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Syntheses of Various 2,5-Disubstituted Oxazole Derivatives Related to Natural Products

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The alkaloidal pigment annuloline (I), isolated from the roots of *Lolium multiflorum* (1), the quaternary alkaloid N-methylhalfordine (II), a natural constituent of *Halfordia scleroxyla* (2) and the mold metabolite pimprinine (III), a fermentation product of *Streptomyces pimprina* (3), are 2,5-disubstituted oxazole derivatives.

The preparation of various oxazole derivatives related to these natural products is described in this paper. Annuloline (I) has been synthesized by cyclizing an appropriate N-acylated 4-methoxy-ω-aminoacetophenone derivative of type A - R_1 = -CH=CH-C_6H_3(3,4-di-OCH_3) (R_2 = $-CH_3$) by means of phosphorus oxychloride (4). By this method we have prepared the five oxazole derivatives V, VII, IX, XI and XIII of type B from their corresponding N-acyl-ω-aminoacetophenone derivatives IV, VI, VIII, X and XII of type A.

The oxazole derivative V is identical with dihydroannuloline, already described by other investigators (4). Acid hydrolysis of the oxazole *O*-benzyl ether derivative XIII afforded a phenolic compound melting at 254-255°. This phenol seems to be identical with halfordinol (XIV) (5) described by Crow *et al.*, (2) and obtained by acid hydrolysis of the alkaloid N-methylhalfordinium chloride (II, X = Cl). *O*-Methylation of the phenol XIV with diazomethane yielded *O*-methylhalfordinol (XI) (5), identical with a sample prepared by cyclization of the N-nicotinyl-ω-aminoacetophenone derivative X. The structures of our synthetic halfordinol (XIV) and its *O*-benzyl ether (XIII) have been rigorously established by NMR analysis.

The *p*-chlorostyryl-substituted oxazole derivative IX and its dihydro derivative VII, both close analogs of annuloline (I) and dihydroannuloline (V), respectively, have been synthesized analogously from the *p*-methoxy-substituted N-acyl-ω-aminoacetophenone derivatives VIII and VI, respectively, and correlated with each other by catalytic reduction of IX to yield VII.

Condensation of the known 2-methyl-substituted oxazole derivative XV (6) with veratraldehyde in the presence of acetic anhydride and pyridine yields annuloline (I) directly. This constitutes another easy route to styryl- and 2-phenethyl-substituted oxazole derivatives.

EXPERIMENTAL

The melting points are not corrected. The UV spectra were measured in cyclohexane as solvent, using the Cary Recording Spectrophotometer Model No. 14 M, unless otherwise stated. The NMR spectra were obtained with a Varian A-60 spectrometer, using dimethylsulfoxide-d_6 solutions and tetramethylsilane as the internal reference. The IR spectra were determined on a Beckmann IR-9 spectrophotomer. Unless otherwise specified, all analytical samples were prepared by recrystallization from ethanol.

Dihydroannuloline (V) and analogs VII, IX and XI.

N-(4-Methoxyphenacyl)-3,4-dimethoxydihydrocinnamic acid amide (IV).

A solution of 42 g. of 3,4-dimethoxydihydrocinnamoyl chloride was added slowly to an ice cooled solution of 42 g. of *p*-methoxy-ω-aminoacetophenone hydrochloride (7) in 250 ml. of pyridine. The temperature was kept at 0° for 3 hours, then raised slowly to 25°, and stirring was continued overnight. The mixture was concentrated in vacuum, water was added, and the amide IV was recovered by filtration. Crystallization from ethanol yielded 45 g. of pure amide IV, m.p. 139-140°.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 67.09; H, 6.45.

The amide IV (17 g.) was dissolved in 500 ml. of phosphorus oxychloride and refluxed for 20 hours. The solution was concentrated in vacuum to 50 ml. and poured onto ice. Addition of aqueous ammonia separated an oil which crystallized slowly. The recovered product yielded, after three crystallizations from ethanol, 12 g. of 2-(3,4-dimethoxyphenethyl)-5-(4-methoxyphenyl)oxazole (V), m.p. 98-99° [Lit. (4), m.p. 95-96°]. U.V.: λ max 278 (ε, 26,100), 281 mμ (ε, 25,000).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24. Found: C, 70.87; H, 6.21.

The analogs VII, IX and XI were made as described above by $POCl_3$ cyclization of the corresponding amides VI, VIII and X which were in turn prepared from the requisite acid chlorides and *p*-methoxy-ω-aminoacetophenone hydrochloride.

N-(4-Methoxyphenacyl)-4-chlorodihydrocinnamic acid amide (VI).

M.P. 155-156°.

Anal. Calcd. for $C_{18}H_{18}ClNO_3$: C, 65.18; H, 5.47. Found: C, 65.14; H, 5.42.

2-(4-Chlorophenethyl)-5-(4-methoxyphenyl)oxazole (VII).

M.P. 124-125°. U.V.: λ max 274 mμ (ε, 25,500).

Anal. Calcd. for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14. Found: C, 69.11; H, 4.99.

