UDC 547.865.7 + 542.95

STUDY OF DERIVATIVES OF THE ISOALLOXAZINE SERIES

II. Synthesis of Some 9-Substituted Isoalloxazines*

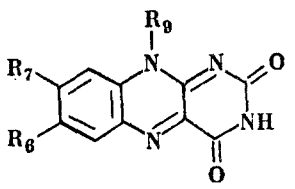
Z. V. Pushkareva, V N. Konyukhov, and G. S. Sakovich

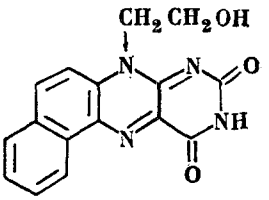
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 4, pp. 604-607, 1965

Five new isoalloxazine derivatives are synthesized by condensing o-diamines with alloxan. A method of synthesizing ring-substituted monoalkylphenylenediamines by reducing the corresponding o-nitro-N-alkylanilines with hydrazine hydrate in the presence of Raney nickel is developed.

Among isoalloxazine derivatives 6, 7-dichloro-9-(1'-D-ribityl)isoalloxazine, 6-methyl-7-chloro-9-(1'-D-ribityl)-isoalloxazine, and other halogen-substituted derivatives are riboflavin bacterial inhibitors [1]. Replacement of the ribityl portion of riboflavin by β-hydroxyethyl gives a compound inhibiting tumor growth in the rat [2]. 5, 6-Benzoisoalloxazine derivatives possess some anti-tumor activity and solubility in lipids [3, 4].

The isoalloxazine derivatives I-IV have been synthesized as potential riboflavin antimetabolites

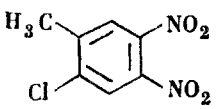




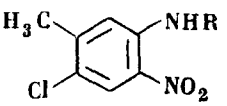
V

I $R_6=Cl$, $R_7=CH_3$, $R_9=CH_2CH_2OH$,
II $R_6=Cl$, $R_7=CH_3$, $R_9=CH_2C_6H_5$,
III $R_6=Cl$, $R_7=CH_3$, $R_9=C_6H_{11}$,
IV $R_6=R_7=H$, $R_9=p\text{-}C_6H_4CH_3$,

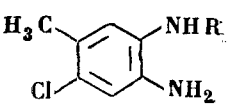
and so has 9-β-hydroxyethyl-5, 6-benzoisoalloxazine V.



VI



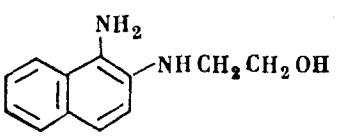
VII



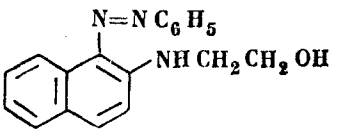
VIII

Refluxing the dinitro derivative of o-chlorotoluene VI [5] in isoamyl alcohol with monoethanolamine, benzylamine, or cyclohexylamine readily converts it to nitroalkylamino derivatives. By analogy with what has been demonstrated previously [6], these compounds are 2-nitro-4-chloro-5-methyl-N-alkylanilines (VIIa-c). Use of a reported method of reducing nitro compounds with hydrazine hydrate and Raney nickel [7] made it possible to prepare substituted o-diamines (VIIIa-c), which, without further purification, were quite suitable for subsequent condensation with alloxan to give compounds I-III.

9-p-Tolylisoalloxazine (IV) is prepared from 2-amino-4'-methyldiphenylamine [8] and alloxan in acetic acid. 9-β-Hydroxyethyl-5, 6-benzoisoalloxazine (V) was also prepared by condensing alloxan with 2-(β-hydroxyethyl)-1, 2-naphthylenediamine (IX), the latter being in its turn prepared by reduction of 1-phenyl-2-(β-hydroxyethyl)naphthylamine (X). The latter was obtained in the usual way, by diazo coupling between a phenyldiazonium compound and (β-hydroxyethyl)-2-naphthylamine [9].



IX



X

*For Part I see [10].

The isoalloxazines obtained are orange crystalline compounds with melting points over 300°. Some properties of the compounds synthesized are given in Tables 1 and 2.

Experimental

2-Nitro-4-chloro-5-methyl-N-(β-hydroxyethyl)aniline (VIIa). 11 g 2-chloro-4, 5-dinitrotoluene (VI) and 4 g monoethanolamine in 32 ml isoamyl alcohol were refluxed for 6 hr. The red crystalline precipitate which separated on cooling was filtered off and recrystallized from isoamyl alcohol. Yield 5.2 g (44.5%).

2-Nitro-4-chloro-5-methyl-N-benzylaniline (VIIb) and 2-nitro-4-chloro-5-methyl-N-cyclohexylaniline (VIIc) were prepared similarly to VIIa.

