and diluting with an equal volume of petroleum ether (b.p. 90–100°). The product, after drying at 60° *in vacuo* for one hour, melted with decomposition at about 195–200°. All other properties of this compound were identical to those already described.[8]

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

Synthesis of Some Substituted Benzimidazolones

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RECEIVED NOVEMBER 2, 1957

A number of benzimidazolones, substituted in the aromatic ring and on the nitrogen atoms, and the necessary intermediates, were synthesized. Some of them possessed anti-convulsant, antimitotic and anti-leukemic activity.

This paper deals with the synthesis of substituted benzimidazolones. Although a number of benzimidazolones are reported in the literature, very few data are available on their pharmacological activity. It has now been found that many of them protect rats from convulsions due to electro shock, one of the better ones being 5-tetradecylbenzimidazolone.[1] Also, some, especially 5-*t*-butylbenzimidazolone, have an anti-mitotic effect.[1] Several of the compounds showed activity against mouse leukemia; one of the best compounds was 1,3-dimethyl-5-*t*-butylbenzimidazolone.[2]

The benzimidazolone ring was formed from substituted *o*-diaminobenzene derivatives by one of two methods, either the diamine was allowed to react with phosgene, or heated with urea. In the former case phosgene was bubbled into an aqueous acid solution of the diamine. In most cases the benzimidazolone separated almost immediately and could be washed free of impurities. A solution resulting from a stannous chloride reduction of an *o*-nitroamine could be used directly with phosgene, without isolation of the diamine.

In the latter case an intimate mixture of the *o*-diamine (or acid salt) and urea was heated slowly to 140°. At this temperature a melt usually resulted. With continued heating the liquid solidified to give the benzimidazolone which could be purified by crystallization.

The diamine intermediates, listed in Table II, were prepared by more or less standard procedures from the most available starting materials. All other intermediates leading up to the *o*-diamine are listed in Table III along with their method of preparation.

The N-alkylated derivatives were prepared by the use of the method Kloetzel[3] developed for alkylating amides. A suspension of the benzimidazolone, powdered potassium hydroxide and the alkyl halide in acetone was heated under reflux to give, in most cases, a good yield of the dialkylated benzimidazolone.

To prepare monoalkylbenzimidazolones it was necessary to form first the N-alkylnitroamine. This was done by tosylating an *o*-nitroaniline and then alkylating the nitrogen of the sulfonamide. The tosyl group was then hydrolyzed and the nitro group reduced to give the monoalkylated *o*-diamine.

Acylation of the benzimidazolone nitrogen was readily carried out using acid anhydrides at elevated temperatures.

The benzene ring of benzimidazolone can be acylated by a Friedel–Crafts reaction using an acid chloride in carbon disulfide in the presence of aluminum chloride.[4] These acyl compounds can then be reduced to give the alkyl derivatives.

All of the benzimidazolones prepared, along with their method of preparation and physical constants, are listed in Table I.

Experimental[5]

A. **Reaction of *o*-Diamines with Phosgene.**—Phosgene was bubbled into an aqueous hydrochloric acid solution of the *o*-diamine. In some cases the product precipitated in a very short time, while others required several hours. After precipitation was complete the benzimidazolone was collected and washed well with water. This product was fairly pure but generally could be recrystallized if desired. The phosgene method was superior to the urea method in that a whiter, purer product was obtained in better yields (75–95%).

B. **Reaction of *o*-Diamines with Urea.**—A mixture of 1.0 mole of aromatic *o*-diamine, or its hydrochloride, and 1.1 moles of urea was heated in an oil-bath at 140° or higher, depending upon the melting point of the mixture. A clear melt formed which was followed by effervescence. Heating was continued, and in most cases the substituted benzimidazolone soon solidified. After heating 15 minutes more the solid mass was cooled and dissolved in 2.5 *N* sodium hydroxide. After filtration it was reprecipitated with concentrated hydrochloric acid. The benzimidazolone was then crystallized or purified further by repetition of the base–acid treatment. The yields ranged from 40 to 75%.

C. **Catalytic hydrogenation of nitro groups** was accomplished by shaking an alcohol solution of the nitro compound under hydrogen at 40 p.s.i. in the presence of 5% palladium-on-charcoal. After removing the catalyst by filtration the filtrate was either evaporated to give the free amines, or hydrogen chloride was passed into the solution. Often the hydrochloride separated immediately but sometimes ether had to be added to precipitate it.

