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SYNTHESIS OF N-ALLYLSALICYLAMIDE AND o, (N-ALLYLCARBAMYL)-PHENOXYACETIC ACID

by

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and
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(*) Directorate-General for Research and Training
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By a reaction analysis study, we found optimum reaction conditions for the synthesis of I, yielding 40 %.

The reaction conditions for the synthesis of II also had to be changed.

A yield of 50 % was obtained. The infra-red spectra are given.

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by

W.H. MÜLLER (*) and A. HEYNDRICKX (**)

o, (N-Allylcarbamyl)-phenoxyacetic acid is expected to be a complexing agent with decontaminating effects for some transition elements.

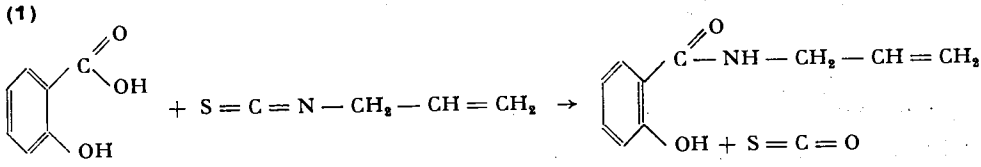
This compound and its precursor N-allylsalicylamide are already known substances but the synthetic methods given in the pertinent literature (4, 5, 6) are not sufficient.

N-Allylsalicylamide (I).

The synthesis, which is given in Equation 1, is described by W.Q. FOYE, H.M. KOTAK and J.J. HEFFEREN (1), who used salicylic acid (III) and allylisothiocyanate (IV) and yielded 25 mole-% of I, calculated on III.

In our experiments we could not reach this value, so the reaction was not always reproducible. Therefore, in order to determine the optimum reaction conditions, a reaction analysis study was carried out by volume measurement of the gaseous carbonoxysulphide (V), Equation 1.

(1)



III IV I V

Optimum reaction conditions were found at a molar ratio of salicylic acid to allylisothiocyanate of 1 : 2, a bath temperature of 150°C and a reaction time of 30 minutes, with a yield of about 40 mole-% of V.

The conditions given by W.Q. FOYE *et al.* (1) were therefore changed as follows : the molar ratio of III to IV was raised from 1 : 1.1 to 1 : 2, the reaction time reduced from 20 to 2 hours and a definite bath temperature of 140-150°C chosen for the original reaction. The obtained yields of 38.7 and 39.5 mole-% of I confirmed the results of the reaction analysis.

(*) Department of Radiobiology, Euratom, Ghent Centre.
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Competition reactions are responsible for the relatively low yield of about 40 %.

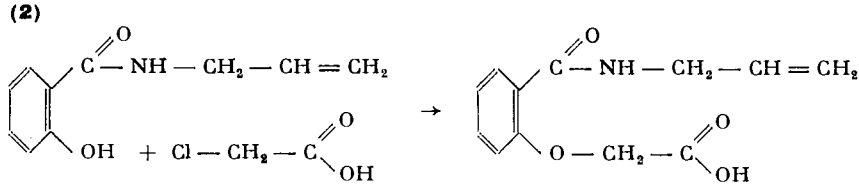
It is a colourless crystalline substance with a m.p. of 50°C. The infra-red spectrum of I in CCl_4 shows an NH stratching vibration at 3460 K (w.), an amide-I-band at 1650 K (s.) and an amide-II-band at 1525 K (s.) (Fig. 1).

Three by-products — needles with a m.p. of 246-248°C, platelets with a m.p. of 250-252°C, both of them containing sulphur, and crystals with a m.p. of 96°, all of them containing nitrogen, were isolated.

o, (N-Allylcarbamyl)-phenoxyacetic Acid (II).

According to Equation 2, O. Foye *et al.* synthesized II with a yield of 40 mole-%. This prescription was not reproducible in our laboratory. Therefore, the procedure was changed as described below.

(2)



I II

II was obtained in colourless needles m.p. 120°C as described (1), with a yield of 50-52 % calculated on reacted I.

Alkaline degradation of II yields salicylic-O-acetic acid, m.p. 190-192°C (2), m.p. 190°C.

