144. *A Series of 9-Dialkylaminoalkyl*isoalloxazines.

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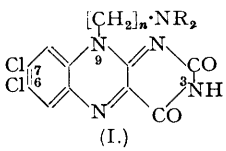
A series of 6 : 7-dichloro-9-dialkylaminoalkyl*iso*alloxazines and some related compounds have been prepared and tested as antimalarial and trypanocidal agents.

Since 1945 numerous papers have appeared describing the preparation of *iso*alloxazine derivatives containing a basic side chain (Hall and Turner, *J.*, 1945, 699; Neeman, *J.*, 1946, 811; King and Acheson, *J.*, 1946, 681; 1948, 1926; Adams, Weisel, and Mosher, *J. Amer Chem. Soc.*, 1946, **68**, 883; Kipnis, Weiner, and Spoerri, *ibid.*, 1947, **69**, 799; Burkett, *ibid.*, 1947, **69**, 2555; Hippchen, *Ber.*, 1947, **80**, 263). When the work to be described herein was begun, in May 1944, it was proposed to prepare 6 : 7-dichloro*iso*alloxazines (I) with a basic side chain attached in the 9-position in the hope that they would prove to have antimalarial activity. It was known that mepacrine antagonized riboflavin in some micro-organisms and the 6 : 7-dichloro-compounds were chosen for the same reason as led Kuhn, Weygand, and Möller (*Ber.*, 1943, **76**, 1044) to synthesise the 6 : 7-dichloro-analogue of riboflavin, although at the time this work of the German authors was unknown to us.



(I.)

The first compound to be prepared, 9-(3′-*piperidinopropyl*)-6 : 7-*dichloro*isoalloxazine *hydrochloride* (I; $n = 3$, $NR_2 = N{<}C_5H_{10}$), gave promise of being a member of an interesting new series; it was tested (serial number 5115) in the laboratories of Imperial Chemical Industries Ltd., and found by Dr. D. G. Davey to have definite antimalarial activity against *Plasmodium gallinaceum* in chicks, and by Dr. J. Madinaveitia to exert an antibacterial action against *Lactobacillus casei*, which was to some extent antagonized by riboflavin. Later, Dr. Davey found that the same substance had some trypanocidal activity *in vitro*, but not *in vivo* (against *Trypanosoma rhodesiense*).

After some delay the work was resumed and Table I gives a list of the *compounds* prepared. The first four differ only in the length of the polymethylene chain. One 7-chloro-compound (8021) and one 6-chloro-compound (5374) were prepared for comparison with their dichloro-analogues, 5115 and 5291, respectively. The 6 : 7-dichloro-3-methyl compound (8956) was made in order to discover the effect of blocking the possibility of lactam–lactim tautomerism in the *iso*alloxazine nucleus, and the methochloride (8955) to discover the effect of quaternizing the basic group; compound 8957 combines both these structural changes. Some difficulty was

encountered in preparing the last compound in Table I, which contains the same side chain as mepacrine, and it has so far only been tested *in vitro*.

TABLE I.

iso*Alloxazines*.

Serial number.	Substituents in positions: 3.	6.	7.	9.	pK_a (±0·3) at 21°.
8776	—	Cl	Cl	$[CH_2]_2$·NHEt$_2$}Cl	7·7
5291	—	Cl	Cl	$[CH_2]_3$·NHEt$_2$}Cl	9·1
8778	—	Cl	Cl	$[CH_2]_4$·NHEt$_2$}Cl	9·7
8779	—	Cl	Cl	$[CH_2]_5$NHEt$_2$}Cl	9·6
5115	—	Cl	Cl	$[CH_2]_3$·NH<C_5H_{10}}Cl	8·9
8021	—	—	Cl	$[CH_2]_3$·NH<C_5H_{10}}Cl	9·0
5374	—	Cl	—	$[CH_2]_3$·NHEt$_2$}Cl	9·8
8777	—	Cl	Cl	$[CH_2]_3$·NHBu$_2$}Cl	8·0
8955	—	Cl	Cl	$[CH_2]_3$·NMeEt$_2$}Cl	—
8956	Me	Cl	Cl	$[CH_2]_3$·NHEt$_2$}Cl	9·7
8957	Me	Cl	Cl	$[CH_2]_3$·NMeEt$_2$}Cl	—
9163	—	Cl	Cl	CHMe·$[CH_2]_3$·NHEt$_2$}X *	9·6

* X = Picrate anion.

