[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

NITRO AND AMINO TRIPHENYLGUANIDINES[1]

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The present investigation was undertaken in order to prepare a series of amino derivatives of triphenylguanidine for pharmacological use in a coöperative study of the chemotherapy of tuberculosis. Hesse has shown[2] that the only organic compounds, so far examined, which inhibit the growth of tubercle bacilli are basic in character. Inasmuch as the aminotriphenylguanidines should possess high basicity, it was suggested by Professor Hesse that the study of the bactericidal power of this type of compound be incorporated in our systematic study of tuberculosis chemotherapy.

The preparation of some aminotriphenylguanidines, as well as the pharmacological results obtained in Professor Hesse's experiments, are described in Section D. Inasmuch as the amino compounds were prepared from the corresponding nitro derivatives, it was necessary to develop adequate methods of synthesizing the latter, which are discussed in Sections B and C.

The preparation of the nitrotriphenylguanidines involved, first, the synthesis of a series of thioureas.

A. Preparation of Thioureas.—The nitroarylthioureas were prepared by the addition of an aniline derivative to an isothiocyanate. A study of this reaction has revealed the inactivity of *p*-nitraniline, in many cases, toward isothiocyanates with which aniline combines at once. For example, *p*-nitraniline could not be made to combine with phenyl isothiocyanate. This result confirms a similar observation by Losanitsch.[3] Moreover, *p*-nitraniline reacted with *p*-nitrophenyl isothiocyanate only in the presence of pyridine as a catalyst, whereas aniline combined quickly and quantitatively with the same isothiocyanate in the absence of catalysts. On the other hand, the reaction between *p*-nitraniline and benzoyl isothiocyanate took place with ease, giving the desired thiourea derivative.

The three *p*-nitrophenylarylthioureas prepared in the above ways have not been previously described. There is in the literature, however, a confusion of the known di-*m*-nitrophenylthiourea with the previously unknown di-*p*-nitrophenylthiourea. Brückner,[4] in 1873, reported the preparation of di-*p*-nitrophenylthiourea, melting at 161°. Later work by

[1] Constructed from a dissertation presented by Elizabeth Dyer to the Faculty of the Graduate School of Yale University in June, 1931, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Meissner and Hesse, *Arch. Exp. Path. Pharm.*, **147**, 339 (1930); Hesse and Meissner, *ibid.*, **159**, 679 (1931).

[3] Losanitsch, *Ber.*, **14**, 2365 (1881).

[4] Brückner, *ibid.*, **6**, 1103 (1873).

three independent investigators[5] showed that di-*m*-nitrophenylthiourea melted at 161°, and indicated that the corresponding para derivative had never been prepared. Loh and Dehn,[6] in 1926, referring to the early article by Brückner, assumed that a di-nitrophenylthiourea obtained by them, and which melted at 161°, was the para derivative. The above evidence indicates that their compound was probably di-*m*-nitrophenylthiourea.

B. Preparation of Nitrotriphenylguanidines.—Two nitro derivatives of triphenylguanidine are described in the literature, namely, *m*-nitrophenyldiphenylguanidine[7,8] and tri-*m*-nitrophenylguanidine.[8] Both substances were prepared by methods involving desulfurization of thioureas. The procedures used, however, resulted in low yields of the guanidines due to the formation of several by-products.

In the present investigation more successful methods of preparing nitrotriphenylguanidines have been developed. The most satisfactory of these consists in the use of a mixture of iodine and pyridine to destroy hydrogen sulfide during interaction of thiourea and amine

$$RNHCSNHR' + R''NH_2 + I_2 + 2C_5H_5N \longrightarrow R''N{=}C(NHR)NHR' + 2C_5H_5N{\cdot}HI + S$$

Former investigators have described the use of either iodine[8,9] or pyridine[10] alone as desulfurizing agents in the preparation of guanidines, but the combination of these two reagents has previously been applied only to the synthesis of thioureas.[11] A summary of the results obtained by the application of this procedure to the preparation of *p*-nitrotriphenylguanidines is given in Table I.

TABLE I

PREPARATION OF *p*-NITROTRIPHENYLGUANIDINES

	Thioureas used	Amines used	Guanidines formed	Yield, %
1	$C_6H_5NHCSNHC_6H_4NO_2$[a]	$NH_2C_6H_5$	$C_6H_5N{=}C(NHC_6H_5)NHC_6H_4NO_2$	80
2	$CS(NHC_6H_4NO_2)_2$	$NH_2C_6H_5$	$C_6H_5N{=}C(NHC_6H_4NO_2)_2$	85
3	$CS(NHC_6H_4NO_2)_2$	$NH_2C_6H_4NO_2$	$NO_2C_6H_4N{=}C(NHC_6H_4NO_2)_2$	73
4	$C_6H_5NHCSNHC_6H_4NO_2$	$NH_2C_6H_4NO_2$	(a) $NO_2C_6H_4N{=}C(NHC_6H_5)NHC_6H_4NO_2$	34
			(b) $NO_2C_6H_4N{=}C(NHC_6H_4NO_2)_2$	30
5	$CS(NHC_6H_5)_2$	$NH_2C_6H_4NO_2$	(a) $NO_2C_6H_4N{=}C(NHC_6H_5)NHC_6H_4NO_2$	4
			(b) $NO_2C_6H_4N{=}C(NHC_6H_4NO_2)_2$	3

[a] Nitro group in *p*-position.

