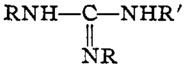
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF WASHINGTON]

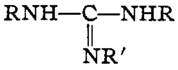
Isomerism of the Guanidines

BY ROBERT P. SIEG AND WILLIAM M. DEHN

When three groups, of which two are identical, are attached to the three nitrogen atoms of guanidine, two isomers are possible

(a) 

$$\mathrm{RNH{-}\underset{\underset{NR}{\|}}{C}{-}NHR'}$$

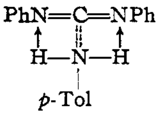
(b) 

$$\mathrm{RNH{-}\underset{\underset{NR'}{\|}}{C}{-}NHR}$$

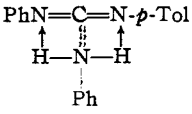
Several unsuccessful attempts to prepare these isomers and to locate the positions of their double bonds have been made. In 1886 Huhn[1] attempted to prepare two pairs of these isomers. He treated di-substituted thioureas with mercuric oxide, and, to the resulting carbodiimides, he added a base to form the guanidine. Marckwald[2] found that Huhn's compounds were contaminated by impurities that caused the differences in melting points submitted by Huhn as proof of formation of isomers. Dyer and Johnson[3] prepared and proved two isomers of di-p-nitrophenylphenylguanidine. However, they had insufficient proof of the location of the gamma double bonds and their surmise of these positions was erroneous. Bly, Perkins and Lewis[4] prepared a monochlorotriphenylguanidine which evidently was a mixture of isomers. They did not locate the double bond.

Because of the recited differences of opinion, "Beilstein" always gives two formulas for the guanidines, thus indicating that the existence of isomers and the location of the double bond in the respective structures have not been established. We have isolated twelve pairs of isomers conforming to formulas (a) and (b) and have found convincing proof of their structures. Also, contradictions of the mentioned and other investigators have been clarified.

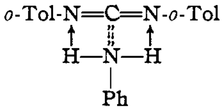
Huhn assumed shifting of the two hydrogen atoms of the primary base, when it reacts with the carbodiimide, as is indicated in the following pairs of isomers that he reported.



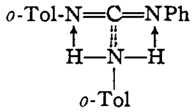
$$\begin{array}{c}\mathrm{PhN{=}C{=}NPh}\\ \uparrow\quad\Vert\quad\uparrow\\ \mathrm{H{-}N{-}H}\\ |\\ p\text{-Tol}\end{array}$$



$$\begin{array}{c}\mathrm{PhN{=}C{=}N}\text{-}p\text{-Tol}\\ \uparrow\quad\Vert\quad\uparrow\\ \mathrm{H{-}N{-}H}\\ |\\ \mathrm{Ph}\end{array}$$



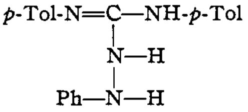
$$\begin{array}{c}o\text{-Tol-}\mathrm{N{=}C{=}N}\text{-}o\text{-Tol}\\ \uparrow\quad\Vert\quad\uparrow\\ \mathrm{H{-}N{-}H}\\ |\\ \mathrm{Ph}\end{array}$$



$$\begin{array}{c}o\text{-Tol-}\mathrm{N{=}C{=}NPh}\\ \uparrow\quad\Vert\quad\uparrow\\ \mathrm{H{-}N{-}H}\\ |\\ o\text{-Tol}\end{array}$$

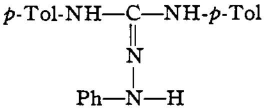
We submit evidences that only one hydrogen atom of the base shifts when the respective carbodiimides yield the guanidines and also that Huhn's assigned structures are erroneous because they are interchanged.

When phenylhydrazine is the added base, colorless anilino-diaryl guanidines are formed and these oxidize in air to yield colored compounds. For example, when treating di-p-tolylcarbodiimide with phenylhydrazine, Schall[5] found that the colorless crystals oxidized to an azo compound. This must be



$$\begin{array}{l}p\text{-Tol-}\mathrm{N{=}C{-}NH}\text{-}p\text{-Tol}\\ \qquad\qquad |\\ \qquad\quad \mathrm{N{-}H}\\ \qquad\qquad |\\ \quad \mathrm{Ph{-}N{-}H}\end{array}$$

or



$$\begin{array}{c}p\text{-Tol-}\mathrm{NH{-}C{-}NH}\text{-}p\text{-Tol}\\ \Vert\\ \mathrm{N}\\ |\\ \mathrm{Ph{-}N{-}H}\end{array}$$

