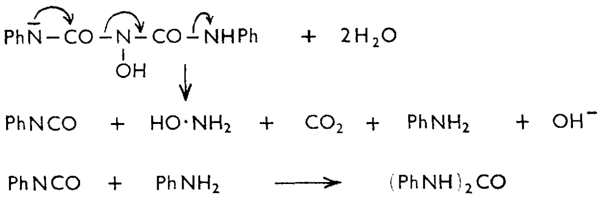
The Synthesis and Some Reactions of Dihydroxyurea

By E. Boyland and R. Nery

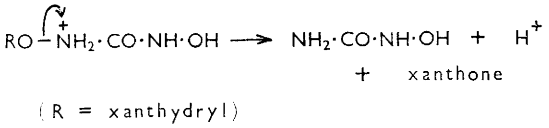
Hydroxylamine and *O*-methylhydroxylamine react with phosgene to yield *NN'*-dihydroxyurea or *NN'*-dimethoxyurea. Dihydroxyurea forms a tetrabenzoyl derivative which gives *O*-benzoyl benzhydroxamate in hot aqueous ethanol. With phenyl isocycanate, dihydroxyurea gave hydroxydiphenylbiuret; with xanthydrol, xanthone and hydroxyurea were produced. Hydroxyurea and dihydroxyurea were determined colorimetrically with amminoprusside. In alkali, dihydroxyurea formed cyanate and hydroxyurea; hydroxyurea formed cyanate. Hydroxyurea was more stable than dihydroxyurea.

THE reaction of phosgene or hydroxyurethane with hydroxylamine in alkali gave hydroxyurea. When phosgene and hydroxylamine reacted in the presence of potassium acetate, the mixture became acidic and dihydroxyurea was obtained. Phosgene and *O*-methylhydroxylamine gave *NN'*-dimethoxyurea. On alkaline hydrolysis, dihydroxyurea gave hydroxyurea and cyanate; on reaction with benzoyl chloride, it gave *NN'*-dibenzoyl-*NN'*-dibenzoyloxyurea which, in boiling aqueous ethanol, yielded *O*-benzoyl benzhydroxamate. With phenyl isocyanate in dimethylformamide or dioxan, dihydroxyurea gave an unstable product, probably the tetraphenyl carbamoyl derivative, which formed diphenylcarbamoylhydroxylamine in hot aqueous ethanol. Diphenylcarbamoylhydroxylamine is isomeric with the compounds *N*-anilinocarbonyloxy-*N'*-phenylurea (PhNH·CO·NH·O·CO·NHPh) [1,2] and hydroxydiphenylbiuret [$(PhNH{\cdot}CO)_2N{\cdot}OH$].[3,4] It gave a red colour with ferric chloride and decomposed in alkali into carbon dioxide, hydroxylamine, aniline, and *NN'*-diphenylurea.[3] The alkaline decomposition probably occurred as follows:



The latter reaction is known.[1,5] When *N*-hydroxy-*N'*-phenylurea was boiled in ethanol in the presence of aniline, neither *NN'*-diphenylurea nor phenyl isocyanate was formed;[1] when *N*-hydroxy-*N'*-phenylurea was treated with aniline in ethanolic potassium hydroxide in the present experiments, *NN'*-diphenylurea was isolated in 45% yield. Diphenylcarbamoylhydroxylamine similarly gave 57% *NN'*-diphenylurea. As *N*-hydroxy-*N'*-phenylurea forms diphenylcarbamoylhydroxylamine in boiling ethanolic solutions,[3] these results support the proposed structure of hydroxydiphenylbiuret.

When dihydroxyurea was treated with xanthydrol in acetic–sulphuric acid mixture, xanthone and hydroxyurea were produced, probably through the intermediate formation of *N*-hydroxy-*N'*-xanthydryloxyurea, *e.g.*,



In phosphate buffer at pH 7·5, hydroxyurea and dihydroxyurea, like *N*-arylhydroxylamines [6] and *N*-hydroxycarbamates,[7] formed coloured pentacyanoferrate(II) complexes, $Na_3[Fe(CN)_5X]$, where X is a molecule of the hydroxyamino-derivative, to extents proportional to the concentration of X. This reaction formed the basis of a sensitive method for the colorimetric determination of hydroxyurea and dihydroxyurea (see Figure 2), although the complexes were less stable (see Figure 1) than those formed from the arylhydroxylamines [6] and *N*-hydroxycarbamates.[7] The measurements of the concentration of hydroxyurea and dihydroxyurea by the colour given with amminoprusside

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[1] C. D. Hurd, *J. Amer. Chem. Soc.*, 1923, **45**, 1473.

