tained was 0.9 g. of recovered *o*-benzoylbenzoic acid (45% of the starting amount).

Oxidation of Dimeric Styrene.—Three grams of dimeric styrene, $n^{20}D$ 1.5900 was oxidized, and the oxidation products isolated, in accordance with the usual procedure. The products obtained were: benzoic acid, 1.8 g. (51%), *o*-benzoylbenzoic acid, 0.2 g. (7%), and anthraquinone, 70 mg. (2.3%).

Oxidation of 1,3-Diphenylbutene-1.—Three grams of 1,3-diphenylbutene-1 was oxidized and the products isolated by the usual procedure.

The only oxidation product obtained was benzoic acid, 1.8 g. (51%).

Oxidation of 1-Methyl-3-phenylindane, Prepared from 1,3-Diphenylbutene-1.—Three grams of 1-methyl-3-phenylindane, $n^{20}D$ 1.5805, was oxidized and the products isolated by the usual procedure. The oxidation products obtained were: *o*-benzoylbenzoic acid, 1.3 g. (40%) and anthraquinone, 102 mg. (3.4%).

Oxidation of 1-Methyl-3-phenylindane, Prepared from Dimeric Styrene, in Anhydrous Medium.—The oxidation procedure and product separation scheme was the same as usual, but the chromic acid used was dissolved, without the use of water, in fifteen times its weight of glacial acetic acid, and the reaction mixture was protected from moisture by means of a calcium chloride drying tube placed on top of the reflux condenser. Under these conditions, the products obtained were: *o*-benzoylbenzoic acid (34%), anthraquinone (3.4%), and benzoic acid, 6 mg. (0.18%).

Ultraviolet Absorption of 1-Methyl-3-phenylindane.—A solution of 1-methyl-3-phenylindane, $n^{20}D$ 1.5805, in isopropyl alcohol, containing 0.1375 g. of 1-methyl-3-phenylindane per 100 ml. of solution, was diluted 1:9 with isopropyl alcohol and the ultraviolet absorption of the resulting solution measured with a Beckman quartz spectrophotometer.

Summary

Evidence has been obtained from a study of oxidation products and ultraviolet absorption which confirms the 1-methyl-3-phenylindane structure postulated for one of the dimers of styrene.

The presence of anthraquinone among the oxidation products of this hydrocarbon is not due to cyclodehydration of the *o*-benzoylbenzoic acid formed or to an impurity present, but is formed during the oxidation of the hydrocarbon itself.

BROOKLYN 10, N. Y. RECEIVED MARCH 20, 1950

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Migrations of Acyl Groups in Aminoethanols. II.[1] Analogy with Mixed Diacyl *o*-Aminophenols

BY ARTHUR P. PHILLIPS AND ALLISON MAGGIOLO

Numerous examples of acyl migrations between oxygen and nitrogen have been reported for derivatives of *o*-aminophenols.[2,3,4,5]

Very recently careful work by LeRosen and Smith[6] has demonstrated that, in contrast with some of the earlier findings, in the introduction of a second, different acyl group into an *o*-acylaminophenol a mixture, in varying proportions, of the two isomers results regardless of the order of introducing the groups. They also showed that half hydrolysis of *either* of the purified isomeric diacyl *o*-aminophenols gave not a single product but a mixture of the two possible N-acylaminophenols in nearly constant proportions, independent of which isomer was hydrolyzed.

This earlier work showed that acyl migrations in *o*-aminophenols occur very frequently both during the formation as well as during the half hydrolyses of mixed diacyl compounds. These facts as well as the facile rearrangements known to occur with monoacylethanolamines[1] warranted the anticipation of similar acyl shifts during the preparation and hydrolysis of the mixed diacyl ethanolamines described below.

The two isomers, 2-acetamidoethyl *p*-nitrobenzoate (I) and 2-(*p*-nitrobenzamido)-ethyl acetate (II) were obtained by appropriate acylation of the ethanolamides.

Compounds I and II had different melting points and mixtures of the two showed marked depressions of the melting temperature. Hydrolysis of I with dilute aqueous alkali gave a quantitative amount of *p*-nitrobenzoic acid while II gave the calculated quantity of *p*-nitrobenzoic acid ethanolamide as the readily isolable hydrolysis product.

Compound I was treated under a variety of conditions thought likely to favor acyl wandering: (1) refluxing several hours with sodium in xylene; (2) heating two hours at 70° in pyridine solution; (3) heating two hours at 70° in pyridine solution containing one mole of hydrogen chloride; (4) heating for two hours at 70° in alcoholic hydrogen chloride. In every case a nearly theoretical recovery of unchanged I was obtained. Samples of I and II refluxed separately for five hours in triethylamine gave back all of the unchanged starting compound.

