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The Chemistry of Heterocycles. III. 2H-1,3-Benzoxazine-2,4(3H)-dione and Some 3-Substituted Derivatives. (1-3)

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The preparation of 2H-1,3-benzoxazine-2,4(3H)-dione, the sodium salt, and the *p*-anisoyl, benzoyl, *m*-bromobenzoyl, benzyl, *trans*-cinnamoyl, ethyl, myristoyl, *p*-nitrobenzyl, phenyl and *p*-phenylphenacyl derivatives substituted on 2H-1,3-benzoxazine-2,4(3H)-dione (I) at position 3 together with their infrared and ultraviolet spectra are described.

The impetus to begin this investigation was based on the improved synthesis of 2H-1,3-benzoxazine-2,4(3H)-dione (I) and the consideration of the close structural similarity of this compound to the known medicinally active barbiturates and salicylates (12). Limited investigations involving I have been cited by various authors (6-11), however, in most cases the isolation of I was tedious or of low yield. Employing the improved procedure of Hoback and co-workers (12), I was easily prepared for use in this investigation by the reaction of salicylamide and ethyl chlorocarbonate in pyridine solution.

The facile synthesis of the sodium salt (II), by reaction of I with ethanolic sodium ethoxide, led to the preparation of derivatives in which other moieties of various types were conveniently attached in good yields. In general, acylations were accomplished by reaction of the sodium salt (II) with the appropriate acid chloride in anhydrous benzene or anhydrous benzene-pyridine solution while the alkyl derivatives were prepared from the sodium salt (II) and the alkyl halide in absolute ethanol.

Examination of the infrared spectrum of I showed two carbonyl absorption bands at 1770 and 1724 cm^{-1} . From comparisons with the spectra of salicylamide and compounds of similar structure it was deduced

that the carbonyl peak at 1770 cm^{-1} corresponds to the carbonyl ester of I, whereas the peak at 1724 cm^{-1} corresponds to the amide I carbonyl absorption. Also noted in the spectrum of I was the presence of N-H absorption at 3200 cm^{-1} , this absorption being absent in the spectrum of II and the other substituted compounds. In the spectrum of the sodium derivative (II), it was noted that the ester and amide carbonyl peaks had shifted with reduced intensity to 1717 and 1681 cm^{-1} respectively, while two additional broad peaks had appeared at 1618 and 1560 cm^{-1} . The latter peaks may be attributed to the increased contribution of amide II bands of both carbonyls of the sodium salt (II).

Examination of the spectra of the alkyl compounds revealed two carbonyl absorption bands generally between 1700-1800 cm^{-1} . In each case absorption at the higher frequency was representative of the ester group while the absorption band at the lower frequency represented the amide I carbonyl. In the spectrum of every acyl compound, a third carbonyl peak always appeared between the principle ester and amide I carbonyl bands. As noted in Bellamy (14) and the spectra of related compounds, the presence of this third carbonyl absorption when located

