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Resynthesis of NSC 341,964, which had been assigned structure **1** (1-[[3-(7-chloro-4-oxo-4*H*-3,1-benzoxazin-2-yl)phenyl]methyl]pyridinium chloride) was approached *via* 7-chloro-2-(3-methylphenyl)-4*H*-3,1-benzoxazin-4-one (**5**) obtained from 3-methylbenzoyl chloride (**2**) and 2-amino-4-chlorobenzoic acid (**3**) followed by dehydration in acetic anhydride. Radical bromination provided **6** which with pyridine afforded the bromide analog **7** of **1**. Ion exchange, however, gave ring-opened benzoic acid **8** rather than **1**. The original sample of NSC 341,964 also proved to be ring-opened material. However, **7** upon standing exhibited slow hydrolysis to **8** so that the structure of the original NSC 341,964 remains uncertain. A more direct route to compound **8** is also described.

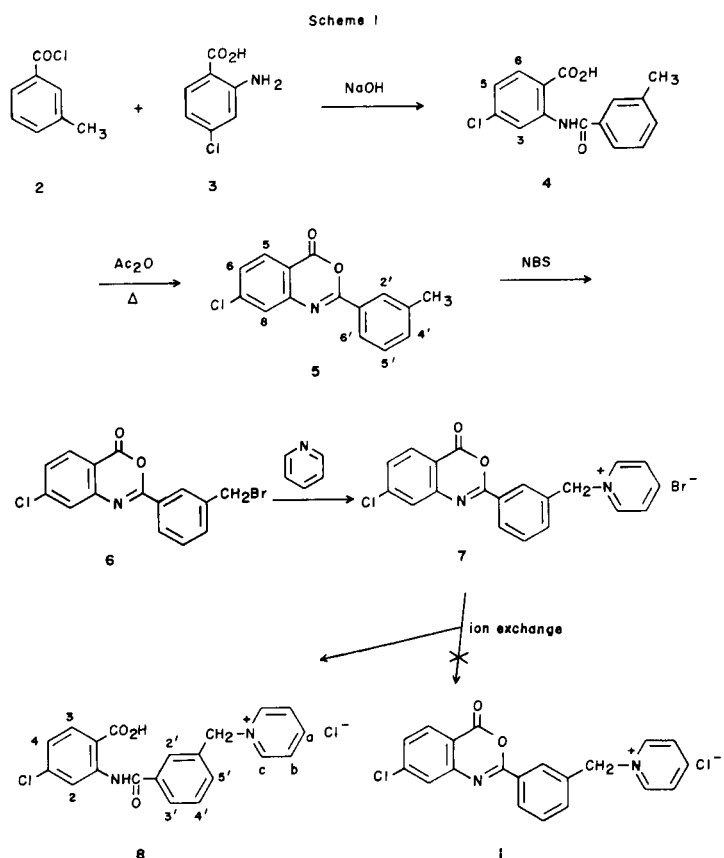
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In order to provide the National Cancer Institute with additional material for biological evaluation, we were asked to prepare NSC-341,964. This compound had been assigned the structure 1-[[3-(7-chloro-4-oxo-4*H*-3,1-benzoxazin-2-yl)phenyl]methyl]pyridinium chloride (**1**, Scheme I) by the original submitter. However no experimental details of its preparation were available nor was the compound reported in the literature.

We approached the target compound **1** by first forming the benzoxazine heterocycle utilizing a method described by Zentmyer and Wagner [2] (Scheme 1). The reaction [3] of 3-methylbenzoyl chloride (**2**) with 2-amino-4-chlorobenzoic acid (**3**) afforded 4-chloro-2-[(3-methylbenzoyl)amino]benzoic acid (**4**), which was dehydrated in boiling acetic anhydride [2] to produce the ring-closed product, 7-chloro-2-(3-methylphenyl)-4*H*-3,1-benzoxazin-4-one (**5**). The ir spectra clearly demonstrated this conversion: the major absorbance at 1670  $\text{cm}^{-1}$  for the 2-(benzoylamino)benzoic acid (**4**) was shifted to 1765  $\text{cm}^{-1}$  for the anhydride-like 4*H*-3,1-benzoxazin-4-one (**5**). Bromination of compound **5** with *N*-bromosuccinimide in fluorobenzene gave 7-chloro-2-[3-(bromomethyl)phenyl]-4*H*-3,1-benzoxazin-4-one (**6**) which, when treated with pyridine, afforded 1-[[3-(7-chloro-4-oxo-4*H*-3,1-benzoxazin-2-yl)phenyl]methyl]pyridinium bromide (**7**). An attempt to convert an aqueous solution of the pyridinium bromide **7** to the chloride **1** by ion exchange chromatography resulted in hydrolytic ring-opening to give **8**. This ring-opening was demonstrated by the ir spectrum: the strong absorbance at 1765  $\text{cm}^{-1}$ , a characteristic of the 4*H*-3,1-benzoxazin-4-one, was absent and was replaced by one at 1670  $\text{cm}^{-1}$ , characteristic of the benzoic acid, **4**.

