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Studies on the Syntheses of Heterocyclic Compounds. DCCXXVIII.[1] A Simple Synthesis of 1,3-Benzoxazin-4-ones from Salicylic Acid

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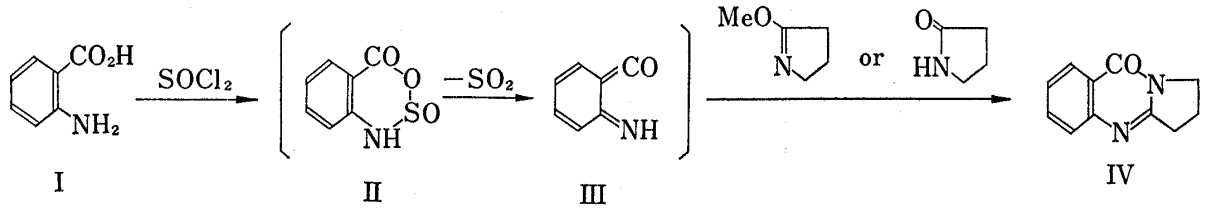
Condensation of salicylic acid chloride (VI) with 3,4-dihydro-β-carboline (VII) gave 6,7,8,13b-tetrahydro-5-oxo-5*H*-β-carbolino[1,2-*b*][1,3]benzoxazine (X), which was also synthesised by a reaction of VI with N-formyltryptamine (VIII). The same reaction of VI with isoquinoline (XIV) and 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (XVI) afforded the corresponding benzoxazinones (XV and XVII), respectively.

Keywords——simple synthesis of 1,3-benzoxazin-4-one; salicylic acid chloride; oxoketene; 6,7,8,13b-tetrahydro-5-oxo-5*H*-β-carbolino[1,2-*b*][1,3]benzoxazine; 5-oxoisoquinolino[1,2-*b*][1,3]benzoxazine

In the previous papers[3–6] we have developed a novel and simple synthetic reaction of quinazolones (IV) along the retro mass spectral synthesis[7] by a cycloaddition reaction[8] of the iminoketene (III), generated *in situ* from anthranilic acid (I) *via* the sulfinamide anhydride (II), to imines and amides as shown in Chart 1. This type of the cycloaddition reaction could be successfully applied for a total synthesis of evodiamine[4–6] and other several alkaloids.[6,9] In an extension of this investigation, we examined a reactivity of salicylic acid chloride (VI), which would form the oxoketene (XIII) in the presence of an appropriate base, instead of anthranilic acid (I). Here we wish to report a novel and simple synthesis of 1,3-benzoxazin-4-one system by the reaction with imines and amides.

Heating salicylic acid (V) with an excess of thionyl chloride in dry benzene for 4 hr in a current of nitrogen gave salicylic acid chloride (VI),[10] which was treated with an equimolar



I II III IV

Chart 1

1) Part DCCXXVII: D. Tourwé, G. Van Binst, and T. Kametani, *Org. Mag. Resonance*, **9**, 341 (1977).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Kametani, T. Higa, K. Fukumoto, and M. Koizumi, *Heterocycles*, **4**, 23 (1976).
4) T. Kametani, T. Higa, C.V. Loc, M. Ihara, M. Koizumi, and K. Fukumoto, *J. Am. Chem. Soc.*, **98**, 6186 (1976).
5) T. Kametani, C.V. Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *Heterocycles*, **4**, 1487 (1976).
6) T. Kametani, C.V. Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *J. Am. Chem. Soc.*, **99**, 2306 (1977).
7) T. Kametani and K. Fukumoto, *Account Chem. Res.*, **9**, 319 (1976); *Yuki Gosei Kagaku Kyokaishi*, **34**, 934 (1976).
8) R.B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, GmbH, Weinheim/Bergstr., 1970.
9) T. Kametani, C.V. Loc, T. Higa, M. Ihara, and K. Fukumoto, *J. Chem. Soc. Perkin I*, in press.
10) E. Ziegler and H.D. Hanus, *Monatsh.*, **95**, 1053 (1964).

