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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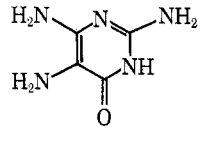
have also been used.[2,7] The results reported by Semb[7] using sodium bisulfite in the preparation of **2c** are similar to those reported here, although his yields are much lower. Angier[8] observed that the condensation of phenylglyoxal diethyl acetal led to a good yield of 2-amino-4-hydroxy-6-phenylpteridine (**2a**). Baugh and Shaw[9] used cysteine as an antioxidant to protect **1** from self-condensation in the reaction of **1** with dihydroxyacetone to give **2e**. Since the cysteine was present in a much smaller amount than the carbonyl compound, it is unlikely that a directive effect such as reported here was operating. We have observed that



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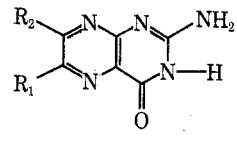

2a, $R_1 = C_6H_5$; $R_2 = H$
b, $R_1 = H$; $R_2 = C_6H_5$
c, $R_1 = CH_3$; $R_2 = H$
d, $R_1 = H$; $R_2 = CH_3$
e, $R_1 = CH_2OH$; $R_2 = H$

methyl glyoxal and phenyl glyoxal will condense with **1** under mild basic conditions in the presence of 2-mercaptoethanol to give **2c** and **2a** as the predominant isomers. Furthermore, the pure 6 isomers may be obtained by simple crystallization from base. By analogy to Angier's results, we believe the reactive intermediate to be the thiohemiacetal of the diketo compound. An even more direct route to **2a** is to simply carry out the condensation of the phenyl glyoxal and **1** at pH 4. Under these conditions pure **2a** is obtained. At pH 8 pure **2b** is obtained; at intermediate pH a mixture of isomers is obtained. It is interesting to note that the directive effects of the mercaptoethanol are in the opposite sense of the directive effects of pH on this condensation. In other instances when one has acid or base sensitive functional groups in the α-keto aldehyde, the direction of condensation may be controlled in either acidic or basic solution. This is illustrated by the preparation of **2c** and **2d** under identical conditions of pH.

Analysis of mixtures of pterin isomers has also been a problem in the past. The most satisfactory method to date has been that of Petering and Schmitt.[10] They demonstrated that the isomer content of crude mixtures of 2-amino-4-hydroxy-6- (and 7-) alkylpteridines can be determined by measuring the ratio of the absorbances at two specific wavelengths in the ultraviolet region of the absorption spectrum. Pmr studies of pterins in trifluoroacetic acid solution did not reveal[11] any difference in the chemical shift of the vinyl protons in the pterin isomers. We have observed the pmr spectra of these compounds under basic conditions and in all cases the vinyl protons in the different isomers are separated by 0.1 ppm or more and the isomer ratios are easily determined by proton integration. This technique is not susceptible to interference by colored side products and is more accurate for assaying crude mixtures than the ultraviolet-peak ratio technique. The activity of **2c** and **2d**, after reduction to the tetrahydro form, as cofactors in the enzymatic hydroxylation of phenylalanine to tyrosine have been discussed earlier by Storm and Kaufman.[5]

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Experimental Section

Methods.—Absorption spectra were obtained with a Cary Model 14 recording spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60 spectrometer using sodium 2,2-dimethyl-2-silapentanesulfonate (DDS) as an internal standard. Chemical shifts are reported as δ values in parts per million with DDS = 0 ppm. The results are reported in Table I.

TABLE I
PROTON RESONANCE DATA ON PTERIDINES[a]

Compd	Vinyl proton	Methyl group	Phenyl group
2a	8.50		(*m*, *p*) 7.22; (*o*) 7.39
2b	8.39		(*m*, *p*) 7.39; (*o*) 7.49
2c	8.45	2.55	
2d	8.16	2.52	

[a] Pmr spectra were run at 0.20 *M* concentration in 1 *M* NaOD. Chemical shifts are reported in parts per million relative to DDS internal standard with DDS = 0 ppm.

Materials.—Chemicals were obtained from the following sources: 2,4,5-triamino-6-hydroxypyrimidine sulfate from K and K Laboratories; methyl glyoxal (pyruvaldehyde) obtained as the 40% aqueous solution from Aldrich; phenyl glyoxal from Pierce Chemical Co.

