3. S. P. Épshtein, A. F. Rukasov, V. P. Tashchi, T. G. Simonova, and Yu. G. Putsykin, Khim. Geterotsikl. Soedin., No. 9, 1240 (1983).

FRIES REACTION AND DAKIN REARRANGEMENT IN BENZO-2,1,3-THIADIAZOLES

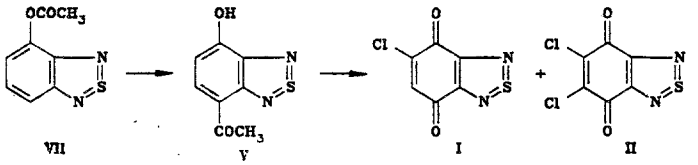
I. A. Belen'kaya, G. P. Krokhina, S. A. Sirik, and S. A. Andronati

UDC 547.567.3'572.1'655.6'794.3

The Fries rearrangement of 4- and 5-acetoxybenzo-2,1,3-thiadiazoles has given 4-hydroxy-7-acetyl- and 5-hydroxy-4-acetylbenzo-2,1,3-thiadiazoles, which on oxidation afford mixtures of 5-chloro-4,7-dioxo- and 5,6-dichloro-4,7-dioxobenzo-2,1,3-thiadiazole and of 6-chloro-4,5-dioxo- and 6,7-dichloro-4,5-dioxobenzo-2,1,3-thiadiazole. Reaction of 6,7-dichloro-4,5-dioxobenzo-2,1,3-thiadizole with ortho-phenylenediamine gives 4,5-dichloro-2,1,3-thiadiazolo[4,5-a]phenazine.

5-Chloro-4,7-dioxo- and 5,6-dichloro-4,7-dioxobenzo-2,1,3-thiadiazole (I, II) are known to possess high antiviral activity in ovo [1]. It is noteworthy that 4-hydroxy- and 4-aminobenzo-2,1,3-thiadiazole (III, IV), which give the quinone (I) on oxidation in the presence of HCl [2, 3], also exhibit antiviral activity [1, 4]. It might be expected that other benzo-2,1,3-thiadiazoles, which undergo oxidation under these conditions to give the chloro-compounds, would be viral inhibitors. To test this theory, 4-hydroxy-7-acetyl- and 5-hydroxy-4-acetylbenzo-2,1,3-thiadiazoles (V, VI) were selected.

The hydroxyketones (V) and (VI) were obtained by the Fries rearrangement of 4- and 5-acetoxybenzo-2,1,3-thiadiazole (VII, VIII). The acetoxy-compounds (VII, VIII) were obtained by reacting 4- and 5-hydroxybenzo-2,1,3-thiadiazole (III, IX) with acetic anhydride.



Oxidation of (V) and (VI) with hydrogen peroxide in alkaline media (the Dakin reaction) as for the oxidation of p-hydroxyacetophenone [5] failed to give the dihydroxy-compounds. Only when the alkali was replaced by concentrated hydrochloric acid and the reaction was carried out in acetonitrile were mixtures of quinones obtained, these being in the first case 5-chloro,4-7-dioxo- and 5,6-dichloro-4,7-dioxobenzo- (I, II), and in the second case 6-chloro-4,5-dioxo- and 6,7-dichloro-4,5-dioxobenzo-2,1,3-thiadiazole (X, XI). Treatment of a mixture of (I) and (II) with chlorine in acetic acid in the presence of iodine gave the quinone (II), identical with that described in [2]. Prolonged chlorination of the mixture of quinones (X) and (XI) failed to give the pure dichloro-compound (XI), but its concentration in the mixture was increased to such an extent that it was possible to separate (XI) from (X).

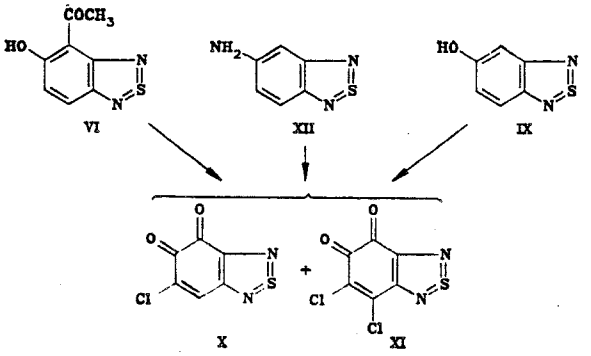
Oxidation of the hydroxy-compound (IX) and 5-aminobenzo-2,1,3-thiadiazole (XII) under conditions similar to those used to oxidize ketone (VI) likewise gave a mixture of quinones (X) and (XI).

