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DERIVATIVES OF SALICYLIC ACID

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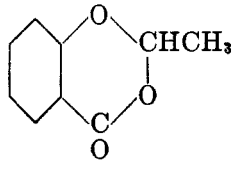
Received April 16, 1948

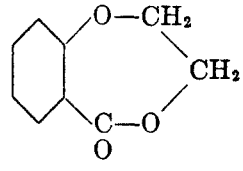
In the hope that the combination of the aspirin and the phenacetin structures in one molecule may give rise to pharmacologically interesting substances, older preparative experiments in the series of N-salicoyl-*p*-aminophenol (1) (III) were repeated and extended. [Salicoyl phenetidide (I) has been described by Bolezzi (1b) and by Cohn (1a), and also by Cohn (2), Anschütz (3), and in a U. S. Patent (4).] The results of this investigation are summarized in Charts A and B.

Some of the observations made are believed to be of interest. The hydroxyl groups of (I) and (III) are converted into the corresponding *carbonates* (IIa and VIII) by treatment with methyl chloroformate in pyridine and under fairly mild conditions. [This type of reaction is, of course, not new (5).] Salol reacts with *p*-aminophenol in an unsatisfactory manner, but using a diluent such as 1,2,4-trichlorobenzene or 1-methylnaphthalene (6), VanAllan (1d) reported good results. Acetylsalicoyl chloride, too, reacts smoothly with *p*-aminophenol, and IV can, therefore, be prepared easily by hydrolysis of its diacetyl and its two monoacetyl derivatives. Acetylation of IV attacks first the hydroxyl group of the *p*-aminophenol radical (VI), so that the isomeric monoacetyl compound (III) is only accessible by the condensation of acetylsalicoyl chloride with *p*-aminophenol.

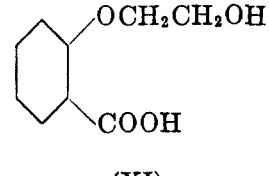
In connection with these experiments, β-hydroxyethyl salicylate, $HOC_6H_4COOCH_2CH_2OH$, was prepared from sodium salicylate and ethylene chlorohydrin.[1] As by-product, a crystalline compound was observed (m.p. 82°) which gave analysis for $C_9H_8O_3$. Its melting point excluded the possibility that it was 2-methyl-4-keto-1,3-benzodioxane (IX) which has recently been described as melting at 33° (7). We assume, therefore, that the substance is the seven-membered cyclic ether (X) of the ester. It could also have formed through *o*-(β-hydroxyethoxy)benzoic acid (XI).



(IX)



(X)



(XI)

EXPERIMENTAL

Acetylsalicoyl phenetidide (II). To a solution of 514 g. (2 moles) of salicoyl phenetidide (from alcohol, m.p. 146°) in 790 cc. of pyridine, 188 g. of acetyl chloride was gradually added

[1] See *Chem. Zentr.*, **1906**, II, 934. The reaction of ethylene chlorohydrin with sodium salts of organic acids has been studied before in only one other case, that of benzoic acid (*Chem. Zentr.*, **1912**, I, 1407). We have investigated its reaction with sodium propionate, cinnamate, and phenylcinchonate; they all give easily β-hydroxyethyl esters.