amount of 3,4-dihydro-β-carboline (VII) in dry benzene for 2 hr at room temperature to give the condensation product, mp 234—235°, in 81.4% yield after purification on silica gel column chromatography. This compound has the molecular formula $C_{18}H_{14}N_2O_2$, which has been verified by microanalysis and mass spectrometry [*m/e* 290 (M^+)], and showed a presence of indole NH (3500 cm^{-1}) and tertiary amide (1660 cm^{-1}) groups in the infrared (IR) spectrum. Moreover, the nuclear magnetic resonance (NMR) spectrum (δ) showed a methine proton at 6.4 ppm as a singlet in addition to two pairs of methylene protons (2.8—3.0 ppm) and nine aromatic protons (7.2—8.1 ppm). On the basis of these data, the product could be assigned to 6,7,8,13b-tetrahydro-5-oxo-5*H*-β-carbolino[1,2-*b*][1,3]benzoxazine (X).

Furthermore, treatment of salicylic acid chloride (VI) with 1.2 molar equivalent of *N*-formyltryptamine (VIII), a precursor of 3,4-dihydro-β-carboline (VII) in dry chloroform and benzene under the same conditions as above afforded, in 65% yield, the benzoxazin-4-one (X), which was identical with the authentic sample, prepared from 3,4-dihydro-β-carboline (VII), in mp and spectral comparisons.

The mechanism of these reactions could be explained as follows; the condensation of salicylic acid chloride (VI) with 3,4-dihydro-β-carboline (VII) would proceed *via* the cationic intermediate (IX) in the similar manner with Reissert reaction, and the reaction with N-formyltryptamine (VIII) forms firstly the iminium cation (XI), which is attacked by indole ring or phenolic hydroxyl group to generate the intermediate (IX) and (XII). The latter is converted into the final product by the Mannich type cyclization.

