Enamine Intermediates in the Synthesis of Analogs of Pyrrolnitrin

E. E. Garcia, L. E. Benjamin and R. Ian Fryer

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, N. J. 07110

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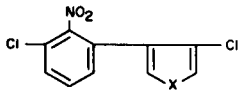
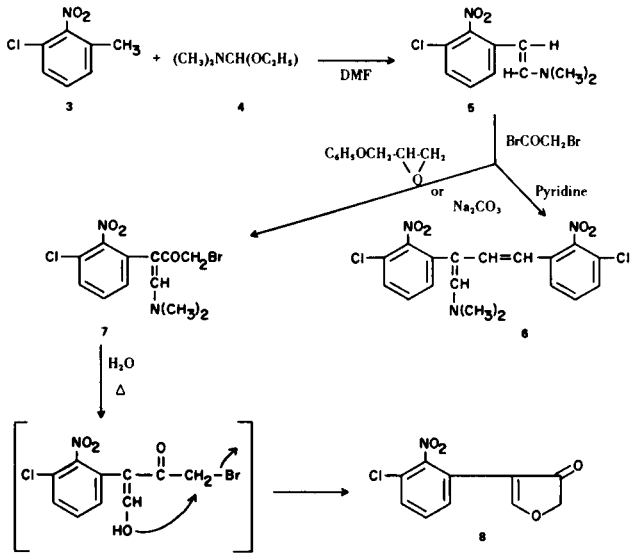
Analogs of the antibiotic pyrrolnitrin (**1**) bearing furan (**2**), pyrazole and isoxazole rings were prepared to determine the effect of such heterocyclic substitution on the biological activity (1,2). All the analogs reported here were found to be devoid of pyrrolnitrin-type of biological activity.



1, X = NH
2, X = O

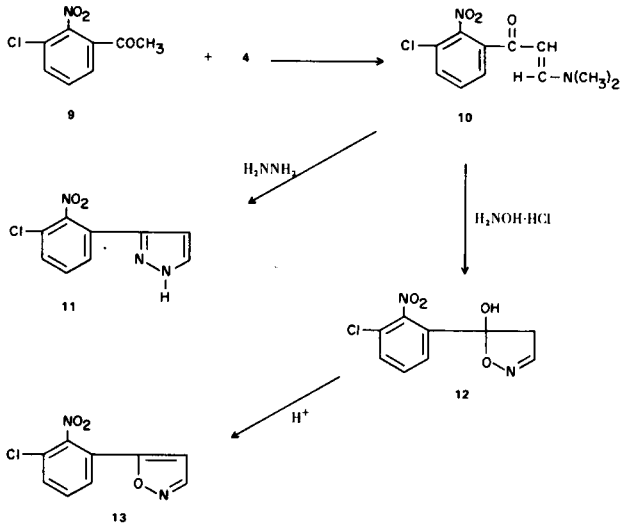
The reaction of 3-chloro-2-nitrotoluene (**3**) with *N,N*-dimethylformamide diethylacetal (**4**) (3) in refluxing dimethylformamide for 24 hours afforded the desired enamine derivative **5** in 40% yield (Scheme I). Attempted acylation of **5** with bromoacetyl bromide in the presence of pyridine resulted instead in the self condensation of the enamine to give compound **6** (4). When sodium carbonate or 1,2-epoxy-3-phenoxypropane was used as a scavenger for the hydrogen bromide liberated in the reaction, bromoacetylation was successful and compound **7** was obtained in 30% and 60% yields, respectively. Compound **7** when exposed to refluxing aqueous dioxane or aqueous *t*-butyl alcohol underwent hydrolysis and concomitant cyclization to yield the desired furanone derivative **8** in 65% yield. The ketonic nature of this product was substantiated by the infrared spectrum which exhibited a carbonyl absorption at 1690 cm^{-1}. All efforts to convert **8** to the chloro derivative **2** were unsuccessful, apparently as a result of furanone ring instability.

