[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

Pyrimidines. V. Analogs of 2-(*o*-Chlorobenzylthio)-4-dimethylamino-5-methylpyrimidine (Bayer DG-428)[1]

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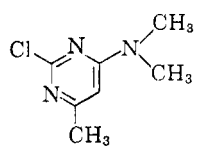
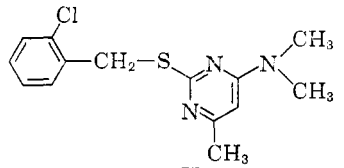
Bayer DG-428 and its analogs were synthesized by two different methods. These compounds were found to be inactive against the CA-755, SA-180, and L-1210 tumor systems.

Westphal and Bierling[2] reported that the toxicity of the compound "Castrix"[3] (I) was greatly reduced when the 2-chloro group was replaced by an *o*-chlorobenzylthio group. The resulting compound, Bayer DG-935 (II), possessed slow but certain

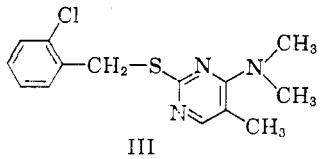


I



II

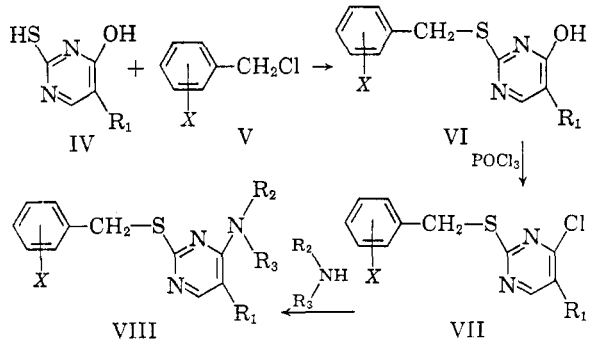
cytostatic action on certain tumor cells in tissue culture. When the structure of compound II was further modified by changing the position of the methyl group from 6 to 5 (the "thymine" position), a compound, Bayer DG-428 (III), was obtained. This compound was reported by Westphal and Bierling[2] to exhibit strong inhibitory effects against certain human tumors in tissue culture without damaging the normal tissue.



III

A search of the literature has revealed that, although carcinostatic activity has been claimed by several investigators,[4] others have obtained less satisfactory results in certain testing systems.[5] This controversy prompted us, in connection with our studies in pyrimidine chemistry, to direct our attention to this type of compound.

In order to obtain additional information with regard to the biological activity and the trend of the antitumor properties that are associated with this type of compound, DG-428 and several of its analogs were synthesized in our laboratories by two methods. Both methods are different from those previously described in the patent of the Farbenfabriken Bayer.[6]



IV V VI VII VIII

2-Thiothymine (IV. $R_1 = CH_3$), when treated with aralkyl chlorides (V) in base, gave the corresponding substituted thio derivatives (VI. $R_1 = CH_3$) in nearly quantitative yield. Phosphorus oxychloride then converted VI ($R_1 = CH_3$) to VII ($R_1 = CH_3$) in 80–90% yield. The latter was changed to the desired product (VIII. $R_1 = CH_3$) by nucleophilic substitution in a sealed vessel at elevated temperature with primary and secondary alkyl amines.

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) K. Westphal and R. Bierling, *Naturwissenschaften*, **46**, 230 (1959).

(3)(a) K. Westphal, Ger. Patent, **703,068**, Jan. 30, 1941; (b) K. P. DuBois, *J. Am. Pharm. Assoc.*, **37**, 307 (1948); (c) K. P. DuBois, K. W. Cochran, and J. F. Thomson, *Proc. Soc. Exptl. Biol. Med.*, **67**, 169 (1948); (d) H. Freytag, *Z. anal. Chem.*, **129**, 366 (1949); (e) W. A. McDougall, *Queensland J. Agr. Sci.*, **6**, 54 (1949); (f) H. J. Goldbach, *Med. Klin.* (*Munich*), **45**, 963 (1950); (g) F. Hüter, *Anz. Schädlingskunde*, **24**, 23 (1951); (h) M. A. Miller, *Hilgardia*, **22**, 131 (1953).

