TABLE III (*Continued*)

R_1	R_2	R_3	R_4	R_5	R_6	Method of prepn.	Formula	Recrystn. solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
NH_2	NO_2		OEt			*a*							
NH_2	NO_2		F			J			*h*				
NH_2	NO_2		Br		*i*-C_3H_7	J			*b*				
NH_2	NO_2		Br			J			*h*				
NHEt	NO_2		CH_3			*i*	$C_9H_{12}N_2O_2$	EtOH–H_2O	56–57	59.98	59.70	6.71	6.40
NHMe	NO_2		CH_3			*i*			*j*				
NHAc	NO_2		*n*-C_3H_7			1	$C_{11}H_{14}N_2O_5$	EtOH–H_2O	135	59.44	59.62	6.35	6.17
NHAc	NO_2		*i*-C_3H_7			1	$C_{11}H_{14}N_2O_5$	EtOH–H_2O	81–82	59.44	59.30	6.35	6.32
NHAc	NO_2		*s*-C_4H_9			1			*c*				
NHAc	NO_2		*s*-C_5H_{11}			I			*b*				
NHAc	NO_2		*t*-C_5H_{11}			I	$C_{13}H_{18}N_2O_5$	Petr. eth.	53–54	62.39	62.53	7.25	7.09
NHAc	NO_2		*n*-C_6H_{13}			I	$C_{14}H_{20}N_2O_5$	EtOH–H_2O	51–52	63.62	63.41	7.63	7.26
NHAc	NO_2		Ac			I			*k*				
NHAc	NO_2		F			I	$C_8H_7N_2O_4F$	EtOH–H_2O	72–73	48.48	48.84	3.56	3.70
NHAc	NO_2		Br	*i*-C_3H_7		1	$C_{11}H_{13}N_2O_5Br$	EtOH	139–141	43.86	44.01	4.35	4.05
NH-tosyl	NO_2		CH_3			*l*			*j*				
NHAc			*n*-C_3H_7			E			*m*				
NHAc			*i*-C_3H_7			E			*n*				
NHAc			*s*-C_5H_{11}			E	$C_{13}H_{19}NO$	Et_2O–petr. eth.	122–124	76.05	76.14	9.33	9.60
NHAc			*t*-C_5H_{11}			E			*m*				
NHAc			*n*-C_6H_{13}			E	$C_{14}H_{21}NO$	Petr. eth.	74–76	76.66	76.88	9.65	9.87
NHAc			F			E			*o*				
NHAc			Br	*i*-C_3H_7		*p*	$C_{11}H_{14}NOBr$	Et_2O–petr. eth.	136–137	51.57	50.95	5.51	4.97
NH_2			*n*-C_6H_{13}			C	$C_{12}H_{19}N\cdot HCl$	EtOH–Et_2O	153–154	67.42	67.39	9.43	9.10
NHAc			*i*-C_3H_7			E			*q*				
NO_2			*n*-C_6H_{13}			I			*b*				
NHAc				*i*-C_3H_7		E			*q*				
			n-C_6H_{13}			H			*r*				

[a] Not characterized. In general these were oils that were not purified but immediately carried on to the next step. [b] J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **117**, 117 (1920). [c] H. J. B. Bickart, H. B. Dessens, P. E. Verkade and B. M. Wepstev, *Rec. trav. chim.*, **71**, 321 (1952). [d] W. Birsche and J. Barthenhin, *Ann.*, **553**, 250 (1942). [e] H. Hähle, *J. prakt. Chem.*, **43**, 64 (1891). [f] W. Heimisch, *Monatsh.*, **15**, 233 (1894). [g] Commercially available. [h] J. Frejka and F. Vezmetal, *Collection Czechoslov. Chem. Comm.*, **7**, 436 (1935). [i] The tosyl group was removed by heating 10 g. of the tosyl derivative with 10 ml. of concentrated H_2SO_4 and 5 ml. of HOAc on the steam-bath for 1.5 hours. The homogeneous solution was poured into 25 ml. of ice-water to precipitate the product. [j] F. Ullman and C. Gross, *Ber.*, **43**, 2698 (1910). [k] N. J. Leonard and S. N. Boyd, *J. Org. Chem.*, 11, 405 (1946). [l] Tosylation was performed in pyridine solution. [m] V. N. Ipatieff and L. Schmerling, THIS JOURNAL, **59**, 1056 (1937). [n] E. C. Sterling and M. T. Bogert, *J. Org. Chem.*, 4, 25 (1939). [o] O. Wallach and F. Hensler, *Ann.*, **243**, 223 (1888). [p] Bromination with N-bromosuccinimide in carbon tetrachloride. [q] E. J. Costam and H. Goldschmidt, *Ber.*, **21**, 1160 (1888). [r] D. Nightingale and H. D. Radford, *J. Org. Chem.*, 14, 1089 (1949).

