Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88; S, 11.16. Found: C, 62.99; H, 4.59; N, 5.15; S, 11.19.

2,3-Dihydro-3-keto-1H-pyrido[3,2,1-kl]phenothiazine Sulfoxide (XI).—In a similar way this was prepared from 10.0 g. (0.04 mole) of the corresponding keto compound.[17] The product was recrystallized from 95% ethanol giving 7.0 g. (65%) of solid, m.p. 198–200°.

Anal. Calcd. for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.18; N, 5.20; S, 11.90. Found: C, 66.86; H, 4.07; N, 5.19; S, 11.95.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, ASSIUT UNIVERSITY]

Synthesis of Oxazolo-phenoxazines

BY ABDEL-MEGUD OSMAN AND ISMAIL BASSIOUNI

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2-Aryl-5*H*-oxazolo[4,5-*b*]phenoxazines (II) were synthesized by heating 3-aminophenoxazone-2 (I) with aromatic aldehydes in the absence of solvents and basic catalysts. The oxazol-phenoxazines (II) were attacked by concentrated hydrochloric acid giving 2-hydroxy-3-aminophenoxazine hydrochloride (III). When III was heated with aromatic aldehydes, it was reconverted to the corresponding oxazolo-phenoxazines. The action of benzyl chloride on I gave 2-phenyl-5-benzyl-oxazolo[4,5-*b*]phenoxazine (VIII). This also was obtained by the action of benzyl chloride on 2-phenyl-5*H*-oxazolo[4,5-*b*]-phenoxazine. Mechanisms explaining the formation of II and VIII are discussed.

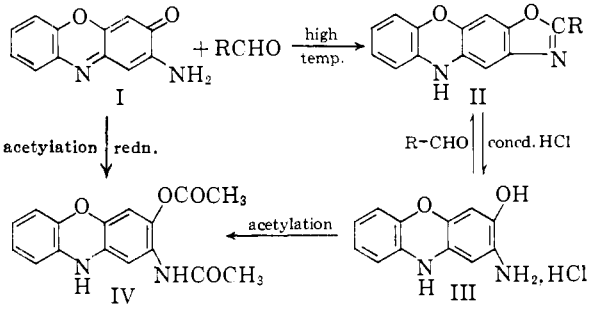
The remarkable antibacterial and antifungal activities of some oxazoles[1] has prompted us to synthesize new oxazoles. It was thought that the combination of an oxazole ring with a heterocyclic nucleus might increase these biological activities, and so the synthesis of previously unknown oxazolophenoxazines(II) was undertaken.

The route (chosen) for the synthesis involves the action of aldehydes on 3-aminophenoxazone-2 (I), to form an intermediate Schiff base which was expected to cyclize and rearrange forming oxazolo-phenoxazines (II). 3-Aminophenoxazone-2 (I) is known to be an oxidation product of *o*-aminophenol,[2] and it was conveniently prepared by oxidation of *o*-aminophenol with an equivalent amount of *p*-benzoquinone in alcohol.

The reaction between 3-aminophenoxazone-2 (I) and aldehydes was tried several times using the procedure usually applied to the preparation of oxazoles, *i.e.*, use of a suitable solvent and a basic catalyst[3]; however, the reaction did not proceed and the aminophenoxazone was recovered unchanged. It was discovered that by heating the reactants alone in the direct flame or better by refluxing them for a short time at the boiling point of the aldehyde, the required condensations were effected giving yellow products. The reaction was positive only with aromatic aldehydes, while aliphatic aldehydes failed to react even when heated in a sealed tube for a long time. The products showed strong fluorescence in different solvents and in concentrated sulfuric acid, a property which is usually exhibited by oxazoles. On investigation, the yellow compounds were found to be devoid of carbonyl groups or conjugated systems. This was also confirmed by the infrared absorption spectra which showed no characteristic bands for these groups, but a medium band was shown at 3340 cm.$^{-1}$, indicating a secondary amino group.[4,5]

These facts together with the analytical results were in full agreement with structure II originally proposed for these compounds.

