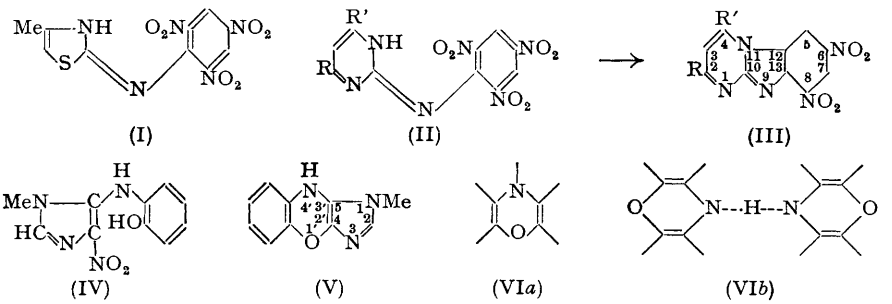
141. *New Syntheses of Heterocyclic Compounds. Part XVI.* Some Further Observations on Ring Closures involving Loss of Nitrous Acid.*

By S. S. Berg and V. Petrow.

Study of the picryl derivatives of 2-amino-4-methylthiazole, 8-amino-1 : 2 : 3 : 4-tetrahydrocarbazole, 1-aminocarbazole, 2-amino-, 2-amino-6-methyl-, and 2 : 4-diamino-6-methyl-pyrimidine has revealed that only those derived from 2-aminopyrimidine undergo ring closure by loss of nitrous acid. *Inter alia* it was observed that reaction of 2 : 4 : 6-trinitroanisole with 2-aminopyridine, 2-aminothiazole, and 2-aminopyrimidine, in the presence of fused sodium acetate, leads to formation of the corresponding 2-*N*-methyl-*N*-picrylamino-derivatives.

Removal of nitrous acid from 5-*o*-hydroxyanilino-1-methyl-4-nitroglyoxaline (IV) furnished a blue derivative of (V) for which the azyl (VI*a*) or azhydrin (VI*b*) structure is proposed.

The facile synthesis of dinitrophenoxazine from picryl chloride and *o*-aminophenol in the presence of alkali (Turpin, *J.*, 1891, 722) has formed the basis of many preparations of heterocyclic compounds of various types. By this reaction, or modifications thereof



(I) (II) (III) (IV) (V) (VI*a*) (VI*b*)

phenothiazines (Kehrmann, *Ber.*, 1899, **32**, 2603), phenazines (Kehrmann and Messinger, *Ber.*, 1893, **26**, 2372; Leemann and Grandmougin, *Ber.*, 1908, **41**, 1308), phenoxadiazines (Plazek, *Rocz. Chem.*, 1936, **16**, 504; Petrow and Rewald, *J.*, 1945, 313), phenothiadiazines (*idem*, *J.*, 1946, 588), diazafluorenes (Morgan and Stewart, *Chem. and Ind.*, 1937, 670), and triazafluorenes (Ochiai and Yanai, *J. Chem. Soc., Japan*, 1940, **60**, 192; Petrow and Saper, *J.*, 1946, 588) have been prepared, in many cases in extremely good yield. The extension of the reaction to such compounds as aminothiazole and aminocarbazole forms the subject of the present communication.

Attempts to condense picryl chloride with 2-aminothiazole proved unsuccessful. 2-Amino-4-methylthiazole, in contrast, readily gave 2 : 3-dihydro-4-methyl-2-picryliminothiazole (I), but the ring closure of this compound could, unfortunately, not be effected.

