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Reactions in the Salicylic Acid Series. A New Rearrangement of Acylsalicylic Acid Derivatives

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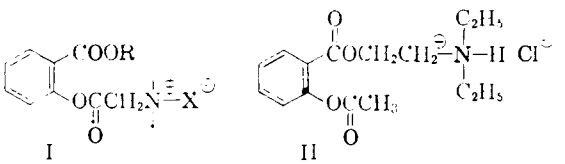
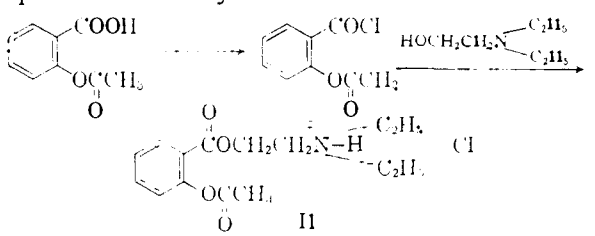
Reactions are described which support the hypothesis that the carboxylate anion of acylsalicylates can participate in a neighboring group nucleophilic attack on the carbonyl group of the acyl moiety to form a hypothetical six-membered cyclic intermediate which can then undergo further reaction with other nucleophilic species. Other reactions show that in certain α-substituted acylsalicylic acids, the carboxylate group can displace the α-subtituent to yield a seven-membered cyclic intermediate, 1,4-benzodioxepin-2,5-(3H)-dione (XXV), which can then react with nucleophilic reagents to yield rearrangement products such as 1-pyrrolidinylcarbonylmethyl salicylate (XII). The course of the reaction is determined by the reactivity of the substituent X in nucleophilic displacement reactions. The preparation of a few representative protonated acylsalicylic acid derivatives is reported.

The instability of aspirin in aqueous acid solutions (*p*H 1–3) has been attributed to the facile attack of hydrogen ions on the carbonyl oxygen of the acetyl group.[1-3] Any structural modification that could hinder the approach of the elements of water could theoretically impart increased acid stability to acyl salicylate derivatives. Such inhibition of reaction might be due to steric factors which could mechanically hinder nucleophilic attack or they could be electronic factors such as positive centers in the molecule which could repel proton attack. Murray and Heinzelman[4] of these laboratories have prepared a group of hindered acylsalicylic acid derivatives which proved to be more resistant to acid-catalyzed hydrolysis than aspirin.[5] To determine the efficacy of an electrostatic "proton shield," we prepared a group of acylsalicylates containing positive centers in the acyl moiety as in I and in the alcohol portion of an aspirin ester as in II.



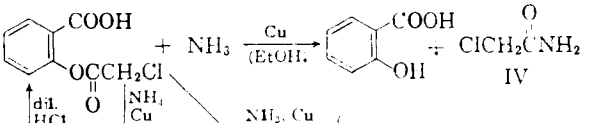
I II

The synthesis of II from aspirin[6] was accomplished by conversion to the acid chloride with thionyl chloride[7] followed by treatment with one equivalent of diethylaminoethanol.



II

Kaufman and Thomas[8] reported the preparation of glycylsalicylic acid hydrochloride (III), m.p. 70°, by treatment of chloroacetylsalicylic acid with alcoholic ammonia in the presence of copper powder in the cold. We have repeated this reaction at 0° and at −20° and found in both cases that the main products (75–80%) were salicylic acid and chloroacetamide. When the reaction was carried out in ether solution, a solid was obtained, m.p. 70–72°, which corresponded in melting point and solubility behavior to glycylsalicylic acid hydrochloride, m.p. 70°, reported by Kaufmann and Thomas. We believe, however, that the structure of the material can best be represented by V, ammonium chloroacetylsalicylate, rather than by III, the isomeric glycylsalicylic acid hydrochloride. This follows from the fact that solution in ice-water followed by acidification and rapid filtration of the product yielded chloroacetylsalicylic acid in 91–98% yield, good evidence that the salt was a carboxylate and not an amine hydrochloride. The infrared spectrum of V was very similar to that of the ammonium salt of aspirin prepared in a similar fashion.

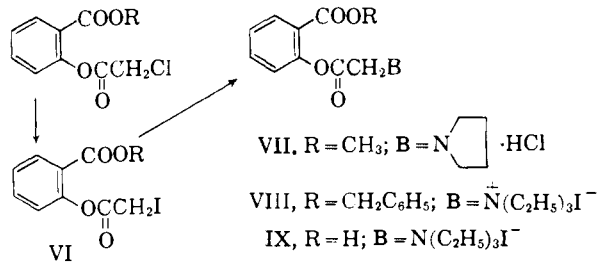


III

IV V III

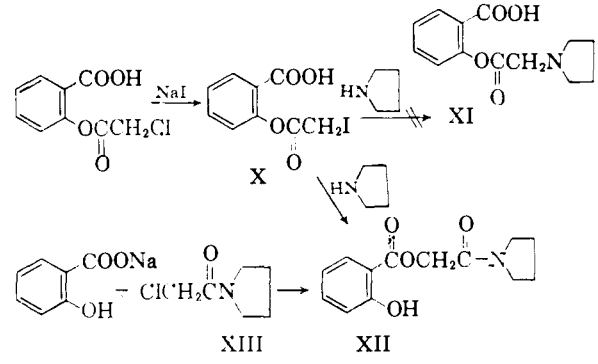
Hahn and Loos[9] prepared aminoacylsalicylate esters by treating chloroacetylsalicylate esters with sodium iodide to form the corresponding iodo compounds which were then treated with amines. This procedure proved satisfactory for the preparation of methyl pyrrolidylacetylsalicylate hydrochloride (VII) and benzyl triethylammoniumacetylsalicylate iodide (VIII). Attempted hydrogenolysis of VIII failed to yield IX. No hydrogen uptake was observed with 10% palladium-on-charcoal, and cleavage of the acyl group occurred in the presence of Raney nickel due to its basic character.