2-Chloro-4-amino-5-(β-hydroxyethylamino)toluene (VIIIa). 5 g VIIa and 8 g hydrazine hydrate in 50 ml absolute alcohol was refluxed and Raney nickel added until the mixture was decolorized, after which boiling was continued for

Table 1

2-Nitro-4-chloro-5-methyl-alkylanilines (VII)

Compound No.	Mp, °C	Formula	Cl, %		N, %		Yield, %
			Found	Calc.	Found	Calc.	
VIIa	165—166 (isoamyl alcohol)	$C_9H_{11}ClN_2O_3$	15.10 14.82	15.40	11.89 12.03	12.14	44.5
VIIb	99—101 (isoamyl alcohol)	$C_{14}H_{13}ClN_2O_2$	12.23 11.71	11.97	—	—	31.4
VIIc	120 (isoamyl alcohol)	$C_{13}H_{17}ClN_2O_2$	13.74	13.13	10.05	10.38	26.3

1 hr. The nickel was filtered off, VIIIa precipitated from the filtrate with water, filtered off, and dried. Yield 3 g (68.7%), mp 121-124°. A specimen for analysis was recrystallized from alcohol, mp 125°. Found: N 13.65%. Calculated for $C_9H_{13}ClN_2O$: N 13.90%.

2-Chloro-4-amino-5-benzylaminotoluene (VIIIb) was prepared from VIIb, in a way similar to VIIIa, yield 84.2%, mp 45-46°.

2-Chloro-4-amino-5-cyclohexylaminotoluene (VIIIc) was prepared similarly to VIIIa, yield 48%, mp 77°.

Table 2

Isoalloxazine Derivatives

Compound No.	Formula	Cl, %		N, %		Yield, %
		Found	Calculated	Found	Calculated	
I	$C_{13}H_{11}ClN_4O_3$ . .	—	—	18.14 18.32	18.36	21.7
II	$C_{18}H_{13}ClN_4O_2$ . .	10.35 9.87	10.09	15.94 15.60	15.88	57.5
III	$C_{17}H_{17}ClN_4O_2$ . .	10.16	10.30	—	—	61.0

6-Chloro-7-methyl-9-(β-hydroxyethyl)isoalloxazine (I). A hot solution of 3 g VIIIa in 25 ml glacial acetic acid was added to a hot solution of 7 g boric acid and 5 g alloxan in 150 ml glacial acetic acid, and the whole refluxed for 1 hr, diluted with water, and left for 12 hr. The precipitate was filtered off and recrystallized from 80% acetic acid.

6-Chloro-7-methyl-9-benzylisoalloxazine (II) and 6-chloro-7-methyl-9-cyclohexylisoalloxazine (III) were prepared similarly to I, and recrystallized respectively from glacial and 80% acetic acid.

9-p-Tolylisoalloxazine (IV). This was prepared similarly to I, by condensing 2-amino-4'-methyldiphenylamine with alloxan in acetic acid. Recrystallized from acetic acid, yield 43%. Found: C 67.23, 67.07; H 3.91, 3.87%. Calculated for $C_{17}H_{12}N_4O_2$: C 67.10; H 3.94%.

1-Phenylazo-2-(β-hydroxyethyl)naphthylamine (X). A solution of 5.5 g 2-(β-hydroxyethyl)naphthylamine in 300 ml alcohol was mixed with cooling with a solution of 2.88 g diazotized aniline. After 2 hr the dyes which had separated

were filtered off, and recrystallized from alcohol, yield 5.4 g (42%). Red crystals mp 136°. Found: C 73.92, 74.05; H 5.85, 5.93%. Calculated $C_{18}H_{17}N_3O$: C 74.22; H 5.84%.

9-(β-Hydroxyethyl)-5, 6-benzoylalloxazine (V). A solution of 5.4 g X in 500 ml alcohol was refluxed, and an aqueous solution of sodium hydrosulfite added until decolorization was complete. The solution was filtered and concentrated under reduced pressure, the resultant residue was condensed, under conditions similar to those used for I, with alloxan. After recrystallizing the product from 80% acetic acid, the yield was 31.1%. Found: C 62.12, 62.13; H 4.02, 3.88; N 18.34, 18.20%. Calculated for $C_{16}H_{12}N_4O_3$: C 62.33; H 3.89; N 18.14%.

REFERENCES

1. V. M. Berezovskii and T. V. Eremenko, Usp. khim., 32, 671, 1963.
2. L. F. Larionov, Chemotherapy of Malignant Tumors [in Russian], Medgiz, 1962.
3. M. Fernholz and H. Fernholz, Ber., 94, 257, 1951.
4. W. S. J. Ross, J. Chem. Soc., 219, 1948.
5. G. T. Morgan and H. D. K. Drew, J. Chem. Soc., 117, 784, 1920.
6. G. T. Morgan and L. A. Jones, J. Chem. Soc., 119, 187, 1921.
7. D. Balcon and A. Furst, J. Am. Chem. Soc., 75, 1953.
8. G. N. Tyurenkova and I. Ya. Postovskii, ZhPKh, 34, 2327, 1961.
9. M. S. Malinovskii, Olefin Oxides and Their Derivatives [in Russian], Goskhimizdat, 265, 1961.
10. Z. V. Pushkareva, L. F. Petrova, and V. F. Gryazev, KhGS, 438, 1965.

3 August 1964

Kirov Urals Polytechnic Institute,
Sverdlovsk