The compounds were tested as antimalarial and trypanocidal agents in the laboratories of Imperial Chemical (Pharmaceuticals) Ltd. through the courtesy of the late Dr. F. H. S. Curd and Dr. D. G. Davey, but none of the compounds fulfilled the expectations aroused by the early tests on 5115; nor in later tests did the latter substance prove to be so active an antimalarial as had at first been thought. The 7-chloro-compound (8021) had slight activity against *T. congolense* in mice, and so had the quaternary salt 8955. The two 3-methyl compounds had slight to moderate activity against *T. rhodesiense* in mice, but none of the other compounds had any curative action against either parasite *in vivo*. The lack of curative activity in experimental malaria and trypanosomiasis may be partly due to the high toxicity of these compounds to chicks and mice, since positive effects were only observed with doses within the toxic range. The cause of this toxicity is unknown, but an action on the central nervous system is suspected.

The compounds were also tested in this laboratory, with the help of Dr. E. M. Lourie, against *T. rhodesiense in vitro*; they were trypanocidal in a dilution range of 1—2·5 million. Dr. Lourie tells us that with the same organism stilbamidine and pentamidine are trypanocidal in the ranges 1—4 and 6—8 million respectively (unpublished results), whereas undecanediamidine and tervalent arsenicals are active in dilutions of 1 in 100 million or more (King, Lourie, and Yorke, *Ann. Trop. Med. Parasit.*, 1938, **32**, 177).

On three flavoprotein enzymes, *viz.*, D-amino-acid oxidase, monoamine oxidase, and diamine oxidase, these compounds exerted only feeble inhibition; they had, however, the peculiar property of increasing the oxygen uptake of certain enzyme preparations, in particular those prepared from acetone-dried powders of liver and kidney. Dr. Madinaveitia had previously observed that, whereas 5115 inhibited the alcohol, citrate, and glycerophosphate dehydrogenases of yeast, yet it accelerated the action of yeast lactic acid dehydrogenase.

The pK_a values of all the tertiary bases were measured by the method of Albert and Goldacre (*J.*, 1943, 454); the results, included in Table I, are subject to an error of ±0·3 owing to the use of a mains-operated meter.

Professor Adrien Albert very kindly tested two of our compounds (5291 and its 3-methyl derivative 8956) for chelation effects by electrometric titration in the presence of cupric chloride. He reports that neither of these gave evidence of chelation; both behaved in the same way, although the former contains the unit ·N:C·C(OH):N·, which might be expected to give rise to chelation, and the latter does not.

With the exception of the substance containing the 4-diethylamino-1-methylbutyl side chain, all the *iso*alloxazines were prepared by condensing suitably substituted *o*-phenylenediamines with alloxan monohydrate in methanol containing hydrogen chloride (Kuhling, *Ber.*, 1891, **24**,2363); they were isolated as their crystalline *hydrochlorides*, which were usually hydrated, and occasionally as their *picrates*. The *o*-phenylenediamine derivatives were not usually isolated; they were obtained by catalytic reduction of the corresponding *o*-nitroaniline derivative in methanol and, after the removal of the catalyst, they were immediately condensed with alloxan. At first the *o*-nitroaniline derivatives were prepared by heating the appropriate ω-dialkylaminoalkylamine with 4 : 5-dichloro-1 : 2-dinitrobenzene, but as the preparation of the latter substance in quantity

is exceedingly tedious (cf. Kuhn, Weygand, and Möller, *loc. cit.*), it was replaced by 2 : 4 : 5-trichloronitrobenzene, which is readily obtained by nitrating 1 : 3 : 4-trichlorobenzene; that it is the chloro-substituent *ortho* to the nitro-group which is replaced by the substituted alkylamine was proved by preparing three of the nitroaniline derivatives from both of these starting materials (see Table II). The *o*-nitroaniline derivatives were usually isolated as hydrochlorides or perchlorates, but reduction (with hydrogen and Raney nickel at atmospheric pressure) was best effected with the free bases in methanol; reduction of the hydrochlorides with hydrogen and palladium–charcoal was exceedingly slow.

