Synthesis of 2-Alkyl-4H, 1, 3-benzoxazine-4-ones

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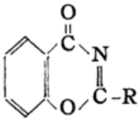
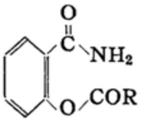
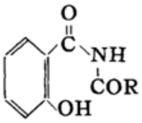
4*H*,1,3-Benzoxazine-4-one derivatives are expected to show interesting chemical and biological properties, owing to the characteristic structure that the carbonyl group adjacent to N=C double bond is present in them. However, only a few 2-aryl derivatives have been reported[1,2], and no literature has appeared concerning 2-alkyl derivative. Titherley[1] reported the preparation of 2-phenyl-4*H*, 1, 3-benzoxazine-4-one (I: R=Ph) from *O*- or *N*-benzoylsalicylamide by the action of hydrogen chloride in boiling xylene. But Titherley et al.[3] failed in the preparation of 2-methylbenzoxazinone (Ia) from *O*-acetylsalicylamide (IIa) by the same procedure, and isolated only *N*-acetylsalicylamide (IIIa) produced by O→N acyl rearrangement. They assumed that the abortive isolation of 2-methylbenzoxazinone was due to its decomposition by alkali which was present.



I



II



III

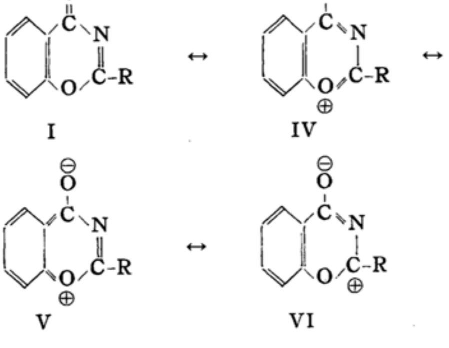
(a: $R=CH_3$, b: $R=C_2H_5$, c: $R=C_3H_7$)

In the present experiment *O*-acetylsalicylamide (IIa) was treated with hydrogen chloride in boiling xylene according to the procedure of Titherley[1], and without using alkali there were isolated yellow crystals, $C_9H_7O_2N$, m. p. 217°C, together with *N*-acetylsalicylamide (IIIa) produced by the acyl rearrangement. The yellow compound was considered to be 2-methyl-4*H*, 1, 3-benzoxazine-4-one (Ia). Its infrared spectrum showed carbonyl band at 1680 cm^{-1}, and C=N band at 1645 cm^{-1}, and indicated also the absence of both OH and NH group. This was insoluble in cold dilute aqueous alkali and showed no coloration with ferric chloride in chloroform. It also was produced from *N*-acetylsalicylamide (IIIa) in low yield under similar conditions.

Similarly, 2-ethyl- and 2-propyl-benzoxazinone (Ib and Ic) were synthesized from *O*-propionyl- and *O*-butyrylsalicylamide (IIb and IIc) respectively, though in poor yield. Their chemical and physical properties were very similar to those of the 2-methyl compound. It is noticeable that the infrared spectra of these compounds are essentially identical in the region below 7μ, while the 2-phenyl homologue shows an infrared band of carbonyl group at 1665 cm^{-1} and of C=N group at 1645 cm^{-1}.

2-Methyl-4*H*, 1, 3-benzoxazine-4-one was stable towards acid in contrast with the 2-phenyl homologue, but very sensitive to alkali; it was easily hydrolyzed to salicylamide by boiling with 1 N-sodium hydroxide for a few minutes. When heated with dilute aqueous ammonia it produced an alkali-soluble compound, m. p. 227°C (empirical formula, $C_{18}H_{15}O_3N_3$), of which the structure is now under investigation.

2-Alkyl-benzoxazinone contains a characteristic skeleton, $-CO-N=\overset{|}{C}-$, which has not yet been studied well and is assumed to be stabilized by a hydrid among the structures I, IV, V, and VI. It is supposed that the carbon atom at the 2-position is easily attacked by the nucleophilic reagent owing to the influence of the carbonyl group.



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[1] A. W. Titherley, *J. Chem. Soc.*, **97**, 200 (1910).

