decitol[11] would be expected to oxidize via malondialdehyde, or hydroxymalondialdehyde, this reaction should be considered in any interpretation of the periodate oxidation of these compounds. For example, if the simplifying assumption is made that the rate of cleavage of glycol carbon bonds is equivalent to the rate of cleavage of hydroxyaldehyde carbon bonds, 5.5% of the carbon in dodecitol should appear as carbon dioxide. Wolfrom found a consumption of 11.5 mole of periodate instead of the theoretical values of eleven and only 9.5 mole of formic acid instead of 10. His failure to find carbon dioxide is understandable if a terminal assay of the acidic solutions was used. Our results on polyvinylene glycol and its vinyl alcohol copolymer are consistent with this interpretation of the periodate oxidation and will be published elsewhere.

EXPERIMENTAL

All periodate oxidations were carried out in the dark at room temperature using paraperiodic acid (H_5IO_6) or occasionally sodium meta periodate ($NaIO_4$). Sufficient sample to reduce 1 mmol. of oxidant was weighed into a 100 ml. volumetric flask, and enough .05–.1M oxidant solution to give 1.25 mmol. of oxidant was added and the flask was diluted to the mark. At the same time a blank containing the identical amount of oxidant was prepared. After the sample was observed to be dissolved, aliquots were withdrawn at intervals for titration. This procedure was followed in all cases except for the oxidations of mannitol and glycerol where the initial oxidant concentrations were .0045 and .01M respectively, and consequently less sample was used.

Oxidant consumption was determined by the method of Malaprade.[12] A 5 ml. aliquot was added to a 125 ml. Erlenmeyer flask containing a few crystals of iodate-free potassium iodide in 20 ml. of distilled water. Two drops of 6N hydrochloric acid were then added and the liberated iodine was immediately titrated with .02N thiosulfate to a Thyodene (Fisher Scientific Co. substitute for starch indicator) endpoint. The difference between the titer of the blank and the sample, $\bar{D}$, is a measure of the oxidant consumed by the sample; Periodate consumed = $10\ \bar{D}\ N_{(thio)}$.

The formic acid liberated during the oxidation was estimated by the total acidity of the solutions according to the iodometric procedure of Hallsall, Hirst and Jones.[2] The iodometric procedure was checked by titrations with 0.02N barium hydroxide solutions to a phenophthalein endpoint and good agreement was obtained.

A terminal assay of the carbon dioxide evolved in periodic acid oxidations was performed using the high vacuum technique of Levy and Szwarc.[13,14]

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Preparation and Properties of N^{α}-Acyl Lysine Esters[1]

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The syntheses of the free bases, N^{α}-tosyl-L-lysine methyl ester, m.p. 93–95°, and N^{α}-tosyl-DL-lysine benzyl ester, m.p. 104°, are described. A number of other N^{α}-acyl lysine esters, obtained as hygroscopic hydrochlorides or hydrobromides, have also been prepared.

It has recently been suggested that the proximate metabolite of the carcinogen *N*-(2-fluorenyl)acetamide which is bound to proteins is the *o*-quinone imine, 1,2-fluorenoquinone-2-imine,[2,3] and that the ϵ-amino group of lysine is implicated in the binding reaction.[4] N^{α}-acyl lysine esters in which the ϵ-amino group is free and the carboxyl and the α-amino group are protected, were therefore desired for a study of their reactions with model quinone imides.[5] A search of the literature showed that such N^{α}-acyl lysine esters have not been prepared and we have therefore undertaken the synthesis of a number of these lysine derivatives.[6] Since recent evidence indicates that peptide linkages involving

