sulfuryl chloride (3% excess) in 25 ml. of acetic acid was added slowly with constant mechanical stirring. The mixture was then warmed gradually to room temperature and finally was heated for 20 min. on the steam bath at 70–75°. The reaction mixture was then poured into a solution of 40 g. sodium acetate in 300 ml. water. The precipitate of crude product was removed by filtration, washed with water, dried and recrystallized from acetic acid.

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Some Observations on the Preparation of Salicylamide Esters of Acylated α-Amino Acids

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Acyl salicyclic acid esters frequently have been used as substrates in enzyme and non-enzyme catalyzed hydrolyses because of the ease with which such reactions may be followed spectrophotometrically.[1-8] However, these substrates when used in systems more alkaline than *p*H 5 will be present as the corresponding anions thus introducing a possible complication that would not be encountered with an uncharged substrate. Because of interest in the behavior of neutral as well as anionic substrates our attention was directed to the preparation of acyl esters of salicylamide whose spectral properties and those of the parent phenol[9,10] would be expected to be similar to those of salicyclic acid and its analogous esters.

The successful use of trifluoroacetic anhydride as a condensing agent in the synthesis of benzoyl-DL-phenylalanine α-naphthyl ester[11] suggested the use of this reagent for the preparation of the salicylamide esters of acetyl-DL- and L- and benzoyl-DL- and L-phenylalanine. While the two DL-compounds were obtained in good yield the attempted preparation of benzoyl-L-phenylalanine salicylamide ester gave a racemized product, even when the reaction was conducted at −20 to −30°. This result was not totally unexpected since it is known that many optically active α-acylamino acids are readily racemized in the presence of acetic or trifluoroacetic anhydride[12-16] presumably *via* an intermediate mixed anhydride and oxazolonium ion.[17-20]

The observations of Weygand *et al.*[14-16] and of Schallenberg and Calvin[21] relative to the preparation of optically active α-trifluoroacetamido acid chlorides and their use in the acylation of amines without attendant racemization led us to investigate the usefulness of such acid chlorides in the synthesis of the desired salicylamide esters.

Trifluoroacetyl-DL-phenylalanine was prepared by a procedure similar to that described by Weygand and Leising[15] and was converted to the acid chloride by treatment with phosphorus pentachloride. Reaction of the acid chloride with the sodium salt of salicylamide gave the DL-ester in good yield. However, when the above reaction sequence was repeated with L-phenylalanine a substantially racemized product was obtained.

In order to locate the point at which racemization had occurred the above synthesis was repeated, this time isolating each intermediate and determining its optical purity. As before,[14-17,21] it was found that trifluoroacetyl-L-phenylalanyl chloride could be prepared without difficulty but in contrast to previous experience with the reaction of this acid chloride with aniline,[15,21] its reaction with the sodium or triethylamine salt of salicylamide led to a substantially racemized product.

The absence of racemization in the preparation of trifluoroacetyl-L-phenylalaninanilide[21] and of trifluoroacetyl-L-alaninanilide[15] suggested the desirability of examining the reaction of trifluoroacetyl-L-phenylalanyl chloride with anthranilamide. Because of the poor yields obtained in the ammonolysis of methyl anthranilate,[22,23] the amide was prepared from *o*-nitrobenzamide by reduction

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with Raney nickel and hydrazine.[24] The reaction of trifluoroacetyl-L-phenylalanyl chloride with anthranilamide, in the presence of triethylamine, gave the desired L-amide in good yield. The synthesis of this latter compound was of importance not only in respect to the interpretation of the reaction of the above acid chloride with salicylamide, *vide ante*, but also because it may be inferred from the spectral properties of anthranilamide and acylated anthranilamides[25] that the spectra of the above amide and anthranilamide would be sufficiently different to permit the use of the former compound as a specific substrate in studies involving α-chymotrypsin where the extent of reaction is to be determined spectrophotometrically. It may be noted that Ellman[26] has found that the α-chymotrypsin-catalyzed hydrolysis of methyl acetyl-L-phenylalaninanthranilate, present in the DL-mixture, may be followed fluorometrically.