Because the first molecule, rather than the second, can more readily oxidize in air to give the azo compound, it is probable that only one hydrogen atom shifts. Also it must be remembered that Schall used a symmetrical carbodiimide and obtained only one isomer and this oxidized to the pure azo compound. That only one hydrogen shifts is also confirmed by the converse experiments of Marckwald and Wolff.[6] They obtained a mixture of two isomers when they treated an unsymmetrical carbodiimide with phenylhydrazine. This is possible only on the basis that one hydrogen atom shifts.

A further proof that one hydrogen atom shifts from the base to the carbodiimide is observed when guanidines are formed by treatment of diphenylcarbodiimide with secondary bases, as dimethylamine or piperidine.[7]

In the study of the twelve pairs of isomers described herein we always found that a symmetrical carbodiimide yielded with a primary base only one easily isolated compound, and an unsymmetrical carbodiimide yielded two isomers that were difficult to separate. Therefore the

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[1] Huhn, *Ber.*, **19**, 2404 (1886).

[2] Marckwald, *Ann.*, **286**, 343 (1895).

[3] Dyer and Johnson, THIS JOURNAL, **54**, 777 (1932).

[4] Bly, Perkins and Lewis, *ibid.*, **44**, 2902 (1922).

[5] Schall, *J. prakt. Chem.*, [2] **61**, 445 (1900).

[6] Marckwald and Wolff, *Ber.*, **25**, 3117 (1892).

[7] Meis, U. S. Patent 1,850,682 (1932).

conclusion is drawn that only one hydrogen atom shifts and the location of the double bond can be determined when the melting points of the products of the two reactions are studied. For example in the following table the double bonds are attached as indicated:

	Order of introduction of groups	Huhn's m. p., °C.	Our m. p., °C
(4b)	*o*-TolNH—(*o*-Tol—N=)C—NH—Ph	102	97
(4a)	*o*-TolNH—(Ph—N=)C—NH—*o*-Tol	97–98	93.5
(3b)	PhNH—(Ph—N=)C—NH—*p*-Tol	120–121	121
(3a)	PhNH—(*p*-Tol—N=)C—NH—Ph	126–127	104.5

Because diphenylthiourea and di-*o*-tolylthiourea each gave only one isomer, 3b and 4b, respectively, and because phenyl-*p*-tolylthiourea and phenyl-*o*-tolylthiourea gave two isomers, 3a and 3b and 4a and 4b, respectively, it must be concluded that always only one hydrogen atom of the base shifts to the carbodiimide to form a guanidine.

When unsymmetrical carbodiimides are used, probability alone would indicate that equimolecular mixtures of the two isomers would be formed. However, because of relative reactivities of the different aryl-nitrogen groups, most often equimolecular mixtures were not formed.

Carbodiimides usually have been prepared by heating thioureas in benzene with mercuric oxide.[8] Other desulfurizing reagents are lead oxide,[9] lead peroxide,[10] zinc hydroxide in alkaline solution,[11] iodine,[12] pyridine,[13] combination of these last two,[14] bromates and iodates in alkaline solutions.[15] With nitroaryl thioureas and lead hydroxide, Dyer and Johnson[16] obtained only the corresponding ureas. With lead hydroxide, and thioureas in benzene at room temperatures we obtained nearly pure carbodiimides. With lead hydroxide, thioureas, benzene and primary organic bases we obtained guanidines practically free from ureas and polymerized carbodiimides. In all cases extraction with phosphoric or acetic acid, and precipitation by ammonium hydroxide, yielded guanidines free from these by-products.

The conditions favoring our method of preparation of guanidines are desulfurization of the thioureas in benzene by lead hydroxide at room temperatures, extraction of the guanidines by weak acids, and separation of the isomers by fractional crystallization.