N-(4-Methoxyphenacyl)-4-chlorocinnamic acid amide (VIII).

M.P. 201-202°.

Anal. Calcd. for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89. Found: C, 65.62; H, 4.95.

2-(4-Chlorostyryl)-5-(4-methoxyphenyl)oxazole (IX).

M.P. 154-155°. U. V.: λ max 270 (ε, 19,900), 348 (ε, 34,100), 365 mμ (ε, 33,250).

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: C, 69.34; H, 4.53. Found: C, 69.57; H, 4.45.

Catalytic hydrogenation of this oxazole derivative IX in ethanol over platinum oxide yielded the oxazole derivative VII.

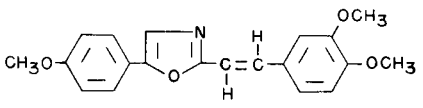
N-(4-Methoxyphenacyl)nicotinamide (X).

M.P. 148-149°.

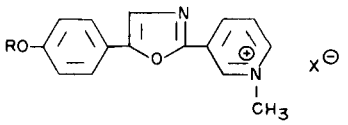
Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22. Found: C, 66.85; H, 5.19.

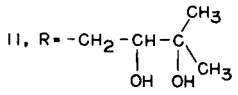
2-(3-Pyridyl)-5-(4-methoxyphenyl)oxazole hydrochloride (XI HCl).

This compound was prepared from the oily base with methanolic hydrogen chloride, m.p. 243-244°. U. V. (2-propanol): λ max 247 (ε, 9,000), 325 mμ (ε, 21,900).

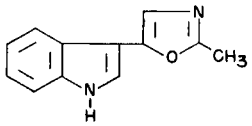


I

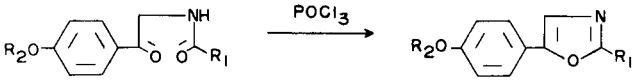




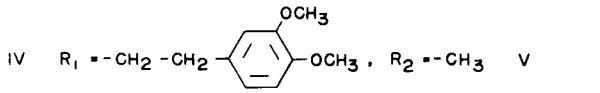
II, R = $-CH_2-CH(OH)-C(OH)(CH_3)-CH_3$



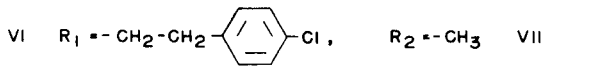
III



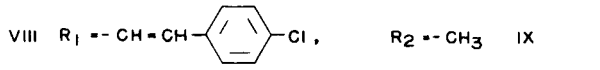
A B



IV $R_1 = -CH_2-CH_2-$(3,4-dimethoxyphenyl), $R_2 = -CH_3$ V



VI $R_1 = -CH_2-CH_2-$(4-chlorophenyl), $R_2 = -CH_3$ VII



VIII $R_1 = -CH=CH-$(4-chlorophenyl), $R_2 = -CH_3$ IX

X R_1 = (4-pyridyl), $R_2 = -CH_3$ XI

XII R_1 = (4-pyridyl), $R_2 = -C_7H_7$ XIII

R_1 = (4-pyridyl), $R_2 = -H$ XIV

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54. Found: C, 62.49; H, 4.44.

The methosulfate of XI was prepared in nitromethane from the free base and dimethylsulfate, m.p. 217-219°. U. V. (2-propanol): λ max 262 (ε, 15,250), 352 mμ (ε, 15,800).

Anal. Calcd. for $C_{16}H_{15}N_2O_2^+ \cdot CH_3SO_4^-$: C, 53.97; H, 4.80. Found: C, 53.82; H, 5.03.

O-Benzylhalfordinol (XIII).

4-Benzyloxy-ω-bromoacetophenone.

4-Benzyloxyacetophenone (45.2 g.) (8) was dissolved in 600 ml. of ethanol and 5 drops of concentrated hydrochloric acid was added. The solution was cooled to 15° and 32 g. of bromine dissolved in 100 ml. of methanol was added within 30 minutes. The mixture was stirred for 1 additional hour at 15° and then it was cooled to -20°. The solid was filtered and recrystallized from ethanol, yield 59 g., m.p. 83-84°.

Anal. Calcd. for $C_{15}H_{13}BrO_2$: C, 59.03; H, 4.29. Found: C, 58.94; H, 4.07.

4-Benzyloxy-ω-aminoacetophenone.

A solution of 45.7 g. of the ω-bromo compound described above in 100 ml. of chloroform was added to a solution of 22 g. of hexamethylene tetramine in 100 ml. of chloroform. The reaction mixture was refrigerated overnight and the precipitate which formed was filtered, washed with chloroform and ether and dried, yield 26.9 g. of a mixed salt with m.p. 133-134°. This material was added to a mixture of 27 ml. of concentrated hydrochloric acid and 54 ml. of water. After stirring for 1 hour, 80 ml. of ethanol was added and the stirring was continued for 1 additional hour at room temperature. The undissolved material which was a mixture of 4-benzyloxy-ω-aminoacetophenone hydrochloride and hydrobromide was filtered and used directly in the next step, yield 14.5 g., m.p. 228-230°.

