing the uv spectra of the 3-oxo compounds (**4** and **5**) with the spectra of the corresponding N-2 and N-4 methylated derivatives (**7e** and **12e**, respectively).

The condensation of 2-methylsemicarbazide with benzil has been reported[9] to afford the same 2,3-dihydro-3-oxo-1,2,4-triazine (**7e**) as is obtained from the treatment of an alkali metal salt of 5,6-diphenyl-3-hydroxy-1,2,4-triazine with methyl iodide. Thus, the site of N-alkylation is established and one of the reference compounds needed for the uv study is available. The other needed isomer (**12e**) was prepared by condensing benzil with 4-methylsemicarbazide under acidic conditions (Scheme II).

A comparison of the uv spectrum of the nonalkylated derivative (**4e**) with the spectra of the N-2 and N-4 methyl derivatives (**7e** and **12e**) (see Table I) clearly shows that the equilibrium **4e** $\rightleftharpoons$ **5e** lies essentially totally in favor of the N_2H tautomer **4e**. Consequently, it appears that the tautomer possessing a N=N bond (**5e**) is considerably less stable than the one (**4e**) where this structural feature is not present. Whether this conclusion is also valid for those 3-oxo derivatives where C-5 and C-6 are either unsubstituted or have a methyl substituent, cannot be answered because of the complications to be discussed in the next section. However, there seems to be no *a priori* reason to suspect that the 5,6-diphenyl compound would behave substantially different from the other 3-oxo derivatives.

The direct alkylation with methyl iodide of the sodium salts of the other 3-hydroxy-1,2,4-triazines (**2a–d**) yielded the expected N-2 alkylated derivatives in satisfactory yields. That alkylation has indeed occurred at N-2 and not at N-4 is evident from the similarity of the proton chemical shifts of the N-CH_3 groups in all of these compounds, with the proton chemical shifts of the methyl group in the authentic N-2 methyl derivative **2e** (the methyl proton chemical shift in the N-4 methyl compound **12e** is significantly different).

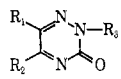
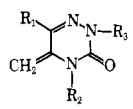
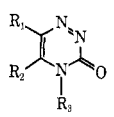
When the sodium salt of 3-hydroxy-1,2,4-trazine (**2a**) is treated with aqueous acid, there is obtained a compound whose molecular formula, $C_3H_5N_3O_2$, differs from the expected one, $C_3H_3N_3O$, by the elements of water. We have already commented on the propensity with which the 1,2,4-triazines undergo convalent hydration across the 4–5 bond,[2] an observation which has recently been confirmed.[10] Consequently, we can

(9) M. Polonovski, M. Pesson, and P. Rajzman, *Bull. Soc. Chim. Fr.*, 240 (1955).

(10) N. Vinot and J.-P. M. Packo, *ibid.*, 12 (1970).

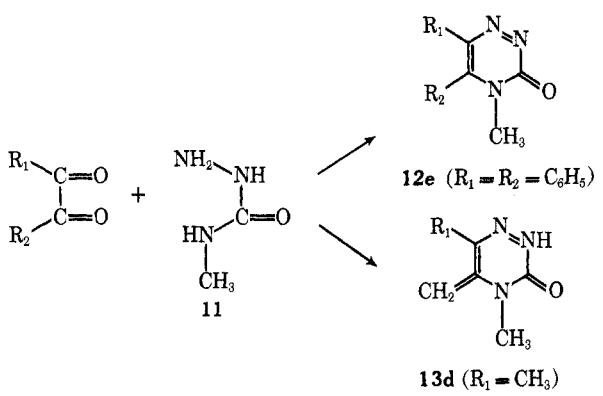
TABLE I

UV SPECTRAL DATA FOR VARIOUS 1,2,4-TRIAZIN-3-ONES[a]

