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HYDROXAMIC ACIDS AND THEIR DERIVATIVES—II[†]

REACTION OF HYDROXAMIC ACIDS WITH DICYCLOHEXYL CARBODIIMIDE[*]

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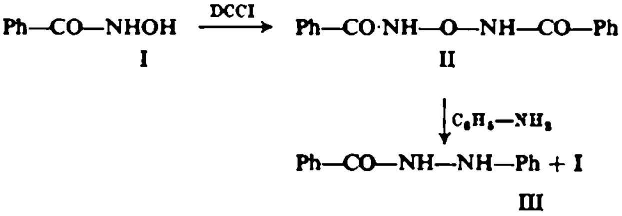
Abstract—The reaction of hydroxamic acids with DCCI leads to O-carbamoylhydroxamic acids.

It has been reported[1] that benzohydroxamic acid (I) reacts with dicyclohexylcarbodiimide (DCCI) to form an "anhydride" (II), which in turn reacts with aniline to form N-benzoyl-N′-phenylhydrazine (III) and benzohydroxamic acid (I). Our interest in benzohydroxamic acid chemistry[2] prompted a reinvestigation of this reaction.



$$\underset{\text{I}}{\text{Ph—CO—NHOH}} \xrightarrow{\text{DCCI}} \underset{\text{II}}{\text{Ph—CO·NH—O—NH—CO—Ph}}$$

$$\Big\downarrow C_6H_5\text{—}NH_2$$

$$\text{Ph—CO—NH—NH—Ph} + \text{I} \qquad \text{III}$$

At room temperature the reaction of two molar equivalents of benzohydroxamic acid with one molar equivalent of DCCI in tetrahydrofuran was slow; at the end of 60 hr the dicyclohexylurea (DCU) which had separated was filtered off and from the filtrate, was isolated in 45% yield a crystalline compound, melting around 170° with decomposition, solidifying and remelting around 220°. The empirical formula, $C_{14}H_{12}N_2O_3$, did indeed correspond to a bimolecular "anhydride" of benzohydroxamic acid; but the IR spectrum of the compound showed bands at 1770 and 1740 cm^{-1}, suggesting the presence of an "activated carbonyl" group.[3] The product was identified as O-phenylcarbamoyl-benzohydroxamic acid (IV) by comparison with an authentic sample made by the known procedure[4] involving the action of phenylisocyanate on sodium benzohydroxamate.

[*] Contribution No. 63 from CIBA Research Centre
[†] Ref. 2 is considered Part I of this series.

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[1] M. Löw and L. Kisfaludy, *Acta Chim. Hung. Tomus*, **44**, 61 (1965). Experimental details are not available.

[2] T. R. Govindachari, K. Nagarajan, S. Rajappa, A. S. Akerkar and V. S. Iyer, *Tetrahedron* **22**, 3367 (1966).

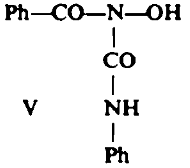
[3] cf. H. A. Staab, *Angew. Chem.* (Intern. Ed. Engl.) **1**, 351 (1962); L. A. Paquette, *J. Amer. Chem. Soc.* **87**, 5186 (1965).

[4] C. D. Hurd and L. Bauer, *J. Amer. Chem. Soc.* **76**, 2791 (1954).

Interestingly, when phenylisocyanate was heated with a solution of benzohydroxamic acid in the absence of a base, a significant quantity of a compound, $C_{14}H_{12}N_2O_3$, isomeric with IV was obtained. This gave a ruby-red ferric color and the IR spectrum showed bands at 1635 and 1720 cm^{-1}, leading to its identification as V, the hitherto unknown N-phenylcarbamoyl benzohydroxamic acid.[5,6] Compound IV was also isolable from this reaction.