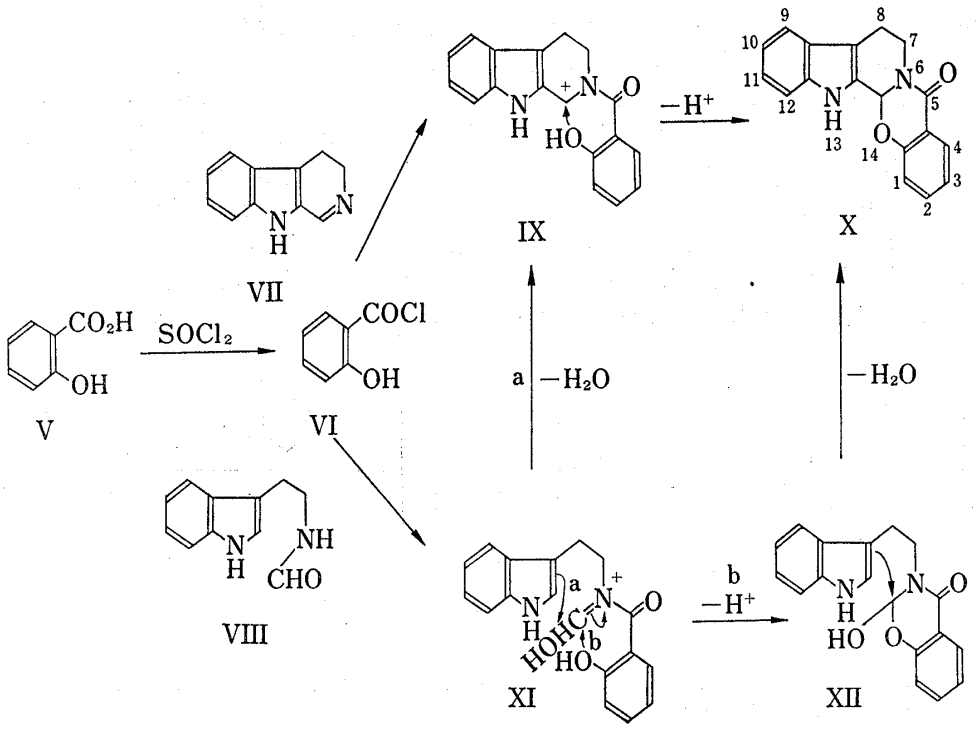


Chart 2

However, the following mechanism could not be ruled out; salicylic acid chloride (VI) might be firstly converted into the more reactive oxoketene (XIII)[10,11] by an intramolecular elimination of hydrogen chloride and then the oxoketene would react with 3,4-dihydro-β-carboline (VII) or *N*-formyltryptamine (VIII) in a manner due to an intermolecular cycloaddition as shown in Chart 3.

11) M. von Strandtman, M. P. Cohen, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **6**, 429 (1969).

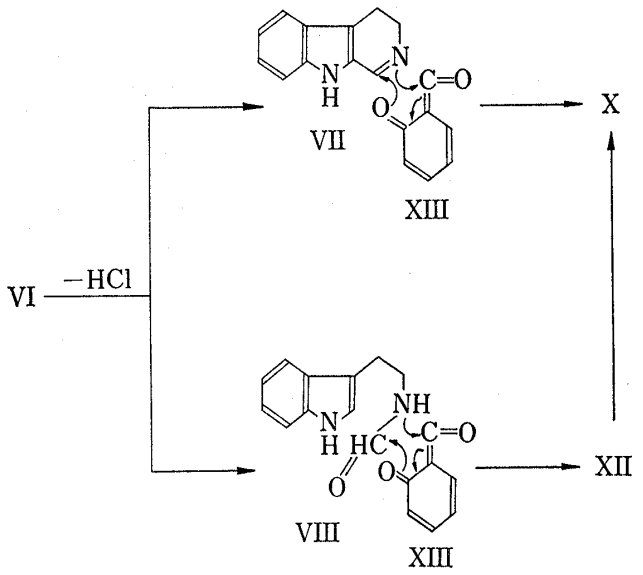


Chart 3

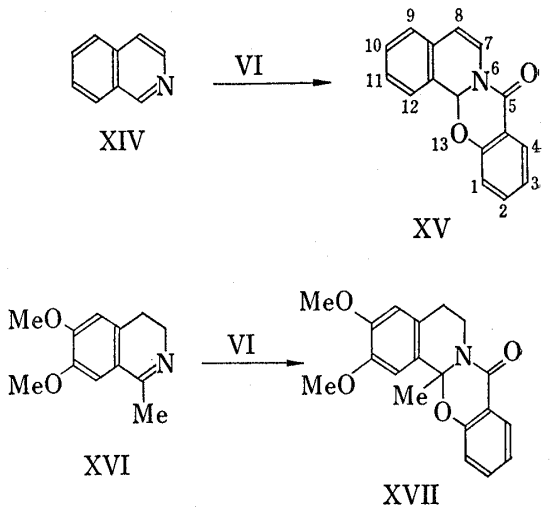


Chart 4

The reaction of isoquinoline (XIV) with salicylic acid chloride (VI) in dry benzene at room temperature for 2 hr gave, in 75% yield, the isoquinolinobenzoxazinone (XV), mp 130—132° [*m/e* 249 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675, δ ($CDCl_3$) 6.7 (1H, s, methine proton)]. Similarly, 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (XVI) reacted with an excess of VI under the same conditions afforded the 1,3-benzoxazin-4-one (XVII), mp 180—182° [*m/e* 323 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650, δ ($CDCl_3$) 1.85 (3H, s, Me)], in 65% yield.

Thus, we have developed a novel and simple synthetic method for 1,3-benzoxazin-4-one system by the reaction of salicylic acid with imines and amides.

