to afford XI, 193 mg. (85%), m.p. 138–139°, $[\alpha]^{20}\text{D}$ −31° (*c* 1, $CHCl_3$), $\lambda_{\max}^{\mathrm{CH_3OH}}$ 316 mμ (ϵ 11,000).

Anal. Calcd. for $C_{12}H_{16}O_5S_3$: C, 42.9; H, 4.8; S, 28.6. Found: C, 42.7, H, 4.9; S, 28.2.

1,2-*O*-Isopropylidene-5,6-dithio-3-*O*-(*p*-tolylsulfonyl)-β-L-idofuranose 5,6-Trithiocarbonate (XIII).—To a solution of 200 mg. of IX in 4 ml. of anhydrous pyridine, *p*-toluenesulfonyl chloride (1 g.) was added. The solution after standing at 25° for 3 days was poured into ice–water. The precipitate thus formed was collected by filtration, washed with water, and crystallized from ethanol–water mixture to afford XIII, 285 mg. (94%), m.p. 153–155°, $[\alpha]^{20}\text{D}$ −15° (*c* 1, $CHCl_3$), $\lambda_{\max}^{\mathrm{CH_3OH}}$ 316 mμ (ϵ 13,800).

Anal. Calcd. for $C_{17}H_{20}O_6S_4$: C, 45.6; H, 4.5; S, 28.6. Found: C, 45.7; H, 4.7; S, 28.0.

Lead Tetraacetate Oxidation of IX, XI, XIII, and Ethylene Trithiocarbonate and Isolation of the Corresponding Oxythiocarbonyl Products.—A solution of 1.0 g. of IX in 100 ml. of lead tetraacetate stock solution was allowed to stand at 25° for 10 min. before addition of 300 ml. of stopping solution. Aqueous sodium thiosulfate was then added to react with the free iodine, and the solution was extracted twice with 250-ml. portions of chloroform. The chloroform extract was washed with three 100-ml. portions of water and dried over anhydrous magnesium sulfate. After filtration, the chloroform was evaporated to yield 620 mg. of crude sirup, which partially crystallized from ethanol–water mixture to yield 350 mg. (33%) of 1,2-*O*-isopropylidene-5,6-dithio-β-L-idofuranose oxythiocarbonyl-5,6-trithiocarbonate (X), m.p. 185–187°, $[\alpha]^{20}\text{D}$ +262° (*c* 0.5, $CHCl_3$), $\lambda_{\max}^{\mathrm{CH_3OH}}$ 348 mμ (ϵ 10,600) and 284 (4900).

Anal. Calcd. for $C_{10}H_{14}O_5S_3$: C, 38.7; H, 4.5; S, 31.0; mol. wt., 310. Found: C, 38.7; H, 4.7; S, 31.0; mol. wt., 292 (Rast in camphor).

Similarly, oxidation of 1.0 g. of XI gave 843 mg. of crude amorphous product, which crystallized from a benzene–hexane mixture to yield 500 mg. (48%) of 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-dithio-β-L-idofuranose oxythiocarbonyl-5,6-trithiocarbonate (XIII), m.p. 160–161°, $[\alpha]^{20}\text{D}$ +203° (*c* 0.32, $CHCl_3$), $\lambda_{\max}^{\mathrm{CH_3OH}}$ 347 mμ (ϵ 10,250) and 285 (4400).

Anal. Calcd. for $C_{12}H_{16}O_6S_3$: C, 40.9; H, 4.5; S, 27.2. Found: C, 41.3; H, 4.7; S, 26.8.

The oxidation of 1.0 g. of XIII by a similar procedure gave 920 mg. (89%) of a crude amorphous product, m.p. 82–90°, $[\alpha]^{20}\text{D}$ +16° (*c* 0.5, $CHCl_3$), $\lambda_{\max}^{\mathrm{CH_3OH}}$ 347 mμ (ϵ 10,100) and 282 (5100).