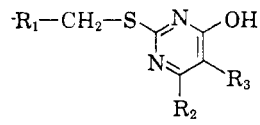
(4)(a) "A solution containing 1/1,000,000 DG-428 stops the growth of Yoshida sarcoma or Ehrlich. The resulting material, when inoculated into animals, has lost the ability to form tumors," *La Prensa Médica Argentina*, **46**, 2005 (1959); (b) H. G. Sievers and J. P. Marzoli, *Med. Klinik*, **54**, 366 (1959); (c) M. Oberneder, *Med. Welt*, **27/28**, 1497 (1960); (d) "Clinically we have sometimes observed good success in carcinoma and papilloma of the bladder," private communication through Professor Gerhard Domagk, Farbenfabriken Bayer, August 25, 1960.

(5)(a) "Contrary to the reports of other authors, complete clinical and histological cures were not achieved," A. Ravina and T. Grosz, *La Presse Medicale*, **68** (54), 2075 (1960); (b) "In concentrations of 5×10^{-8} *M*, DG-428 was completely inactive, while at 5×10^{-7}*M* it became lethal within a few hours . . . . The cells which were treated became rapidly drug-resistant, and the drug ceased to be active 24 hours after," R. Truhaut and G. Deysson, *C. R. Acad. Sci.* (*Paris*), **251**, 593 (1960).

(6) Farbenfabriken Bayer A.-G., Brit. Patent **810,846**, March 25, 1959.

TABLE I

4-HYDROXYPYRIMIDINES[a]

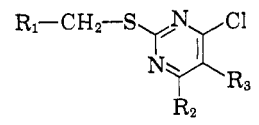


R_1	R_2	R_3	M.P.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
C_6H_5	H	H	192–194	60.5	4.6	12.8	60.6	4.4	12.6
o-Cl—C_6H_4	H	H	218–219	52.3	3.5	11.1	52.4	3.3	11.0
p-Cl—C_6H_4	H	H	200–202	52.3	3.5	11.1	52.2	3.3	11.2
2,4-$Cl_2C_6H_3$	H	H	208–210	45.8	2.6	9.7	46.2	2.2	9.8
C_6H_5[b]	H	CH_3	204–205	61.1	4.2	12.1	61.1	4.2	11.9
o-Cl—C_6H_4	H	CH_3	172–174	53.7	4.1	10.4	53.3	4.0	10.7
p-Cl—C_6H_4	H	CH_3	192–193	53.7	4.1	10.4	54.0	4.2	10.6
2,4—$Cl_2C_6H_3$	H	CH_3	216–217	47.8	3.3	9.3	48.1	3.5	9.1
o-Cl—C_6H_4	CH_3	H	206–207	53.7	4.1	10.4	53.6	4.1	10.8
2,4-$Cl_2C_6H_3$	CH_3	H	218–219	47.8	3.3	9.3	48.2	3.4	9.3

[a] All hydroxypyrimidines were recrystallized from ethyl acetate. [b] H. L. Wheeler and D. F. McFarland, *Am. Chem. J.*, **43**, 19 (1910).

TABLE II

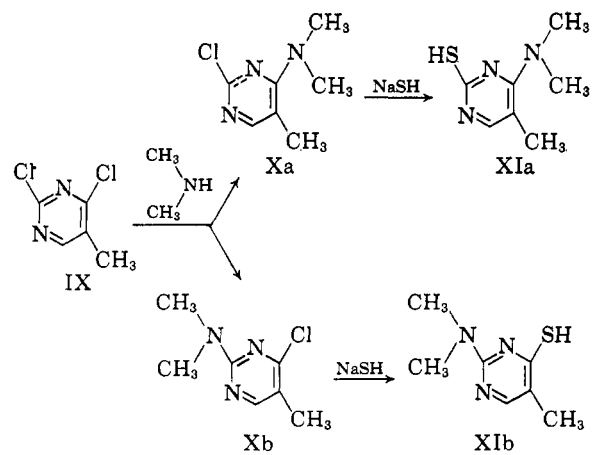
4-CHLOROPYRIMIDINES[a]