Experimental Part

The thiourea (1 mole) was dissolved in a beaker with benzene and then was treated with freshly precipitated and practically dry lead hydroxide (2–3 moles). The base (1 mole) was then added and the mixture was stirred by a spatula or by a mechanical stirrer. The mixture can conveniently be placed in a bottle and agitated by a mechanical shaker. Most frequently orange, red or brown colors appear before the black of lead sulfide. After a day or more, finely divided lead sulfide settles as a compact mass. The end of the reaction is indicated by a negative test for sulfur in the benzene solution.[16] The benzene solution is filtered on a Büchner funnel and, if the lead sulfide is bulky, it should be extracted with hot alcohol. The benzene solution and the alcohol solution are poured into a large beaker containing water and the solvents are evaporated on the water-bath. The mixture of heavy oil and water is boiled to volatilize unfixed base remaining because side reactions yielded ureas and polymerized carbodiimides. Taking the odor of the steam will usually indicate the removal of the base. The heavy oil, or the gummy mass resulting from cooling, is separated from the water. The mass is then advantageously dissolved in a small volume of hot alcohol and poured, while stirring, into the calculated quantity of dilute phosphoric acid[17] to dissolve the guanidine. At this stage an insoluble mass composed of a urea, unchanged thiourea, and polymerized carbodiimide may appear. This is filtered off and the filtrate is treated with dilute ammonium hydroxide to precipitate the guanidine or the mixture of the two guanidines, depending on the thioureas used. This precipitate is filtered off, washed and recrystallized.

Because the guanidines are very soluble in most organic solvents and often supercool without yielding crystals, different methods were employed to obtain the pure compounds. A saturated benzene solution was poured into petroleum ether. After standing a number of days, often beautiful crystals were formed. Hot saturated alcohol solutions yielded crystals. When mixtures of two isomers, always obtained from asymmetrical thioureas, are to be separated to yield the respective isomers, two methods are available. These methods are dependent upon the lesser solubility in alcohol of the higher melting isomer. The successive crops of crystals are obtained either by concentrating the filtrates or by adding water. Addition of water usually proved to be the better method. As the successive crops of crystals were obtained and their melting points were taken, it was found that the first fraction was predominantly the higher melting isomer and most often was the lone isomer obtained with symmetrical thioureas. The other fractions melted successively lower and the last fraction melted sharply and was the

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(8) Weith, *Ber.*, **7**, 10 (1874). This was employed by Huhn, Marckwald and others.

(9) Berger, *ibid.*, **12**, 1857 (1879).

(10) Raiford and Daddow, THIS JOURNAL, **53**, 1552 (1931).

(11) Meis, U. S. Patents 1,850,682, 1,953,494.

(12) Hofmann, *Ber.*, **2**, 456 (1869); Losanitsch, *ibid.*, **16**, 49 (1883).

(13) *Chem. Abstracts*, **8**, 2638 (1914); **12**, 1170 (1918).

(14) Dyer and Johnson, THIS JOURNAL, **54**, 785 (1932).

(15) Capps and Dehn, *ibid.*, **54**, 4301 (1932).

(16) Sometimes this benzene solution blackened either by heating or on standing, indicating a soluble intermediate lead compound.

(17) Dyer and Johnson observed that continued heating with hydrochloric acid isomerized a high melting isomer to the low melting isomer. We observed no such isomerization when employing the weak acids phosphoric or acetic acid.

