A solution of 110 mg. of $\Delta^{4,6,8(14),22}$-ergostatetraene in ethyl acetate in the presence of used platinum catalyst absorbed three moles of hydrogen in 30–40 min. and the reaction then stopped. The resulting colorless oil slowly crystallized from ether–methanol at 5° to give 80 mg. of crystals, m.p. 71–74°, α_D +16° Chf. Recrystallized material melted at 74.5–75.5°, α_D +15° Chf; positive test with tetranitromethane. The constants reported[41] for $\Delta^{8(14)}$-ergostene are: m.p. 77–78°, α_D +11°.

The tetraene (110 mg.) was reduced when sodium (4 g.) was added over a 4-hr. period to a refluxing solution in redistilled *n*-propyl alcohol (25 cc.). The solution was let stand overnight, ether was added and the cake broken up, and then successive small portions of methanol were added to decompose the sodium. The washed, dried, and clarified ethereal solution on concentration (3–4 cc.) and cooling (5°) afforded two crops of product: 46 mg. of long thick plates, m.p. 68.5–69.5°, α_D −124° Chf, λ_{max}^{EtOH} 252 mμ (4,600); 33 mg., m.p. 58–59.5°, λ_{max}^{EtOH} 251.5 mμ. The material is probably a mixture, since in known instances chemical reduction of trienes involve 1,2-, 1,4- and 1,6-addition.

(41) I. M. Heilbron, F. S. Spring and R. T. Webster, *J. Chem. Soc.*, 1705 (1932).

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES[a] AND THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH[b]]

The Formation of 1,3,5-Triazines by the Reaction of α-Cyanocarbonyl Compounds with Guanidine

BY PETER B. RUSSELL,[a] GEORGE H. HITCHINGS,[a] B. H. CHASE[b] AND JAMES WALKER[b]

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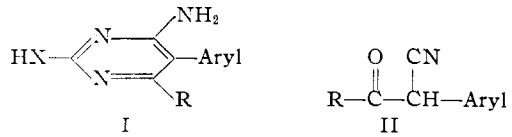
Contrary to reports in the literature it has been shown that the condensation of cyandesoxybenzoin and guanidine does not result in 2,4-diamino-5,6-diphenylpyrimidine but gives 2-amino-4-benzyl-6-phenyl-1,3,5-triazine. In a similar manner α-formylphenyl- and *p*-chlorophenylacetonitrile condense with guanidine to give 2-amino-4-benzyl- and 4-*p*-chlorobenzyltriazines. These compounds were synthesized by an alternate route. The courses of the above reactions are discussed.

The condensation of an α-cyanocarbonyl compound with a urea derivative would appear to be an attractive method of preparation of 4-aminopyrimidines. This is especially the case with 4-amino-5-arylpyrimidines (I), since the required α-acylarylacetonitriles (II) are readily available by the acylation of arylacetonitriles with esters. However, there appears to be only one instance of such a synthesis reported in the literature. Zerweck and Keller[1] state that the reaction of cyandesoxybenzoin (III) with guanidine yielded 2,4-diamino-5,6-diphenylpyrimidine (IV). All attempts to prepare IV from these two compounds failed and IV, prepared by the condensation of α,β-diphenyl-β-methoxyacrylonitrile and guanidine,[2] did not correspond in properties with the compound described by Zerweck and Keller.

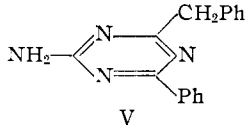
When cyandesoxybenzoin and guanidine were refluxed together in alcoholic solution no product was isolated and the greater part of the ketonitrile was recovered unchanged. However, when the heating was carried out at 180° the solvent being allowed to evaporate, a crystalline product $C_{16}H_{14}N_4$, isomeric with IV, was obtained and the oily residues from the reaction had the odor of ethyl benzoate. The ultraviolet spectrum of the product (Table I) suggested that it was a phenyl-1,3,5-triazine and it was formulated as 2-amino-4-benzyl-6-phenyl-1,3,5-triazine (V).