The infra-red spectrum in KBr shows an NH stretching vibration at 3350 K (m.), a CO stretching vibration at 1755 K (s.), belonging to the carboxylic acid group, the amide-I-band at 1615 K (s.), the amide-II-band at 1555 K (s.), and an ether band at 1215 K (s.) (Fig. 2).

EXPERIMENTAL PROCEDURE (3)

N-Allylsalicylamide.

138 g salicylic acid (1 mole) and 200 g allylisothiocyanate (Fluka), both of commercial grade, are placed in a 500 ml round-bottom flask, which is equipped with a long reflux condenser. The flask is placed in an oil bath, which is heated to 150°C and kept at that temperature, after the reaction starts, for two hours. The start of the reaction manifests itself in a kind of boiling, caused by an intensive gas development (outlet).

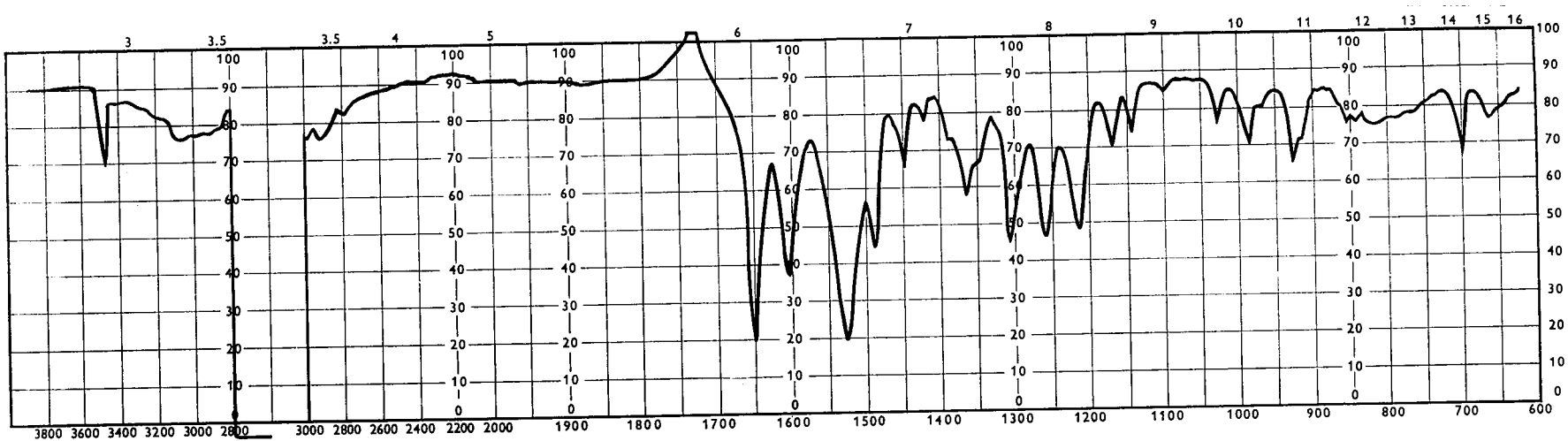


Fig. 1. — N-Allylsalicylamide in CCl_4

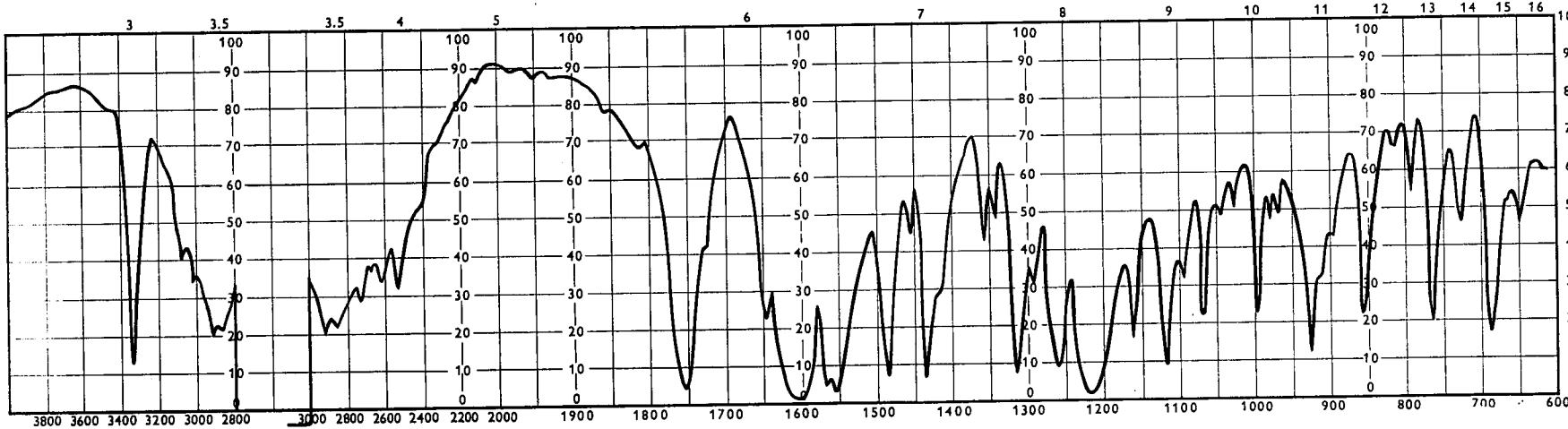


Fig. 2. — o, (N-Allylcarbamyl)-phenoxyacetic Acid in KBr

After this time the flask is cooled directly at room temperature. Further gas development is ignored and the content is mixed with 200 ml of ether. The solution is cooled in a refrigerator for two hours. The crystalline precipitate (13.3-15.0 g) is separated off by suction. The filtrate is evaporated under reduced pressure and the residual oil distilled. After the first fraction (33.8-39.0 g; b.p. 40-100°C; 15 mm Hg; water jet suction) containing allylisothiocyanate, the Liebig condenser is removed and the Claisen stillhead connected directly to the vacuum receiver adaptor. Distillation is recommenced with the aid of a mechanical oil vacuum pump connected to a refrigerating trap.

The fraction between 100 and 160°C, 0.3 mm Hg, is collected (156.3-164.3 g of a yellow oil), and the residue (53.8-54.1 g) discarded. The yellow oil is poured in a cold solution containing 60 g of sodium hydroxide in 400 ml of water. This mixture is extracted five times with 100 ml of ether. The ether layer is rejected.