A consideration of the table shows that reactions 1, 2 and 3 were satisfactory for the preparation of *p*-mononitro-, *p*-dinitro- and *p*-trinitro derivatives of triphenylguanidine, respectively. In the first two cases the reaction was practically instantaneous when a hot pyridine solution of

[5] Losanitsch, *Ber.*, **15**, 470 (1882); Steudemann, *ibid.*, **16**, 550 (1883); Fry, THIS JOURNAL, **35**, 1541 (1913).

[6] Loh and Dehn, *ibid.*, **48**, 2958 (1926).

[7] Brückner, *Ber.*, **7**, 1236 (1874).

[8] Losanitsch, *ibid.*, **16**, 49 (1883).

[9] Hofmann, *ibid.*, **2**, 456 (1869).

[10] Raffo, *et al.*, *Chemical Abstracts*, **8**, 2683 (1914); **12**, 1170 (1918).

[11] Fry, THIS JOURNAL, **35**, 1543 (1913).

the thiourea and amine was treated with an equivalent of iodine. In the third case the reaction was complete after the mixture had been boiled for four hours.

Reactions 4 and 5 did not proceed in a single direction. In the case of reaction 4, nearly half of the product consisted of the trinitrotriphenylguanidine (b) in addition to the expected dinitrotriphenylguanidine (a). Evidence as to the mechanism of the formation of the trinitrotriphenylguanidine was furnished by one experiment in which di-*p*-nitrophenylthiourea was isolated from the reaction mixture. If this substance is assumed to be the precursor of the trinitrotriphenylguanidine, the formation of the latter may be represented as:

$$C_6H_5NHCSNHC_6H_4NO_2 \longrightarrow [NO_2C_6H_4NCS] \xrightarrow[NO_2C_6H_4NH_2]{}$$

$$CS(NHC_6H_4NO_2)_2 \xrightarrow[NO_2C_6H_4NH_2]{} NO_2C_6H_4N{=}C(NHC_6H_4NO_2)_2$$

Reaction 5 resulted in the formation of dinitro- and trinitrotriphenylguanidines in small yields instead of the mononitrotriphenylguanidine expected. It may be assumed that the mechanism of this reaction is analogous to that of reaction 4.

A second method of preparing nitrotriphenylguanidines consisted in the condensation of phenylisocyandichloride with nitranilines. This method, originally used by Sell and Zierold, and developed by Nef, Hantzsch and Johnson,[12] was successfully applied in the present investigation to the preparation of di-*p*-nitrophenylphenylguanidine and di-*m*-nitrophenylphenylguanidine.

A third means of obtaining nitrotriphenylguanidines was the condensation of alkyl pseudothioureas with the necessary aniline derivatives.[13] Although this reaction was investigated in the preparation of various nitrotriphenylguanidines, a good yield (70% of calcd.) was obtained in one case only, namely, by the action of aniline on S-methyl-*p*-nitrophenylphenylpseudothiourea.

C. The Isomerism of the Di-*p*-nitrophenylphenylguanidines.—Two di-*p*-nitrophenylphenylguanidines have been obtained, which melt at 168–169° and 191–193°, respectively. The methods of preparing these substances and the relationships between them are shown in Table II.

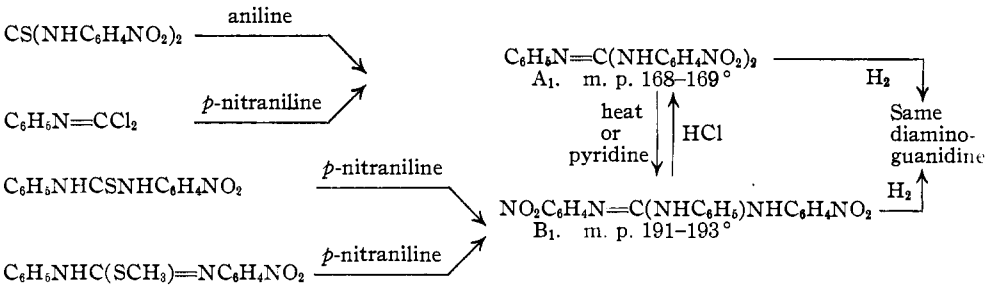
It is to be noted that the chemical differences in the methods of preparation, and the varying behavior of the two substances toward such agents as heat, pyridine or acids, exclude the possibility that the two forms are polymorphic varieties. The type of isomerism exhibited by these substances may be interpreted (1) as desmotropism, in which the compounds

[12] Sell and Zierold, *Ber.*, **7**, 1231 (1874); Nef, *Ann.*, **270**, 283 (1892); Hantzsch and Mai, *Ber.*, **28**, 982 (1895); Johnson and Chernoff, THIS JOURNAL, **34**, 166 (1912).

