

# 1,4-BENZODIAZEPINES AND THEIR DERIVATIVES

## VII.\* ACTIVITY OF THE METHYLENE GROUP OF 1,3-DIHYDRO-2H-

### 1,4-BENZODIAZEPIN-2-ONES AND -2-THIONES

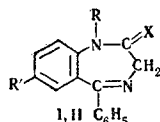
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A series of compounds of the merocyanine dye type was obtained by the reaction of 1-acetyl-1,3-dihydro-2H-1,4-benzodiazepin-2-ones and 1,3-dihydro-2H-1,4-benzodiazepine-2-thiones with 2-methylmercapto-3-ethylbenzothiazolium tosylate, 2-methylmercapto-3,4,5-trimethylthiazolium bromide, 2-methylmercapto-3-methyl-5-phenyloxazolium methosulfate, and 1,3,3-trimethyl-2-formylmethyleneindoline. The hydrogen atoms of the methylene group of the 1-unsubstituted and 1-alkyl-substituted 1,3-dihydro-2H-1,4-benzodiazepin-2-ones are of low mobility, and the indicated compounds do not undergo condensation reactions with electrophilic agents.

In the chemistry of 1,4-benzodiazepines the problem of the activity of the methylene group of 1,3-dihydro-2H-1,4-benzodiazepin-2-ones (I) and -2-thiones (II) has not been studied at all. There are papers [1,2] in which the condensation of tetrahydro-1,4-benzodiazepin-2,5-dione with benzaldehyde, which proceeds with the participation of the methylene group of this 1,4-benzodiazepine derivative, is described.

We felt that it would be interesting to investigate the activity of the methylene group in substituted 1,3-dihydro-2H-1,4-benzodiazepin-2-ones and -2-thiones (A).



R=H, CH<sub>3</sub>, CH<sub>3</sub>CO; R'=CH<sub>3</sub>, Cl, Br; I X=O; II X=S

Proceeding from the structure of compounds of the A type, it could be assumed that they are capable of reacting with electrophilic agents like other substances that contain active methylene groups. We have previously shown that I (X = O, R = H) undergoes tautomeric transformation as the pH is changed. In neutral media, these compounds have a lactam structure, but have the lactim structure in alkali [3,4]. The shift of the electron density in the I system, which is responsible for this form of tautomerism, suppresses the formation of the enol form via the second form of tautomerism possible here, viz., keto-enol tautomerism. The methylene group in such compounds is of low activity.

It seemed possible that the introduction of an electron-acceptor substituent into the 1-position could increase the lability of the hydrogen atoms of the methylene group. Proceeding from this assumption, we synthesized the corresponding acetyl derivatives of I (R = CH<sub>3</sub>CO) [4] and condensed them with the intermediates commonly used in the synthesis of cyanine dyes - 2-methylmercapto-3-ethylbenzothiazolium tosylate (III), 2-methylmercapto-3,4,5-trimethylthiazolium bromide (IV), 2-methylmercapto-3-methyl-5-

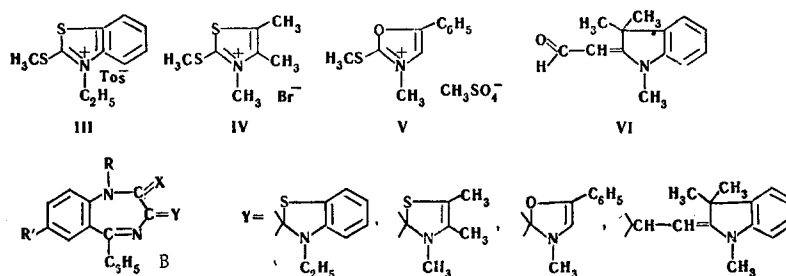
\*See [6] for communication VI.

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TABLE 1.

Comp.	R'	R	X	Y	mp	$\lambda_{max}$ , nm	Empirical formula	Found %		Calc. %		Yield, %
								N	S	N	S	
VII	Cl	CH <sub>3</sub> CO	O		93-94	440	C <sub>26</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>2</sub> S	8,9	6,7	8,9	6,8	47
VIII	Br	CH <sub>3</sub> CO			94-95	440	C <sub>26</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>2</sub> S	8,2	6,1	8,3	6,2	45
IX	CH <sub>3</sub>	CH <sub>3</sub> CO			89-90	430	C <sub>27</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> S	9,2	6,9	9,3	7,0	33
X	Cl	CH <sub>3</sub> CO	O		73-75	470	C <sub>23</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>2</sub> S	9,8	7,5	9,6	7,3	25
XI	Br	CH <sub>3</sub> CO			75-77	475	C <sub>23</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>2</sub> S	8,8	6,7	8,7	6,6	30
XII	CH <sub>3</sub>	CH <sub>3</sub> CO			70-72	460	C <sub>24</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> S	10,0	7,7	10,1	7,6	25
XIII	Cl	CH <sub>3</sub> CO	O		78-80	520	C <sub>29</sub> H <sub>26</sub> ClN <sub>3</sub> O <sub>2</sub>	8,7		8,7		62
XIV	Br	CH <sub>3</sub> CO			78-79	522	C <sub>29</sub> H <sub>26</sub> BrN <sub>3</sub> O <sub>2</sub>	8,0		8,0		66
XV	CH <sub>3</sub>	CH <sub>3</sub> CO			75-77	516	C <sub>30</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	9,0		9,1		63
XVI	Cl	CH <sub>3</sub> CO	O		52-54		C <sub>27</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub>	9,0		8,9		43
XVII	Br	CH <sub>3</sub> CO			52-55		C <sub>27</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>3</sub>	8,2		8,2		39
XVIII	CH <sub>3</sub>	CH <sub>3</sub> CO			50-52		C <sub>28</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub>	9,4		9,3		33
XIX	Cl	H	S		78-80	462	C <sub>24</sub> H <sub>18</sub> ClN <sub>3</sub> S <sub>2</sub>	9,5	14,6	9,4	14,3	33
XX	Br	H			84-86	464	C <sub>24</sub> H <sub>18</sub> BrN <sub>3</sub> S <sub>2</sub>	8,0	12,8	8,5	13,0	36