The structure of quinone (XI) was confirmed by its IR spectrum, elemental analysis (Table 1), the formation therefrom with o-phenylenediamine of 4,5-dichloro-2,1,3-thiadiazolo[4,5-a]-phenazine (XIII), and the presence of (XI) amongst the chlorination products of 4,5-dioxobenzo-2,1,3-thiadiazole (XIV) [6].

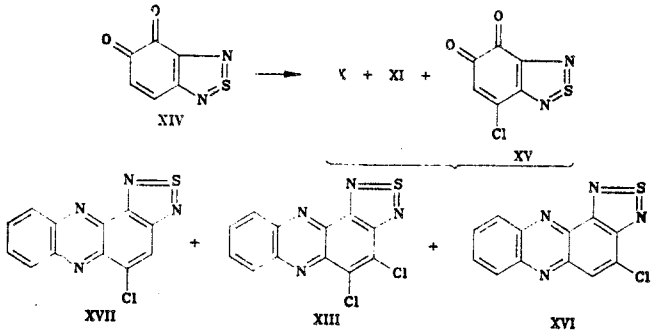
The quinone (X) and 7-chloro-4,5-dioxobenzo-2,1,3-thiadiazole (XV) could not be obtained analytically pure. The position of the chlorine in quinones (X) and (XV) was established from the TLC data for the phenazine (XIII), 4-chloro-2,1,3-thiadiazolo[4,5-a]phenazine (XVI) (obtained as in [7]), a mixture of the phenazine (XIII) and 5-chloro-2,1,3-thiadiazolo[4,5-a]-

A. V. Bogatskii Institute of Physical Chemistry, Academy of Sciences of the Ukrainian SSR, Odessa 270080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1683-1687, December, 1987. Original article submitted July 2, 1986; revision submitted August 17, 1987.

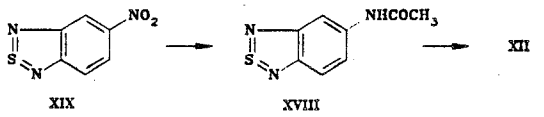
 0009-3122/87/2312-1356$12.50



phenazine (XVII) [obtained from a mixture of quinones (X) and (XI)], and a mixture of phenazines (XIII), (XVI), and (XVII), obtained by reacting o-phenylenediamine with a mixture of quinones (X), (XI), and (XV).



The amine (XII) required for this investigation was obtained by hydrolyzing 5-acetamidobenzo-2,1,3-thiadiazole (XVIII), obtained by reacting 5-nitrobenzo-2,1,3-thiadiazole (XIX) with acetic anhydride, alcohol, and iron.



It has been found that the hydroxyketones (V) and (VI) possess moderate antiviral activity in ovo against A_2 Leningrad influenza virus (protective index 50 and 45.35%, respectively).

In conclusion, it is worthy of note that the oxidation of hydroxyketones with 30% hydrogen peroxide and concentrated hydrochloric acid in acetonitrile to give chlorinated quinones is not restricted to benzo-2,1,3-thiadiazoles. We have found that p-hydroxyacetophenone (XX) and p-hydroxyacetonaphthone (XXI) are oxidized under these conditions to give tetrachloro-1,4-benzoquinone (XXII) and 2,3-dichloro-1,4-naphthoquinone (XXIII).

EXPERIMENTAL

The progress of the reactions and the purity of the products were assessed by TLC on Silufol UV-254 in the systems acetone–chloroform–hexane, 2:1:2 (system A), 1:1:2 (system B), and benzene–acetone–acetic acid, 100:50: 1 (system C). The compounds were visualized in UV on a Chromatoscope-M, the quinones also with iodine vapor. IR spectra were obtained on a Perkin-Elmer 580B spectrophotometer in KBr disks, and mass spectra on a Varian MAT-112 at an ionizing electron energy of 70 eV.

The properties of the ketones, quinones, and acetoxy-compounds obtained here are shown in Table 1.

Hydroxyketones (V) and (VI). To a mixture of 2 g (10.3 mmole) of (VII) or (VIII) and 17 ml of nitrobenzene was added at 65°C 3 g (22.5 mmole) of anhydrous aluminum chloride. After 6 h, the mixture was cooled, 17 ml of alcohol and 68 ml of water added, and the nitrobenzene steam-distilled. The residue (100 ml) was filtered hot, and cooled to give the hydroxyketone (V) or (VI).