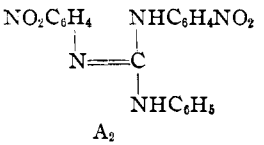
[13] Bernthsen and Friese, *Ber.*, **15**, 567 (1882).

TABLE II

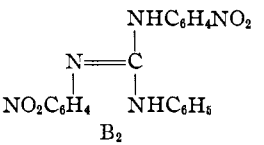
ISOMERIC DI-*p*-NITROPHENYLPHENYLGUANIDINES



are represented by formulas A_1 and B_1, or (2) as geometrical isomerism, in which the configurations may be represented by formulas A_2 and B_2



A_2



B_2

The reactions by which the substances were prepared furnish evidence in support of formulas A_1 and B_1, as shown in Table II. The assignment of formulas A_2 and B_2 to the compounds would necessitate the assumption of a shift in the position of the double bond in both reactions, resulting in the formation of the substance melting at 168–169°. On the other hand, the ease of interconversion of the two guanidines is comparable to that of geometrical isomers.

Both isomers, when reduced catalytically, yielded the same amino compound. The possibility that the double bond in the guanidine nucleus may have been reduced as well as the nitro group seems very unlikely, since this linkage is ordinarily resistant to reduction.[14] Since the reduction was a vigorous exothermic reaction, it might be assumed that isomerization of one form to the other was brought about by the action of heat.

The formation of these two structural isomers of di-*p*-nitrophenylphenylguanidine is of interest in view of numerous previous attempts to demonstrate the existence of isomerism of this type among guanidine derivatives. Huhn's results,[15] which reported the isolation of two pairs of desmotropic varieties of triarylguanidines, were later discredited by Marckwald.[16] Likewise, Forster[17] and Schenck[18] obtained only *one* form of each of the guanidines studied, although two were theoretically possible.

[14] Thiele, *Ann.*, **273**, 133 (1893).
[15] Huhn, *Ber.*, **19**, 2404 (1886).
[16] Marckwald, *Ann.*, **286**, 343 (1895).
[17] Forster, *ibid.*, **175**, 56 (1875).
[18] Schenck, *Z. physiol. Chem.*, **77**, 328 (1912).

D. Aminotriphenylguanidines.—The aminotriphenylguanidines were obtained by catalytic reduction of the corresponding nitro compounds. The results of this research are summarized in Table III.

TABLE III

PREPARATION OF AMINOTRIPHENYLGUANIDINES

	Nitro compound used	Amino compound produced	Yield, %
1	p-$C_6H_5N{=}C(NHC_6H_5)NHC_6H_4NO_2$	p-$C_6H_5N{=}C(NHC_6H_5)NHC_6H_4NH_2$	69
2	p-$C_6H_5N{=}C(NHC_6H_4NO_2)_2$	p-$C_6H_5N{=}C(NHC_6H_4NH_2)_2$ or	61–78
3	p-$NO_2C_6H_4N{=}C(NHC_6H_5)NHC_6H_4NO_2$	p-$NH_2C_6H_4N{=}C(NHC_6H_5)NHC_6H_4NH_2$	
4	m-$C_6H_5N{=}C(NHC_6H_4NO_2)_2$	m-$C_6H_5N{=}C(NHC_6H_4NH_2)_2$	80–90
5	p-$NO_2C_6H_4N{=}C(NHC_6H_4NO_2)_2$	p-$NH_2C_6H_4N{=}C(NHC_6H_4NH_2)_2$	66

The reduction took place most readily in the case of tri-p-nitrophenylguanidine (Expt. 5), least readily in the case of p-nitrophenyldiphenylguanidine (Expt. 1). It should be noted that the two isomeric di-p-nitrophenyl phenylguanidines yielded the same aminoguanidine (Expts. 2 and 3).

Both the nitro and amino derivatives of triphenylguanidine prepared in this investigation were sent for pharmacological study to Professor Erich Hesse, at the Institute for Pharmacology and Experimental Therapy at the University of Breslau. The nitro compounds were found to be entirely inactive toward the tubercle bacilli, a result which is in accord with Hesse's theory of the relation between the basicity of organic compounds and their bactericidal effect.[2] Contrary to expectations, the aminoguanidine derivatives, which we have prepared, likewise have been shown by Hesse[19] to possess no bactericidal activity. Hesse found, after an exhaustive study of many different types of guanidine derivatives, that the only representative of this series which retarded the growth of the tubercle bacillus *in vivo* was a tri-p-ethoxyphenylguanidine of unknown constitution. This was supplied for his researches by the I. G. Farbenindustrie, Hochst in Germany. It will be of especial interest to examine the behavior of several of the possible alkoxy substituted guanidines and also to study the effect of varying the structure of the alkoxy grouping.