N-(4-Benzyloxyphenacyl)nicotinamide (XII).

The above-mentioned material (14.5 g.) was dissolved in 250 ml. of pyridine and a solution of 9.2 g. of nicotinoyl chloride in 100 ml. of pyridine was added over a period of 30 minutes. The reaction mixture was stirred overnight and then concentrated in vacuum to 50 ml. Water was added and the solid was filtered after 1 hour. Crystallization from methanol yielded 6.8 g. of the amide XII, m.p. 166-167°.

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24. Found: C, 72.69; H, 5.53.

O-Benzylhalfordinol (XIII).

The amide (6.5 g.) XII was refluxed for 5 hours with 250 ml. of phosphorus oxychloride. The solution was evaporated to a small volume, treated with ice water and the *p*H was adjusted to 9.0 with aqueous ammonia. The oily material was extracted with chloroform and after evaporation the hydrochloride was prepared by treatment with methanolic hydrogen chloride. Crystallization from methanol yielded 5.2 g. of *O*-benzylhalfordinol hydrochloride, m.p. 224-226°. The free base XIII prepared from the hydrochloride in the usual way melted at 160-161°.

UV (free base in ethanol): λ max 228 (ε, 10,500), 249 (ε, 11,950), 260 (ε, 11,700), 326 mμ (ε, 26,500). IR (free base in chloroform): cm^{-1} 2940, 1617, 1600, 1585, 1500, 1250, 830, 700. IR (HCl salt in KBr pellet): cm^{-1} 2100, 1975, 1620, 1610, 1570, 1525, 1500, 1250, 830, 760, 750, 713, 707. NMR (free base): The NMR spectrum shows a singlet at τ 4.82 (2 hydrogens, $-CH_2O-$) and a complex aromatic region from τ 1.25 to τ 3.10 (~ 14 hydrogens).

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91. Found: C, 76.91; H, 4.79.

Halfordinol (XIV).

The *O*-benzyl ether XIII (0.9 g.) was refluxed with 210 ml. of 4 *N* hydrochloric acid. The acid solution was cooled, extracted with ether, made strongly alkaline with sodium hydroxide and extracted with chloroform to remove any non-phenolic basic materials. The aqueous alkaline solution was then adjusted to *p*H 8.0 and extracted three times with chloroform. The chloroform extracts were combined, evaporated to dryness and the crystalline residue was crystallized three times from methanol to yield 42 mg. of pure halfordinol (XIV), m.p. 254-255°.

UV (free base in ethanol): λ max 230 (ε, 10,800), 250 (ε, 12,400), 330 mμ (ε, 25,100). UV (0.1 *N* KOH): λ max 261 (ε, 14,600), 348 mμ (ε, 23,950). IR (free base in KBr): cm^{-1} 2800-2600, 1615, 1590, 1510, 830, 810, 700. NMR: The NMR spectrum shows nine protons from τ 1.25 to τ 3.25 and an exchangeable singlet (1 hydrogen) at τ = 0.17.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23. Found: C, 70.53; H, 4.56.

Methylation of halfordinol (XIV) with an ethereal solution of diazomethane yielded *O*-methylhalfordinol (XI), m.p. hydrochloride 243-244°. The compound gave no depression in the melting point when mixed with the hydrochloride prepared as described in the literature (4).

A New Synthesis of Annuloline (I).

2-Methyl-5-(4-methoxyphenyl)oxazole (17.1 g.) (6), 27 ml. of acetic anhydride, 45 g. of veratraldehyde and 1.5 ml. of piperidine were refluxed for 17 hours. The mixture was poured into ice water and extracted with ether. The deep blue fluorescent ether layer was

extracted four times with 500 ml. of 2 *N* hydrochloric acid. The acid solutions were combined, made alkaline with ammonia and re-extracted with ether to yield 10 g. of crude annuloline. For the preparation of pure annuloline, 2.2 g. of the crude material was dissolved in a mixture of cyclohexane-acetone (3:2) and chromatographed through a column of 60 g. of aluminum oxide (Activity II). The various fractions were analyzed by using thin layer techniques (aluminum oxide, solvent system: cyclohexane-acetone (3:2); detection: UV light). The fractions containing annuloline (1.2 g.) were combined, evaporated to dryness and the resulting residue was crystallized from benzene-Skellysolve B (1:3) to give an over-all yield of 800 mg. (12%) of annuloline (I), m.p. 107-108° [Lit. (1) m.p. 105-106°C]. UV: λ max 274 (ε, 12,400), 353 mμ (ε, 33,250). This material was identical with a sample prepared by the published procedure (4).

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(5) The identity of our two synthetic products (XIV) and (XI) with the corresponding compounds prepared from the natural alkaloid N-methylhalfordine (II) by Crow *et al.*, (2) has been established by Mr. S. Teitel (m.p., m.m.p., IR, UV and TLC). We are grateful to Dr. W. D. Crow of The Australian National University, Canberra, Australia, for supplying us with the comparison samples.

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