I

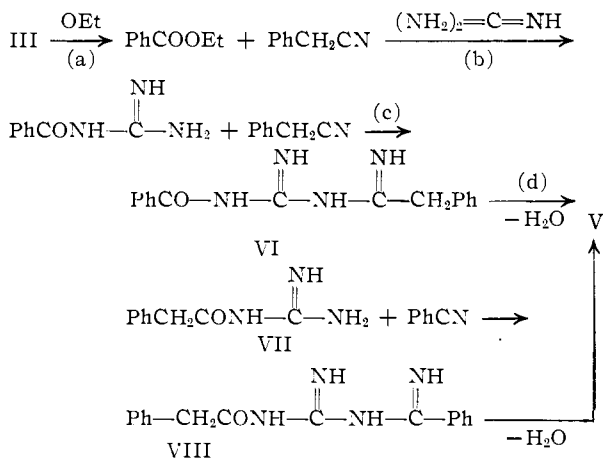
II

IV (R = Aryl = Ph, X = NH) III (R = Aryl = Ph)



V

The formation of V was believed to occur by the following steps: (a) the cleavage of III to ethyl benzoate and phenylacetonitrile by the strongly alkaline solution, a reversal of the formation of III; (b) the reaction of guanidine with ethyl benzoate to give benzoylguanidine; (c) the addition of benzoylguanidine to phenylacetonitrile to give N′-phenyliminoaceto-N″-benzoylguanidine (VI) followed by (d) the cyclization of this compound with loss of water to give V.



If this formulation is correct the condensation of benzoylguanidine and phenylacetonitrile at 180° should give rise to V and further phenylacetylguanidine (VII) and benzonitrile might be expected to give the same product *via* the intermediate N′-benzoylimino-N″-phenylacetylguanidine (VIII). In fact, both these reactions gave rise to V in good yield, thus giving strong support to the assigned structure and mode of formation.

(1) W. Zerweck and K. Keller, U. S. Patent 2,211,710.

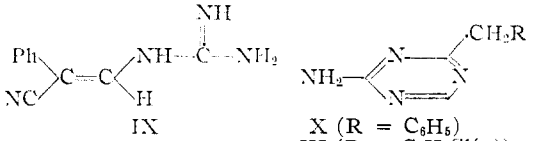
(2) P. B. Russell and G. H. Hitchings, THIS JOURNAL, **73**, 3763 (1951).

TABLE I

	Compound[a]	λ_{min}, mμ	$\epsilon \times 10^{-3}$	λ_{max}, mμ	$\epsilon \times 10^{-3}$
1	2,4-Diamino-1,3,5-triazine[b,d]	242	2.8	248–253	2.9
2	2,4-Diamino-6-*p*-chlorobenzyl-1,3,5-triazine	248	3.1	259	4.0
3	2,4-Diamino-6-phenyl-1,3,5-triazine[c,d]	...	..	249	25.0
4	2-Amino-4-benzyl-1,3,5-triazine (XII)	252	2.5	259–261	2.8
5	2-Amino-4-(3′4′-dichlorobenzyl)-1,3,5-triazine[e]	250–253	2.5	265	2.7
6	2-Amino-4-benzyl-6-phenyl-1,3,5-triazine (VI)	243	17.0	253	20.0
7	2-Amino-4,6-diphenyl-1,3,5-triazine[e]	...	..	256	30.0

[a] All spectra determined on a Beckman model DU quartz spectrophotometer in ethanol, cell length 1 cm. Concentrations: [b] 20 mg./l. [c] 40 mg./l., otherwise 10 mg./l. [d] K. Rackmann, *Ann.*, **376**, 180 (1910). [e] P. B. Russell and G. H. Hitchings, THIS JOURNAL, **72**, 4922 (1950).

Attempts to combine α-formylphenylacetonitrile and its *p*-chloro analog (II, R = H, Aryl = C_6H_5 and C_6H_4Cl, respectively) with guanidine did not give the desired pyrimidines (I, R = H, Aryl = C_6H_5 and C_6H_4Cl, X = NH)[3,4] but resulted in two compounds $C_{10}H_{10}N_4$ and $C_{10}H_9N_4Cl$ isomeric with the required products. Chase, Thurston and Walker[3] considered these compounds to be *trans*-(α-guanidinomethylene)-phenylacetonitrile (IX) and its *p*-chloro analog. However, the compound $C_{10}H_{10}N_4$ on hydrolysis with acid gave phenylacetylguanidine (VII), a reaction difficult to formulate on the basis of structure IX, and, further, it was shown to be identical with the product obtained by Russell and Hitchings[2,5] from the condensation of formylguanidine and phenylacetonitrile.