[2] V. D. Kall, *Annalen*, 1891, **263**, 263.

[3] C. Kjellin, *Ber.*, 1893, **26**, 2384.

[4] O. Exner, *Coll. Czech. Chem. Comm.*, 1961, **26**, 706.

[5] A. W. Hofmann, *Annalen*, 1850, **74**, 1.

[6] E. Boyland and R. Nery, *Analyst*, 1964, **89**, 95.

[7] E. Boyland and R. Nery, *Analyst*, 1964, **89**, 520.

show that dihydroxyurea decomposed rapidly in 0·5N-potassium hydroxide at 25° (half-life = 128 sec.; see Table 1) by a pseudounimolecular mechanism with a first-order rate constant of $5{\cdot}4 \times 10^{-2}$ sec.$^{-1}$ to give hydroxyurea, cyanate, and hydroxylamine. This was followed by a change of rate of decomposition which approximated to that of hydroxyurea under similar conditions after about 1 hour (see Table 1 and Figure 3). The same phenomenon was observed in solutions of dihydroxyurea in phosphate buffer at pH 7·5, but the initial first-order rate of decomposition ($k = 5{\cdot}7 \times 10^{-4}$ sec.$^{-1}$) was slower (half-life = 20 min.), and the attainment of a rate approximating to that of hydroxyurea occurred after about 25 hours. In 0·5N-potassium hydroxide at 25°, both compounds produced cyanate at rates which were initially faster in solutions containing dihydroxyurea (see Table 2) and did not follow simple kinetics. Chromatography revealed that alkaline solutions of dihydroxyurea contained hydroxurea which was isolated during attempts to prepare dihydroxyurea in alkaline media. Hydroxyurea was more stable than dihydroxyurea under all conditions examined; in neutral solutions the half-life of hydroxyurea was 384 times that of dihydroxyurea (see Table 1).

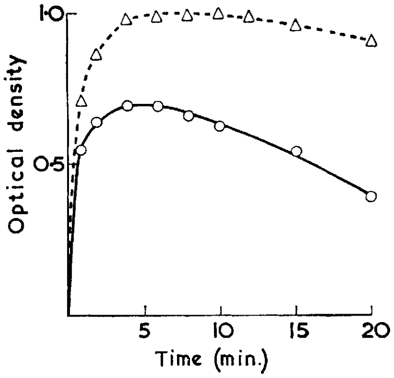

FIGURE 1 The formation, stability, and decomposition of the sodium amminoprusside complexes of hydroxyurea and dihydroxyurea at pH 7·5

△, Hydroxyurea complex. ○, Dihydroxyurea complex

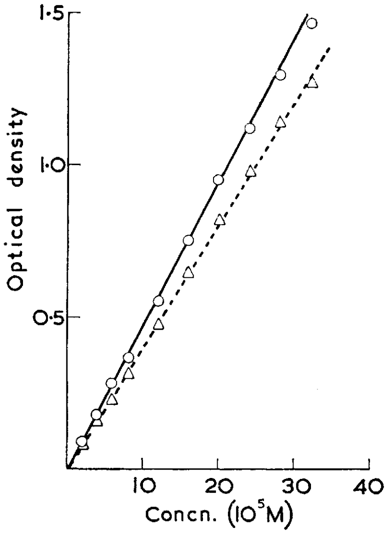

FIGURE 2 The variation of optical density with concentration of the sodium amminoprusside complexes of hydroxyurea and dihydroxyurea at pH 7·5

△, Dihydroxyurea complex. ○, Hydroxyurea complex

TABLE 1

Half-lives and first-order rate constants for the decomposition of hydroxyurea and dihydroxyurea in solutions of different pH at 25°

		Hydroxyurea	
pH	0·8	7·5	12·8
k (sec.$^{-1}$)	$1{\cdot}4 \times 10^{-6}$	$1{\cdot}5 \times 10^{-6}$	$9{\cdot}6 \times 10^{-5}$
$t_{0{\cdot}5}$	137 hr.	128 hr.	2 hr.
		Dihydroxyurea	
pH	0·8	7·5	12·8
k (sec.$^{-1}$)	$3{\cdot}0 \times 10^{-6}$	$5{\cdot}7 \times 10^{-4}$ * $1{\cdot}8 \times 10^{-6}$ †	$5{\cdot}4 \times 10^{-2}$ ‡ 10^{-4} §
$t_{0{\cdot}5}$	64 hr.	20 min.*	128 sec.‡

* Applicable to first 30 min. only. † From 25 to 48 hr. ‡ First 2 min. § From 1 to 4 hr.