R_1	R_2	R_3	M.P.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
C_6H_5	H	H	49–50	55.7	3.8	11.8	56.0	3.6	11.8
C_6H_5	H	CH_3	49–51	57.6	4.0	11.2	57.5	4.4	11.0
o-Cl—C_6H_4	H	CH_3	45–47	50.3	3.4	9.8	50.6	3.4	9.7
p-Cl—C_6H_4	H	CH_3	67–69	50.3	3.4	9.8	50.7	3.3	9.9
2,4-$Cl_2C_6H_3$	H	CH_3	74–75	45.1	2.8	8.7	45.1	2.8	8.6
2,4-$Cl_2C_6H_3$	CH_3	H	85–87	45.1	2.8	8.7	45.5	3.0	8.7

[a] All chloropyrimidines were recrystallized from *n*-heptane.

The second method utilized the readily available 2,4-dichloro-5-methylpyrimidine (IX)[7] as the starting material. It was reported[8] that 2,4-dichloropyrimidine and ammonia gave a mixture of 2-amino-4-chloropyrimidine and 4-amino-2-chloropyrimidine. However, the reaction of 2,6-dichloro-6-methylpyrimidine with amines yielded exclusively 4-substituted amino derivatives.[3a] In our laboratories the behavior of the corresponding 5-methyl isomer (IX)[7] toward nucleophilic displacement was investigated. When IX was treated with dimethylamine, the product isolated was carefully examined. Only one absorption spot was detected in each of three different paper chromatographic systems, and elementary analysis indicated that only one chlorine atom was replaced. Hence the product was either 2 - chloro - 4 - dimethylamino - 5 - methylpyrimidine (Xa) or its position isomer, Xb. The aminated product was then treated with sodium hydrosulfide to replace the second chlorine atom. The thiated product was again found to be paper chromatographically pure. Examination of the ultraviolet absorption spectra of the thiated product indicated that the thio group is attached to position 2 (XIa), rather than position 4 (XIb), as the absorption maxima in both *p*H 1 and *p*H 11

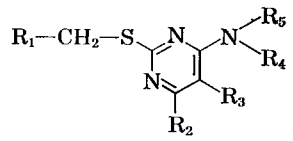


(7) O. Gerngross, *Ber.*, **38**, 3411 (1905).

(8) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 1152 (1930).