(1) These biological results will be presented in more detail in a publication from the Merck Institute for Therapeutic Research by Drs. J. Hawkins, Jr., and H. Stoerk.

(2) Private communication from the Division of Chemotherapy of Sloan-Kettering Institute.

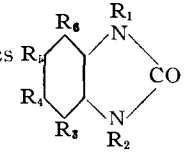
(3) I. J. Pachter and M. C. Kloetzel, THIS JOURNAL, **74**, 1321 (1952).

(4) J. R. Vaughan and J. Blodinger, *ibid.*, **77**, 5757 (1955).

(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.

TABLE I

BENZIMIDAZOLONES



R_1	R_2	R_4	R_4	R_5	R_5	Method of prepn.	Formula	Recrystn. solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
		CH_3				A	$C_8H_8N_2O$	MeOH	302–303	64.85	65.08	5.44	5.33	18.91	19.09
		CH_3		CH_3		A	$C_9H_{10}N_2O$	HOAc	337	66.65	66.65	6.22	5.99	17.28	16.85
			CH_3	CH_3		B	$C_9H_{10}N_2O$	HOAc	>345	66.65	66.90	6.22	6.11	17.28	17.31
		CH_3	CH_3	CH_3	CH_3	B	$C_{11}H_{14}N_2O$	HOAc–H_2O	313–314	69.44	69.79	7.42	6.80	14.73	14.46
			C_2H_5			A	$C_9H_{10}N_2O$	EtOH	264–265	66.65	66.58	6.22	5.98	17.28	17.26
		C_2H_5				A	$C_9H_{10}N_2O$	EtOH	261–262	66.65	66.40	6.22	6.20	17.28	17.11
		i-C_3H_7				[a]	$C_{10}H_{12}N_2O$	EtOH–H_2O	232–233	68.14	68.28	6.87	7.06	15.90	15.58
			n-C_3H_7			A	$C_{10}H_{12}N_2O$	EtOH–H_2O	239–241	68.14	68.16	6.87	6.51	15.90	16.14
			i-C_3H_7			A	$C_{10}H_{12}N_2O$	EtOH	270–272	68.14	67.90	6.87	6.83	15.90	15.78
			n-C_4H_9			A	$C_{11}H_{14}N_2O$	EtOH–H_2O	250	69.43	69.28	7.42	7.54	14.73	14.39
			s-C_4H_9			A	$C_{11}H_{14}N_2O$	EtOH–H_2O	253–254	69.43	69.61	7.42	7.28	14.73	15.07
			t-C_4H_9			A	$C_{11}H_{14}N_2O$	EtOH–H_2O	310	69.43	69.54	7.42	7.47	14.73	15.16
			n-C_5H_{11}			H	$C_{12}H_{16}N_2O$	EtOH–H_2O	261–264	70.55	70.26	7.90	7.79	13.72	13.86
			t-C_5H_{11}			A	$C_{12}H_{16}N_2O$	EtOH–H_2O	284–285	70.55	70.46	7.90	7.89	13.72	13.57
			s-C_5H_{11}			A	$C_{12}H_{16}N_2O$	EtOAc	217–218	70.55	70.77	7.90	7.83	13.72	14.00
			i-C_5H_{11}			H	$C_{12}H_{16}N_2O$	EtOH–H_2O	256–259	70.55	70.66	7.90	7.58	13.72	13.90
			n-C_6H_{13}			A	$C_{13}H_{18}N_2O$	EtOAc	250–252	71.53	71.38	8.31	8.10	12.84	12.70
			n-C_8H_{17}			H	$C_{15}H_{22}N_2O$	EtOH	240–242	73.22	73.18	9.01	8.44	11.39	11.34
			C_6H_5			B	$C_{13}H_{10}N_2O$	HOAc	350	74.27	74.21	4.80	4.77	13.33	13.51
			n-$C_{14}H_{29}$			H	$C_{21}H_{34}N_2O$	EtOH	226	76.31	76.49	10.37	10.10	8.48	8.61
			Ac			A	$C_9H_8N_2O_2$	EtOH–H_2O	296–297	61.36	61.70	4.58	4.71	15.91	15.57
			COC_4H_9			G	$C_{12}H_{14}N_2O_2$	EtOH–H_2O	269–271	66.02	65.89	6.46	6.39	12.84	13.10
			i-COC_4H_9			G	$C_{12}H_{14}N_2O_2$	EtOH	268–270	66.02	66.26	6.46	6.45	12.84	12.76
			COC_7H_{15}			G	$C_{15}H_{20}N_2O_2$	EtOH	246–247	69.20	69.53	7.75	7.20	10.76	10.57
			$COC_{13}H_{27}$			G	$C_{21}H_{32}N_2O_2$	EtOH	229	73.21	73.49	9.37	9.28	8.13	8.39
			OH			A	$C_7H_6N_2O_2$	EtOH–H_2O	307–309	55.99	56.15	4.03	3.80	18.66	18.56
			OCH_3			A	$C_8H_8N_2O_2$	EtOH	256–257	58.52	58.32	4.91	5.03	17.06	16.81
			OCH_3	OCH_3		B	$C_9H_{10}N_2O_3$	Dioxane	268	55.69	55.69	5.19	5.73	14.43	14.31
			OC_2H_5			A	$C_9H_{10}N_2O_2$	HOAc	272–273	60.66	60.77	5.66	5.80	15.73	15.31
			NH_2			C	$C_7H_7N_3O$·HCl	EtOH–Et_2O	>340	45.29	45.08	4.35	3.92	22.64	22.44
			F			A	$C_7H_5N_2OF$	EtOH–H_2O	303	55.26	55.57	3.31	3.39	18.42	18.38
		i-C_3H_7		Br		A	$C_{10}H_{11}N_2OBr$	EtOH–H_2O	245–249	47.07	47.12	4.35	4.11	10.98	10.95
			Br			A	$C_7H_5N_2OBr$	HOAc	336–337	39.46	39.47	2.37	2.43	13.16	13.47