Surprisingly, these seem to represent examples in which no acyl migrations occurred either in the formation or hydrolysis of I and II, nor could I or II be induced to rearrange under various "forced conditions."

This difference in migration aptitude may be attributable to a less favorable steric configuration in the open chain ethanolamine derivatives.

(1) Paper I of this series, Phillips and Baltzly, THIS JOURNAL, **69**, 200 (1947).

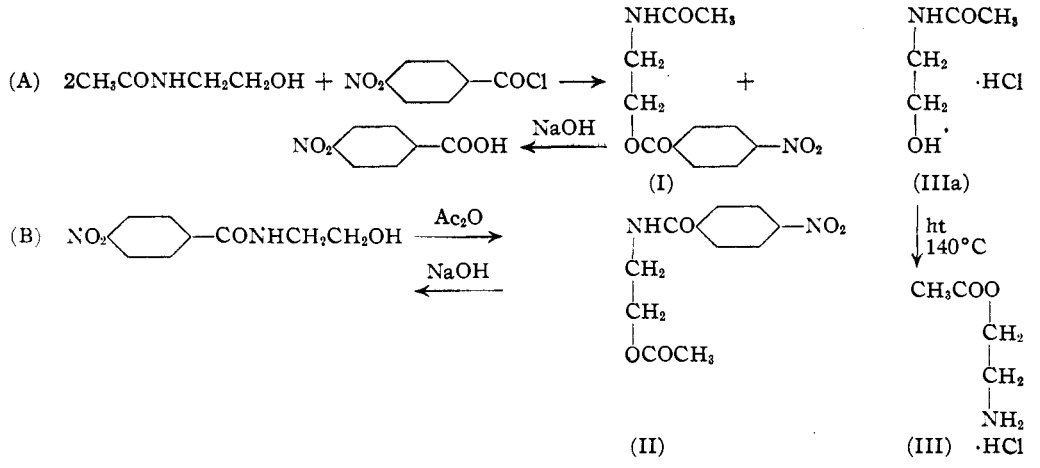
(2) Böttcher, *Ber.*, **16**, 629 (1883).

(3) Raiford, THIS JOURNAL, **41**, 2068 (1919).

(4) Bell, *J. Chem. Soc.*, 2962 (1931).

(5) Raiford and LeRosen, THIS JOURNAL, **67**, 2163 (1945).

(6) LeRosen and Smith, *ibid.*, **71**, 2815 (1949); **70**, 2705 (1948).



In the analogous *o*-aminophenols the amino and hydroxyl are held rigidly in a "*cis*" configuration (as demanded by the valence structure of benzene) this configuration being particularly favorable to participation in the five membered rings believed to mediate these intramolecular rearrangements.[1,6] Because of the possibility of free rotation about the central C—C bond the O and N of the ethanolamine compounds might be expected to be more stable in a "*trans*" configuration by virtue of electrostatic repulsions between these similar groups. While with a single acyl group present rearrangements occur readily, under the burden of another acyl, migrations appear to be excluded. Other factors significant in producing these differences may be: (1) the greatly different acidities and basicities of O and N when attached to resonating benzenoid systems as compared with attachment to saturated aliphatic carbons; (2) possible greater resonance stabilization in the cyclic intermediates derived from the benzenoid than from the open chain aliphatic compounds.

Further studies concerned with O⟷N rearrangements are in progress.

Experimental

2-Acetamidoethyl *p*-Nitrobenzoate (I).—A mixture of 9 g. (0.05 mole) of *p*-nitrobenzoyl chloride and 12 g. (0.12 mole) of 2-acetamidoethanol was heated for four hours on a steam-bath. The originally fluid mixture gradually precipitated a solid until finally the entire mass comprised a cake of white crystals. The crystals were triturated with hexane after which 21 g. of white solid was collected by filtration. This was expected to be a mixture of the desired substance (I) and the hydrochloride adduct (IIIa) of the 2-acetamidoethanol, analogous to the hydrochloride adducts of N-acetylephedrine and N-acetyl-ψ-ephedrine reported by Welsh[7] which on heating at 110° were shown to rearrange to the hydrochlorides of the isomeric O-acetylephedrines. More than two molecular proportions of 2-acetamidoethanol were used with the object of obtaining this second product IIIa by reaction with the hydrogen chloride liberated in the principal reaction of ester formation.

To separate I from IIIa the mixture was digested with hot ethyl acetate in which I, but not IIIa, was soluble. After filtration I was precipitated with hexane. The white crystals of I obtained were treated with a saturated aqueous sodium bicarbonate solution to remove any acidic impurities. The insoluble matter was further purified by crystallization from ethyl acetate–hexane mixtures. The yield of I purified in this way was about 65% calculated on the *p*-nitrobenzoyl chloride used; m. p. 114–115°. *Anal.* Calcd. for $C_{11}H_{12}O_5N_2$: C, 52.3; H, 4.8. Found: C, 52.0; H, 4.9.

