Some Substituted Amides of Salicylic Acid

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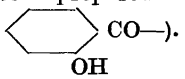
In connection with investigations on heterocyclic substituted amides of 4-aminosalicylic acid some amides of salicylic acid have been prepared (Table 1, R = ).

These compounds were prepared by the reaction of the appropriate amino compound with acetylsalicylic acid chloride in pyridine.

By the preparation of the first-mentioned compound 0.01 mole of acetylsalicylic acid chloride was added under cooling to a solution of 0.01 mole of 2-aminothiazole in 5 ml of pyridine. After standing for two hours at room temperature the solution was diluted with 50 ml of water and the precipitate which separated was filtered after 24 hours and recrystallized from ethanol. Compounds nos. 2 and 3 were prepared in a similar way; the thiadiazole compound was recrystallized from a mixture of ethanol and pyridine and subsequently treated with boiling ethanol.

The compounds nos. 1 and 2 form long, white needles which are readily soluble in ethanol; compound no. 3 which is almost insoluble in ethanol, separates in very small crystals.

For the preparation of compounds nos. 4—6, 0.01 mole of the amino compound was dissolved in the necessary amount of pyridine and 0.01 mole (resp. for no. 4: 0.02 moles) of acetylsalicylic acid chloride was added with cooling and stirring. After standing for 24 hours the solutions were diluted with their own volume of ethanol, neutralized with sodium carbonate, filtered and the filtrate poured into 200 ml of water. In the case of nos. 4 and 6 a white precipitate was obtained, which was filtered and recrystallized from ethanol. The derivative of sulphathiazole, however, separated as an oil, which was turned into solid form by dissolving in 25 ml of 1 *N* NaOH and precipitating with hydrochloric acid. The yield of this compound was small. The yields of the other compounds were about 80 %.

The sulphanilamide derivative has previously been prepared by essentially the same method by v. Euler and Hasselquist [1]. For comparison we prepared this compound in the same way as the first three compounds. The two products were found to be identical.

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two ε-bonds are not parallel, each of them making an angle of about 7° with the principal axis of the carbon ring. We may add that this deformation was observed also in the electron diffraction examination.

The proof has thus been given, that the tetrachlorocompound of m. p. 174° corresponds to the tetrabromocyclohexane of m. p. 185° [3]. It is highly probable that the substance will be the chief reaction product when a solution of chlorine is added to a solution of 1,4-cyclohexadiene in a suitable organic solvent.

The shape of the (optically active) molecule is not altered by a conversion of the carbon ring. A study of the optical antipodes should therefore be possible even in solution.

1. Sabatier, P., and Mailhe, A. *Compt. rend.* **137** (1903) 240.
2. Hetland, E. *Acta Chem. Scand.* **2** (1948) 678.
3. Halmøy, E., and Hassel, O. *J. Am. Chem. Soc.* **61** (1939) 1601.

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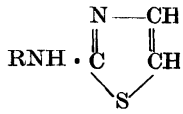
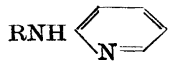
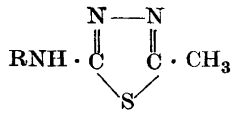
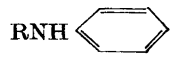
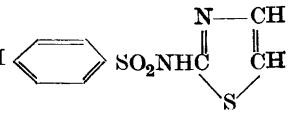
Table 1.

	M. p. °C	(% N) calc.	found
1. N-Salicyloyl-2-aminothiazole 	258	12.73	12.92
2. N-Salicyloyl-2-aminopyridine 	210	13.10	13.32
3. N-Salicyloyl-2-amino-5-methyl-1,3,4-thiadiazole 	298	17.90	17.74
4. N^4-Salicyloyl-sulphanilamide 	257	9.60	9.50
5. N^4-Salicyloyl-sulphathiazole 	268	11.20	11.40
6. bis-(4-Salicyloylamino)-diphenylsulphone 	265	5.74	5.87

During these processes the acetyl group of acetylsalicylic acid is split off. Compound no. 1 was also prepared by the reaction of 2-aminothiazole with benzoylsalicylic acid chloride; in this case, too, the unacylated compound resulted. Nos. 1 and 2 were further prepared by the reaction of salicylic acid chloride with the amine in pyridine solution. In addition to the inconvenience of working with the unstable salicylic acid chloride, this method gave only small yields. The identity of the products prepared by the different methods was shown by analyses and mixed melting points.

Acetylsalicylic acid chloride was prepared by heating equivalent amounts of acetylsalicylic acid and thionyl chloride at 60° for 30 minutes and distilling the product *in vacuo* (b. p. 140° at 15 mm). Yield almost 100 %.

Salicylic acid chloride was prepared by the method of Kirpal [2].

The compounds prepared were tested for antibacterial effect against *Diplococcus pneumoniae* (type I), *Eberthella typhosa*. *Staphylococcus aureus* and *Escherichia coli*, but were found to be without effect in the concentration 1 : 5000.

We thank Dr. K. Kjerulf Jensen for carrying out the bacteriological tests.

1. v. Euler, H., and Hasselquist, H. *Arkiv Kemi, Mineral. Geol.* **A 24** (1947) no. 9.
2. Kirpal, A. *Ber.* **63** (1930) 3190.

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