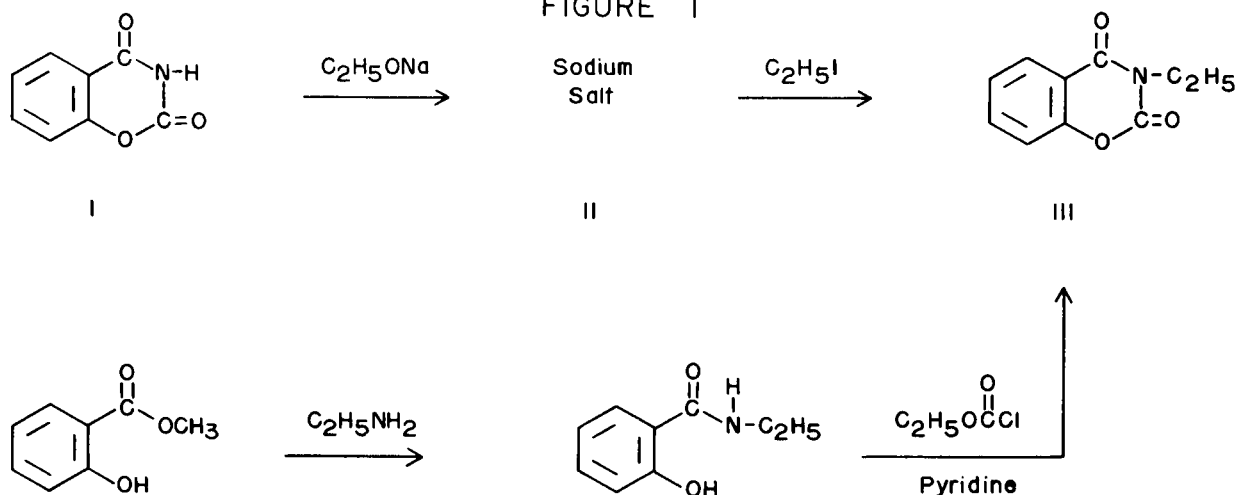


TABLE I

Spectral Data of 2H-1,3-Benzoxazine-2,4(3H)-dione (I) and 3-Substituted Derivatives

Compound	Group	Infrared Carbonyl Absorption (cm ⁻¹)	Ultraviolet Absorption, λ max (CH ₃ OH) $m\mu$ ($\epsilon \times 10^4$)
I	H	1770a, 1724b	205(3.4), 236bs(0.80), 293bp(0.19)
II	Na	1717a, 1681b	206(3.0), 236(0.77), 293bp(0.15)
III	C ₂ H ₅	1763a, 1700b	205(3.2), 236(0.80), 290bp(0.10)
IV	C ₆ H ₅ CH ₂	1770a, 1708b	207(3.9), 240(0.96), 290bs(0.18)
V	<i>p</i> -O ₂ NC ₆ H ₄ CH ₂	1760a, 1704b	206(5.1), 243bp(1.39), 270bp(1.24)
VI	<i>p</i> -C ₆ H ₅ C ₆ H ₄ COCH ₂	1767a, 1710b and c	204(5.7), 235s(1.13), 290bp(2.20)
VII	C ₆ H ₅	1770a, 1710b	206(3.9), 240(0.95), 290bp(0.15)
VIII	C ₆ H ₅ CO	1784a, 1739c, 1712b	205(3.9), 246bp(1.62), 290bp
IX	<i>m</i> -BrC ₆ H ₄ CO	1785a, 1745c, 1714b	207(4.5), 248bp(1.52), 295bs(0.27)
X	<i>trans</i> -C ₆ H ₅ CH=CHCO	1782a, 1735c, 1713b	206(3.4), 230s(1.42), 303bp(2.20)
XI	<i>p</i> -H ₃ COC ₆ H ₄ CO	1779a, 1734c, 1710b	206(3.7), 238s(1.42), 243s(0.87), 293bp(1.97)
XII	H ₃ C(CH ₂) ₁₂ CO	1805a, 1760c, 1710b	206(3.6), 238bp(0.87), 290bp
XIII	<i>p</i> -O ₂ NC ₆ H ₄ CO	1785a, 1742c, 1712b	205(5.2), 250s(1.85), 263bp(2.10), 290bp
XIV	-----	1735a, 1652b	205(3.7), 239(0.86), 305bp(0.37)

a, urethane carbonyl (2-position); b, amide carbonyl (4-position); c, derivative carbonyl (on 3-position); bp, broad peak; s, shoulder; bs, broad shoulder. The ultraviolet values near 205 $m\mu$ are only approximate since the spectra were recorded in methanol.

in this manner is representative of such a trisubstituted nitrogen. Observed in the infrared spectra of all compounds (I-XIII) was a peak at 1210 cm⁻¹ which is indicative of the -C-O-C- asymmetric stretch of the benzoxazine ring.

The ultraviolet spectra of I and the 3-substituted compounds when compared to the spectrum of salicylamide showed almost identical characteristic carbonyl-aromatic ring absorptions near 205 $m\mu$. In general, the substituted aryl derivatives showed a broadening of the second characteristic peak and a shift to a longer wavelength. The alkyl derivatives showed no marked changes in the ultraviolet spectra when compared to I except in the case of the 3-(*p*-nitrobenzyl)- (V) and 3-(*p*-phenylphenacyl)- (VI) derivatives which absorbed more strongly in the 270 and 290 $m\mu$ regions respectively.