The reaction of trifluoroacetyl-L-phenylalanyl chloride with anthranilamide to give the L-amide and with salicylamide to give the DL-ester raises the question of whether racemization occurred during the formation of the ester or in a subsequent process. An attempt was made to answer this question by a proposed synthesis of methanesulfonyl-L-phenylalanine salicylamide ester through the intermediate methanesulfonyl-L-phenylalanyl chloride which might be expected to exhibit less tendency to form an oxazolonium chloride than the trifluoroacetyl derivative even though there is no evidence presently available that such a cyclic isomer can be formed from the latter compound. However, when the proposed synthesis was tested with DL-phenylalanine the yields were so unsatisfactory that no attempt was made to use the procedure for the preparation of the L-compound. Thus, while the point at which racemization occurred in attempted preparation of trifluoroacetyl-L-phenylalanine salicylamide ester remains unknown it should be noted that although phenolic esters would be expected to be subject to facile racemization Iselin *et al.*[27] recently have reported the preparation of the *p*-nitrophenyl esters of carbobenzoxy-L-leucine, carbobenzoxy-L-valine, and carbobenzoxy-*S*-benzyl-L-cysteine by the condensation of the appropriate acid with di-*p*-nitrophenyl sulfite in the presence of pyridine. The applicability of this latter procedure to the synthesis of optically active esters of salicylamide and various acylated α-amino acids is currently under investigation.

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Bader and Kontowicz[28] reported the successful preparation of phenolic esters by simply heating the acid with phenol in the presence of polyphosphoric acid. The application of this procedure to the attempted synthesis of benzoylglycine salicylamide ester gave none of the desired product but instead benzoic acid, disalicylamide, and a compound $C_{16}H_{19}O_2N_2$ which appeared to arise from the condensation of 1 mole of benzoylglycine and 1 mole of salicylamide with the elimination of 3 moles of water. An attempted condensation of hydrocinnamic acid with salicylamide gave only disalicylamide, the dimer of α-hydrindone, *i. e.*, anhydrobishydrindone,[29] and α-truxene. It is known that disalicylamide may be obtained from salicylamide by reaction with phosphorus pentoxide[30] and in this study it was obtained in good yield using polyphosphoric acid in lieu of the anhydride. It also was found that anhydrobishydrindone was converted into α-truxene with the same reagent. Liebermann[31] and Kipping[29] prepared α-truxene by reaction of α-hydrindone with sulfuric acid and Kipping[29] also isolated anhydrobishydrindone from the reaction mixture. Since Snyder and Werber[32] obtained α-hydrindone and presumably α-truxene from the reaction of hydrocinnamic acid with polyphosphoric acid and 1-methylisoquinoline from the reaction of acetyl-DL-phenylalanine with the same reagent[33] it is clear that polyphosphoric acid offers little or no promise as a condensing agent for the preparation of phenolic esters of acylated α-amino acids because of side reactions involving the substituted phenol and acylated α-amino acid.

The reports of the usefulness of cyanomethyl esters[34-36] in peptide synthesis led to the attempted acylation of salicylamide with acetyl-DL-phenylalanine cyanomethyl ester. However, the desired product was not obtained. Similar results were observed in an attempt to extend the reaction of phenyldiazonium fluoroborate with acetic acid, to give phenyl acetate,[37] to the acylated α-amino acids and in an attempt to effect condensation of salicylamide and an acylated α-amino acid with

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dicyclohexylcarbodiimide.[38–43] In these latter three attempts no reaction was observed in the first and third and in the second only intractable products were formed, presumably arising from the reaction of the diazonium compound with acetonitrile or dimethylformamide which were used as solvents.

EXPERIMENTAL[44,45]

Benzoyl-DL-phenylalanine salicylamide ester. Acylation of 66 g. (0.40 mole) of DL-phenylalanine with 60 g. (0.43 mole) of benzoyl chloride under Schotten-Bauman conditions gave 82.4 g. (78%) of benzoyl-DL-phenylalanine, m.p. 179–182°, lit.,[46] m.p. 181–182°.