for three hours or by the method of Verkade and Witjens[7] using sodium methoxide.

(7) P. E. Verkade and P. H. Witjens, *Rec. trav. chim.*, **62**, 201 (1943).

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[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

Synthesis of Some Substituted Benzoxazolones

BY ROBERT L. CLARK AND ARSENIO A. PESSOLANO

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A number of benzoxazolones substituted in the aromatic ring and on the nitrogen atom were synthesized. Some of them possessed anticonvulsant activity.

Since a number of benzimidazolones possessed interesting biological activity[1] a group of benzoxazolones was prepared to see whether any of them also had activity. They were less effective in protecting rats from lethal convulsions due to electro shock, but were very effective in protecting mice from lethal doses of metrazol.[2] 6-Carbamidobenzoxazolone was the most potent compound found, and it had approximately the same activity as trimethadione.

The benzoxazolone ring was prepared from the appropriate *o*-aminophenols, either by fusion with urea or by bubbling in phosgene.[3]

The manipulations on the benzoxazolone ring were carried out by standard chemical reactions, *i.e.*, the amines were prepared from the nitro compounds by hydrogenation, and acylated with acid anhydrides or acid chlorides. Carbamates and

(1) R. L. Clark and A. A. Pessolano, THIS JOURNAL, **80**, 1657 (1958).

(2) These biological results will be published in more detail in a publication from the Merck Institute for Therapeutic Research by Dr. J. Hawkins, Jr., and his associates.

(3) W. J. Close, B. D. Tiffany and M. A. Spielman, THIS JOURNAL, **71**, 1265 (1949).

thiocarbamates were prepared from the amine and potassium cyanate or ammonium thiocyanate. The nitrogen could be alkylated by the method used by Kloetzel[4] for alkylating amides. A second nitro group was introduced into 6-nitrobenzoxazolone by fuming nitric acid at room temperature.

Experimental[5]

5-Carbomethoxybenzoxazolone was prepared by the method of Einhorn.[6]

5-Carboxybenzoxazolone.—The methyl ester was hydrolyzed by 1 *N* sodium hydroxide for three hours at 100°, and crystallized from sodium hydroxide–acetic acid, m.p. 336–338°.

Anal. Calcd. for $C_8H_5NO_4$: C, 53.63; H, 2.81. Found: C, 53.98; H, 2.51.

5-*t*-Butylbenzoxazolone.—A solution of 130 g. of 4-*t*-butylphenol was added to a mixture of 100 ml. of nitric acid in 200 ml. of acetic acid cooled to −10°. After four hours the solution was poured into ice containing 110 ml. of 30% sodium hydroxide. The product was extracted 3 times with benzene, the combined benzene washed and then steam distilled. The oil that distilled was extracted with ether and then after removing the ether distilled *in vacuo*, distilling at 83–88° (1 mm.), yield 81.4 g. This material was hydrogenated in 700 ml. of ethanol by the use of 4 g. of 5% palladium-on-Darco. After removing the catalyst the solvent was evaporated to give 4-*t*-butyl-2-aminophenol, m.p. 156–157°.

A mixture of 16 g. of 4-*t*-butyl-2-aminophenol and 13 g. of urea was heated over an open flame to a liquid. Heating was continued until no more bubbling occurred. After cooling, the solid was extracted with 30 ml. of warm ethanol. This alcohol extract was diluted with water to give 15.5 g. of material melting at 143–145°. Recrystallization from 50 ml. of absolute ethanol gave 11.7 g. of 5-*t*-butylbenzoxazolone melting at 146–147°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.13; H, 6.65.