The oxazolo-phenoxazines (II) were unstable in concentrated mineral acids, and when warmed with concentrated hydrochloric acid the oxazole ring was readily cleaved giving 2-hydroxy-3-aminophenoxazine hydrochloride (III). This on acetylation gave a colorless diacetate (IV), identical with that obtained by reductive acetylation of I. When III was heated with aromatic aldehydes (but not aliphatic aldehydes), the corresponding oxazolophenoxazines were produced.



The mechanism of formation of the oxazolophenoxazines (II) from I and aromatic aldehydes apparently involves an aminoaldehyde condensation forming an intermediate Schiff base (V). This intermediate is expected to undergo electronic displacements across the conjugated double bonds with simultaneous cyclization forming a molecule of the type VI. The extra hydrogen atom attached to the oxazole ring in VI is probably transferred as a proton to the nitrogen atom in the phenoxazine nucleus thus forming a secondary amino group. This transfer is influenced by the polarity of the molecule VI. At this stage the molecule attains its stability with the formation of the oxazolophenoxazines (II) (*cf.* Scheme A).

The investigation was extended to the action of benzyl chloride and benzyl cyanide on 3-amino-

(1) U. S. Patent 2,630,381 Mar. 3, 1953; L. Katz, *et al.*, THIS JOURNAL, **75**, 712 (1953); *J. Org. Chem.*, **19**, 756 (1954).

(2) O. Fisher, *et al.*, *Ber.*, **27**, 2784 (1894); F. Hepp, *ibid.*, **28**, 297 (1895); Zincke and Heberbrand, *Ann.*, **226**, 61 (1884).

(3) C. W. C. Stein and A. R. Day, THIS JOURNAL, **64**, 2567 (1942); A. M. Osman, *ibid.*, **79**, 966 (1957).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 212.

(5) We wish to thank Prof. F. G. Baddar, Chem. Dept., Faculty of Science, Ain-Shams University, for the determination of the infrared absorption spectra.

TABLE I

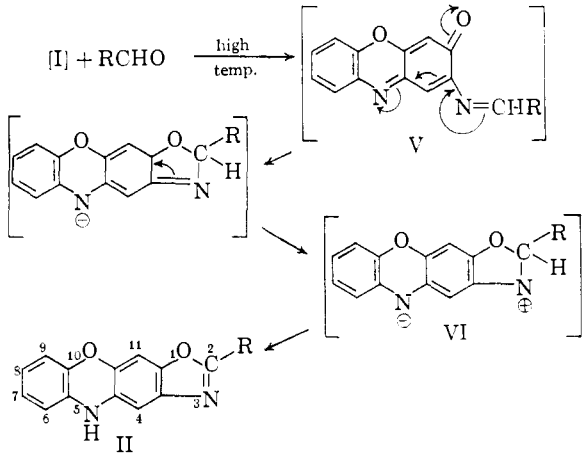
2-Aryl-5*H*-oxazolo-(4,5-*b*)phenoxazine	Color of the product	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Fluoresence in benzene	Color with concd. H_2SO_4
2-Phenyl-	Golden-yell.	275	$C_{19}H_{12}O_2N_2$	76.00	76.18	4.00	3.99	9.33	9.32	Bluish-gr.	Pink
2-Anisyl-	Yellow	250	$C_{20}H_{14}O_3N_2$	72.72	72.40	4.24	4.58	8.48	8.57	Blue	Pale blue
2-(*o*-Hydroxyphenyl)-	Greenish-yell.	307	$C_{19}H_{12}O_3N_2$	72.15	72.52	3.79	3.73	8.86	8.83	Greenish-bl.	Pale bluish-viol
2-(*o*-Chlorophenyl)-	Yellowish-br.	235	$C_{19}H_{11}O_2N_2Cl$	...	...	..	..	8.37	7.83	Greenish-bl.	Pink
2-(3,4-Oxymethylenephenyl)-	Yellow	320	$C_{20}H_{12}O_4N_2$	69.76	69.58	3.48	3.50	8.13	8.10	Bluish-gr.	Blue