Although 4*H*-3,1-benzoxazin-4-ones, substituted in the 2-position with hydrogen or lower alkyl, are known to be susceptible to ring-opening hydrolysis, the 2-aryl-benzoxazin-4-ones are reportedly more stable, at least as solids [3,4] and indeed, in the preparation of some 2-aryl-benzox-

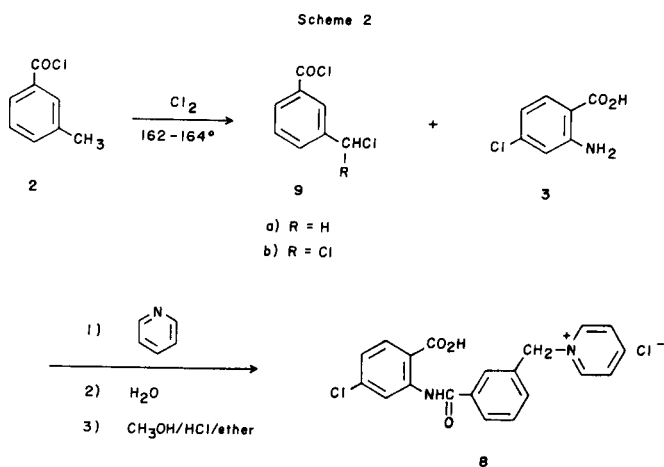
azin-4-ones, work-up has involved treatment with cold water [5,7]. Thus, the ring-opening of **7** was not entirely expected.



Our observation of the ring-opening of **7** prompted us to obtain and evaluate a sample of the NSC-341,964 submitted originally. Analysis and spectral data indicated this material to be the open chain benzoic acid **8** rather than the cyclized heterocycle **1**. Since it was not clear whether the original structure had been misassigned or the sample

had changed with time it was decided to provide the National Cancer Institute with both ring-opened and ring-closed material for biological evaluation. Thus we submitted a sample of the ring-closed bromide salt **7** and prepared a larger sample of the open chain material **8** by the more direct route depicted in Scheme 2.

Chlorination [7] of 3-methylbenzoyl chloride (**2**) with chlorine gas afforded a 5:3 mixture of the desired 3-(chloromethyl)benzoyl chloride (**9a**) and 3-(dichloromethyl)benzoyl chloride (**9b**), which could not be separated by the



usual distillation methods. Treatment of the mixture **9a,b** with 2-amino-4-chlorobenzoic acid (**3**) in the presence of pyridine afforded the desired product **8** which precipitated from the mixture.

In view of the instability of 1-[[3-(7-chloro-4-oxo-4H-3,1-benzoxazin-2-yl)phenyl]methyl]pyridinium bromide (**7**) in solution, we examined the storage stability of both the ionic material, **7**, and the neutral 4H-3,1-benzoxazin-4-one, **5**, in the solid state. After standing in a sealed bottle for one year, the neutral compound **5** had, according to its ir spectrum, remained unchanged. However, the pyridinium bromide, **7**, over the same period, had hydrolyzed partially, as demonstrated by the appearance of the band at 1670 cm<sup>-1</sup>. Thus, it is difficult to assess whether NSC-341,964 was misassigned initially or ring-opened upon standing. However, for the purpose of biological evaluation, it matters not, for once taken up in aqueous medium its ring opens readily.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. EM-390, XL200, and XL300 spectrophotometers (all Varian) were used to obtain nmr spectra. Ir spectra were recorded on a Nicolet 20SX FT-IR spectrophotometer.

### 4-Chloro-2-[(3-methylbenzoyl)amino]benzoic Acid (**4**) [3].

To a stirred, chilled mixture of 36.1 g (0.2 mole) of 2-amino-4-chlorobenzoic acid (**3**) were slowly added, 26.4 ml (0.2 mole) of 3-methylbenzoyl chloride (**2**) and 100 ml of 2*N* sodium hydroxide (0.2 mole) so that each