5-*n*-Octylbenzoxazolone.—4-*n*-Octylphenol was nitrated like 4-*t*-butylphenol; however, the yield of steam-distilled material was only 17%. This was directly hydrogenated and the hydrochloride of the product prepared. It was crystallized from a small amount of alcohol by the addition of ether and petroleum ether, m.p. 218–220°. A solution of 8 g. of the above was dissolved in 200 ml. of ethanol and 200 ml. of water. When phosgene was added a gum separated which slowly solidified. This solid was dissolved in 40 ml. of absolute alcohol and after treatment with Darco was crystallized by the slow addition of water. It was recrystallized by solution in 25 ml. of ether and, after concentrating to 10 ml., petroleum ether was added; yield 3.0 g., m.p. 118–119°.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.56. Found: C, 72.13; H, 8.96.

6-Nitrobenzoxazolone was prepared using the method of St. Von Chelmicki.[7]

Fifty grams of benzoxazolone was added in portions to 240 ml. of concd. nitric acid. Slight warming was necessary to start the reaction, then it was kept at 50° by addition of benzoxazolone. Product began to separate toward the end of the addition. After standing 20 minutes the mixture was diluted with water to give 55 g. of 6-nitrobenzoxazolone. Recrystallization from ethanol–water raised the m.p. to 146°.

6-Aminobenzoxazolone.—The above nitro compound was hydrogenated in 70% alcohol using 5% palladium-on-Darco. It was crystallized from methanol, m.p. 310°.

Anal. Calcd. for $C_7H_6N_2O_2 \cdot HCl$: C, 45.05; H, 3.78. Found: C, 45.25; H, 4.00.

6-Carbamidobenzoxazolone.—To a suspension of 4.2 g. of 6-aminobenzoxazolone in 75 ml. of dilute hydrochloric acid was added 2.43 g. of potassium cyanate in 10 ml. of water. There was a complete solution at first and then a solid separated. The solid was recrystallized from 200 ml. of 50% ethanol, m.p. >340°.

Anal. Calcd. for $C_8H_7N_3O_3$: C, 49.74; H, 3.65. Found: C, 49.72; H, 3.69.

6-Thiocarbamidobenzoxazolone was prepared similarly to the 6-carbamidobenzoxazolone except ammonium thiocyanate was used. It was necessary to heat under reflux three hours. Upon cooling the solid separated and was crystallized from pyridine–petroleum ether, m.p. 243°.

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.92; H, 3.37. Found: C, 46.26; H, 3.51.

6-(N,N-Diphenylcarbamido)-benzoxazolone.—To a solution of 4 g. of 6-aminobenzoxazolone in 75 ml. of warm pyridine was added 7.0 g. of diphenylcarbamyl chloride. The solution soon turned dark red and the temperature went from 40 to 60°. After standing overnight 8.5 g. of solid separated. Recrystallization from 50 ml. of pyridine by the addition of water gave 5.0 g., m.p. 206° (never a complete melt).

Anal. Calcd. for $C_{20}H_{15}N_3O_3$: C, 69.57; H, 4.38. Found: C, 69.87; H, 4.04.

3-Acetyl-6-acetylaminobenzoxazolone.—Thirty ml. of acetic anhydride was added to 5.0 g. of 6-aminobenzoxazolone and the suspension heated on the steam-bath for two hours. Most of the solid was in solution. After two more hours, a different solid had separated. After cooling, ether was added and the solid separated. It was recrystallized from aqueous acetone, m.p. 234°. Desai, *et al.*,[8] claim they obtained a monoacetyl derivative.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.40; H, 4.31; $COCH_3$, 36.70. Found: C, 56.18; H, 4.08; $COCH_3$, 35.60.

3-Diphenylacetyl-6-diphenylacetylaminobenzoxazolone.—Three grams of 6-aminobenzoxazolone was dissolved in 9.0 ml. of 2.5 *N* sodium hydroxide and 25 ml. of water. To this stirred solution was added simultaneously 9 ml. of 2.5 *N* sodium hydroxide in 30 ml. of water and 4.6 g. of diphenylacetyl chloride in 30 ml. of ether. A solid formed during the addition. After stirring one hour the mixture was made acidic and a new solid separated. This was crystallized from pyridine by the addition of water, m.p. 247°. The molecular weight and the analysis indicated the diacyl derivative.