Ochiai and Yanai (*loc. cit.*) had described the condensation of picryl chloride with 2-amino-, 2-amino-6-methyl-, and 2 : 4-diamino-6-methyl-pyrimidine, and the cyclisation of the resulting picryl derivatives (II) to the corresponding 6 : 8-dinitro-1 : 9 : 11-triaza-

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fluorenes (III). In our hands, however, the high yields claimed by the Japanese authors for the cyclisation could not be reached, in spite of much systematic study of the reaction conditions. Whilst, therefore, the reduction of 6 : 8-dinitro-, 2-methyl-6 : 8-dinitro-, and 4-acetamido-2-methyl-6 : 8-dinitro-1 : 9 : 11-triazafluorene to the corresponding 6 : 8-diamino-derivatives was successfully accomplished, further extension of the work was not undertaken. *Inter alia*, the observation was made that whereas reaction of 2 : 4 : 6-trinitroanisole (cf. Messlin and Bau, *Helv. Chim. Acta*, 1919, **2**, 295) with 2-aminopyrimidine in methanol leads to 2-aminopyrimidine picrate, reaction in the presence of fused sodium acetate gives 2-*N*-methylpicrylaminopyrimidine. The new reaction appears to possess some general character, as both 2-aminothiazole and 2-aminopyridine behave in the same way, giving 2-*N*-methylpicrylaminothiazole and 2-*N*-methylpicrylaminopyridine, respectively. The structure of the latter product was confirmed by direct comparison with authentic material (Morgan and Stewart, *J.*, 1938, 1298). Ethyl picrate behaved in the same way, yielding 2-*N*-ethylpicrylaminopyridine with 2-aminopyridine. 2 : 4 : 6-Trinitrodiphenyl ether similarly gave 2-*N*-phenylpicrylaminopyridine, though in poor yield.

8-Picrylamino-1 : 2 : 3 : 4-tetrahydrocarbazole and 1-picrylaminocarbazole were readily prepared by reaction of the corresponding bases with picryl chloride in benzene solution in the presence of fused sodium acetate, but could not be cyclised under a variety of experimental conditions. The result is particularly surprising in the latter case, since it bears a close resemblance to that of 2-picrylaminodiphenylamine, cyclisation of which proceeds with great facility (Kehrmann and Messinger, *loc. cit.*).

Some interesting results were obtained during experiments on the preparation of benzoxazinoglyoxaline. 5-Chloro-1-methyl-4-nitroglyoxaline (Sarason and Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713) condensed smoothly with *o*-aminophenol in ethanol in the presence of fused sodium acetate and potassium iodide, to give 1-methyl-4-nitro-5-*o*-hydroxyanilinoglyoxaline (IV) in *ca.* 50% yield. Ring closure of this compound presented initial difficulty. It was ultimately found that ethanolic diethylamine at 120° led to a low yield of a brilliant blue crystalline compound of empirical formula *ca.* $C_{10}H_7ON_3$. Formulation of this product as 1-methylbenzoxazino(2′ : 3′-4 : 5)glyoxaline (V), though supported by analytical data, is hardly feasible in view of the intense blue colour of the compound. At the same time, the structural characteristics of (V) impose restrictions on the existence of quinonoid forms. It is, therefore, suggested that this product be assigned the free-radical azyl structure (VI*a*) or the " azhydrin " structure (VI*b*). Of these, the latter is preferred in view of the marked insolubility of the compound in the usual solvents.

The formation of blue azyl and azhydrin structures has previously been recorded in the dihydrophenazine series, to which (V) bears a formal resemblance. Thus McIlwain (*J.*, 1937, 1704) has shown that 3-cyano-5 : 10-dihydro-5-methylphenazine undergoes ready oxidation to the stable blue free radical 2-cyano-5 : 10-dihydro-10-methylphenaz-5-yl. Again, Clemo and McIlwain (*J.*, 1934, 1991; 1935, 738) have found that admixture of phenazine and dihydrophenazine in equimolar amounts leads to the formation of a crystalline blue " phenazhydrin " which contains the system of hydrogen bonds shown in (VI*b*). The formulation of the blue product in this manner is further supported by the observation that reduction with zinc dust in concentrated sulphuric acid leads to a pink compound which is presumably a reduced form. Its isolation and characteristics have not, however, proved possible, in view of the extreme facility with which it reverts to the blue product in the presence of traces of air.