Anal. Calcd. for $C_{17}H_{20}O_7S_4$: C, 44.0; H, 4.3; S, 27.6. Found: C, 44.6; H, 4.7; S, 27.0.

Ethylene trithiocarbonate prepared according to the procedure of Culvenor, Davies, and Pausacker[25] gave m.p. 34–35° (reported 36°), $\lambda_{\max}^{\mathrm{CH_3OH}}$ 316 mμ (ϵ 13,900). The product obtained by oxidation of ethylene trithiocarbonate with lead tetraacetate was isolated. The procedure, similar to that used to isolate X, gave a sirup that crystallized from a benzene–hexane mixture as yellow needles in 30% yield, m.p. 61°, $\lambda_{\max}^{\mathrm{CH_3OH}}$ 347 mμ (ϵ 10,000) and 284 (5100).

Anal. Calcd. for $C_3H_4OS_3$: C, 23.7; H, 2.6; S, 63.2. Found: C, 23.7; H, 2.8; S, 63.4.

Reduction of X by L-Cysteine.—To a solution of 50 mg. of X in 4 ml. of methanol, 200 mg. of L-cysteine hydrochloride monohydrate was added along with 1 ml. of water. Upon standing at 25° for 15 hr. a white precipitate formed which was filtered and dried to yield 29 mg. of L-cystine (identified by comparing its infrared spectrum with an authentic sample). The filtrate was evaporated to dryness and extracted with chloroform; the extract was washed with water and dried over anhydrous magnesium sulfate. The inorganic salt was discarded by filtration, and the clear chloroform solution was evaporated to yield 33 mg. of yellow crystals identified as IX by infrared, melting point, and mixture melting point with an authentic sample.

Reduction of Ethylene Oxythiocarbonyltrithiocarbonate.—The reduction was followed spectrometrically since the oxidized product showed absorption maxima at 347 and 285 mμ, but the absorption maximum of the parent compound was at 315 mμ. Hence, 30.4 mg. of the oxidized ethylene trithiocarbonate was dissolved in 8 ml. of methanol to which 105 mg. of cysteine hydrochloride in 2 ml. of water was added. A blank solution containing 105 mg. of cysteine hydrochloride was run simultaneously. Both solutions were kept at 25°. Measurements in the spectrometer were made periodically by taking 1-ml. aliquots and diluting to 250 ml. with methanol. After 45 hr. no absorption maxima were found at 347 or 285 mμ, and a new peak at 315 mμ appeared with a molar extinction coefficient that corresponded to 75% of the theoretical value of the reduced product. A white precipitate, identified as L-cystine, was isolated from the flask containing the oxythio compound, whereas the blank solution was still clear. The ultraviolet spectrum of a solution of the oxythio compound in methanol–water was unchanged on standing at 25° for 5 days.

Acknowledgment.—We are grateful to Mrs. Clara McGrew, Mrs. Bonita Heaton, and Mrs. Anita Dirks for microanalysis and the molecular weight determination by vapor pressure osmometry.

[25] C. C. J. Culvenor, W. Davies, and K. H. Pausacker, *J. Chem. Soc.* 1050 (1946).

Reissert Compound Studies. VIII. The Preparation and Reactions of 2-Arylsulfonyl- and 2-Alkylsulfonyl-1,2-dihydroisoquinaldonitriles[1,2]

JOHN M. WEFER, ADRIA CATALA, AND FRANK D. POPP

Department of Chemistry, Clarkson College of Technology, Potsdam, New York 13676

Received March 9, 1965

The title compounds (II) are prepared from isoquinolines, potassium cyanide, and sulfonyl chlorides. Basic cleavage of these compounds yields isoquinaldonitrile and acid hydrolysis yields isoquinoline. Treatment of quinoline with potassium cyanide and benzenesulfonyl chloride yields only quinaldonitrile.

