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REACTION OF DEHYDRO-D-ERYTHORBIC ACID AND ITS ARYL ANALOGS WITH *ortho*-DIAMINES*

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ABSTRACT

Condensation of 3-(D-*erythro*-2,3,4-trihydroxy-1-oxobutyl)-2-quinoxalinone and its 6-chloro derivative (obtained by the reaction of D-*erythro*-2,3-hexodiulosono-1,4-lactone with *ortho*-diamines) with aryl- or aroyl-hydrazines gave 3-[1-(phenylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]-2-quinoxalinone (**5**) and relatives. Whereas boiling acetic anhydride causes the loss of two molecules of water per molecule of such hydrazones, affording the 3-[5-(acetoxymethyl)-1-arylpyrazol-3-yl]-2-quinoxalinones, identical with those obtained from the L-*threo* isomer, alkali causes the loss of only one molecule, affording the corresponding flavazoles. Periodate oxidation of **5** gave 3-[1-(phenylhydrazono)glyoxal-1-yl]-2-quinoxalinone, which afforded the corresponding mixed bis(hydrazones). A similar sequence of reactions was conducted with the aryl analogs, 4-phenyl-2,3-dioxobutano-1,4-lactone and its *p*-chlorophenyl derivative, whereby the 3-[2-aryl-1-(arylhydrazono)-2-hydroxyethyl]-2-quinoxalinones, were prepared; these were transformed into 3-(α-hydroxybenzyl)-flavazoles that gave monoacetyl derivatives.