Experimental

M. p.s are uncorrected. Microanalyses are by Mr. S. Bance, B.Sc., A.R.I.C.

Reaction of Picryl Chloride and 2-Aminothiazole.—Picryl chloride (2·5 g.) was added to 2-aminothiazole (2·0 g.) in dry benzene (30 ml.), and the solution heated under reflux for 5 hours. Addition of light petroleum (30 ml.; b. p. 40—60°) to the cooled solution leads to the separation of a *complex* (2·3 g.), m. p. 80—110°, of 2-aminothiazole picryl chloride (Found : N, 19·6; Cl, 9·7. $C_3H_4N_2S,C_6H_2O_6N_3Cl$ requires N, 20·1; Cl, 10·2%).

2 : 3-*Dihydro*-4-*methyl*-2-*picryliminothiazole* (I), prepared by treating a boiling solution of 2-amino-4-methylthiazole (10 g.) in toluene (100 ml.) with picryl chloride (11 g.) in toluene

(100 ml.) and refluxing the whole for 3 hours, formed crimson prisms (10·2 g.), m. p. 184—185°, from benzene (Found : N, 21·6; S, 10·1. $C_{10}H_7O_6N_5S$ requires N, 21·5; S, 9·8%). Attempts at ring closure included treatment with potassium hydroxide–methanol under reflux, phenol–nitrobenzene under reflux, redistilled dimethylaniline at 200°, and sublimation at 170—175°/0·03 mm.

6 : 8-*Diamino*-1 : 9 : 11-*triazafluorene*.—6 : 8-Dinitro-1 : 9 : 11-triazafluorene (500 mg.) in warm methanol (25 ml.) was reduced catalytically at atmospheric pressure with Adams's platinum oxide catalyst (100 mg.). Reduction was complete in 1 hour, the colour of the solution changing to green. 6 : 8-*Diamino*-1 : 9 : 11-*triazafluorene*, isolated in the usual way, formed green prisms (200 mg.), m. p. >300° (Found : C, 60·0; H, 4·3; N, 35·4. $C_{10}H_9N_5$ requires C, 60·3; H, 4·5; N, 35·2%).

6 : 8-*Diamino*-2-*methyl*-1 : 9 : 11-*triazafluorene dihydrochloride*, prepared by reduction of the corresponding dinitro-compound (400 mg.) in warm methanol (20 ml.) containing dilute hydrochloric acid (2 ml.) at 35—45° in the presence of Adams's catalyst (100 mg.) for 3 hours, formed pale yellow prisms (150 mg.), m. p. >300°, from 3N-hydrochloric acid (Found : N. 24·6; Cl, 24·3. $C_{11}H_{11}N_5$,2HCl requires N, 24·6; Cl, 24·8%).

4 : 6 : 8-*Triamino*-2-*methyl*-1 : 9 : 11-*triazafluorene trihydrochloride*, prepared by reduction of the acetamido-dinitro-compound (8 g.) in warm methanol (2500 ml.) over Adams's catalyst (1 g.) for 1 hour, formed pink prisms (3·2 g.), m. p. >300°, from dilute hydrochloric acid (Found : N, 25·1; Cl, 31·2. $C_{11}H_{12}N_6$,3HCl requires N, 25·0; Cl, 31·6%).

Attempts to Condense Bromo-2 : 4-*dinitrobenzene with* 2-*Amino*-4-*methylpyridine*.—(*a*) Reaction was not observed when 2-amino-4-methylpyridine (1 g.), 1-bromo-2 : 4-dinitrobenzene (2·5 g.), fused sodium acetate, and anhydrous toluene (20 ml.) were heated under reflux for 5 hours.

(*b*) 2-Amino-4-methylpyrimidine (2 g.) and 1-bromo-2 : 4-dinitrobenzene (12 g.) failed to condense at 120—125° during 3 hours, but reacted explosively with total charring when the temperature was raised to 150°.