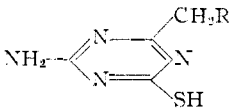


IX

X (R = C_6H_5)
XI (R = $C_6H_4Cl(p)$)

The facts recorded above, together with the ultraviolet absorption spectrum of the compound, suggested that it was in fact 2-amino-4-benzyl-1,3,5-triazine (X). It is apparent that X can arise in an exactly similar manner to that discussed for V.

The constitutions X and XI for the condensation products of α-formylphenyl- and *p*-chlorophenylacetonitriles with guanidine were proven by an alternative synthesis. Phenylthioacetic and *p*-chlorophenylthioacetic acids reacted with dicyandiamide to give 2-amino-4-benzyl-6-mercapto-1,3,5-triazine[6] (XII) and the corresponding 4-*p*-chlorobenzyl compound (XIII), respectively.



XII (R = C_6H_5)
XIII (R = C_6H_4Cl-*p*)

The desulfurization of these two compounds to give X and XI was accomplished with Raney nickel in ethanol.

The ultraviolet absorption spectra of several amino-1,3,5-triazines, of value in assigning the triazine structures to the above compounds, are given in Table I. It is seen that when a phenyl nucleus is conjugated with the triazine nucleus there is a great increase in intensity of absorption but no marked wave length change (see Table I, 1 and 3 or 4 and 6). Introduction of a second phenyl group causes a further marked increase in intensity (see Table I, 3 and 7).

Experimental

Condensation of Cyandesoxybenzoin with Guanidine.—Cyandesoxybenzoin (11 g.) was treated with an alcohol solution of guanidine (from 4.75 g. of the hydrochloride and 1.15 g. of sodium in 50 ml. of ethanol) and the mixture heated at 150–170° (with evaporation of the alcohol) for one hour. The mixture was then cooled. The solid product, which smelled strongly of ethyl benzoate, was washed free from oil with a little ethanol and recrystallized from ethanol-benzene. After a further recrystallization from ethyl acetate it was obtained as colorless plates, m.p. 206–207°.

Anal. Calcd. for $C_{16}H_{14}N_4$: C, 73.2; H, 5.3; N, 21.4. Found: C, 73.0; H, 5.4; N, 21.1.

Condensation of Benzoylguanidine with Phenylacetonitrile.—Benzoylguanidine[7] (15 g.) was heated with phenylacetonitrile (30 g.) at 180° in an open vessel for one hour. After cooling the solid was washed with ethanol and recrystallized from ethyl acetate. It melted at 206° and was identical with the sample prepared above.

Condensation of Phenylacetylguanidine with Benzonitrile.—Phenylacetylguanidine[8] (18 g.) was heated with benzonitrile (20 g.) at 180° for one hour. The mixture was cooled and the solid washed with ethanol. The crystalline material after recrystallization from ethyl acetate melted at 206° and was identical with the two samples prepared above.

Formylguanidine and Phenylacetonitrile.—The product, m.p. 139°, obtained by Russell and Hitchings[2] was recrystallized several times from ethyl acetate. It then formed colorless needles, m.p. 140°.

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.9; H, 5.3; N, 30.5.

This compound was identical in every respect with the material, m.p. 139.5°, obtained by condensation of α-formylphenylacetonitrile and guanidine.[3]

It is believed that the high nitrogen and low carbon values previously obtained[2] were due to the presence of some melamine or guanamine which is difficult to remove.

Formylguanidine and 3,4-Dichlorophenylacetonitrile.—The nitrile (18.6 g.) and formylguanidine[7] (8.7 g.) were heated together at 180° for two hours. After cooling the solid 2-amino-4-(3′,4′-dichlorobenzyl)-1,3,5-triazine was washed with ether and recrystallized from ethyl acetate and then benzene-ligroin. It formed small colorless needles, m.p. 155°.

Anal. Calcd. for $C_{10}H_8N_4Cl_2$: C, 47.1; H, 3.1; N, 21.9. Found: C, 47.4; H, 2.7; N, 21.6.