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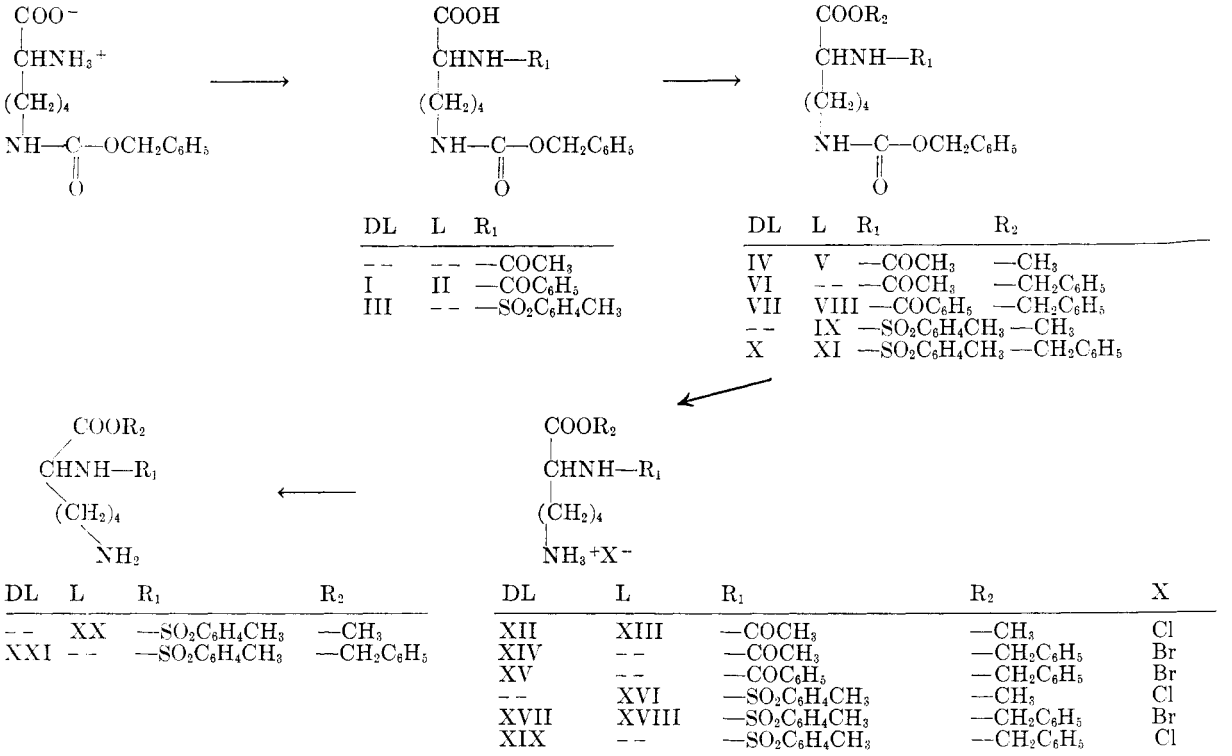
(6) While this work was in progress, the synthesis of N^{α}-tosyl-L-lysine ethyl ester hydrochloride and N^{α}-tosyl-L-lysine benzyl ester hydrochloride were reported (D. L. Swallow, I. M. Lockart, and E. P. Abraham, *Biochem. J.*, **70**, 359 (1958)).

the ε-amino group of lysine are found in naturally occurring peptides[7] and in collagen,[8] these lysine derivatives would also be useful for the synthesis of ε-lysyl peptides.

The compounds prepared in the course of these studies and the synthetic routes are indicated in Fig. 1. The free bases, N^{α}-tosyl-L-lysine methyl ester (XX) and N^{α}-tosyl-DL-lysine benzyl ester (XXI) were obtained in crystalline form, but we have been unable to crystallize N^{α}-tosyl-L-lysine benzyl ester. The preparation of a number of other N^{α}-acyl lysine esters, obtained as the hydrochlorides or hydrobromides, is also described. These compounds (XII, XIII, XIV, and XV) are hygroscopic oils or hygroscopic semisolids. It is of interest that most of the compounds of the DL series obtained in these studies have higher melting points than the corresponding L isomers. This indicates that these members of the DL series are racemic compounds rather than racemic mixtures.[9]



DL	L	R_1
--	--	$-COCH_3$
I	II	$-COC_6H_5$
III	--	$-SO_2C_6H_4CH_3$

DL	L	R_1	R_2
IV	V	$-COCH_3$	$-CH_3$
VI	--	$-COCH_3$	$-CH_2C_6H_5$
VII	VIII	$-COC_6H_5$	$-CH_2C_6H_5$
--	IX	$-SO_2C_6H_4CH_3$	$-CH_3$
X	XI	$-SO_2C_6H_4CH_3$	$-CH_2C_6H_5$

DL	L	R_1	R_2
--	XX	$-SO_2C_6H_4CH_3$	$-CH_3$
XXI	--	$-SO_2C_6H_4CH_3$	$-CH_2C_6H_5$

DL	L	R_1	R_2	X
XII	XIII	$-COCH_3$	$-CH_3$	Cl
XIV	--	$-COCH_3$	$-CH_2C_6H_5$	Br
XV	--	$-COC_6H_5$	$-CH_2C_6H_5$	Br
--	XVI	$-SO_2C_6H_4CH_3$	$-CH_3$	Cl
XVII	XVIII	$-SO_2C_6H_4CH_3$	$-CH_2C_6H_5$	Br
XIX	--	$-SO_2C_6H_4CH_3$	$-CH_2C_6H_5$	Cl

Fig. 1. N^{α}-acyl lysine esters and intermediates

EXPERIMENTAL

DL- and L-lysine were obtained from the Mann Research Laboratories, New York, N. Y. N^{ϵ}-carbobenzoxy lysine (DL or L) was prepared by a modification[10] of the procedure of Neuberger and Sanger.[11] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Amino nitrogen was determined manometrically.[12] The petroleum ether used had a boiling range of 30–60°.