(1) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).
(2) L. J. Edwards, *ibid.*, **48**, 696 (1952).
(3) E. R. Garrett, THIS JOURNAL, **79**, 5206 (1957).
(4) M. F. Murray and R. V. Heinzelman, unpublished.
(5) E. R. Garrett, THIS JOURNAL, **79**, 3401 (1957).
(6) Since this work was done, compound II has been reported by Z. Jerzmanowska and Z. Orchowicz, *Acta Polon. Pharm.*, **13**, 11 (1956); see *C. A.*, **50**, 16, 671 (1956). Their melting point, 135–136° from acetone, agrees well with ours, 136.5–137.5° from ethanol.
(7) R. Wolffenstein, German Patent 277,659 (1911); *C. A.*, **9**, 1096 (1915).
(8) H. P. Kaufmann and M. Thomas, *Arch. Pharm.*, **262**, 117 (1924).
(9) F. L. Hahn and M. Loos, *Ber.*, **51**, 1436 (1918).



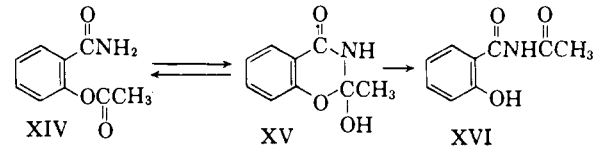
Garrett has studied the rates of hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride (II)[10] and methyl pyrrolidylacetylsalicylate hydrochloride[3] (VII). He found that II, as predicted, was much more stable to acid hydrolysis than aspirin, 15 times more stable at *p*H 3 and 20 times more stable at *p*H 5. The situation in the case of VII proved to be more complicated. Although VII was completely resistant to hydrogen ion-catalyzed hydrolysis as proposed, it proved to be highly susceptible to nucleophilic catalysis (*e.g.*, OH^-, water, acetate ion)[11] and was therefore easily hydrolyzed.

Although nucleophilic attack by pyrrolidine proceeded as expected in the iodoacetylsalicylic acid ester series, it led to an unexpected reaction product when applied to free iodoacetylsalicylic acid. Conversion of chloroacetylsalicylic acid to its iodo analog X followed by treatment with pyrrolidine in acetone solution did not yield the expected product, pyrrolidylacetylsalicylic acid (XI). Instead, a weakly

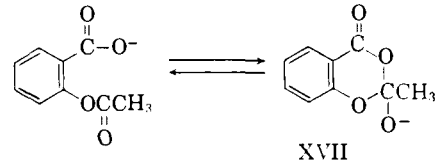


acidic rearrangement product (XII) was isolated which was isomeric with XI and which gave a positive ferric chloride test. The infrared spectrum showed hydroxyl absorption at 3230 cm.$^{-1}$, strong amide carbonyl absorption at 1650 cm.$^{-1}$ and a shoulder at 1668 cm.$^{-1}$, typical of salicylate esters. An ethanolic solution of the rearrangement product absorbed at 239 and 308 mμ in the ultraviolet spectrum. When the solution was made alkaline and was stored at room temperature, a flex appeared at 252 mμ with maximum absorption at 298 mμ and less absorption at 334 mμ. Methyl salicylate behaved similarly showing absorption at 239 and 305 mμ in ethanol. In alkaline solution absorption increased at 298 and decreased at 333 mμ as hydrolysis proceeded. The spectral characteristics and elemental analysis of the rearrangement product were in accord with the assigned structure, XII, which was proved unequivocally by synthesis from sodium salicylate and chloroacetylpyrrolidine (XIII).

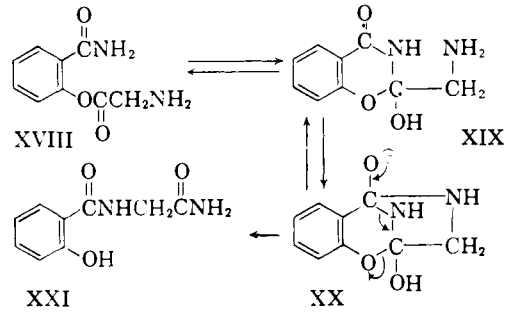
Many of the reported anomalous reactions of acylsalicylic acid derivatives have been explained by assuming an equilibrium between the acylsalicylic acid derivative and a six-membered cyclic intermediate. McConnan and Titherley[12] postu-



lated a six-membered cyclic intermediate XV to account for the rearrangement of O-acetylsalicylamide (XIV) to the N-acetyl derivative XVI. Similarly, a six-membered cyclic intermediate XVII, has been proposed to rationalize the independence of the hydrolysis rates of aspirin on *p*H in the range 5–8[3,13] and to explain the "anhydride" character of aspirin.[14] Brenner, *et al.*,[15] have recently announced a novel peptide synthesis based on this type of reaction. Under basic conditions amino-



acetylsalicylamide (XVIII) rearranges to transfer its side chain from the phenolic oxygen to the amidic



carbonyl group. This rearrangement, like the others cited above, was thought to proceed through a six-membered cyclic intermediate (*cf.* XIX) formed by a nucleophilic attack of a neighboring group on the carbonyl group of the acyl moiety.