The alkaline water layer is subsequently mixed, in portions, with 160 ml of a 36 % hydrochloric acid (gas development; outlet) and 200 ml of ether added. This mixture is neutralized with sodium bicarbonate (40-50 g); after intensive shaking the ether layer is separated, combined with two more 200 ml ether extracts, dried over sodium sulphate for eight hours, and double-distilled under reduced pressure as described above.

Should any crystalline salicylic acid appear at the beginning, the distillation process should be interrupted, all the oil absorbed in ether, washed with sodium bicarbonate water solution, and, after drying, the ether solution again distilled.

Yield : 68-70 g; 38.7-39.5 mole-%, calculated on salicylic acid. b.p. 134-136°C; 1.0 mm Hg. Yellow oil with crystallizing tendency.

In this condition, N-allylsalicylamide is clean enough for further synthetic work. From di-n-butyl ether, long, firm, obtuse, colourless needles are obtained, m.p. 50°C.

Analysis :

Calculated N : 7.90 %.

Found N : 7.92 %.

o, (N-Allylcarbamyl)-phenoxyacetic Acid.

In a 250 ml three-necked round-bottom flask, fitted with a mechanical stirrer and a tap funnel, 10.4 g of monochloroacetic acid and 8.0 g of dry potassium carbonate react at room temperature in 20 ml of water. As soon as the carbon dioxide development is finished, 17.7 g (0.1 mole) of N-allylsalicylamide are placed in the flask, which is then heated on a boiling water bath. To the stirred hot mixture a fresh solution of 5.0 g sodium hydroxide in 20 ml of water is added dropwise for a period of 10 minutes.

The alkaline mixture is stirred and heated for one hour and then extracted twice with 50 ml of ether. About 4.3 g of N-allylsalicylamide are recovered from the ether layer.

