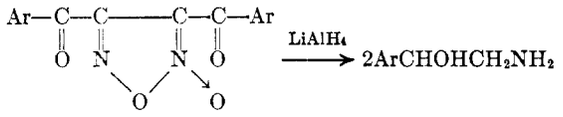
TABLE I

Ketone (ArCOCH$_3$)	Diaroylfurazan oxide: Yield, %	Mp, °C (found)	Mp, °C (reptd)	N-Benzamide, derivative of redn prod, ArCHOHCH$_2$NHCOC$_6$H$_5$: Yield, %	Mp, °C (found)	Mp, °C (reptd)
Ar = phenyl	70	85.5–86.5	86–87[a]	43	148.5–150	149.5–150[c]
Ar = *p*-anisyl	73	140–140.5	139[b]	35	152.5–153	152.0[d]
Ar = 2-thienyl	72	114–115	New	58	122–123	121–122[e]
Ar = 1-naphthyl	48	151–152	New	56	145–146.5 (acetamide derivative)	145–146[f]

[a] A. F. Holleman, *Ber.*, **20**, 3360 (1887); **21**, 2838 (1888). [b] A. F. Holleman, *Rec. Trav. Chim*, **10**, 216 (1891) [c] S. M. Gordon, *J. Am. Pharm. Assoc.*, **17**, 1195 (1928). [d] V. Evdokimoff, *Gazz. Chim. Ital.*, **81**, 725 (1951). [e] C. F. Huebner, P. A. Diassi, and C. R. Scholz, *J. Org. Chem.*, **18**, 21 (1953). [f] A. Pictet and B. Manevitch, *Arch. Sci. Phys. Nat.*, **35**, 40 (1913).

We considered that the reduction of a molecule of diaroylfurazan oxide with lithium aluminum hydride might lead to two molecules of the corresponding β-aryl-β-hydroxyethylamine. Should the reaction produce the substituted ethanolamine in good yield, it would afford a simple, two-step procedure for obtaining these physiologically active types from methyl ketones. This has proved to be the case.



The amines appeared to be the only organic product. They were converted into benzamide or acetamide derivatives for identification.

Four typical aryl methyl ketones were converted to the diaroylfurazan oxides which were reduced to the amines. The results are summarized in Table I.

Experimental Section

Reaction of Methyl 2-Thienyl Ketone with Nitric Acid.—To a mixture of 50 ml of nitric acid (sp gr 1.42) and 100 ml of glacial acetic acid containing a small amount of sodium nitrite, was added, over a period of 10 min, 31.6 g (0.25 mole) of methyl 2-thienyl ketone dissolved in 50 ml of glacial acetic acid. The solution became pale yellow after addition but slowly darkened to a deep amber color after 2.5 hr. The temperature rose slowly from 30 to 50° over a 3-hr period. No external cooling was required. The mixture was then allowed to stand overnight. The resulting mass of needlelike crystals was filtered out, washed with cold ethanol, and air dried. A further yield of crystals could be obtained by pouring the filtrate over 200 g of ice; however, much by-product was mixed with the furazan oxide and purification was difficult. The furazan oxide was recrystallized from ethanol–ethyl acetate and the pale yellow product melted at 114–115°. The yield was 72%.

Anal. Calcd for $C_{12}H_6N_2O_4S_2$: C, 47.05; H, 1.97; N, 9.15. Found: C, 47.17; H, 1.99; N, 9.19.

Similar runs were carried out with acetophenone and *p*-methoxyacetophenone. Both furazans have been previously reported as indicated in Table I. In the case of the reaction of acetophenone, the temperature of the reaction mixture rose to 90° at which point the mixture was cooled to prevent further temperature rise.

1-Acetylnaphthalene was likewise converted into furazan oxide. In the first trial the temperature was raised to 86° and in the second to 51°. No furazan oxide could be isolated but a heavy, oily liquid, which set up as a glassy solid on cooling, was formed. In the third trial the temperature was held below 35°. After standing overnight a yellow, crystalline mass of furazan oxide had separated. No furazan oxide could be isolated from the filtrate.

Anal. Calcd for $C_{24}H_{14}N_2O_4$: N, 7.10. Found: N, 7.00, 7.22.