Experimental Part

p-Nitrophenyl Isothiocyanate.—The isothiocyanate was prepared in 65–85% yields by treating thiophosgene with p-nitraniline. Coghill and Johnson's method[20] was modified by the use of two additional equivalents of p-nitraniline as hydrogen chloride acceptor. A mixture of 20 g. of thiophosgene with 72 g. of p-nitraniline suspended in 800 cc. of dry benzene was boiled for one hour with frequent shaking. The mixture was then cooled and the precipitate of p-nitraniline hydrochloride filtered. The benzene filtrate, when concentrated under reduced pressure, deposited, first at a volume of 100 cc., 1.0 g. of p-nitraniline, then at a volume of 70 cc., 11 g. of p-nitrophenyl isothiocyanate, m. p. 112–113°. The mother liquor on further evaporation yielded a total of 10.8 g. of the same substance. The last precipitate from the concentrated mother liquor was contaminated with di-p-nitrophenylthiourea, from which the iso-

[19] Private communication from Professor Hesse.

[20] Coghill and Johnson, THIS JOURNAL, **47**, 187 (1925).

thiocyanate could be separated by extraction with cold benzene. Too long heating or local superheating of the reaction mixture increased the quantity of thiourea formed.

Nitroaryl Thioureas.—The thioureas were prepared by the addition of an aniline derivative to an isothiocyanate. The most successful methods of procedure are shown in Table IV and the properties of the thioureas are given in Table V.

TABLE IV

PREPARATION OF NITROARYLTHIOUREAS

	Reactants	Cc. solvent	Time of boiling	Yield of thiourea, %	
1	20 g. p-$NO_2C_6H_4NCS$ 10.5 cc. $C_6H_5NH_2$	90 C_6H_6	3 min.	p-$C_6H_5NHCSNHC_6H_4NO_2$[21]	97
2	5 g. p-$NO_2C_6H_4NCS$ 3.8 g. p-$NO_2C_6H_4NH_2$	100 C_6H_5 2 C_5H_5N as catalyst[22]	1 hr.	p-$CS(NHC_6H_4NO_2)_2$	94
3	10 g. C_6H_5CONCS 8.5 g. p-$NO_2C_6H_4NH_2$	70 C_6H_6	15 min.	p-$C_6H_5CONHCSNHC_6H_4NO_2$	96
4	10 g. C_6H_5CONCS 8.5 g. m-$NO_2C_6H_4NH_2$	125 C_6H_6	Stood in cold 2 hr.	m-$C_6H_5CONHCSNHC_6H_4NO_2$	96

TABLE V

PHYSICAL PROPERTIES OF NITROARYLTHIOUREAS

	Thiourea	M. p., °C.	Crystalline form	Analyses, % Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
1	p-$C_6H_5NHCSNHC_6H_4NO_2$	160	Pale yellow plates from acetone	15.38	15.22	11.71	11.81
2	p-$CS(NHC_6H_4NO_2)_2$	195–196	Orange needles[23] from acetone	17.61	17.50	10.06	10.35
3	p-$C_6H_5CONHCSNHC_6H_4NO_2$[24]	182	Pale yellow needles from acetic acid	14.00	13.93	10.63	10.75
4	m-$C_6H_5CONHCSNHC_6H_4NO_2$[24]	164–165	Pale yellow needles from acetic acid	14.00	13.92	10.63	10.65

S-Methylphenyl-p-nitrophenylpseudothiourea.—Phenyl-p-nitrophenylthiourea was alkylated in 72% yield by treatment with methyl iodide in methanol solution. Ten grams of thiourea was suspended in 40 cc. of absolute methanol, 5.5 g. of methyl iodide was added and the mixture was boiled for half an hour. The resulting clear solution was iced and treated with 3 cc. of pyridine, when, on stirring, 6 g. of a precipitate of the free base, melting at 120–122°, was obtained. From the filtrate, by adding 200 cc. of cold water, 3.5 g. melting at 103–105° was precipitated. This mixture was resolved, by repeated fractional crystallization from absolute methanol, into 1.6 g. of the alkylated pseudothiourea, melting at 118–120°, and 0.3 g. of the original thiourea, melting at 160°. When recrystallized from absolute methanol, the alkylated product separated in the form of long yellow needles, melting at 121–122°.

Anal. Calcd. for $C_{14}H_{13}O_2N_3S$: N, 14.63; S, 11.15. Found: N, 14.62; S, 11.28.