A solution of 11 ml of 36 % hydrochloric acid in 10 ml of water is now added dropwise to the alkaline water layer. The acid solution is extracted rapidly three times with 50 ml of ether. A yellow white crystalline precipitate appears very soon in the separated ether layer. 150 ml of petroleum ether are added. After three hours the precipitate is removed by suction (15.3-16.0 g), washed with petroleum ether and recrystallized from a water-alcohol mixture (7 + 3).

Colourless needles of o, (N-allylcarbamyl)-phenoxyacetic acid are obtained. m.p. 120°C.

Yield : 9.0-9.4 g; 50-52 mole-% calculated on reacted N-allylsalicylamide.

Analysis :

Calculated N : 5.96 %.

Found N : 6.07 %.

Summary

The synthesis of N-allylsalicylamide (I) and o, (N-allylcarbamyl)-phenoxyacetic acid (II), described by W.Q. Foye et al. (1) were not sufficiently reproducible.

By a reaction analysis study, we found optimum reaction conditions for the synthesis of I, yielding 40%.

The reaction conditions for the synthesis of II also had to be changed.

A yield of 50% was obtained. The infra-red spectra are given.

Zusammenfassung

Die Darstellungen von N-Allylsalicylamid (I) und o, (N-Allyl-carbamyl)-phenoxiessigsäure (II) nach W.Q. Foye und Mitarbeitern (1), waren nicht befriedigend reproduzierbar.

Durch eine Reaktionsanalyse wurden optimale Reaktionsbedingungen für die Darstellung von I mit einer Ausbeute von 40 % gefunden.

Die Reaktionsbedingungen für die Darstellung von II mussten ebenalls verändert werden, wobei eine Ausbeute von 50 % erzielt werden konnte.

Die Infra-rot-Spektren wurden aufgenommen.

Samenvatting

De bereiding van N-allylsalicylamide (I) en o, (N-allylcarbamyl)-phenoxiazijnzuur (II) volgens W.G. Foye en medewerkers (1) waren niet voldoende reproduceerbaar.

Door de studie van de reaktie, vonden we de optimale voorwaarden voor de bereiding van I met een opbrengst van 40 %.

De reaktievoorwaarden voor de bereiding van II, moesten eveneens veranderd worden, waarbij wij een rendement van 50 % konden verkrijgen.

De infra-rood spektra zijn weergegeven.

Résumé

La préparation de la N-allylsalicylamide (I) et de l'acide o, (N-allylcarbamyl)-phénoxyacétique (II) selon la méthode de W.Q. Foye et ses collaborateurs (1) ne donna pas entière satisfaction en ce qui concerne la reproduction de la technique.

En changeant la préparation, nous avons pu obtenir, par une étude approfondie de la réaction, un rendement de 40 % pour la synthèse du composé I.

Pour la préparation du produit II, nous avons pu obtenir un rendement de 50 % en modifiant les conditions de la réaction.

Les spectres infrarouges de ces produits ont été enregistrés.

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(1) *J. Amer. Pharmac. Ass.*, **41**, 273 (1952).

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(3) We are indebted to Prof. Dr. Verzele of the Department of Organic Chemistry of the State University of Ghent (Belgium), for the nitrogen analyses which were carried out in his laboratories.

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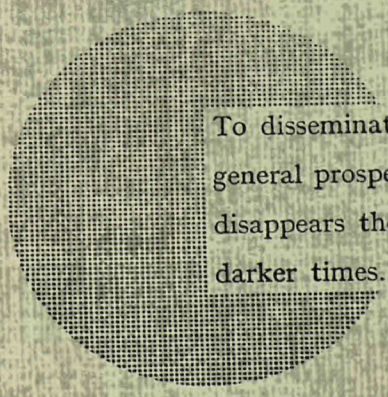
(5) Bockmühl M. and Schwarz A., United States Patent 1.693, 432, German Pat. 423.031 (1924).

(6) W.H. Feinstone, United States Patent 2.581.397.



To disseminate knowledge is to disseminate prosperity — I mean general prosperity and not individual riches — and with prosperity disappears the greater part of the evil which is our heritage from darker times.

Alfred Nobel