TABLE III

BAYER DG-428 AND RELATED COMPOUNDS



R_1	R_2	R_3	R_4	R_5	Method of Synthesis	Recrystallization Solvents[a]	M.P.	Yield, %	Calcd., %			Found, %		
									C	H	N	C	H	N
C_6H_5	H	CH_3	H	CH_3	A	(e)	105–106	72	63.6	6.1	17.1	63.6	5.9	17.0
C_6H_5	H	H	C_2H_5	C_2H_5	A	(e)	79–81	70	65.9	7.0	15.3	66.1	7.0	15.3
C_6H_5	H	CH_3	CH_3	CH_3	A	(c) + (e)	86–87	68	64.6	6.5	16.2	64.3	6.5	16.4
o-Cl—C_6H_4	H	CH_3	CH_3	CH_3	A	(c) + (e)	226–228[b]	61	50.9[c]	4.8	12.7	51.1	4.9	12.7
o-Cl—C_6H_4	H	CH_3	C_2H_5	C_2H_5	A	(c) + (e)	211–213	64	53.6[c]	5.9	11.7	53.8	6.0	11.7
o-Cl—C_6H_4	H	CH_2OH	CH_2 ———	CH_2	[d]	(a) + (f)	120–121	23	54.9	4.5	13.7	54.8	4.9	14.0
p-Cl—C_6H_4	H	CH_3	CH_3	CH_3	A	(c) + (e)	208–211	83	51.3[c]	4.6	12.8	51.0	4.8	13.1
p-Cl—C_6H_4	H	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	A	(c) + (e)	256–258	53	71.6	6.3	9.4	71.9	6.5	9.1
p-F—C_6H_4	H	CH_3	H	CH_3	B	(d) + (e)	84–86	50	59.3	5.5	15.9	59.3	5.3	16.0
p-F—C_6H_4	H	CH_3	CH_3	CH_3	B	(c) + (e)	202–204	58	53.6[c]	5.1	13.4	53.3	4.9	13.5
p-F—C_6H_4	CH_3	H	CH_3	CH_3	B	(c) + (e)	219–221	38	53.3[c]	5.1	13.4	53.7	5.2	13.3
2,4-$Cl_2C_6H_3$	H	H	CH_3	CH_3	A	(c) + (e)	208–210	56	44.6[c]	4.0	12.0	44.6	4.0	12.2
2,4-$Cl_2C_6H_3$	CH_3	H	CH_3	CH_3	B	(c) + (e)	220–224	66	46.3[c]	4.4	11.5	46.6	4.2	11.4
2,4-$Cl_2C_6H_3$	H	CH_3	H	CH_3	A	(b) + (h)	113–114	87	49.6	4.1	13.4	49.4	4.1	13.1
2,4-$Cl_2C_6H_3$	H	CH_3	CH_3	CH_3	A	(e)	79–80	69	51.3	4.5	12.8	51.5	4.7	13.0
2,4-$Cl_2C_6H_3$	H	CH_3	C_2H_5	C_2H_5	A	(c) + (e)	220–222	53	48.9[c]	5.1	10.9	48.6	5.0	10.7
2,4-$Cl_2C_6H_3$	H	CH_3	H	C_4H_9	A	(e)	90–91	50	54.0	5.3	11.8	54.4	5.3	11.5
3,4-$Cl_2C_6H_3$	H	CH_2OH	CH_2 ———	CH_2	[d]	(a) + (f)	140–142	29	49.3	3.9	12.3	49.7	4.2	12.0

[a] Recrystallization solvents: (a) = benzene, (b) = dimethylformamide, (c) = ethanol, (d) = ethyl acetate, (e) = *n*-heptane, (f) = petroleum ether (b.p. 60–70°), (g) = toluene, and (h) = water. [b] Bayer DG-428, m.p. 224°. [c] Monohydrochloride. [d] Prepared from the lithium aluminum hydride reduction of the corresponding ethyl 5-carboxylate. See H. C. Koppel, R. H. Springer, and C. C. Cheng, *J. Org. Chem.*, **26**, 1884 (1961).

were in the neighborhood of 280 mμ and none passed 300 mμ. Upon the basis of our present knowledge[9] as well as the characteristic absorption of 2-thiocytosine[10] and 2-amino-4-pyrimidinethiol,[9] it was concluded that the product was 4-dimethylamino - 5 - methyl - 2 - pyrimidinethiol (XIa). Compound XIa was then reacted with *o*-chlorobenzylchloride to give DG-428 (III), identical to that prepared by the action of dimethylamine on 2 - (*o* - chlorobenzylthio) - 4 - chloro - 5 - methylpyrimidine. This serves as a proof that when 2,4-dichloro-5-methylpyrimidine is subject to nucleophilic attack by an amine, the product is exclusively 4-(substituted amino)-2-chloro-5-methylpyrimidine.

The second method of synthesis of Bayer DG-428 and its analogs is more convenient, as the reactions proceed smoothly without use of a sealed vessel and elevated temperature.

The analogs of 2 - (*o* - chlorobenzylthio) - 4 - dimethylamino - 5 - methylpyrimidine are listed in Table III.

In preliminary screening against SA-180, CA-755 and L-1210, these compounds, including DG-428, were found to be quite toxic and inactive.[11] In view of the extensive claims made concerning the value of this type of compound as antitumor agents, it was felt that they should be further tested in a broader spectrum of tumor systems. This testing is now in progress.

EXPERIMENTAL[12]

Method A is illustrated by the following example.

