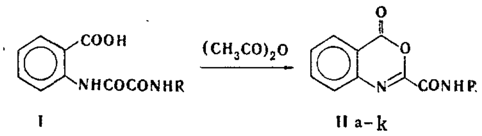
SYNTHESIS AND TRANSFORMATION OF AMIDES OF 4H-3,1-BENZOXAZIN-4-ONE-2-CARBOXYLIC ACID*

P. A. Petyunin, V. A. Bulgakov,
and G. P. Petyunin

UDC 547.867.2.07 : 543.422.4

A method for the preparation of amides of 4H-3,1-benzoxazin-4-one-2-carboxylic acid was developed, and N-R-amides of 3-R-4(3H)-quinazolone-2-carboxylic acid were synthesized from them.

Amides of 4H-3,1-benzoxazin-4-one-2-carboxylic acid are unknown. The synthesis of N-R-substituted amides of 4H-3,1-benzoxazin-4-one-2-carboxylic acid (II) is accomplished by heating N-R-oxamoylanthranilic acids (I) with acetic anhydride:



Benzoxazinones II (Table 1) are readily converted to the starting acids (I) by the action of aqueous alkalis and acids and also by heating with water.

The spectral properties of benzoxazinones II are presented in Table 2. The ν_{CO} bands are absent in the spectra of solutions, and the amide band is shifted by 50 cm^{-1}. This indicates that association of II is realized through the amido group. The UV spectra are characterized by the presence of two absorption bands at 270 and 300 nm. As compared with I [R=CH_3, λ_{max}, nm (log ε): 260 (4.95) and 305 (4.88)], the band is shifted to longer wavelengths by 10 nm.

---

*Communication LVII from the series "Research on the Chemistry of Heterocycles." See [1] for the preceding communication.

TABLE 1. Amides of 4H-3,1-Benzoxazin-4-one-2-carboxylic Acid

Compound	R	mp, °C	Empirical formula	N, %		Yield, %
				found	calc.	
II a	H	205	$C_9H_6N_2O_3$	14,9	14,7	75
II b	CH_3	190—191	$C_{10}H_8N_2O_3$	14,0	13,7	85
II c	C_2H_5	125—126	$C_{11}H_{10}N_2O_3$	12,8	12,8	75
II d	n-C_3H_7	80—81	$C_{12}H_{12}N_2O_3$	12,5	12,0	77
II e	n-C_4H_9	100—101	$C_{13}H_{14}N_2O_3$	11,5	11,4	65
II f	i-C_4H_9	120—121	$C_{13}H_{14}N_2O_3$	11,6	11,4	71
II g	n-C_5H_{11}	70—71	$C_{14}H_{16}N_2O_3$	11,1	11,3	73
II h	n-C_6H_{13}	78—79	$C_{15}H_{18}N_2O_3$	10,3	10,2	54
II i	n-C_7H_{15}	81—82	$C_{16}H_{20}N_2O_3$	10,1	9,7	39
II j	$CH_2{=}CH{-}CH_2$	116—117	$C_{12}H_{10}N_2O_3$	12,2	12,2	87
II k	$C_6H_5CH_2$	138—139	$C_{16}H_{12}N_2O_3$	10,2	10,0	40

Kharkov Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 609-612, May, 1974. Original article submitted April 11, 1973.

TABLE 2. Spectra of N-R-Amides of 4H-3,1-Benzoxazin-4-one-2-carboxylic Acid

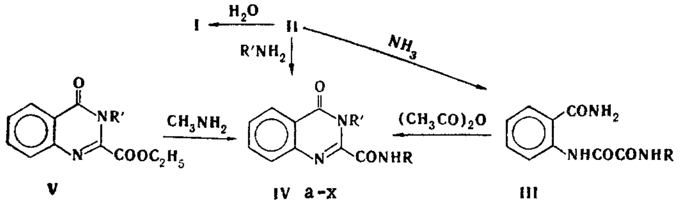
Compound	UV spectrum, λ_{max}, nm ($\log \varepsilon$) in dioxane	IR spectrum, cm^{-1}							
		ν_{NH}		ring ν_{CO}[3]		amide ν_{CO}		ring ν	
		CCl$_4$	KBr	CCl$_4$	KBr	CCl$_4$	KBr	CCl$_4$	KBr
IIa	270 (4,91); 303 (4,67)	—	3360, 3300	—	1790	—	1690	—	1640, 1610, 1330
IIb	270 (4,93); 303 (4,73)	3450	3360, 3300	1790	1780	1730	1680	1640 1310	1640, 1610, 1310
IIe	— —	—	3370, 3300	—	1770	—	1680	—	1640, 1610, 1320
IIi	— —	—	3370, 3310	—	1760	—	1700	—	1650, 1610, 1330