N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-DL-lysine (I). Crude I was obtained by benzoylation[13] of 3.00 g. of N^{ϵ}-carbobenzoxy-DL-lysine. The crude oil was purified by two extractions with 25 ml. of boiling water. The wash water was discarded and the residual oil was taken up in 20 ml. of *N* NaOH. The mixture was filtered and the filtrate was acidified with 6*N* HCl. The oil which precipitated solidified on standing overnight. The material was collected and washed with water. After drying over phosphoric anhydride *in vacuo* there was obtained 3.70 g. of I, m.p. 130–131°, 90% yield. I was recrystallized from benzene; m.p. 132–133° (reported[14] m.p. 130°).

N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-L-lysine (II). Three g. of N^{ϵ}-carbobenzoxy-L-lysine (10.7 mmol.) was benzoylated[13] yielding 4.6 g. of a gummy product after drying *in vacuo* over phosphoric anhydride. The crude product was washed with petroleum ether, dissolved in a small amount of hot acetone and the solution was filtered. The filtrate was heated to boiling and water was added dropwise to incipient turbidity. Upon standing, the compound precipitated as an oil which crystallized when left at 4° for 2 days, yielding 2.5 g. of II m.p. 132–133°, after drying *in vacuo* over sulfuric acid; 61% yield. II was recrystallized from benzene; m.p. 132–133°. For analysis, II was dried *in vacuo* at 78°. $[\alpha]_D^{23}$ +2.5° (*c* 2.4, 0.1*N* NaOH).

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.29; N, 7.29. Found: C, 65.5; H, 6.23; N, 7.18.

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*N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-*DL*-lysine* (III). III was prepared by the procedure reported by Swallow *et al.*[6] for the synthesis of the corresponding L-isomer. The yield was 86%; m.p. 130–132°. III was recrystallized from benzene[15] and dried *in vacuo* at 78°; m.p. 132–133°.

Anal. Calcd. for $C_{21}H_{26}N_2O_6S$: C, 58.1; H, 6.03; N, 6.50. Found: C, 58.1; H, 6.00; N, 6.70.

*N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-*DL*-lysine methyl ester* (IV). (a) By esterification of N^{α}-acetyl-N^{ϵ}-carbobenzoxy-DL-lysine. N^{α}-acetyl-N^{ϵ}-carbobenzoxy-DL-lysine,[16] 3.72 g. (11.5 mmol.), m.p. 119–121°, was suspended in 150 ml. of benzene and diazomethane[17] was passed through the solution. When all of the solid had dissolved and the yellow color of the diazomethane persisted, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The resulting oil crystallized upon cooling and addition of ether to give 3.55 g. of IV after drying *in vacuo* over calcium chloride; m.p. 78–80°; 85% yield. Recrystallization from benzene-petroleum ether gave pure IV, m.p. 81–83°, after drying *in vacuo* over paraffin chips.

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.19; N, 8.33. Found: C, 60.8; H, 7.15; N, 8.55.

(b) IV was obtained in lower yields by methanolysis[18] of N^{α}-carboxy-N^{ϵ}-carbobenzoxy-DL-lysine anhydride[19] followed by acetylation of the resulting oil. The product melted at 81–82° and the mixed melting point with authentic IV was not depressed.

*N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-*L*-lysine methyl ester* (V). N^{ϵ}-carbobenzoxy-L-lysine, 0.850 g. (3.1 mmol.), m.p. 247–250°, was acetylated according to Neuberger and Sanger.[11] The oil, which was obtained when the reaction mixture was acidified with concentrated hydrochloric acid, solidified on cooling and scratching to give 0.503 g. of N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine after drying *in vacuo* over calcium chloride; m.p. 85–87°; 52% yield. In large scale preparations yields ranging from 66 to 77% were realized. Solution of this product in ethyl acetate and precipitation with petroleum ether gave amorphous N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine, m.p. 82–84°.

Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.6; H, 6.88; N, 8.69. Found: C, 59.6; H, 6.93; N, 8.88.