TABLE 1, Properties of Ketones, Quinones, and Acetoxy-Compounds Obtained

Compound*	T_{mp}** °C	R_f (system)	IR spectrum, $\nu_{C=O}$ (ν_{C-OH}), cm^{-1}	Mass spectrum, M^+	Found, % Cl (S)	Found, % N	Empirical formula	Calculated, % Cl (S)	Calculated, % N	Yield, %
II	233—235***	0,62 (B)	1705	—	30,3	10,7	$C_6Cl_2N_2O_2S$	30,2	10,9	50 (calculated on ketone V)
V	197—198	0,6 (A)	1650 (3400)	194	(16,2)	13,8	$C_8H_6N_2O_2S$	(16,5)	14,4	50
VI	157—158	0,74 (A)	1620, 1630 (3450)	194	(16,3)	13,9	$C_8H_6N_2O_2S$	(16,5)	14,4	50
VII	53—54	0,86 (A)	—	—	(16,3)	14,3	$C_8H_6N_2O_2S$	(16,5)	14,4	87
VIII	69—70	0,89 (A)	—	—	(16,9)	14,3	$C_8H_6N_2O_2S$	(16,5)	14,4	93
XI	179—181	0,34 (B)	1770, 1780	—	30,0 (13,5)	—	$C_6Cl_2N_2O_2S$	30,2 (13,6)	—	13 (calculated on ketone VI)
XXII	288—289	0,93 (C)	1670	246	57,4	—	$C_6Cl_4O_2$	57,7	—	20
XXIII	192—193	0,86 (C)	—	227	31,3	—	$C_{10}H_4Cl_2O_2$	31,67	—	21

*Compound (II) was crystallized from dichloroethane, (V) and (VI) from water, (VII), (VIII), and (XXIII) from ethanol, (XI) from light petroleum, and (XXII) from benzene.
**According to [8], mp 53-54°C (VII) and 68-69°C (VIII); according to [9], mp 290°C (XXII) and 193°C (XXIII).
***Before fusion in a sealed capillary, (II) darkened and sublimed at 189-190°C, similar to the quinone (II) described in [2].

Acetoxybenzo-2,1,3-thiadiazoles (VII, VIII). A mixture of 6 g (40 mmole) of (III) or (IX), 40 ml (423 mmole) of acetic anhydride, and 0.33 ml (2.35 mmole) of triethylamine was boiled for 20 min, cooled, poured into water, and extracted with chloroform. The chloroform extract was filtered through a fluted filter paper and evaporated. The residue crystallized, giving (VII) or (VIII).

Oxidation of (V, VI, IX, XII, XX, and XXI). Each of these compounds (13.15 mmole) was mixed with 60 ml of acetonitrile and 34 ml of conc. hydrochloric acid, the mixture heated to 50°C, and treated with 66.6 ml of 30% hydrogen peroxide at such a rate that vigorous foaming did not occur. The mixture was boiled for 30 min,* cooled, and poured into ice and water (130 ml), when either a solid (quinones XXII and XXIII), or an oil separated, the latter being extracted with chloroform. After filtration, the chloroform extract was filtered through a fluted filter paper, and the solvent removed to give an oil, in which were detected (TLC) either quinones (I) and (II)† (R_f 0.8 and 0.62, system B), or quinones (X) and (XI) (R_f 0.9 and 0.34, system B).

6,7-Dichloro-4,5-dioxobenzo-2,1,3-thiadiazole (XI). The oil (3 g) obtained by oxidizing (VI), (IX), or (XII) was heated to the boil with 20 ml of light petroleum, filtered through a fluted filter paper, the filtrate cooled, and the solid which separated [2 g of a mixture of quinones (X) and (XI)] filtered off, dried, and dissolved in 16.6 ml of glacial acetic acid. The mixture was treated with 0.77 g of iodine, heated to the boil, and gaseous chlorine passed through the solution for 7 h with continuous heating. The mixture was then cooled and poured onto ice, the solid which separated filtered off, washed with water, dried, suspended (1.2 g) in 5 ml of chloroform, filtered and the solid on the filter washed successively with 5 ml of dichloroethane and 5 ml of light petroleum. This solvent treatment was repeated until the solid remaining on the filter was chromatographically pure (XI).

4,5-Dichloro-2,1,3-thiadiazolo[4,5-a]phenazine (XIII). A solution of 0.5 g of the quinone (XI) (2.1 mmole) in 5 ml of ethanol was mixed with a solution of 0.24 g (2.2 mmole) of

*In the oxidation of (XXI), for one hour.

†A similar mixture of quinones (I) and (II) was obtained by oxidizing the quinone (V) with 30% hydrogen peroxide and conc. hydrochloric acid in acetonitrile in amounts half those given above.

o-phenylenediamine in 6 ml of ethanol, and the mixture kept overnight. The reaction mixture was then diluted with water, and the solid filtered off and dried to give 0.3 g of a solid which was dissolved in 10 ml of alcohol, 3 g of cation-exchanger KU-1 added, the mixture brought to the boil, cooled, and after 2 h filtered and the filtrate evaporated to give 0.1 g (15%) of the phenazine (XIII), mp 224-226°C (darkens and decomposes), R_f 0.63 (system B). Found: Cl 22.7; N 17.8%. $C_8H_4Cl_2N_4S$. Calculated: Cl 23.1; N 18.2%.