TABLE 3. N-R-Amides of 3-R'-R-4(3H)-Quinazolone-2-carboxylic Acids

Compound	R'	R	mp °C (from aqueous DMF)	Empirical formula	N, % found	N, % calc.	Yield, %
IVa	H	CH$_3$	192—194	$C_{10}H_9N_3O_2$	21,0	20,7	78
IVb	CH$_3$		212—213	$C_{11}H_{11}N_3O_2$	19,3	19,3	75
IVc	*n*-C$_3$H$_7$		176—178	$C_{13}H_{15}N_3O_2$	17,1	17,1	58
IVd	*n*-C$_4$H$_9$		172—173	$C_{14}H_{17}N_3O_2$	16,3	16,2	72
IVe	*iso*-C$_4$H$_9$		180—181	$C_{14}H_{17}N_3O_2$	16,0	16,2	72
IVf	*tert*-C$_4$H$_9$		212—213	$C_{14}H_{17}N_3O_2$	15,9	16,2	83
IVg	*n*-C$_5$H$_{11}$		180—181	$C_{15}H_{19}N_3O_2$	15,1	15,4	75
IVh	CH$_2$CH$_2$Cl		206—207	$C_{12}H_{12}ClN_3O_2$	16,0	15,8	62
IVi	CH$_2$COOC$_2$H$_5$		251	$C_{14}H_{15}N_3O_4$	14,7	14,5	53
IVj	C$_6$H$_5$		249—251	$C_{16}H_{13}N_3O_2$	14,9	15,0	81
IVk	*o*-CH$_3$C$_6$H$_4$		228—229	$C_{17}H_{15}N_3O_2$	14,1	14,3	70
IVl	*o*-ClC$_6$H$_4$		226—227	$C_{16}H_{12}ClN_3O_2$	13,5	13,4	74
IVm	*o*-CH$_3$OC$_6$H$_4$		226—227	$C_{17}H_{15}N_3O_3$	13,9	13,6	77
IVn	*m*-CH$_3$OC$_6$H$_4$		201—202	$C_{17}H_{15}N_3O_3$	13,8	13,6	87
IVo	*p*-CH$_3$OC$_6$H$_4$		179—180	$C_{17}H_{15}N_3O_3$	13,4	13,6	86
IVp	*o*-HOOCC$_6$H$_4$		248—249	$C_{17}H_{13}N_3O_4$	13,3	13,0	85
IVq	*m*-HOOCC$_6$H$_4$		232—233	$C_{17}H_{13}N_3O_4$	13,1	13,0	93
IVr	*n*-HOOCC$_6$H$_4$		262—263	$C_{17}H_{13}N_3O_4$	12,7	13,0	76
IVs	*cyclo*-C$_6$H$_{11}$		247—248	$C_{16}H_{19}N_3O_2$	14,6	14,7	71
IVt	*p*-H$_2$NSO$_2$C$_6$H$_4$		266—267	$C_{16}H_{14}N_4O_4S$	15,9	15,6	66
IVu	**α-Pyridyl**		199—200	$C_{15}H_{13}N_4O_2$	20,2	19,9	87
IVv	**β-Quinolyl**		241—242	$C_{19}H_{14}N_4O_2$	17,2	17,0	59
IVw	**iso**-C$_4$H$_9$	H	235—236	$C_{13}H_{15}N_3O_2$	17,3	17,1	92
IVx	C$_6$H$_5$		262—264	$C_{15}H_{11}N_3O_2$	15,6	15,8	69
IVy	*p*-HOOCC$_6$H$_4$		262—263	$C_{16}H_{11}N_3O_4$	13,4	13,6	88