SCHEME I



The starting material for the synthesis of the pyrazole and isoxazole analogs was 3-chloro-2-nitroacetophenone (**9**). Compound **9** was converted in high yield with DMF-acetal to the enamine (**10**), which in turn was transformed to the desired pyrazole (**11**) and isoxazole (**13**) derivatives with hydrazine and hydroxylamine, respectively. In the hydroxylamine reaction, 5-(3-chloro-2-nitrophenyl)-4-isoxazolin-4-ol (**12**) was an isolable intermediate.

Scheme II



EXPERIMENTAL

All melting points are corrected. Ir spectra were determined using a Beckmann IR-9 spectrophotometer, nmr spectra with a Varian A-60 spectrometer and mass spectra with a CEC 21-100 spectrometer.

3-Chloro-2-nitrotoluene (**3**).

In a 5 l. 3-necked flask equipped with a thermometer, dropping funnel and mechanical stirrer was placed 600 ml. of chloroform. The flask was cooled in ice, and with stirring, 20 drops of concentrated sulfuric acid was added followed by the dropwise addition of 136 ml. of 90% hydrogen peroxide. The temperature

was maintained below 10° during this addition. This was followed by the dropwise addition of 570 ml. of acetic anhydride, once again, at a temperature below 10°. After this addition was completed (*ca.* 80 minutes), the mixture was stirred in ice until the internal temperature dropped below 3°. The ice bath was then removed and the clear, colorless solution was stirred at room temperature for 15 minutes. An additional 400 ml. of chloroform was added and the solution was rapidly heated to boiling. The heating source was then removed and a solution of 142 g. (1 mole) of 2-amino-3-chlorotoluene in 250 ml. of chloroform was added dropwise at such a rate as to maintain moderate refluxing. The resultant green solution was then heated under reflux for 2 hours and after standing at room temperature overnight was poured into 3 ℓ. of ice-water. The organic layer was separated, washed successively with 1 ℓ. of 5 *N*-sodium hydroxide and 1 ℓ. of 3 *N*-hydrochloric acid and dried. After the absence of peroxides was demonstrated, the solution was concentrated at 50°, *in vacuo*, to give 157 g. of a dark, orange liquid. This was dissolved in petroleum ether and filtered over 480 g. Florisil. Elution with petroleum ether afforded 124 g. (72%) of **3** as a pale orange liquid which was spectrally identical to an authentic sample prepared according to the procedure of Singer and Shine (5).

trans-3-Chloro-2-nitro-β-dimethylaminostyrene (**5**).

A solution of 103 g. (0.6 mole) of **3** and 103 g. (0.695 mole) of *N,N*-dimethylformamide diethylacetal (**4**) in 210 ml. of DMF was heated in an oil bath at 180-190° for 20 hours. The excess acetal and DMF were removed by distillation at ca. 100°/30 mm and unreacted **3** was distilled at 80°/2 mm. The remaining dark, red residue was stirred with petroleum ether to give 89 g. (65%) of crude **5** as red crystals. A small sample was purified for microanalysis by recrystallization from 2-propanol to yield red plates, m.p. 89-90°; nmr (DMSO-d_6): δ 5.9 (s, 6H), α-vinyl proton at δ 4.63 (d, 1H, J = 13.5 Hz).

Anal. Calcd. for $C_{10}H_{11}ClN_2O_2$: C, 52.99; H, 4.89; N, 12.36. Found: C, 53.04; H, 4.96; N, 12.07.

1-Dimethylamino-2,4-bis(3-chloro-2-nitrophenyl)-1,3-butadiene (**6**).

Method a.