TABLE II

2-Aryl-5-benzyl-oxazolo-(4,5-*b*)phenoxazine	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Fluoresence in benzene	Color with concd. H_2SO_4
2-Anisyl-	226	68	$C_{27}H_{20}O_3N_2$	77.14	77.61	4.76	4.91	6.66	6.40	Violet	Violet
2-Phenyl-[a]	246	55	$C_{26}H_{18}O_2N_2$	80	79.59	4.61	4.37	7.17	7.34	Bluish-gr.	Pink
2-Phenyl-[b]	246	65	$C_{26}H_{18}O_2N_2$	80	80.28	4.61	4.77	7.17	7.29	Bluish-gr.	Pink
2-(*o*-Benzyloxyphenyl)-[c]	232	84	$C_{33}H_{24}O_3N_2$	79.83	79.14	4.83	4.96	5.64	6.18	Bluish-gr.	Violet

[a] Prepared from 3-aminophenoxazone-2 and benzaldehyde. [b] Prepared from 2-phenyl-5*H*-oxazolo[4,5-*b*]phenoxazine and benzyl chloride. [c] The benzyloxyphenyl radical has resulted from the reaction of benzyl chloride with the hydroxyl group of salicylaldehyde (comp. Perkin, *Ann.*, **148**, 24 (1868)).

SCHEME A

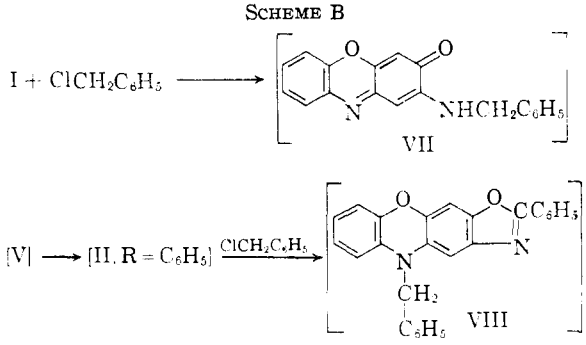


R = C_6H_5 *o*-OHC_6H_4, *o*-$OCH_3C_6H_4$, *o*-ClC_6H_4, $CH_2O_2C_6H_3$

phenoxazine-2 (I) with the view of obtaining the same 2-phenyl-5*H*-oxazolo(4,5-*b*)phenoxazine (II, R = C_6H_5) *via* another route.[6] Benzyl cyanide did not react, while benzyl chloride gave a new substance or $C_{26}H_{18}O_2N_2$ which also showed strong fluorescence in solution. The properties and analytical data agree fairly well with structure VIII, the N-benzyl derivative of II, R = C_6H_5. The relation between II, R = C_6H_5, and VIII was established by transforming the former to the latter by allowing it to react with benzyl chloride at a high temperature. That benzyl chloride had reacted with the secondary amino group of II was confirmed by the infrared absorption spectra which indicated the absence of the band previously shown at 3340 $cm.^{-1}$ which is characteristic for a secondary amino group. Other N-benzyl derivatives were prepared by the action of benzyl chloride on 2-anisyl- and 2-salicyl-oxazolo-phenoxazines (II, R = *o*-OCH_3-C_6H_4 or *o*-OHC_6H_4). It should be noted that with 2-salicyl-oxazolo-phenoxazine, two molecules of benzyl chloride reacted, apparently one with the secondary amino group and the other with the hydroxyl group of the salicyl residue (*cf.* Table II).

The reaction between I and benzyl chloride can be interpreted as follows: A molecule of benzyl chloride reacts with I giving an intermediate (VII) which is oxidized to the Schiff base (V) and the reaction then proceeds to form II as described before in Scheme A. Compound II being formed reacts with another molecule of benzyl chloride giving 2-phenyl-5-benzyloxazolo[4,5-*b*]phenoxazine (VIII) (*cf.* Scheme B).

SCHEME B



The biological testings are in progress and the results will be published later.

Experimental

3-Aminophenoxazone-2 (I).—Ten grams of pure *o*-aminophenol and 10 g. of *p*-benzoquinone were dissolved separately each in 100 cc. of ethyl alcohol, then mixed and refluxed for 20 minutes. The alcohol was distilled over to half its volume; the remaining mixture was cooled and the deposited product was collected, washed with a small amount of alcohol and crystallized from the same solvent as red needles, m.p. 249°, yield 5 g. The aminophenoxazone gave a blood-red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.77; N, 13.20. Found: C, 67.98; H, 3.94; N, 13.08.