α-p-Nitrophenyl-β,γ-diphenylguanidine.—This guanidine was obtained (a) in 80%

[21] This thiourea could not be prepared by treating phenyl isothiocyanate with p-nitraniline, neither by fusion of the two substances, nor by heating a solution of the two in the presence of hydrochloric acid or pyridine as catalyst.

[22] No reaction took place unless catalyzed by pyridine.

[23] The thiourea separated from solutions in the form of curved yellow needles, which became orange on exposure to the air.

[24] Neither of these products is the same as a nitrophenylbenzoylthiourea prepared by Miquel by direction nitration; *Ann. chim. phys.*, [5] **11**, 322 (1877).

yield by treating *p*-nitrophenylphenylthiourea with aniline in the presence of pyridine and iodine, and (b) in 70% yield by fusing S-methyl-*p*-nitrophenylphenylpseudothiourea with aniline.

(a) Ten grams of *p*-nitrophenylphenylthiourea and 3.5 cc. of aniline were dissolved in 20 cc. of pyridine, a solution of 9.3 g. of iodine in 40 cc. of pyridine was added together with 20 cc. of pyridine for washing, and the mixture was heated to boiling. After one minute of boiling the starch test showed the absence of free iodine. When the reaction mixture was cooled and treated with 300 cc. of cold water, a gummy precipitate was obtained which became crystalline on standing for three hours in an ice-bath. The precipitate was filtered, dried and treated with 125 cc. of cold acetone. The acetone solution, when filtered from the undissolved sulfur and concentrated to a volume of 40 cc., yielded 7.3 g. of the guanidine, melting at 170–171°. By concentrating the filtrate and adding cold alcohol, an additional 2.3 g. of the guanidine was obtained. When purified by recrystallization from acetone, the guanidine separated in the form of yellow leaves, which melted at 172–173°. One gram dissolved in 12 cc. of boiling, and in 20 cc. of cold acetone. The guanidine was extremely resistant to hydrolysis. It was recovered unchanged after heating for several hours in contact with concentrated hydrochloric acid, 70% sulfuric acid, or 40% sodium hydroxide.

Anal. Calcd. for $C_{19}H_{16}O_2N_4$: C, 68.68; H, 4.82; N, 16.87. Found: C, 68.49; H, 4.85; N, 16.74.

It is to be noted that all attempts to prepare a mononitrotriphenylguanidine by treating diphenylthiourea with *p*-nitraniline, a reaction analogous to (a), were unsuccessful. When a pyridine solution containing 5 g. of diphenylthiourea and 3.0 g. of *p*-nitraniline was treated with iodine according to the procedure described above, the only products isolated from the reaction mixture were 0.3 g. of di-*p*-nitrophenylphenylguanidine, melting at 191–193°, and 0.3 g. of tri-*p*-nitrophenylguanidine, melting at 244–245°. The rest of the material was an oil. The use of basic lead carbonate or mercuric chloride as desulfurizing agent was likewise unsuccessful.

(b) Two grams of S-methyl-*p*-nitrophenylphenylpseudothiourea and 0.9 g. of aniline were heated at the fusion temperature for fifteen minutes. The melt was cooled, dissolved in alcohol, and the alcohol solution concentrated to a volume of 30 cc. On cooling, 1.1 g. of the guanidine, melting at 170–171°, was precipitated. The filtrate yielded 0.5 g. of the same product.

β-Phenyl-α,γ-di-*p*-nitrophenylguanidine.—This di-*p*-nitrophenylphenylguanidine was obtained (a) by the reaction between di-*p*-nitrophenylthiourea and aniline in the presence of iodine and pyridine, (b) by the isomerization of the higher-melting di-*p*-nitrophenylphenylguanidine, and (c) by the condensation of phenyl-isocyan-dichloride with *p*-nitraniline.

(a) Five grams of di-*p*-nitrophenylthiourea was suspended in 30 cc. of pyridine, and 1.9 cc. of aniline was added. When a solution of 4.0 g. of iodine in 20 cc. of pyridine was added, together with 15 cc. of pyridine for washing, an immediate exothermic reaction took place. The reaction was complete after boiling for one minute. The product was isolated by a procedure analogous to that described above for the preparation of *p*-nitrophenyldiphenylguanidine. By treatment with ice water, acetone and alcohol, 5 g. of the guanidine was obtained which melted at 166–168°. The alcohol filtrate yielded 0.5 g., melting at 165–192°, which consisted of a mixture of the guanidine melting at 168–169°, and the isomeric form melting at 191–193°.

The guanidine, when recrystallized from alcohol, separated in the form of yellow prismatic needles containing one mole of alcohol of crystallization. One gram dissolved in 48 cc. of hot, and in 400 cc. of cold alcohol. When alcohol-free after heating at 120°, the substance melted at 168–169°.

Anal. Calcd. for $C_{19}H_{15}O_4N_4$: C, 60.43; H, 4.09; N, 18.57. Found: C, 60.77; H, 3.85; N, 18.65.