The 6-chloro-compound (5374) was prepared by condensing 5-chloro-2-iodonitrobenzene with diethylaminopropylamine, reducing the *o*-nitroaniline derivative so formed, and condensing the product with alloxan. The 7-chloro-compound (8021) was similarly prepared from 2 : 4-dichloronitrobenzene and piperidinopropylamine.

Quaternary metho-salts of 9-dialkylaminoalkyl*iso*alloxazines could not be obtained by direct addition of methyl iodide to the free bases, or by condensing alloxan with the reduction products of *o*-nitro-*N*-dialkylaminoalkylaniline methiodides; intractable red products were formed by both methods. When, however, the *o*-nitro-*N*-dialkylaminoalkylaniline was converted into its methochloride (by the addition of methyl sulphite and subsequent hydrolysis of the metho-methylsulphite with hydrochloric acid), condensation with alloxan was satisfactorily effected after reduction of the nitro-group. The 3-methyl*iso*alloxazines were prepared by using methyl-alloxan in place of alloxan.

6 : 7-Dichloro-9-(4-diethylamino-1-methylbutyl)*iso*alloxazine hydrochloride could not be obtained by condensing the appropriate *o*-phenylenediamine derivative with alloxan in methanol containing hydrogen chloride; the only product isolated was 6 : 7-*dichloroalloxazine*. Other authors have found a similar difficulty in preparing *iso*alloxazines with the " mepacrine side chain " in position 9 (cf. Hall and Turner, *loc. cit.*; Kipnis, Weiner, and Spoerri, *loc. cit.*; McCombrey and Webster, *J.*, 1948, 1719), and Neeman (*loc. cit.*), who used boric acid in acetic acid as the condensing agent (Kuhn and Weygand, *Ber.*, 1935, **68**, 1282), was only able to isolate his products as reineckates. Condensation of alloxan with the reduction product of 4 : 5-*dichloro*-2-(4-*diethylamino*-1-*methylbutylamino*)*nitrobenzene* certainly occurs in acetic acid solution in the presence of boric acid, since we were able to isolate the *iso*alloxazine as its *picrate*, but we were unable to isolate the hydrochloride in an analytically pure state.

Experimental.

(All analyses are by Drs. Weiler and Strauss. All m. p.s are uncorrected.)

Dialkylaminoalkylamines.—We are indebted to Messrs. Imperial Chemical Industries Ltd. for generous supplies of diethylamino-ethylamine and -propylamine, dibutylaminopropylamine, and 4-diethylamino-1-methylbutylamine. Diethylamino- and piperidino-propylamines were prepared by the method of Whitmore *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 725), the intermediate nitriles being reduced by sodium and ethanol. Diethylaminobutylamine was prepared from γ-chlorobutyronitrile (Utermohlen and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 156; Strukov, *Chem. Abs.*, 1934, **28**, 3714), and the homologous amylamine from phthalo-5-bromoamylimide (Magidson and Grigorowsky, *Ber.*, 1936, **69**, 396).

2-*Nitro*-N-*dialkylaminoalkylanilines.*—The 4 : 5-dichloro-2-nitrodialkylaminoalkylanilines were all prepared by boiling a solution of the dialkylaminoalkylamine and 2 : 4 : 5-trichloronitrobenzene (10% excess) in toluene or xylene for 5—12 hours; yields of 40—50% were obtained. Three of them (see Table II) were also prepared in a similar way from the alkylamine and 4 : 5-dichloro-1 : 2-dinitrobenzene. 5-*Chloro*-2-*nitro*-N-3′-*piperidinopropylaniline hydrochloride* was obtained similarly from piperidinopropylamine and 2 : 4-dichloronitrobenzene. The reaction mixtures were cooled and shaken with dilute hydrochloric acid; if the solid hydrochloride separated, it was collected and crystallized from water or alcohol; otherwise, the free base was liberated to ether and converted into the perchlorate. Only one base was obtained crystalline, *viz.*, 4 : 5-*dichloro*-2-*nitro*-N-2′-*diethylaminoethylaniline*.

