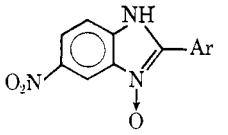
TABLE I
2-ARYL-5-NITROBENZIMIDAZOLE 3-OXIDES FROM ALDEHYDES (ArCHO)

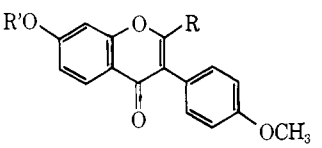


Ar	Yield, %[a]	Mp, °C[b]	Vol. of recrystn solvent, ml/g	Color	Formula	N, % Calcd	N, % Found
C_6H_5	56	272–273	25	Cream	$C_{13}H_9N_3O_3$[c]	16.47	16.20[d]
4-ClC_6H_4	64	249–250[e]	20	Yellow	$C_{13}H_8N_3O_3Cl$	14.50	14.39[f]
2-$MeOC_6H_4$	64	255–257	30	Yellow	$C_{14}H_{11}N_3O_4$	14.74	14.58
3-$MeOC_6H_4$	62	267–269	20	Cream	$C_{14}H_{11}N_3O_4$	14.74	14.52
4-$MeOC_6H_4$	64	273–274	35	Pale yellow	$C_{14}H_{11}N_3O_4$	14.74	14.39
3,4-$(MeO)_2C_6H_3$	62	268–270	30	Pale yellow	$C_{15}H_{13}N_3O_5$	13.33	12.89
2-Naphthyl	62	258–259	20	Pale yellow	$C_{17}H_{11}N_3O_3$	13.75	13.56
4-Pyridyl[g]	59	279–280	25	Pale yellow	$C_{12}H_8N_4O_3$	21.87	21.82

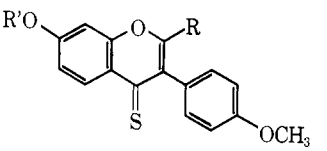
[a] Of recrystallized product. Crude yields were generally in excess of 70%. [b] All compounds melted with decomposition. [c] This compound was identical (melting point, mixture melting point, infrared spectrum) with a sample prepared by photolysis of N-(2,4-dinitrophenyl)-C-phenylglycine at pH 3 as described by R. J. Pollitt, *Chem. Commun.*, 262 (1965). [d] *Anal.* Calcd: C, 61.18; H, 3.55. Found: C, 61.39; H, 3.72. [e] This compound resolidified on further heating and melted again at 296–298° dec. [f] *Anal.* Calcd: Cl, 12.24. Found: Cl, 12.03. [g] The reaction mixture contained an additional 2.2 mmoles of *p*-toluenesulfonic acid, and water (20 ml) instead of ethanol was used to precipitate the product.

mmoles) in glacial acetic acid (2.5 ml) containing *p*-toluenesulfonic acid (33 mg)[7] was boiled under reflux for 30 min, during which time part of the product generally crystallized. The hot reaction mixture was cautiously diluted with ethanol (7 ml) and set aside overnight at room temperature to complete the precipitation. The product after being washed with ethanol was crystallized from 1-butanol–pyridine (3:2) with addition of a little decolorizing charcoal. Compounds prepared by this procedure are given in Table I.

(7) Reaction was faster in glacial than in the 50% AcOH originally used[2] and was still more rapid in the presence of catalytic amounts of the sulfonic acid.



1a, R' = C_7H_7; R = H
b, R' = CH_3CO; R = H
c, R' = CH_3CO; R = CH_3
d, R' = C_2H_5CO; R = C_2H_5



2a, R' = C_7H_7; R = H
b, R' = CH_3CO; R = H
c, R' = CH_3CO; R = CH_3
d, R' = C_2H_5CO; R = C_2H_5

Flavonoids. V. Thiation of Isoflavones[1,2]

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A biological significance of isoflavonoids is well documented in the example of genistein, an isoflavone which occurs in clover and has been responsible for the failure of ewes to lamb.[3] In this connection we have prepared for biological evaluation a few isoflavthiones (**2**): the synthetic method employed here has precedent in Baker's thiation of flavone.[4]

The general procedure described herein (Experimental Section) was inadequate for the thiation of 3-(*p*-methoxyphenyl)-7-methoxycoumarin.[5]

Experimental Section[6]