TABLE I (*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	Nitrogen, % Calcd.	Nitrogen, % Found
		Cl				A	$C_7H_5N_2OCl$	EtOH–H_2O	335–336	49.87	50.26	2.99	2.87	16.62	16.81
		Cl		Cl		B	$C_7H_4N_2OCl_2$	Diox.–H_2O	>340	41.41	41.86	1.99	1.59	13.80	14.23
			Cl	Cl		B	$C_7H_4N_2OCl_2$	Base–acid	345	41.41	41.58	1.99	2.05	13.80	13.75
		Cl	Cl	Cl		B	$C_7H_3N_2OCl_3$	Base–acid	342	35.40	35.73	1.27	1.29	11.80	11.99
			$NHCONH_2$			[b]	$C_8H_8N_4O_2$	Base–acid	345	50.00	50.13	4.20	4.42	29.16	28.55
$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$					F	$C_{13}H_{14}N_2O$	Petr. eth.	53–54	72.86	73.12	6.59	6.51	13.08	12.83
$CH_2C_6H_5$	$CH_2C_6H_5$					F	$C_{21}H_{18}N_2O$	Et_2O	107–108	80.24	80.08	5.77	5.53	8.92	8.65
C_2H_5			CH_3			A	$C_{10}H_{12}N_2O$	EtOH–H_2O	115	68.14	68.31	6.87	6.61	15.90	16.01
CH_3	CH_3		*t*-C_4H_9			F	$C_{13}H_{18}N_2O$	EtOH–H_2O	180–181	71.53	71.44	8.31	8.00	12.84	12.93
CH_3	CH_3		*i*-C_3H_7			F	$C_{12}H_{16}N_2O$	EtOH–H_2O	142–143	70.55	70.20	7.90	7.84	13.72	13.24
$CH_2C(CH_3){=}CH_2$	$CH_2C(CH_3){=}CH_2$					F	$C_{15}H_{18}N_2O$	Et_2O–petr. eth.	85–86	74.34	74.07	7.49	7.30	11.50	11.64
CH_3	CH_3		CH_3	CH_3		F	$C_{11}H_{14}N_2O$	EtOAc	153–154	69.28	69.55	7.42	7.35	14.73	14.70
C_6H_5						A	$C_{13}H_{10}N_2O$	EtOH	206–207	74.27	73.97	4.80	5.00	13.33	13.48
CH_3	CH_3		Cl			F	$C_9H_9N_2OCl$	EtOH–H_2O	163–164	54.97	55.25	4.61	4.83	14.25	14.03
CH_3	CH_3		CH_3			F	$C_{10}H_{12}N_2O$	Et_2O–petr. eth.	103–105	68.14	68.34	6.87	6.57	15.90	16.24
CH_3	CH_3		OCH_3			F	$C_{10}H_{12}N_2O_2$	C_6H_6–petr. eth.	92–93	62.47	62.90	6.30	5.93	14.58	14.38
C_2H_5	C_2H_5					F	$C_{11}H_{14}N_2O$	Petr. eth.	68–69	69.44	69.55	7.42	7.20	14.73	14.47
