RING CONTRACTION OF 3-CARBOXAMIDE OR 3-CARBOXYLATE OF 4-HYDROXY-2-METHYL -2*H*-1,2-BENZOTHIAZINE -1,1-DIOXIDE AND ANALOGOUS 1(2*H*)-ISOQUINOLINONE-3-CARBOXYLATE

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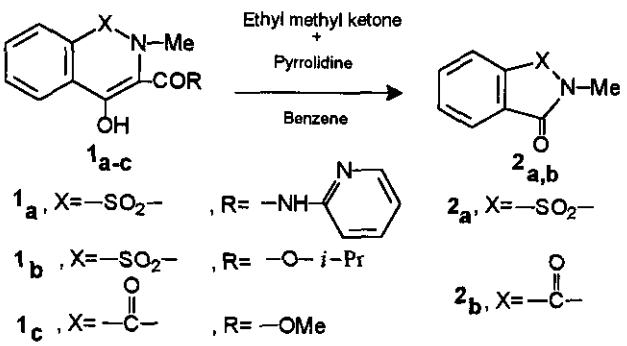
Abstract-A novel ring transformation of 3-carboxylate or 3-carboxamide of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-1,1-dioxide and analogous 1(2*H*)-isoquinolinone-3-carboxylate to the 5-membered rings upon the reaction with carbonyl compounds in the presence of primary or secondary amines is described.

During the course of our investigations for the synthesis of prodrugs of the popular antiinflammatory agent piroxicam (**1a**)[1] through the reaction with ethyl methyl ketone in the presence of pyrrolidine in benzene, the only product isolated was shown by spectroscopic and analytical data to be 2-methyl-1,2-benzoisothiazol-3(2*H*)-one 1,1-dioxide (**2a**)[2] which is a known metabolite of **1a**.[3] Compound (**2a**) was also obtained when we carried out the same reaction with isopropyl 4-hydroxy-2-methyl -2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**1b**) instead of **1a**. These findings led us to investigate the utility of this reaction for the ring transformation of 1,2-dihydro-4-hydroxy-2-methyl-1-oxo-3-isoquinolinecarboxylic acid methyl ester (**1c**)[4] under similar conditions and the structure of the product of this reaction was established as 2-methyl-1*H*-isoindole-1,3(2*H*)-dione (**2b**)[2] (Scheme 1).



Scheme 1

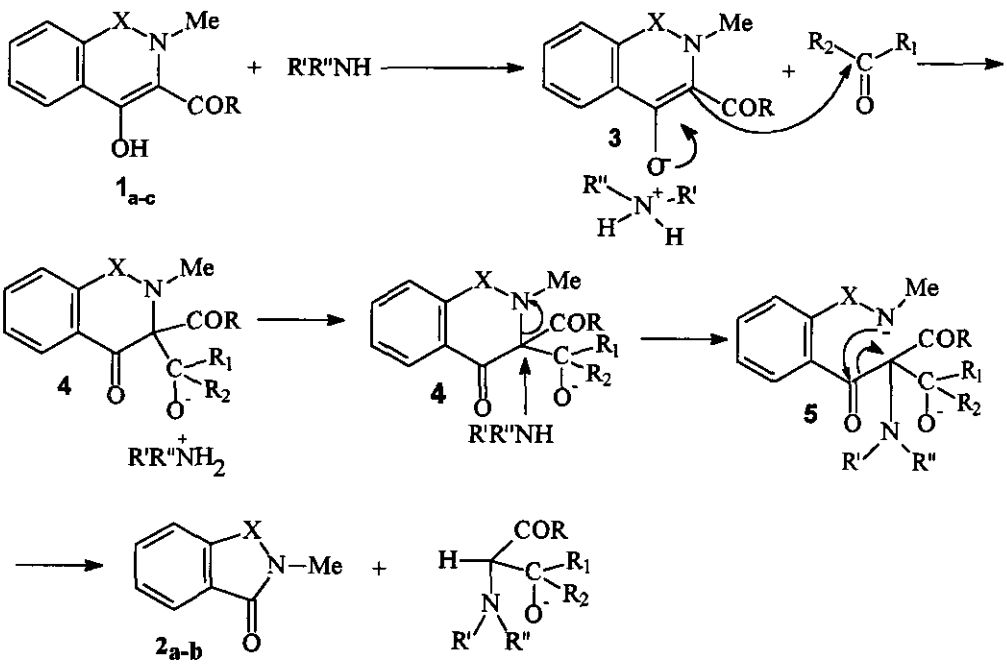
Further experiments showed that the ring contraction of **1a-c** was also successful for the reaction with other carbonyl compounds in the presence of primary or secondary amines (Table1), but failed with tertiary amines.