(b) The guanidine melting at 168–169° was also obtained by the action of hydrogen chloride upon the isomeric guanidine melting at 191–193°. Five-tenths of a gram of the latter was suspended in 100 cc. of concd. hydrochloric acid, and the mixture was heated on the steam-bath for eight hours. The mixture was then neutralized with ammonia, the precipitate taken up in hot alcohol and treated again with ammonia. On cooling the solution, 0.3 g. of the guanidine, melting at 165–167°, was obtained. The filtrate yielded 0.1 g. of the original higher melting form.

(c) Inasmuch as the yield of guanidine from condensation of phenyl-isocyandichloride with *p*-nitraniline was only 40% of the theoretical, the details of this procedure will be omitted.

α,β-Di-*p*-nitrophenyl-γ-phenylguanidine.—The di-*p*-nitrophenylphenylguanidine melting at 191–193° was prepared: (a) by treating *p*-nitrophenylphenylthiourea with *p*-nitraniline in the presence of iodine and pyridine, (b) by isomerization of the di-*p*-nitrophenylphenylguanidine melting at 168–169°, and (c) by fusing S-methyl-*p*-nitrophenylphenylpseudothiourea with *p*-nitraniline.

(a) Ten grams of *p*-nitrophenylphenylthiourea and 5.1 g. of *p*-nitraniline were suspended in 30 cc. of pyridine, a solution of 9.3 g. of iodine in 35 cc. of pyridine was added, and the mixture was boiled for five minutes. On cooling the resulting solution and adding 400 cc. of water, a gum was obtained. When the aqueous pyridine solution was decanted and the gum stirred with 50 cc. of alcohol, a crystalline precipitate (A) was obtained which weighed 5 g. and melted at 220–238°. The filtrate, when evaporated to a gum and stirred with 50 cc. of alcohol, yielded a second crop (B) of crystalline precipitate, which weighed 5.2 g. and melted partially with the evolution of a gas at 90°, solidified at 115°, and melted to a clear oil at 190–280°.

Precipitate (A), when extracted three times with 30-cc. portions of boiling acetone yielded, by evaporation of the extracts, 4.0 g. of tri-*p*-nitrophenylguanidine.

Precipitate (B) was treated with 50 cc. of cold acetone, filtered from sulfur, and the filtrate concentrated to a volume of 10 cc. When 15 cc. of alcohol was added, 4.3 g. of the di-*p*-nitrophenylphenylguanidine crystallized from the cold solution. The filtrate yielded 0.5 g. of the same product. The guanidine was recrystallized from alcohol, from which it separated in the form of yellow prisms, which held one mole of alcohol of crystallization. One gram dissolved in 40 cc. of boiling, and in 200 cc. of cold alcohol. The pure guanidine, when heated in a melting point tube, melted partially with the evolution of alcohol of crystallization at 90–105°, solidified at 120°, and melted sharply at 191–193°. When alcohol-free, the substance melted at 191–193°.

Anal. Calcd. for $C_{19}H_{15}O_4N_5$: C, 60.43; H, 4.09; N, 18.57. Found: C, 60.09; H, 4.02; N, 18.39. Calcd. for $C_{19}H_{15}O_4N_5 \cdot C_2H_6O$: N, 16.55. Found: N, 16.45.

The products of the reaction between *p*-nitraniline and *p*-nitrophenylphenylthiourea in the presence of pyridine and iodine are, therefore, the di-*p*-nitrophenylphenylguanidine, melting at 191–193°, obtained in 34% yield, and the tri-*p*-nitrophenylguanidine, obtained in 30% yield. Evidence as to the mechanism of the formation of the latter was secured from a reaction carried out in chloroform solution. Under these conditions di-*p*-nitrophenylthiourea was isolated from the reaction mixture in addition to the above products. The occurrence of this substance indicates that it is a possible precursor of the tri-*p*-nitrophenylguanidine formed.

(b) The higher melting di-*p*-nitrophenylphenylguanidine was also obtained by isomerization of the lower melting form by heat or pyridine.

The guanidine melting at 168–169° was transformed quantitatively into the guanidine melting at 191–193° when 0.5-g. specimens of the former were heated for thirty

minutes at 170–175°. Partial isomerization was brought about by heating at lower temperatures (130–170°), when mixtures melting from 164 to 193° were obtained.

The guanidine melting at 168–169° was partially converted into the higher melting guanidine by heating in pyridine solution. When a pyridine solution of 4 g. of the former substance was boiled for one hour, a mixture of the two isomers was obtained which was separated by repeated fractional extractions with acetone and alcohol into 2.2 g. of the guanidine melting at 191–193°, and 1.4 g. of the guanidine melting at 168–169°.

(c) The guanidine melting at 191–193° was obtained in 26% yield by fusing S-methyl-*p*-nitrophenylphenylpseudothiourea with *p*-nitraniline.