was added at about the same molar rate. The stirred mixture was allowed to warm to room temperature overnight. The resulting white precipitate was collected, washed with a small amount of water, and suspended in 1 l of water. The suspension was acidified to pH 1 with hydrochloric acid, stirred for 0.5 hour, and filtered. The filter cake was washed with water and dried under vacuum at 55° to afford 31.5 g (53%) of **4**, mp 196-197°; nmr (d<sub>6</sub>-DMSO): δ 2.36 (s, 3, CH<sub>3</sub>), 7.17 (dd, 1, 5H), 7.3-7.5 (m, 2), 7.5-7.8 (m, 2), 7.95 (d, 1, 6H), 8.72 (d, 1, 3H), 12.2 (s, 1, exchangeable H) (see numbering of aromatic protons of **4** in Scheme 1); ir (potassium bromide): 3020 (broad), 1670, 1580, 1410, 1280, and 1250 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>12</sub>ClNO<sub>3</sub> (289.72): C, 62.18; H, 4.18; N, 4.84; Cl, 12.24. Found: C, 61.90; H, 4.38; N, 4.78; Cl, 12.54.

### 7-Chloro-2-(3-methylphenyl)-4H-3,1-benzoxazin-4-one (**5**).

A mixture of 7.24 g (0.025 mole) of 4-chloro-2-[(3-methylbenzoyl)amino]benzoic acid (**4**) and 20 ml of acetic anhydride was heated under reflux for one hour, then distilled to remove about 12 ml of liquid which included acetic acid and water, and allowed to cool. The reaction mixture was diluted with ethyl acetate and hexane and filtered to afford the crude product, mp 164-169°. Recrystallization from toluene afforded 3.5 g (51%) of **5**, mp 166-168°; nmr (d<sub>6</sub>-DMSO): δ 2.45 (s, 3, CH<sub>3</sub>), 7.49 (m, 2, 4'H & 5'H), 7.66 (dd, 1, 6H), 7.8 (d, 1, 8H), 8.0 (m, 2, 2'H & 6'H), 8.17 (d, 1, 5H) (see numbering of aromatic protons of **5** in Scheme 1); ir (potassium bromide): 1765, 1605, and 1590 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>15</sub>H<sub>10</sub>ClNO<sub>2</sub> (271.71): C, 66.30; H, 3.71; N, 5.16; Cl, 13.05. Found: C, 66.56; H, 3.97; N, 5.17; Cl, 12.96.

### 7-Chloro-2-[3-(bromomethyl)phenyl]-4H-3,1-benzoxazin-4-one (**6**).

In an atmosphere of argon, a mixture of 10 g (0.056 mole) of *N*-bromosuccinimide, which had been dried over phosphorous pentoxide at 0.5 mm at room temperature, and 15 g (0.055 mole) of 7-chloro-2-(3-methylphenyl)-4H-3,1-benzoxazin-4-one (**5**) in 300 ml of fluorobenzene was irradiated in a quartz photochemical reaction vessel with a 450 watt Hanovia photochemical immersion lamp under gentle reflux for five hours. An additional 5 g of dried *N*-bromosuccinimide and 200 ml of fluorobenzene were added and irradiation was continued for four hours. The mixture was allowed to cool and filtered to remove the precipitate which was washed with dichloromethane. The filtrate and wash were combined, washed with water, dried over magnesium sulfate, and filtered. Tlc (Silica gel-toluene) demonstrated a major spot (R<sub>f</sub> = 0.57 which represented the desired product and two minor spots, one at R<sub>f</sub> = 0.67, and one at the origin. The solution was chromatographed over 200 g of silica gel with dichloromethane to afford about 10 g (52%) of crude **6** which was used in the next step without further purification.

### 1-[[3-(7-Chloro-4-oxo-4H-3,1-benzoxazin-2-yl)phenyl]methyl]pyridinium Bromide (**7**).

A solution of 10 g (about 0.028 mole) of crude 7-chloro-2-[3-(bromomethyl)phenyl]-4H-3,1-benzoxazin-4-one (**6**) in about 400 ml of dichloromethane and 100 ml of ethanol was treated with 50 ml of pyridine, gently warmed on the steam bath for one hour, and allowed to stand at room temperature overnight. The resulting precipitate was collected, washed with a little ethanol and with dichloromethane, and dried under vacuum at 50° to afford 9.0 g (73%) of **7**, mp 267-270° (dec) with prior shrinking; nmr (d<sub>6</sub>-DMSO): δ 6.02 (s, 2, CH<sub>2</sub>), 7.6-7.81 (m, 4), 8.1-8.24 (m, 4), 8.4 (s, 1), 8.64 (t, 1, γH of pyridinium), 9.29 (d, 2, αH of pyridinium); ir (KBr): 3400 (broad), 1760, 1610, and 1600 cm<sup>-1</sup>; tlc [silica gel-acetonitrile:0.2*N* ammonium chloride (3:1)]: R<sub>f</sub> = 0.73 with a trace at R<sub>f</sub> = 0.45.