Acetylation of 3-aminophenoxazone-2 by the usual methods gave a yellow monoacetate which crystallized from glacial acetic acid into brown-yellow needles, m.p. 285°.

Anal. Calcd. for $C_{14}H_{10}O_3N_2$: C, 66.29; H, 3.90; N, 11.02. Found: C, 66.34; H, 4.26; N, 10.84.

Reductive acetylation of I by zinc dust, acetic anhydride and fused sodium acetate gave a colorless diacetate which was crystallized from petroleum ether (b.p. 80–100°) as colorless needles, m.p. 236°.

Anal. Calcd. for $C_{16}H_{14}O_4N_2$: C, 64.98; H, 4.37; N, 9.42. Found: C, 64.64; H, 4.57; N, 9.90.

2-Aryl-5H-oxazolo(4,5-b)phenoxazines (II).—The aminophenoxazone (I) (0.6 g.) was covered with the aromatic aldehyde and then allowed to reflux gently in an oil-bath for about 20 minutes while keeping the temperature of the oil-bath just above the boiling point of the aldehyde. The re-

(6) Comp. A. Schönberg and W. Awad, *J. Chem. Soc.*, 72 (1950); A. S. Wheeler, *Am. Chem. J.*, **17**, 397 (1895).

action mixture was cooled until it solidified, then heated with a small amount of alcohol to remove any resinous materials. The yellowish reaction product was collected after cooling, washed several times with alcohol and crystallized from benzene as fluffy yellowish needles which exhibited strong fluorescence in solution.

With heliotropin the reaction was better carried out by fusing the reactants together in the direct flame for a few minutes. The reaction mixture was cooled, a small amount of alcohol was added, and the mixture was heated gently and cooled again. The precipitated yellowish material was collected and purified as described above.

The yields in all cases were almost quantitative, and the products were fairly soluble in acetone, glacial acetic acid and nitrobenzene from which they can also be crystallized. The solubility of the products in alcohol and petroleum ether was very limited. The analyses and some other properties are recorded in Table I.

Attempted Reactions of I with Aromatic Aldehydes in the Presence of Solvents and Basic Catalysts.—A pure sample of aminophenoxazone (I) was covered with the aldehyde and refluxed for 5 hours in excess alcohol containing a few drops of piperidine or dimethylaniline. The reaction mixture was cooled, the product was collected and crystallized from alcohol as red needles, m.p. and mixed m.p. with 3-aminophenoxazone-2 249°.

In the above experiment the alcohol could be replaced by benzene, decalin, dioxane, nitrobenzene or acetic acid with the same result.

Interaction of Aliphatic Aldehydes with I.—(a) A pure sample of the aminophenoxazone (I) was covered with acetaldehyde or propionaldehyde and allowed to reflux for one hour in an oil-bath. The reaction product was collected, washed with alcohol and crystallized also from alcohol as red needles, m.p. and mixed m.p. with 3-aminophenoxazone-2, 249°.

(b) Five-tenths gram of the aminophenoxazone (I) was suspended in 10 cc. of propionaldehyde in a sealed tube and placed in an electric furnace at 120° for 12 hours. The tube was cooled, opened and the contents were collected. The excess aldehyde was removed leaving a resinous material from which no pure substance could be obtained.

Action of Concd. Hydrochloric Acid on 2-Phenyl-5*H*-oxazolo[4,5-*b*]phenoxazine.—One gram of the substance was heated with 10 cc. of concd. hydrochloric acid for a few minutes. The yellow material changed readily to reddish-brown, then was collected and washed with few cc. of concd. hydrochloric acid. The product could not be crystallized as it was readily oxidized in the air. It was identified as 2 hydroxy-3-aminophenoxazone hydrochloride (III) since it dissolved readily in water, gave a positive Beilstein test for chlorine, precipitated silver chloride when treated with silver nitrate solution and on acetylation a colorless diacetate was given which was identical to that obtained by reductive acetylation of aminophenoxazone (I).