The preparation of Reissert compounds[3] (such as I) from a wide variety of quinolines[4] or isoquinolines,[5] potassium cyanide, and an acyl halide[6] or anhydride[6] is a well-known reaction.

We have now observed that a similar reaction occurs with isoquinoline, potassium cyanide, and an alkyl- or arylsulfonyl chloride to lead to the formation of 2-arylsulfonyl- and 2-alkylsulfonyl-1,2-dihydroisoquinaldonitriles (II, Chart I). The compounds of the type II which we have prepared are included in Table I. In general the methylene chloride–water method[4–7] of Reissert compound formation was used with no attempt to find ideal conditions. In the reaction of isoquinoline,

---

[1] Part VII: H. W. Gibson, F. D. Popp, and A. Catala, *J. Heterocyclic Chem.*, **1**, 251 (1964).

[2] Presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

[3] W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

[4] F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.*, **26**, 4930 (1961).

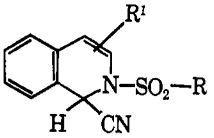
[5] F. D. Popp and W. Blount, *ibid.*, **27**, 297 (1962).

[6] F. D. Popp and A. Soto, *J. Chem. Soc.*, 1760 (1963).

[7] F. D. Popp and W. Blount, *Chem. Ind.* (London), 550 (1961); F. D. Popp, W. Blount, and A. Soto, *ibid.*, 1022 (1952).

TABLE I

2-ARYLSULFONYL- AND 2-ALKYLSULFONYL-1,2-DIHYDROISOQUINALDONITRILES

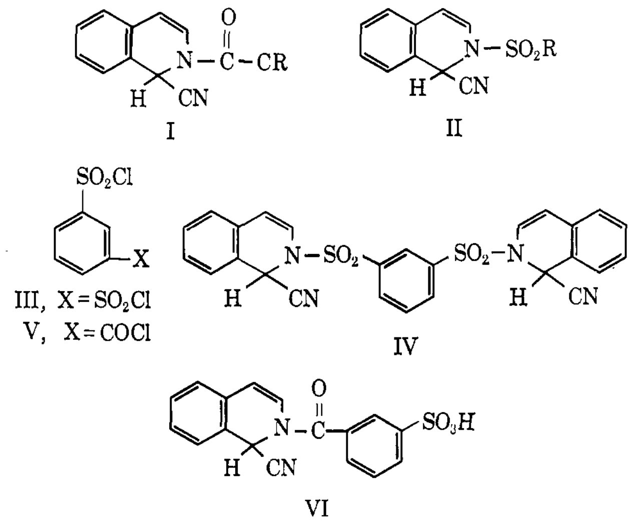


R	R'	Yield, %[a]	M.p., °C.[b]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Me	H	7	130–132	56.39	4.30	11.96[c]	56.31	4.18	11.96
n-Pr	H	12	85–86	59.52	5.38	10.68	59.39	5.25	10.60
Benzyl	H	21	134–136	65.78	4.55	9.03	65.61	4.86	9.29
Ph	H	15	109–112	64.85	4.08	9.45[d]	64.94	4.26	9.44
Ph	H	90[e]	109–112	...	...	...	...	...	...
Ph	3-Me	53	132–134	65.78	4.55	9.03	65.83	4.52	9.22
Ph	4-Br	37	149–150	51.21	2.95	7.47	50.99	2.80	7.38
Ph	7-CH_3O	15[e]	91–93	62.56	4.32	8.58	62.45	4.42	8.74
p-CH_3O-Ph	H	60	131–134	62.56	4.32	8.58	62.50	4.31	8.65
p-Me-Ph	H	32	101–103	65.78	4.55	9.03[f]	65.73	4.69	8.96
p-Fl-Ph	H	21	131–132[g]	61.13	3.53	8.91	61.16	3.52	8.95
p-Cl-Ph	H	50	93–96[g]	58.09	3.35	8.47	58.33	3.28	8.44
p-Br-Ph	H	10	119–122[g]	51.21	2.95	7.47	51.02	2.96	7.42
p-NO_2-Ph	H	43	143–146	56.30	3.25	12.31	56.07	3.12	12.30