The rearrangement which occurred in the transformation X → XII can also be explained by invoking cyclic intermediates; however, three routes are possible, only one of which involves a six membered cyclic intermediate. In route A, the action of base establishes an equilibrium between X and the "pseudo anhydride" XXII. The latter can open to the bona fide anhydride XXIIa which in turn can react with pyr-

(10) E. R. Garrett, THIS JOURNAL, **80**, 4049 (1958).

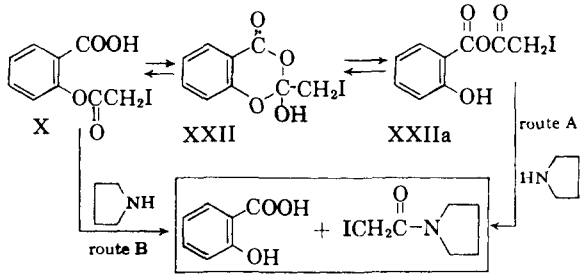
(11) M. L. Bender, Y. Chow and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(12) J. McConnan and A. W. Titherley, *J. Chem. Soc.*, 1318 (1906).

(13) J. D. Chanley, E. M. Gindler and H. Sobotka, THIS JOURNAL, **74**, 4347 (1952).

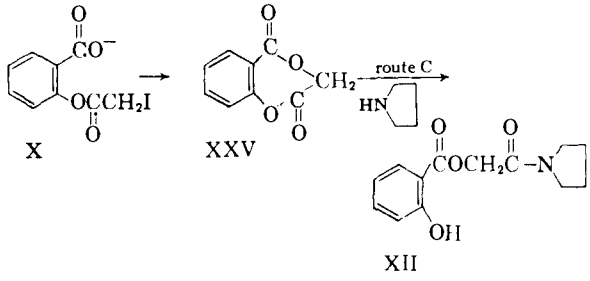
(14) D. Davidson and L. Auerbach, *ibid.*, **75**, 5984 (1953).

(15) M. Brenner, J. P. Zimmermann, J. Wehrmuller, P. Quitt, A. Hartmann, W. Schneider and W. Beglinger, *Helv. Chim. Acta*, **40**, 1497 (1957).

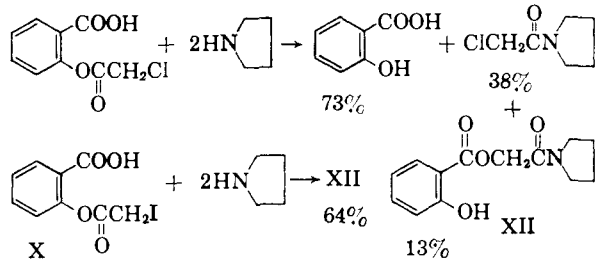


rolidine to yield the mixture XXIII, iodoacetylpyrrolidine and the salicylate ion. Alternatively, pyrrolidine can attack X directly to yield XXIII (route B). In either case the mixture XXIII could then yield XII.

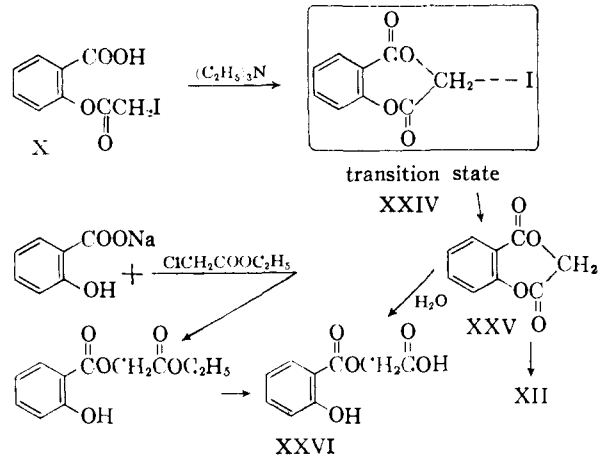
In route C, a seven-membered ring intermediate (XXV) arising from an internal nucleophilic displacement of halogen by the carboxylate anion is postulated. Subsequent attack by pyrrolidine should yield the rearrangement product XII. This mechanism is attractive because of its intramolecular nature, neighboring group facilitation of reaction, the excellent "leaving" properties of the iodo group and the steric compatibility of the ring system, easily demonstrated with models.