[2] A. Mustafa and A. E. A. A. Hassan, *J. Am. Chem. Soc.*, **79**, 3846 (1957).

[3] A. W. Titherley and W. L. Hicks, *J. Chem. Soc.*, **99**, 866 (1911).

Experimentral

***O*-Acetylsalicylamide (IIa).**—McConnan and Titherley[4] prepared this compound by the action of acetyl chloride on salicylamide in pyridine at −15°C. In the present study it was obtained by the following procedure: a few drops of concentrated sulfuric acid were added to a mixture of 20 g. of salicylamide and 50 ml. of acetic anhydride. After this mixture was kept for about 10 min., 500 ml. of water was added in order to decompose the excess of acetic anhydride. Upon filtration and washing with water, 18.5 g. (71%) of crude product was obtained and used for the next step without further purification. Recrystallization from ethyl acetate gave colorless needles, m. p. 138°C (Reported m. p. 138°C.).

***O*-Propionylsalicylamide (IIb).** — A solution of 10 g. of salicylamide in 20 ml. of pyridine was cooled to −15°C and 6.8 g. of propionyl chloride was added dropwise under vigorous stirring. After the addition, the mixture was kept for 30 min. at the same temperature, and 100 ml. of ether was added under stirring and then the ether was decanted off. To the remaining pasty mixture was added 1 N-sulfuric acid at 0°C, under stirring, in the course of ca. 10 min. The solid was filtered and washed with water. After the above ethereal solution had been allowed to stand for several hours, an additional small quantity of crystals was separated. The combined solids (9.1g.; 65%) were recrystallized from benzene to give colorless needles, m. p. 112∼113°C, which showed no coloration with ethanolic ferric chloride.

Anal. Found: C, 62.27; H, 5.93. Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74%.

***N*-Propionylsalicylamide (IIIb).** — When dilute aqueous ammonia was added to IIa, the solid was dissolved gradually and a yellow solution was obtained. By acidification with dilute hydrochloric acid colorless crystals were obtained, m. p. 123∼125°C. Recrystallization from benzene gave colorless needles, m. p. 126∼127°C, readily soluble in ethanol and ether; they revealed a purple-brown color with ethanolic ferric chloride.

IIIb was also obtained by boiling IIb with water for 30 min.

Anal. Found: C, 62.68; H, 5.92. Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74%.

***O*-Butyrylsalicylamide (IIc).**—To a solution of 10 g. of salicylamide in 20 ml. of pyridine, was added 7.8 g. of butyryl chloride at −15°C following the same procedure as in the case of IIb. A solid thus obtained was crystallized from benzene to yield colorless needles, but the melting point was not sharp (m. p. ca. 90∼110°C) because of persistent contamination of IIIc.

Anal. Found: C, 64.02; H, 6.59. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32%.

***N*-Butyrylsalicylamide (IIIc)**,—This material was prepared by the action of dilute aqueous ammonia on IIc, or by boiling IIc with water for 20 min. Recrystallization from benzene gave colorless needles, m. p. 128∼129°C, readily soluble in ethanol and ether. They produced an orange brown color with ethanolic ferric chloride.

Anal. Found: C, 63.64; H. 6.55. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32%.

2-Methyl-4*H*, 1, 3-benzoxazine-4-one (Ia).—a) *From O-Acetylsalicylamide* (*IIa*).—A mixture of 15 g. of IIa and 200 ml. of xylene was heated in a bath to 145°C, and when the solution became clear, a stream of dry hydrogen chloride was passed through for several min. By gradually raising the temperature of the bath to 155°C, the xylene was allowed to distil out, carrying with it the water formed during the reaction. In order to make up for the loss of hydrogen chloride by distillation, a few bubbles of the gas were passed into the solution at an interval of several minutes. When the greater part of the solvent was distilled off, the residue solidified on cooling. It was treated with warm ethanol to remove IIIa. The remaining yellow solid (7.4g.; 50%) was repeatedly crystallized from benzene to yield yellow needles (Ia), m. p. 217°C. It was insoluble in ethanol and ether, soluble in dioxane, pyridine and chloroform. The infrared spectrum showed bands at 1684 cm⁻¹ (C=O) and 1645 cm⁻¹ (C=N).