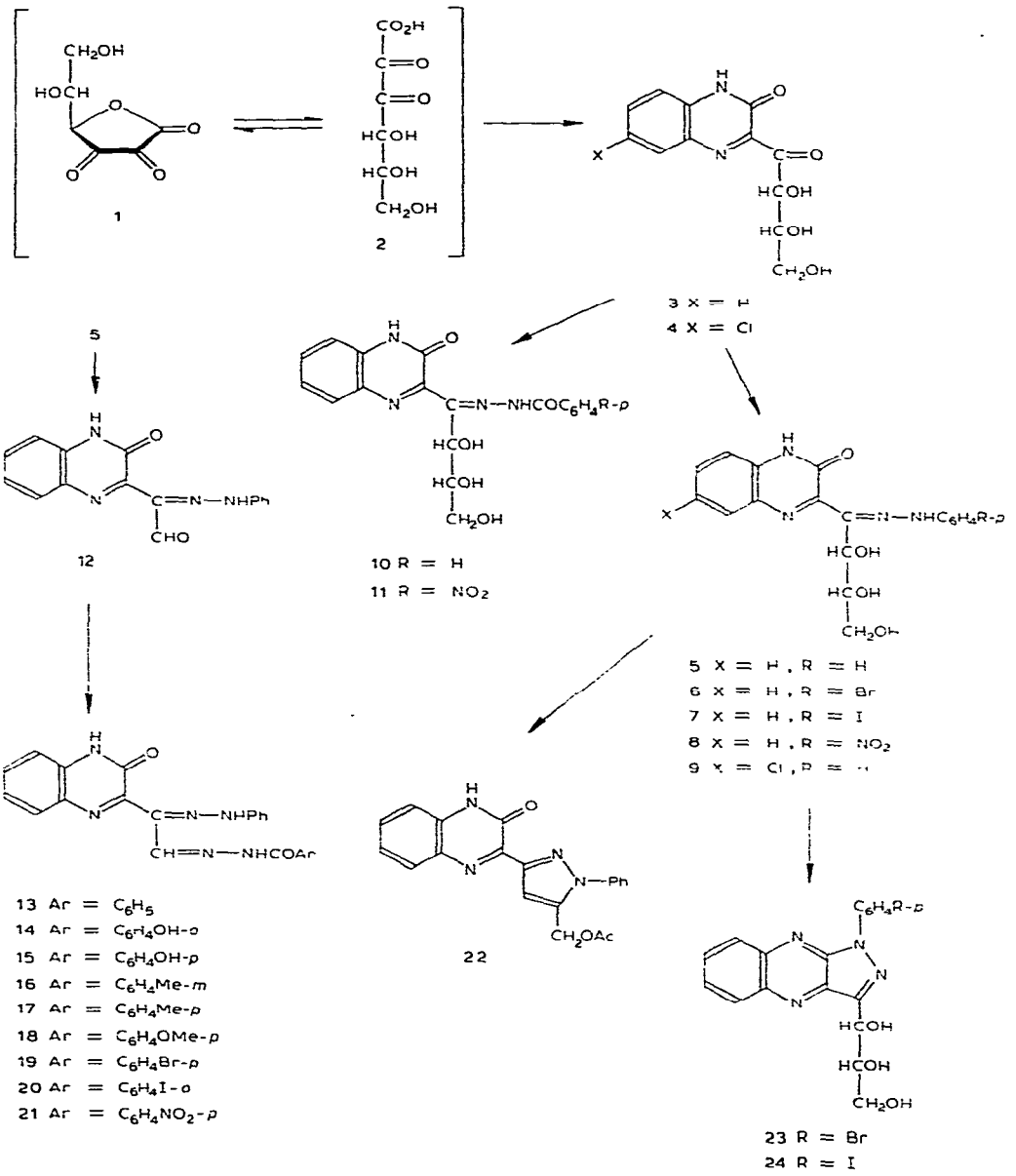
INTRODUCTION

In a program in this laboratory devoted to the synthesis of heterocyclic compounds in the carbohydrate series, hydrazines[1–8] and diamines[9–13] have been used to produce such heterocycles (or functional groups capable of heterocyclization). L-Ascorbic acid is one of these carbohydrate precursors, and one of the approaches entailed the use of its mono- and bis-arylhydrazones, whereas, in the other, *o*-phenylenediamine was employed. In this way, excellent intermediates for the synthesis of various heterocycles[9–13] were prepared. The generality of the latter reactions using various *ortho*-diamines[13] and arylhydrazines[9] was described in previous reports. In the present work, we have extended these reactions to D-erythorbic acid and its phenyl analog, in order to ascertain the effect of changing the hydroxypropyl side-chain to an isomeric analog or replacing it with an aromatic residue.

*Heterocycles from Carbohydrate Precursors, Part XIII. For Part XII, see E. S. H. El Ashry, Y. El Kilany, and F. Singab, *Carbohydr. Res.*, 67 (1978) 415–422.

