Reaction of 2-Chlorobenzoxazole with Anthranilic Acids and 2-Amino-1-naphthalenesulfonic Acid

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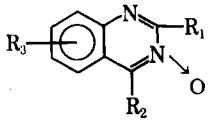
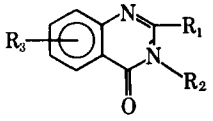
The preparation of 1-carboxy-12-benzo(*d*)quinazo(2,3-*b*)oxazole-12-one and 2-chloro-12-benzo(*d*)quinazo(2,3-*b*)oxazole-12-one are reported. The reaction of 2-chlorobenzoxazole with 2-amino-1-naphthalenesulfonic acid gave 2-(2-naphthylamino)benzoxazole. Preliminary pharmacological screening indicates mild sedative properties for the described compounds.

NUMEROUS CNS properties have been attributed to quinazoline-3-oxides (I) (1) and quinazolones (II) (2). The incorporation of the latter moiety into a tetraheterocyclic system (*e.g.*, VII)



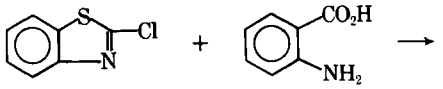
I



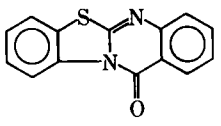
II

which also includes the benzoxazole nucleus was undertaken in order to obtain compounds which might exhibit interesting CNS properties. Benzoxazole derivatives are known to exhibit CNS effects (3).

The preparation of 12-benzo(*d*)quinazo(2,3-*b*)-thiazole-12-one (V) from 2-chlorobenzothiazole (III) and anthranilic acid (IV) has been described by Katz (4); Katz also mentioned 12-benzo(*d*)quinazo-(2,3-*b*)-oxazole-12-one (VII*a*) but did not describe

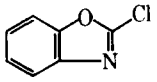


III IV

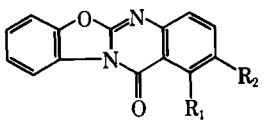


V

its preparation. More recently Sam and Plampin (5) described the preparation of VII*a* *via* condensation of 2-chlorobenzoxazole (VI) and IV. Two related substances, *viz.*, VII*b* and VII*c*, have been



VI

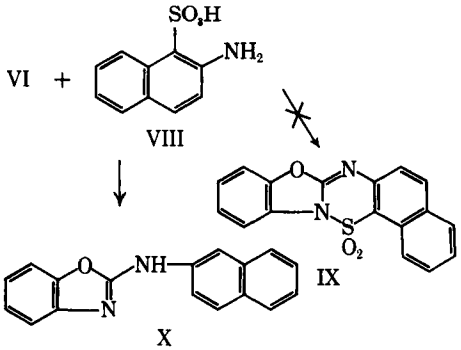


VII

a, $R_1 = R_2 = H$
b, $R_1 = CO_2H, R_2 = H$
c, $R_1 = H, R_2 = Cl$

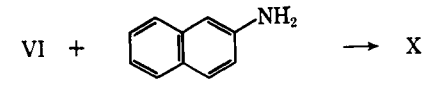
prepared from VI and an appropriately substituted anthranilic acid.

The above results prompted the investigation of the preparation of 12-benzo(*d*)naphtha(*a*)thiadiazo-(2,3-*b*)oxazole-12,12-dioxide (IX) by the condensation of VI with 2-amino-1-naphthalenesulfonic acid (VIII). However, the condensation of VI and VIII



VIII IX X

in either acidic, basic, or neutral medium resulted in either starting materials or intractable residues. The fusion of VI and VIII resulted in 2-(2-amino-naphthyl)benzoxazole (X) which was identified on the basis of physical data and unequivocal synthesis from VI and 2-naphthalamine (XI). The desulfonation inherent in this fusion reaction has not been



XI

previously observed for VIII although the related *1*-naphthalenesulfonic acid is known to undergo desulfonation under acid conditions at 140° (6).

Pharmacological Results[1]—Fasted male albino mice (25–50 g.) were used. The animals were observed closely for signs of pharmacological and toxic effects during the first 2 hr. following intraperitoneal injection. Posttreatment observations were made at 4, 6, 18, 24, and 72 hr. The vehicle for all compounds was a 10% suspension of the respective compound in a 5% acacia solution.

Compound VII*b* exhibited sedation and analgesia at 500 mg./kg. The same effects were noted at 1,000 mg./kg. and 2,000 mg./kg. in addition to ataxia, hypothermia, and opaque clouding of the eyes.