β-Phenyl-α,γ-di-*m*-nitrophenylguanidine.—This guanidine was prepared in 65% yield by treating phenyl-isocyan-dichloride with *m*-nitraniline. A solution containing 8 g. of phenyl-isocyan-dichloride and 14 g. of *m*-nitraniline in 80 cc. of dry chloroform was boiled for three hours. The hydrochloride obtained on cooling and filtering the reaction mixture was changed into 5.8 g. of the free guanidine by treating its alcohol solution with ammonia. By continued boiling of the mother liquor from the reaction with fresh *m*-nitraniline, an additional 5.6 g. of the guanidine was obtained.

When recrystallized from alcohol, the guanidine separated in the form of yellow plates, melting at 175–176°. One gram of the substance was soluble in 50 cc. of boiling alcohol and in 75 cc. of cold alcohol.

Anal. Calcd. for $C_{19}H_{15}O_4N$: C, 60.43; N, 18.57. Found: C, 60.61; N, 18.69.

α,β,γ-Tri-*p*-nitrophenylguanidine.—The most successful method of preparing tri-*p*-nitrophenylguanidine consisted in desulfurizing a mixture of di-*p*-nitrophenylthiourea and *p*-nitraniline by means of iodine and pyridine. Other desulfurizing agents, such as lead hydroxide, led to the formation of the oxygen urea, di-*p*-nitrophenylurea.

Fifteen grams of di-*p*-nitrophenylthiourea and 6.6 g. of *p*-nitraniline were dissolved in 90 cc. of hot pyridine, a solution of 12 g. of iodine in 40 cc. of pyridine was added, and the mixture was boiled for four hours. It was then cooled, and the product precipitated by adding water gradually with stirring. The yellow precipitate was filtered, washed with water to remove pyridine hydriodide and with carbon bisulfide to remove sulfur. The product was purified by extracting it three times with 100 cc. of acetone, and once with 50 cc. of acetone. The extracts, when concentrated, deposited a total of 14.6 g. of the guanidine, melting at 241–243°. The yield was 73%. The residue insoluble in acetone consisted of 0.9 g. of di-*p*-nitrophenylurea, melting with decomposition at 310°.

The guanidine was purified by recrystallization from acetone. Twelve grams dissolved in 320 cc. of boiling acetone, and the solution, when concentrated to 50 cc., deposited 8.8 g. of transparent yellow plates, melting at 244–245°. The guanidine was very slightly soluble in alcohol or chloroform.

Anal. Calcd. for $C_{19}H_{14}O_6N_6$: C, 54.02; H, 3.32; N, 19.90. Found: C, 53.82; H, 3.42; N, 19.79.

α-*p*-Aminophenyl-β,γ-diphenylguanidine.—Four grams of α-*p*-nitrophenyl-β,γ-diphenylguanidine was dissolved in 95 cc. of hot ethyl acetate, 0.42 g. of platinum oxide catalyst[25] was added, and the mixture was shaken in an atmosphere of hydrogen under twenty pounds pressure. After a slow absorption of hydrogen during the first hour, 0.15 g. of fresh catalyst was added, and the shaking was continued for three hours. At the end of this time a sample of the solution, filtered from platinum, gave a red coloration with sodium hydroxide. Since this test is characteristic of the nitro com-

[25] Adams, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 92.

pound, 0.15 g. of fresh catalyst was added, the mixture was shaken for five hours longer, and then allowed to stand without shaking for twelve hours under twenty pounds pressure. After this treatment the solution gave no coloration with alkali. The catalyst was then filtered off, and the solution concentrated under reduced pressure at 60° to a gum. The gum was dissolved in absolute alcohol, the alcohol distilled off, and the process repeated until a crystalline precipitate separated from the concentrated alcohol solution. This consisted of 2.3 g. of the amino compound, melting at 152–153°. An additional 0.2 g. of the same product was obtained from the filtrate, which gave a total yield of amino compound amounting to 69%.

The guanidine derivative, when recrystallized from absolute alcohol, separated in the form of short, colorless needles, melting at 152–153°. One gram dissolved in 25 cc. of boiling alcohol and in 30 cc. of cold alcohol. The substance was slightly soluble in water, giving a basic solution.

Anal. Calcd. for $C_{19}H_{18}N_4$: N, 18.54. Found: N, 18.53, 18.33.

β-Phenyl-α,γ-di-*p*-aminophenylguanidine.—This amino compound was obtained by reduction of either the nitro compound melting at 168–169°, or the nitro compound melting at 191–193°.

Ten grams of the nitro compound, melting at 168–169°, was dissolved in 100 cc. of hot purified ethyl acetate and shaken with 0.2 g. of platinum oxide in an atmosphere of hydrogen for fifty-five minutes. The solution was then filtered from the platinum, and concentrated under reduced pressure to a volume of 40 cc. At this point a yellowish precipitate separated, which consisted of 3.9 g. of the amino compound, melting at 166–167°. By evaporation of the filtrate, 3.7 g. more of the same product was obtained (a 78% yield).