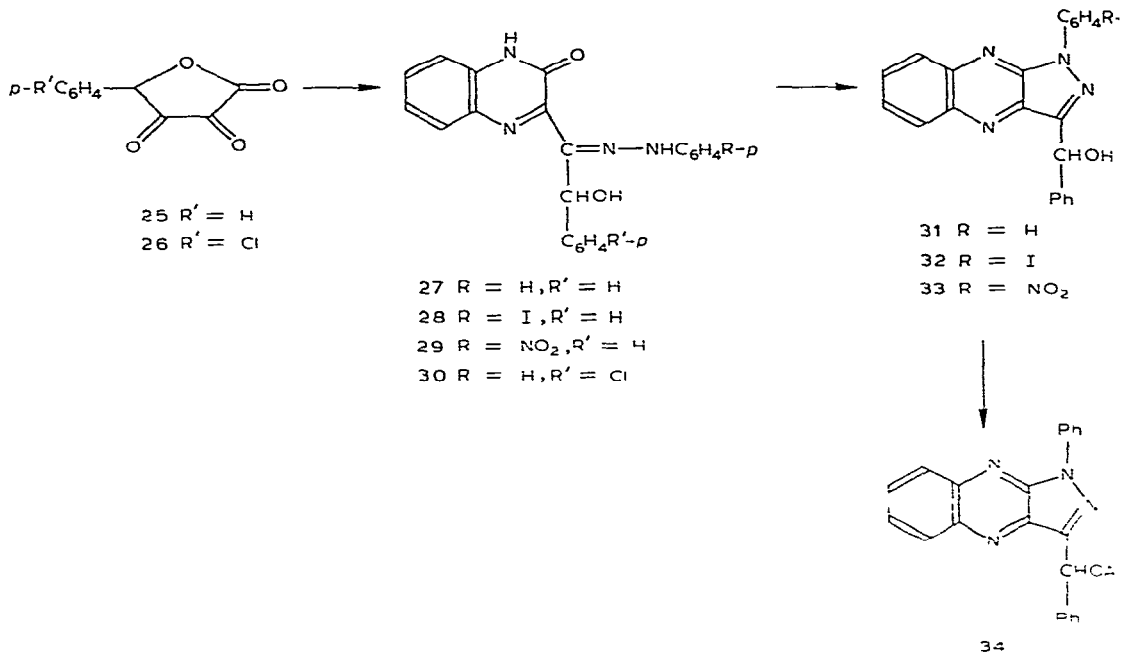
DISCUSSION AND RESULTS

Unimolecular condensation of dehydro-D-erythorbic acid (D-*erythro*-2,3-hexodiulosono-1,4-lactone; **1**) with *o*-phenylenediamine was first studied by Erlbach and Ohle[14], who isolated 3-(D-*erythro*-2,3,4-trihydroxy-1-oxobutyl)-2-quinoxalinone (**3**); this gave the monophenylhydrazone **5**. When D-erythorbic acid was oxidized in aqueous solution with *p*-quinone, and without isolation, was allowed to react with 4-chloro-*o*-phenylenediamine, it afforded a yellow, crystalline product identified as



6-chloro-3-(D-*erythro*-2,3,4-trihydroxy-1-oxobutyl)-2-quinoxalinone (**4**), the structure of which was deduced from its similar method of preparation to that of **3**, as well as by its giving a red product on condensation with phenylhydrazine. The infrared (i.r.) spectra of **3** and **4** showed a band in the carbonyl frequency region at 1675 and 1665 cm^{-1}, respectively, due to CO and OCN groups which overlap. The selectivity of the reaction of 4-chloro-*o*-phenylenediamine with **1**, which is present in equilibrium with acid **2**, could be explained as due to the difference in reactivity of the amino groups, as previously noted for its reaction with the L-*threo* epimer, and this was confirmed by the isolation of only one isomer, which was chromatographically homogeneous. During our studies with the L-*threo* epimer, no attempt was made to isolate such an intermediate, but it was transformed directly, in solution, into the corresponding hydrazone; however, its formation was presumed[9]. The phenylhydrazone of **3** was isolated as a red-orange product, and, similarly, the reaction with *p*-bromo-, *p*-iodo-, and *p*-nitro-phenylhydrazines afforded the corresponding 3-[1-(arylhydrazono)-D-*erythro*-2,3,4-trihydroxybutyl]-2-quinoxalinones (**5–8**), having the characteristic, red-orange color. Similarly, reaction of **4** with phenylhydrazine afforded **9**, the 6-chloro isomer of **5**. When aroylhydrazines were used in the condensation with **3**, the products (**10** and **11**) were yellow. The i.r. spectra of **5–11** showed bands at 1665–1640 cm^{-1} due to the OCN groups, in addition to bands at 1630–1625 cm^{-1} due to C=N. Such characteristic bands appeared in the i.r. spectra of similar compounds prepared from the L-*threo* epimer, which was taken as an argument[9] (in addition to the results of periodate oxidation[10], and mass spectrometric[12] studies) for the presence of these groups in the acyclic structures. Periodate oxidation of **5** afforded a product identical with that obtained from the L-*threo* epimer, namely, 3-(1-phenylhydrazono-glyoxal-1-yl)-2-quinoxalinone (**12**), a compound of interest as a glyoxalyl derivative suitable for further use in heterocyclic synthesis. Reaction of **12** with aroylhydrazines gave the corresponding mixed bis(hydrazones) **13–21**.