N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-L-lysine, 0.50 g. (1.55 mmol.), m.p. 82–84°, was hydrogenolyzed[11] to give 0.27 g. of $N\alpha$-acetyl-L-lysine.[11] m.p. 250° (dec.), $[\alpha]_D^{20}$ +4.4° (*c* 2.4, water); 93% yield.

Crystalline N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine, m.p. 107–110°, was obtained in poor yield by recrystallization of the amorphous product from chloroform–petroleum ether. Neuberger and Sanger[11] reported a melting point of 105–115° for N^{α}-acetyl-N^{ϵ}-carbobenzoxy-L-lysine.

N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-L-lysine, 0.52 g. (1.62 mmol.), m.p. 85–87°, was esterified with diazomethane in benzene as described for IV to yield 0.322 g. of V, m.p. 66–67°, 62% yield. In large scale preparations, yields ranging from 80 to 90% were realized. After recrystallization from ether or ether–petroleum ether, V melted from 67–68°; $[\alpha]_D^{23}$ −23.7° (*c* 3.0, methanol).

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.19; N, 8.33. Found: C, 60.9; H, 7.10; N, 8.43.

*N^{α}-Acetyl-N^{ϵ}-carbobenzoxy-*DL*-lysine benzyl ester* (VI). N^{α}-acetyl-N^{ϵ}-carbobenzoxy-DL-lysine,[16] 7.72 g. (24 mmol.), was suspended in 150 ml. of benzene. Benzyl alcohol, 4.0 ml. (39 mmol.) and 0.36 g. of *p*-toluenesulfonic acid were added and the mixture was refluxed for 17 hr., the water formed being removed azeotropically.[20] The reaction mixture was cooled, filtered, and extracted twice with 50 ml. of 5% sodium bicarbonate. After drying over anhydrous sodium sulfate, the benzene layer was taken to dryness under reduced pressure (30–40°). The resulting oil crystallized when triturated with petroleum ether, yielding 9.00 g. of VI, m.p. 86–87°, 91% yield. VI was recrystallized from benzene–petroleum ether; m.p. 87–88°.

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 67.0; H, 6.84; N, 6.79. Found: C, 67.0; H, 7.05; N, 6.95.

*N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-*DL*-lysine benzyl ester* (VII). I, 2.40 g. (6.25 mmol.), was esterified in 600 ml. of benzene containing 1.0 ml. of benzyl alcohol (9.6 mmol.) and 0.25 g. of *p*-toluenesulfonic acid by the above procedure to give 2.44 g. of VII, m.p. 92–95°, 82% yield. VII was recrystallized from benzene-petroleum ether (activated charcoal added); m.p. 94–95°.

Anal. Calcd. for $C_{28}H_{30}N_2O_5$: C, 70.9; H, 6.37; N, 5.91. Found: C, 71.0; H, 6.38; N, 6.02.

*N^{α}-Benzoyl-N^{ϵ}-carbobenzoxy-*L*-lysine benzyl ester* (VIII). One g. of II (2.61 mmol.) in 250 ml. of benzene containing 0.40 ml. of benzyl alcohol (3.87 mmol.) and 0.10 g. of *p*-toluenesulfonic acid was esterified by the above procedure to give 1.11 g. of VIII, m.p. 93–97°, 90% yield. VIII was recrystallized from benzene–petroleum ether; m.p. 94–95°. $[\alpha]_D^{23}$ +2.2° (*c* 2.5, methanol).

Anal. Calcd. for $C_{28}H_{30}N_2O_5$: C, 70.9; H, 6.37; N, 5.91. Found: C, 71.0; H, 6.34; N, 6.01.

*N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-*L*-lysine methyl ester* (IX). N^{α}-tosyl-N^{ϵ}-carbobenzoxy-L-lysine,[6] 1.50 g. (3.34 mmol.), m.p. 127–128°, was suspended in 75 ml. of benzene and esterified with diazomethane as described above. Evaporation of the benzene under reduced pressure gave an oil which was taken up in 5 ml. of benzene. Addition of petroleum ether and cooling gave 1.32 g. of crystalline material, m.p. 72–76°, 88% yield. In another run, the yield of IX, m.p. 76–78°, was 88%. The crude IX, m.p. 72–76°, was recrystallized twice from benzene–petroleum ether to give pure IX, m.p. 78–80°; $[\alpha]_D^{22}$ +4.9° (*c* 3.0, methanol).

Anal. Calcd. for $C_{22}H_{28}N_2O_6S$: C, 58.9; H, 6.29; N, 6.25. Found. C, 58.9; H, 6.26; N, 6.08.