Preparation of 2-Phenyl-5*H*-oxazolo(4,5-*b*)phenoxazine from 2-Hydroxy-3-aminophenoxazine Hydrochloride and Benzaldehyde.—A sample of 2-hydroxy-3-aminophenoxazine hydrochloride obtained from the above experiment was covered with benzaldehyde and heated in the direct flame for a few minutes. The reaction product was collected, washed with alcohol and crystallized from benzene as golden yellow needles, m.p. 275°, undepressed when mixed with a pure sample obtained from 3-aminophenoxazone-2 and benzaldehyde as described before.

2-Phenyl-5-benzyloxazolo(4,5-*b*)phenoxazine (VIII).—(a) One gram of 3-aminophenoxazine-2 was covered with 6 g. of benzyl chloride and the mixture was refluxed on the direct flame for about 1.5 hours. The excess benzyl chloride was removed and the reaction mixture on cooling deposited a yellow solid which was collected, washed with a few drops of benzene and crystallized from the same solvent as light yellow needles of 2-phenyl-5-benzyl-oxazolo[4,5-*b*]phenoxazine, m.p. 246°. The substance exhibited a bluish-green fluorescence in benzene and a violet fluorescence in concd. sulfuric acid.

(b) 2-Phenyl-5*H*-oxazolo(4,5-*b*)phenoxazine (II, R = C_6H_5) was refluxed in a slight excess of benzyl chloride in the direct flame for 3 hours. The excess benzyl chloride was removed and the reaction mixture was cooled. The precipitated yellow product was collected, washed with a small amount of benzene and crystallized from the same solvent as light yellow needles, m.p. 246°, undepressed when mixed with a sample of 2-phenyl-5-benzyloxazolo[4,5-*b*]phenoxazine prepared in the previous experiment.

The N-benzyl derivatives of the 2-anisyl- and the 2-salicyloxazolo-phenoxazines were prepared similarly.

Analytical results of the N-benzyl derivatives and some other properties are summarized in Table II.

Attempted Reaction of 3-Aminophenoxazine-2 (I) with Benzyl Cyanide.—A pure sample of the aminophenoxazone (I) was covered with benzyl cyanide and the reaction was carried out as described for benzyl chloride. After isolating the reaction product, it proved to be unchanged material, m.p. and mixed m.p. 249°.

ASSIUT, EGYPT, U. A. R.

[CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH]

5-Sulfanilamidotetrazole[1]

BY HANNA KOVACS NAGY,[2] ARTHUR J. TOMSON AND JEROME P. HORWITZ

RECEIVED AUGUST 24, 1959

The reaction of 5-aminotetrazole (I) and an arensulfonyl chloride (II) in either pyridine or aqueous sodium carbonate is shown to lead directly to a guanyl azide (IV) rather than the previously reported 5-arenesulfonamidotetrazole (V). Similarly, 1-amino-3-(*p*-acetamidobenzenesulfonyl)-guanidine affords the corresponding guanyl azide IVa on treatment with nitrous acid. The presence of an azide group in IV is established from infrared absorption measurements together with the fact that reduction of IV yields the corresponding guanidine VII. Furthermore, the cyclization of IV to a 5-arenesulfonamidotetrazole is readily effected with dilute base.

The successful application of several sulfanilamido heterocycles as chemotherapeutic agents for the treatment of bacterial infections prompted several independent attempts to prepare 5-sulfanilamidotetrazole (sulfatetrazole) (VI) between 1940 and 1952. The interaction of 5-aminotetrazole (I) and *p*-acetamidobenzenesulfonyl chloride (IIa) in either an aqueous suspension of calcium carbonate[3] or pyridine[4] yields a solid to which the structure N^1-(5-tetrazolyl)-N^4-acetylsulfanilamide (Va) was assigned. On the other hand, the same reactants, I and IIa, in aqueous sodium carbonate afford still another product, following *special treatment* with dilute sodium hydroxide, to which structure Va was also assigned.[5] These observa-

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(2) Research Fellow.

(3) G. Tappi and C. Migliardi, *Arch. sci. biol. Italy*, **27**, 164 (1941); *C. A.*, **36**, 1023 (1942).

(4) K. A. Jensen and O. Rosenlund Hansen, *Dansk. Tids. Farm.*, **15**, 229 (1941); *Chem. Zentr.*, **113** (I), 2528 (1942).

(5) H. Veldstra and P. W. Wiardi, *Rec. trav. chim.*, **61**, 627 (1942).