A choice between the three routes cannot be made on steric grounds since a study of models indicates that the carboxylate anion is in a favorable position to participate in a neighboring group nucleophilic attack on either the carbonyl group (route A) or the adjacent methylene group (route C). Since previous workers[1-3,11] have demonstrated the facile attack of the carboxylate anion on the carbonyl group of the *o*-acyloxy group in the hydrolysis of aspirin, one might predict even greater ease of attack in the case of the α-haloacyloxy derivatives due to the inductive effect of the halogen atom. In order for route C to compete effectively in determining the course of a reaction between an α-haloacylsalicylic acid and a base, the halogen must be an exceptionally good leaving group. To determine the role of halogen in the reaction, chloroacetylsalicylic and iodoacetylsalicylic acids were treated with pyrrolidine under identical conditions. The chloro compound yielded mainly salicylic acid (73% yield) and a low yield of XII (13% yield), the product distribution one might predict if the reaction proceeded through routes A or B. In contrast, the iodo derivative yielded 64% of the rearranged product XII, the product to be expected from route C. These results indicated clearly that the reactivity of the halogen atom was critical in determining the course which the reaction followed. To demonstrate



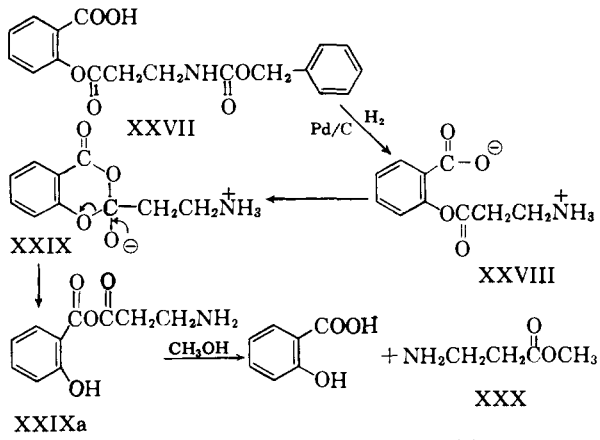
that route C actually described the course of the reaction between iodoacetylsalicylic acid and pyrrolidine, an attempt was made to isolate the seven-membered cyclic intermediate XXV. Treatment of X with one equivalent of triethylamine under anhydrous conditions yielded a crystalline material which gave a negative ferric chloride test and a negative Beilstein test. Elemental analysis and



the infrared spectrum were in accord with the assigned structure, XXV, 1,4-benzodioxepin-2,5-(3H) dione. Treatment with pyrrolidine converted XXV quantitatively to the rearranged amide XII. Water at room temperature converted XXV to a new solid whose elemental analysis, spectral characteristics and melting point corresponded with the known acid XXVI, previously prepared[16] from sodium salicylate and ethyl chloroacetate followed by saponification of the terminal ester. The isolation of XXV, its quantitative conversion to XII, and the demonstration that the type of halogen controlled the course of the reaction indicated that the rearrangement which took place in the conversion of X to XII proceeded by route C. To the best of our knowledge, *this is the first demonstration of a rearrangement in the acylsalicylate series which proceeds through a cyclic seven-membered intermediate.*

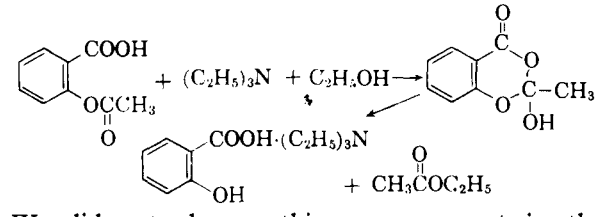
Another reaction which can be explained by postulating a nucleophilic attack on a neighboring group was encountered during an attempted synthesis of β-aminopropionylsalicylic acid (XXVIII). Hydrogenolysis of carbobenzyloxy-β-aminopropionylsalicylic acid (XXVII) in the presence of palladium-on-charcoal in methanol solution did not yield XXVIII as expected. Instead, the main products of the reaction were methyl β-aminopropionate (XXX) and salicylic acid. It would ap-

(16) German Patent 125,988 (1901); *Chem. Zentr.*, **72**, II, 1220 (1901).

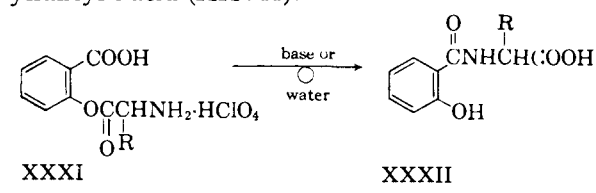


XXIXa

pear that the carboxylate anion formed in XXVIII participated in a nucleophilic attack on the carbon atom of the carbonyl group in the adjacent acyl chain to form the "pseudo anhydride" XXIX which could react with methanol through the anhydride XXIXa to yield salicylic acid and XXX. Since the carbobenzyloxy derivative XXVII is stable in alcohol solution, the sequence of events must be first hydrogenolysis, second salt formation and third nucleophilic attack by the carboxylate anion. To test this hypothesis in an analogous system, aspirin was treated with one equivalent of triethylamine in ethanol solution overnight. The solvent was removed under reduced pressure to yield the theoretical amount of triethylammonium salicylate in the residue and the theoretical amount of ethyl acetate in the distillate as determined by vapor phase chromatography.[17] This system simulates the conditions encountered after the hydrogenolysis of XXVII to XXVIII. The decomposition of XXVIII to XXX by methanol and the aspirin anion to ethyl acetate by ethanol are very similar in character. Since this work was done, Brenner and Wehrmuller[18] have successfully hydrogenolyzed carbobenzyloxy derivatives of α-aminoacylsalicylic acids in acetic acid–perchloric acid to prepare glycylsalicylic acid perchlorate derivatives (XXXI). These compounds when treated with base or water rearranged to salicyloylglycine derivatives (XXXII).