CHART A

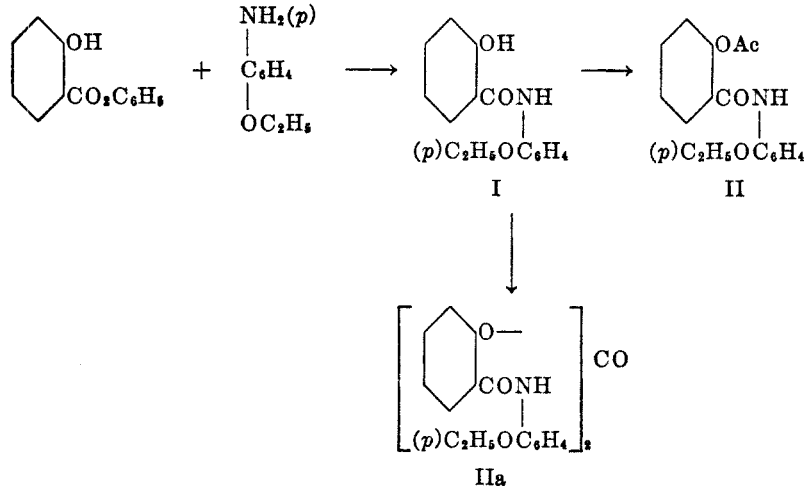
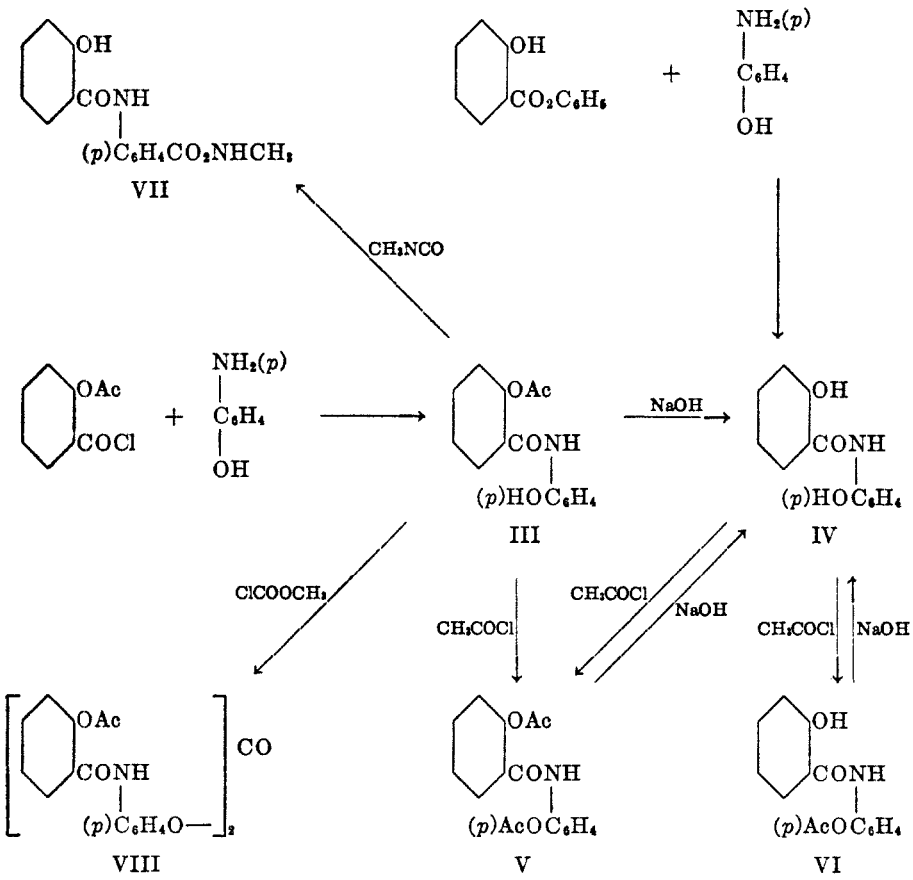


CHART B



in the course of two hours with cooling (0°) and stirring. The stirring was continued for two hours, and the reaction completed by refluxing for one hour. Dilute sulfuric acid precipitated the product, which was recrystallized from acetone or butyl acetate, and melted at 134°; yield 545 g. (91%).

Anal. Calc'd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7.
Found: C, 68.0; H, 5.8; N, 4.5.

Acetylation with acetyl chloride and acetic anhydride at 100° led, by displacement of the acetylsalicoyl radical, to phenacetin (from butyl acetate, m.p. 134°), which depressed the m.p. of II considerably.

Carbonate of salicoyl phenetidide (IIa). Methyl chloroformate (1.1 cc.) in chloroform (5 cc.) reacted with salicoyl phenetidide (2.6 g.) in pyridine (10 cc.) with liberation of heat. After twenty-four hours at room temperature, the mixture was heated at 100° for one hour and poured into dilute sulfuric acid. The product which separated was recrystallized from pyridine, and formed aggregates of fine prisms, which melted at 256–257°.

Anal. Calc'd for $C_{31}H_{28}N_2O_7$: C, 68.9; H, 5.2; N, 5.2.
Found: C, 68.9; H. 5.0; N, 5.4.

For the synthesis of *N-acetylsalicoyl-p-aminophenol (III)*, the following method has proved satisfactory: (a) The chloride of acetylsalicylic acid was best prepared (8) by adding the free acid (720 g., 4 moles) to a solution of thionyl chloride (952 g., 8 moles) in benzene (1300 cc.) and refluxing the mixture for six hours. The volatile components of the product were removed by distillation and finally by heating at 110° under 15 mm. pressure for about two hours. Upon cooling, the oil crystallized spontaneously. It did not require further purification, *e.g.*, by distillation (b.p. 135°/12 mm.; 99°/3.5 mm.); m.p. 43–44°; yield 745 g. (94%).

(b) A solution of 397 g. (2 moles) of the chloride in 600 cc. of ether was added at 0° to the vigorously stirred suspension of 436 g. (4 moles) of *p*-aminophenol in 1400 cc. of anhydrous ether. The reaction was completed by continuing the stirring at room temperature (two hours) and finally at the boiling point of ether (three hours). The solid product was filtered, dried, digested with water, and subsequently with very dilute hydrochloric acid, and washed chloride-free. (The mother liquor contained the excess of aminophenol, which could be recovered in the normal way by use of sodium sulfite.) From butyl acetate, the product crystallized in glistening needles, m.p. 167°; yield 490 g. (90%).

Anal. Calc'd for $C_{15}H_{13}N_4O_3$: N, 5.2. Found: N, 5.1, 5.2.

The carbonate (VIII) of (III) was prepared as described for the salicoyl phenetidide (IIa). After recrystallization from a mixture of equal volumes of benzene and light petroleum, it formed fine needles, melting at 134–135°.