*N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-*DL*-lysine benzyl ester* (X). III, 17.4 g. (40 mmol.), was esterified in 400 ml. of benzene containing 6.4 ml. of benzyl alcohol (62 mmol.) and 0.9 g. of *p*-toluenesulfonic acid by the above procedure to give 19.5 g. of X, m.p. 91–92°, 92% yield. X was recrystallized from benzene–petroleum ether, m.p. 92°.

Anal. Calcd. for $C_{29}H_{32}N_2O_6S$: C, 64.1; H, 6.15; N, 5.34. Found: C, 63.9; H, 6.14; N, 5.42.

*N^{α}-Tosyl-N^{ϵ}-carbobenzoxy-*L*-lysine benzyl ester* (XI). One g. of N^{α}-tosyl-N^{ϵ}-carbobenzoxy-L-lysine[6] (1.95 mmol.) was esterified in 20 ml. of benzene containing 0.31 ml. of benzyl alcohol (3.00 mmol.) and 0.55 g. of *p*-toluenesulfonic acid by the above procedure to give 0.95 g. of XI, m.p. 90–91°, 93% yield. XI was recrystallized from benzene–petroleum ether (activated charcoal added) and dried *in vacuo* at 78°, m.p. 92–93°, $[\alpha]_D^{23}$ +2.3° (*c* 3.0, methanol).

Anal. Calcd. for $C_{29}H_{32}N_2O_6S$: C, 64.1; H, 6.15; N, 5.34. Found: C, 64.2; H, 6.08; N, 5.20.

*N^{α}-Acetyl-*DL*-lysine methyl ester hydrochloride* (XII). A 0.440 g. sample of IV (1.30 mmol.) was dissolved in 50 ml. of methanol and 0.2 ml. of concentrated hydrochloric acid. The solution was hydrogenolyzed in the presence of 0.06 g. of Palladium black[21] at a hydrogen pressure of 33 lb. per in.^{2} for 1 hr. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure (35–40°) to yield a clear oil. The oil was washed with ether and then dried to

(15) Swallow *et al.*[6] reported the L-isomer with 1 mole of benzene of crystallization. In contrast, the DL-isomer did not contain benzene of crystallization since the compound did not lose weight on drying *in vacuo* at 78° and the elemental analysis of the dried compound did not indicate the presence of benzene.

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constant weight (0.292 g., 98% yield) *in vacuo* over phosphoric anhydride.

Anal. Calcd. for $C_9H_{19}N_2O_3Cl$: NH_2—N, 5.87. Found: NH_2—N, 5.81.

To provide further evidence for the identity of the oil, N^{α}-acetyl-N^{ϵ}-phthaloyl-DL-lysine methyl ester was prepared.

N^{α}-Acetyl-N^{ϵ}-phthaloyl-DL-lysine methyl ester from XII. To a solution of 0.337 g. of XII (1.41 mmol.) in 6 ml. of glacial acetic acid were added 0.306 g. of phthalic anhydride (2.1 mmol.) and 0.525 g. of sodium acetate trihydrate and the mixture was heated under reflux for 15 min. After cooling, the mixture was diluted with water and allowed to stand at room temperature for 1 hr. The clear solution was then taken to dryness under reduced pressure (30–40°) and the residue was dissolved in 50 ml. of warm benzene. The benzene solution was washed with 25 ml. of 5% sodium bicarbonate and 25 ml. of water. After drying over anhydrous sodium sulfate, the benzene was evaporated under reduced pressure (30–40°) to give 0.187 g. of N^{α}-acetyl-N^{ϵ}-phthaloyl-DL-lysine methyl ester, m.p. 132–133°, after washing with petroleum ether and drying in air, 42% yield. The compound was recrystallized twice from benzene–petroleum ether to give needles, m.p. 133–134°. For analysis, the compound was dried *in vacuo* at 78° over paraffin chips for 24 hours. Drying at lower temperatures resulted in the retention of benzene.

Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.4; H, 6.07; N, 8.43. Found: C, 61.5; H, 6.10; N, 8.40.

N^{α}-Acetyl-L-lysine methyl ester hydrochloride (XIII). A 0.400 g. sample of V (1.19 mmol.), m.p. 66–68°, was dissolved in 25 ml. of methanol and 0.1 ml. of concentrated hydrochloric acid. After addition of 0.075 g. of Palladium black, hydrogenolysis was carried out at atmospheric pressure. The reaction mixture was worked up as described for XII and the resulting oil was dried to constant weight (0.274 g., 98% yield) *in vacuo* over potassium hydroxide and phosphoric anhydride.

Anal. Calcd. for $C_9H_{19}N_2O_3Cl$: NH_2—N, 5.87. Found: NH_2—N, 5.87.