4-*Chloro*-2-*nitro*-N-3′-*diethylaminopropylaniline hydriodide* was obtained by heating together diethylaminopropylamine and 5-chloro-2-iodonitrobenzene (Korner, *Gazzetta*, 1875, **4**, 381) without a solvent at 100° until a test drop gave a clear solution in dilute acid (4 hours). The product was diluted with water and acidified with hydriodic acid, the salt then crystallizing; it was recrystallized by the addition of ether to its solution in hot ethanol.

Table II gives a list of the compounds prepared, their m. p.s, and analytical results. The salts tend to crystallize in orange or yellow hydrated forms; the anhydrous salts are red, but become yellow in a damp atmosphere. The hydrochlorides are soluble in water and alcohol, but only sparingly so in acetone; the perchlorates are less soluble in water and alcohol. The *methochloride* of 4 : 5-dichloro-2-nitro-*N*-3′-diethylaminopropylaniline was obtained by heating the free base in methanol with methyl sulphite (1 mol.; excess must be avoided); after 1 hour, excess of hydrochloric acid was added, and heating continued for 4 hours; the solution was then evaporated and the residue taken up in ethanol and again evaporated; it was finally crystallized from ethanol. Both the methochloride (orange) and the *methiodide* (yellow) were hydrated; they lost water, becoming red, a few degrees above 100°.

2 : 4 : 5-Trichloronitrobenzene was prepared by adding 1 : 2 : 4-trichlorobenzene (25 c.c.) gradually to nitric acid (*d* 1·5; 120 c.c.) cooled in ice–salt; the solution was poured on ice, and the mixture left at 0°

Table II.

2-Nitro-N-dialkylaminoalkylanilines.

Method.	Substituents. 4.	5.	*N*.	Salt.	M. p.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
a	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	—	102° *	$C_{12}H_{17}O_2N_3Cl_2$	47·1	5·4	—	47·1	5·6	—
a, *b*	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	HCl	214	$C_{13}H_{20}O_2N_3Cl_3$ †	—	—	11·5	—	—	11·8
				MeI	215	$C_{14}H_{22}O_2N_3Cl_2I,H_2O$	35·0	5·0	—	35·0	5·0	—
				MeCl	216	$C_{14}H_{22}O_2N_3Cl_3,H_2O$	43·2	5·7	—	43·3	6·2	—
a	Cl	Cl	$[CH_2]_4{\cdot}NEt_2$	HCl	133 ‡	$C_{14}H_{22}O_2N_3Cl_3,\frac{1}{2}H_2O$	44·2	6·1	10·8	44·3	6·1	11·1
				$HClO_4$	143 ‡	$C_{14}H_{22}O_6N_3Cl_3$	—	—	9·8	—	—	9·7
a	Cl	Cl	$[CH_2]_5{\cdot}NEt_2$	$HClO_4$	133 ‡	$C_{15}H_{24}O_6N_3Cl_3$	39·7	4·9	—	40·2	5·4	—
a, *b*	Cl	Cl	$[CH_2]_3{\cdot}NC_5H_{10}$	HCl	215	$C_{14}H_{20}O_2N_3Cl_3$	—	—	11·2	—	—	11·4
a	Cl	Cl	$[CH_2]_3{\cdot}NBu_2$	$HClO_4$	140 ‡	$C_{17}H_{28}O_6N_3Cl_3$	42·9	5·8	—	42·8	5·9	—
a, *b*	Cl	Cl	$CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	$HClO_4$	109	$C_{15}H_{24}O_6N_3Cl_3$	—	—	9·5	—	—	9·4
c	Cl	H	$[CH_2]_3{\cdot}NEt_2$	HI	157	$C_{13}H_{21}O_2N_3ClI$	37·9	5·0	—	37·7	5·1	—
d	H	Cl	$[CH_2]_3{\cdot}NC_5H_{10}$	HCl §	210	$C_{14}H_{21}O_2N_3Cl_2$	49·3	6·0	—	49·0	6·4	—

(*a*) Prepared from 2 : 4 : 5-trichlorobenzene. (*b*) Prepared from 4 : 5-dichloro-1 : 2-dinitrobenzene.
(*c*) Prepared from 5-chloro-2-iodonitrobenzene. (*d*) Prepared from 2 : 4-dichloronitrobenzene.
* Free base, crystallized from ether. † Found : Cl, 29·8. $C_{13}H_{20}O_2N_3Cl_3$ requires Cl, 29·9%.
‡ Melting with decomposition.
§ Crystallized with $\frac{1}{2}H_2O$ (Found : H_2O, 2·7. $C_{14}H_{20}O_2N_3Cl,HCl,\frac{1}{2}H_2O$ requires H_2O, 2·6%) but the analysis in the Table is for the anhydrous salt.