The ethyl acetate insoluble IIIa, 6 g. (85%), was heated two hours at 140°, after which crystallization from methanol–ethyl acetate–ether mixtures gave 4.5 g. of the rearranged product III, the hydrochloride of the aminoethyl ester of acetic acid, m. p. 125–126°. *Anal.* Calcd. for $C_4H_{10}O_2NCl$: C, 34.4; H, 7.2. Found: C, 35.1; H, 7.2.

Compound III was readily soluble in water and after treatment with alkali, back titration with hydrochloric acid showed it had lost its acid binding properties similarly to the earlier described[1] aminoesters.

2-(*p*-Nitrobenzamido)-ethyl Acetate (II).—The ethanolamide of *p*-nitrobenzoic acid, 10.5 g. (0.05 mole), was heated one hour at 100° with 20 cc. of acetic anhydride containing 5 drops of concentrated sulfuric acid. The reaction mixture was poured into 150 cc. of cold water and 10 g. of sodium acetate was added. The white crystalline product which resulted was collected and weighed 11 g. (90%). After several recrystallizations from ethyl acetate–hexane mixtures it melted at 108–109°. *Anal.* Calcd. for $C_{11}H_{12}O_5N_2$: C, 52.3; H, 4.8. Found: C, 52.1; H, 4.5. A mixture of I and II melted at 95–103°.

Hydrolysis of I and II: I.—A sample of 1.2 g. of I was heated for five minutes on a steam-bath with 30 cc. of 1 *N* potassium hydroxide. The originally insoluble compound dissolved rapidly to a clear solution. Cooling and acidification with hydrochloric acid to pH_2 gave 0.83 g. (100%) of white crystals, m. p. 233–235° (for *p*-nitrobenzoic acid lit. gives m. p. 241°).

II.—A 1.2-g. sample of II treated similarly gave after acidification 1 g. (95%) of white crystals of m. p. 131–132° (for *p*-nitrobenzoic acid ethanolamide lit. gives m. p. 132–133°).

Attempted Rearrangement of I.—A. To 0.005 mole of sodium in 20 cc. of xylene was added 0.005 mole of I. The mixture was refluxed for two hours during which the sodium remained unchanged. After cooling the sodium was removed mechanically and the organic material was precipitated by the addition of petroleum ether. A quantitative recovery of unchanged I was obtained; m. p. 113–114°.

B. A solution of 0.005 mole of I in 5 cc. of pyridine was heated two hours at 70°. Removal of solvent *in vacuo* followed by dilution with water gave back all the unchanged I; m. p. 113–115°.

C. Conditions of B plus 1 cc. of 34% alcoholic hydrogen chloride. Recovered unchanged I; m. p. 113–114°.

D. To 0.005 mole of I in 5 cc. of ethanol was added 1 cc. of 34% alcoholic hydrogen chloride. After heating two hours at 70° the solution was neutralized, solvent was

(7) Welsh, THIS JOURNAL, **69**, 128 (1947).

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.

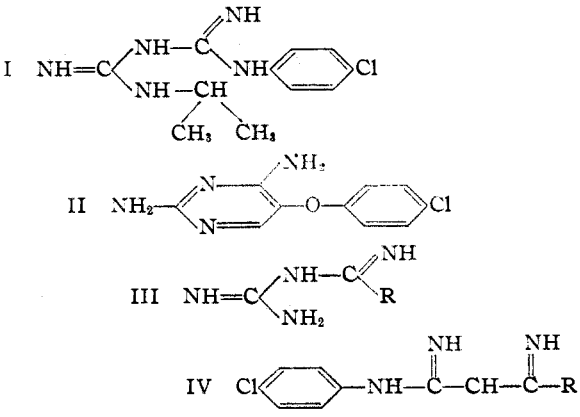
TUCKAHOE 7, N. Y. RECEIVED APRIL 14, 1950

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

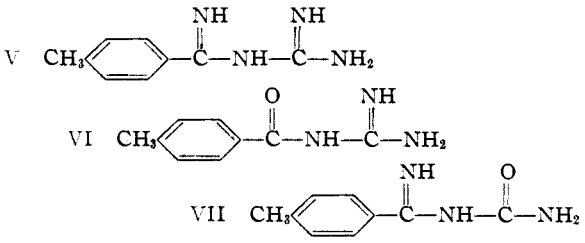
The Reaction of Aromatic Nitriles with Guanidine[1]

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).