XIII was converted to N^{α}-acetyl-N^{ϵ}-phthaloyl-L-lysine methyl ester as described above, m.p. 126–128°, 43% yield. The product was recrystallized once from benzene and three times from benzene–petroleum ether to give needles, m.p. 127–128°.

Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.4; H, 6.07; N, 8.43. Found: C, 61.7; H, 6.12; N, 8.63.

N^{α}-Acetyl-DL-lysine benzyl ester hydrobromide (XIV). Attempts to prepare XIV by treatment of VI with 35% hydrogen bromide in glacial acetic acid and isolation[20] of the product yielded gummy material which retained excess hydrogen bromide even when dried *in vacuo* over potassium hydroxide for several days. The following method gave pure XIV. VI, 0.83 g. (2.0 mmol.), was treated with 1.5 ml. of 35% hydrogen bromide in glacial acetic acid in a flask closed with a calcium chloride drying tube. After 15 min., 20 ml. of dry acetone-ether[22] (1:1, v/v) was added, the stoppered flask was shaken vigorously for 5 min. and then cooled in an ice bath for 30 min. The mother liquor was decanted and the residual oil was washed four times with 20 ml. of the acetone-ether mixture and twice with 20 ml. of ether. The resulting semisolid was dissolved in 5 ml. of methanol and treated batchwise with Amberlite IR-45 (OH) until the excess hydrogen bromide had been removed as indicated by the use of methyl yellow. The mixture was filtered and the ion-exchange resin was washed twice with 3 ml. of methanol. The combined methanolic solutions were treated with activated charcoal and filtered through Celite. The filtrate was taken to dryness under reduced pressure (40°) yielding a clear oil which, after drying *in vacuo* over calcium chloride and phosphoric anhydride, weighed 0.58 g., 80% yield.

Anal. Calcd. for $C_{15}H_{23}N_2O_3Br$: NH_2—N, 3.90. Found: NH_2—N, 3.97.

N^{α}-Benzoyl-DL-lysine benzyl ester hydrobromide (XV). VII, 0.95 g. (2.0 mmol.), was treated with 1.5 ml. of 35% hydrogen bromide in glacial acetic acid. XV was isolated and purified as described above for the preparation of XIV to yield a clear oil (0.48 g., 57% yield) after drying *in vacuo* over calcium chloride and phosphoric anhydride.

Anal. Calcd. for $C_{20}H_{25}N_2O_3Br$: NH_2—N, 3.33. Found: NH_2—N, 3.49.

N^{α}-Tosyl-L-lysine methyl ester hydrochloride (XVI). A 0.350 g. sample of IX (0.78 mmol.), m.p. 78–80°, was dissolved in 25 ml. of methanol and 0.1 ml. of concentrated hydrochloric acid. Hydrogenolysis was carried out at atmospheric pressure in the presence of 0.09 g. of 10% palladium on charcoal. The oil which remained after evaporation of the solvent under reduced pressure (30–40°) solidified on cooling and triturating with ether to give 0.235 g. of XVI, m.p. 147–148°, after drying *in vacuo* over calcium chloride and potassium hydroxide, 86% yield. In large scale runs the yields of XVI ranged from 72 to 90%. XVI was recrystallized from ethanol ether to give long needles, m.p. 148–150°; $[\alpha]_D^{22}$ −10.2° (*c* 4.0, water).

Anal. Calcd. for $C_{14}H_{23}N_2O_4SCl$: C, 47.9; H, 6.60; S, 9.14; NH_2—N, 3.99. Found: C, 48.0; H, 6.64; S, 9.13; NH_2—N, 3.95.

N^{α}-Tosyl-DL-lysine benzyl ester hydrobromide (XVII). X, 18.3 g. (35 mmol.), was treated with 26 ml. of 35% hydrogen bromide in glacial acetic acid[20] in a flask closed with a calcium chloride drying tube. After 20 min., 350 ml. of ether was added to complete the precipitation of XVII. The product was collected and washed with ether to give 15.3 g. of crude XVII, m.p. 150–160°, 93% yield. The crude hydrobromide was crystallized from water (activated charcoal added) and dried *in vacuo* over phosphoric anhydride and potassium hydroxide; m.p. 182–183°. For analysis, XVII was recrystallized from water and dried *in vacuo* at 78° over phosphoric anhydride, m.p. 184–185°.

Anal. Calcd. for $C_{20}H_{27}N_2O_4SBr$: C, 51.0; H, 5.77; N, 5.94. Found: C, 51.2; H, 5.76; N, 5.70.

