DERIVATIVES OF 2-BENZAZEPINE-1,3-DIONE

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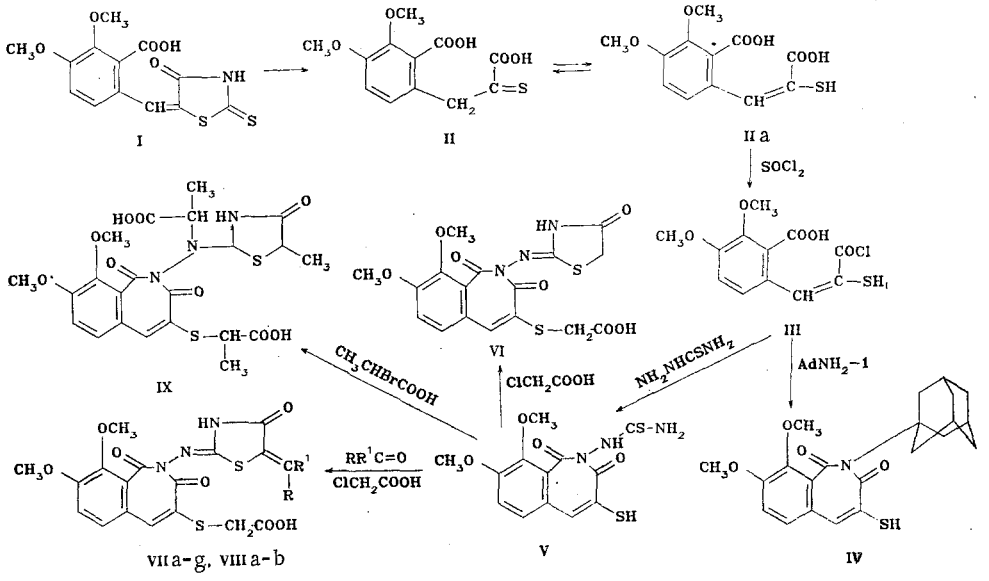
The reactions of the di(acid chloride) of 2-carboxy-3,4-dimethoxyphenylthiopyruvic acid with 1-aminoadamantane and with thiosemicarbazide take place with the closure of a seven-membered ring and the formation of 1,2-dihydro-(3H)-2-benzazepine-1,3-dione. On reaction with monochloroacetic acid, 4-mercapto-8,9-dimethoxy-2-(N-thioureido)-1,2-dihydro-(3H)-2-benzazepine-3-dione is converted into a derivative of thiazolidine-2,4-dione 2-hydrazone, which readily takes part in condensation reactions with oxo compounds forming 5-ylidene derivatives.

2-Benzazepine derivatives are arousing definite interest, since they include the alkaloid galanthamine, two isomeric benzocaprolactams, etc. The production of 2-benzazepine-1,3-diones by the cyclization of the acid chloride of the o-carboxycinnamonitrile under the action of gaseous HCl in dioxane has been described [1]. We set ourselves the task of synthesizing 2-benzazepine-1,3-dione derivatives using opianic acid as the starting material in order to study their properties and find effective foam suppressants.

We have shown for the first time that for the synthesis of 1,2-dihydro-(3H)-2-benzazepine-1,3-dione derivatives it is possible to start from the readily accessible 5-opianylidenerhodanine (I), the alkaline hydrolysis of which forms 2-carboxy-3,4-dimethoxyphenylthiopyruvic acid (II). Compound II is readily converted under the action of thionyl chloride into the di(acid chloride) (II) which forms, on condensation with 1-aminoadamantane or thiosemicarbazide, the 1,2-dihydro-(3H)-2-benzazepine-1,3-dione derivatives (IV, V).



VII R^1=H; a R=*p*-ClC_6H_4; b R=2,4-$Cl_2C_6H_3$; c R=3-OH—4-$OCH_3C_6H_3$; d R=*o*-$NO_2C_6H_4$, e R=*m*-$O_2NC_6H_4$, f R=C_6H_5CH=CH, g R=*p*-$NO_2C_6H_4CH$=CH; VIII a R+R^1= isatinylidene; R+R^1= 1-methylisatinylidene

When compound (V) was condensed with monochloroacetic acid, not only the closure of a thiazolidine ring but also the alkylation of the mercapto group took place, as a result of which the thiazolidine-2,4-dione 2-hydrazone derivative with a 4-carboxymethylmercaptobenzazepine substituent (VI) was formed. A proof of the structure of (V) is its capacity for condensation with monochloroacetic acid in the presence of aldehydes and ketones, which takes place

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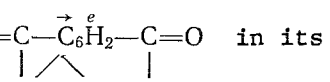
TABLE 1. Derivatives of Opianic Acid and 2-Benzazepine-1,3-dione