Table1. Ring contraction of **1a-c** to **2a-b** upon the reaction with carbonyl compounds in the presence of primary or secondary amines.

Substrate	Aldehyde or Ketone	Amine	Product Yield %
			2a
1a	ethyl methyl ketone	pyrrolidine	48
	acetone	butylamine	39
	benzaldehyde	pyrrolidine	52
1b	ethyl methyl ketone	pyrrolidine	32
	methyl isopropyl ketone	morpholine	43
			2b
1c	ethyl methyl ketone	pyrrolidine	35
	propionaldehyde	aniline	28

While we are not certain about the fate of the extruded ring carbon (C-3) with the attached substituents as well as that of the amine and aldehyde or ketone reactants, following important parameters for transformation of **1a-c** to **2a,b** have been investigated. No reaction occurs in the absence of either amines or carbonyl compounds, confirming the requirement for participation of both reactants in the ring contraction. No reaction occurs between **1a-c** and preformed *N*-(2-buten-2-yl)pyrrolidine[5] even in the presence of pyrrolidine, eliminating the possibility that ring contraction might proceed through the reaction of **1a-c** with *in situ* generated enamines from the carbonyl compounds and amines.

From these results it seems that the mechanism of the reaction may involves the nucleophilic addition of the enolate ions of the amine salts (**3**) resulting from the reaction of **1a-c** with amines to the carbonyl group to give the intermediate (**4**). Inductive influences of the C-3 bearing two electron withdrawing groups as well as the carbonyl group increase the positive character of C-3 and make it susceptible to the nucleophilic substitution. The steric interference between the substituents at C-3 and the methyl group at N-2 assisted by the nucleophilic addition of the amine nitrogen to C-3 would force the amide nitrogen of the intermediate (**4**) out of the plane and result in the formation of the ring-opened intermediate (**5**). The final step of the reaction may involve nucleophilic attack of the sulfonamide nitrogen of the intermediate (**5**) to the carbonyl group to give products (**2a,b**) with concurrent elimination of C-3 and attached substituents. (Scheme 2)



Scheme 2

The lack of reactivity of tertiary amines compared with primary and secondary amines for conversion of **1a-c** to **2a,b** may be attributed to the greater steric hindrance and lower nucleophilicity to induce conversion of the intermediate (**4**) to **2a,b.** Consistent with this mechanism ring transformation failed with *N*-demethyl analogue (**1c**)[6] in which nitrogen atom is less nucleophilic in comparison with that of **1c** and it lacks the steric hindrance of the methyl group.

Further support for the mechanism was given by the experiment in which preformed crystalline (**3**) prepared from the reaction of **1a** with morpholine in EtOH[7] was treated with ethyl methyl ketone to give **2a**.

In summary, although ring expansion of *N*-substituted derivatives (**2a**)[6] and (**2b**)[8] is a general synthetic route for the preparation of the six membered rings (**1a-c**), the findings described in this paper is the first example for the reverse ring contraction.