[a] Methylene chloride–water method unless otherwise noted. [b] Recrystallized from 95% ethanol unless otherwise noted. [c] *Anal.* Calcd.: S, 13.69. Found: S, 13.80. [d] *Anal.* Calcd.: S, 10.82. Found: S, 10.88. [e] Aqueous method. [f] *Anal.* Calcd.: S, 10.33. Found: S, 10.39. [g] Recrystallized from absolute ethanol.

potassium cyanide, and benzenesulfonyl chloride the aqueous method[3] gave a greatly improved yield but this method was not practical with solid sulfonyl chlorides. The structure of these compounds (II) is assigned on the basis of elemental analysis, the isolation of isoquinaldonitrile as discussed below, the infrared spectra, and analogy to Reissert compound formation.

CHART I



I

II

III, X = SO_2Cl

V, X = COCl

IV

VI

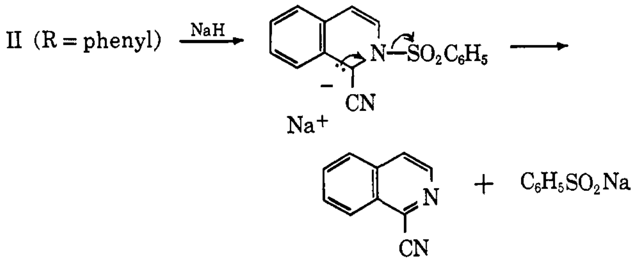
As in the case with Reissert compounds (as I)[3] the analogs did not exhibit any nitrile absorption in the infrared. All of the compounds exhibited peaks at 1150–1160 and 1340–1350 cm.$^{-1}$ which are typical for N,N-disubstituted sulfonamides.

Use of the disulfonyl chloride III gave the bis compound IV in low yield. The mixed compound V, however, reacted only at the carbonyl group to give rise to a normal Reissert compound VI as indicated by its absorption at 1660 cm.$^{-1}$ and lack of absorption at 1150–1175 cm.$^{-1}$. Further evidence for structure VI was obtained by acid hydrolysis of VI to *m*-formylbenzenesulfonic acid (isolated as its 2,4-dinitrophenylhydrazone).

Attempts to extend the reaction to quinoline did not lead to products of the type II. It should be noted, however, that low yields of quinaldonitrile were obtained, indicating that perhaps the quinoline analog of II was formed but was unstable. Use of 6-methoxyquinoline led to the isolation of 6-methoxyquinaldonitrile.

3-Methyl-, 4-bromo-, and 7-methoxyisoquinoline all gave rise to compounds of type II as indicated in Table I. The latter base, however, gave II only under aqueous condition, 7-methoxyisoquinaldonitrile being obtained in methylene chloride–water.

The chemical behavior of compound II (R = phenyl) has been found to be quite different from that of classical Reissert compounds (I, R = phenyl). It has been reported[8] that I (R = phenyl) rearranges to 1-benzoylisoquinoline when refluxed with sodium hydride in xylene. It is also known[3] that I (R = phenyl) reacts with phenyllithium at low temperatures to give a relatively stable anion which can then undergo various reactions, such as condensation with aldehydes.[9,10] We have found that, when II (R = phenyl) reacts with a base such as sodium hydride, phenyllithium, or 5% sodium hydroxide, isoquinaldonitrile is



---

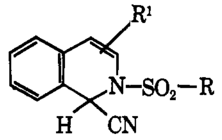
(8) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

(9) L. R. Walters, N. T. Dyer, and W. E. McEwen, *ibid.*, **80**, 1177 (1958).

(10) F. D. Popp and H. W. Gibson, *J. Heterocyclic Chem.*, **1**, 51 (1964).