A mixture of 10 g. (.037 mole) of the above acid and 12 g. (.057 mole) of trifluoroacetic anhydride was warmed on a steam bath until a clear solution resulted. The excess trifluoroacetic anhydride was removed *in vacuo* and to the orange solution was added 5 g. (.037 mole) of salicylamide. The mixture was warmed on the steam bath for one hour, evaporated to dryness *in vacuo*, the residue washed with cold methanol and dried to give 10.4 g. (73%) of benzoyl-DL-phenylalanine salicylamide ester. Recrystallization from a mixture of dioxane and cyclohexane gave the desired ester, m.p. 198–199°.

Anal. Calcd. for $C_{23}H_{20}O_4N_2$: C, 71.1; H, 5.2; N, 7.2. Found: C, 71.0; H, 5.3; N, 7.2.

The compound gave a positive ferric hydroxamate test, was soluble in dimethylformamide and dioxane and insoluble in water, methanol, and ethanol.

Acetyl-DL-phenylalanine salicylamide ester. Acylation of 9 g. (.054 mole) of DL-phenylalanine with 19.2 ml. (0.21 mole) of acetic anhydride under Schotten-Bauman conditions gave 9.4 g. (84%) of acetyl-DL-phenylalanine, m.p. 152–155°.

The above product (.045 mole) was mixed with 12 g. (.060 mole) of trifluoroacetic anhydride and warmed on a steam bath to effect solution. The excess anhydride was removed *in vacuo*, 5 g. (.037 mole) of salicylamide added and the solution heated for ten minutes on a steam bath. Upon cooling a white solid precipitated. The solid was collected, washed with methanol, and dried to give 9 g. (76%) of acetyl-DL-phenylalanine salicylamide ester. Recrystallization from dimethylformamide gave the desired product, m.p. 208–209°.

Anal. Calcd. for $C_{18}H_{18}O_4N_2$: C, 66.2; H, 5.6; N, 8.6. Found: C, 66.3; H, 5.6; N, 8.7.

The compound gave a positive ferric hydroxamate test, was soluble in acetic acid, Methyl Cellosolve, and dimethylformamide, slightly soluble in acetonitrile and insoluble in water, ethanol, and methanol.

Attempted synthesis of acetyl-L-phenylalanine salicylamide ester using trifluoroacetic acid anhydride as a condensing agent. Acylation of 7.5 g. (.046 mole) of L-phenylalanine with 12 ml. (0.128 mole) of acetic anhydride under Schotten-Bauman conditions gave, after one recrystallization from water, 9.0 g. (94%) of acetyl-L-phenylalanine, m.p. 171–172°. Proceeding as described for the DL-compound 5 g. (.024 mole) of acetyl-L-phenylalanine gave 2.8 g. (37%) of ester, m.p. 207–208°. The low rotation initially observed disappeared upon recrystallization from dimethylformamide. When the recrystallized product was mixed with an authentic sample of the DL-compound the melting point was not depressed.

An attempt was made to conduct the above esterification at −40 to −50° but under these conditions the mixed anhydride was not formed as indicated by the fact that the solution never cleared. At −20° it appeared that the anhydride had formed since a clear solution resulted. Upon the addition of salicylamide the solution remained thick for an extended period. A small amount of racemic product was isolated.

Trifluoroacetyl-DL-phenylalanine salicylamide ester. Acylation of 20 g. (0.121 mole) of DL-phenylalanine with 18.8 ml. (0.119 mole) of trifluoroacetic anhydride as described by Weygand and Leising[15] gave 30.4 g. (95%) of crude trifluoroacetyl-DL-phenylalanine. Recrystallization from a mixture of benzene and hexane gave colorless crystals, m.p. 121–122°, lit.,[21] m.p. 125.6–126.8°. A solution of 5.2 g. (0.0191 mole) of the preceding acid in 100 ml. of dry ether was cooled in an ice-salt bath, an excess of phosphorus pentachloride added portionwise with vigorous shaking and the reaction mixture allowed to stand for three hours with intermittent shaking. The solvent was removed *in vacuo*, the residue washed with petroleum ether (30–60°), collected, and dried to give 4.5 g. (84%) of trifluoroacetyl-DL-phenylalanyl chloride, m.p. 96–98°, lit.[15] m.p. 99–100°.