EXPERIMENTAL

Melting points were determined with a Reichert hot plate melting point apparatus and are uncorrected. TLC analyses were performed on 250-Eastman 13181 silicagel sheets; spots were visualized under ordinary fluorescent light or 254 nm UV light. MS spectra were recorded with a Finnigan TSQ-70 instrument .^{1}H NMR spectra were measured in deuterochloroform with a Bruker AC-80 (80 MHz) spectrometer relative to TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Elemental analyses were performed by the microanalytical laboratory, Iran National Oil Company. Piroxicam (**1a**) was

supplied by the Alhavi Pharmaceutical Company in Iran. The known isoquinoline (**1c**) used in the present study was prepared according to the reported method in the literature.[4]

Isopropyl 4-hydroxy-2-methyl -*2H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (1b).

To a stirred solution of 0.8 g (0.2 mol) of sodium hydroxide in water (50 mL) and EtOH (65 mL) at rt was added 6 g (0.2 mol) of isopropyl 4-hydroxy-*2H*-1,2-benzothiazine-3-carboxylate 1,1-dioxoide[6] and the mixture was heated at reflux for 20 min. To the resulting solution after cooling to rt was added 6.3 mL (0.1 mol) of methyl iodide and stirring was continued for 8 h. The obtained precipitate was collected by filteration, washed with water (20 mL) and the crude product was recrystallized from MeOH to give 5 g (86%) of **1b**: mp 105°C ; IR(KBr): 1600, 1340, and 1190 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.22 (s, 1H, OH), 7.99-7.76 (m, 4H, aromatic), 5.32 (m, J = 6.3 Hz, 1H, -CH-), 2.95 (s, 3H, N-CH_3), and 1.35 (d, J = 6.3 Hz, 2H, CH_3) ppm; MS: *m/z* 297(M^+). Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.54; H,5.04; N,4.71. Found: C, 52.23; H, 4.95; N, 4.43.

General procedure for the ring transformation of 1a-c to 2a,b is as follows :

The appropriate primary or secondary amine (9 mmol) was added to a stirred mixture of **1** (6 mmol) in anhydrous benzene (10 mL) at rt and the resulting clear yellow solution after heating at reflux for 10 min gave a suspension which upon addition of the carbonyl compound (6 mmol) was changed to a solution. The solution was then allowed to stir at reflux for 4 h and the progress of the formation of the product was checked by TLC analyses (benzene/chloroform= 6/4). After cooling to rt unreacted **1** was filtered and the organic solution was washed successively with 5% HCl (2 mL), 5% sodium hydroxide solution (2 mL), and water (2 mL ×2) and dried over anhydrous $MgSO_4$. The residue after evaporation of the solution under reduced pressure was crystallized from EtOH to give **2**.

2a: mp 131-132°C (lit.,[2] 130 °C); IR (KBr): 1720,1375,1330, and 1160 cm^{-1}; ^1H NMR($CDCl_3$): δ 8.05-7.82 (m, 4H, aromatic), and 3.27 (s, 3H, N-CH_3) ; MS m/z:197 .

2b:mp 130°C(lit.,[2] 126 -128°C); IR (KBr): 1725, 1610, and 1450 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 8.12-7.76 (m, 4H, aromatic),and 3.47 (s, 3H, N-CH_3); MS m/z: 161.

REFERENCES

1. R.N. Brogden, R.C. Heel, T.M. Speight, and G.S. Avery, *Drugs,* 1984, **28**, 292 .

2. Y. Inoue, M. Taguchi, and H. Hashimoto, *Synthesis* ,1986, 332.

3. J. G. Lombardino, *J. Med. Chem.*, 1981, **24**, 39.

4. J. G. Lombardino, *J. Heterocycl. Chem.*, 1970, **7**, 1057.

5. R. Jacquier, C. Petrus, and F. Petrus, *Bull. Chem. Soc. Fr.*, 1966, 2845.

6. C. B. Schapira, I. A.Perillo, and S. Lamdan, *J. Heterocycl. Chem.*, 1980, **17**, 1281.

7. R. G. W. Spickett, J. Moragues Mauri, A. Vega Noverola and J. M. Prieto Soto, Span. ES.507,666, 1982 (*Chem. Abstr.*, 1982, **98**, 179396g).

8. L. R. Caswell and R. D. Campbell , *J. Org. Chem.*, 1961, **26**, 4175.

Received, 14th November, 1997