Compound	mp, °C	UV spectrum, λ_{max} nm (log ε)	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
II	254—255	241 (4,48); 326 (4,08); 370 (3,96)	51,0	4,0	—	11,3	$C_{12}H_{12}O_6S$	50,7	4,3	—	11,3	88
III	165—166	—	45,2	3,4	—	10,0	$C_{12}H_{10}Cl_2O_4S$	44,9	3,1	—	9,9	93
IV	198—199	246 (4,47); 320 (4,02); 374 (3,91)	66,4	6,0	3,7	8,0	$C_{22}H_{25}NO_4S$	66,1	6,3	3,7	8,0	50
V	215 dec.	247 (4,51); 227 (4,16); 370 (3,99)	46,2	3,7	12,6	18,7	$C_{13}H_{13}N_3O_4S_2$	46,0	3,9	12,4	18,9	95
VI	222—224	250 (4,32); 339 (3,96); 389 (3,92)	46,8	3,2	9,8	14,7	$C_{17}H_{15}N_3O_7S_2$	46,7	3,5	9,6	14,7	82
VIIa	192—194	250 (4,61); 334 (4,32); 389 (4,34)	51,7	3,2	7,6	11,8	$C_{24}H_{18}ClN_3O_7S_2$	51,5	3,2	7,5	11,5	88
VIIb	184—185	250 (4,62); 335 (4,36); 392 (4,34)	48,2	2,8	7,0	11,1	$C_{24}H_{17}Cl_2N_3O_7S_2$	48,5	2,9	7,1	10,8	88
VIIc	174—176	224 (4,65); 251 (4,70); 335* (4,45); 388 (4,38)	52,8	3,5	7,6	10,9	$C_{25}H_{21}N_3O_9S_2$	52,5	3,7	7,4	11,2	62
VIId	156—157	247 (4,65); 334 (4,32); 390 (4,31)	50,6	3,2	10,0	11,2	$C_{24}H_{18}N_4O_9S_2$	50,5	3,2	9,8	11,2	84
VIIe	169—171	251 (4,62); 334 (4,32); 391 (4,25)	50,6	2,9	9,9	11,0	$C_{24}H_{18}N_4O_9S_2$	50,5	3,2	9,8	11,2	70
VIIf	194—195	250 (4,61); 345 (4,33); 387 (4,34)	56,4	3,7	7,9	11,3	$C_{26}H_{21}N_3O_7S_2$	56,6	3,8	7,6	11,6	88
VIIg	194—195	250 (4,55); 340* (4,34); 382 (4,41)	49,3	3,0	8,7	10,3	$C_{26}H_{19}ClN_4O_9S_2$	49,5	3,0	8,9	10,2	82
VIIIa	227—228	250 (4,63); 335* (4,29); 386 (4,40)	52,7	3,4	10,1	11,1	$C_{25}H_{18}N_4O_8S_2$	53,0	3,2	9,9	11,3	87
VIIIb	229—230	250 (4,54); 335* (4,17); 386 (4,31)	54,1	3,5	9,7	10,7	$C_{26}H_{20}N_4O_8S_2$	53,8	3,5	9,7	11,0	90
IX	208—210	251 (4,59); 342 (4,11); 402 (4,14)	49,2	4,0	8,0	11,7	$C_{22}H_{23}N_3O_9S_2$	49,2	4,3	7,8	11,9	93

*Inflections.

with the formation of the 5-ylidene derivatives (VII) and (VIII). It is interesting that when compound (V) was condensed with α-bromopropionic acid, 3 moles of the latter were consumed, as a result of which compound (IX) with an α-carboxyethyl substituent on both the sulfur atom and the nitrogen atom separated out from the reaction mixture.

The UV spectrum of 2-carboxy-3,4-dimethoxyphenylthiopyruvic acid (II) is characterized by three absorption bands, with maxima at 244, 334-328, and 369-372 nm. The first band is connected with the presence of the substituted benzoyl chromophore [2], and the second band with π-π* benzene absorption of the L_b type. The presence of the third band at about 370 nm gives grounds for assuming that (II) also exists in the tautomeric form (IIa) and contains the chromophore  in its molecule. Compounds (III-IX) are characterized by maxima or inflections at 243-257, 317-358, and 368-420 nm.

For compounds containing only a carboxy group in the molecule, strong νC=O bands are observed at 1762 cm^{-1} (opianic acid) and 1724 cm^{-1} (II); for compounds containing only amide groups there are bands at 1658 cm^{-1} (IV) and 1685 cm^{-1} (V); and for compounds containing both carboxy and amide groups in the molecule there are bands at (cm^{-1}) 1750 and 1650 (I), 1780 and 1695 (VI), 1705 and 1642 (VIId), 1705 and 1685 (VIIf), and 1762 and 1690 (VIIIa).