Boiling the L-*threo* analogs of **5–9** with acetic anhydride had been reported[9] to be an effective method for inducing them to undergo the loss of two molecules of water per molecule, to give pyrazole derivatives. It was of interest to ascertain the effect on such reactions of varying the stereochemistry. Thus, the hydrazone **5** was boiled with acetic anhydride, whereby a colorless product was isolated that was identical with 3-[5-(acetoxymethyl)-1-phenylpyrazol-3-yl]-2-quinoxalinone (**22**) that had been obtained from the L-*threo* analog. Whereas acidic reagents cause the elimination of two molecules of water, involving the sugar residue, alkali causes **6** and **7** to undergo the elimination of only one molecule of water, from the C-2 quinoxalinone ring and the imino proton of the hydrazone residue, to afford the corresponding pyrazoloquinoxalines (flavazoles), **23** and **24**, respectively. Such derivatives could be prepared from D-glucose and D-allose, and their epimers, D-mannose and D-altrose. Flavazoles are important derivatives for the identification of sugars, as well as for use of their mass spectra in studying oligosaccharide sequencing[9,15–18]. The n.m.r. spectra of **24** showed the methylene protons at δ 4.8, H-2 at δ 5.6, and H-1 at δ 6.2, in addition to the aromatic protons as a multiplet in the region δ 7.6–8.5.



Reaction of the phenyl analog, 4-phenyl-2,3-dioxobutano-1,4-lactone (**25**) with *o*-phenylenediamine was studied by Dahn and co-workers[19]. In the present study, the foregoing sequence of reactions used for the D-*erythro* analog was extended to the phenyl and *p*-chlorophenyl analogs of L-ascorbic acid. Thus, 4-phenyl-2,3-dioxobutano-1,4-lactone reacted with *o*-phenylenediamine and arylhydrazines, affording red products identified as 3-[2-aryl-2-hydroxy-1-(phenylhydrazono)-ethyl]-2-quinoxalinone (**27–29**). Similarly, 4-(*p*-chlorophenyl)-2,3-dioxobutano-1,4-lactone (**26**) gave **30**, which is a chloro derivative of **27**. Their i.r. spectra showed the OCN bands at 1660 cm^{-1}. When the hydrazones **27–29** were subjected to the action of alkali, they lost one molecule of water per molecule, affording yellow products formulated as 1-aryl-3-(α-hydroxybenzyl)flavazoles (**31–33**). The presence of the hydroxyl groups in these compounds was confirmed by the acetylation of **31**, whereby 3-(α-acetoxybenzyl)-1-phenylflavazole (**34**) was obtained; its i.r. spectrum showed the presence of an acetyl band (at 1740 cm^{-1}), and that hydroxyl group originated in these compounds on opening of the lactone ring. The n.m.r. spectrum of **31** showed a one-proton singlet, at δ 3.64, of a CH, and a multiplet (aromatic protons) at δ 7.2–7.8.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with a Unicam SP200 spectrometer, and n.m.r. spectra (for solutions in pyridine-d_5), with a Jeol-100

spectrometer, with tetramethylsilane as the standard. Chemical shifts are given on the δ scale. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

3-(D-erythro-*2,3,4-Trihydroxy-1-oxobutyl)-2-quinoxalinone* (**3**). — A solution of D-erythorbic acid (1.8 g) in water (15 mL) was stirred with benzoquinone (1.08 g) for 3 h at 20°, and the mixture was then treated with *o*-phenylenediamine (1.08 g), whereby the product separated out within 24 h. It was filtered off, washed with ethanol, and dried; m.p. 124° (lit.[14] 125°); ν_{max}^{Nujol} 3400 (OH) and 1675 cm^{-1} (CO and OCN).

