[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

A Novel Rearrangement of Hydroxamic Acids Using Sulfonyl Chlorides

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Direct rearrangement of monohydroxamic acids without the necessity of isolating a dihydroxamic acid occurs on reaction of the monohydroxamic salts with arenesulfonyl chlorides. The product from benzohydroxamic acid is benzo-(phenylcarbamylhydroxamic) acid, that from hydrocinnamohydroxamic acid is hydrocinnamo-(phenethylcarbamylhydroxamic) acid, and that from succinohydroxamic acid (with benzenesulfonyl chloride) is 3-benzenesulfonoxy-5,6-dihydrouracil. The steps leading to the formation of these substances are discussed, and certain of their reactions are developed.

The Lossen rearrangement of a hydroxamic acid as usually performed involves acylation and heating a salt of the acyl derivative

$$\text{RCONHOH} \longrightarrow \text{RCONHOCOR}' \longrightarrow \text{RCONaOCOR}' \xrightarrow{-\text{R}'\text{COONa}} \text{RNCO} \xrightarrow{\text{H}_2\text{O}} \text{RNHCONHR (or RNH}_2\text{)}$$

Since this is usually performed in water, a urea or an amine is the anticipated product, but modifications are known wherein the intermediate isocyanate may be isolated, one such being a direct reaction of the hydroxamic acid with thionyl chloride.[2,3]

Acetic anhydride and benzoyl chloride are the conventional acylating agents used in the above process. No attempted acylation of a hydroxamic acid by any sulfonyl chloride has been reported. The present study bears on this problem.

The sodium salt of benzohydroxamic acid was treated with *p*-toluenesulfonyl chloride. Reaction was vigorous but the product was not the simple derivative I which would be formed by direct acylation.

$\text{PhCONHOSO}_2\text{C}_6\text{H}_4\text{CH}_3$ (I) $\qquad$ PhCONHOCONHPh (II)

The substance contained no sulfur, nor was it the original monohydroxamic acid since it no longer showed the ferric chloride color reaction. It did dissolve in alkali, however, as a dihydroxamic acid should, and heating the latter solution gave rise to *sym*-diphenylurea.

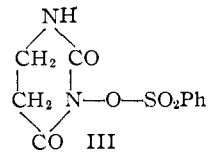
This and other evidence all support structure II for the compound in question. It may be assumed that I is formed initially but, being a much stronger acid than benzohydroxamic, it converts the sodium benzohydroxamate into benzohydroxamic acid. The new sodium salt of I then undergoes a spontaneous concerted cleavage and rearrangement into sodium toluenesulfonate and phenyl isocyanate. The latter is captured by the benzohydroxamic acid to yield benzo-(phenylcarbamylhydroxamic) acid (II). This is a novel variation of the Lossen rearrangement. Two features stand out: (1) a diacylhydroxylamine (II) is formed during a Lossen rearrangement, (2) a hydroxamic acid rearranges directly without the necessity of first preparing and isolating its acyl derivative.

Marquis[2] reported the preparation of II by interaction of benzohydroxamic acid and phenyl isocyanate in pyridine. His compound melted at 209–210° whereas our compound, which also gave the correct analysis, melted at 180° dec. We have no suggestion to explain this difference. Marquis obtained none of this compound during the synthesis of phenyl isocyanate by the action of thionyl chloride on benzohydroxamic acid. Hurd[4] found that when no solvent was used in the reaction of phenyl isocyanate and benzohydroxamic acid two moles of isocyanate were taken up, whereas if ethyl acetate was present as solvent no reaction occurred. Hence, it was interesting in the present work to discover the facile formation of II by reaction of phenyl isocyanate with sodium benzohydroxamate, suspended in cold chloroform.

Sodium hydrocinnamohydroxamate was next investigated. It behaved exactly as sodium benzohydroxamate toward *p*-toluenesulfonyl chloride. The product of interaction was hydrocinnamo-(phenethylcarbamylhydroxamic) acid, $\text{C}_6\text{H}_5\text{CH}_2\text{-CH}_2\text{CO-NH-O-CONHCH}_2\text{CH}_2\text{C}_6\text{H}_5$. As before, this compound was capable of undergoing a second rearrangement to yield *sym*-diphenethylurea, $\text{CO(NHCH}_2\text{CH}_2\text{Ph)}_2$.

