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RESEARCH ON ISOALLOXAZINE DERIVATIVES

I. Preparation and Properties of Some 7-Aminoisoalloxazine Derivatives

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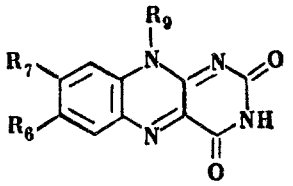
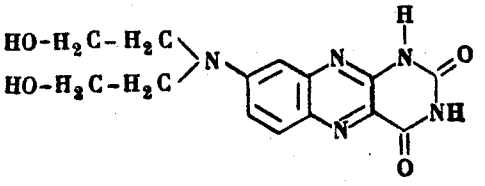
Starting from the corresponding 7-chloro- derivatives, 7-aminoalloxazines are synthesized as potential antimetabolites. A comparative study is made of the UV spectra of 7-chloro- and 7-aminoalloxazines in formic acid.

Among the numerous derivatives of isoalloxazine, there is a large group possessing biological activity, and among other things, a capacity for retarding malignant tumor growth [1-7]. Compounds of general formula I with a secondary or tertiary amino group at position 7 of the isoalloxazine ring have now been synthesized as possible antimetabolites of vitamin B_2. The known biochemical analogy between 7-methyl- and 7-aminoisoalloxazines [8] was the reason for synthesizing substituted 7-aminoisoalloxazines.



I



II

For preparing amino- derivatives of isoalloxazines, use was made of the comparative reactivity of the halogen at position 7 in the isoalloxazine ring, due to diminished electron density at the carbon atom [9].

The table gives the structures and some properties of the aminoalloxazine derivatives synthesized.

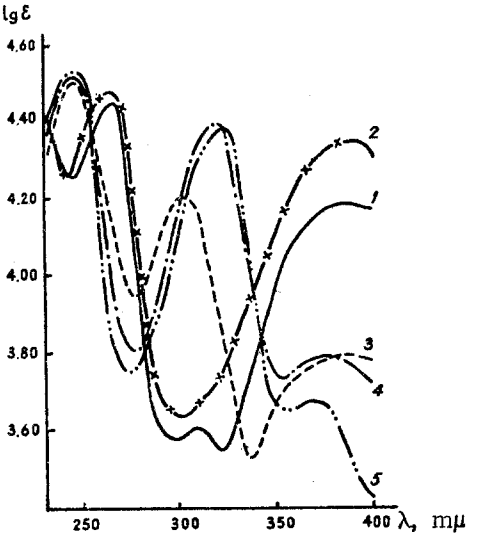
The starting material, 7-chloro-9-phenylisoalloxazine [7] used in synthesizing the isoalloxazines III-VI, was prepared by condensing alloxan with 2-amino-5-chlorodiphenylamine. The latter in its turn was prepared by reducing 2-nitro-5-chlorodiphenylamine with stannous chloride in hydrochloric acid [10]. 6, 9-Dimethyl-7-chloroisoalloxazine, an intermediate in synthesizing isoalloxazines VII-IX, was prepared by a known method [11] from p-toluidine. Reaction of the 7-chloro derivatives with the appropriate amines for preparing isoalloxazines III-IX took place upon heating in dimethylformamide solution.

In carrying out amination, it became evident that halogen in the 6, 9-dimethyl-7-chloroisoalloxazine is comparatively unreactive, apparently because of both the electron-donor effect of the substituent at position 6 and steric hindrance. Only strongly basic amines react with it, while 7-chloro-9-phenylisoalloxazine, without a substituent at position 6, readily reacts with such a weakly basic amine as diethanolamine.

All the aminoisoalloxazines synthesized were red crystalline compounds, decomposing above 300°. They are readily soluble in strong mineral acids, formic acid, solutions of alkalies, and dimethylformamide. They have poor solubilities in most organic solvents. They crystallize with a molecule of solvent, and therefore, for analysis they must be dried for a long time in a vacuum at 110-140°.

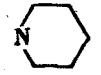
Halogen at position 7 in alloxazine, unlike isoalloxazine, is unreactive. Consequently 7-bis-(β-hydroxyethyl)aminoalloxazine (II) was prepared by condensing N, N-bis-(β-hydroxyethyl)-m-phenylenediamine [12] with violuric acid.

Since none of the aminoisoalloxazines synthesized had a sharp melting point, an attempt was made to utilize UV spectroscopy for identification, and UV spectra were measured with an SF-4 spectrophotometer in formic acid, at a concentration of 10^{-3} M. The comparison standard was the known 6, 9-dimethyl-7-aminoisoalloxazine.



UV absorption spectra: 1) 6, 9-dimethyl-7-chloroisoalloxazine; 2) 7-chloro-9-phenylisoalloxazine; 3) 6, 9-dimethyl-7-aminoisoalloxazine; 4) 7-morpholyl-9-phenylisoalloxazine; 5) 7-bis(β-hydroxyethyl)amino-9-phenylisoalloxazine.