6-Chloro-3-(D-erythro-*2,3,4-trihydroxy-1-oxobutyl)-2-quinoxalinone* (**4**). — A solution of D-erythorbic acid (1.8 g) in water (15 mL) was stirred with benzoquinone (1.08 g) for 3 h at 20°, then treated with 4-chloro-*o*-phenylenediamine (1.4 g), and kept overnight at room temperature, whereby the product separated out. It was filtered off, washed with ethanol, and dried (yield 62%). The product was recrystallized from ethanol, giving pale-yellow needles, m.p. 165–167°; ν_{max}^{Nujol} 3400 (OH), 3250 (NH), and 1665 cm^{-1} (CO and OCN).

Anal. Calc. for $C_{12}H_{11}ClN_2O_5$: C, 48.3; H, 3.7; Cl, 11.9; N, 9.4. Found: C, 48.5; H, 3.6; Cl, 11.9; N, 9.2.

*3-[1-(Arylhydrazono)-*D-erythro-*2,3,4-trihydroxybutyl]-2-quinoxalinones* (**5–8**). — A hot solution of compound **3** (0.01 mol) in ethanol (10 mL) was treated with the respective arylhydrazine (0.01 mol), and the mixture was left to cool, whereby the respective hydrazone separated out. They were recrystallized from ethanol in red-orange needles (see Table I).

6-Chloro-3-[D-erythro-*2,3,4-trihydroxy-1-(phenylhydrazono)butyl]-2-quinoxalinone* (**9**). — A solution of compound **4** (0.2 g) in ethanol (10 mL) was treated, while hot, with phenylhydrazine (0.1 mL), and the mixture was left to cool, whereby the hydrazone separated out. It was filtered off, washed, and recrystallized from ethanol, giving orange needles, m.p. 180–182°; ν_{max}^{Nujol} 3445 (OH) and 1665 cm^{-1} (OCN).

Anal. Calc. for $C_{18}H_{17}ClN_4O_4$: C, 55.6; H, 4.4; Cl, 9.1; N, 13.8. Found: C, 55.8; H, 4.0; Cl, 9.0; N, 13.5.

*3-1-(Aroylhydrazono)-*D[-erythro-*2,3,4-trihydroxybutyl]-2-quinoxalinones* (**10, 11**). — A solution of compound **3** (0.01 mol) in ethanol (10 mL) was treated, while hot, with the respective aroylhydrazine (0.01 mol), and the reaction mixture was left to cool, whereupon the product that had separated out was filtered off, and washed with ethanol. It was recrystallized from ethanol, to give yellow needles (see Table II).

3-[1-(Phenylhydrazono)glyoxal-1-yl]-2-quinoxalinone (**12**). — To a stirred solution of sodium metaperiodate (0.3 g) in distilled water (10 mL) was added compound **5** (0.2 g), and the mixture was kept overnight in the dark at room temperature. The suspension was filtered, and the solid product was recrystallized from 1-butanol, giving orange needles, m.p. 242° (lit.[20] m.p. 244°).

3-[2-(Aroylhydrazono)-1-(phenylhydrazono)glyoxal-1-yl]-2-quinoxalinones (**13–21**). — A solution of compound **12** (2 mmol) in 1-butanol (10 mL) was treated, while

TABLE I

MICROANALYTICAL AND SPECTRAL DATA FOR 3-[1-(ARYLHYDRAZONO)-D-*erythro*-2,3,4-TRIHYDROXYBUTYL]-2-QUINOXALINONES (6–8)

Compound No.	*R*	*Yield* (%)	*M.p.* (*degrees*)	*Molecular formula*	*Calculated* (%)				*Found* (%)				ν_{max}^{Nujol} (cm^{-1})
					C	*H*	*X*	*N*	*C*	*H*	*X*	*N*	
5	H	93	205[a]										1660, 3350
6	Br	87	214	$C_{18}H_{17}BrN_4O_4$	49.9	4.0	18.4	12.9	49.6	4.3	18.0	13.1	1645, 3400
7	I	90	227	$C_{18}H_{17}IN_4O_4$	45.0	3.6	26.4	11.7	45.2	3.4	26.1	12.0	1665, 3350
8	NO_2	83	238	$C_{18}H_{17}N_5O_6$	54.1	4.2		17.5	54.1	4.5		17.8	1645, 3350

[a]Lit. m.p. 203°.