Preparation of 2,4-Dinitrophenylhydrazone of 3,4-Bis(2′-thienoyl)furazan Oxide.—Hayes and O'Keefe[5] had carried out the preparation of a 2,4-dinitrophenylhydrazone of 3,4-di(2-furoyl)furazan oxide in which they use iodine to catalyze the reaction. To 3.0 g of furazan in 100 ml of 95% EtOH was added several small crystals of iodine, 4.0 g of 2,4-dinitrophenylhydrazine, and 5 ml of concentrated HCl. The mixture was heated under reflux for 1 hr. The resulting, orange powder was filtered off and recrystallized from ethanol–ethyl acetate mixture. The product melted with decomposition at 180.5–182°. Although Hayes and O'Keefe obtained the bis-2,4-dinitrophenylhydrazone of the 2-furoyl compound, only one molecule of 2,4-dinitrophenylhydrazine was taken up by the 2-thienoyl compound.

Anal. Calcd for $C_{18}H_{10}N_6O_7S_2$: C, 44.44; H, 2.07; N, 17.27. Found: C, 44.70; H, 2.14; N, 17.60.

Reduction of Furazan Oxides with Lithium Aluminum Hydride.—A solution of the furazan oxide in 1,4-dioxane was prepared. In the typical case, 1.53 g (0.005 mole) of 3,4-bis(2′-thienoyl)furazan oxide was dissolved in 25 ml of dioxane and mixed with 25 ml of anhydrous ether. The solution was added dropwise to a well-stirred mixture of 0.88 g of $LiAlH_4$ suspended in 100 ml of dry ether. A vigorous reaction resulted in a heavy, white precipitate. Excess $LiAlH_4$ was destroyed with moist ether and water. The ether layer was separated and the water layer was twice extracted with 50-ml portions of ether. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed by distillation under reduced pressure. The oily ethanolamine was not crystallized but was converted into the benzamide.[6] Data from individual reactions are given in Table I.

Registry No.—$C_{12}H_6N_2O_4S_2$, 7733-96-2; $C_{24}H_{14}N_2O_4$, 7757-40-6.

Acknowledgment.—The authors wish to thank the National Science Foundation for a Research Participation grant for the summer of 1966 which made this study possible.

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Reduction of Silyl Esters of Amino Acids[1]

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Received November 28, 1966

A number of methods are available for the reduction of optically active amino acids to the corresponding optically active amino alcohols, but none is entirely satisfactory for use on a preparative scale. Direct reduction of the free amino acids with lithium aluminum

(1) This investigation was supported by a research grant (CA-06695) from the U. S. Public Health Service, National Cancer Institute, and by a fellowship grant (F-66-UB-6) from the United Health Foundation of Western New York.

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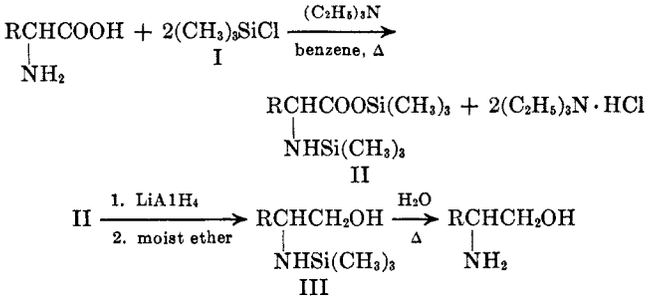
hydride is not feasible on a large scale because of the low solubility of free amino acids in ether and because of the subsequent formation of insoluble metal complexes which prevent the reaction to proceed to completion. With mixtures of ether and tetrahydrofuran[3] or hot tetrahydrofuran alone,[4] reduction was accomplished only with small quantities of amino acids. More useful methods involve the reduction of the organic solvent soluble N-acyl and/or O-alkyl (ester) derivatives of the amino acids.[3,5-14] Except in the case of the N-benzoyl derivatives[9,10,13] where the resulting N-benzylamino alcohols can be debenzylated by catalytic hydrogenolysis,[13] the removal of the N-protecting groups requires undesirable drastic conditions. While the ethyl or methyl esters of amino acids can be smoothly reduced to the corresponding amino alcohols,[6,11,13] the N-unprotected esters are not always obtained in high yield. Liberation and isolation of the free esters from their amine salts requires an additional cumbersome step,[6] or, if the latter are used directly,[14] they react exothermically while using up a second equivalent of the metal hydride.

Birkofer and Ritter[15] and Rühlmann[16] reported the synthesis of the trimethylsilyl esters of N-trimethylsilylamino acids, with the use of hexamethyldisilazane and N-trimethylsilyldiethylamine, respectively. These esters are obtained in good yields without racemization,[17] they are easily purified by distillation, are highly soluble in aprotic solvents, and, most importantly, their trimethylsilyl groups can be quantitatively removed by hydrolysis in water, under neutral conditions. We wish to report the successful reduction of these silyl esters to the corresponding optically active amino alcohols.