phenyloxazolium methosulfate (V), and 1,3,3-trimethyl-2-formylmethylenindoline (VI),\* as a result of which we obtained a series of compounds of the merocyanine dye type B.



Like the 1-unsubstituted 1,3-dihydro-2H-1,4-benzodiazepin-2-ones (I, R = H), the 1-methyl derivatives of I (R = CH<sub>3</sub>) do not condense with III-VI, which might have been expected considering the electron-donor character of the methyl radical and what was stated above relative to the reactivity of the methylene group in such compounds.

A similar condensation of III-VI with thiones II gave the corresponding dyes B (X = S). Here it is interesting to note that the reaction also proceeds with 1-unsubstituted thiones II (R = H). This sort of activation of the methylene group apparently occurs due to the great polarizability of the C=S bond (as compared with the C=O group). It is possible that the thione-thiol tautomerism predominates over the thio-lactam-thiolactim tautomerism in the case of thiolactams II. However, this assumption requires experimental confirmation.

Compounds B are brightly colored, crystalline substances (see Table 1). The spectra of VII-IX, XIX, and XX contain a band at 430-460 nm characteristic for merocyanine dyes of this type [5]. This band undergoes a considerable bathochromic shift in the spectra of XIII-XV, which is probably explained by the greater conjugation in such systems than in systems of the VII-IX type.

\*Compounds III-VI were synthesized in the Institute of Organic Chemistry of the Academy of Sciences of the Ukrainian SSR (Kiev).

## EXPERIMENTAL

7-Chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-3-[2-(1-ethylbenzothiazolydene)]-1,4-benzodiazepin-2-one (VII). Several drops of triethylamine were added to a hot solution of 0.62 g (0.002 mole) of 7-chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one and 0.76 g (0.002 mole) of 2-methylmercapto-3-ethylbenzothiazolium tosylate in 10 ml of absolute ethanol. The mixture was refluxed for 1 h, during which the solution took on a yellow-orange color. The solution was then cooled and diluted with water, during which a brightly colored amorphous precipitate formed. The precipitate was filtered and dried. Purification of VII by column chromatography on aluminum oxide with elution by chloroform gave 0.45 g (47%) of a product with mp 93-94°.

Products VIII and IX were similarly obtained.

7-Chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-3-[2-(3,4,5-trimethylthiazolydene)]-1,4-benzodiazepin-2-one (X). A solution of 0.62 g (0.002 mole) of 7-chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one and 0.508 g (0.002 mole) of 2-methylmercapto-3,4,5-trimethylthiazolium bromide in 10 ml of absolute ethanol was heated on a water bath, and several drops of triethylamine were added to the hot solution. The solution was then refluxed for 1 h, cooled, and diluted with water. The resulting precipitate was filtered, dried, and purified by column chromatography on  $Al_2O_3$  with elution by  $CHCl_3$  to give 0.2 g (25%) of X.

Compounds XI and XII were synthesized under the same conditions.

3-[2-(1,3,3-Trimethyl-2-indolinydene)ethylidene]-7-chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (XIII). A solution of 0.31 g (0.001 mole) of 7-chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one and 0.20 g (0.001 mole) of 1,3,3-trimethyl-2-formylmethyleneindoline in 3 ml of acetic anhydride was heated to the boiling point. After 1 h, the reaction mixture was cooled, and the precipitate was filtered and dried. Chromatographic purification with  $Al_2O_3$  as the adsorbent and elution by chloroform gave 0.30 g of reddish-violet crystalline substance with mp 78-80°.

Compounds XIV and XV were similarly synthesized.

7-Chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-3-[2-(1-methyl-5-phenyloxazolydene)]-1,4-benzodiazepin-2-one (XVI). Several drops of triethylamine were added to a hot solution of 0.31 g (0.001 mole) of 7-chloro-5-phenyl-1-acetyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one and 0.32 g (0.001 mole) of 2-methylmercapto-1-methyl-5-phenyloxazolium methosulfate in 3 ml of absolute ethanol. The solution acquired a lemon-yellow color in the process. The mixture was heated for 1 h, cooled, and several drops of water were added to it. The precipitate of unchanged starting 1,4-benzodiazepine was removed by filtration, and an amorphous reaction product was isolated from the mother liquor on standing; this was purified by column chromatography (on  $Al_2O_3$  with elution by chloroform) to give 0.2 g (43%) of a product with mp 52-54°.

Products XVII and XVIII were obtained under similar conditions. Compounds XIX and XX were synthesized from 7-chloro- and 7-bromo-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-thione under the conditions described above for the synthesis of VII-IX.

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