N^{α}-Tosyl-L-lysine benzyl ester hydrobromide (XVIII). XI was converted to XVIII by the method used above to prepare XVII. The crude product, m.p. 156–159°, obtained in 95% yield, was recrystallized from water and dried *in vacuo* at 78° over phosphoric anhydride, m.p. 172–173°,[23] $[\alpha]_D^{23}$ +10.4° (*c* 2.2, 95% ethanol).

Anal. Calcd. for $C_{20}H_{27}N_2O_4SBr$: C, 51.0; H, 5.77; NH_2—N, 2.97. Found: C, 51.0; H, 5.86; NH_2—N, 2.92.

N^{α}-Tosyl-DL-lysine benzyl ester hydrochloride (XIX). XIX was prepared by esterification of N^{α}-tosyl-DL-lysine. (a) N^{α}-tosyl-DL-lysine.[24] III, 2.00 g. (4.6 mmol.), was dissolved in 25 ml. of methanol. Six ml. of water, 0.15 ml. of glacial acetic acid, and 0.10 g. of palladium black were added and the mixture was hydrogenolyzed at atmospheric pressure for 1.5 hr. After 30 ml. of water had been added, the reaction mixture was heated to boiling and filtered hot. The filtrate was taken to dryness under reduced pressure (60°), yielding 0.99 g. of N^{α}-tosyl-DL-lysine, m.p. 260–262°

(22) The acetone was dried over anhydrous calcium sulfate for several days and then distilled with careful exclusion of moisture.

(23) While this manuscript was in preparation, the syntheses of N^{α}-tosyl-N^{ϵ}-carbobenzoxy-L-lysine benzyl ester m.p. 86–87°, and N^{α}-tosyl-L-lysine benzyl ester hydrobromide, m.p. 160–161°, were reported.[8] The compounds were not characterized by elemental analysis and, as judged from the reported melting points, were not obtained in pure form.

(24) N^{α}-Tosyl-DL-lysine has been prepared by Steib according to the following sequence of reactions: N^{ϵ}-benzoyl-DL-lysine ⟶ N^{α}-tosyl-N^{ϵ}-benzoyl-DL-lysine ⟶ N^{α}-tosyl-DL-lysine. [H. Steib, Hoppe-Seyler's *Z. physiol. Chem.*, **155**, 292 (1926).] However, no melting point was given for N^{α}-tosyl-DL-lysine.

(dec.), 72% yield. The compound was recrystallized from water and dried *in vacuo* at 78° over phosphoric anhydride; m.p. 262–263° (dec.).

Anal. Calcd. for $C_{13}H_{20}N_2O_4S$: C, 52.0; H, 6.71; N, 9.33. Found: C, 52.1; H, 6.76; N, 9.22.

(b) XIX from N^{α}-tosyl-DL-lysine. N^{α}-tosyl-DL-lysine, 0.765 g. (2.55 mmol.), was esterified[6] by heating at 100° for 3 hr. with 12 ml. of benzyl alcohol saturated with dry hydrogen chloride, to give 0.860 g. of XIX, m.p. 163–165° (with softening at 160–163°), 79% yield. XIX was recrystallized from 2*N* hydrochloric acid and dried *in vacuo* at 78° over phosphoric anhydride and potassium hydroxide, m.p. 176–177°.

Anal. Calcd. for $C_{20}H_{27}N_2O_4SCl$: C, 56.3; H, 6.38; N, 6.56. Found: C, 55.6; H, 6.36; N, 6.57.

N^{α}-Tosyl-L-lysine methyl ester (XX). Dry ammonia was passed through a solution of 0.431 g. of XVI (1.23 mmol.), m.p. 148–150°, in dry chloroform for 15 min. The solution was cooled in an ice bath to 0°. The reaction mixture was then washed twice with 25 ml. of water. After drying over anhydrous sodium sulfate, the chloroform was evaporated under reduced pressure (30–40°). The residual oil solidified on cooling and triturating with petroleum ether to give 0.306 g. of XX, m.p. 93–95°, after drying *in vacuo* over calcium chloride, 79% yield. Recrystallization of XX from benzene–petroleum ether gave needle clusters, m.p. 93–95°. The recrystallized XX was dried *in vacuo* at room temperature over paraffin chips for 24 hr.; $[\alpha]_D^{23}$ −5.4° (*c* 2.5, 95% ethanol).

Anal. Calcd. for $C_{14}H_{22}N_2O_4S$: C, 53.5; H, 7.05; S, 10.2; NH_2—N, 4.46. Found: C, 53.7; H, 7.06; S, 10.5; NH_2—N, 4.26.