Ph—CO—NH—O—CO—NH—Ph

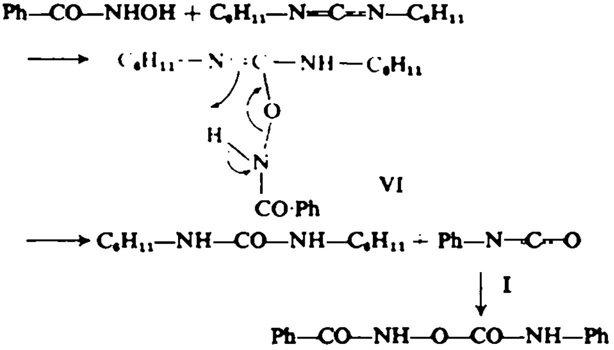
IV



V

$$\text{Ph—CO—N(—CO—NH—Ph)—OH}$$

It is interesting to speculate on how IV could be formed from benzohydroxamic acid (I) in the DCCI reaction. Addition of I to DCCI can be postulated to give an intermediate of the type VI, which could be expected to be an unstable species. Compound VI could undergo a Lossen-type rearrangement with DCU as the leaving group, to yield phenylisocyanate, which would be expected to undergo a fast reaction with I to account for the formation of IV. Alternatively, VI can be attacked by a second molecule of benzohydroxamic acid to produce the anhydride II, which can lose the stabilized benzohydroxamate ion in a Lossen-type rearrangement to produce phenylisocyanate and thence IV. At any rate, II is not an isolable intermediate.



VI

$$\mathrm{VI} \xrightarrow{\text{Ph—CONHOH}} \text{Ph—CO—NH—O—NH—CO—Ph} + \text{DCU}$$
$$\downarrow \ \mathrm{II}$$
$$\text{Ph—N=C=O} + \text{Ph—CO—NH—OH}$$
$$\downarrow \ \mathrm{IV}$$

The thermal decomposition of O-carbamoylhydroxamic acids to ureas is a well-documented phenomenon.[4,7,8] Pyrolysis of IV gave diphenylurea in near quantitative

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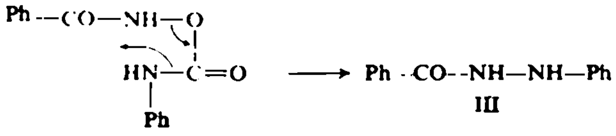
[5] It has been reported that there is no reaction between benzohydroxamic acid and phenylisocyanate in solution in the cold. C. D. Hurd, *J. Amer. Chem. Soc.* **45**, 1478 (1923).

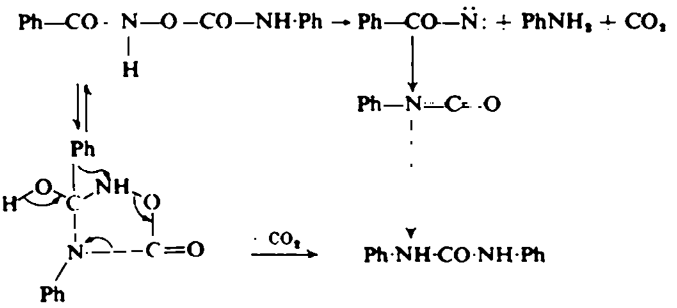
[6] For the addition of hydroxylamine to phenylisocyanate see G. Zinner, R. O. Weber and W. Ritter, *Arch. Pharm.* **298**, 869 (1965) and references cited therein.

[7] T. Mukaiyama and H. Nohira, *J. Org. Chem.* **26**, 782 (1961).

[8] M. A. Stolberg, R. C. Tweit, G. M. Steinberg and T. Wagner-Jauregg, *J. Amer. Chem. Soc.* **77**, 765 (1955).

yield, with only a trace of impurity showing up in TLC on silica plates. N-Benzoyl-N'-phenylhydrazine (III), a product possible by the mechanism shown was thus not an important side-product. The formation of diphenylurea itself has been considered in the literature to go in discrete steps. The authors, while postulating this mechanism, have noted that isocyanates were not isolable in this reaction.[7] It is tempting to speculate for this reason that the alternate cyclic mechanism shown below may be operative:





