removed and worked up as above; recovered 85% unchanged I; m. p. 113–114°.

E. Separate 0.01 mole samples of I and II were refluxed for six hours in 25 cc. of triethylamine. Evaporation of the triethylamine gave back quantitative recoveries of the unchanged starting compound in each case.

Acknowledgment.—The authors are indebted to Mr. Samuel W. Blackman for the microanalyses reported here.

Summary

A pair of mixed diacyl derivatives of ethanolamine has been made and characterized. No evidence of the acyl migrations, common in the analogous *o*-aminophenol derivatives, has been observed under a variety of conditions.

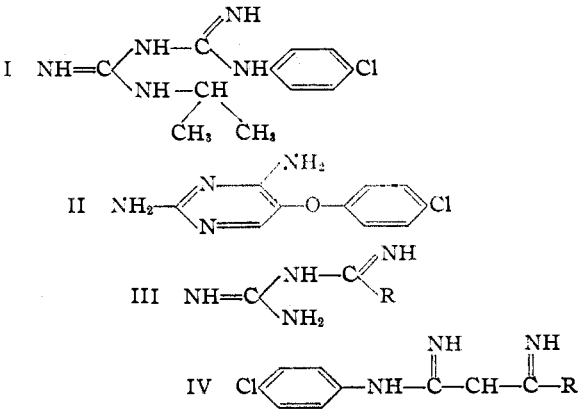
TUCKAHOE 7, N. Y. RECEIVED APRIL 14, 1950

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

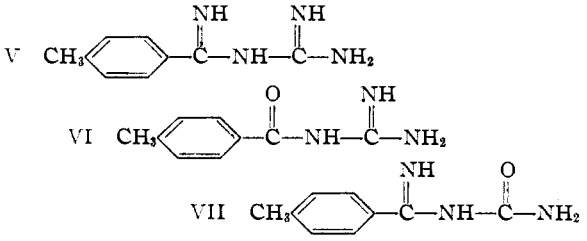
The Reaction of Aromatic Nitriles with Guanidine[1]

BY PETER B. RUSSELL AND GEORGE H. HITCHINGS

The formal analogy in structure between N^1-*p*-chlorophenyl-N^1-isopropylbiguanide (I)[2] and 2,4-diamino-5-*p*-chlorophenoxypyrimidine (II) and their similarities in microbiological and antimalarial behavior were noted recently.[3] Since the hitherto unknown acylimidoguanidines (III) represent a second type of open chain analog of 2,4-diaminopyrimidines an investigation of the methods for their preparation was initiated. Subsequently Birtwell[4] reported the preparation of a series of N-acylimido-N′-*p*-chlorophenylguanidines (IV) by the action of alkylmagnesium iodides on N-cyano-N′-*p*-chlorophenylguanidine. All the compounds (IV) were inactive against *Plasmodium gallinaceum* in chicks.[4]



Malonitrile, its substitution products and ethyl cyanoacetate condense with guanidine to give 2,4,6-triaminopyrimidine[5,6] or 2,4-diamino-6-hydroxyprimidine,[7] respectively. Thus it might be expected that a mononitrile would condense with guanidine to give an acylimidoguanidine (III). With aromatic nitriles this reaction does occur, but the isolation of such a compound was found to be possible in only one instance, that of *p*-toluimidoguanidine (V).



When *p*-toluonitrile was treated with guanidine in boiling alcohol, the ether soluble product gave a hydrochloride $C_9H_{11}ON_3 \cdot HCl$ on treatment with dilute aqueous hydrochloric acid. This compound proved to be the hydrochloride of *p*-toluoguanidine (VI) rather than *p*-toluimidourea (VII). By avoiding the use of aqueous solutions the hydrochloride and the acetate of *p*-toluimidoguanidine (V) were readily prepared. Both salts are easily hydrolyzed to salts of VI by cold water or dilute acids so that the compound is too unstable for biological studies. This facile hydrolysis may be likened to the hydrolysis of salts of IV to salts of N-acyl-N′-*p*-chlorophenylguanidine by water or dilute acids,[4] and less closely to the hydrolysis of I to N-*p*-chlorophenyl-N′-isopropylguanylurea by cold dilute acids.[8]