To an ice-cooled, stirred solution of 9 g. (0.04 mole) of **5** in a mixture of 90 ml. of ether and 3.2 g. (0.04 mole) of pyridine was added dropwise 8.1 g. (0.04 mole) of bromoacetyl bromide in 10 ml. of ether. After stirring in ice for 25 minutes, the suspension was filtered to remove a small amount of oily solid (discarded) and additional ether was added to the filtrate. After refrigeration, filtration gave a red solid which was dissolved in chloroform, washed, dried and concentrated to yield 1.3 g. of **6** as a brick-red solid, m.p. 202-206°. Recrystallization from dichloromethane-hexane gave brick-red needles, m.p. 211-213° dec.; nmr (DMSO-d_6): δ 2.7 (s, 6H), 4.89 (d, 1H, J = 15 Hz), 7.06 (d, 1H, J = 15 Hz) and δ 7.3-7.8 (m, 8H); MS: Mol. ion at 407.

Anal. Calcd. for $C_{18}H_{15}Cl_2N_3O_4$: C, 52.96; H, 3.73; N, 10.29. Found: C, 53.19; H, 3.98; N, 10.24.

Method b.

A solution of 0.9 g. (4 mmoles) of **5** dissolved in a mixture of 3:1 ethyl acetate-hexane was absorbed on 20 g. of silica gel and allowed to stand for 1 hour. The silica gel was washed with 3:1 ethyl acetate-hexane and the eluant concentrated to give a red solid which was filtered and washed with ether to yield 0.5 g. (62%) of **6**, m.p. 208-210° dec. This substance was identical in all respects to the product obtained using method a.

2-Bromoacetyl-2-(3-chloro-2-nitrophenyl)-1-dimethylaminoethylene (**7**).

A solution of 9.1 g. (0.04 mole) of **5** in 45 ml. of dichloromethane was treated with 7.5 g. (0.05 mole) of 1,2-epoxy-3-phenoxypropane. (6) The solution was placed in an ice-bath and a solution of 9.1 g. (4 ml., 0.045 mole) of bromoacetyl bromide in 15 ml. of dichloromethane was added dropwise. The resultant mixture was stirred for 30 minutes at room temperature and then evaporated at reduced pressure. The residual oil was treated with 300 ml. of ether and then decanted from a small amount of insoluble oil. The ether solution was concentrated to half volumn and then allowed to stand at room temperature. Filtration gave 6.9 g. (50%) of yellow crystals, m.p. 120-122°. Recrystallization from dichloromethane-hexane gave yellow prisms, m.p. 123-124° dec.; ir (chloroform): 1668 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.83 (s, 6H), 3.76 (s, 2H), 7.69 (s, 1H).

The use of sodium carbonate in place of 1,2-epoxy-3-phenoxypropane in the above procedure gave 7 g. (29%) of 7, m.p. 120-122°.

Anal. Calcd. for $C_{12}H_{12}BrClN_2O_3$: C, 41.46; H, 3.48; N, 8.06. Found: C, 41.76; H, 3.23; N, 8.10.

4-(3-Chloro-2-nitrophenyl)-3(2*H*)furanone (**8**).

A solution of 5 g. (0.014 mole) of **7** in a mixture of 50 ml. of *t*-butyl alcohol and 15 ml. of water was heated under reflux for 20 hours and concentrated at reduced pressure to remove the organic solvent. The aqueous oily residue was extracted with dichloromethane and the organic layer was separated, washed, dried and concentrated. The residual oil which crystallized upon scratching was washed with a small amount of 2-propanol to yield 4 g. (56%) of **8** as tan crystals, m.p. 130-132°. Recrystallization from dichloromethane-hexane yielded pale-yellow rods, m.p. 134-135°: MS: mol ion at 239; ir (potassium bromide): 1690 cm^{-1}.

Anal. Calcd. for $C_{10}H_6ClNO_4$: C, 50.13; H, 2.52; N, 5.85. Found: C, 50.11; H, 2.56; N, 5.82.

3-Chloro-2-nitroacetophenone (**9**).

This substance was prepared from commercially available 3-chloro-2-nitrobenzoic acid using the procedure (7) employed for the synthesis of 2-nitroacetophenone. Compound **9** was obtained as white crystals from ethanol, m.p. 94-95° (lit. (8) 94-95°).

trans-2-Dimethylaminovinyl 3-chloro-2-nitrophenyl Ketone (**10**).