TABLE II

MICROANALYTICAL AND SPECTRAL DATA FOR 3-[1-(AROYLHYDRAZONO)-D-*erythro*-2,3,4-TRIHYDROXYBUTYL]-2-QUINOXALINONES (10 AND 11)

Compound No.	*R*	*Yield* (%)	*M.p.* (*degrees*)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
					C	*H*	*N*	*C*	*H*	*N*	
10	H	86	135	$C_{19}H_{18}N_4O_5$	59.7	4.7	14.7	59.5	4.7	14.8	1640, 1660
11	NO_2	89	179	$C_{19}H_{17}N_5O_7$	53.4	4.0	16.4	53.7	4.3	16.0	1645, 1665, 1675

TABLE III

MICROANALYTICAL AND SPECTRAL DATA FOR 3-[2-(AROYLHYDRAZONO)-1-(PHENYLHYDRAZONO)GLYOXAL-1-YL]-2-QUINOXALINONES (13–21)

Compound No.	*Ar*	*Yield* (%)	*M.p.* (*degrees*)	*Molecular formula*	*Calculated* (%)				*Found* (%)				ν_{max}^{Nujol} (cm^{-1})
					C	*H*	*X*	*N*	*C*	*H*	*X*	*N*	
13	Ph	92	273	$C_{23}H_{18}N_6O_2$	67.3	4.4		20.5	67.5	4.5		20.7	1645, 1660
14	C_6H_4OH-*o*	90	268	$C_{23}H_{18}N_6O_3$	64.8	4.3		19.7	64.5	4.3		19.5	1655
15	C_6H_4OH-*p*	89	292	$C_{23}H_{18}N_6O_3$	64.8	4.3		19.7	64.7	4.2		19.8	1645, 1675
16	C_6H_4Me-*m*	95	252	$C_{24}H_{20}N_6O_2$	67.9	4.7		19.8	67.6	4.7		19.6	1650, 1660
17	C_6H_4Me-*p*	97	266	$C_{24}H_{20}N_6O_2$	67.9	4.7		19.8	68.2	4.6		20.1	1645, 1660 (sh)
18	C_6H_4OMe-*p*	92	255	$C_{24}H_{20}N_6O_3$	65.4	4.6		19.1	65.2	4.5		19.3	1640, 1665
19	C_6H_4Br-*p*	90	270	$C_{23}H_{17}BrN_6O_2$	56.5	3.5	16.3	17.1	56.2	3.5	16.2	16.8	1640, 1655
20	C_6H_4I-*o*	87	264	$C_{23}H_{17}IN_6O_2$	51.5	3.2	23.7	15.7	51.6	3.5	23.6	15.7	1645, 1655
21	$C_6H_4NO_2$-*p*	96	262	$C_{23}H_{17}N_7O_4$	60.7	3.8		21.5	60.5	4.0		21.4	1645, 1665

TABLE IV

MICROANALYTICAL AND SPECTRAL DATA FOR 1-ARYL-3-(D-*erythro*-GLYCEROL-1-YL)FLAVAZOLES (23 AND 24)

Compound No.	*R*	*Yield* (%)	*M.p.* (*degrees*)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
					C	*H*	*N*	*C*	*H*	*N*	
23	Br	82	195	$C_{18}H_{15}BrN_4O_3$	52.1	3.6	13.5	52.0	3.4	13.2	3328
24	I	76	240	$C_{18}H_{15}IN_4O_3$	46.8	3.3	12.1	46.9	3.1	12.0	3330

TABLE V

MICROANALYTICAL AND SPECTRAL DATA FOR 3-[2-ARYL-1-(ARYLHYDRAZONO)-2-HYDROXYETHYL]-2-QUINOXALINONES (27–30)