In other instances either the nitrile was recovered unchanged or a product was obtained which, with one exception, appeared to arise from the condensation of two molecules of the nitrile and one of guanidine with the elimination of one molecule of ammonia. This suggests the 2-amino-4,6-diaryl-1,3,5-triazine structure (VIII) for these compounds, a formulation which is in agreement with the physical and chemical properties of the products. For example, 3-cyanopyridine reacted smoothly with guanidine to give a colorless, rather insoluble compound $C_{13}H_{10}N_6$ which formed a trihydrochloride and a dimethiodide. The absorption spectrum of the com-

(1) Presented before the Division of Organic Chemistry at the 117th Meeting of the A. C. S., Philadelphia, Pa., April 1950.

(2) "Paludrine," now known as "Chlorguanide" in the U. S. and "Proguanil" in England.

(3) Falco, Hitchings, Russell and VanderWerff, *Nature*, **164**, 107 (1949).

(4) Birtwell, *J. Chem. Soc.*, 2561 (1949).

(5) Traube, *Ber.*, **37**, 4544 (1904).

(6) Merck, German Patent 165,692 (1905), *Frdl.*, **8**, 1073 (1908).

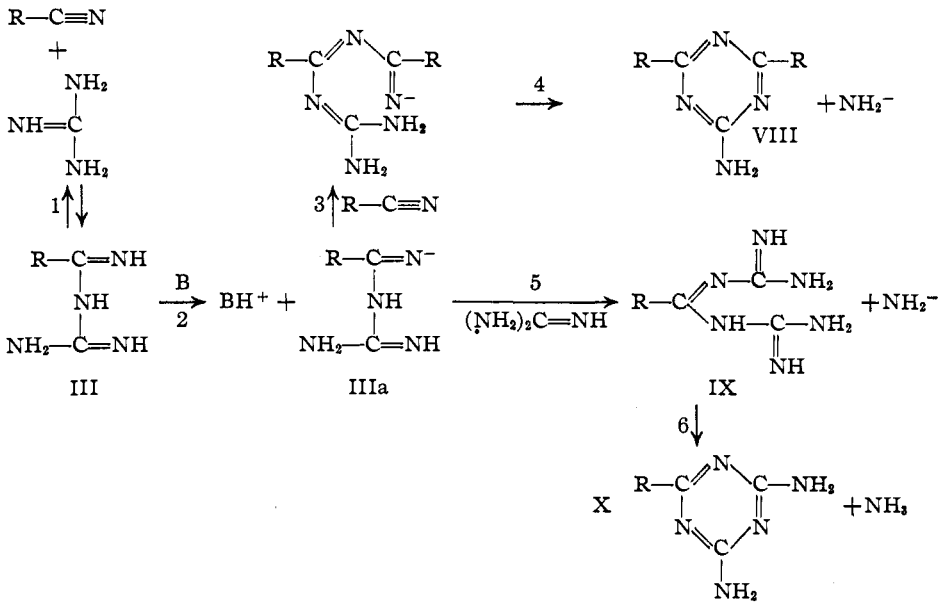
(7) Cain, Mallette and Taylor, THIS JOURNAL, **68**, 1996 (1946).

(8) Curd, Davey and Richardson, *J. Chem. Soc.*, 1732 (1949).

pound had an intense band at 235 mμ similar to that seen in the spectrum of melamine (2,4,6-triamino-1,3,5-triazine). Members of this class of triazines which lack basic groupings in the radical R do not exhibit basic characteristics, and salts with sulfuric or hydrochloric acids could not be isolated.

The course of the reaction was found to be influenced markedly by the nature of the substituent in the aromatic nucleus. The nitriles giving rise to 1,3,5-triazines (Table I) are benzonitrile, benzonitriles substituted with electron attracting groups or heterocyclic nitriles of similar electronic character. Two nitriles carrying electron releasing substituents were examined and one, *p*-toluonitrile, gave *p*-toluimidoguanidine (V), while the other, 3,4-methylenedioxybenzonitrile, failed to react.