Anal. Calcd. for $C_{35}H_{26}N_2O_4$: C, 77.91; H, 5.05. Found: C, 77.95; H, 4.53.

3-Methyl-6-nitrobenzoxazolone.—To a suspension of 9 g. of 6-nitrobenzoxazolone in acetone was added in portions 9.0 g. of powdered potassium hydroxide. A thick yellow-orange solid formed. To this was added 14.2 g. of methyl iodide in 30 ml. of acetone over ten minutes. After stirring three hours at room temperature the solid was removed and the filtrate evaporated. This residue was extracted with water leaving 3.0 g. of yellow solid. It was crystallized from 40 ml. of acetic acid to give 1 g., m.p. 183–184°. Re-extraction of the original solid with acetone gave more material.

Anal. Calcd. for $C_8H_6N_2O_4$: C, 49.49; H, 3.12. Found: C, 49.72; H, 2.81.

3-Methyl-6-aminobenzoxazolone.—3-Methyl-6-nitrobenzoxazolone was hydrogenated in ethanol using 5% palladium-on-Darco as the catalyst. The hydrochloride was crystallized from alcohol, m.p. 315°.

Anal. Calcd. for $C_8H_8N_2O_2 \cdot HCl$: C, 58.52; H, 4.91. Found: C, 58.78; H, 4.64.

3-Methyl-6-carbamidobenzoxazolone was prepared like 6-carbamidobenzoxazolone, and was crystallized from water, m.p. 359°.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.18; H, 4.38. Found: C, 52.58; H, 4.44.

5-Nitrobenzoxazolone.—To a solution of 100 g. of 2-amino-4-nitrophenol in dilute hydrochloric acid was added phosgene. After several minutes the benzoxazolone sepa-

(4) I. J. Pachter and M. C. Kloetzel, THIS JOURNAL, **74**, 1321 (1952).

(5) We are indebted to Mr. R. N. Boos and his associates for the microanalyses, and to Dr. W. H. Jones and his associates for the hydrogenations.

(6) A. Einhorn and E. Ruppert, *Ann.*, **325**, 324 (1902).

(7) St. Von Chelmicki, *J. prakt. Chem.*, [2] **42**, 441 (1890).

(8) R. D. Desai, R. F. Hunter and A. R. K. Khaliki, *J. Chem. Soc.*, 321 (1938).

rated. After two hours 48 g. of product was collected, m.p. 229–232°. Recrystallization from dioxane raised the melting point to 231–232°.

Anal. Calcd. for $C_7H_4N_2O_4$: C, 46.68; H, 2.24. Found: C, 46.56; H, 2.35.

5-Aminobenzoxazolone.—The 5-nitrobenzoxazolone was hydrogenated using 5% palladium-on-Darco as catalyst. It was crystallized from alcohol–water, m.p. 223°.

Anal. Calcd. for $C_7H_6N_2O_2$: C, 55.99; H, 4.03. Found: C, 55.92; H, 4.03.

5-Carbamidobenzoxazolone was prepared like 6-carbamidobenzoxazolone. It was crystallized from water, m.p. 356°.

Anal. Calcd. for $C_8H_7N_3O_3$: C, 49.74; H, 3.65. Found: C, 49.90; H, 3.59.

5,6-Dinitrobenzoxazolone.—A solution of 15 g. of 6-nitrobenzoxazolone in 100 ml. of fuming nitric acid was warmed to 40° on the steam-bath, it was then removed and the temperature climbed to 60°. After standing overnight it was diluted with water to give 17.5 g. Recrystallization from alcohol–water gave 14 g., m.p. 190–195°. A sample was recrystallized for analysis and the melting point was 199–201°.

Anal. Calcd. for $C_7H_3N_3O_6$: C, 37.34; H, 1.34. Found: C, 37.13; H, 1.32.

5,6-Ureidobenzoxazolone.—5,6-Dinitrobenzoxazolone was hydrogenated in alcohol using 5% palladium-on-Darco. The diamine was quite insoluble and considerable difficulty was encountered getting it separated from the catalyst. Some hydrochloride was prepared and this was dissolved in water and phosgene bubbled into it. A pink solid separated. It was purified by dissolving in sodium hydroxide and precipitating with hydrochloric acid.