Anal. Calc'd for $C_{31}H_{24}N_2O_9$: N, 4.9. Found: N, 4.6.

N-Salicoylaminophenol (IV). (a) The N-acetylsalicoyl compound (III) was hydrolyzed when dissolved in cold 0.1 *N* NaOH solution and kept at room temperature for five minutes. Addition of 0.1 *N* HCl precipitated the desired compound in quantitative yield. From very dilute alcohol or xylene, it crystallized in needles of m.p. 178°. Ferric chloride solution gave a purple color reaction; the solution of the substance in aqueous ammonia turned blue on exposure to air.

(b) The reaction of salol (125 g.) and *p*-aminophenol (22 g.) at 200° (one hour) gave a resinous product which crystallized upon trituration with acetone (50 cc.), but could be purified only with some difficulty. Acetylation of the crude product with boiling acetic anhydride and anhydrous sodium acetate, however, gave the pure diacetyl derivative of m.p. 151° (see below). Method (a) is preferable in our experience.

N-Acetylsalicoyl-p-aminophenyl acetate (V). (a) A mixture of 54.2 g. (0.2 mole) of

N-acetylsalicoyl-*p*-aminophenol (III) and 80 cc. of acetyl chloride was refluxed for four hours. The excess of the chloride was removed from the crystalline product by distillation and the residue recrystallized from alcohol. It formed colorless needles of m.p. 151°; yield 53 g. (93%).

Anal. Calc'd for $C_{17}H_{15}NO_5$: N, 4.5. Found: N, 4.4, 4.6.

(b) N-Salicoyl-*p*-aminophenol (IV) was refluxed with an excess of acetyl chloride for six hours. The product was isolated in the manner described under (a).

Hydrolysis with 2 moles of aqueous 0.1 *N* NaOH brought the diacetyl compound (V) into solution very slowly; it produced first N-salicoyl-*p*-aminophenyl acetate (VI), described presently, then N-salicoyl-*p*-aminophenol (IV).

N-Salicoyl-p-aminophenyl acetate (VI). Equimolecular quantities of N-salicoyl-*p*-aminophenol (IV) and acetyl chloride were refluxed for two hours. The reaction product was triturated with water, dried, and recrystallized from ethyl alcohol. It formed needles, melting at 181°; yield 61%.

Anal. Calc'd for $C_{15}H_{13}NO_4$: C, 66.4; H, 4.8; N, 5.2.
Found: C, 66.1; H, 5.0; N, 5.0.

Methylurethan (VII) of N-salicoylaminophenol (IV). The reaction of N-acetylsalicoyl-*p*-aminophenol (III) with methyl isocyanate is accompanied by deacetylation. It was carried out by heating 3.3 g. of (III) and 2.5 g. of methyl isocyanate at 60° for 10 hours (sealed tube). The reaction product was freed from excess reagent and triturated with methanol, which left a small amount of the starting material undissolved. The solution was evaporated to dryness, and the residue recrystallized from a small quantity of propyl alcohol. The methylurethan formed aggregates of needles, m.p. 199°, which gave a positive response to ferric chloride solution.

Anal. Calc'd for $C_{15}H_{14}N_2O_2$: C, 62.9; H, 4.9; N, 9.8.
Found: C, 62.8; H, 5.1; N, 9.6, 9.9.

β-Hydroxyethyl salicylate. A mixture of 20 g. of sodium salicylate, 8 cc. of ethylene chlorohydrin, and 0.5 g. of copper-bronze was heated at 140° for four hours. The reaction product was treated with water and ether and the residue of the ethereal layer fractionated. The desired ester boiled at 166°/13 mm.; yield 12 g. (53%).

The residue crystallized upon standing. From methyl alcohol, the cyclic ether (IX) formed either leaflets or prisms (dimorphism) and melted at 82°; it has no free hydroxyl group.

Anal. Calc'd for $C_9H_8O_3$: C, 66.0; H, 5.0.
Found: C, 66.0; H, 5.2.

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REFERENCES

(1) (a) COHN, *J. prakt. Chem.*, (2) **61**, 551 (1900). (b) BOLEZZI, *Gazz. chim. ital.*, **28**, 200 (1898). (c) FARGHER, GALLOWAY, AND PROBERT, *J. Textile Inst.*, **21**, 245 T (1930); *Chem. Abstr.*, **24**, 6026 (1930). (d) VANALLAN, *J. Am. Chem. Soc.*, **69**, 2913 (1947).
(2) COHN, *J. prakt Chem.*, (2) **60**, 404 (1899).
(3) ANSCHÜTZ, *Ber.*, **37**, 3976 (1904).
(4) U. S. Patent 706,356 (1902).
(5) MOREL, *Bull. soc. chim.*, (3) **21**, 829 (1899).
(6) *Org. Syntheses*, **26**, 92 (1946).
(7) MOWRY, YANKO, AND RINGWALD, *J. Am. Chem. Soc.*, **69**, 2358 (1947).
(8) MCCONNAN, *J. Chem. Soc.*, **89**, 1333 (1906). WOLFFENSTEIN, German Patent, 277,659.