The results mentioned above are perhaps best explained by the scheme



Electron releasing substituents in R would tend to hinder reactions 1, 2 and 3: in the case of *p*-toluonitrile reaction 1 is permitted while 2 and 3 are inhibited leading to III. The methylenedioxy group, however, appears to prevent even reaction 1. Electron attractive groups in R aid reactions 1, 2 and 3, reactions 1 and 3 by an increase in the electrophilic nature of the nitrile carbon while reaction 2 is aided by an increase in the ease of ionization of III to IIIa. The postulated reversibility of reaction 1 is indicated by the observation that if *p*-toluimidoguanidine (V) (III, R = *p*-tolyl) is treated with a nitrile possessing a strong electron attractive group, the triazine isolated does not contain the *p*-tolyl radical, both aromatic groups arising from the second nitrile. Thus, 3-cyanopyridine and V gave 2-amino-4,6-di-(3′-pyridyl)-1,3,5-triazine while *p*-chlorobenzonitrile and V gave the di-*p*-chlorophenyltriazine.

When the nitrile is substituted in the *ortho* position the reaction may follow a different course, presumably because of steric factors. When 4-cyanoquinoline reacted with guanidine in alcohol the product was 4′-quinolylguanamine (2,4-diamino-6-(4′-quinolyl)-1,3,5-triazine) (X, R = 4-quinolyl) as shown by its alternative preparation from 4-quinolylguanidine at 200–230°, a well-known guanamine synthesis.[9,10,11] Presumably the formation of X in alcoholic solution proceeds by the addition of guanidine to IIIa to give IX and ammonia (reaction 5) followed by cyclization of IX to X with elimination of ammonia (reaction 6). The N,N′-diguanylamidine (IX) was suggested by Weith[12] as the intermediate in the formation of guanamines from guanidine salts of organic acids,[9] and from acylguanidines.[10,11]

The question as to whether reaction 3 or 5 will be favored is doubtless determined by a combination of the steric and electronic factors. Several nitriles, for example α-naphthonitrile or 2-methoxy-6-nitrobenzonitrile, both of which are heavily substituted in the *ortho* position, do not have a sufficiently strong electron attractive nucleus and fail to react.

Experimental

Condensation of *p*-Toluonitrile with Guanidine.—To a solution of guanidine (prepared from 19.1 g. of the hydrochloride (0.2 mole) and 4.6 g. of sodium (0.2 mole) in 100 cc. of ethanol) was added 23.4 g. of *p*-toluonitrile and the solution was refluxed for five hours.

(a) Isolation of *p*-Toluoguanidine Hydrochloride.—The clear alcoholic solution was evaporated to half volume and 225 ml. of ether was added. The ether solution was extracted with 100 ml. of 2 *N* hydrochloric acid. On standing the acid solution deposited 3.0 g. of fine needles, which melted with foaming at 287–289°. The needles were quite soluble in water and alcohol and gave a pink precipitate in the biuret reaction.

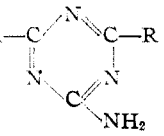
Anal. Calcd. for $C_9H_{11}ON_3 \cdot HCl$: C, 50.6; H, 5.6; N, 19.7; Cl, 16.6. Found: C, 50.3; H, 5.4; N, 19.6; Cl, 16.3.

(b) Isolation of *p*-Toluimidoguanidine Dihydrochloride.—An alcoholic solution of toluimidoguanidine, prepared as above using only 0.1 mole of guanidine, was treated with an excess of alcoholic hydrogen chloride solution and the toluimidoguanidine dihydrochloride was precipitated by ether. After recrystallization from alcohol–ether mixture it melted at 210–212°; yield 6 g., 25%.

(9) Nencki, *Ber.*, **7**, 775 (1874).
(10) Haaf, *J. prakt. Chem.*, [2] **43**, 75 (1890).
(11) Simons and Weaver, U. S. Patent 2,408,694 (1946).
(12) Weith, *Ber.*, **9**, 454 (1876).