The benzohydroxamic acid 'anhydride' was reported to react with aniline to form III.[1] As this appeared to be a novel route for the conversion of amines to hydrazines, we have examined the reaction of IV with aniline in some detail. Under mild conditions, N,N'-diphenylurea was almost exclusively the only product formed. Reaction of O-phenylcarbamoylbenzohydroxamic acid (IV) with a molar equivalent of aniline at 160° for 5 min gave a complex mixture of products as revealed by the silica-plate TLC. The pattern was substantially the same, when ten molar equivalents of aniline were used and the reaction conducted at 160° for 15 min. The major product (~55%) was identified as diphenylurea. In addition, benzanilide (VII) and 1,4-diphenylsemicarbazide (VIII) were isolated in about 10% yield. Traces of N-benzoyl-N'-phenylhydrazine (III) could be detected on TLC plates, but III was not isolated. The formation of diphenylurea is most likely to occur in this reaction by Lossen rearrangement, followed by reaction of the resultant phenylisocyanate with aniline. The formation of VII and VIII is explained by the following scheme.

$$\underset{\text{IV}}{\text{Ph—CO—NH—O—CO·NH—Ph}} \xrightarrow{\text{Ph·NH}_2} \underset{\text{III}}{\text{Ph·CO—NH—NH—Ph}} + \text{CO}_2$$

$$\text{III} \xrightarrow{\text{Ph—NH}_2} \underset{\text{VII}}{\text{Ph—CO—NH—Ph}} + \text{Ph·NH·NH}_2$$

$$\text{Ph—NH—NH}_2 \xrightarrow{\text{Ph—NCO}} \underset{\text{VIII}}{\text{Ph·NH·NH·CO·NH·Ph}}$$

Thus the reaction of IV with aniline does lead to a derivative of phenylhydrazine, but its synthetic utility is doubtful, as the course of the reaction is not simple.

The reaction of cyclohexanecarbohydroxamic acid (IX) with DCCI at room temperature was likewise slow, and at the end of 46 hr led to DCU and about 40% yield of O-cyclohexane-carbamoyl-cyclohexanecarbohydroxamic acid (X). The product was identical with an authentic sample synthesized by the reaction of cyclohexyl isocyanate with cyclohexanecarbohydroxamic acid. Compound X was also isolated

$$\underset{\text{IX}}{C_6H_{11}CONHOH} \xrightarrow[C_6H_{11}-N=C=O]{\text{DCCI or}} \underset{\text{X}}{C_6H_{11}CONHOCONHC_6H_{11}}$$

in the Schotten-Baumann acylation of IX with *m*-trifluoromethylbenzoyl fluoride. In this reaction, X must have been formed by a facile Lossen rearrangement of the normal product XI to produce cyclohexylisocyanate which would then react with available IX to lead to the observed product.

$$\underset{\text{XI}}{C_6H_{11}CONHOCOC_6H_4(m\text{CF}_3)}$$

EXPERIMENTAL

M.ps are uncorrected. IR spectra refer to nujol mulls.

Reaction of benzohydroxamic acid with DCCI

Commercial benzohydroxamic acid was purified by washing with $NaHCO_3$aq and recrystallizing from EtOH. A soln of this benzohydroxamic acid (2·74 g; 0·02 mole) in dry THF (30 ml) was treated with DCCI (2·1 g; 0·01 mole) at room temp, and left for 60 hr. The DCU that separated, was filtered off, the filtrate evaporated to dryness at reduced press, the residue dissolved in AcOEt, filtered, concentrated and crystallization induced by addition of petrol. The crystals (1·15 g) were collected and recrystallized from AcOEt-petrol to afford O-phenylcarbamoylbenzohydroxamic acid, m.p. 169–170°, solidifying and remelting at ~220°. The IR spectrum was identical with that of an authentic sample. (Found: C, 65·93; H, 4·97. Calc. for $C_{14}H_{12}O_3N_2$: C, 65·62; H, 4·72%.)

Action of heat on O-phenylcarbamoylbenzohydroxamic acid

The compound was heated in an oil-bath at 180° for ½ hr. The crude solid showed a major spot on TLC corresponding to diphenylurea, and a faint trace of a slightly slower-moving material. This was not further investigated.

Reaction of O-phenylcarbamoylbenzohydroxamic acid with aniline

(a) *In the cold.* A mixture of O-phenylcarbamoylbenzohydroxamic acid (1·02 g; 0·004 mole) and aniline (0·37 g; 0·004 mole) in THF (20 ml) was left at room temp for 60 hr. The soln was then evaporated to dryness *in vacuo*, the residue taken in AcOEt, extracted with ice-cold 1 N NaOH, and then washed with water.