A solution of 4.5 g. (0.0161 mole) of the above acid chloride in 50 ml. of dry benzene was added to a suspension of 2.4 g. (0.0161 mole) of the sodium salt of salicylamide in dry benzene and the resulting slurry was stirred vigorously at room temperature for twelve hours and at 50° for one hour. The solvent was removed *in vacuo*, the residue washed repeatedly with water, and dried to give 3.6 g. (59%) of the desired ester. Recrystallization from a mixture of ethanol and hexane gave a product, m.p. 223–224° with decomp.

Anal. Calcd. for $C_{18}H_{15}O_4N_2F_3$: C, 56.8; H, 4.0; N, 7.4. Found: C, 56.8; H, 3.9; N, 7.3.

The ester was soluble in hot ethanol and insoluble in water.

Attempted synthesis of trifluoroacetyl-L-phenylalanine salicylamide ester. To a solution of 10 g. (0.0605 mole) of L-phenylalanine in 100 ml. of dry benzene, contained in a 3-necked flask fitted with a mechanical stirrer, dropping funnel, and drying tube, was added with vigorous stirring 9.4 ml. (0.0595 mole) of trifluoroacetic anhydride. The reaction mixture was slowly warmed to 70° and then cooled to room temperature. The colorless solid was collected and dried to give 7.2 g. of trifluoroacetyl-L-phenylalanine, m.p. 117–119°. Removal of benzene and trifluoroacetic acid from the mother liquor gave an additional 4.9 g., m.p. 116–118°. The total yield was 12.1 g. (78%). Recrystallization from a mixture of benzene and hexane gave 10.4 g. of acid, m.p. 119–120°, lit.[21] m.p. 119.4–120.6°. $[\alpha]_D^{25}$ + 35.2 ± 0.6° (c, 2.6% in glacial acetic acid), lit.,[21] $[\alpha]_D^{25}$ + 36.4° (c, 0.4% in glacial acetic acid).

A solution of 7.2 g. (0.0276 mole) of the acid in 250 ml. of dry ether was treated in the usual manner with phosphorus pentachloride. Recrystallization of the crude product from a mixture of benzene and petroleum ether gave 6.5 g. (84%) of trifluoroacetyl-L-phenylalanyl chloride, m.p. 108–110°, lit.[21] m.p. 109.5–111.5°. $[\alpha]_D^{25}$ + 17.1 ± 0.4° (c, 3.3% in glacial acetic acid), lit.[21] $[\alpha]_D^{28.3}$ + 15.5° (c, 0.16% in glacial acetic acid).

Reaction of a solution of 6.5 g. (0.0232 mole) of the acid chloride in 250 ml. of benzene with 3.5 g. (0.0220 mole) of the sodium salt of salicylamide gave 7.6 g. (90%) of a compound m.p. 214.5–218° with decomp. Three recrystallizations from ethanol gave a compound with no optical rotation, m.p. 218–219°. The melting point was not depressed on admixture with an authentic sample of trifluoroacetyl-DL-phenylalanine salicylamide ester, m.p. 223–224°.

Anal. Calcd. for $C_{18}H_{15}O_4N_2F_3$; C, 56.8; H, 4.0; N, 7.4. Found: C, 56.8; H, 4.0; N, 7.2.

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Anthranilamide. Repeated reaction of 100 g. (0.66 mole) of methyl anthranilate with saturated methanolic ammonia over a 5-month period gave an oil. The oil was taken up in ether and hexane added to give 22.2 g. (27%) of anthranilamide, m.p. 108.5–111°, lit.,[22,23] m.p. 109–111°.