Of interest was the preparation of β -carboethoxy-salicylhydrazide formed from the reaction of salicylhydrazide with ethyl chlorocarbonate. The 3-amino derivative of I was not formed as anticipated, but under a large variety of conditions, the β -substituted hydrazide (XIV) was produced instead. Examination of the infrared spectrum of XIV showed the characteristic urethane ester carbonyl absorption at 1735 cm⁻¹ and strong broad amide II absorption at 1652 cm⁻¹. Since the amide II band is not present in disubstituted amides (13) the carboethoxy group in this compound is therefore located not on the *alpha* but the *beta* nitrogen atom. A sharp peak present at 1162 cm⁻¹, the strongest region of phenolic OH

absorption, was also consistent with the open-chain formula.

EXPERIMENTAL

All chemical analyses were performed by Galbraith Laboratories, Inc., Knoxville 21, Tennessee, except as noted. All melting points, taken on a Thomas-Hoover Capillary Melting Point Apparatus, are uncorrected.

All solvents used were Baker Analyzed Reagent grade. Benzene and petroleum ether (b.p. 30-60°) were dried over sodium, and pyridine was dried by distilling with barium oxide. All reagents used were Eastman Kodak White Label materials.

2H-1,3-Benzoxazine-2,4(3H)-dione (I).

This compound was prepared according to the procedure of Hoback, Crum and Carroll (12). To a solution of 411 g. (3.0 moles) of salicylamide in 483 ml. (6.0 moles) of anhydrous pyridine at 0° was added slowly with stirring 572 ml. (6.0 moles) of ethyl chlorocarbonate. The resulting orange solution was refluxed for 5 hr. and poured into 2 l. of ice-water. The filtered product was washed twice with 0.5 l. of water and recrystallized three-times from acetone-ethanol (50:50) giving white needles (83% yield), m.p. 227.5-228.5° (lit. 12), m.p. 227-228°, which gave no coloration with ethanolic ferric chloride.

Anal. Calcd. for C₈H₉NO₃: C, 58.88; H, 3.09; N, 8.59. Found: C, 59.07; H, 3.13; N, 8.82.

2H-1,3-Benzoxazine-2,4(3H)-dione-sodium (II).

The sodium salt of I was prepared according to the method of Hoback, Crum and Carroll (12). To a solution of 32.6 g. (0.20 mole) of I in 2 l. of boiling absolute ethanol was added slowly with stirring 400 ml. of an ethanolic solution of sodium ethoxide (9.2 g., 0.40 gram atom of sodium). The mixture was cooled to 0° and filtered yielding 29.4 g. (80% yield) of II, m.p. 352-357°.

Anal. Calcd. for C₈H₉NO₃Na: C, 51.89; H, 2.18; N, 7.57; Na, 12.43. Found: C, 52.10; H, 2.30; N, 7.67; Na, 12.19.

3-Ethyl-2H-1,3-benzoxazine-2,4(3H)-dione (III) from II and ethyl iodide.

A solution of 7.4 g. (0.04 mole) of II in 100 ml. of absolute ethanol and 32.3 ml. (0.40 mole) of ethyl iodide was refluxed for 5 hr., the mixture poured into water and the resulting oil separated by decantation. The oil was dissolved in ethanol and the alcoholic solution poured into water giving 2.10 g. (0.011 mole, 27%) of product. Recrystallization from boiling water gave white flakes, m.p. 107.5-108°, in agreement with that (107°) previously reported (7).

3-Ethyl-2H-1,3-benzoxazine-2,4(3H)-dione (III) from N-ethyl salicylamide and ethyl chlorocarbonate.

To a cold solution (0°) of 1.6 g. (0.01 mole) of N-ethyl salicylamide in 25 ml. of pyridine was added slowly with stirring 1.9 ml. (0.02 mole) of ethyl chlorocarbonate. The reaction mixture was refluxed for 5 hr., cooled to room temperature, poured into water and refrigerated overnight. The resulting solid was filtered and recrystallized from hot water giving short, white needles, m.p. 107.5-108.0°. This product gave no melting point depression on admixture with the product obtained from the reaction of II with ethyl iodide.

3-Benzyl-2H-1,3-benzoxazine-2,4(3H)-dione (IV).

To a solution of 9.25 g. (0.05 mole) of II in 125 ml. of pyridine was added 6.33 g. (0.05 mole) of benzyl chloride, the reaction mixture refluxed for 4 hrs. and poured over ice. Three recrystallizations from hot absolute ethanol yielded a white flocculent precipitate, m.p. 133-134°, in agreement with that (130°) previously reported (6,12).

3-(p-Nitrobenzyl)-2H-1,3-benzoxazine-2,4(3H)-dione (V).