General Procedure for the Thiation of Isoflavones 1a–d.—A suspension of equal weights of isoflavone and P_2S_5[7] in benzene (20 ml/g of isoflavone) was stirred and heated under reflux (bath temperature, 80–85°), protected from atmospheric moisture. The reaction progress was followed by tlc; chromatograms were eluted in 10% ethyl acetate–benzene (the isoflavones fluoresce blue light under an ultraviolet light source; the isoflavthiones move as yellow zones, are nonfluorescent, and are further developed by 5% phosphomolybdic acid in ethanol reagent). The remainder of the total quantity of P_2S_5 was added during the course of the reaction. At the end of the refluxing period (2–4 hr), as judged by tlc, the hot reaction solution was decanted through a fluted filter and the residual solids were washed with two small portions of hot benzene. The crude isoflavthione was precipitated (or crystallized) by adding a 4–5-fold volume of petroleum ether (bp 30–60°), keeping the solution at ~−10°. In the case of **2d** (the slowest to crystallize), the precipitation of yellow solid preceded the crystallization of product; this being the case, the supernatant was decanted into a clean flask, and cooling was continued until separation of product was complete. The yields and melting points of the isoflavthiones reported in Table I (on the following page) were obtained after one recrystallization from ethyl acetate.

(1) This research was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) Paper IV in this series: K. H. Dudley, H. W. Miller, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **32**, 2317 (1967).

(3) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 3447 (1951).

(4) W. Baker, J. B. Harborne, and W. D. Ollis, *ibid.*, 1303 (1952).

(5) N. Campbell in "Chemistry of Carbon Compounds," Vol. IVB, E. H. Rodd, Ed., Elsevier Publishing Co., Amsterdam, 1959, p 877.

(6) Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. Ultraviolet spectra were measured with a Cary Model 14 spectrophotometer, infrared spectra with a Perkin-Elmer 221 spectrophotometer (KBr disks). Microanalyses were carried out by Triangle Chemical Laboratories, Carrboro, N. C., and Micro-Tech Laboratories, Skokie, Ill.

(7) P_2S_5 (Matheson Coleman and Bell) was employed without further purification.

TABLE I

Isoflavthione (yield, %)	Ratio [g] isoflavone P_2S_5	Mp, °C	Color[a]	Infrared data (cm^{-1})	λ_{max}^{MeOH}, mμ (ε)	Formula	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
2a (51)	0.50	180–191	Magenta prisms	1610, 1510, 1440	385 (17,200),[b] 282 (11,200),[b] 355 (10,700)[b,c]	$C_{30}H_{18}O_2S$	73.79	1.85	8.56	73.32	1.54	8.51
2b (84)	0.38	163–164	Magenta prisms	1770, 1615, 1610, 1510	381 (14,100), 276 (11,500)	$C_{31}H_{20}O_2S$	66.25	1.32	9.81	66.23	1.35	9.61
2c (85)	0.71	181–185	Purple rods	1780, 1600, 1546, 1505	373 (16,800), 278 (11,900)	$C_{30}H_{16}O_2S$	67.05	1.75	9.10	67.30	1.81	9.31
2d (38.4)	0.50	93 and 110–112 (dimorphous)	Purple-black rods	1770, 1620, 1602, 1550, 1520	377 (16,300), 285 (12,600)	$C_{34}H_{24}O_2S$	68.17	5.47	8.69	68.63	5.86	8.58

[a] The color is undoubtedly due to solid-state and association phenomena, for it was imparted only to very concentrated solutions and was unmeasurable in the region 400–600 mμ employing 10^{-3} to 10^{-5} *M* solutions of the isoflavthiones **2** in methanol, benzene, and hexane. [b] Benzene, not methanol, was the solvent. [c] Shoulder.

Synthesis of Potential Antineoplastic Agents. XVIII. Synthesis of New Alkylating Agents[1]

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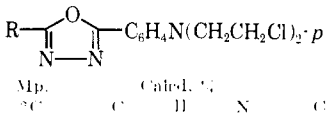
The preparation of a number of potential biological alkylating agents and related compounds is reported.

Experimental Section[3]

2-{*p*-[Bis(2-chloroethyl)amino]phenyl}-5-alkyl-1,3,4-oxadiazole.—Following the procedure of Ainsworth,[4] 2.0 g of *p*-[bis(2-chloroethyl)amino]benzhydrazide[5] was heated to reflux in 15 ml of the appropriate, freshly distilled, triethylorthoalkyl ester. The mixture was refluxed overnight and the excess orthoester was removed *in vacuo*. The oxadiazoles were recrystallized from ethanol–water and are shown in Table I.

TABLE I



R	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H[a]	55	68–70	50.36	4.58	14.69	50.56	4.60	14.62
CH_3	79	122–125	52.01	5.04	14.00	52.11	5.13	13.92
C_2H_5	84	109–113	53.14	5.45	13.37	53.35	5.58	13.12

[a] We should like to thank Dr. D. W. Alwani for assistance with this compound. This compound was inactive[7] against Walker carcinosarcoma.