The third monohydroxamic salt to be tested with an arenesulfonyl chloride was sodium succinohydroxamate. In its reaction with benzenesulfonyl chloride a crystalline product was obtained which differed from the preceding in that it did contain sulfur. As before, the first mole of benzenesulfonyl chloride to react promoted the new type of Lossen rearrangement. The crystalline product obtained was 3-benzenesulfonoxy-5,6-dihydrouracil (III) and these steps in its formation seem probable

$$(\text{—CH}_2\text{CONHONa})_2 \xrightarrow{\text{PhSO}_2\text{Cl}} \text{OCN—CH}_2\text{CH}_2\text{—CO—NHONa} \longrightarrow$$



III

Thus, only one of the two hydroxamic groups rearranged during the formation of III. In keeping with its structure as a triacylhydroxylamine, III did not give a color reaction with ferric chloride. The details of further rearrangement of III into ethylenediamine will be reported in a forthcoming paper by C. M. Buess and L. Bauer.

It is of interest to point out that the facile rearrangements in the sulfonyl series are related to the findings of Hauser and co-workers.[5] They prepared several derivatives of dibenzohydroxamic

(1) Holder of a fellowship sponsored by Swift and Company.

(2) R. Marquis, *Compt. rend.*, **143**, 1163 (1906).

(3) W. B. Dickey, *et al.*, U. S. Patent 2,394,597; *C. A.*, **40**, 2848 (1946).

(4) C. D. Hurd, THIS JOURNAL, **45**, 1478 (1923).

(5) W. B. Renfrow, Jr., and C. R. Hauser, *ibid.*, **59**, 2308 (1937); R. D. Bright and C. R. Hauser, *ibid.*, **61**, 618 (1939).

acid, $C_6H_5CONHOCOAr$, and found a direct relationship between the ease of these Lossen rearrangements and the strengths of the analogous carboxylic acids, ArCOOH. The stronger sulfonic acids, therefore, should promote a still faster Lossen rearrangement, and such was the observation in the present work.

Experimental

Benzo-(phenylcarbamylhydroxamic) Acid. Using Toluenesulfonyl Chloride.—Benzohydroxamic acid was converted into its sodium salt. Then a solution of 4.2 g. of *p*-toluenesulfonyl chloride in 10 ml. of chloroform was added dropwise during 15 minutes to a stirred, cold (10°) suspension of 3.2 g. of the salt in 40 ml. of chloroform. The reaction was vigorous. The mixture was stirred for 15 more minutes, then the solid was collected on a filter, washed with chloroform, ligroin and finally with water to remove sodium salts. That there was some unused benzohydroxamic acid was evident since the wash water gave a strong ferric chloride color test. The yield of insoluble product was 2.45 g. It crystallized from ethanol in flat needles. The compound gave no coloration with ferric chloride and it dissolved readily in cold alkali. It decomposed at about 180°, then resolidified and melted to a clear meniscus at 232°. The second m.p. was that of *sym*-diphenylurea. A smaller yield (1.3 g.) was obtained by refluxing for one hour after the initial 15 minutes at 10°.

Anal. 180° product (by C. White, J. Sorensen). Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.72; N, 10.9. Found: C, 65.8; H, 4.85; N, 10.9.

Using Phenyl Isocyanate.—One ml. of phenyl isocyanate was added to an ice-cold suspension of 1.6 g. of sodium benzohydroxamate in 20 ml. of chloroform. The temperature immediately rose to 20°. After half an hour and recooling to 5°, 0.5 ml. more phenyl isocyanate was added. The mixture was processed 30 minutes later by adding 1 ml. of acetic acid and 20 ml. of petroleum hexane. The solid was collected, rinsed free of inorganic salts and crystallized from 95% ethanol (20 ml.); yield 1.2 g., and another 0.4 g. from the filtrate by precipitating it with an equal volume of water. The same decomposition and fusion behavior was shown as was described above.

Rearrangement.—A solution of 0.97 g. of this compound in water containing 0.14 g. of sodium hydroxide was heated to 100° for 30 minutes. *sym*-Diphenylurea separated promptly; yield 0.58 g., m.p. 232°. One recrystallization from ethanol brought the m.p. (and mixture m.p.) to 235°.

Hydrocinnamohydroxamic Acid and Its Benzoyl Derivative.—Hydrocinnamohydroxamic acid was prepared by reaction of equimolar portions of ethyl hydrocinnamate, hydroxylamine and sodium ethoxide, with ultimate acidification by carbon dioxide. Crystallization from benzene yielded lustrous plates, m.p. 82° (lit.,[6] 78°). The benzoyl derivative, prepared by Schotten–Baumann procedure and crystallized from benzene, melted at 131° which agrees with Bright and Hauser's value[5] of 132–133° but is noticeably higher than the 117° reported by Thiele and Pickard.[6] It underwent a satisfactory rearrangement into *sym*-diphenethylurea of m.p. 137° (lit.[6] 137°).