TABLE 2

The production of cyanate by hydroxyurea and dihydroxyurea in alkali at 25°

Time (min.)		15	25	45	85	130	190	250
Cyanate (mole %)	Hydroxyurea	1·0	3·0	7·0	14	27	45	48
	Dihydroxyurea	7·3	9·0	13	18	28	40	42

The reactions of dihydroxyurea in alkali probably occurred as follows:

$$\mathrm{CO(NH{\cdot}OH)_2 + H_2O + {}^{-}OH \longrightarrow 2\,NH_2{\cdot}OH + HCO_3^-} \qquad (1)$$

$$\mathrm{{}^{-}O{-}NH{-}CO{-}NH{-}OH \longrightarrow NOH + HO{\cdot}CN + {}^{-}OH} \qquad (2)$$

$$\mathrm{HO{\cdot}CN + NH_2{\cdot}OH \rightleftharpoons HO{\cdot}NH{\cdot}CO{\cdot}NH_2} \qquad (3)$$

Reactions (1) and (2) predominated during the initial rapid decomposition, and reaction (3) during the intermediate stage which was followed finally by the slow decomposition of the hydroxyurea formed. Other reactions, including the alkaline decomposition of hydroxylamine,[8] probably also occurred. Reaction (3) is reversible. The forward reaction has been utilised in the synthesis of hydroxyurea;[9,10] the reverse reaction has been suggested by Dresler and Stein,[9] and is now shown to occur in cold alkali (see Table 2). In hot alkali, urea and carbamates were converted into cyanate to the extent of 10 and 50—56%; alkyl hydroxycarbamates did not produce cyanate.[11]

A preliminary report of part of this work has been published.[12]

EXPERIMENTAL

1,4-Dioxan was freed from peroxides and distilled before use.

Chromatography.—Glass plates coated with films of Silica Gel G (Merck) of 0·25 mm. thickness were used for ascending development in (A) acetone–light petroleum

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[8] K. A. Hofmann and F. Kroll, *Ber.*, 1924, **578**, 937.

[9] W. F. C. Dresler and R. Stein, *Annalen*, 1869, **150**, 242.

[10] A. Hantzsch, *Annalen*, 1898, **299**, 99.

[11] E. Boyland and R. Nery, *Biochem. J.*, 1965, **94**, 198.

[12] E. Boyland and R. Nery, *Nature*, 1964, **203**, 1379.

(b. p. 40—60°) (2 : 3), (B) as (A) (3 : 7), (C) propan-1-ol–ethanol (7 : 3), and (D) butan-1-ol–acetic acid (19 : 1). The following reagents were used: (i) aq. 2% (w/v) silver nitrate, (ii) 1% (w/v) sodium amminoprusside in 0·5M-sodium hydrogen carbonate, and (iii) 1% (w/v) ferric chloride in aq. 50% (v/v) ethanol. Hydroxyurea had R_{F} 0·06, 0·02, 0·59, and 0·47, and dihydroxyurea 0·04, 0, 0·71, and 0·58 in solvents (A), (B), (C), and (D), respectively. *NN'*-Dimethoxyurea had R_{F} 0·50 and 0·18 in solvents (A) and (B), respectively. All three compounds reduced reagent (i); the first two gave brick-red spots with reagent (ii) and bluish-purple spots with reagent (iii); the last gave no colours with reagents (ii) and (iii).