7-Amino- Derivatives of Isoalloxazines

Compound no.	R_6	R_7	R_9	Formula	C, %		H, %		N, %		Yield, %
					Found	Calculated	Found	Calculated	Found	Calculated	
III	H	$NHCH_2CH_2OH$	C_6H_5	$C_{18}H_{15}N_5O_3$	61.27; 61.45	61.80	4.64; 4.80	4.30	20.33; 20.40	20.01	75
IV	H	$N(CH_2CH_2OH)_2$	C_6H_5	$C_{20}H_{19}N_5O_4$	61.37	61.00	4.88	4.84	17.70	17.78	78
V	H		C_6H_5	$C_{21}H_{19}N_5O_2$	67.16; 67.82	67.56	5.19; 5.27	5.09	19.14	18.80	80
VI	H		C_6H_5	$C_{20}H_{17}N_5O_3$	63.91; 64.00	64.00	4.68; 4.74	4.53	18.85; 18.59	18.70	78
VII	CH_3	$N(CH_2CH_2OH)_2$	CH_3	$C_{16}H_{19}N_5O_4$	55.15	55.65	5.35	5.51	—	—	56
VIII	CH_3		CH_3	$C_{17}H_{19}N_5O_2$	62.49; 62.50	62.77	6.02; 5.97	5.84	21.91	21.53	70
IX	CH_3		CH_3	$C_{16}H_{17}N_5O_3$	58.62	58.72	5.21	5.19	21.35	21.41	65

Comparison of the spectrum curves shows that the starting halogen compounds have absorption maxima in the regions 262-265 and 385-390 mμ, while the presence of a main absorption maximum in the region 244 and 303-335 mμ is characteristic of 7-amino- derivatives of isoalloxazine. The figure shows that the positions of the absorption maxima in the UV region depend on the nature of the substituent at position 9 in the isoalloxazine ring, and this is apparently due to the weak participation of the hetero-atom at position 9 in the conjugation of the electronic system of the isoalloxazine.

Experimental

7-(β-Hydroxyethyl)amino-9-phenylisoalloxazine (III). 0.9 g monoethanolamine was added to a suspension of 1 g 7-chloro-9-phenylisoalloxazine in 100 ml dimethylformamide, and the mixture heated with stirring at 100-110° for 1 hr 30 min. The solvent was distilled off under reduced pressure, the residue washed with cold water, and the insoluble material filtered off. It was purified by precipitation from 6N HCl by dilute ammonia.

7-Bis-(β-hydroxyethyl)amino-9-phenylisoalloxazine (IV). 1 g 7-chloro-9-phenylisoalloxazine, 1.5 g diethanolamine, and 150 ml dimethylformamide were stirred together for 3 hr at 110-120°. The reaction product was isolated in the way described above, precipitated from 2N NaOH with dilute acetic acid, and crystallized from dimethylformamide.

7-Piperidyl-9-phenylisoalloxazine (V), and 7-morpholyl-9-phenyl-isoalloxazine (VI) were prepared similarly to III, and crystallized from dimethylformamide.

6,9-Dimethyl-7-bis(β-hydroxyethyl)aminoisoalloxazine (VII). 0.83 g 6,9-dimethyl-7-chloroisoalloxazine, 1.9 g diethanolamine, 2 ml triethylamine, and 100 ml dimethylformamide were stirred together for 8 hr at 130-140°, when the suspension gradually dissolved. The solvent was evaporated off in a vacuum, the residue washed with alcohol, and the insoluble material filtered off, and crystallized from dimethylformamide.

6,9-Dimethyl-7-piperidylisoalloxazine (VIII). 0.83 g 6,9-dimethyl-7-chloroisoalloxazine, 1.53 g piperidine, and 100 ml dimethylformamide were stirred together for 4 hr at 130°. The product was isolated similarly to VII. To purify it, a solution of 0.5 g VIII in 6 ml formic acid was cautiously diluted with twice its volume of water. On cooling the resultant solution (VIII) gradually precipitated as fine needles.

6,9-Dimethyl-7-morpholylisoalloxazine (IX). Obtained similarly to VII. Reaction time 4 hr. Crystallized similarly to VIII.

7-Bis-(β-hydroxyethyl)aminoalloxazine (II). 2N NaOH was added dropwise to a hot solution of 3.01 g violuric acid in 50 ml water to which a solution of 2.69 g N,N-bis-(β-hydroxyethyl)-m-phenylenediamine hydrochloride in 20 ml water had been added, until the mixture was slightly alkaline to phenolphthalein. Then it was refluxed for 2 hr, diluted with an equal volume of water, the precipitate filtered off, and reprecipitated from 2N NaOH with dilute acetic acid. Orange crystals, soluble in mineral acids, formic acid, and alkalies, insoluble in water and in most organic solvents. Mp 340-345° (decomp). Yield 81%. Found: C 53.04; H 4.79; N 22.36, 21.98%. Calculated for $C_{14}H_{15}N_5O_4$: C 52.90; H 4.73; N 22.10%.

REFERENCES

1. V. M. Berezovskii, Usp. khim., 18, 737, 1949.
2. V. M. Berezovskii and T. V. Erememko, Usp. khim., 32, 671, 1963.
3. L. F. Larionov, Chemotherapy of Malignant Tumors [in Russian], Medgiz, 196, 1962.
4. F. Weygand, R. Löwenfeld, and E. F. Möller, Ber., 84, 101, 1951.
5. F. W. Holly, E. W. Peel, R. Mozingo, and K. Folkers, J. Am. Chem. Soc., 72, 5416, 1950.
6. M. Lane, J. L. Fahey, R. D. Sullivan, and C. G. Zubrod, C. A., 52, 11267, 1958.
7. M. E. Fernholz and H. Fernholz, Ber., 84, 257, 1951.
8. Sumi Nishida, C. A., 46, 6715, 1952.
9. P. Hemmerich, B. Prijs, and H. Erlenmeyer, Helv. Chim. Acta, 42, 2164, 1959.
10. O. Ernst, Ber., 23, 3423, 1890.
11. P. Hemmerich, B. Prijs, and H. Erlenmeyer, Helv. Chim. Acta, 42, 1604, 1959.
12. O. F. Ginzburg, B. A. Porai-Koshits, and K. Yu. Mar'yanovskaya, ZhOKh, 30, 571, 1960.

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