Birkofer and Ritter pointed out[15,17] that trimethylchlorosilane (I) cannot be used for the silylation of free amino acids. We found that amino acids do not, indeed, react with I (in the presence of triethylamine) at room temperature but the reaction proceeded satisfactorily in refluxing benzene. Under the latter conditions, the amino acids were essentially quantitatively converted within 6 hr to the corresponding disilyl derivatives (II). Reduction of the latter with lithium aluminum hydride in ether proceeded smoothly at room temperature. If the intermediate complex and excess reagent were decomposed with moist ether at 0–5°, the N-trimethylsilylamino alcohol (III) could be isolated from the ether extract, while decomposition of the complex in excess amounts of water at 25° gave the free amino alcohol directly. We found that, particularly in the case of water-soluble amino alcohols, it was advantageous to isolate III by ether extraction, and then hydrolyze the latter by heating with a twofold excess of water. The free amino alcohol could then be isolated in excellent yield by saturation of the hydrolysis mixture with potassium carbonate and subsequent extraction with ether.



The amino alcohols prepared by this method from both L-alanine and L-phenylalanine gave optical rotation values slightly above, while that from L-proline slightly below, the highest corresponding values reported in the literature. Thus, there is no evidence of racemization in the course of the above procedure. The reactions reported here were carried out with 0.1–0.2 mole of the amino acids without difficulty, and there is no apparent reason to prevent the application of this procedure to much larger quantities.

Experimental Section

Silylation of Amino Acid.—The amino acid (0.1 mole) was suspended in 400 ml of benzene and to this was added 69.3 ml of triethylamine (0.50 mole) and 23.8 g of trimethylchlorosilane (0.22 mole). The mixture was refluxed while stirring vigorously under anhydrous conditions for 6 to 12 hr. The precipitated triethylamine hydrochloride was filtered, the filtrate was dried with anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. The resulting liquid residue showed the expected infrared absorption bands (SiC at 1245–1250, C=O at 1740 cm^{-1}) for the disilyl derivatives (II) and was used without distillation in the subsequent reduction step. It is essential that the trimethylsilyl esters be kept free from moisture.

Preparation of Amino Alcohol.—The above product (II) was dissolved in 200 ml of ether and slowly added (over 2 hr) to a well-stirred suspension of lithium aluminum hydride (0.10 mole) in 200 ml of ether at 0°. The mixture was then slowly brought to room temperature, held there for 2 hr, and then refluxed for another 2 hr. The mixture was cooled in an ice bath, and 350 ml of moist ether was added over 1 hr. The solid was filtered off and washed with ether; the combined ether extracts were dried with K_2CO_3 and the solvent was evaporated under reduced pressure. The residue which showed the expected infrared absorption bands (SiC at 1250, OH at 3300 cm^{-1} and absence of C=O) for the silylamino alcohol (III), was added to 3.6 ml of water (0.20 mole) and heated on a steam bath for 1 hr. The aqueous mixture was cooled to room temperature, then saturated with anhydrous K_2CO_3 and extracted with ether. After evaporation of the solvent *in vacuo*, the residue was purified by distillation or crystallization. Over-all yields and physical data of the amino alcohols and their oxalate salts are given below.

L-Alaninol was obtained in 79% yield, bp 59–60° (5 mm), $[\alpha]^{22}D$ +20.8° (*c* 4.0, ethanol) [lit.[4] bp 85° (10 mm), $[\alpha]^{17}D$ +20.3° (ethanol)]; the oxalate (netural) had mp 165–166° (lit.[4] 165–166°).

L-Phenylalaninol was obtained in 70% yield, mp 91–92°, $[\alpha]^{22}D$ −24.8° (*c* 3.0, ethanol) [lit.[13] mp 90–91°, $[\alpha]^{23}D$ −24.7° (*c* 3.1, ethanol)]; the oxalate (acid) had mp 175–176° (lit.[13] 177°).

L-Prolinol was obtained in 58% yield, bp 64–65° (1.25 mm), $[\alpha]^{22}D$ +25.2° (*c* 1.7, 0.2 *N* HCl) [lit.[14] bp 98° (10 mm), $[\alpha]^{23}D$ +27.4 (*c* 1.1, 0.2 *N* HCl)]; the oxalate (neutral) had mp 159°, $[\alpha]^{22}D$ +20.1° (*c* 2.0, H_2O) [lit.[4] mp 159–160°, $[\alpha]^{18}D$ +21.5° (*c* 2.0, H_2O)].

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