TABLE II

HYDROLYSIS OF COMPOUND OF TYPE II



R	R′	Reagent[a]	Product	Yield, %	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ph	H	NaH	Isoquinaldonitrile	100	87–89	*b*	...	...	...	...	...
			Sodium benzenesulfinate	99	...	*c*	...	...	...	...	...
Ph	H	5% NaOH	Isoquinaldonitrile	63[d]	86–88	*b*	...	...	...	...	...
Ph	H	PhLi[e]	Isoquinaldonitrile	43	87–89	*b*	...	...	...	...	...
Ph	H	50% NaOH	Isoquinaldamide	95	168–170	*b*	...	...	...	...	...
p-Me–Ph	H	NaH	Isoquinaldonitrile	72	87–89	*b*	...	...	...	...	...
			Sodium *p*-toluenesulfinate	73	...	*c*	...	...	...	...	...
Ph	3-Me	NaH	3-Methylisoquinaldonitrile	99	103–104[f]	78.56	4.80	...	78.14	4.74	...
Ph	3-Me	50% NaOH	3-Methylisoquinaldamide	99	181–182[f]	70.95	5.41	15.05	71.06	5.32	15.06
Ph	4-Br	NaH	4-Bromoisoquinaldonitrile	81	122–123[f]	51.53	2.16	12.02	51.68	2.15	11.94
Ph	4-Br	50% NaOH	4-Bromoisoquinaldamide	94	169–170[f]	47.83	2.81	11.16	47.68	2.75	11.16

[a] See Experimental. [b] Identical melting point, mixture melting point, and infrared spectrum with authentic sample. [c] Identical infrared spectrum with authentic sample. [d] Plus 28% recovered starting material. [e] In presence of methyl iodide or benzaldehyde.[9,10] [f] Recrystallized from 95% ethanol.

obtained.[11] Sodium benzenesulfinate has also been isolated in the sodium hydride reaction. The elimination scheme shown above can account for these results.[12] That this is a general procedure for the preparation of isoquinaldonitriles in high yield was demonstrated by the use of 3-methyl- and 4-bromoisoquinoline as indicated in Table II. Use of 50% sodium hydroxide gave rise to the isoquinaldamides indicated in Table II. With 50% sodium hydroxide the Reissert compound I (R = phenyl) gave isoquinoline. It is of interest to note that isoquinaldonitrile can be obtained when I (R = *p*-nitrophenyl) is treated with basic reagents, the electron-withdrawing nitro group aiding the elimination reaction.

Acid-catalyzed hydrolysis of Reissert compounds has been much studied,[3] the major products being the aldehyde derived from the acyl group and the acid or amide derived from the heterocyclic base. Under these conditions[14] II (R = phenyl) is hydrolyzed to isoquinoline.

Experimental[15]

Preparation of Compound II. A. Methylene Chloride–Water Method.—A solution of 6.2 g. of potassium cyanide in 16 ml. of water was added to a solution of 0.031 moles of the appropriate isoquinoline in 40 ml. of methylene chloride. The sulfonyl chloride (0.062 mole) was added dropwise (solid sulfonyl chlorides were dissolved in a minimum of methylene chloride) with stirring over 0.5–2 hr. (The shorter time and external cooling of the reaction mixture was used with aliphatic sulfonyl chlorides.) After stirring an additional 4–6 hr., the layers were separated and the aqueous layer was washed with methylene chloride. The combined methylene chloride solutions were washed with water, 10% hydrochloric acid, water, 5% sodium hydroxide, and water and dried over magnesium sulfate. Concentration of the solvent gave the products indicated in Table I.

With 7-methoxyisoquinoline and benzenesulfonyl chloride in this method a 67% yield of 7-methoxyisoquinaldonitrile, m.p. 152–153°, was obtained.

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.39; N, 15.21. Found: C, 71.69; H, 4.48; N, 15.16.

With *m*-benzenedisulfonyl chloride (III) and isoquinoline a 4.5% yield of IV, m.p. 184–185°, was obtained.