(*c*) Condensation could not be effected by heating the components under reflux in *cyclo*hexanol in the presence of a trace of copper bronze for 5 hours.

Condensation Reactions employing 2 : 4 : 6-*Trinitroanisole*.—(*a*) Reaction of 2 : 4 : 6-trinitroanisole (2·5 g.) with 2-aminopyrimidine (1 g.) in dry methanol (15 ml.) under reflux for 45 minutes produced 2-aminopyrimidine picrate (2·7 g.), m. p. 234—235°, alone or in admixture with an authentic specimen.

(*b*) 2-N-*Methylpicrylaminopyrimidine* (0·6 g.), yellow prisms or rhombs (from acetic acid or benzene), m. p. 225—226° (Found : C, 41·1; H, 2·75; N, 26·2. $C_{11}H_8O_6N_6$ requires C, 41·2; H, 2·5; N, 26·2%), was obtained by heating trinitroanisole (2·4 g.), 2-aminopyrimidine (0·95 g.), fused sodium acetate (3 g.), and dry methanol (40 ml.) under reflux for 5 hours.

(*c*) 2-N-*Methylpicrylaminothiazole* (700 mg.), similarly prepared from 2-aminothiazole (1·0 g.), formed blood-red rhombs, m. p. 206—208°, from dry benzene (Found : C. 36·9; H, 2·5; N, 21·6; S, 10·2. $C_{10}H_7O_6N_5S$ requires C, 36·9; H, 2·2; N, 21·5; S, 10·2%).

(*d*) 2-*N*-Methylpicrylaminopyridine formed red prisms, m. p. 240—242°, from acetic acid (Found : C, 45·2; H, 2·6; N, 21·7. Calc. for $C_{12}H_9O_6N_5$: C, 45·1; H, 2·8; N, 21·9%), not depressed on admixture with an authentic specimen (Morgan and Stewart, *loc. cit.*).

(*e*) Reaction of trinitroanisole (12 g.) with 2-picrylaminopyridine (1·5 g.) and fused sodium acetate (1·5 g.) in dry methanol (20 ml.) for 5 hours under reflux gave the *N*-methyl derivative (200 mg.), m. p. 242—243°, not depressed on admixture with a sample prepared as under (*d*).

(*f*) *N*-Methylation of carbazole and diphenylamine could not be effected.

2-N-*Ethylpicrylaminopyridine*, similarly prepared from ethyl picrate (2·6 g.) and 2-aminopyridine (950 mg.), formed red rhombs (500 mg.) (from acetic acid), m. p. 234—236° (Found : C, 47·0; H, 3·5; N, 20·9. $C_{13}H_{11}O_6N_5$ requires C, 46·8; H, 3·3; N, 21·0%).

2-N-*Phenylpicrylaminopyridine*, prepared from 2 : 4 : 6-trinitrodiphenyl ether (3·0 g.; Willgerodt, *Ber.*, 1879, **12**, 1277) and 2-aminopyridine (950 mg.), formed red prisms (100 mg.), m. p. 229—231°, from acetic acid (Found : C, 53·7; H, 3·2; N. 18·4. $C_{17}H_{11}O_6N_5$ requires C, 53·5; H, 2·9; N, 18·4%).

1 : 2 : 3 : 4-*Tetrahydro*-8-*picrylaminocarbazole*, prepared by heating 8-amino-1 : 2 : 3 : 4-tetrahydrocarbazole (9·3 g.; Edwards and Plant, *J.*, 1923, 2398), fused sodium acetate (8·0 g.), and anhydrous benzene (100 ml.) for 1 hour, then cooling the solution and adding ligroin (200 ml.), formed red prismatic needles (13.5 g.), m. p. 248° (decomp.), from toluene (1 l.) (Found : C, 54·8; H, 4·1; N, 17·4. $C_{18}H_{15}O_6N_5$ requires C, 54·4; H, 3·8; N, 17·6%).