Compd		λ_{max}, mμ ($\epsilon \times 10^3$)	λ_{min}, mμ ($\epsilon \times 10^3$)	Compd no.
	$R_1 = R_3 = H$; $R_2 = CH_3$[b]	300 (2.17) 220 (3.96) sh	258 (0.50)	9b
	$R_1 = R_2 = CH_3$; $R_3 = H$[b]	295 (3.03) 215 (9.14)	253 (0.63)	9d
	$R_1 = R_3 = H$; $R_2 = C_6H_5$	292 (13.28) 222 (11.07)	246 (1.71)	4c
	$R_1 = R_2 = C_6H_5$; $R_3 = H$	335 (4.17) sh 295 (6.55) sh 252 (14.88)	233 (13.39)	4e
	$R_1 = H$; $R_2 = R_3 = CH_3$	303 (2.82)	256 (0.61)	7b
	$R_1 = R_2 = R_3 = CH_3$	308 (2.88) 213 (9.92) sh	248 (0.69)	7d
	$R_1 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$	295 (12.67) 223 (10.89)	248 (1.78)	7c
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$	338 (4.97) 290 (6.16) 254 (14.30)	320 (4.77) 233 (11.93)	7e
	$R_1 = R_2 = CH_3$; $R_3 = H$	286 (4.76) 227 (13.89)	252 (1.79)	13d
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$	292 (10.72) 230 (10.92) sh 215 (15.43) sh	255 (5.81)	12e

[a] In 95% EtOH. [b] Tautomeric mixture of CH_3- and $CH_2=$ at R_2.

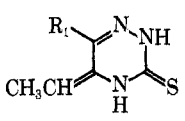
SCHEME II



assign structure **6a** to this covalently hydrated species. That we are indeed dealing with this compound is supported by its nmr spectrum, which is composed of an AB proton-on-carbon system (τ_5 4.62, τ_6 2.92, $J_{5,6}$ = 3.0 Hz) which is analogous to those previously described by us[2] as being typical of this type of triazine derivative. All attempts to date (sublimation, heating in toluene in the presence of a Dean–Stark trap) have failed to yield the dehydrated compound **4a**. Treatment with base does, however, regenerate the salt of 3-hydroxy-1,2,4-triazine (**2a**) quantitatively.

The remaining two alkali metal salts (**2b** and **2d**), when treated with aqueous acetic acid, afforded compounds with the expected molecular formulas. However, their nmr spectra are rather unique in that, in addition to the patterns expected for structures **9b** and **9d**, one observes an olefinic AB system (τ_1 5.9, τ_2 5.7, $J_{1,2}$ = 1.0 Hz) as well as the presence of an "additional" methyl peak (τ 8.05) in the case of the 5,6-dimethyl derivative and an "additional" highly deshielded singlet (τ 2.82) in the 5-methyl compound.

Since Adams and Shepherd[11] have recently shown that 5-ethyl derivatives of some 2,3-dihydro-3-thio-1,2,4-triazines exist in the ethylidene form **14**, one



$R_1 = CH_3, C_2H_5$

14

can conclude that the new peaks observed in the nmr spectra of the mono- and dimethyl derivatives of the oxo compounds are due to the methylene forms **8b** and **8d**, respectively. Thus, the equilibria **8b** ⇄ **9b** and **8d** ⇄ **9d** can be written to account for these observations.

The equilibrium constants of these equilibria can conveniently be determined by nmr as well as by ultraviolet spectroscopy. The latter technique would be applicable if one could obtain the uv spectra of the pure isomers (**8** and **9**).

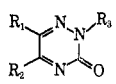
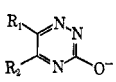
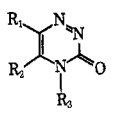
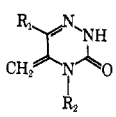
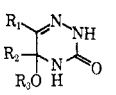
Since the nmr spectra of the N-2 alkylated compounds (**7b** and **7d**) are devoid of any methylene protons, we can assume that these substances exist, at least to the extent of 95%, in the methyl forms (**7b** and **7d**).