Preparation of 2-(o-chlorobenzylthio)-4-dimethylamino-5-methylpyrimidine. 2-(o-Chlorobenzylthio)-4-hydroxy-5-methylpyrimidine (VI. X = *o*-Cl, R_1 = CH_3). To 800 ml. of 1*N* sodium hydroxide were added 71 g. (0.5 mole) of 5-methyl-2-thiouracil,[13] 150 ml. of *p*-dioxane, and 80.5 g. (0.5 mole) of *o*-chlorobenzyl chloride. The resulting mixture was heated at 80° for 4 hr. with stirring. The hot solution was then treated with charcoal and filtered. The filtrate was acidified with glacial acetic acid to give VI (X = *o*-Cl, R_1 = CH_3) as a white precipitate. The product was filtered and washed with water and petroleum ether. The yield was 126 g. (94%), m.p. 172–174° (recrystallized from ethyl acetate). $\lambda_{max}^{pH\ 1}$ 271 mμ (ε 8,700); $\lambda_{shoulder}^{pH\ 11}$ 242 mμ (ε 8,900); $\lambda_{max}^{pH\ 11}$ 279 mμ (ε 8,450).

4-Chloro-2-(o-chlorobenzylthio)-5-methylpyrimidine (VII. X = *o*-Cl, R_1 = CH_3). A mixture of 115 g. of 2-(*o*-chlorobenzylthio)-4-hydroxy-5-methylpyrimidine and 1 l. of phosphorus oxychloride was refluxed for 1 hr. Excess phosphorus oxychloride was distilled under reduced pressure and the residue was poured onto crushed ice with vigorous stirring. The icy residue was extracted twice (2 × 1 l.) with ether, and the ethereal extract was washed with dilute sodium bicarbonate solution, and then dried over anhydrous magnesium sulfate. Evaporation of the ether yielded a light yellow powder. Recrystallization from *n*-heptane gave the product as white needles, m.p. 45–47°. The yield was 110 g. (89%); $\lambda_{max}^{ethanol}$ 257 mμ (ε 25,400), 293 mμ (ε 3,600).

Anal. Calcd. for $C_{12}H_{10}N_2SCl_2$: C, 50.5; H, 3.5; N, 9.8. Found: C, 50.6; H, 3.4; N, 9.7.

2-(o-Chlorobenzylthio)-4-dimethylamino-5-methylpyrimidine hydrochloride (VIII. X = *o*-Cl; R_1, R_2,R_3 = CH_3). A mixture of 20 g. 4-chloro-2-(*o*-chlorobenzylthio)-5-methylpyrimidine, 150 ml. of 25% aqueous dimethylamine, and 100 ml. of 95% ethanol was heated at 130° for 4 hr. in a stainless steel bomb. The reaction mixture was evaporated to dryness under reduced pressure and the oily residue was taken up in 200 ml. of absolute ethanol. The ethanol solution was decolorized with charcoal and filtered. The filtrate was chilled to 10° and saturated with dry hydrogen chloride. A white precipitate formed. After 6 hr. of standing at low temperature the precipitate was filtered and washed with ligroin. The crude product was recrystallized from a mixture of ethanol and *n*-heptane to yield 14.0 g. (67%) of the product as white needles, m.p. 226–228°; $\lambda_{max}^{ethanol}$ 257 mμ (ε 23,400); $\lambda_{shoulder}^{ethanol}$ 290 mμ (ε 11,800).

(An alternate method of isolating the desired compound is to take the oil residue from the bomb reaction, suspend it in 200 ml. of boiling water, and add just enough 6*N* hydrochloric acid to form a clear solution. The boiling solution is then treated with charcoal, filtered, and chilled to yield the desired product.)

Anal. Calcd. for $C_{14}H_{16}N_3SCl \cdot HCl$: C, 50.9; H, 4.8; N 12.7. Found: C, 51.1; H, 4.9; N, 12.7.

Method B is illustrated by the following example.

Preparation of 2-(o-chlorobenzylthio)-4-dimethylamino-5-methylpyrimidine. 2,4-Dichloro-5-methylpyrimidine (IX). The following method is simpler than that employed by Gerngross.[7] A mixture of 150 g. of 5-methyluracil and 1 l. of phosphorus oxychloride was refluxed for 2 hr. The excess phosphorus oxychloride was distilled from the reddish solution under reduced pressure and the residue was poured onto crushed ice with vigorous stirring. The yellow precipitate formed during this process was filtered and washed with ice water until the *p*H of the washings was approximately 5. The yield was 130 g. The end product, m.p. 27–29°, was sufficiently pure for the next preparation without further recrystallization.