When decolorized with norite and recrystallized from alcohol, the substance separated in the form of rosets of colorless plates, m. p. 167–168°. A mixture of the amino derivative with the original nitro compound melted at 120–130°. The amino compound was moderately soluble in water, giving a strongly basic solution. Solutions of the amino compound discolored when allowed to stand in the air.

Anal. Calcd. for $C_{19}H_{19}N_5$: N, 22.08. Found: N, 21.98, 21.94.

The same amino compound was obtained in 61% yield by reduction of the nitro compound melting at 191–193°. The two specimens were identical in mixed melting point, crystalline form, and percentage of nitrogen.

β-Phenyl-α,γ-di-*m*-aminophenylguanidine.—This *m*-amino derivative was obtained in 80–90% yields by reduction of the *m*-nitro compound, m. p. 175–176°, according to a procedure similar to that described for the preparation of the *p*-amino compound. When purified by recrystallization from alcohol, the substance was obtained as a white powder, melting at 138–139°. It was moderately soluble in hot water, giving a strongly basic solution, but separated as an oil on cooling. One gram dissolved in 10 cc. of boiling alcohol and in 30 cc. of cold alcohol.

Anal. Calcd. for $C_{19}H_{19}N_5$: N, 22.08. Found: N, 22.09, 21.91.

α,β,γ-Tri-*p*-aminophenylguanidine.—Three grams of tri-*p*-nitrophenylguanidine suspended in 100 cc. of hot ethyl alcohol was shaken with 0.3 g. of platinum oxide under 23 pounds pressure of hydrogen. A rapid absorption of hydrogen occurred at once with the evolution of heat. As the nitro compound dissolved, a white amino compound was precipitated on the walls of the flask. The reaction was complete in less than an hour. The resulting mixture was poured into a beaker, treated with 12 cc. of water, and heated to boiling to dissolve the amino compound. The platinum was filtered off, and the solution concentrated at once under reduced pressure to a volume of 40 cc. On cooling, the solution deposited a gray precipitate of 0.9 g., melting at 211°, and

from the filtrate 1.1 g. of the same substance was obtained. The residue was a black gum.

The product, when treated with norite and crystallized from 80% aqueous alcohol, melted at 215°. Two grams dissolved in 100 cc. of 80% aqueous alcohol and, on cooling the solution, 0.7 g. separated in the form of long, colorless needles. One gram was soluble in 400 cc. of boiling acetone and did not crystallize on cooling. The substance was only slightly soluble in pure alcohol or water. Solutions of the compound quickly turned purple when exposed to the air. This triamino compound was by far the least soluble and the most sensitive to decomposition of any of the amino derivatives studied.

Anal. Calcd. for $C_{19}H_{20}N_6$: N, 25.30. Found: N, 25.10, 25.08.

Summary

1. A new method for the synthesis of nitrotriarylguanidines has been developed. By desulfurization of a mixture of the thiourea and amine through the combined action of iodine and pyridine, *p*-nitrophenyldiphenylguanidine, two di-*p*-nitrophenylphenylguanidines, and tri-*p*-nitrophenylguanidine have been prepared. A di-*m*-nitrophenylphenylguanidine has also been obtained.

2. An instance of guanidine isomerism has been observed in the case of the two di-*p*-nitrophenylphenylguanidines. These substances are interconvertible isomers, which differ widely in melting points and in behavior toward heat, acids and pyridine.

3. Four previously undescribed nitroarylthioureas have been prepared.

4. Four amino derivatives of triphenylguanidine have been obtained, and their pharmacological effect on the tubercle bacillus has been investigated.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NOTRE DAME]

IODINATION IN LIQUID AMMONIA

BY THOMAS H. VAUGHN AND J. A. NIEUWLAND

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Solutions of iodine in liquid ammonia have been used by several investigators as a nitridizing agent.[1] In these reactions hydrogen has been nitridized off of organic compounds with the subsequent formation of ammonium iodide. A survey of the literature shows that no substitutions of iodine for hydrogen have been reported.

It has been pointed out by Richter[2] and shown by Datta and Chatterjee[3] that iodination generally takes place most readily in the presence of sub-

[1] Shurman and Fernelius, THIS JOURNAL, **52**, 2425–30 (1930); Strain, *ibid.*, **51**, 272 (1929); **49**, 1564 (1927); Bergstrom, *J. Phys. Chem.*, **32**, 440 (1928).

[2] Richter, "Organic Chemistry," translation by Spielmann, Blakiston's Son & Co., Philadelphia, 1919, Vol. I, p. 92.

[3] Datta and Chatterjee, THIS JOURNAL, **39**, 439 (1917).