Dihydroxyurea.—A suspension of hydroxylamine hydrochloride (32·3 g.) and potassium acetate (70 g.) in water (20 ml.) was stirred rapidly at 0° and diluted with dioxan (50 ml.). A solution of phosgene (21 g.) in dioxan (150 ml.) was added dropwise during 1·5 hr. After 3 hr., the mixture (pH 3·5) was filtered, the residue washed with ethanol (100 ml.), the combined filtrate and washings were evaporated *in vacuo*, and the residue was fractionally recrystallised from ethanol, to yield (*a*) colourless needles of hydroxylamine hydrochloride (2·5 g.), m. p. and mixed m. p. 165°, (*b*) colourless plates of an unknown compound (2·5 g.), m. p. 95°, with explosive decomposition, and (*c*) colourless prisms of *dihydroxyurea* (9·1 g.) which decomposed with partial melting at 102—106° (Found: C, 13·0; H, 4·7; N, 30·6. $CH_4N_2O_3$ requires C, 13·0; H, 4·4; N, 30·4%). Compound (*b*) behaved like dihydroxyurea on chromatography in solvents (A)—(D) and in its reactions with reagents (i)—(iii), but it was less stable in the solid state or in solution. On keeping at 5°, it exploded violently after several days or weeks and sometimes on being jarred, emitting a grey cloud and leaving a dark, sticky residue; at 23°, it decomposed similarly within minutes or after several hours. The amount of this material isolated varied in different preparations, and violent decompositions sometimes occurred when the crude reaction mixtures or the ethanolic extracts were evaporated.

When no water was used in the above preparation, hydroxylamine hydrochloride was recovered. When larger amounts of water or equivalent amounts of sodium hydroxide, sodium carbonate, or sodium hydrogen carbonate were used instead of potassium acetate, hydroxyurea was obtained in varying amounts as colourless needles (from ethanol), m. p. and mixed m. p. 140—142° (decomp.) (lit.,[9] 139—140°) (Found: C, 16·1; H, 5·5; N, 37·0. Calc. for $CH_4N_2O_2$: C, 15·8; H, 5·3; N, 36·6%). A solution of hydroxyurethane (12·6 g.), hydroxylamine hydrochloride (10·4 g.), and sodium hydroxide (10·3 g.) in water (50 ml.), after 2 days at 23°, was neutralised with 6N-hydrochloric acid, evaporated *in vacuo*, the residue extracted with ethanol (100 ml.), and the extract evaporated *in vacuo*, to give colourless needles of hydroxyurea (from ethanol) (2·4 g.), m. p. and mixed m. p. 140—142° (decomp.). Dihydroxyurea was not detected in the ethanolic filtrate (by chromatography in solvents C and D).

NN'-*Dimethoxyurea.*—Phosgene (7 g.) in dioxan (100 ml.) was added dropwise during 30 min., at 0°, to a stirred suspension of *O*-methylhydroxylamine hydrochloride (12 g.) and potassium hydrogen carbonate (50 g.) in dioxan (50 ml.) and water (20 ml.). After 16 hr., the mixture was filtered, the residue washed with ethanol (25 ml.), and the combined filtrate and washings were evaporated *in vacuo*. The residue was extracted with ethanol (100 ml.), and the extract dried ($MgSO_4$) and diluted with ether at 0° until the precipitation of inorganic salts ceased. The mixture was filtered and the filtrate evaporated *in vacuo*, to give the *product* (6·2 g.) as a colourless oil, b. p. 112—114°/0·7 mm. (Found: C, 30·4; H, 6·9; N, 23·2. $C_3H_8N_2O_3$ requires C, 30·0; H, 6·7; N, 23·3%). It reduced reagent (i) after 1 hr., gave a red colour with 1% (w/v) *p*-dimethylaminocinnamaldehyde in 6N-hydrochloric acid–ethanol (1 : 1 v/v), and no colour with reagents (ii) and (iii).

Reactions of Dihydroxyurea.—(a) *With benzoyl chloride.* Benzoyl chloride (1·8 g.) was added slowly to dihydroxyurea (0·23 g.) in pyridine (5 ml.) at 0°. After 30 min., ice–water (100 ml.) was added, the gummy precipitate formed was washed with ice–water until free from pyridine and fractionally crystallised from aqueous ethanol, to give (i) colourless prisms of NN'-*dibenzoyl*-NN'-*dibenzoyloxyurea* (0·4 g.), m. p. 144° (decomp.) (Found: C, 68·4; H, 4·3; N, 5·3. $C_{29}H_{20}N_2O_7$ requires C, 68·5; H, 4·0; N, 5·5%), and (ii) colourless needles of *O*-benzoyl benzhydroxamate, (0·29 g.), m. p. 168° (lit.,[13] 153, 156—158, 158—159, 161, 165°) (Found: C, 69·8; H, 5·0; N, 5·9. Calc. for $C_{14}H_{11}NO_3$: C, 69·7; H, 4·6; N, 5·8%).