2-Chloro-4-dimethylamino-5-methylpyrimidine (Xa). A mixture of 130 g. of IX and 800 ml. of 25% aqueous dimethylamine was stirred vigorously at room temperature. The temperature of the reaction mixture rose rapidly. After the reaction had subsided, a second layer was formed which gradually solidified on cooling and continuous stirring. After 1 hr. the reaction mixture was chilled and the product was filtered. The crude product was washed with petroleum ether (b.p. 60–70°) and dried to give 110 g. (73% over-all yield from 5-methyluracil) of Xa as white needles, m.p. 69–71° (recrystallized from *n*-heptane); $\lambda_{max}^{ethanol}$ 258 mμ (ε 12,700); 289 mμ (ε 7400).

The theoretically possible isomer, 4-chloro-5-methyl-2-dimethylaminopyrimidine, was not isolated.

Anal. Calcd. for $C_7H_{10}N_3Cl$: C, 48.8; H, 5.8; N, 24.4. Found: C, 48.8; H, 5.9; N, 24.4.

2-Chloro-5-methyl-4-methylaminopyrimidine was similarly prepared, m.p. 180–182°.

4-Dimethylamino-5-methyl-2-pyrimidinethiol (XIa). A mixture of 30 g. of Xa, 90 g. of sodium hydrosulfide, and 200 ml. of 2-ethoxyethanol was heated at 135–140° for 30 min. The resulting dark solution was cooled and poured into 800 ml. of hot water. The straw-colored solution was treated with charcoal, filtered, and the filtrate acidified with glacial acetic acid. Upon cooling, a precipitate had formed, which was filtered and washed with water. The crude product was reprecipitated from dilute aqueous ammonia with acetic acid

(9) H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 792 (1961).

(10) G. H. Hitchings, *J. Biol. Chem.*, **177**, 357 (1949).

(11) All the tumor screening was done at Battelle Memorial Institute, Columbus, Ohio, under the contract with the Cancer Chemotherapy National Service Center.

(12) All melting points were taken on a Thomas-Hoover melting point apparatus. The infrared spectra were taken with a Perkin-Elmer Infracord and the ultraviolet absorption spectra were determined with a Beckman DK-2.

(13) H. L. Wheeler and D. McFarland, *Am. Chem. J.*, **43**, 25 (1910).

to give 18 g. (61%) of light yellow solid. Recrystallization from water yielded XIa as light yellow needles, m.p. 242–245°. $\lambda_{max}^{pH\ 1}$ 282 mμ (ε 18,200); $\lambda_{max}^{pH\ 11}$ 269 mμ (ε 17,500).

Anal. Calcd. for $C_7H_{11}N_3S$: C, 49.7; H, 6.5; N, 24.8. Found: C, 49.6; H, 6.4; N, 24.8.

Similarly prepared were 5-methyl-4-methylamino-2-pyrimidinethiol, m.p. 237–241°, and 4-dimethylamino-6-methyl-2-pyrimidinethiol, m.p. 292–296°.

2-(o-Chlorobenzylthio)-4-dimethylamino-5-methylpyrimidine (VIII. X = *o*-Cl; R_1, R_2, R_3 = CH_3). A mixture of 16.9 g. (0.1 mole) of XIa, 16.1 g. (0.1 mole) of *o*-chlorobenzylchloride, 75 ml. of *p*-dioxane, and 250 ml. of 0.5*N* sodium hydrochloride was heated at 70° for 3 hr. with stirring. After cooling, the aqueous layer was decanted and the oily residue was triturated several times with ice water, the water being decanted each time. Finally 250 ml. of boiling water was added to the only residue, and just enough 6*N* hydrochloric acid was added to form a clear solution. The solution was decolorized with charcoal, filtered, and the filtrate was chilled to give 15 g. (46%) of white solid. Recrystallization from a mixture of ethanol and *n*-heptane gave the product as white needles, m.p. 226–228°.