On the other hand, when biacetyl is condensed with 4-methylsemicarbazide (**11**), the N-4 methyl derivative **13d** that is obtained exists exclusively in the methylene form (Scheme II and Table II). Thus, the

(11) J. Adams and R. G. Shepherd, *Tetrahedron Lett.*, 2747 (1968).

TABLE II

NMR SPECTRAL DATA FOR SOME 1,2,4-TRIAZINES

Compd		Chemical shifts, τ					Solvent	$J_{1,2}$, cps	Compd no.
		R_1	R_2	R_3	CH_2=	C_6H_5			
	$R_1 = R_3 = H$; $R_2 = CH_3$[a]	2.07	7.62				DMSO		9b
	$R_1 = H$; $R_2 = R_3 = CH_3$	2.32	7.55	6.24			$CDCl_3$		7b
	$R_1 = R_2 = CH_3$; $R_3 = H$[b]	7.60	7.74				DMSO		9d
	$R_1 = R_2 = R_3 = CH_3$	7.55	7.68	6.28			$CDCl_3$		7d
	$R_1 = R_3 = H$; $R_2 = C_6H_5$[c]	1.22				(1.77, 2.36)	DMSO		4c
	$R_1 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$[c]	1.71		6.17		(1.89, 2.50)	$CDCl_3$		7c
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$[c]			6.10		(2.62)	$CDCl_3$		7e
	$R_1 = R_2 = C_6H_5$; $R_3 = H$[c]					2.38	DMSO		4e
	$R_1 = R_2 = H$	1.64	1.72				D_2O		2[a]
	$R_1 = H$; $R_2 = CH_3$	1.73	7.64				D_2O		2b
	$R_1 = R_2 = CH_3$	7.66	7.69				D_2O		2d
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$[c]			7.03		(3.38)	$CDCl_3$		12e
	$R_1 = R_2 = H$[a]	2.82			5.88 5.80		DMSO	1.0	8b
	$R_1 = CH_3$; $R_2 = H$[b]	8.05			5.88 5.72		DMSO	1.0	8d
	$R_1 = R_2 = CH_3$	7.94	6.90		5.79 5.66		$CDCl_3$	2.0	13d
		7.98	6.98		5.69 5.59		DMSO	2.0	
	$R_1 = R_2 = R_3 = H$	2.92	4.62				D_2O	3.0	6a
	$R_1 = R_2 = R_3 = CH_3$	8.57	8.14	7.06			DMSO		10d

[a] These values represent data taken from the equilibrium mixture of the $CH_3 \rightleftarrows CH_2$= tautomeric mixture of the 3-oxo-2,3-dihydro-5-methyl-1,2,4-triazine. The two species are present in the relative amounts indicated in the text. [b] These values represent data taken from the equilibrium mixture of the 3-oxo-2,3-dihydro-5,6-dimethyl-1,2,4-triazine. The two species are present in the relative amounts indicated in the text. [c] Chemical shift of middle point, indicated by parentheses.

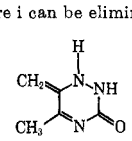
means of establishing the equilibrium constant for the system **8d** ⇄ **9d** by ultraviolet spectroscopy is now available.[12] The equilibrium constant for this equilibrium, determined in 95% ethanol, is 0.71, with the methylene tautomer (**8d**) being the minor component. This value compares well with the equilibrium constant (0.83) determined in DMSO by means of nmr.[13]

An analysis of the nmr spectrum of the equilibrium **8b** ⇄ **9b** in DMSO gives a value of 0.20 for the 5-methyl isomer (**9b**), with the methylene form (**8b**) again being the minor component.

When the 5,6-dimethyl mixture (**8d** ⇄ **9d**) is heated in methanol, one obtains compound **10d**, resulting from addition of 1 mol of methanol across the N_4–C_5 bond in compound **9d**. The nmr spectrum (Table II) and elemental analysis of this compound confirm its structure. Interestingly when this compound is sublimed, it readily reverts to the 3-oxo mixture **8d** ⇄ **9d**. This is in contrast to the stability of the covalently hydrated 2,3-dihydro-3-oxo-1,2,4-triazine (**6a**).