Anal. Calcd. for $C_8H_5N_3O_3$: C, 50.27; H, 2.64. Found: C, 49.39; H, 2.78.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Utilization of α,γ-Dialkoxyacetoacetates in the Synthesis of Certain 2-Thiouracils and Uracils[1]

BY HENRY R. HENZE AND EILHARD N. KAHLENBERG[2]

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A series of *sec*-butyl alkoxyacetates was converted into a new series of *sec*-butyl α,γ-dialkoxyacetoacetates, and the latter yielded the corresponding thiouracils by interaction with thiourea. Uracils were formed more readily by desulfurization of the thiouracils than from interaction of the alkoxyacetoacetates with urea.

In light of the early interest in thiouracils[3] and uracils,[4] and more recently, in connection with a study of compounds of possible use as metabolic inhibitors, it was decided to attempt the synthesis of certain pyrimidines containing alkoxy substituents. Production of these compounds was visualized through utilization of well-established procedures involving condensation of substituted acetoacetates with thiourea or urea. During the preliminary investigations in this work, it was demonstrated that *sec*-butyl alkoxyacetates gave better yields of dialkoxyacetoacetates, upon condensation, than did the corresponding methyl, ethyl and propyl alkoxyacetates. Using a method described by Johnson and Caldwell,[5] the *sec*-butyl alkoxyacetoacetates were converted into the corresponding 5-alkoxy-6-alkoxymethyl-2-thiouracils by allowing the esters to react with thiourea in the presence of sodium methoxide. When it was found that the corresponding uracils were better prepared from the thiouracils than from condensation of the keto esters with urea, each thiouracil derivative was in turn desulfurized through use of chloroacetic acid.

It was next of interest to investigate the cleavage of the ether linkages of both the thiouracil and uracil derivatives, since the ease of cleavage and/or replacement of their alkoxyl groups would have a direct bearing on their possible use as intermediates in the synthesis of pyrimidines of more complex structure. It was recalled that, in a search for a synthesis of orotic acid,[5] the cleavage of both ethoxyl groups of 5-ethoxy-6-ethoxymethyluracil had been accomplished under pressure by means of concentrated hydrochloric acid at 120–140°; such treatment resulted in formation of 5-hydroxy-6-hydroxymethyluracil. Since hydrogen iodide is the common reagent for scission of ether linkages, although frequently extensive reduction of the product is noted, the behavior of certain thiouracil and uracil derivatives toward hot concentrated hydriodic acid was investigated. It was found that 5-isobutoxy-6-isobutoxymethyl-2-thiouracil could be reductively cleaved in a stepwise fashion. The initial stage involved cleavage of the alkoxyl group at the 6-position with reduction to form 5-isobutoxy-6-methyl-2-thiouracil. The next step comprised splitting, unaccompanied by reduction at the 5-position, resulting in formation of 5-hydroxy-6-methyl-2-thiouracil. The latter resulted, also, from similar treatment of 5-isopropoxy-6-isopropoxymethyl-2-thiouracil.

Similarly, reductive cleavage was found to occur with the corresponding uracils. Thus, using boiling, concentrated hydriodic acid, 5-isobutoxy-6-isobutoxymethyluracil was converted into 5-isobutoxy-6-methyluracil and 5-hydroxy-6-methyluracil. The latter compound had previously been prepared through oxidation of 6-methyluracil by Behrund and Grünewald.[6] They reported that uracils containing an hydroxyl substituent at the 5-

(1) From the Ph.D. dissertation of E. N. Kahlenberg at the University of Texas, June, 1954.

(2) Eastman Kodak Company Research Fellow, 1953–1954.

(3) W. B. Baker, *J. Am. Pharm. Assoc., Pract. Pharm. Ed.*, **6**, 359 (1945).

(4) T. G. Klumpp and J. B. Rice, *Record Chem. Progr., Kresge-Hooker Sci. Lib.*, **7**, 15 (1946).

(5) T. B. Johnson and W. T. Caldwell, THIS JOURNAL, **51**, 873 (1929).

(6) R. Behrund and R. Grünewald, *Ann.*, **323**, 186 (1902).