Anal. Found: C, 67.05; H, 4.18; N, 8.74. Calcd. for $C_9H_7O_2N$: C, 67.06; H, 4.35; N, 8.69%.

From the ethanolic solution, by evaporation of the solvent and recrystallization from benzene, colorless needles, m. p. 140∼141°C, were obtained. The melting point was not depressed on admixture with IIIa.

b) *From N-Acetylsalicylamide* (*IIIa*).—A solution of 6.5 g. of IIIa in 25 ml. of dry xylene was heated for ca. 5 hr. under passage of dry hydrogen chloride. After removal of the greater part of the solvent under reduced pressure, yellow crystals deposited on cooling. After recrystallization from benzene, the compound had m. p. 217°C; mixed m. p. with Ia prepared from IIa, 217°C.

2-Ethyl-4*H*, 1, 3,-benzoxazine-4-one (Ib). — A solution of 15 g. of IIb in 200 ml. of dry xylene or toluene was heated in the presence of dry hydrogen chloride following the same procedure as above. The product, after removal of the ethanol-soluble part, was crystallized from benzene to yield yellow needles m. p. 212∼213°C, insoluble in ethanol and ether. The infrared spectrum showed bands at 1680 cm⁻¹ (C=O) and 1645 cm⁻¹ (C=N).

Anal. Found: C, 68.48; H, 5.40; N, 8.23. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00%.

The ethanol extracts obtained above were concentrated to a solid, which on crystallization from benzene gave colorless needles, m. p. 126∼127°C, undepressed on admixture with IIIb.

2-Propyl-4*H*, 1, 3-benzoxazine-4-one (Ic).— A solution of 15 g. of IIc in 180 ml. of toluene was heated with dry hydrogen chloride in the same manner as described above. In this case, the residue was wholly soluble in ethanol, but on standing overnight, a small quantity of crystals separated out from the ethanol solution. Recrystallization from benzene gave yellow plates, m.p. 142∼143.5°C, soluble in ethanol and benzene.

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[4] J. McConnan and A. W. Titherley, *J. Chem., Soc.*, **89**, 1333 (1906).

The infrared spectrum showed bands at 1680 cm^{-1} (C=O) and 1645 cm^{-1} (C=N).

Anal. Found: C, 69.77; H, 6.06. Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86%.

Further concentration of ethanolic mother liquor gave crystals which on repeated recrystallizations from benzene had m. p. 124~128°C. The material did not depress the melting point of an authentic sample of IIIc.

Alkaline Hydrolysis of Ia. — When Ia was boiled for a few minutes with 1 N sodium hydroxide, a pale yellow solution was formed. After acidification with diluted hydrochloric acid, the precipitates formed were collected and recrystallized from water to give colorless needles, m. p. 136~137°C. The material was identified as salicylamide on the basis of the mixed melting-point test.

Reaction of Ia with Aqueous Ammonia.— A mixture of 2 g. of Ia, 60 ml. of 3N aqueous ammonia and 60 ml. of ethanol was heated for 30 min. on a steam bath. After cooling the yellow solution was acidified with dilute hydrochloric acid, and the precipitates were collected and recrystallized twice from benzene (once using charcoal) to give colorless needles, m. p. 227°C, in almost quantitative yield. The material was soluble in ether, ethanol and chloroform, and showed no color with ferric chloride in ethanol. It was dissolved in dilute sodium hydroxide solution to give a yellow solution, and was recoverable, as it was, from this solution, after ten minutes' heating in a water bath.

Anal. Found: C, 67.55; H, 4.31; N, 13.09; Mol. wt. (Rast), 323. Calcd. for $C_{18}H_{15}O_3N_3$: C, 67.28; H, 4.71; N, 13.08%; mol. wt., 321.

The infrared spectrum showed bands at 3390 cm^{-1} (OH) and 1640 cm^{-1} (C=O).

Summary

2-Alkyl-4*H*, 1, 3-benzoxazine-4-ones (Ia, Ib, and Ic) were synthesized from the corresponding *O*-acylsalicylamides (II), and some of the properties of I were studied.

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