TABLE I

2-AMINO-4,6-DIARYL-1,3,5-TRIAZINES



Nitrile	Triazine R—	M. p., °C.	Cryst. form and solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Benzonitrile	C_6H_5	168–170	Colorless needles EtOH	$C_{15}H_{12}N_4$	72.6	72.6	4.8	4.8	22.6	22.8
p-Chlorobenzonitrile	*p*-ClC_6H_4-	254	Colorless silky needles EtOH	$C_{15}H_{10}N_4Cl_2$	56.9	57.1	3.2	3.1	17.7	18.0
p-Nitrobenzonitrile	*p*-$NO_2C_6H_4$-	>320	Insol. light brown powder	$C_{16}H_{10}N_6O_4$	53.2	52.9	3.0	2.6	24.9	25.4
3-Cyanopyridine	3′-C_5N_5N	320–323	Colorless prisms EtOH	$C_{13}H_{10}N_6$	62.4	62.1	4.0	4.0	33.6	33.1
	Hydrochloride of above	322–323	Colorless needles concd., HCl	$C_{13}H_{10}N_6 \cdot 3HCl$	43.4	43.0	3.6	3.3	..	..
2-Methyl-4-amino-5-cyanopyrimidine	2′-Methyl-4′-amino-pyrimidyl-5′-	>300	Colorless prisms EtOH	$C_{13}H_{14}N_{10}$	50.3	49.8	4.5	4.3	45.2	45.6
	Hydrochloride of above	>350	Pale yellow prisms concd. HCl	$C_{13}H_{14}N_{10} \cdot 5HCl$	31.8	32.1	4.1	4.3	28.5	29.0

Anal. Calcd. for $C_9H_{14}N_4 \cdot 2HCl$: C, 43.4; H, 5.6; N, 22.5. Found: C, 43.0; H, 5.8; N, 22.0.

The acetate was prepared and purified in similar manner. The first crop of crystals from alcohol–ether consisted of guanidine acetate, m. p. 223–225° (Found: N, 35.0; Calcd. N, 35.2). Successive crops melted at 134–140° and on recrystallization four times from ethanol–ether were obtained as shiny plates, m. p. 164–165° (4.0 g.), 18%.

Anal. Calcd. for $C_{11}H_{16}O_2N_4$: C, 56.0; H, 6.8; N, 23.8. Found: C, 55.7; H, 7.0; N, 24.2.

Hydrolysis of *p*-Toluimidoguanidine.—One hundred milligrams of the above dihydrochloride was dissolved in 2 ml. of water. The solid dissolved readily in the cold. On standing for two hours the solution deposited fine needles (in all 75 mg.). The melting point (287–288° with foaming) was undepressed on admixture with an authentic sample of *p*-toluguanidine (see below). After removal of the crystals, the presence of ammonia in the solution was demonstrated. The acetate was hydrolyzed in a like manner using dilute hydrochloric acid in place of water.

***p*-Toluoguanidine.**—A solution of 8.2 g. of ethyl *p*-toluate and 8.8 g. of guanidine in 100 ml. of ethanol was allowed to stand at room temperature. After three days the ethanol was evaporated on the steam-bath and the resulting *Brei* pressed dry on an unglazed tile. After washing with a little ether, it was recrystallized from ethanol–ether (1:1). It formed colorless needles, m. p. 224–225 (dec.).

Anal. Calcd. for $C_9H_{11}ON_3$: N, 23.7. Found: N, 23.4.

The compound was converted to its hydrochloride by solution in warm 3 *N* hydrochloric acid. On cooling, colorless needles separated, m. p. 287–289° (dec.). The hydrochloride was shown to be identical with the previously described hydrolysis products.