N^{α}-Tosyl-DL-lysine benzyl ester (XXI). A suspension of 1.08 g. of XVII (2.29 mmol.) in 25 ml. of chloroform was cooled to −15° in an ice-salt mixture. Dry ammonia was passed into the suspension for 10 min. The resulting clear solution was allowed to warm slowly to room temperature and the ammonium bromide which precipitated from the reaction mixture was removed by filtration and washed with chloroform. The slightly turbid filtrate and washings were combined and extracted twice with 15 ml. of water. The chloroform solution was dried over anhydrous sodium sulfate and then taken to dryness under reduced pressure (35–40°). The residual oil crystallized when it was covered with petroleum ether and cooled, to give 0.80 g. of XXI, m.p. 103–104°, 90% yield. XXI was recrystallized from chloroform–petroleum ether, m.p. 104°.

Anal. Calcd. for $C_{20}H_{26}N_2O_4S$: C, 61.5; H, 6.71; NH_2—N, 3.59. Found: C, 61.3; H, 6.61; NH_2—N, 3.52.

Attempts to prepare N^{α}-acetyl-DL-lysine methyl ester by esterification of N^{α}-acetyl-DL-lysine[16] with diazomethane[17] yielded a basic oil which, as judged from the elemental analysis, appeared to be N^{α}-acetyl-N^{ϵ}-methyl-DL-lysine methyl ester.

Anal. Calcd. for $C_{10}H_{20}N_2O_3$: C, 55.5; H, 9.32; N, 12.96. Found: C, 54.9; H, 8.99; N, 12.84.

N-Methylation of primary amines by diazomethane is a known reaction.[25] The reaction here probably proceeds *via* the intermediate formation of N^{α}-acetyl-DL-lysine methyl ester.

MINNEAPOLIS, MINN.

(25) L. I. Smith, *Chem. Revs.*, **23**, 193 (1938).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Chemistry of the 1,2,4-Thiadiazine Ring System. II. A New Synthesis of 1,2,4,2*H*-Thiadiazine-3,5(4*H*,6*H*)-dione-1,1-dioxide

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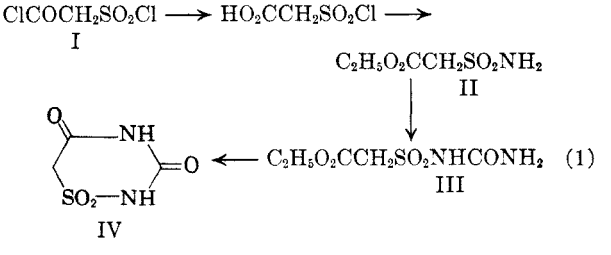
1,2,4,2*H*-Thiadiazine-3,5(4*H*,6*H*)-dione-1,1-dioxide (IV) has been synthesized in 25% over-all yield by the following sequence: sulfoacetic acid, sulfoacetic diacid chloride (I), diphenyl sulfoacetate (V), sulfamylacetamide (VI), carbamylmethanesulfonylurea (VII). The final ring closure of VII to IV was carried out in refluxing pyridine; other bases were ineffective. The same method was used to cyclize β-ureidoethanesulfonamide (XI) to 1,2,4(2*H*)-thiadiazine-3(4*H*,5*H*,6*H*)-one-1,1-dioxide (XII), an analog of dihydrouracil. Attempted ring closure of sulfamylacetylurea (IX) to IV was unsuccessful as were attempts to synthesize IV from sulfamylacetamide by reaction with ethyl carbonate, ethyl chloroformate, or urea

1,2,4(2*H*)-Thiadiazine-3,5(4*H*,6*H*)-dione-1,1-dioxide (IV) has recently been synthesized and its properties have been fully described for the first time.[2] Attention has been called to its similarity to barbituric acid, particularly its pronounced acidity (*p*Ka′ 2.7). The method used is shown in Equation 1. To circumvent difficulties in the conversion of sulfoacetic diacid chloride (I) to ethyl sulfamylacetate (II),[2] an alternative synthesis of IV was sought.



The present paper describes several new approaches to the synthesis of IV, including one new and improved method, summarized in Equation 2. Sulfoacetic diacid chloride (I) was converted to diphenyl sulfoacetate (V) which reacted with liquid ammonia in a sealed tube, forming sulfamylacetamide (VI). (Only the more reactive[2] carboxyl end of

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(2) R. L. Hinman and L. Locatell, Jr., *J. Am. Chem. Soc.*, **81**, 5655 (1959). Previously reported attempts to synthesize IV are discussed in this reference.