Attempts at ring closure included treatment with quinoline under reflux, dimethylaniline at 200°, and hot alcoholic potassium hydroxide, and sublimation at 205—210°/0·03 mm. Phenol–nitrobenzene at 200° (0·5 hour) gave a brown amorphous *substance* (200 mg.), m. p. >310° (Found : C, 62·5; H, 3·7; N, 15·0. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·0; N, 16·0%).

1-*Picrylaminocarbazole* formed crimson prisms (80%) (from acetic acid), m. p. 274—275° (decomp.) (Found : C, 55·2; H. 2·9; N, 18·1. $C_{18}H_{11}O_6N_5$ requires C, 55·0; H, 2·8; N, 17·8%). When phenol–nitrobenzene was used to effect ring closure, a red-brown amorphous *substance* was obtained, having m. p. >300° (Found : C, 64·1; H, 2·7; N, 15·3. $C_{18}H_{10}O_4N_4$ requires C, 62·4; H, 2·9; N, 16·2%).

1-*Methyl*-4-*nitro*-5-o-*hydroxyanilinoglyoxaline* (IV).—5-Chloro-1-methyl-4-nitroglyoxaline (8·0 g.), *o*-aminophenol (5·0 g.), fused sodium acetate (5·0 g.), potassium iodide (1 crystal), and ethanol (100 ml.) were heated under reflux for 24 hours. After cooling to 5° the solids were collected and crystallised from ethanol to give 1-*methyl*-4-*nitro*-5-o-*hydroxyanilinoglyoxaline*, yellow needles (6·0 g.), m. p. 222—224° (decomp.) (Found : C, 51·1; H, 4·4; N, 24·1. $C_{10}H_{10}O_3N_4$ requires C, 51·3; H, 4·3; N, 23·9%). The compound dissolved in sodium hydroxide to give a red solution.

Ring closure was effected by heating the foregoing compound (5·0 g.) in ethanol (400 ml.) and diethylamine (40 ml.) in a sealed tube at 120° for 16 hours. Blue needles (1·1 g.) were collected. The *substance* was recrystallised from amyl alcohol (1·5 l.), to give blue needles, m. p. >310° (Found : C, 63·8; H. 4·1; 3·8; N, 21·9. $C_{10}H_8ON_3$ requires C, 64·5; H, 4·3; N, 22·5. $C_{10}H_7ON_3$ requires C, 64·8; H, 3·8; N, 22·7%). The compound is slightly soluble in dioxan and in concentrated sulphuric acid, to give intense blue solutions. The absorption spectrum in sulphuric acid and dioxan were kindly determined for us by Dr. H. Campbell (see table for the approximate figures). Considerable changes occurred when the sulphuric acid solution was kept, with marked intensification of the spectrum.

Conc. H_2SO_4 solution [4×10^{-3} g. per litre]		Dioxan solution [concn. unknown]
$\lambda_{max.}$	$E^{1\%}_{1\ cm.}$	$\lambda_{max.}$
260	300	—
380	300	320
480	230	[480] *
510	420	500
550	480	540

* Submerged maximum.

Reduction. The blue compound (4·0 g.) in concentrated sulphuric acid (200 ml.) was treated at 10—20° with zinc dust (4·0 g.). As the reduction proceeded the deep violet colour faded and, after an hour, the pale red suspension was filtered and the filtrate added to oxygen-free water (5 l.). The pink solution was treated with barium hydroxide solution at 15—30° in an atmosphere of hydrogen to precipitate sulphate, and the pink filtrate concentrated *in vacuo* to 100 ml. in a stream of hydrogen. The pink *substance* thus obtained had m. p. 250—255° (Found : N, 22·1; 22·0. $C_{10}H_7ON_3$ requires N, 22·7%), but could not be recrystallised owing to extremely rapid oxidation to the blue compound.

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