Anal. Calcd. for $C_{26}H_{18}N_4O_4S_2$: C, 60.68; H, 3.53; N, 10.89. Found: C, 60.60; H, 3.47; N, 10.84.

With V and isoquinoline a low yield of VI, m.p. 175–176°, was obtained.

Anal. Calcd. for $C_{17}H_{12}N_2O_4S$: C, 59.99; H, 3.55; N, 8.23; S, 9.42. Found: C, 60.18; H, 3.26; N, 8.30; S, 9.50.

With 6-methoxyquinoline and benzenesulfonyl chloride a 49% yield of 6-methoxyquinaldonitrile, m.p. 177–178° (lit.[16] m.p. 178°), was obtained.

B. Aqueous Method.—To a mixture of 77.5 g. of potassium cyanide and 45.5 ml. (0.356 mole) of isoquinoline in 625 ml. of water was added over 2 hr. with stirring 95 ml. of benzenesulfonyl chloride. After stirring for an additional 4 hr., the product described in Table I was obtained.

With quinoline a 24% yield of quinaldonitrile, m.p. 93–94° (lit.[17] m.p. 95°), was obtained.

Reaction of II With Base. A. Sodium Hydride.—A mixture of 3.55 g. (0.012 mole) of II (R = phenyl) and 0.58 g. of 50% sodium hydride in oil in 30 ml. of xylene was refluxed for 1 hr. and filtered to give sodium benzenesulfinate which was identical with authentic material. Concentration of the filtrate gave isoquinaldonitrile as indicated in Table II.

B. 5% Sodium Hydroxide.—A mixture of 1.0 g. of II (R = phenyl) and 15 ml. of 5% sodium hydroxide was heated on a steam bath for 10 min. On cooling a solid was obtained. Digestion of the solid with hexane gave starting material (insoluble in hot hexane) and isoquinaldonitrile (soluble in hot hexane) as indicated in Table II.

C. 50% Sodium Hydroxide.—A mixture of 1.0 g. of II and 15 ml. of 50% sodium hydroxide was heated on a steam bath for 10 min. and poured into 250 ml. of water. Filtration gave the products indicated in Table II.

Acid Hydrolysis of II.—A mixture of 4.9 g. (0.017 mole) of II (R = phenyl), 4.2 ml. of glacial acetic acid, and 4.2 ml. of fuming hydrobromic acid was refluxed for 1.25 hr. and cooled. The mixture was made basic and extracted with ether. Concentration of the extract gave a nearly quantitative yield of isoquinoline identified as its picrate, m.p. 224–226°.

Acid Hydrolysis of VI.—Acid-catalyzed hydrolysis of VI in the presence of 2,4-dinitrophenylhydrazine[18] gave the 2,4-dinitrophenylhydrazone of *m*-formylbenzenesulfonic acid, m.p. 268–269.

Anal. Calcd. for $C_{13}H_{10}N_4O_7S$: C, 42.62; H, 2.75; N, 15.30; S, 8.75. Found: C, 42.75; H, 2.58; N, 15.02; S, 8.69.

---

[11] J. M. Wefer, A. Catala, and F. D. Popp, *Chem. Ind.* (London), 140 (1965).

[12] The basic cleavage of arylsulfonamides has recently been discussed.[13]

[13] E. Negishi and A. R. Day, *J. Org. Chem.*, **30**, 43 (1965); W. Paterson and G. R. Proctor, *J. Chem. Soc.*, 485 (1965).

[14] J. W. Davis, Jr., *J. Org. Chem.*, **24**, 1691 (1959).

[15] Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

[16] F. Montanari and L. Pentimalli, *Gazz. chim. ital.*, **83**, 273 (1953).

[17] F. M. Hamer, *J. Chem. Soc.*, 1008 (1939).

[18] W. E. McEwen, R. H. Terss, and I. W. Elliott, *J. Am. Chem. Soc.*, **74**, 3605 (1952).