The mass spectra of the adamantyl derivative (IV) show the strongest peaks with m/z 399 [M^+], 370, 249, 221, and 135.

The compounds synthesized are listed in Table 1.

EXPERIMENTAL

UV spectra were taken on an SF-16 spectrophotometer in methanol, and IR spectra on a UR-20 spectrometer in tablets with KBr. The mass-spectrometric analysis of compound (IV) was performed on an MS 2H instrument (AEI).

The compounds synthesized consist of crystalline substances, colorless (IV) or with various shades of yellow (II, III, V, VI, VIIa, b, d, e), orange (VIIc, VIIIb), light brown (VIIe, g, IX), and red (VIIIa), soluble (with the exception of (IV)) in the cold or on gentle heating in NH_4OH and NaOH solutions and on heating (with the exception of (III, V, VII, and VIIIa) in ethanol and insoluble (with the exception of (IV)) in ether and benzene.

2-Carboxy-3,4-dimethoxyphenylthiopyruvic Acid (II) and Its Dichloride (III). A mixture of 10.74 g (33 mmole) of 5-opianylidenerhodanine (I) and 26 ml of 30% aqueous NaOH was boiled for 30 min. The cherry-red solution formed was poured into 80 ml of concentrated HCl and, after cooling, the precipitate was filtered off, washed with water, and recrystallized from dioxane, to give 7.96 g (28 mmole) of the acid (II) in the form of yellow crystals. A mixture of 3.89 g (13.7 mmole) of the acid (II) and 30 ml of thionyl chloride was boiled for 30 min, the resulting solution was evaporated to dryness, and the residue was recrystallized from toluene, to give 4.11 g (12.8 mmole) of the dichloride (III) in the form of yellow crystals.

2-(Adamant-1-yl)-4-mercapto-8,9-dimethoxy-1,2-dihydro-(3H)-2-benzazepine-1,3-dione (IV). A mixture of 0.6 g (4 mmole) of 1-aminoadamantane and 0.64 g (2 mmole) of the dichloride (III) in 20 ml of xylene was boiled for 36 min. The boiling solution was filtered and cooled, and the resulting precipitate was filtered off and recrystallized from toluene, to give 0.40 g (1.0 mmole) of compound (IV) in the form of colorless crystals.

4-Mercapto-8,9-dimethoxy-2-(N-thioureido)-1,2-dihydro-(3H)-2-benzazepine-1,3-dione (V). A mixture of 0.36 g (4 mmole) of thiosemicarbazide and 0.64 g (2 mmole) of compound (III) in 20 ml of dioxane was boiled for 30 min and the precipitate that deposited was filtered from the still hot mixture, washed with water, and recrystallized from 50% DMSO. This gave 0.64 g (1.9 mmole) of the benzazepinedione (V) in the form of yellow crystals.

4-Carboxymethylthio-8,9-dimethoxy-2-(4-oxothiazolidin-2-ylidineamino)-1,2-dihydro-(3H)-2-benzazepine-1,3-dione (VI). A mixture of 1.36 g (4 mmole) of compound (V) and 0.76 g (8 mmole) of monochloroacetic acid was heated at 210°C for 30 min. The resulting melt was recrystallized from propanol, giving 1.43 g (3.28 mmole) of compound (VI) in the form of large brown crystals.

5'-Ylidene Derivatives of 4-Carboxymethylthio-8,9-dimethoxy-2-(4'-oxothiazolidin-2'-ylidineamino)-1,2-dihydro-(3H)-benzazepine-1,3-dione (VII, VIII). A mixture of 1.36 g (4 mmole) of substance (V), 0.76 g (8 mmole) of monochloroacetic acid, and 4 mmole of an oxo compound was heated at 210°C for 30 min. The resulting melts were recrystallized from propanol, butanol, or acetic acid. The yields and properties are given in Table 1.

4-(α-Carboxyethylthio)-2-[N-(α-carboxyethyl)-N-(5-methylthiazolin-2-yl)amino]-8,9-dimethoxy-1,2-dihydro-(3H)-2-benzazepine-1,3-dione (IX). A mixture of 1.36 g (4 mmole) of compound (V) and 1.53 g (10 mmole) of α-bromopropionic acid was heated at 210°C for 30 min. The resulting melt was recrystallized from butanol, giving 2.0 g (3.72 mmole) of substance (IX) in the form of large brown crystals.

LITERATURE CITED

1. M. S. Puar and B. R. Vogt, Tetrahedron, 34, 2887 (1978).
2. A. I. Scott, Experientia, 17, 68 (1961).