2-Amino-4,6-diaryl-1,3,5-triazines. General Method.—The triazines are listed in Table I. The preparation of 2-amino-4,6-di-(3′-pyridyl)-1,3,5-triazine is given as an example. A solution of 20.8 g. (0.2 mole) of 3-cyanopyridine and guanidine (from 19.1 g. (0.2 mole) of the hydrochloride) was refluxed for sixteen hours; crystals began to separate soon after the heating was commenced. After cooling and filtration the precipitate (15.0 g.) was recrystallized from a large volume of boiling alcohol, m. p. 320–323°.

Conversion to the Hydrochloride.—Four grams of the triazine was dissolved in 30 ml. of concentrated aqueous hydrochloric acid with gentle warming. On cooling the hydrochloride (4.1 g.) crystallized as white needles which were very soluble in water, m. p. 322–323°.

Dimethiodide of 2-Amino-4,6-di-(3′-pyridyl)-1,3,5-triazine.—Four grams of the base was refluxed with 10 g. of methyl iodide in 100 ml. of acetone for five hours. The yellow solid which formed was filtered off and extracted with cold 90% ethanol. The methiodide was precipitated from the extract with ether–acetone (7:3). It was a canary yellow powder which was not molten below 300°.

Anal. Calcd. for $C_{15}H_{16}N_6I_2$: C, 33.9; H, 3.0. Found: C, 34.4; H, 2.9.

Reaction of *p*-Toluimidoguanidine with *p*-Chlorobenzonitrile.—Four grams of *p*-toluimidoguanidine dihydrochloride was dissolved in 25 ml. of ethanol and a solution of sodium ethoxide (from 0.4 g. sodium) in 20 ml. of alcohol was added. The precipitated sodium chloride was removed and 1.8 g. of *p*-chlorobenzonitrile was added. The mixture was heated under reflux on the steam-bath for sixteen hours. On cooling, clusters of colorless needles separated which, after recrystallization from ethanol, melted at 252–254°, undepressed on admixture with 2-amino-4,6-di-*p*-chlorophenyl-1,3,5-triazine, m. p. 254°. Repetition of the above experiment using 3-cyanopyridine in place of *p*-chlorobenzonitrile gave 2-amino-4,6-di-(3′-pyridyl)-1,3,5-triazine, m. p. 320° (dec.).

Condensation of 4-Cyanoquinoline with Guanidine.—The two compounds were refluxed together as previously described for the preparation of 2-amino-4,6-di-(3′-pyridyl)-1,3,5-triazine. After four hours the crystalline precipitate was filtered off and washed with boiling ethanol; it melted at 315–320° (unsharp).

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.6; H, 4.2. Found: C, 60.9; H, 4.1.

The compound was converted to its hydrochloride by solution in concentrated hydrochloric acid, the hydrochloride separated as rosettes of small needles, m. p. 320° (dec.). The ultraviolet absorption spectrum at *p*H 1.0 was characterized by two bands; an intense band at 237 mμ ($E^{1\%}_{1cm.}$ = 1,650) similar to that of melamine and other aminotriazines, and a secondary band at 320 mμ ($E^{1\%}_{1cm.}$ = 380).

Anal. Calcd. for $C_{12}H_{10}N_6 \cdot 3HCl$; C, 41.6; H, 3.7. Found: C, 41.9; H, 3.7.

4-Quinoloylguanidine.—Ten grams (0.05 mole) of ethyl quinoline-4-carboxylate was added to a solution of guanidine (0.05 mole) in 30 ml. of ethanol. The solution was allowed to stand for about sixteen hours, during which time crystals were deposited slowly. The crystalline material, after filtration, weighed 8.2 g. On heating in a capillary tube it softened at 230° with darkening and melted at 267–274°. The melting point varies with the rate of heating.

Anal. Calcd. for $C_{11}H_{10}ON_4$: C, 61.6; H, 4.7. Found: C, 61.7; H, 4.8.

4'-Quinolylguanamine (2,4-Diamino-6-(4'-quinolyl)-1,3,5-triazine).—One gram of the above compound was heated in a test-tube in a metal-bath. Ammonia began to be evolved at about 200° and the solid turned a pinkish color. The temperature was kept at 200–230° until no more ammonia was evolved. The residue was then washed with hot alcohol and dissolved in 5 ml. of concentrated hydrochloric acid. After addition of charcoal and filtration the solution was made alkaline with sodium hydroxide when the guanamine (0.1 g.) separated as a slightly pinkish crystalline powder, m. p. 318–322° (dec.). It was shown to be identical with the condensation product of 4-cyanoquinoline and guanidine by melting point and ultraviolet absorption spectrum measurements.