Hydrocinnamo-(phenethylcarbamylhydroxamic) Acid.—Sodium hydrocinnamohydroxamate (2.0 g.) was treated in chloroform suspension (20 ml.) at 5–10° with *p*-toluenesulfonyl chloride in the manner detailed above for the benzohydroxamic salt. After an hour of reaction time the mixture was diluted with an equal volume of petroleum hexane and filtered. The solid was washed with hexane and with water; yield 0.8 g. After crystallization from benzene it melted with gas evolution at 133–134°.

Anal. (by White and Sorensen). Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.45; N, 8.97. Found: C, 69.2; H, 6.53; N, 8.98.

Rearrangement.—The acid (1.06 g.), when dissolved in cold sodium hydroxide solution (0.13 g. in 3.5 ml. of water) and heated at 100° for half an hour, gave rise to 0.82 g. of *sym*-diphenethylurea which separated during this period. Crystallization from 2-propanol produced lustrous plates, m.p. 137°.

3-Benzenesulfonoxy-5,6-dihydrouracil.—To a rapidly stirred suspension of 2.4 g. of sodium succinohydroxamate in 25 ml. of chloroform at 25° was added dropwise during about half an hour a solution of benzenesulfonyl chloride in toluene (5.3 g. in 10 ml.). Addition at this rate kept the temperature nearly constant. After 45 minutes, the mixture was diluted with two volumes of hexane. The solid was collected, triturated with water containing 1% of acetic acid (15 ml.), and the mixture filtered; yield 0.9 g., after one crystallization from 2-propanol, m.p. 158–160°. Lustrous plates were obtained after recrystallization from 2-propanol or water.

The substance was soluble in hot water or ethanol and insoluble in chloroform. It dissolved in warm alkali. It gave no coloration with ferric chloride solution. It depressed the m.p. of N,N'-ethylenedibenzenesulfonamide (m.p. 168°).

Anal. (by White and Sorensen for C, H, N and Micro-Tech Lab. for S). Calcd. for $C_{10}H_{10}N_2O_5S$: C, 44.42; H, 3.73; N, 10.36; S, 11.86. Found: C, 44.75; H, 3.63; N, 9.93; S, 12.25.

(6) J. Thiele and R. H. Pickard, *Ann.*, **309**, 197 (1899).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO., DECATUR, ILLINOIS]

Bis Ammonium Salts. Derivatives of Some Carboline and Related Heterocyclic Bases[1]

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A group of bis salt derivatives of some relatively large heterocyclic bases, twinned by an alkylene chain (4 to 10 carbons) attached to nitrogen, has been prepared. The bases involved include substituted β-carbolines, α-carboline, yohimbine and tetrahydroberberine. Several methods have been employed for the preparation of the β-carboline derivatives. Many of the salts produced transitory hypotensive effects; a few exhibited strong curare-like activity.

As a part of an extensive examination of the effects of variations in structure of bis ammonium salts on biological properties,[2] a group of derivatives of some carbolines, yohimbine and tetrahydroberberine, in which these large, relatively flat structures are twinned by alkylene bridges through a ring nitrogen, has been prepared. Variations in size, flatness, electrostatic charge distribution, steric hindrance about bonding functions, and distance between such functions have been introduced.[3a,b]

(1) Presented in part before the Division of Medicinal Chemistry at the 124th National Meeting of the American Chemical Society, Chicago, Illinois, September 6–11, 1953.

(2) Preceding paper, C. J. Cavallito A. P. Gray and E. E. Spinner, THIS JOURNAL, **76**, 1862 (1954).

(3) (a) The effects of variations of biological activity with distances between ionic groups have been reported by a number of investigators. *Cf.* R. B. Barlow and H. R. Ing, *Nature*, **161**, 718 (1948); *Brit. J. Pharmacol.*, **3**, 298 (1948); W. D. M. Paton and E. J. Zaimis, *Nature*, **161**, 718 (1948); H. O. J. Collier, *Brit. J. Pharmacol.*, **7**, 392 (1952); D. Bovet, *Ann. N. Y. Acad. Sci.*, **54**, 407 (1951). See also H. King, E. M. Lourie and W. Yorke, *Ann. Trop. Med.*, **31**, 435 (1937); *ibid.*, **33**, 289 (1939). (b) The effect of flatness and van der Waals bonding on antimicrobial action has been elegantly demonstrated; *cf.* A. Albert, S. D. Rubbo and M. I. Burvill, *Brit. J. Exptl. Path.*, **30**, 159 (1949).