2-Amino-4-benzyl-6-mercapto-1,3,5-triazine.—A mixture of dicyandiamide (7.0 g.) and phenylthioacetic acid[9] (14 g., 10% excess) in ethyl acetate (75 ml.) was boiled under re-

(3) B. H. Chase, J. P. Thurston and J. Walker, *J. Chem. Soc.*, 3439 (1951).

(4) P. B. Russell and G. H. Hitchings, unpublished work.

(5) In the reference cited[2] the melting point of the compound agrees with that of Chase, *et al.*, but the analysis does not agree for $C_{16}H_{10}N_4$. This discrepancy is believed to be due to small quantities of nitrogen-rich impurities which were removed only after several further recrystallizations (see Experimental).

(6) A. Ostrogovich and V. Galea, *Atti. Acad. Lincei*, **162**, 12 (1930).

(7) W. Traube, *Ber.*, **43**, 3586 (1910).

(8) J. K. Simons and W. I. Weaver, U. S. Patent 2,403,694.

(9) T. B. Johnson, THIS JOURNAL, **28**, 1457 (1906).

flux for three hours on a steam-bath. After standing at room temperature overnight the crude cream-colored triazine (9.35 g., 51%) was collected and washed with ethyl acetate. The substance was dissolved in cold *N* potassium hydroxide and the solution was treated with charcoal, filtered and acidified with acetic acid, when the triazine was precipitated. Recrystallization from ethoxyethanol gave the pure triazine as small colorless needles which melted at 265°, with darkening and gassing below the melting point.[10]

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.0; H, 4.6; N, 25.7; S, 14.7. Found: C, 55.3; H, 4.7; N, 25.4; S, 14.3.

The picrate separated from aqueous alcohol in yellow needles, m.p. 187–188°.[10]

Anal. Calcd. for $C_{10}H_{10}N_4S \cdot C_6H_3O_7N_3$: C, 42.9; H, 2.9; N, 21.9; S, 7.2. Found: C, 42.4; H, 3.1; N, 21.4; S, 7.4.

2-Amino-4-*p*-chlorobenzyl-6-mercapto-1,3,5-triazine.—This compound was prepared in a manner analogous to that described above for the unsubstituted compound. The crude triazine was obtained in 58% yield. It was purified by solution in dilute ammonium hydroxide followed by precipitation with acetic acid, and finally by recrystallization from ethoxyethanol. It formed colorless prisms, m.p. 268–269° (dec.).

Anal. Calcd. for $C_{10}H_9N_4ClS$: C, 47.6; H, 3.6; N, 22.2. Found: C, 47.6; H, 3.6; N, 22.2.

The picrate separated from ethanol in clusters of tiny yellow needles, m.p. 196–197°.

Anal. Calcd. for $C_{10}H_9N_4ClS \cdot C_6H_3O_7N_3$: N, 20.4; S, 6.7. Found: N, 20.3; S, 6.9.

2-Amino-4-benzyl-1,3,5-triazine.—2-Amino-4-benzyl-6-mercapto-1,3,5-triazine (2.0 g.) was treated with Raney nickel (2.0 g., prepared without allowing the temperature to rise above 50°) in boiling ethanol (100 ml.), two further portions of Raney nickel (each of 2 g.) being added after one-half and 1.5 hours, respectively. After refluxing for two hours, the suspension was filtered and the nickel washed with hot ethanol. The combined ethanolic solutions were evaporated *in vacuo* and the greenish residue was shaken with a slight excess of cold *N* hydrochloric acid. The solution, freed from a small amount of insoluble material, was basified with an excess of *N* sodium hydroxide solution and extracted with ether (twice with 250 ml.). The colorless residue (0.55 g., 32%) obtained on evaporation of the ether gave, on recrystallization from benzene, colorless flattened needles of 2-amino-4-benzyl-1,3,5-triazine, m.p. 139–140°, identical with the product, m.p. 138.5–139.5°, obtained from formylphenylacetonitrile and guanidine[3] or from formylguanidine and phenylacetonitrile.

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.2; H, 5.3; N, 30.1.