The authors' thanks are due to S. Blackman and N. Martinez, Jr., for the microanalyses reported here.

Summary

Aromatic nitriles appear to react with guanidine to form acylimidoguanidines as primary products, but this reaction fails when the aromatic nucleus is substituted with certain electron donating groups. The acylimidoguanidines may react further, depending on electronic and steric factors, giving 2-amino-4,6-diaryl-1,3,5-triazines as the usual product, but in one instance an arylguanamine was isolated.

TUCKAHOE 7, N. Y. RECEIVED APRIL 3, 1950

[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

The Chemistry of 2,2-Diphenyl-4-pentenoic and 2,2-Diphenyl-4-methyl-4-pentenoic Acids[1]

BY PAUL N. CRAIG AND IVAN H. WITT[2]

Because of the recent availability of 2,2-diphenyl-4-pentenoic (I) and 2,2-diphenyl-4-methyl-4-pentenoic (II) acids[3,4] these compounds were examined as starting materials for the synthesis of compounds which might show pharmacological activity. These acids are of particular interest because their bifunctional nature allows the possibility of effecting transformations through a single function or by reactions involving both functions simultaneously. The present paper deals with the basic chemistry of these two γ,δ-unsaturated acids.

1. Reduction.—Reduction with either platinum or palladium catalysts gave excellent yields of 2,2-diphenylpentanoic (III)[5] and 2,2-diphenyl-4-methylpentanoic (IV) acids. This was the sole reaction thus far observed which affected only the double bond in I and II.

2. Ester Formation.—The methyl ester (VI) was prepared from the acid (I) by the action of dimethyl sulfate on the potassium salt (V). The methyl ester (XIII) was prepared from the acid (II) by diazomethane. Either method of esterification may be used for these acids.

3. Acid Chloride Formation.—The acid chloride (VII) was prepared from I by both thionyl chloride and phosphorus pentachloride; VII was characterized by preparation of the amide (VIII). When the 4-methylpentenoic acid (II) was treated with thionyl chloride, an anomalous reaction occurred (discussed in Section 4) unless pyridine was also employed as a reagent, in which case the corresponding acid chloride (XVIII) was readily prepared. The acid chloride (XVIII) was characterized by preparation of the diethylamide (XIX). The reaction of the 4-methylpentenoic acid (II) with phosphorus pentachloride did not yield the acid chloride, but led to the formation of a cyclopentenone (discussed below).

4. Lactone Formation.—When the unsaturated acids (I and II) were dissolved in sulfuric acid and then diluted with ice-water, lactonization occurred to give the valerolactones, IX and XIV, respectively. Lactonization occurred most readily with II, but excellent yields of both lactones were obtained. When the temperature exceeded 50° during the lactonization of the acid (I) with sulfuric acid, large amounts of water-soluble products were obtained.[6] The best method for the lactonization of I utilized hot sirupy phosphoric acid.

Interaction of the 4-methylpentenoic acid (II) with thionyl chloride gave a mixture from which only the lactone (XIV) was isolated. Apparently the hydrogen chloride initially formed acted to lactonize the acid (II) in preference to the formation of the acid chloride (XVIII).

5. Bromolactone Formation.—Both of the pentenoic acids (I and II) reacted with bromine in the cold with evolution of hydrogen bromide

(1) Allyldiphenylacetic and β-methallyldiphenylacetic acids, respectively.

(2) Deceased.

(3) Arnold and Searles, THIS JOURNAL, **71**, 1150 (1949).

(4) Obtained from Research Dept., General Mills, Inc., Minneapolis, Minn.

(5) May and Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(6) Presumably this was due to the addition of sulfuric acid to the double bond, but this reaction was not further examined.