Compound No.	*R*	*R'*	*Yield* (%)	*M.p.* (*degrees*)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
						C	*H*	*N*	*C*	*H*	*N*	
27	H	H	90	195	$C_{22}H_{18}N_4O_2$	71.3	4.9	15.1	71.5	4.9	15.3	1660
28	I	H	95	223	$C_{22}H_{17}IN_4O_2$	55.2	3.6	11.7	55.5	3.8	11.7	1665
29	NO_2	H	97	235	$C_{22}H_{17}N_5O_4$	63.6	4.1	16.9	63.8	4.2	17.1	1660
30	H	Cl	89	230	$C_{22}H_{17}ClN_4O_2$	65.3	4.2	13.8	65.6	4.6	14.2	1660

TABLE VI

MICROANALYTICAL AND SPECTRAL DATA FOR 1-ARYL-3-(α-HYDROXYBENZYL)FLAVAZOLES (31–33)

Compound No.	*R*	*Yield* (%)	*M.p.* (*degrees*)	*Molecular formula*	*Calculated* (%)			*Found* (%)			ν_{max}^{Nujol} (cm^{-1})
					C	*H*	*N*	*C*	*H*	*N*	
31	H	82	177–179	$C_{22}H_{16}N_4O$	75.0	4.6	16.0	57.2	4.8	16.5	3300
32	I	89	230–232	$C_{22}H_{15}IN_4O$	54.2	3.1	13.3	54.2	3.5	13.0	3250
33	NO_2	75	207–209	$C_{22}H_{15}N_5O_3$	66.5	3.8	17.6	66.8	3.8	17.9	3220

hot, with the respective aroylhydrazine (2 mmol) in ethanol (3 mL), whereby the mixed bis(hydrazones) readily separated out in yellow needles (see Table III).

3-[5-(Acetoxymethyl)-1-phenylpyrazol-3-yl]-2-quinoxalinone (**22**). — A solution of compound **5** (0.5 g) in acetic anhydride (5 mL) was boiled under reflux for 15 min, and the mixture was cooled, and poured onto crushed ice. The product was recrystallized from ethanol, giving colorless needles, m.p. 249–250° (lit.[21] m.p. 244°; lit.[9] m.p. 249–250°).

1-Aryl-3-(D-erythro-*glycerol-1-yl)flavazoles* (**23**, **24**). — A suspension of compound **6** or **7** (5 mmol) in 0.01M sodium hydroxide (60 mL), 1-butanol (6 mL), and methanol (10 mL) was boiled under reflux for 2 h, and then cooled, whereupon the respective flavazole derivative separated out. They were recrystallized from ethanol–1,4-dioxane, giving yellow needles (see Table IV).

3-[2-Aryl-1-(arylhydrazono)-2-hydroxyethyl]-2-quinoxalinones (**27–30**). — A solution of compound **25** or **26** (0.01 mole) in methanol (10 mL) was treated with a solution of *o*-phenylenediamine (0.01 mol) in a mixture of methanol (10 mL) and water (60 mL), the mixture was boiled for 2 min, and the respective arylhydrazine (0.01 mol) was then added. The mixture was boiled under reflux for 10 min, and the respective product that separated was recrystallized from ethanol, giving red needles (see Table V).

1-Aryl-3-(α-hydroxybenzyl)flavazoles (**31–33**). — A suspension of each of compounds **27–29** (3 mmol) in 0.01M sodium hydroxide solution (60 mL) and 1-butanol (2 mL) was boiled under reflux for 1 h. The mixture was then filtered, and the yellow product washed with water, and recrystallized from ethanol (see Table VI).

3-(α-Acetoxybenzyl)-1-phenylflavazole (**34**). — A solution of compound **31** (0.1 g) in dry pyridine (3 mL) was treated with acetic anhydride (1 mL), and the mixture was kept overnight at room temperature. It was then poured onto crushed ice, and the acetate that separated was filtered off, and washed with water. It was recrystallized from chloroform–ethanol, giving orange needles, m.p. 192°; ν_{max}^{Nujol} 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{24}H_{18}N_4O_2$: C, 73.1; H, 5.2; N, 14.6. Found: C, 73.5; H, 4.7; N, 14.3.

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