(b) *With phenyl isocyanate.* A solution of dihydroxyurea (0·27 g.) in dimethylformamide (10 ml.), at 0°, was treated with phenyl isocyanate (1·5 g.). After 16 hr., the solution was diluted with ice–water (50 ml.) and the precipitated solid recrystallised from ethanol, to give (i) phenyl isocyanate trimer (0·42 g.), m. p. and mixed m. p. 269° (lit.,[14] 270°), and (ii) colourless prisms (0·84 g.), m. p. 140—160° (decomp.), which became sticky in air and gave colourless needles (0·62 g.) of diphenylcarbamoylhydroxylamine, m. p. 180° (lit.,[3] 178°), after two further crystallisations from ethanol (Found: C, 62·0; H, 4·8; N, 15·4. Calc. for $C_{14}H_{13}N_3O_3$: C, 62·0; H, 4·8; N, 15·5%). It gave a red colour with reagent (iii) and reduced (i) after 2—3 hr. Similar results were obtained when dioxan was used as the solvent and the reaction mixture shaken for 1 hr. at 23° or when no solvent was used.

(c) *With xanthydrol.* A solution of dihydroxyurea (0·27 g.) in acetic acid (10 ml.) at 0°, was treated with xanthydrol (0·6 g.) in acetic acid (10 ml.) containing conc. sulphuric acid (0·1 ml.). The resulting red solution, after 16 hr., was diluted with ice–water (50 ml.). The precipitated solid, after being recrystallised three times from ethanol, gave (i) colourless needles of xanthone (0·45 g.), m. p. and mixed m. p. 173° (lit.,[15] 173°), and (ii) hydroxyurea, which was identified by chromatography in solvents (C) and (D).

(d) *With diazomethane.* Diazomethane (*ca.* 1·5 g.) in ether (100 ml.) was added during 1 hr. to a solution of dihydroxyurea (1·8 g.) in methanol (10 ml.). After 16 hr., the mixture was evaporated *in vacuo*, to give a yellow oil (2 g.), a sample of which decomposed on attempted distillation at 0·5 mm. Chromatography of the oil in solvents (A), (B), and (C) showed that it contained *NN'*-dimethoxyurea together with dihydroxyurea and at least two other components which reduced reagent (i) and had R_{F} 0·30 and 0·52 in solvent (A).

Hydrolysis of Dibenzoyldibenzoyloxyurea.—A solution of

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[13] " Beilstein's Handbuch der Organischen Chemie," Springer, Berlin, 4th edn., 1926, vol. IX, p. 303.

[14] A. W. Hofmann, *Ber.*, 1885, **18**, 765.

[15] V. Merz and W. Weith, *Ber.*, 1881, **14**, 187.

this compound (0·4 g.) in aqueous 80% (v/v) ethanol (10 ml.) was heated under reflux for 40 min. and stored at 0° overnight, to give colourless needles of *O*-benzoyl benzhydroxamate (0·3 g.), m. p. and mixed m. p. 168°.

Comparison of Some Properties of Hydroxyurea and Dihydroxyurea.—(a) *Their colorimetric determination.* Aqueous solutions (1 ml.) of hydroxyurea or dihydroxyurea, in triplicate, were treated with 0·5% (w/v) sodium amminoprusside in 0·2M-phosphate buffer (pH 7·5) (3·5 ml.) and 0·2% (w/v) magnesium chloride hexahydrate in water (0·5 ml.). The test solutions were between $2{\cdot}5 \times 10^{-5}$ and 5×10^{-4}M. The optical densities of the mixed solutions at 465 mμ in a 1-cm. cell were measured against a reagent blank. Readings were taken at 5 and 3 min. after mixing, when absorption was maximal in solutions containing hydroxyurea and dihydroxyurea, respectively. The complexes were stable for 6 and 4 min. longer, respectively (see Figure 1). Beer's law was obeyed within the range of concentration indicated (see Figure 2). The molar extinction coefficients were 3800 and 3220 for the hydroxyurea and dihydroxyurea pentacyanoferrate(II) complexes, respectively. Cyanate and hydroxylamine, which are decomposition products of hydroxyurea and dihydoxyurea (see below), did not interfere with the determination. All results are mean values of three readings (deviation, ±2%).