The organic layer was dried and evaporated. Crystallization of the residue from AcOEt-petrol afforded 100 mg of diphenylurea, m.p. 225°. Recrystallization from EtOH raised the m.p. to 241–243°, undepressed by admixture with an authentic sample.

The alkali layer was cooled, acidified and extracted with AcOEt to give, after crystallization, 0·5 g of recovered starting compound.

(b) *In boiling* THF. A soln of 1·3 g (0·005 mole) of the compound and 1·8 g (0·02 mole) aniline in THF (5 ml) was refluxed on the water-bath for 18 hr. During this time crystals separated. The mixture was cooled and acidified with HCl. The ppt was filtered off and washed with water. The crude product giving no ferric colour was then washed with dil NaOHaq and then with water and dried to yield 1·0 g practically pure diphenylurea, m.p. 238°, with slight softening above 160°.

(c) *At* 160°. (i) A mixture of 0·256 g (0·001 mole) O-phenylcarbamoylbenzohydroxamic acid and 0·09 g (0·001 mole) aniline was heated at 160° for 5 min. A violent reaction occurred and the initial melt solidified. The mixture was cooled, triturated with dil HCl, filtered and washed with water to give about 200 mg slightly tan-coloured solid, with a wide m.p. range between 140 and 220°. TLC on silica plate in chf–AcOEt (5:1) showed the product to be a mixture of 3 or 4 components, with N,N′-diphenylurea as the major product with some 1,4-diphenylsemicarbazide. (ii) A mixture of 0·256 g (0·001 mole) of the compound and 0·93 g (0·01 mole) aniline was heated at 160° for 15 min and worked up to yield about 0·2 g of a product mixture whose TLC pattern was essentially the same as that from the previous experiment, except that the proportion of 1,4-diphenylsemicarbazide seemed to have increased.

About 350 mg of the product from the two experiments was boiled with 10 ml chf and filtered to give as the insoluble part, 130 mg of diphenylurea, m.p. 240°. The filtrate was poured on to a column of 20 g silica gel (E. Merck, 0·05–0·2 mm particle size). The column was developed with chf and 8 fractions of approximately 15–20 ml were collected. Fractions 1, 2 and 8 had negligible solutes and were discarded. Fraction 3 on slow evaporation deposited crystals which on washing with ether became colourless. The product (20 mg) had m.p. 162–163° and was identified as benzanilide by determination of mixed m.p. with an authentic sample. Fraction 4 was likewise found to be benzanilide. Fraction 5 on TLC was found to consist of significant proportions of benzanilide and diphenylurea, a trace of N-benzoyl-N′-phenylhydrazine and an unidentified compound.

Fraction 6 on TLC was found to consist of significant amounts of diphenylurea and 1,4-diphenylsemicarbazide besides traces of N-benzoyl-N′-phenylhydrazine and an unidentified compound.

Fraction 7 on evaporation gave a solid, m.p. 177–178°, which was recrystallized to give 30 mg 1,4-diphenylsemicarbazide, m.p. 178–179°, undepressed by admixture with an authentic sample. IR bands at 1600, 1665, 3210, 3310 and 3345 cm^{-1}. (Found: C, 68·88, 68·73; H, 6·06, 5·92; N, 18·78, 18·75. Calc. for $C_{13}H_{13}N_3O$: C, 68·70; H, 5·77; N, 18·49%.)

Reaction of benzohydroxamic acid with phenylisocyanate

(a) A mixture of 1·4 g (10 mmole) of the hydroxamic acid and 1·2 g (10 mmole) of the isocyanate in 1 ml methylene chloride and 1 ml THF was heated on the water-bath for 1 hr. On cooling and adding hexane, 2·1 g of crude product was obtained, showing a ruby-red ferric colour. Recrystallization from AcOEt afforded 0·5 g N-*phenylcarbamoylbenzohydroxamic acid*, m.p.: softening at 146°, solidifying and finally melting at 230°; ruby-red ferric colour; IR bands at 1595, 1605, 1635, 1720, 3200 and 3240 cm^{-1}. (Found: C, 65·59, 65·42; H, 4·85, 4·86. $C_{14}H_{12}O_3N_2$ requires: C, 65·62; H, 4·72%.)