2-Amino-4-hydroxy-6-methylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine sulfate (10 g, 42 mmol) was suspended in 100 ml of water and 10 g (42 mmol) of $BaCl_2 \cdot 2H_2O$ was added and the solution was stirred for 10 min. The $BaSO_4$ was removed by vacuum filtration on a Büchner funnel, 1 ml of 2-mercaptoethanol was added, and the pyrimidine solution was neutralized with excess $NaHCO_3$. Aqueous 40% pyruvaldehyde (7.56 g, 42 mmol) was diluted with 50 ml of H_2O, 10 g (126 mmol) of 2-mercaptoethanol was added, and the solution was neutralized with excess $NaHCO_3$. The solutions were combined, heated on a steam bath for 30 min, brought to pH 7 with acetic acid, and placed in the cold overnight. The precipitate was filtered, washed with water and then acetone, and dried under high vacuum (7.3 g, 41 mmol, 98%). This material consisted of 75% 6 isomer and 25% 7 isomer by pmr proton integration.

The above isomer mixture (4.5 g) was dissolved in 90 ml of 1 *M* sodium hydroxide with heating, and the solution was filtered and placed in the cold overnight. The sodium salt of **2c** was collected by vacuum filtration. The sodium salt was dissolved in a minimum amount of water, the solution was brought to pH 7.0 with acetic acid, and the precipitate was collected by vacuum filtration. The precipitate was washed successively with cold water, acetone, and ether and finally dried at high vacuum (2.4 g, 53%): λ_{max} (0.1 *N* KOH), 251 mμ (ϵ 1.94 $\times$ 10^4), 362 (6.30 $\times$ 10^3). *Anal.* Calcd for $C_7H_7N_5O$: C, 47.5; H, 3.95; N, 39.5. Found: C, 47.2; H, 4.09; N, 39.8.

2-Amino-4-hydroxy-7-methylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine sulfate (4.0 g, 16.8 mmol) was suspended in 80 ml of H_2O, and $BaCl_2 \cdot 2H_2O$ (4.0 g, 16.8 mmol) was added. The solution was stirred for 10 min and filtered. The filtrate was neutralized with excess $NaHCO_3$. Aqueous 40% pyruvaldehyde (3.5 g, 16.8 mmol) was added to the pyrimidine solution, and the mixture was heated on the steam bath for 30 min and allowed to stand overnight in the cold. The solution was then brought to pH 7 with acetic acid and the precipitate was collected by vacuum filtration. The filter cake was washed with water and then acetone. This material showed no **2c** isomer by pmr analysis. The filter cake was then dissolved in 135 ml of warm 0.1 *M* potassium hydroxide, the solution was passed over a 4 $\times$ 2 cm bed of triethylaminoethyl cellulose on a glass funnel, and the solution was brought to pH 7.0 with acetic acid. The precipitate was collected by vacuum filtration, washed with water

and then acetone, and dried under high vacuum (2 g, 11.3 mmol, 67%): λ_{max} (0.1 *N* KOH) 250 mμ (ϵ 1.72 $\times$ 10^4), 354 (7.17 $\times$ 10^3). *Anal.* Calcd for $C_7H_7N_5O$: C, 47.5; H, 3.95; N, 39.5. Found: C, 47.3; H, 4.08; N, 39.9.

2-Amino-4-hydroxy-6-phenylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine sulfate (2.0 g, 8.4 mmol) was suspended in 30 ml of H_2O, and $BaCl_2 \cdot 2H_2O$ (2.0 g, 8.4 mmol) was added. The solution was stirred for 10 min and filtered. The filtrate was adjusted to a pH of 4.0 with sodium acetate. Phenyl glyoxal (1.1 g, 8.2 mmol) was dissolved in 10 ml of methanol and added to the pyrimidine solution. The resulting mixture was heated on the steam bath for 3 hr. The pale yellow precipitate was collected on a sintered-glass filter and washed with water. This material, pure **2a** by pmr analysis, was dissolved in a minimum amount of 1 *M* sodium hydroxide and the sodium salt was precipitated with 10 *M* sodium hydroxide. The sodium salt was dissolved in a minimum amount of hot 1 *M* sodium hydroxide and cooled overnight. This pale yellow material was taken up in water and the solution was brought to neutrality with acetic acid. The pale yellow precipitate was collected by vacuum filtration, washed with water and acetone, and dried at high vacuum (0.85 g, 3.5 mmol, 41%): λ_{max} (0.1 *M* NaOH) 270 mμ (ϵ 2.38 $\times$ 10^4), 377 (1.00 $\times$ 10^4). *Anal.* Calcd for $C_{12}H_9N_5O$: C, 60.3; H, 3.8; N, 29.3. Found: C, 60.0; H, 3.9; N, 29.6.