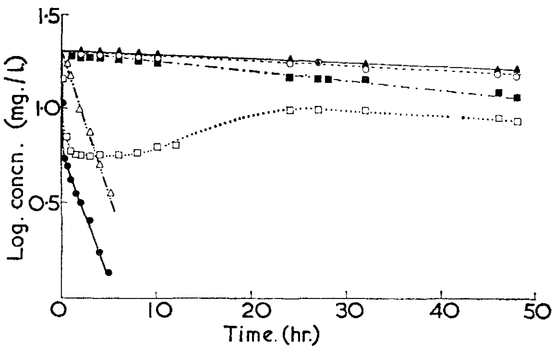

FIGURE 3 The decomposition of hydroxyurea and dihydroxyurea at 25° in different pH media

Hydroxyurea: ▲, pH 0·8; ○, pH 7·5; △ pH 12·8
Dihydroxyurea: ■, pH 0·8; □, pH 7·5; ●, pH 12·8

(b) *Kinetics of decomposition.* Solutions of hydroxyurea or dihydroxyurea (200 μg/ml.) in (i) 0·5N-hydrochloric acid (pH 0·8), (ii) 0·2M-phosphate buffer (pH 7·5), or (iii) 0·5N-potassium hydroxide (pH 12·8) in 90% (v/v) aqueous ethanol were kept at 25°. Aliquots (0·5 ml.), in triplicate, were removed at different times, cooled in ice, and treated with 0·5N-potassium hydroxide (0·5 ml.), water (0·5 ml.), or 0·5N-hydrochloric acid (0·5 ml.), to give neutral solutions. The concentration of the test substances was determined as described above. The results, which represent mean values of three readings (deviation, ±5%), are plotted in Figure 3, and the half-lives and rate constants are given in Table 1.

(c) *Production of cyanate in alkali.* Solutions (0·05M) of hydroxyurea or dihydroxyurea in 0·5N-potassium hydroxide in 90% (v/v) aqueous ethanol were kept at 25°. After different times, aliquots (1·0 ml.), in triplicate, were cooled to 0°, and treated with 0·1% (w/v) cobaltous chloride in ethanol (2·85 ml.) and acetic acid (0·15 ml.). The optical densities were read at 610 mμ in a 1-cm. cell against a reagent blank and related to a standard optical density–concentration curve similarly obtained from potassium cyanate which had ε 88·0 (calculated on the concentration of cyanate in the final solutions). The results which are mean values of three readings (deviation, ±5%) are given in Table 2.

Acid Hydrolysis of Dihydroxyurea and NN′-*Dimethoxyurea.*—Solutions of each compound (0·2 g.) in 4N-hydrochloric acid (5 ml.) were heated at 75° for 2 hr., evaporated *in vacuo*, and the residue was recrystallised from ethanol. Dihydroxyurea gave hydroxylamine hydrochloride (0·14 g.), m. p. and mixed m. p. 165°, and *NN′*-dimethoxyurea gave *O*-methylhydroxylamine hydrochloride (0·17 g.), m. p. and mixed m. p. 149—150°.

The Conversion of N-*Hydroxy*-N′-*phenylurea and Diphenylcarbamoylhydroxylamine into* NN′-*Diphenylurea.*—A solution of *N*-hydroxy-*N′*-phenylurea (1·52 g.), aniline (1·6 ml.), and potassium hydroxide (0·8 g.) in ethanol (50 ml.) was heated under reflux for 1 hr., cooled, and the precipitate of potassium carbonate (0·3 g.) filtered off and washed with ethanol (5 ml.). The filtrate and washings were combined, concentrated *in vacuo* to 15 ml., diluted with ice–water (100 ml.), and the precipitate was recrystallised from aqueous ethanol, to give colourless elongated prisms of *NN′*-diphenylurea (0·95 g.), m. p. and mixed m. p. 239° (lit.,[16] 239·5°). Similar treatment of diphenylcarbamoylhydroxylamine (2·7 g.) in the absence of aniline gave *NN′*-diphenylurea (1·2 g.), m. p. and mixed m. p. 239°.

This investigation was supported by grants to this Institute from the Medical Research Council, The British Empire Cancer Campaign, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

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[5/811 *Received, July 29th*, 1965]

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[16] C. Graebe and S. Rostovzeff, *Ber.*, 1902, **35**, 2750.