Received April 29, 1968, from the Department of Pharmaceutical Chemistry, The University of Mississippi, University, MS 38677

Accepted for publication May 20, 1968.

[1] The authors are grateful to Dr. W. M. Davis, Department of Pharmacology, School of Pharmacy, The University of Mississippi for pharmacological data.

Compound VII*c* produced writhing, sedation, and diarrhea at 1,000 mg./kg. Compound X exhibited sedation at 500 mg./kg. and 1,000 mg./kg. Sedation was apparent at 2,000 mg./kg. along with writhing and ataxia.

EXPERIMENTAL[2]

1 - Carboxy - 12 - benzo(d)quinazo(2,3 - b)oxazole-12-one (VIIb)—The procedure described by Sam and Plampin (5) for the preparation of VII*a* was followed using 21.7 g. (0.1 mole) of 3-aminophthalic acid and 15.4 g. (0.1 mole) of 2-chlorobenzoxazole. Recrystallization from acetone gave 23.8 g. (85%) of product, m.p. 293–294°; $\nu_{max.}^{KBr}$ 1725 cm.$^{-1}$ (C=O), 1650 (CO_2H); NMR (in d_2-DMSO), 7 proton multiplet at 7.43–8.43 (aromatic), 1 proton broad singlet at 13.0–13.3 (carboxyl hydrogen); upon D_2O exchange the absorption at 13.0–13.3 was absent.

Anal.—Calcd. for $C_{15}H_8N_2O_4$: C, 64.29; H, 2.88; N, 10.00. Found: C, 64.41; H, 2.96; N, 9.82.

2 - Chloro - 12 - benzo(d)quinazo(2,3-b)oxazole-12-one (VIIc)—The procedure described above was followed using 17.1 g. (0.1 mole) of 5-chloroanthranilic acid and 15.4 g. (0.1 mole) of 2-chlorobenzoxazole. Recrystallization from isoamyl alcohol gave 21.6 g. (80%) of product, m.p. 228–229°; $\nu_{max.}^{KBr}$ 1700 cm.$^{-1}$ (C=O); NMR (in d_2-DMSO) 7 proton multiplet at 7.43–8.43 (aromatic).

Anal.—Calcd. for $C_{14}H_7ClN_2O_2$: C, 62.12; H, 2.61; N, 10.35. Found: C, 62.18; H, 2.80; N, 10.38.

2-(2-Naphthylamino)benzoxazole (X)—*Method A*—A mixture of 15.4 g. (0.1 mole) of 2-chlorobenzoxazole and 23.1 g. (0.1 mole) of 2-amino-1-naphthalene-sulfonic acid was fused in a preheated oil bath at 180–190° for 3 hr. The crude product was washed with 5% aqueous NaOH, then recrystallized from cellosolve–water and subsequently from benzene to give 9.5 g. (62%) of product, m.p. 245–245.5°; $\nu_{max.}^{KBr}$ 3300 cm.$^{-1}$ (NH); NMR (in d_2-DMSO), 11 proton multiplet at 7.08–7.3 (aromatic), one proton singlet at 12.5 (NH); upon D_2O exchange the absorption at 12.5 was absent.

Anal.—Calcd. for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.45; H, 4.57; N, 10.66.

Method B—A mixture of 15.4 g. (0.1 mole) of 2-chlorobenzoxazole and 14.3 g. (0.1 mole) of 2-naphthylamine was fused in a preheated oil bath at 130–140° for 4 hr. The crude product was treated as in Method A to give 9.5 g. (62%) of product, m.p. 245–245.5°. A mixture melting point with the product from Method A showed no depression. The infrared as well as the NMR spectra were identical.

[2] Melting points were determined on a Fisher-Johns melting apparatus and are corrected. Infrared spectra were obtained on a Perkin-Elmer 137B Infracord spectrophotometer using KBr pellets. The NMR spectra were determined on a Varian A-60A spectrometer using Me_4Si as internal standard; chemical shifts are recorded as δ values.

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Keyphrases

1-Carboxy-12-benzo(*d*)quinazo(2,3-*b*)oxazole-12-one—synthesis
2-Chloro-12-benzo(*d*)quinazo(2,3-*b*)oxazole-12-one—synthesis
2-(2-Naphthylamino)benzoxazole—synthesis
Pharmacological screening
IR spectrophotometry—structure
NMR spectroscopy—structure