(12) We must, of course, assume that the ultraviolet spectrum of **8** and of **9** is not altered by N-alkylation.

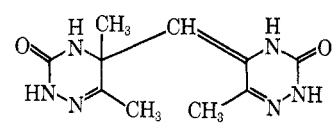
(13) The possibility that the methylene tautomer of the 5,6-dimethyl compound **9d** has the structure i can be eliminated, since the chemical shifts



i

of the methylene protons would be different from those in the 5-methylene cases **8b** and **8d**.

Adams and Shepherd[11] have suggested that 5,6-dimethyl-2,3-dihydro-3-oxo-1,2,4-triazine (**9d**) exists as the dimer **15**.



15

We have found that this dimer is only present in "aged" (2–3 days) and totally absent in freshly prepared solutions. The monomers (**8d** ⇄ **9d**) can be regenerated from the dimer by making an aqueous solution basic and reacidifying it, or by simply subliming it.

Experimental Section

Pmr spectra were obtained, as dilute (5% w/v) solutions in the solvents indicated, with a Varian HA-100 spectrometer. Elemental analyses were done by Mrs. V. Gindelsberger of this department. Mass spectra were obtained on all compounds with a Hitachi Perkin-Elmer RMU-6E mass spectrometer, with an ionization potential of 80 eV. Melting points are corrected.

General Procedure A. Base Hydrolyses of 3-Amino- or 3-Methylthio-1,2,4-triazines.—A solution of the appropriate 3-amino- (**1a–e**, X = NH_2)[14] or 3-methylthio- (**1a–e**, X = SCH_3)[3] 1,2,4-triazine (0.4 mol) in 200 ml of water containing 30 g (0.75 mol) of potassium hydroxide was heated with stirring for 3 hr at 50–60°.

The reaction mixture was then evaporated to dryness under vacuum and the remaining solid was recrystallized from methanol

(14) J. Saikawa and T. Maeda, *Yakugaku Zasshi*, **87**, 1501 (1967), and references cited therein.

to yield the potassium salt of the appropriate 2,3-dihydro-3-oxo-1,2,4-triazine (2a–e) (see Table III for analytical data). This salt was then dissolved in a minimum amount of water and the solution was carefully neutralized by the dropwise addition of acetic acid. The precipitate was collected, and recrystallized from 95% ethanol, and the resulting material was further purified by sublimation (see Table III for analytical data).

Table III
Analytical Data for Various 1,2,4-Triazines[a]

Compd, molecular formula (no.)	Mp, °C	Sublimation temp (at 0.2 mm), °C	Yield, %	Procedure
$C_4H_5N_3O$ (9b)	142	120	56.8	A
$C_5H_7N_3O$ (9d)	224	162	72	A
$C_9H_7N_3O$ (4c)	240	162	75	A
$C_{15}H_{11}N_3O$ (4e)	245	160	68	A
$C_4H_5N_3O$ (7a)	77.5	70	87	B
$C_5H_7N_3O$ (7b)	138	50	<10	B
$C_6H_9N_3O$ (7d)	86	72	82	B
$C_{10}H_9N_3O$ (7c)	158.5	98	79	B
$C_{16}H_{13}N_3O$ (7e)	152	98	72	B
$C_{16}H_{13}N_3O$ (12e)	181	115	<10	C
$C_6H_9N_3O$ (13d)	154	80	75	C
$C_3H_2N_3OK$ (2a)	262–265		23	A
$C_3H_5N_3O_2$ (6a)	320 dec		50 from 18	A
$C_6H_{11}N_3O_2$ (10d)	219		74	D

[a] Satisfactory analytical values (±0.3% for C, H, N) were recorded for all compounds in table: Ed.