Obtained similarly were mixtures of phenazines (XIII) and (XVII) (R_f 0.63 and 0.3, system B; R_f 0.94 and 0.72, system A) and of phenazines (XIII), (XVI), and (XVII) (R_f 0.63, 0.24, and 0.3, system B). These mixtures were not treated with cation-exchanger KU-1.

Chlorination of Quinone (XIV) and a Mixture of Quinones (I) and (II). Quinone (XIV) (0.65 g, 3.9 mmole) or 0.6 g of the oil obtained by oxidation of ketone (V) in 10 ml of acetic acid was treated with 0.52 g (2 mmole) of iodine, and the mixture heated to the boil and saturated with gaseous chlorine for 7 h in the case of (XIV), or for 2 h when the mixture of quinones (I) and (II) was taken. Quinone (II) separated on cooling the reaction mixture. In order to isolate the mixture of quinones (X), (XI), and (XV), the mixture was diluted with water, extracted with chloroform, the extract filtered through a fluted filter paper, and the solvent removed, to give an oily mixture of quinones (X), (XI), and (XV) (R_f 0.9, 0.34, and 0.95, system B).

5-Aminobenzo-2,1,3-thiadiazole (XII). A mixture of 12.4 g (64.2 mmole) of (XVIII), 25.4 ml of conc. HCl, and 68 ml of water was boiled for 20 min. The mixture was then cooled to 20°C, and treated with 365 ml of 10% NaOH to bring the pH to 5-6. The solid was filtered off, washed with water, and dried to give 9.4 g (97%) of (XII), mp 114-116°C (according to [10], mp 117°C), R_f 0.64 (system A).

5-Acetamidobenzo-2,1,3-thiadiazole (XVIII). A mixture of 17.3 g (95.6 mmole) of (XIX), 33.5 g (598.2 mmole) of iron, 83.7 ml (887.9 mmole) of acetic anhydride and 27.9 ml (478.8 mmole) of ethanol was boiled for 30 min. The mixture was then diluted with 120 ml of DMF, heated to 120°C, filtered, the solid on the filter washed with 30 ml of DMF, and the filtrate cooled and diluted with water. The solid which separated was filtered off, washed with water, and dried to give 12.4 g (67%) of (XVIII), mp 186-188°C (according to [10], mp 190°C), R_f 0.58 (system A).

5-Nitrobenzo-2,1,3-thiadiazole (XIX). A mixture of 15 g (98 mmole) of 2-amino-4-nitroaniline, 53.2 ml (739.9 mmole) of thionyl chloride, and 2.8 ml of conc. sulfuric acid was boiled with vigorous stirring for 30 min. The mixture was then cooled, and poured into ice and water. The solid which separated was filtered off, washed with water until neutral, and dried to give 14.6 g (82%) of (XIX), mp 124-126°C (according to [10], mp 127°C), R_f 0.77 (system B).

LITERATURE CITED

1. I. A. Belen'kaya, G. P. Krokhina, V. É. Vignevich, V. P. Lozitskii, O. G. Yasinskaya, and V. V. Ivanova, Khim.-Farm. Zh., No. 1, 46 (1985).
2. I. A. Belen'kaya, G. P. Krokhina, and S. A. Andronati, Khim. Geterotsikl. Soedin., No. 10, 1344 (1982).
3. I. A. Belen'kaya, G. P. Krokhina, S. A. Andronati, K. A. Abramova, and T. D. Panasyuk, Author's Cert. (USSR) No. 1,087,521; Byull. Izobret., No. 15, 86 (1984).
4. I. A. Belen'kaya, N. P. Chizhov, and N. G. Chigareva, Khim.-Farm. Zh., No. 8, 66 (1978).
5. B. A. Kazanskii, I. L. Knunyants, M. M. Shemyakin, and N. N. Mel'nikov (editors), Reactions and Methods of Study of Organic Compounds [in Russian], GONTI, Moscow (1961), Vol. 10, p. 78.
6. I. A. Belen'kaya and G. P. Krokhina, Author's Cert. (USSR), No. 932,801; Byull. Izobret., No. 4, 344 (1983).
7. I. A. Belen'kaya, G. P. Krokhina, and S. A. Andronati, Khim. Geterotsikl. Soedin., No. 6, 850 (1987).
8. V. G. Pesin, I. A. Belen'kaya-Lotsmanenko, and A. M. Khaletskii, Zh. Org. Khim., 34, 3763 (1964).
9. N. N. Mel'nikov, The Chemistry and Technology of Pesticides [in Russian], Khimiya, Moscow (1974), p. 172.
10. L. S. Éfros and R. M. Levit, Zh. Org. Khim., 25, 199 (1955).