1,4-Bis[(2-chloroethyl)thio]-2,3,5,6-tetrafluorobenzene. A mixture of 1 g of 1,4-bis[(2-hydroxyethyl)thio]-2,3,5,6-tetrafluorobenzene[6] and 5 ml of $SOCl_2$ was refluxed for 3 hr and the excess $SOCl_2$ was removed *in vacuo* to give 1.3 g of solid, mp 110–116°. Recrystallization from ethanol gave white needles, mp 114–116°.

Anal. Calcd for $C_{10}H_8F_4Cl_2S_2$: C, 35.40; H, 2.37; F, 22.40; Cl, 20.90; S, 18.90. Found: C, 35.30; H, 2.75; F, 22.06; Cl, 20.85; S, 18.90.

This compound was inactive[7] against Walker carcinosarcoma 256.

Diethyl [Bis(2-hydroxyethyl)amino]methylenemalonate.—A mixture of 5.07 g (0.048 mole) of bis(2-hydroxyethyl)amine and 10.5 g (0.048 mole) of diethyl ethoxymethylenemalonate in 60 ml of absolute ethanol was refluxed for 1 hr and the solvent was removed *in vacuo* to give an oil. Distillation gave 9.9 g (74%) of liquid, bp 58–61° (0.8 mm).

Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.09; H, 7.66; N, 4.89.

This compound was inactive[7] against Sarcoma 180 and L1210 lymphoid leukemia.

[Bis(2-hydroxyethyl)amino]methylenemalononitrile.—Using a similar procedure 8.6 g (98%) of solid, mp 86–87° (from ethanol), was obtained.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 53.73; H, 6.12; N, 23.19. Found: C, 52.86; H, 5.93; N, 23.32.

This compound was inactive[7] against L1210 lymphoid leukemia and S91 Clondman melanoma and only very slightly (T/C = 61% at 500 mg/kg) active against Sarcoma 180.

Ethyl [Bis(2-chloroethyl)amino]methylenecyanoacetate.—A solution of 0.05 mole of ethyl ethoxymethylenecyanoacetate and bis(2-chloroethyl)amine (from 0.05 mole of its hydrochloride) in benzene was refluxed for 6 hr. Removal of the solvent *in vacuo* gave an oil which was chromatographed on acid-washed alumina and the solid eluted was recrystallized from ethanol to give 4.7 g (36%) of solid, mp 56–59°.

Anal. Calcd for $C_{11}H_{14}Cl_2N_2O_2$: C, 45.30; H, 5.32; N, 10.57; Cl, 26.74. Found: C, 45.31; H, 5.42; N, 10.52; Cl, 26.78.

This compound was inactive[7] against Walker carcinosarcoma 256. The hydroxyethyl analog of this compound[8] was inactive[7] against L1210 lymphoid leukemia and Friend virus leukemia and only slightly active (T/C = 65% at 62 mg/kg) against Heptoma 129. Preliminary attempts to convert this hydroxyethyl compound directly to the chloroethyl compound with $SOCl_2$ failed.

(8) A. A. Santilli, W. F. Bruce, and T. S. Osdene, *J. Med. Chem.*, **7**, 68 (1964).

Synthesis of Potential Antineoplastic Agents. XIX. Some 5-(ω-Chloroacylamino)quinolines and 4- and 5-(ω-Chloroacylamino)isoquinolines[1]

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A number of 5-(ω-chloroacylamino)quinolines and 4- and 5-(ω-chloroacylamino)isoquinolines were prepared by reaction of

(1) (a) Part XVII: F. D. Popp, F. P. Silver, and D. W. Alwani, *J. Med. Chem.*, **10**, 481 (1967). (b) Supported in part by research grants from the American Cancer Society and from the National Cancer Institute.

(2) Abstracted in part from the M.S. Thesis of F. P. S.

(3) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are taken in capillaries and are corrected.

(4) C. Ainsworth, *J. Am. Chem. Soc.*, **77**, 1148 (1955).

(5) R. C. Elderfield and T. K. Liao, *J. Org. Chem.*, **26**, 4996 (1961).

(6) J. Burdon, V. Damodaran, and J. Tatlow, *J. Chem. Soc.*, 763 (1964).

(7) Screening results were supplied by the DCNSC of the National Institutes of Health.

(1) (a) Part XVIII: F. D. Popp, F. P. Silver, and A. C. Noble, *J. Med. Chem.*, **10**, 986 (1967). (b) Supported in part by research grants from the American Cancer Society and from the National Cancer Institute. (c) A portion of this material is abstracted from the M.S. Thesis of F. P. S., Clarkson College of Technology, 1967.