2-Amino-4-hydroxy-7-phenylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine (4 g, 16.8 mmol) was suspended in 60 ml of H_2O, and $BaCl_2 \cdot 2H_2O$ (4 g, 16.8 mmol) was added. The solution was stirred for 10 min and filtered. The pH of the filtrate was adjusted to 9.0 with 1 *M* sodium hydroxide. Phenyl glyoxal (2.2 g, 16.4 mmol) in 20 ml of methanol was added slowly, and the pH of the solution was kept above 8 with 1 *M* sodium hydroxide. The solution was stirred for 2 hr at room temperature and the pH was adjusted to neutrality with acetic acid. The precipitate was collected by vacuum filtration and washed with water and acetone. This material was pure **2b** by pmr analysis. The filter cake was suspended in 100 ml of hot dimethylformamide and concentrated hydrochloric acid was added until all the material dissolved. The solution was allowed to cool to room temperature and placed in the cold overnight. The crystals were collected by vacuum filtration and taken up in water, the pH was adjusted to neutrality, and the precipitate was collected by vacuum filtration and washed with water and acetone (1.60 g, 6.8 mmol, 41%): λ_{max} (0.1 *M* NaOH) 236 mμ (ϵ 1.97 $\times$ 10^4), 265 (2.00 $\times$ 10^4), 374 (1.28 $\times$ 10^4). *Anal.* Calcd for $C_{12}H_9N_5O$: C, 60.3; H, 3.8; N, 29.3. Found: C, 59.9; H, 3.9; N, 29.5.

Registry No.—**2a**, 25846-86-0; **2b**, 32136-35-9; **2c**, 13165-98-5; **2d**, 13040-58-9.

Novel Imidazole Ring Formation from α Olefins, Carbon Monoxide, and Ammonia

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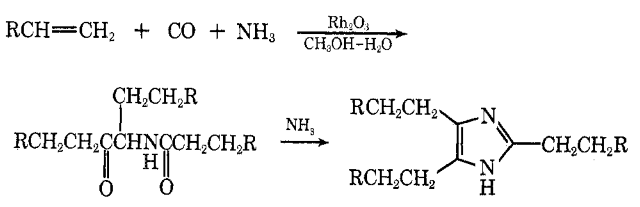
Rhodium-catalyzed reactions of α olefins with carbon monoxide and concentrated aqueous ammonia give 2,4,5-trialkylimidazoles in one step and in 50–60% yields. When dilute aqueous ammonia was used, an *N*-acyl α-amino ketone intermediate was isolated.

Usually the synthesis of imidazole derivatives requires many complicated steps.[1] We now wish to describe a novel method for obtaining 2,4,5-trialkylimidazoles from α olefins, carbon monoxide, and ammonia in one step. In a typical experiment a suspension of rhodium oxide was heated with ethylene, carbon monoxide, and ammonia at 150° for several hours. From the reaction mixture, 2,4,5-triethylimidazole and propionamide were obtained in 52 and 15% yields, respectively.

When a dilute ammonia solution is used in the reaction of ethylene with carbon monoxide, *N*-propionyl-3-amino-4-hexanone was obtained in 40% yield in addition to a small amount of triethylimidazole. The formation of the amino ketone was confirmed by ir, mass spectra, nmr (three ethyl groups and a methine proton, δ 4.5, of the asymmetric carbon), and elemental analysis of the 2,4-dinitrophenylhydrazone derivatives. The analysis of gas remaining in the reactor after completion of the reaction showed the presence of carbon dioxide and a little ethylene. From these results, the reaction may be described as follows.



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In these reactions, the ring carbons of the imidazole ring and the asymmetric carbon of the ketoamide group apparently arise from carbon monoxide. These carbons are probably introduced as carbonyl groups first and then reduced with the aid of the rhodium catalyst.

It is well known that cobalt and rhodium carbonyls are the active catalysts in the carbonylation reaction,[2] and Heck has suggested that $HM(CO)_3$ (M = Co, Rh) is the active species in the catalytic carbonylation.[3]

However, cobalt carbonyl has not shown any catalytic activity for the formation of imidazole rings.

Furthermore, one of the present authors has shown recently that carbon monoxide is easily oxidized to carbon dioxide by a rhodium complex.[4] On the basis of these results, the formation of $HRh(CO)_3$ is assumed to occur as shown below. A similar mechanism of

$$^1/_2Rh_4(CO)_{12} + H_2O + CO \longrightarrow 2HRh(CO)_3 + CO_2$$

hydrorhodium carbonyl formation is found in the reaction of ethylene with carbon monoxide.[5]

Thus, $HRh(CO)_3$ adds to olefin to give an σ-alkyl rhodium carbonyl, which rearranges to an acyl rhodium complex and dimerized to yield an α diketone as reported by Tsutsumi.[6]

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