To a mixture of 1.0 g. (0.0054 mole) of II in 15 ml. of absolute ethanol was added with stirring 0.92 g. (0.0054 mole) of p-nitrobenzyl chloride. The mixture was refluxed for 2.5 hr., poured over ice and filtered yielding 0.90 g. (0.0030 mole, 56%) of product. Recrystallization from boiling absolute ethanol gave white needles, m.p. 186-186.5°.

Anal. Calcd. for C₁₆H₁₀N₂O₆: C, 60.40; H, 3.38; N, 9.39. Found: C, 60.19; H, 3.55; N, 9.15.

3-(p-Phenylphenacyl)-2H-1,3-benzoxazine-2,4(3H)-dione (VI).

To a mixture of 1.0 g. (0.0054 mole) of II in 20 ml. of absolute ethanol was added 1.24 g. (0.0054 mole) of p-phenylphenacyl chloride, the reaction mixture refluxed for 4 hr., cooled, poured over ice and filtered yielding 1.45 g. (0.0041 mole, 75%) of product, m.p. 170-178°. Recrystallization from a boiling solution of benzene and petroleum ether (2:1) yielded light-yellow crystals, m.p. 222-224°.

Anal. Calcd. for C₂₂H₁₅NO₄: C, 73.94; H, 4.23; N, 3.91. Found: C, 74.08; H, 4.48; N, 3.68.

3-Phenyl-2H-1,3-benzoxazine-2,4(3H)-dione (VII).

To a cold solution (0°) of 31.9 g. (0.15 mole) of salicylanilide in 75 ml. of pyridine was added with stirring, 28.7 ml. (0.30 mole) of ethyl chlorocarbonate. The reaction mixture was refluxed for 0.5 hr. and, after cooling and filtration, gave 14.5 g. (0.061 mole, 41%) of product, m.p. 240-244°. Three recrystallizations from boiling benzene gave light flakes of VII, m.p. 244.5-245°, in agreement with that (246°) previously reported (6).

Anal. Calcd. for C₁₄H₉NO₃: C, 70.29; H, 3.79; N, 5.85. Found: (15): C, 70.71; H, 4.04; N, 5.81.

3-Benzoyl-2H-1,3-benzoxazine-2,4(3H)-dione (VIII).

This compound was prepared according to a modification of the method of Einhorn and Mettler (7). To a cold mixture (0°) of 5.0 g. (0.036 mole) of I in 40 g. of pyridine was added 4.5 g. (0.032 mole) of benzoyl chloride yielding, after the addition of water, an oil which solidified, m.p. 160-168°. Three recrystallizations from absolute ethanol gave long, flat, white needles, m.p. 171-172° (lit. (7), m.p. 172°).

3-(m-Bromobenzoyl)-2H-1,3-benzoxazine-2,4(3H)-dione (IX).

To a mixture of 1.0 g. (0.0054 mole) of II in 50 ml. of benzene and 10 ml. of pyridine was added over 5 min., with stirring, a solution of 1.18 g. (0.0054 mole) of m-bromobenzoyl chloride in 40 ml. of benzene. After refluxing 6 hr., the hot reaction mixture was filtered, concentrated to 15 ml. and 75 ml. of petroleum ether added. The mixture was refrigerated overnight (-20°) yielding 1.48 g. (0.0043 mole, 79.5%) of a yellow product, m.p. 132-138° which upon washing with ether and recrystallization from hot absolute ethanol yielded white crystals, m.p. 148-149°.

Anal. Calcd. for C₁₅H₉NO₄Br: C, 52.04; H, 2.33; N, 4.05; Br, 23.09. Found: C, 52.00; H, 2.19; N, 4.08; Br, 23.13.

3-(trans-Cinnamoyl)-2H-1,3-benzoxazine-2,4(3H)-dione (X).

To a mixture of 1.0 g. (0.0054 mole) of II in 50 ml. of benzene and 10 ml. of pyridine was added, over 5 min., a solution of 0.895 g. (0.0054 mole) of trans-cinnamoyl chloride in 30 ml. of benzene. After refluxing 15 min., the mixture was filtered while hot, concentrated to 30 ml., diluted with 150 ml. of petroleum ether and refrigerated (-20°) yielding 1.26 g. (0.0043 mole, 80.5%), m.p. 137-139°. The product was recrystallized from a boiling mixture of 30 ml. of benzene and 42 ml. of petroleum ether giving white crystals, m.p. 149-150°.