Benzoxazinones II are strong electrophiles: N-R-oxamoylanthranilic acid amides (III) are formed with ammonia, while N-R-substituted amides of 4(3H)-quinazolone-2-carboxylic acid (IVa-y) (Table 3) are formed with primary amines. 4(3H)-Quinazolone-2-carboxylic acid methylamide (IVa) is formed when amide (III) is heated with acetic anhydride. The structure of IV was proved by independent synthesis in the case of 3-phenyl-4(3H)-quinazolone-2-carboxylic acid N-methylamide (IVj) as a result of the reaction of 2-ethoxalyl-3-phenyl-4(3H)-quinazolone (V) with methylamine. The spectral properties of amides IV are presented in Table 4.

Tertiary (VI) and secondary (VII) amides of N-R-oxamoylanthranilic acids are formed, respectively, with secondary amines and with dimagnesylamines on reaction with benzoxazinones II.

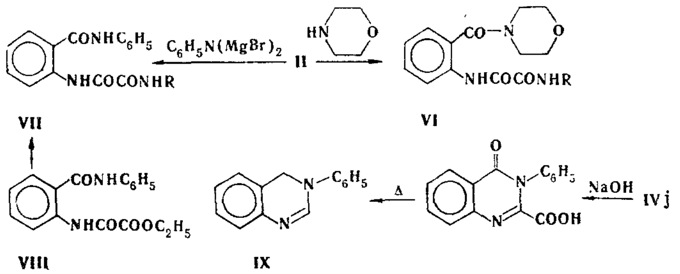


III R=CH$_3$; V R'=C$_6$H$_5$

The structure of secondary amide VII was confirmed by alternative synthesis by reaction of methylamine with N-ethoxalylanthranilic acid anilide (VIII).

TABLE 4. Spectra of N-R-Amides of 3-R'-4(3H)-Quinazolone-2-carboxylic Acids

Compound	UV spectrum, λ_{max}, nm (log ε) in dioxane	IR spectrum, cm^{-1}				
		ν_{NH} (KBr)	ring ν_{CO} [4]	amide I ν_{CO}	amide II ν_{CO}	quinazolone ring
IV a	262 (4,0); 300 (3,81)	3320, 3280	1705	1685	1530	1650, 1610, 1450
IV e	— —	3370, 3320	1700	1690	1530	1650, 1610, 1450
IV j	265 (5,20); 305 (5,03)	3370, 3320	1710	1690	1530	1650, 1610, 1450
IV k	265 (5,15); 305 (4,95)	3370, 3300	1710	1700	1530	1650, 1610, 1450



VI, VII R=CH$_3$

In the case of quinazolone IVj it was shown that 3-phenyl-4(3H)-quinazolone is formed on brief heating with aqueous alkali. Similar behavior was noted for 3-R-4(3H)-quinazolone-2-carboxylic acid ester [2]. A small amount of anthranilic acid anilide, which is converted to IX on treatment with formic acid, is probably also formed along with IX.

EXPERIMENTAL

The UV spectra of dioxane solutions (c $2 \cdot 10^{-3}$-$2 \cdot 10^{-5}$ M) were recorded with an SF-4A spectrophotometer. The IR spectra of KBr pellets (containing 0.5% of the compounds) and CCl_4 solutions (c 0.0015 M) were recorded with a UR-20 spectrometer.

4H-3,1-Benzoxazin-4-one-2-carboxylic Acid N-R-Amides (II). One part of I and two parts of acetic anhydride were heated until the solid dissolved, and the solution was then heated for another 10 min. The mixture was then cooled, and the resulting precipitate was removed by filtration and washed with absolute ether. Analytically pure products were obtained.

N-Methyloxamoylanthranilic Acid Amide (III). Dimethylformamide (6 ml) was saturated with dry ammonia, after which 2 g of IIb was added. The mixture was allowed to stand for 12 h, after which the precipitate was removed by filtration and crystallized from aqueous DMF to give 1.3 g (62%) of needles with mp 236-237°. Found %: N 19.3. $C_{10}H_{11}N_3O_3$. Calculated %: N 19.0.