The mother liquor from the above crystallization deposited crystals on slow evaporation, which were filtered off and washed with hexane to give 0·8 g O-phenylcarbamoylbenzohydroxamic acid, m.p. 180° (d), solidifying and remelting at 240°; negative ferric colour.

(b) O-phenylcarbamoylbenzohydroxamic acid was also made according to the literature procedure[4] from sodium benzohydroxamate and phenyl isocyanate. It had IR bands at 1600, 1640, 1660, 1740, 1770, 3130, 3190, 3240 and 3305 cm^{-1}. (Found: C, 65·98; H, 5·00; N, 11·00. Calc. for $C_{14}H_{12}O_3N_2$: C, 65·62; H, 4·72; N, 10·93%.)

Reaction of cyclohexanecarbohydroxamic acid with DCCI

A soln of cyclohexanecarbohydroxamic acid (1·43 g; 0·01 mole) in DMF (5 ml) and chf (20 ml) was treated at room temp with DCCI (1·03 g; 0·005 mole) in 20 ml chf. At intervals, aliquots were withdrawn and the intensity of the DCCI band at 2100 cm^{-1} in the IR determined. After 46 hr, approximately ¼ of the DCCI was still present. At this stage the soln was evaporated to dryness. From the residue, by a process of fractional crystallization and rapid filtration through a silica-gel column, 550 mg pure O-cyclohexanecarbamoyl-cyclohexanecarbohydroxamic acid was obtained, m.p. 125–127°, solidifying and remelting at 215–220°. The IR spectrum was identical with that of an authentic specimen (see below).

Action of heat on O-*cyclohexanecarbamoyl-cyclohexane-carbohydroxamic acid*

The compound (100 mg) was heated above its m.p. for a few min in an oil-bath. Recrystallization of the solid from EtOH gave an almost quantitative yield of dicyclohexylurea, m.p. 232–233°, undepressed by admixture with an authentic sample. The two samples had superposable IR spectra.

Reaction of cyclohexanecarbohydroxamic acid with cyclohexylisocyanate

A mixture of 1·4 g (10 mmoles) of the hydroxamic acid and 1·3 g (10 mmoles) of the isocyanate in 5 ml chf containing 5 drops EtOH was warmed on the water-bath for a few min until dissolution occurred. The solvent was then mostly removed and the residual syrup left at room temp for 1 hr. Trituration with hexane induced crystallization. The solid was filtered off, washed with hexane and then with water. Recrystallization from CH_2Cl_2–hexane (without heating) afforded *O-cyclohexanecarbamoyl cyclohexanecarbohydroxamic acid* (2·2 g) melting at 126–128° (d), solidifying and remelting at 222°; negative ferric colour; IR bands at 1680, 1728 and 3200 cm^{-1}. (Found: C, 62·37; H, 8·46; N, 10·10. $C_{14}H_{24}O_3N_2$ requires: C, 62·66; H, 9·02; N, 10·44%.)

Reaction of cyclohexanecarbohydroxamic acid with m-*trifluoromethylbenzoyl fluoride*

A soln of 7·2 g (50 mmoles) cyclohexanecarbohydroxamic acid in 50 ml 2·2N NaOH was cooled and, with stirring, treated with 9·1 g (50 mmoles) of the acid fluoride added gradually during ½ hr. After stirring for 2 hr at room temp, 100 ml ether was added to the mixture. The aqueous layer was separated and acidified. The ppt was filtered off and washed with water, then with $NaHCO_3$aq and finally again with water. The bicarbonate extract on acidification gave 6·5 g *m*-trifluoromethylbenzoic acid, m.p. 104–105°. The bicarbonate-insoluble product was recrystallized from chf-hexane to give 3·4 g O-cyclohexane carbamoyl-cyclohexanecarbohydroxamic acid, m.p. 124–125° (d), solidifying and remelting at 220°. The same was identified with an authentic specimen by mixed m.p. and comparison of IR spectra.

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