Anal. Calcd. for $C_{14}H_{16}N_3SCl \cdot HCl$: N, 12.7. Found: N, 12.7.

The ultraviolet, infrared and paper chromatographic determinations of VIII (X = *o*-Cl; R_1, R_2 R_3 = CH_3) by both methods have been found to be identical.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Adjacent Nitro and Guanidino Groups. II. The Base-Catalyzed Rearrangement of Benzotriazine *N*-Oxides to Benzotriazoles[1]

JOHN A. CARBON

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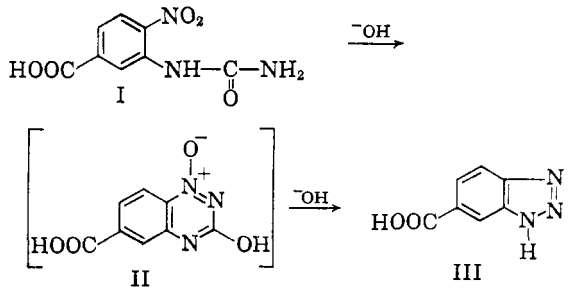
The treatment of 3-amino-1,2,4-benzotriazine 1(or 2)-oxide (IV or IX) with hot alkali results in a molecular rearrangement to form benzotriazole-1-carboxamide (V) plus the hydrolysis product, benzotriazole (VI). The structure of the carboxamide (V) was proven by independent synthesis. Similarly, 3-hydroxy-1,2,4-benzotriazine 1-oxide (VII) rearranges in hot alkali to form benzotriazole (VI). In contrast, a benzotriazine lacking the *N*-oxide function, 3-amino-1,2,4-benzotriazine (VIII), fails to undergo the rearrangement. The mechanism of this interesting reaction is considered to involve an intermediate diazonium hydroxide (IVd), formed by a proton shift within an azoxy intermediate (IVc).

Although the base-catalyzed cyclization of *o*-nitrophenylguanidine (XI) to form 3-amino-1,2,4-benzotriazine 1-oxide (IV) was first reported by Arndt[2] in 1913, an apparently quite closely related transformation, discovered by Griess[3] in 1882, has escaped virtually without notice. Upon treatment of 4-nitro-3-ureidobenzoic acid (I) with hot potassium hydroxide solution, Griess[3] observed the formation of benzotriazole-5-carboxylic acid (III), an interesting reaction which to date has remained unexplained. Considering the work of Arndt[2] on the cyclization of adjacent nitro and ureido groups, the Griess reaction most likely proceeds through the intermediate, 3-hydroxy-1,2,4-benzotriazine 1-oxide-6-carboxylic acid (II), although this has never been demonstrated.



These facts were brought to our attention quite by accident when it was observed[4] that the poor yields encountered in the base-catalyzed cyclization of various compounds containing adjacent nitro and guanidino groups to form fused-ring triazine 1-oxides were due to the formation of acidic by-products, subsequently identified as fused-ring triazoles.

The treatment of 3-amino-1,2,4-benzotriazine 1-oxide (IV) with refluxing 10% sodium hydroxide solution resulted in the formation of two base-soluble compounds, identified as benzotriazole-1-carboxamide (V) and benzotriazole (VI). The structure of benzotriazole-1-carboxamide (V), a compound not described in the literature, was proven by (a) elemental analyses, (b) infrared spectrum, (c) thermal conversion to benzotriazole (VI), and (d) by an unambiguous synthesis from benzotriazole and cyanic acid. This amide (V) possesses a strong carbonyl absorption in the infrared at 5.7 μ and a moderate absorption at 6.2 μ (amide II). Heating of V at 160° results in a quan-

(1) For the preceding paper in this series, see J. A. Carbon, *J. Org. Chem.*, **26**, 455 (1961).

(2) (a) F. Arndt, *Ber.*, **46**, 3522 (1913); (b) F. Arndt and B. Rosenau, *Ber.*, **50**, 1248 (1917).

(3) P. Griess, *Ber.*, **15**, 1878 (1882).

(4) J. A. Carbon, unpublished work.