4(3H)-Quinazolone-2-carboxylic Acid Methylamide (IVa). A solution of 1 g of III in 2 ml of acetic anhydride was heated for 2.5 h, after which it was cooled and diluted with water. The resulting precipitate was removed by filtration and crystallized. The product dissolved in cold aqueous alkali.

3-Phenyl-4(3H)-quinazolone-2-carboxylic Acid Methylamide (IVj). A) A mixture of 1.02 g of IIb and 0.5 g of aniline in 3 ml of DMF was heated for 30 min, after which it was poured into 20 ml of water. The resulting precipitate was removed by filtration and crystallized to give a product with mp 248-249°.

B) A 1-ml sample of a 40% solution of methylamine was added to a solution of 2.8 g of V in 15 ml of ethanol, and the mixture was allowed to stand at room temperature for 16 h. The resulting precipitate was removed by filtration and washed with ethanol to give a product with mp 248-249°. No melting-point depression was observed for a mixture with the product obtained by method A. Compounds IVb-i, k-y were obtained by method A.

Methyloxamoylanthranilic Acid Morpholide (VI). A mixture of 2.04 g of IIb and 0.87 g of morpholine in 6 ml of DMF was heated for 30 min, after which it was poured into 40 ml of water, and the resulting precipitate was removed by filtration and crystallized from glacial acetic acid to give 1.0 g (35.7%) of needles with mp 277-278°. Found %: N 14.2. $C_{14}H_{14}N_3O_4$. Calculated %: N 14.4.

N-Methyloxamoylanthranilic Acid Anilide (VII). A) A suspension of 4 g of IIb in 20 ml of dioxane was added to N,N-bis(bromomagnesyl)aniline, obtained from 0.96 g of magnesium, 5.5 g of butyl bromide, and 1.8 g of aniline in 30 ml of absolute ether, after which the mixture was heated for 30 min and then decomposed with 10% hydrochloric acid. The precipitate was removed by filtration and crystallized from aqueous DMF to give 3.7 g (64%) of needles with mp 256-258°.

B) A 0.3-ml sample of a 40% methylamine solution was added to a solution of 0.9 g of VIII in 10 ml of ethanol, and the mixture was allowed to stand at room temperature for 18 h. It was then diluted with 30 ml of water and acidified with hydrochloric acid. The resulting precipitate was worked up as in the preceding experiment to give 0.85 g (94%) of a product with mp 256-258°. No melting-point depression was observed for a mixture of this product with the material obtained by method A. Found %: N 14.2. $C_{16}H_{14}N_3O_3$. Calculated %: N 14.1.

3-Phenyl-4(3H)-quinazolone (IX). A 1.5-g sample of IVj was refluxed for 30 min with 15 ml of sodium hydroxide solution, after which the hot solution was acidified with 10% hydrochloric acid. After vigorous carbon dioxide evolution had ceased, a 10% sodium hydroxide solution was added until the mixture was strongly alkaline. The resulting precipitate was removed by filtration and air dried. It was then drenched with 1.5 ml of 85% formic acid, and the mixture was refluxed for 1 h and poured into 10 ml of water. The solution was treated with excess 10% sodium carbonate solution, and the resulting precipitate was removed by filtration and crystallized from aqueous ethanol to give 0.9 g (75%) of needles with mp 137-138° [5]. No melting-point depression was observed for a mixture of this product with a genuine sample.

LITERATURE CITED

1. P. A. Petyunin and V. V. Bolotov, Zh. Organ. Khim., 9, 806 (1973).
2. P. A. Petyunin, V. P. Chernykh, G. P. Petyunin, and Yu. V. Kozhevnikov, Khim. Geterotsikl. Soedin., 1575 (1970).
3. K. Lempert and G. Doleshall, Tetrahedron Lett., 781 (1963).
4. H. Culbertson, I. C. Decins, and B. E. Christensen, J. Amer. Chem. Soc., 74, 4834 (1952).
5. P. A. Petyunin and Yu. V. Kozhevnikov, Zh. Obshch. Khim., 30, 2355 (1960).