Anal. Calcd. for C₁₇H₁₁NO₄: C, 69.62; H, 3.78; N, 4.77. Found: C, 69.45; H, 3.66; N, 4.71.

3-(p-Anisoyl)-2H-1,3-benzoxazine-2,4(3H)-dione (XI).

To a mixture of 1.0 g. (0.0054 mole) of II in 45 ml. of benzene and 10 ml. of pyridine was added slowly with stirring over 15 min., a solution of 0.93 g. (0.0055 mole) of p-anisoyl chloride in 30 ml. of benzene. The resulting white mixture was refluxed for 9 hr., filtered, concentrated to 15 ml. and diluted with 85 ml. of petroleum ether giving 1.30 g. (0.0044 mole, 81%) of product, m.p. 191-194°. The product was recrystallized from 15 ml. of hot benzene yielding white crystals of XI, m.p. 205-206°.

Anal. Calcd. for C₁₈H₁₁NO₄: C, 64.64; H, 3.73; N, 4.71. Found: C, 64.82; H, 3.92; N, 4.62.

3-Myristoyl-2H-1,3-benzoxazine-2,4(3H)-dione (XII).

To a mixture of 1.0 g. (0.0054 mole) of II in 50 ml. of benzene was added slowly, with stirring, over 15 min., 1.33 g. (0.0054 mole) of myristoyl chloride. After refluxing for 0.5 hr., 15 ml. of pyridine was added, and refluxing continued for an additional 0.5 hr. The yellow solution was filtered, evaporated to 15 ml. and diluted with 85 ml. of petroleum ether giving 1.40 g. (0.0038 mole, 70%) of material, m.p. 87-93°. Recrystallization of this product from a boiling solution of benzene and petroleum ether (1:6) yielded white fluffly crystals, m.p. 95-96°.

Anal. Calcd. for C₂₂H₃₁NO₄: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.78; H, 8.43; N, 3.81.

3-(p-Nitrobenzoyl)-2H-1,3-benzoxazine-2,4(3H)-dione (XIII).

To a mixture of 1.0 g. (0.0054 mole) of II in 45 ml. of benzene and 10 ml. of pyridine was added slowly with stirring, over 15 min., a solution of 1.0 g. (0.0054 mole) of p-nitrobenzoyl chloride in 30 ml. of benzene. The mixture was refluxed for 1 hr., the resulting light-yellow solution filtered, concentrated to 10 ml. and diluted with 90 ml. of petroleum ether giving 1.35 g. (0.0043 mole, 80.5%) of material, m.p. 205-215°. Recrystallization from a hot solution of benzene and petroleum ether (3:1) gave light-yellow crystals, m.p. 229-230°.

Anal. Calcd. for $C_{15}H_8N_2O_6$: C, 57.70; H, 2.58; N, 8.97. Found: C, 57.90; H, 2.56; N, 8.77.

β -Carboethoxysalicylhydrazide (XIV).

To a solution of 18.8 g. (0.12 mole) of salicylhydrazide in 250 ml. of pyridine was added dropwise 23.4 ml. (0.25 mole) of ethyl chloro-carbonate. After refluxing for 4 hr. the yellow solution was concentrated to a thick syrup, 700 ml. of water was added, the mixture stirred for one day and filtered yielding 18.3 g. (0.082 mole, 66%) of product, m.p. 114-119°. After three recrystallizations from hot water the white needles, m.p. 119.5-120°, gave a purple coloration in ethanolic ferric chloride.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.40; N, 12.49. Found: (15): C, 53.53; H, 5.42; N, 12.59.

Ultraviolet Determinations.

Ultraviolet spectra were recorded in Eastman Kodak Spectro Grade methanol between 195 and 390 $m\mu$ on a double beam Perkin-Elmer Ultraviolet-Visible Spectrophotometer Model 202 in concentrations from 1-3 mg. of compound per 25 ml. of methanol.

Infrared Determinations.

Infrared spectra were recorded on a Beckman IR9 Infrared Spectrophotometer in Eastman Kodak Spectro Grade chloroform at concentrations from 20-50 mg. of compound per ml. of chloroform except I which was determined in pyridine solution and II as a potassium bromide disc. The spectra were recorded in matched KBr cells between 400 and 4000 cm^{-1} .

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