The 2,3-dihydro-3-oxo-1,2,4-triazine (4a) could not be isolated by the above process but was obtained as its crystalline covalently hydrated derivative 6a by addition of acetic acid to an aqueous solution of its potassium salt (2a) (see Table III).

General Procedure B. Direct Alkylation of 2,3-Dihydro-3-oxo-1,2,4-triazines.—A solution of 1 mmol of either the alkali metal salt or the "free" 3-oxo compound obtained from procedure A, in 20 ml of methanol containing 1 mmol of $NaOCH_3$ was vigorously stirred with 5 mmol of CH_3I. After 40 hr, the reaction mixture was evaporated to dryness and the residue was extracted with three 50-ml portions of $CHCl_3$. The dried (anhydrous Na_2CO_3) $CHCl_3$ extracts were evaporated and the residue was sublimed to afford the 2-methyl derivatives of the corresponding 3-oxo compounds (7a–e) (see Table III for the appropriate analytical data).

General Procedure C. Syntheses of 3,4-Dihydro-4-methyl-3-oxo-1,2,4-triazines.—4-Methylsemicarbazone (4 mmol) is treated at room temperature with the appropriate α,β-dicarbonyl compound dissolved in 25 ml of ethanol. The precipitate which formed was collected after 15 min and dissolved in 10 ml of acetic acid. The solution was heated under reflux for 3 hr and evaporated to dryness, and the remaining solid was sublimed at the temperatures indicated in Table III.

Formation of 5,6-Dimethyl-4-methoxy-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (10d) (Procedure D).—A solution of 2,3-dihydro-5,6-dimethyl-3-oxo-1,2,4-triazine (25 mg, 0.2 mmol) was heated in 2 ml of methanol for 3 hr. After concentrating the solution to about 0.5 ml, it was allowed to cool to room temperature to yield 20 mg of compound 10d (see Table III for analytical data).

Registry No.—2a, 31952-58-6; 2b, 31952-59-7; 2d, 31952-60-0; 4c, 31952-61-1; 4e, 4512-00-9; 6a, 31952-63-3; 7a, 31952-64-4; 7b, 31947-27-0; 7c, 31947-28-1; 7d, 31999-38-9; 7e, 18510-97-9; 8b, 31947-30-5; 8d, 31947-31-6; 9b, 31947-32-7; 9d, 31947-33-8; 10d, 31947-35-0; 12e, 31947-34-9; 13d, 31947-36-1.

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Preparation of 6-Substituted Pterins *via* the Isay Reaction

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Various 6-substituted pterins have been prepared by a modification of the Isay reaction. When the condensation of either methyl glyoxal or phenyl glyoxal with 2,4,5-triamino-4-hydroxypyrimidine was carried out in the presence of 2-mercaptoethanol, mixtures of 6- and 7-substituted pterins were obtained with the 6 isomer predominant. The pure 6-methyl- and 6-phenylpterins were obtained from the mixture of isomers by crystallization from alkaline solution.

The Isay reaction is the original method for obtaining pteridines from the condensation of aminopyrimidines and α,β-diketo compounds.[2] We report here our success in using this reaction with α-keto aldehydes to produce 6-substituted 2-amino-4-hydroxypteridines (pterins). This route to pterins, not symmetrically substituted in the 6 and 7 position, has not been very satisfactory in the past for two reasons. The direction of condensation was seldom entirely in one direction, normally with the less desirable 7 isomer predominating. Second, the separation of the resulting mixture of 6 and 7 isomers was extremely difficult.

The ready availability of these compounds is of considerable interest because of their analogy to dihydrofolate[3] and their participation in the tetrahydro form in aromatic hydroxylations.[4,5]

Numerous attempts have been made to direct the Isay condensation in the direction of the 6 isomer. Forrest and Walker[6] examined the effect of hydrazine hydrate on the condensation of both acetol and methyl glyoxal with 2,4,5-triamino-6-hydroxypyrimidine (1). Although the effect was in the desired direction, the yields were low. Sodium bisulfite and strong acid

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