We did not observe this rearrangement in the hydrogenolysis of carbobenzyloxy-β-aminopropionylsalicylic acid (XXVII).



XXXI XXXII

(17) These results agree with those found by Chanley, *et al.*,[18] for the analogous system, salicyl phosphate.

(18) M. Brenner and J. Wehrmuller, *Helv. Chim. Acta*, **40**, 2374 (1957).

In summary, the reactions of α-haloacylsalicylic acid derivatives discussed in this paper indicate that the carboxylate anion is a strong enough nucleophile to participate in neighboring group displacement reactions involving six- and seven-membered ring intermediates. The course of the reaction is determined by the reactivity of the halogen atom.

Experimental[19]

Diethylaminoethyl Acetylsalicylate Hydrochloride (II).—A solution of 39.1 g. (0.2 mole) of acetylsalicyloyl chloride[7] in 800 ml. of dry ether was heated to the reflux temperature. Diethylaminoethanol (23.4 g., 0.2 mole) in 200 ml. of ether was added dropwise with stirring over a one-hour period. After an additional hour at the reflux temperature, the reaction mixture was cooled to 10–15° and the white solid, diethylaminoethanol hydrochloride, was removed by filtration. The filtrate was concentrated to about 150 ml. and stored for 24 hours at room temperature. The white solid which separated was recrystallized from ethyl alcohol–ethyl acetate to a melting point of 136.5–137.5° (6.3 g., 10%). The infrared absorption spectrum showed bands at (cm.$^{-1}$): 2560, 2470, 2360sh, 1609, 1576, 1486, 1261, 1215sh, 1202, 755, 746, 695.

Anal. Calcd. for $C_{15}H_{22}ClNO_4$: C, 57.05; H, 7.02; N, 4.44; Cl, 11.23. Found: C, 57.32; H, 7.15; N, 4.37; Cl, 11.78.

The Reaction of Chloroacetylsalicylic Acid with Ammonia. A. In Ethanol. Cleavage to Ammonium Salicylate and Chloroacetamide.—In a dry 1-l. three-necked flask fitted with a stirrer, Dry Ice condenser, gas inlet tube, and a thermometer were placed 21.5 g. (0.1 mole) of chloroacetylsalicylic acid, 500 mg. of copper powder and 250 ml. of absolute ethanol. After bubbling ammonia through the reaction mixture at −20° for four hours, the deep blue solution was allowed to warm to room temperature while the ammonia was gradually distilled. The remaining ethanol solution was concentrated under reduced pressure at a temperature not exceeding 25°. The residual green solid was slurried with 200 ml. of absolute ether and the solid was removed by filtration. The filtrate, A, and the green solid, B, were worked up separately, A yielding 1.1 g. of chloroacetamide and 2.6 g. of salicylic acid and B yielding 6.1 g. of chloroacetamide and 7.9 g. of salicylic acid. The total chloroacetamide isolated was 7.2 g. (77.7% of theory) and the total salicylic acid was 10.5 g. (76.5% of theory).

B. In Absolute Ether. Formation of Ammonium Chloroacetylsalicylate.—A dry ethereal solution of chloroacetylsalicylic acid was cooled to 0° and ammonia was bubbled into the reaction mixture until no additional solid formed. The solid, removed by filtration, represented an 83 wt. per cent. yield of a water-soluble material melting at 70–72° which gave a negative ferric chloride test. (Kaufmann and Thomas[8] reported a melting point of 70° for the material they called glycylsalicylic acid hydrochloride.) This material on exposure to air decomposed yielding a water-insoluble solid which melted over a broad range, 75–140°, and which gave a positive ferric chloride test. When the 70–72° material was dissolved in ice-water and acidified with dilute hydrochloric acid, a 91% yield (based on ammonium chloroacetylsalicylate) of chloroacetylsalicylic acid was obtained, m.p. 135–137°. An additional 7% yield of less pure material was also obtained, m.p. 132–145°, which was identified as being mainly chloroacetylsalicylic acid by its infrared spectrum.

The ammonium salt of aspirin was prepared by essentially the same procedure described above, m.p. 100–102°. The infrared spectrum of ammonium chloroacetylsalicylate, the compound melting at 70–72°, was very similar to that of the ammonium salt of aspirin. Based on its water solubility, reaction with dilute acid to yield chloroacetylsalicylic acid, and the similarity of its infrared spectrum to that of ammonium acetylsalicylate, the material, m.p. 70–72°, obtained by treating chloroacetylsalicylic acid with ammonia in ether in the presence of copper powder is ammonium chloroacetylsalicylic acid, an isomer of glycylsalicylic acid hydrochloride, the desired product.

(19) All melting points are uncorrected. All infrared spectra were taken on a Perkin-Elmer Model 21 Spectrophotometer, using mineral oil mulls and sodium chloride plates.