Table III.

*9-Dialkylaminoalkyl*isoalloxazines.

Substituents: 3.	6.	7.	9.	Salt.	Cryst. from	M. p.*	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
—	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	HCl	H_2O–MeOH	286°	$C_{16}H_{18}O_2N_5Cl_3,\frac{1}{2}H_2O$	46·0	4·4	16·6	45·9	4·1	16·7
CH_3	Cl	Cl	$[CH_2]_2{\cdot}NEt_2$	HCl	H_2O–EtOH	244	$C_{17}H_{20}O_2N_5Cl_3,H_2O$	45·8	4·9	15·6	45·3	4·9	15·6
				HCl	H_2O–EtOH	244	$C_{17}H_{20}O_2N_5Cl_3,H_2O$	45·5	4·9	15·6	45·3	4·9	15·6
				HCl †	MeOH–Et_2O	244	$C_{17}H_{20}O_2N_5Cl_3,1\frac{1}{2}H_2O$	43·9	5·0	15·0	44·4	4·0	15·2
—	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	MeCl	H_2O–EtOH	276	$C_{18}H_{22}O_2N_5Cl_3,2H_2O$	44·1	5·0	15·0	44·8	5·4	14·5
				Me p.‡	H_2O–EtOH	130	$C_{24}H_{24}O_9N_8Cl_2,H_2O$	43·8	3·7	17·1	43·8	3·9	17·0
				HCl	EtOH	240	$C_{18}H_{22}O_2N_5Cl_3,1\frac{1}{2}H_2O$	45·3	4·8	15·3	45·6	5·3	14·8
				p. ¶	H_2O–EtOH	215	$C_{24}H_{24}O_9N_8Cl_2$	44·6	3·1	17·7	45·1	3·8	17·5
CH_3	Cl	Cl	$[CH_2]_3{\cdot}NEt_2$	MeCl	H_2O–EtOH	248	$C_{19}H_{24}O_2N_5Cl_3,\frac{1}{2}H_2O$	48·2	5·0	15·3	48·6	5·3	14·9
				Me p.	EtOH	204	$C_{25}H_{26}O_9N_8Cl_2$	45·5	3·8	17·3	46·0	4·0	17·2
—	Cl	Cl	$[CH_2]_4{\cdot}NEt_2$	HCl	H_2O–EtOH	259	$C_{18}H_{22}O_2N_5Cl_3,1\frac{1}{2}H_2O$	45·8	5·1	15·1	45·7	5·3	14·8
				p.	H_2O–EtOH	236	$C_{24}H_{24}O_9N_8Cl_2$	45·3	4·0	17·1	45·1	3·8	17·5
—	Cl	Cl	$[CH_2]_5{\cdot}NEt_2$	HCl	AcOH	252	$C_{19}H_{24}O_2N_5Cl_3,H_2O$	47·5	5·0	13·9	47·7	5·4	14·6
				p.	H_2O–EtOH	247	$C_{25}H_{26}O_9N_8Cl_2$	46·3	4·0	17·3	46·0	4·0	17·2
—	Cl	Cl	$[CH_2]_3{\cdot}N{<}C_5H_{10}$	HCl §	AcOH–Et_2O	271	$C_{18}H_{20}O_2N_5Cl_3,H_2O$	46·9	5·0	15·1	46·7	4·8	15·1
—	Cl	Cl	$[CH_2]_3{\cdot}NBu_2$	HCl	EtOH	246	$C_{21}H_{28}O_2N_5Cl_3,\frac{1}{2}H_2O$	50·5	6·1	13·8	50·5	5·8	14·1
				p.	EtOH–$COMe_2$	223	$C_{27}H_{30}O_9N_8Cl_2$	47·5	4·8	16·4	47·6	4·4	16·4
—	Cl	Cl	$CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$	p.	EtOH–$COMe_2$	209	$C_{25}H_{26}O_9N_8Cl_2$	45·6	4·6	17·3	46·0	4·0	17·2
—	Cl	—	$[CH_2]_3{\cdot}NEt_2$	HCl	AcOH–$COMe_2$	282	$C_{17}H_{21}O_2N_5Cl_2$	50·9	4·9	17·7	51·2	5·3	17·6
—	—	Cl	$[CH_2]_3{\cdot}N{<}C_5H_{10}$	HCl	AcOH	275	$C_{18}H_{21}O_2N_5Cl_2$	52·4	5·3	16·6	52·6	5·1	17·1