In an attempt to obtain **1**, a 2.1 g sample of **7** was dissolved in an excess of water and passed through a 50 ml column of Amberlite IRA-410 C.P. (chloride form) and the eluant containing the product was concentrated under vacuum at 40-50° to about 100-150 ml. The precipitate which formed was collected, washed with water, and dried to afford 1.2 g of material which according to its tlc is identical to **8**, mp 276° dec. Physical characteristics are described below.

### 3-(Chloromethyl)benzoyl Chloride (**9a**).

Chlorine gas was bubbled through 31.6 g (0.205 mole) of 3-methylbenzoyl chloride (**2**) at 162-164° for 3.5 hours and the mixture was allowed to

cool. The weight gain of the reaction mixture was 8.85 g or 124% of theoretical. Distillation at 15 torr afforded 37.7 g of clear liquid, bp 144-153° (Literature [7] reports 149-150° at 20 torr for **9a**). Vpc, nmr, and elemental analysis demonstrate that this liquid is a mixture of 3-(chloromethyl)benzoyl chloride (**9a**) and 3-(dichloromethyl)benzoyl chloride (**9b**). The mixture may be used satisfactorily in the next step without further purification; nmr (deuteriochloroform):  $\delta$  4.6 (s,  $\text{CH}_2\text{Cl}$ ), 6.8 (s,  $\text{CHCl}$ ).

*Anal.* Calcd. for  $\text{C}_8\text{H}_6\text{Cl}_2\text{O}$  (**9a**): 0.6  $\text{C}_8\text{H}_5\text{Cl}_3\text{O}$  (**9b**): C, 47.58, H, 2.81; Cl, 41.69. Found: C, 47.29; H, 2.89; Cl, 41.64.

1-[[3-[[[(2-Carboxy-5-chlorophenyl)amino]carbonyl]phenyl]methyl]pyridinium, Chloride (**8**).

To a stirred solution of 38.3 g (0.212 mole) of 2-amino-4-chlorobenzoic acid (**4**) in 600 ml of pyridine at 5° was added dropwise a solution of 45.8 g (about 0.19 mole) of the mixture of 3-(chloromethyl)benzoyl chloride (**9a**) and 3-(dichloromethyl)benzoyl chloride (**9b**) (1:0.6) in 20 ml of dichloromethane. The mixture was allowed to warm to room temperature. After three days, the precipitate which had formed was collected and washed with pyridine and then with dichloromethane. Tlc [silica gel, acetonitrile:0.2N ammonium chloride solution (3:1)] indicated that this solid was primarily **8**, Rf = 0.45, plus some of the ring-closed material, 1-[[3-(7-chloro-4-oxo-4H-3,1-benzoxazin-2-yl)phenyl]methyl]pyridinium, chloride (**1**), Rf = 0.73.

The material was slurried in hot water (55-85°) for 1 3/4 hours, allowed to cool, collected by filtration, washed with water, then with 2-propanol, and finally with hexane, and dried overnight at 50° to afford 38.6 g (50%) of white solid. Elemental analysis indicated that material was a partial pyridinium chloride salt. This material was combined with 10 g obtained in previous runs and dissolved in a boiling mixture of 2800 ml of methanol and 250 ml of 26% hydrogen chloride in 2-propanol. The hot solution was treated with charcoal, filtered through celite, allowed to

cool, and diluted with 1 l of ether. The resulting precipitate was collected, washed with ether, and dried under vacuum at 50° to afford 32.6 g (67% recrystallization yield) of **8**, mp 268-270° dec; nmr ( $d_6$ -DMSO + deuterium oxide):  $\delta$  5.98 (s, 2,  $\text{CH}_2$ ), 7.29 (dd, 1, 4H), 7.68 (t, 1, 4'H), 7.82 (d, 1, 5'H), 7.95 (d, 1, 3'H), 8.05 (d, 1, 3H), 8.09 (s, 1, 2'H), 8.21 (t, 2, bH), 8.65 (t, 1, aH), 8.74 (d, 1, 2H), 9.28 (d, 2, cH), 12.26 (s, 1,  $\text{D}_2\text{O}$  exchangeable) see numbering of aromatic protons of **8** on Scheme 1); ir (potassium bromide): 1206, 1523, 1582, 1601, and 1678  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{16}\text{ClN}_2\text{O}_3\cdot\text{Cl}^-$ : C, 59.56; H, 4.00; N, 6.95; Cl, 17.58;  $\text{Cl}^-$ , 8.80. Found: C, 59.39; H, 3.98; N, 6.91; Cl, 17.64;  $\text{Cl}^-$ , 8.85.

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