	Region of spectrum, cm.$^{-1}$			
	OH/NH	C=O	C=C + salt	C—O
Ammonium salt of aspirin	3240sh, 3160, 2740sh	1765, 1740sh, 1710	1600, 1565	1223, 1195, 1098
Ammonium chloroacetylsalicylic acid	3300sh, 3200, 2800sh	1775, 1743	1600, 1550	1260, 1205, 1095

Methyl pyrrolidylacetylsalicylate hydrochloride (VII) was prepared by a modification of the method of Hahn and Loos.[9] Methyl chloroacetylsalicylate (114 g., 0.5 mole) and sodium iodide (75 g., 0.5 mole) were suspended in 500 ml. of dry acetone and the reaction mixture was shaken under nitrogen at room temperature for 4 hours. The precipitated sodium chloride (26.5 g., theory 26.2 g.) was removed by filtration and the filtrate was cooled to 5° with stirring while pyrrolidine (71 g., 1.0 mole) in 200 ml. of dry ether was added dropwise over a 20-minute period. The reaction mixture was stirred for an additional 2 hours at 5° and for 15 hours at 15°. The solvent was removed under reduced pressure with stirring and the residue was taken up in water and extracted with ether. The aqueous phase was made basic at 5° and extracted immediately with ether. The combined ether layers were concentrated under reduced pressure and dried by repeated distillation of benzene. Last traces of pyrrolidine were removed by evacuating with an oil-pump at 30° for several hours. The residue was dissolved in ether, hydrogen cloride was passed into the solution, and the precipitated solid was removed by filtration. Recrys:allization from ethanol, isopropyl alcohol, ethyl acetate and finally methylcyclohexane yielded 40 g. (27% yield) of methyl pyrrolidylacetylsalicylate hydrochloride, m.p. 131–132°.

Anal. Calcd. for $C_{14}H_{18}ClNO_4$: C, 56.01; H, 6.05; Cl, 11.83; N, 4.67. Found: C, 56.45; H, 6.21; Cl, 11.17; N, 4.65.

In another preparation the analytical sample, recrystallized from ethyl acetate, was a polymorphic form, m.p. 146–147° dec. The infrared spectrum showed the following absorptions: hydrochloride salt at 2510, 2430, 2390 cm.$^{-1}$; carbonyl groups at 1768 (phenol ester) and 1723 cm.$^{-1}$ (benzoate ester); 1611, 1584, 1489 characteristic of benzene hydrogens; 1295, 1206, 1185 characteristic of C–O of esters; 769 characteristic of an *o*-disubstituted phenyl group.

Anal. Calcd. for $C_{14}H_{18}ClNO_4$: C, 56.10; H, 6.05; Cl, 11.83; N, 4.67; equiv. wt., 299.8. Found: C, 56.09; H, 5.86; Cl, 11.85; N, 4.58; equiv. wt., 298.6.

Benzyl triethylammoniumacetylsalicylate iodide (VIII) was prepared in 38% yield by essentially the same procedure as methyl pyrrolidylacetylsalicylate. After recrystallization from acetone–ethyl acetate (1:4) in 90% yield the analytical sample melted at 101–103°.

Anal. Calcd. for $C_{22}H_{28}INO_4$: C, 53.12; H, 5.67; I, 25.52. Found: C, 52.78; H, 5.71; I, 25.26.

1-Pyrrolidinylcarbonylmethyl Salicylate (XII).—In a 1-l., round-bottomed flask were placed 43.0 g. (0.2 mole) of chloroacetylsalicylic acid, 30.0 g. (0.2 mole) of sodium iodide and 250 ml. of acetone. The flask was stoppered and shaken at 25° for 5 hours. Precipitated sodium chloride was removed by filtration and the filtrate was placed in a 1-l., 3-necked flask equipped with a stirrer, dropping funnel and a reflux condenser. Pyrrolidine (28.4 g., 0.4 mole) in 200 ml. of acetone was added dropwise to the stirred solution over a 1-hour period and the reaction mixture was then heated to reflux for one hour. The solvent was removed under reduced pressure at less than 25°, and the solid residue was washed with three 50-ml. portions of water. After drying, the product (32.0 g., 64% yield) was recrystallized from acetone–methylcyclohexane, m.p. 125–127°. Two recrystallizations from ethyl acetate–methylcyclohexane yielded an analytical sample, m.p. 131–132°; infrared absorptions (cm.$^{-1}$): 3230, 1668sh, 1650, 1606, 1579, 1476, 759, 730.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.54; H, 6.11; N, 5.57.

1-Morpholinocarbonylmethyl salicylate was prepared by the same procedure used for the pyrrolidine analog. Recrystallization was carried out from ethyl acetate–methylcyclohexane, m.p. 119–120°.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.54; H, 5.84; N, 5.37.