* All salts melt with decomposition. † Found : H_2O, 5·8. $C_{17}H_{20}O_2N_5Cl_3,1\frac{1}{2}H_2O$ requires H_2O, 5·9%.
‡ Found : H_2O, 2·3. $C_{24}H_{24}O_9N_8Cl_2,H_2O$ requires H_2O, 2·7%. § Found : H_2O, 3·9. $C_{18}H_{20}O_2N_5Cl_3,H_2O$ requires H_2O, 3·9%.
¶ p. = picrate.

overnight. The solid was collected, sucked as dry as possible from oily products, and crystallized twice from methanol; m. p. 57°; yield 20 g., 50—60% (Jungfleisch, *Ann. Chim. Phys.*, 1868, **15**, 273).

The iso*Alloxazine Condensation.*—The 2-nitro-alkylaminoalkylanilines were liberated from their salts to ether, the ethereal extracts dried (Na_2SO_4) and evaporated, and the free bases dissolved in methanol and reduced with hydrogen and Raney nickel at atmospheric pressure. After removal of the catalyst, hydrogen chloride was bubbled into the solution, and alloxan monohydrate (1 mol.) added; the hydrogen chloride stream was continued until the blue colour, which formed round the alloxan crystals, had disappeared and the solution was strongly acid to Congo-red. Sufficient heat was usually generated by this procedure to effect dissolution of the alloxan, but occasionally additional heating was necessary. The deep-brown solution was set aside for at least 12 hours. The *iso*alloxazine hydrochloride sometimes crystallized from the reaction mixture; if not, it was precipitated as a dark brown oil or gum by addition of ether; the mother-liquor from any crystalline material was also treated in this way. The gummy salt often crystallized when stirred with ethanol, but sometimes further washing with ether or acetone was necessary before crystallization could be induced. The *hydrochlorides* were all readily soluble in water with a brilliant green fluorescence, but sparingly so in ethanol. They were usually crystallized from aqueous ethanol and, with the exception of the 6-chloro- and the 7-chloro-compound, they were all hydrated; the two *methochlorides* behaved similarly. The *picrates*, with one exception, crystallized anhydrous and provided a convenient way of characterizing these *iso*alloxazine derivatives. Table III gives a list of the compounds prepared, with m. p.s and analytical results. Usually the yield of recrystallized product was about 30—40%.

4 : 7-Dichloro-9-(4-diethylamino-1-methylbutyl)*iso*alloxazine was prepared in a crude state from the appropriate *o*-nitroaniline derivative by the method of Kipnis, Weiner, and Spoerri (*loc. cit.*). Several attempts were made to prepare a hydrochloride from the crude base, but without success. The *picrate*, however, crystallized from aqueous alcohol–acetone (Table III). When methanolic hydrogen chloride was used as the condensing medium, an insoluble white product separated which appeared to be 6 : 7-*dichloroalloxazine*; it was insoluble in all the usual solvents, but dissolved in aqueous alkali and was reprecipitated by carbon dioxide; it did not melt below 300° (Found: N, 19·8. $C_{10}H_4O_2N_4Cl_2$ requires N, 19·8%).

The methylalloxan used in the preparation of the 3-methyl*iso*alloxazines was prepared from theobromine by the method of Biltz (*Ber.*, 1912, **45**, 3659). In our experience it is essential to use "AnalaR" stannous chloride in the reduction stage and to keep the reaction solution at −15° for 24 hours in order to induce dimethylalloxantin to crystallize.

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