2-Amino-4-*p*-chlorobenzyl-1,3,5-triazine.—2-Amino-4-*p*-chlorobenzyl-1,3,5-triazine was prepared by desulfurization of the corresponding 6-mercapto compound in a manner analogous to that described above. The product was crystallized from *n*-butanol to give colorless flattened prisms, m.p. 205–206° which did not depress the melting point (205–206°) of the product obtained from α-formyl-*p*-chlorophenylacetonitrile and guanidine.[3]

Anal. Calcd. for $C_{10}H_9N_4Cl$; N, 25.4. Found: N, 25.0.

2,4-Diamino-6-*p*-chlorobenzyl-1,3,5-triazine.—This compound was prepared by the method of Ostrogovich and Gheorghiu.[11]

Dicyandiamide (4 g.) and *p*-chlorophenylacetonitrile (8 cc.) in ethanol (10 ml.) were heated in an open flask at 180–200° for two hours. After cooling the residue was washed with ether and then suspended in sodium hydroxide solution. After filtration the solid was recrystallized from ethanol. It formed needles, m.p. 252°.

Anal. Calcd. for $C_{10}H_{10}N_5Cl$: C, 51.0; H, 4.3; N, 29.9. Found: C, 51.2; H, 4.3; N, 30.4.

(10) A. Ostrogovich and V. Galea (ref. 6) who gave scanty details record melting points of 270–271° and 187–188° for the triazine and picrate, respectively.

(11) A. Ostrogovich and G. Gheorghiu, *Gazz. chim. ital.*, **60**, 648 (1930).

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[Contribution from the Lederle Laboratories Division, American Cyanamid Company]

7-Isomer of Pteroylglutamic Acid

By C. W. Waller, M. J. Fahrenbach, J. H. Boothe, R. B. Angier, B. L. Hutchings, J. H. Mowat, J. F. Poletto and J. Semb

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The bromination of 2-amino-4-hydroxy-7-methylpteridine in 48% hydrobromic acid gave a 7-bromomethyl or a 7-dibromomethyl derivative depending upon the quantity of bromine used. From the monobrominated compound was prepared the 7-isomer of pteroylglutamic acid. The instability of this 7-isomer accounts for its absence in purified synthetic pteroylglutamic acid.

In previous communications on the synthesis of pteroylamino acids[1,2] only the 6-isomers have been reported and in the purified compounds[1,2]: the absence of the 7-isomer was proven by oxidation to give only the 2-amino-4-hydroxy-6-pteridinecarboxylic acid. The 7-isomer of pteroic acid was reported to be formed by treating two molecular proportions of *p*-aminobenzoic acid with one of reductone and then treating the product with 2,4,5-triamino-6-hydroxypyrimidine.[3] However, Forrest and Walker did not characterize their product beyond the oxidation of the crude to 2-amino-4-hydroxy-7-pteridinecarboxylic acid.

Disclosed herein is the synthesis of the 7-isomer of pteroylglutamic acid, "7-pteroylglutamic acid" (IV) N-[4-{[(2-amino-4-hydroxy-7-pteridyl)-methyl]-amino}-benzoyl]-glutamic acid.

The bromination[4] of 2-amino-4-hydroxy-7-methylpteridine[5] (I) in 48% hydrobromic acid gave 2-amino-4-hydroxy-7-bromomethylpteridine (II) when one molecular proportion of bromine was used and 2-amino-4-hydroxy-7-dibromomethylpteridine (III) when an excess of bromine was used. The monoacetyl derivative of the latter pterin was prepared by heating at refluxing temperature in acetic anhydride.

The ultraviolet absorption data for the 7-bromomethylpteridine II and 7-dibromomethylpteridine

(1) C. W. Waller, *et al.*, This Journal, **70**, 19 (1948).

(2) (a) R. B. Angier, *et al.*, *ibid.*, **70**, 25 (1948); (b) D. B. Cosulich and J. M. Smith, *ibid.*, **70**, 1922 (1948).

(3) H. S. Forrest and J. Walker, *J. Chem. Soc.*, 79 2002 (1949).

(4) J. H. Boothe, *et al.*, This Journal, **70**, 27 (1948); C. W. Waller, *et al.*, *ibid.*, **72**, 4630 (1950).

(5) J. H. Mowat, *et al.*, *ibid.*, **70**, 14 (1948); R. B. Angier, *et al.* *ibid.*, **70**, 3029 (1948).