1,4-Benzodioxepin-2,5-(3H)-dione (XXV).—In thoroughly dried equipment chloroacetylsalicylic acid (3.3 g., 15.4 millimoles), sodium iodide (2.3 g., 15.4 millimoles) and 60 ml. of acetone were heated to the reflux temperature for two hours under nitrogen. Sodium chloride (810 mg., 90% of theory) was removed by filtration in a nitrogen atmosphere, triethylamine (1.6 g., 15.4 millimoles) was added to the filtrate, and the reaction mixture was heated at the reflux temperature for one hour. The solvent was removed under reduced pressure and the semi-solid orange residue was dissolved in chloroform which was extracted rapidly with three portions of ice-water. After drying over magnesium sulfate, the chloroform solution was concentrated under reduced pressure to an amber oil which, after trituration with ice-cold isopropyl alcohol, solidified on standing, yielding 1.0 g. (36.5%) of a pale yellow solid, m.p. 110–112°. Recrystallization from benzene–methylcyclohexane after decolorization with Darco G-60 yielded an analytical sample, m.p. 115–115.5°, $\lambda_{max}^{(EtOH)}$ 239 mμ a_m 10,400; $\lambda_{max}^{(EtOH)}$ 307 mμ a_m 4,550. This material gave negative Beilstein and ferric chloride tests; infrared absorptions (cm.$^{-1}$): 1795, 1730, 1613, 1586, 1320, 1223, 1205, 797, 785, 765, 702, 685.

Anal. Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.40. Found: C, 60.49; H, 3.30.

Reactions of 1,4-Benzodioxepin-2,5-(3H)-dione. A. With Pyrrolidine. Conversion to 1-Pyrrolidinylcarbonylmethyl Salicylate (XII).—In dried equipment equimolar quantities of pyrrolidine (dried over potassium hydroxide) and 1,4-benzodioxepin-2,5-(3H)-dione in acetone (dried over calcium chloride) were heated to the reflux temperature for one hour. The solvent was removed under reduced pressure yielding a residual white solid, m.p. 128–130°, in quantitative yield. Recrystallization from ethyl acetate–methylcyclohexane yielded melting at 130–131.5°, identical to XII by mixed melting point and comparison of infrared spectra.

B. With Water. Synthesis of Salicyloylglycolic Acid (XXVI).—In one preparation of 1,4-benzodioxepin-2,5-(3H)-dione (XII) the reaction was carried out as usual, the solvent was removed under reduced pressure, and the residue in chloroform was washed with water at *room temperature*. The work-up was then continued as for 1,4-benzodioxepin-2,5-(3H)-dione; however, the solid which was isolated was unlike XII in melting point, 131–132°, (salicycloylglycolic acid melts at 132°[16]), and infrared spectrum. The elemental anaylsis indicated that XII had reacted with one mole of water to yield XXVI which gave a positive ferric chloride test, $\lambda_{max}^{(EtOH)}$ 238 mμ, a_m 12,050; and $\lambda_{max}^{(EtOH)}$ 307 mμ, a_m 5,350. Compound XVI showed absorption at the following frequencies in the infrared spectrum: 3230, 2760sh, 2640, 2540, 1723, 1687, 1615, 1585, 1490, 1283, 1267, 1248, 1235, 945sh, 925sh, 900, 745 and 695.

Anal. Calcd. for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 55.48; H, 4.38.

Proof of Structure of XII by Synthesis. The Preparation of 1-Pyrrolidinylcarbonylmethyl Salicylate.—Sodium salicylate (16 g., 0.1 mole), chloroacetylpyrrolidine (10 g., 0.068 mole), 500 ml. of acetone and enough water to clarify the reaction mixture were heated on a steam-bath for 72 hours. The precipitated sodium chloride was removed by filtration. Upon dilution with cold water, a white solid (10.3 g., 60%) separated from solution, m.p. 130–131°. An analytical sample was prepared by recrystallization from a solution of ethyl acetate and methylcyclohexane, m.p. 131–132°. A mixed melting point with XII was 131–132° and the infrared spectra were identical.

Carbobenzyloxy-β-aminopropionylsalicylic Acid (XXVII).—Salicylic acid (13.3 g., 0.097 mole), 7.9 g. (0.1 mole) of pyridine and 400 ml. of ether were cooled to 5°. To the stirred solution 23.3 g. (0.097 mole) of carbobenzyloxy-β-aminopropionyl chloride dissolved in 100 ml. of ether was added dropwise over a 1-hour period. After being stirred for an additional hour at 30°, the reaction mixture was washed with four 100-ml. portions of water, dried, and the solvent removed under reduced pressure. The solid residue was recrystallized from ethyl acetate–methylcyclohexane, m.p. 121–122°.

Anal. Calcd. for $C_{18}H_{17}NO_5$: C, 62.97; H, 4.99; N, 4.08. Found: C, 62.99; H, 4.77; N, 4.06.