A solution of 20 g. (0.1 mole) of **9** in a mixture of 150 ml. of benzene and 28.4 g. (0.2 mole) of DMF-diethylacetal (**4**) was heated under reflux for 4.5 hours. After standing at room temperature the suspension was filtered to yield 21 g. of yellow crystals, m.p. 164-166°. Evaporation of the filtrate to half volume gave an additional 1.9 g. of product. The total yield of **10** was 22.9 g. (90%). Recrystallization from dichloromethane gave yellow plates, m.p. 166-168°; nmr (DMSO-d_6): δ 3.12 (d, 6H), 5.59 (d, 1H, J = 12 Hz).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_3$: C, 51.88; H, 4.35; N, 11.00. Found: C, 51.98; H, 4.45; N, 10.74.

3(or 5)-(3-Chloro-2-nitrophenyl)pyrazole (**11**).

A solution of 17.8 g. (0.07 mole) of **10** in a mixture of 175 ml. of methanol and 50 ml. of water was treated with 8.3 g. (0.14 mole) of 85% hydrazine hydrate and heated on the steam bath for 1.5 hours. The alcohol was removed at reduced pressure and the resultant suspension was filtered, washed with water and air dried to yield 13.8 g. (88%) of red-brown crystals, m.p. 150-160° dec. Recrystallization from methanol gave cream colored crystals, m.p.

160-165°; ir (potassium bromide): 3300 cm^{-1} (NH).

Anal. Calcd. for $C_9H_6ClN_3O_2$: C, 48.33; H, 2.70; N, 18.79. Found: C, 48.63; H, 2.93; N, 18.40.

5-(3-Chloro-2-nitrophenyl)-4-isoxazolin-4-ol (**12**).

A solution of 17.8 g. (0.07 mole) of **10** in a mixture of 175 ml. of methanol and 75 ml. of water was treated with 9.7 g. (0.14 mole) of hydroxylamine hydrochloride and heated on the steam bath for 2 hours. The alcohol was removed at reduced pressure and the residual oily mixture was extracted with dichloromethane and the organic extracts were washed, dried and concentrated to an oil. This oil was dissolved in ether, and allowed to stand at room temperature until precipitation seemed complete. Filtration gave 6.6 g. of white crystals, m.p. 124-126°. The filtrate was concentrated to dryness and the residue was dissolved in 50 ml. of hot benzene and cooled. In this manner an additional 5.5 g. of product was obtained. The total yield of **12** was 12.1 g. (77%). The microanalytical smaple was prepared by recrystallization from dichloromethane-hexane, to give white rods, m.p. 128-130°; MS: mol. ion at 242; ir (chloroform): 3570 cm^{-1} (OH); nmr (DMSO-d_6): δ 3.26 (broad s, 2H).

Anal. Calcd. for $C_9H_7ClN_2O_4$: C, 44.55; H, 2.90; N, 11.53. Found: C, 44.50; H, 2.67; N, 11.43.

5-(3-Chloro-2-nitrophenyl)isoxazole (**13**).

To a stirred solution of 6.2 g. (0.025 mole) of **12** in 50 ml. of ethanol was added 25 ml. of concentrated hydrochloric acid. After stirring at room temperature for 45 minutes the mixture was poured into 300 ml. of water and extracted with ether. The organic extract was washed, dried and concentrated to yield a yellow oil which slowly crystallized. Recrystallization from hexane (some oily solid which was insoluble was discarded) gave **12** as white rods, m.p. 78-80°; MS: mol. ion at 224; nmr (DMSO-d_6): δ 6.97 (d, 1H, J = 2 Hz), 8.36 (d, 1H, J = 2 Hz).

Anal. Calcd. for $C_9H_5ClN_2O_3$: C, 48.13; H, 2.24; N, 12.47. Found: C, 47.56; H, 2.21; N, 12.30.

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