A mixture of 33.4 g. (0.2 mole) of *o*-nitrobenzoic acid and 43.6 g. (0.22 mole) of phosphorus pentachloride was shaken until reaction began, the semi-solid mass stirred vigorously and slowly heated to 40°, the deep brown solution cooled and added dropwise to 200 ml. of concd. ammonium hydroxide precooled in an ice-salt bath. The light brown solid was collected and dried to give 26.6 g. (80%) of crude *o*-nitrobenzamide. Recrystallization from methanol gave a product, m.p. 173–176°, lit.[47] m.p. 174–176°.

To a warm solution of 26.6 g. (0.16 mole) of the above amide and 16 g. (0.53 mole) of anhydrous hydrazine in 400 ml. ethanol was added a small amount of Raney nickel and the solution was heated for three hours. More Raney nickel was added and the solution heated under refluxing conditions for an additional 30 min. The catalyst was removed, the solution heated with Norit, filtered, and the solvent removed *in vacuo*. The resultant oil was cooled and the solid recrystallized from a mixture of ethanol and hexane to give 16.5 g. (77%) of anthranilamide, m.p. 109–110°, lit.[22,23] m.p. 109–111°.

Trifluoroacetyl-L-phenylalanine anthranilamide. Trifluoroacetyl-L-phenylalanine, $[\alpha]_D^{26}$ + 17.3 ± 0.3° (c, 2% in ethanol), $[\alpha]_D^{25}$ + 35.3 ± 0.4° (c, 2% in glacial acetic acid) was prepared as before. Three and two tenths g. (0.0123 mole) of the above acid was converted into the acid chloride as described above. The acid chloride was dissolved in dry ether, the ethereal solution added to 1.36 g. (0.01 mole) of anthranilamide in dry ether, 2 g. (0.02 mole) of triethylamine added, and the solution stirred at room temperature for 24 hr. The solution was freed of triethylamine hydrochloride and the ether removed *in vacuo*. Recrystallization of the residue from ethanol gave 1.86 g. (49%) of the desired amide, m.p. 191.5–192.0°, $[\alpha]_D^{25}$ −48.8 ± 0.8° (c, 1.3% in dimethylformamide).

Anal. Calcd. for $C_{18}H_{16}O_3N_3F_3$: C, 57.0; H, 4.3; N, 11.1. Found: C, 56.9; H, 4.2; N, 11.0.

Methanesulfonyl-DL-phenylalanine salicylamide ester. Acylation of 25 g. (0.152 mole) of DL-phenylalanine with 12 ml. (0.52 mole) of methanesulfonyl chloride as directed by Helferich and Grünert[48] gave 8.8 g. (0.036 mole) of product, m.p. 96–99°. Recrystallization of this substance from a 1:5 mixture of benzene and acetic acid gave 7.2 g. (19%) of methanesulfonyl-DL-phenylalanine, m.p. 101–102°, lit.,[48] m.p. 104°. Reaction of 7.2 g. of the above acid with an excess of phosphorus pentachloride gave methanesulfonyl-DL-phenylalanyl chloride, as a yellow oil, which was dissolved in 100 ml. of dry benzene. To this solution was added 3.9 g. (.0226 mole) of the sodium salt of salicylamide, the suspension vigorously stirred and heated at 40° overnight. The solid was collected, washed repeatedly with cold water, and recrystallized twice from a mixture of benzene and hexane to give 0.48 g. (1%) of the desired product, m.p. 153.8–155°.

Anal. Calcd. for $C_{17}H_{18}O_5N_2S$: C, 56.3; H, 5.0; N, 7.7. Found: C, 56.2; H, 5.4; N, 7.6.

Reaction of salicylamide with polyphosphoric acid. A mixture of 150 g. of polyphosphoric acid and 41.1 g. (0.3 mole) of salicylamide was heated on a steam cone for 24 hr. The deep red solution was diluted with 400 ml. of hot water, the remaining solid collected and dried *in vacuo*. A colorless crystalline solid separated from the filtrate on cooling. This solid proved to be salicylamide. Removal of most of the water gave a total of 24 g. of salicylamide. Thus, from the remaining 17.1 g. (0.125 mole) of salicylamide there was obtained 8.9 g. (54%) of disalicylamide. Three recrystallizations from hot water gave a product m.p. 188–190°, lit.[30] m.p. 197–199°.