Reaction of Chloroacetylsalicylic Acid with Pyrrolidine.—To a solution of 21.5 g. (0.1 mole) of chloroacetylsalicylic

acid in 200 ml. of dry acetone was added a solution of 14.2 g. (0.2 mole) of pyrrolidine in 200 ml. of dry acetone at 25–35° over a 1-hour period. The clear yellow reaction mixture was heated to the reflux temperature for one hour and the acetone was removed under reduced pressure. The residual yellow oil was dissolved in chloroform (A) and washed with ice-water (B), ice-cold dilute sulfuric acid, and water. The aqueous wash (B), on acidification yielded 8.9 g. of salicylic acid, m.p. 160–162°. A mixed melting point with salicylic acid was not depressed and the infrared spectrum was identical to that of an authentic sample. The chloroform solution (A) was washed with ice-cold sodium carbonate solution which removed an additional 1.2 g. of salicylic acid. The total salicylic acid recovered was 10.1 g. (0.073 mole, 73%). Extraction with ice-cold 0.3 *N* sodium hydroxide yielded 3.25 g. (13%) of 1-pyrrolidinylcarbonylmethyl salicylate (XII), identical by mixed melting point and infrared spectrum to the samples of XII prepared by other methods cited in this paper. The chloroform solution containing neutral material yielded 5.6 g. (38%) of chloroacetylpyrrolidine, m.p. 39–45°. Recrystallization several times from *n*-butyl ether yielded an analytical sample, m.p. 44–46° (Kofler block). The low recovery of chloroacetylpyrrolidine is not too surprising since it has an appreciable solubility in water and continuous extraction of all aqueous phases was not used in its recovery.

Anal. Calcd. for $C_6H_{10}ClNO$: C, 48.82; H, 6.83. Found: C, 48.65; H, 6.41.

Hydrogenolysis of Carbobenzyloxy-β-aminopropionylsalicylic Acid.—A mixture of 22.1 g. (64.5 millimoles) of carbobenzyloxy-β-aminopropionylsalicylic acid, 200 ml. of methanol and 2.0 g. of 5% palladium-on-charcoal was hydrogenated at room temperature at 50–20 p.s.i. The theoretical amount of hydrogen was absorbed in 45 minutes. The amber oil (14.3 g.) was dissolved in ether–ethanol and treated with ethereal hydrogen chloride. A white solid separated from solution, m.p. 104–106° (6.5 g., 72% based on methyl β-aminopropionate hydrochloride). An analytical sample was prepared by recrystallization from ethanol–ethyl acetate, m.p. 106–107°.

Anal. Calcd. for $C_4H_{10}ClNO_2$: C, 34.42; H, 7.22; Cl, 25.40; N, 10.04. Found: C, 34.88; H, 6.94; Cl, 25.38; N, 10.16.

An authentic sample of methyl β-aminopropionate melted at 106–107° and did not depress a mixed melting point with the above compound. The infrared spectra were identical. The filtrate, after collection of the methyl β-aminopropionate, was concentrated to dryness yielding a white solid which after recrystallization from ethyl acetate melted at 155–158°. The infrared spectrum of this material was identical to that of an authentic sample of salicylic acid.

Reaction of Aspirin with Ethyl Alcohol in the Presence of Triethylamine.—Acetylsalicylic acid (90 g., 0.5 mole) and triethylamine (50.5 g., 0.5 mole) were dissolved in 500 ml. of absolute ethyl alcohol and the solution was stored at 25° for 20 hours. The solvent was removed under reduced pressure below 25° and the distillate was collected in a receiver cooled in Dry Ice–acetone. The residue in the distillation flask was dried under reduced pressure yielding 120.4 g. of triethylammonium salicylate (100.5% of theory). The distillate, 500 ml., was analyzed by vapor phase chromatography using helium as the carrier over an "Octoil 5-Celite" column (80" × 0.25") at 75°. This analysis showed that the distillate contained 44 g. or 9.8% by volume of ethyl acetate (quantitative yield).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, WASHINGTON UNIVERSITY, SCHOOL OF MEDICINE]

Oxidation–Reduction Potentials, Ionization Constants and Semiquinone Formation of Indigo Sulfonates and their Reduction Products

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The oxidation-reduction potentials of indigo di-, tri- and tetra-sulfonates in alkaline buffers have been reinvestigated. The ionization constants of these compounds and their corresponding fully reduced derivatives have been estimated from spectrophotometric measurements. The potentials indicate pronounced semiquinone formation in alkaline solutions of about *p*H 10.5 to 12.5. The ionization constants derived from the oxidation-reduction potentials are consistent with those estimated from the spectrophotometric data. The results are of importance in the use of the indigosulfonates as indicators in alkaline solutions.

When indigo[2,3] in alkaline alcoholic solution or indigo disulfonate[4] in aqueous buffers of about *p*H 11 to 12.5 are reduced by the gradual addition of reducing agent, a red intermediate color appears between the initial blue (or green) of the fully oxidized and the yellow of the reduced compound; on reoxidation the red color appears in the reverse color sequence. Outside this *p*H zone, the red color is not observed; in less alkaline solutions of the sulfonates,[4] the color changes from blue, through the green of the mixture, to yellow; in more strongly alkaline solutions, the initial color is a yellow, which on reduction changes to a lighter yellow.

As part of their pioneer work on the oxidation–reduction potentials of organic substances, W. M. Clark,[5] and Sullivan, Cohen and Clark[6] determined the potentials of the indigo systems in various buffers from *p*H 1.2 to 12.6. Above *p*H 9, only a single ratio of oxidant to reductant was measured for each buffer and certain discrepancies noted were ascribed to an effect caused by the borate buffers used rather than to some unique property of the substances themselves.

Our reinvestigation of the oxidation–reduction potentials of the indigo sulfonates and their reduced forms and their absorption coefficients, in alkaline buffers of *p*H 10 to 15, was conducted to find an explanation for the formation of the red intermediate substances.

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