TABLE I

No.	Order of introduction of groups (names indicated)	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
1a	PhNH(*o*-Tol:)C—NHPh	93	13.94	13.89
1b	PhNH(PhN:)C—NH—*o*-Tol	110.5	13.94	13.87
2a	PhNH(*m*-TolN:)CNHPh	101	13.94	14.01
2b	PhNH(PhN:)CNH—*m*-Tol	92	13.94	13.93
3a	PhNH(*p*-TolN:)C—NH—Ph	104.5	13.94	13.95
3b	PhNH(PhN:)C—NH—*p*-Tol	121	13.94	13.86
4a	*o*-TolNH(PhN:)C—NH—*o*-Tol	93.5	13.32	13.30
4b	*o*-TolNH(*o*-TolN:)C—NH—Ph	97	13.32	13.17
5a	*o*-TolNH(*m*-TolN:)C—NH-*o*-Tol	88	12.76	12.80
5b	*o*-TolNH(*o*-TolN:)C—NH—*m*-Tol	86	12.76	12.76
6a	*o*-TolNH(*p*-TolN:)C—NH—*o*-Tol	70.5	12.76	12.77
6b	*o*-TolNH(*o*-TolN:)C—NH—*p*-Tol	83	12.76	12.77
7a	*m*-TolNH(PhN:)C—NH—*m*-Tol	92	13.32	13.32
7b	*m*-TolNH(*m*-TolN:)C—NH—Ph	86	13.32	13.35
8a	*m*-TolNH(*o*-TolN:)C—NH—*m*-Tol	90	12.76	12.63
8b	*m*-TolNH(*m*-TolN:)C—NH—*o*-Tol	84	12.76	12.77
9a	*m*-TolNH(*p*-TolN:)C—NH—*m*-Tol	103	12.76	12.81
9b	*m*-TolNH(*m*-TolN:)C—NH—*p*-Tol	93	12.76	12.80
10a	*p*-TolNH(PhN:)C—NH—*p*-Tol	62	13.32	13.27
10b	*p*-TolNH(*p*-TolN:)C—NH—Ph	82.5	13.32	13.35
11a	*p*-TolNH(*o*-TolN:)C—NH—*p*-Tol	77.5	12.76	12.74
11b	*p*-TolNH(*p*-TolN:)C—NH—*o*-Tol	89.5	12.76	12.86
12a	*p*-TolNH(*m*-TolN:)C—NH—*p*-Tol	83.5	12.76	12.74
12b	*p*-TolNH(*p*-TolN:)C—NH—*m*-Tol	101	12.76	12.76

pure lower melting isomer. Thus both isomers could be obtained pure.

In Table I are given twelve pairs of isomers, (a) and (b), in all combinations of phenyl and the tolyl groups, and in conformity with the general formulas (a) and (b). The compounds are arranged to show the order of introduction of groups. The first group indicates the mustard oil used to form the thiourea. The first two groups indicate the thiourea used to form the carbodiimide. The third group indicates the primary base used to yield the guanidine. In the table isomers are adjacent, the established locations of double bonds are given, also the melting points and analytical data. All of these compounds crystallize as needles or as rosettes of needles. Analyses were made by the Kjeldahl method. In general the symmetrical carbodiimides yield the higher melting isomers. When a *m*-tolyl group is present, this does not always hold true.

Summary

When a primary base adds to a carbodiimide to yield a guanidine, only one hydrogen atom of the base shifts to a nitrogen atom of the carbodiimide. This rule is established by study of the lone isomer obtained with a symmetrical carbodiimide and also of the two isomers always obtained with the symmetrical carbodiimide. This knowledge leads to determination of location of gamma double bonds. Twelve pairs of isomers were prepared and their structural relations were established.

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[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH FOUNDATION OF THE FRANKLIN INSTITUTE]

The Preparation of Some 2-Pyridyl and 8-Quinolyl Phenyl Sulfides and Sulfones

BY HARRY C. WINTER AND FRANCIS E. REINHART

The discovery of the powerful antistreptococcal properties of sulfanilamide, 4,4′-dinitrodiphenyl sulfone, and some of their derivatives has led to the investigation of a large number of related compounds of the benzene series. Very little attention, however, has been directed to the pyridine and quinoline analogs of these active therapeutic agents. In fact, only two such compounds, 6-sulfonamidoquinoline[1] and 2,2′-dipyridyl sulfide,[2] had been studied when an investigation of these analogs was begun in this Laboratory. Recently, there has been reported the preparation of a number of sulfonamides,[3] sulfides[4,5] and sulfones[5] of pyridine and of quinoline. The value of these compounds as antistreptococcal agents has not yet been established.

The compounds prepared in this investigation have been chiefly 2-pyridyl or 8-quinolyl sulfides and sulfones in which a phenyl or *p*-nitrophenyl group was present as the second substituent. In all of these, a nitro or amino group occupied that position in the heterocyclic nucleus para to the sulfur linkage thus simulating the relative

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[1] J. Tréfouël, Mme. J. Tréfouël, F. Nitti and D. Bovet, *Ann. Inst. Pasteur*, **58**, 30 (1937).

[2] J. A. Kolmer, H. Brown and G. W. Raiziss, *J. Pharmacol.*, **61**, 253 (1937).

[3] C. Naegeli, W. Kündig and H. Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938); **22**, 912 (1939).

[4] M. Colonna, *Gazz. chim. ital.*, **70**, 154 (1940).

[5] A. R. Surrey and H. G. Lindwall, THIS JOURNAL, **62**, 173 (1940).