Experimental[12]

6,7,8,13b-Tetrahydro-5-oxo-5*H*-β-carbolino[1,2-*b*][1,3]benzoxazine (X)——a) From 3,4-Dihydro-β-carboline (VII). A mixture of salicylic acid (V) (150 mg), thionyl chloride (1.5 g) and dry benzene (10 ml) was refluxed for 4 hr in a current of nitrogen. The excess of reagent and solvent were distilled *in vacuo* at room temperature to leave a pale yellow viscous syrup, to which was added 3,4-dihydro-β-carboline (VII) (180 mg) in dry benzene (20 ml). After the mixture had been kept aside at room temperature for 2 hr, the solvent was evaporated at reduced pressure. The residue was basified with 10% NaOH and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a yellow powder (310 mg), which was subjected to silica gel (10 g) column chromatography. The benzene eluate gave the benzoxazinone (X) (250 mg, 81.4%), mp 234—235°, as colourless crystals after recrystallisation from AcOEt–hexane. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (indole NH) and 1660 (CO); NMR ($CDCl_3$) δ: 2.8—3.0 (4H, m, CH_2CH_2), 6.4 (1H, s, >CH), and 7.2—8.1 (8H, m, ArH); MS *m/e* 290 (M^+). *Anal.* Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.82; N, 9.65. Found: C, 74.28; H, 4.87; N, 9.38.

b) From *N*-Formyltryptamine (VIII): To salicylic acid chloride (VI), prepared from salicylic acid (V) (200 mg), was added a solution of N-formyltryptamine (VIII) (150 mg) in dry benzene–chloroform (v/v 1: 1, 20 ml). After the reaction mixture had been allowed to stand at room temperature for 2 hr, usual work-up and purification as above afforded the benzoxazinone (X) (200 mg, 65%), whose mp and spectral data were identical with those of the sample prepared by method (a) mentioned above.

6,13-Dihydro-5-oxo-5*H*-isoquinolino[1,2-*b*][1,3]benzoxazine (XV)——To the salicylic acid chloride (VI), prepared from salicylic acid (VI) (200 mg), was added isoquinoline (XIV) (300 mg) in dry benzene (15 ml), and the mixture was allowed to stand at room temperature for 2 hr. Work-up and purification as above gave the benzoxazin-4-one (XV) (430 mg, 75%), mp 130—132°, as colourless needles (from EtOAc), IR

12) All melting points are uncorrected and were measured with Yanagimoto micro melting point apparatus (MP-22). IR spectra were taken with a Hitachi 215 grating spectrophotometer, NMR spectra with a JEOL PMX-60 spectrometer with Me_4Si as internal standard, and MS with a Hitachi RMU-7 spectrometer.

$\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (CO); NMR ($CDCl_3$) δ: 5.75 (1H, d, J=8 Hz, CH=CHN), 6.7 (1H, s, CH), 6.9—7.6 (8H, m, ArH) and 7.95 (1H, d, J=8 Hz, CH=CHN); MS *m/e* 249 (M^+). *Anal.* Calcd. for $C_{16}H_{11}NO_2$: C, 77.11; H, 4.42; N, 5.62. Found: C, 77.06; H, 4.06; N, 5.46.

6,7,8,12b-Tetrahydro-10,11-dimethoxy-13a-methyl-5-oxo-5*H*-isoquinolino[1,2-*b*][1,3]benzoxazine (XVII) ——To the salicylic acid chloride (VI), prepared from salicylic acid (V) (400 mg), was added a solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (XVI) (200 mg) in dry benzene (20 ml). After being kept aside for 2 hr at room temperature, the mixture was worked up and purified as above to give the benzoxazinone (XVII) (240 mg, 65%), mp 180—182°, as colourless crystals (from AcOEt–hexane), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (CO); NMR ($CDCl_3$) δ: 1.85 (3H, s, Me), 2.5—3.2 (4H, m, CH_2CH_2), 3.9 (3H, s, OMe), 4.0 (3H, s, OMe), and 6.9—8.6 (6H, m, ArH); MS *m/e*: 323 (M^+). *Anal.* Calcd. for $C_{19}H_{17}NO_4 \cdot 0.5H_2O$: C, 68.88; H, 5.44; N, 4.23. Found: C, 68.70; H, 5.84; N, 4.10.

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