Anal. Calcd. for $C_{14}H_{11}O_4N$: C, 65.4; H, 4.3; N, 5.5. Found: C, 65.4; H, 4.4; N, 5.5.

Reaction of hippuric acid with polyphosphoric acid. Reaction of 36 g. (0.2 mole) of hippuric acid with polyphosphoric acid in a manner analogous to that described above gave 26 g. of starting material. There also sublimed from the reaction mixture 4 g. of benzoic acid, m.p. 121–123°; anilide, m.p. 158–159.5°. Thus, based upon the unrecovered starting material, 65% of the hippuric acid was converted to benzoic acid.

Reaction of salicylamide and hippuric acid with polyphosphoric acid. A solution of 9 g. (0.05 mole) of hippuric acid and 10 g. (0.073 mole) of salicylamide in 150 g. of polyphosphoric acid was heated on a steam bath for 24 hr. during which time 2.1 g. of benzoic acid sublimed into the neck of the flask. The reaction mixture was diluted with water, and triturated with 5% aqueous sodium carbonate to give a brown clay-like friable mass. The dark brown solid was collected, dried, and powdered. Acidification of the aqueous sodium carbonate solution gave a small amount of disalicylamide, m.p. 186–189°. The brown solid was extracted with ethyl acetate, the solution filtered through 8 cm. of activated alumina, and the yellow filtrate evaporated to dryness to give 3.8 g. of a substance which was very slightly soluble in 5% aqueous hydrochloric acid, was readily oxidized by aqueous potassium permanganate, rapidly decolorized a solution of bromine in carbon tetrachloride, gave a negative ferric chloride test and a negative ferric hydroxamate test. Recrystallization of the crude product from ethanol gave light yellow needles, m.p. 131.5–132.5°.

Anal. Calcd. for $C_{16}H_{10}O_2N_2$: C, 73.3; H, 3.8; N, 10.7. Found: C, 73.1; H, 3.9; N, 10.5.

The ultraviolet spectrum of 4 mg. of the above substance in 100 ml. of chloroform was characterized by three peaks, *i.e.;* 247–248 mμ, $E_{1\,cm}^{1\%}$ 740; 264–265 mμ, $E_{1\,cm}^{1\%}$ 380 and 347–348 mμ, $E_{1\,cm}^{1\%}$ 90. Its chemical behavior, empirical formula, and ultraviolet and infrared spectra suggested that the compound was 4-phenylimidazolo[3,4-*b*]benzopyranone-2.

Reaction of salicylamide and hydrocinnamic acid with polyphosphoric acid. A mixture of 15 g. (0.10 mole) of hydrocinnamic acid and 20 g. (0.146 mole) of salicylamide in 150 g. of polyphosphoric acid was heated on a steam bath for 24 hr. Trituration of the green clay-like residue, resulting from dilution of the reaction mixture with water, with 5% aqueous sodium carbonate gave a green solid and a clear solution. The solution was acidified, the solid collected, and dried to give 10.2 g. (55%) of disalicylamide, m.p. 186–189°.

The green solid was extracted with ethyl acetate to give a yellow solution and a greenish yellow solid. Filtration of the solution through 8 cm. of activated alumina and removal of the solvent *in vacuo* gave 2.1 g. of a pale yellow compound, m.p. 140–143°. Recrystallization from ethyl acetate gave the dimer of α-hydrindone, called by Kipping[29] anhydrobishydrindone, m.p. 142–144°, lit.[29] m.p. 142–143°.

Anal. Calcd. for $C_{18}H_{14}O$: C, 87.8; H, 5.9. Found: C, 87.6; H, 5.9.

The greenish yellow solid remaining after extraction with ethyl acetate was recrystallized from tetrahydrofuran to give 4.4 g. of α-truxene, silky yellow needles, m.p. 376.1–378.0°, lit.,[29] m.p. 365–368°.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.5; H, 5.3. Found: C, 94.2; H, 5.5.

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