CH_3			CH_3			A	$C_9H_{10}N_2O$	EtOH–H_2O	197–199	66.65	66.65	6.22	6.67	17.28	17.02
C_2H_5						A	$C_9H_{10}N_2O$	Et_2O–petr. eth.	117–118	66.65	66.75	6.22	6.07	17.28	17.10
$CH_2CH_2C_6H_5$	$CH_2CH_2C_6H_5$					F	$C_{23}H_{22}N_2O$	Et_2O–petr. eth.	74–75	80.67	80.94	6.48	6.44	8.18	8.17
CH_3	CH_3		Br			F	$C_9H_9N_2OBr$	EtOH	166–167	44.83	45.06	3.76	3.91	11.62	11.05
CH_3	CH_3		OC_2H_5			F	$C_{11}H_{14}N_2O_2$	EtOH–H_2O	104–105	64.05	64.20	6.84	6.57	13.59	13 84
CH_3	Ac					E	$C_{10}H_{10}N_2O_2$	EtOH	120–121	63.14	63.2	5.30	5.28	14.73	14.56
C_6H_5	Ac					E	$C_{15}H_{12}N_2O_2$	EtOH	137–138	71.42	71.43	4.80	4.92	11.11	11.27
Ac	Ac		NHAc			E	$C_{13}H_{13}N_3O_4$	HOAc–H_2O	260–261	56.73	56.70	4.76	4.71	15.27	15.57
COC_2H_5						[c]	$C_{14}H_{10}N_2O_2$	EtOH	212–213	70.58	70.74	4.23	4.32	11.76	11.46
Ac	Ac		*t*-C_4H_9			E	$C_{15}H_{18}N_2O_3$	EtOAc-petr. eth.	127–130	65.68	66.17	6.61	6.29	10.22	10.62
COC_2H_5	COC_2H_5					E	$C_{13}H_{14}N_2O_3$	EtOAc	169–170	63.40	63.69	5.73	5.70	11.38	11.71
Ac	Ac		Cl			E	$C_{11}H_9N_2O_3Cl$	EtOAc	172–173	52.29	52.41	3.59	3.26	11.09	11.02
Ac	Ac		NO_2			E	$C_{11}H_9N_3O_5$	EtOH	131–132	50.19	50.33	3.45	3.70	15.97	16.45
Ac	Ac		Cl	Cl		E	$C_7H_3N_2O_3Cl_2$	Dioxane	218–219	46.01	46.28	2.81	2.68	9.76	9.75
Ac	CH_3					E	$C_{10}H_{10}N_2O_2$	EtOH	120–121	63.14	63.23	5.30	5.28	14.73	14.56
CH_3	CH_2OH					[d]	$C_9H_{10}N_2O_2$	EtOH	153–154	60.66	60.87	5.66	5.36	15.73	15.31
CH_3	CH_2OAc					E	$C_{11}H_{12}N_2O_3$	EtOAc	115–116	59.99	60.05	5.50	5.39	12.73	12.56
$CH_2COC_6H_5$	$CH_2COC_6H_5$					F	$C_{23}H_{18}N_2O_3$	HOAc–H_2O	197–198	74.56	74.09	4.90	4.60	7.57	7.59
$CH_2CH_2NMe_2$	$CH_2CH_2NMe_2$					F	$C_{15}H_{24}N_4O{\cdot}2HClO_4$	H_2O–EtOH	238	37.74	37.58	5.49	5.57	11.74	11.48
1-Xanthyl			*t*-C_4H_9			[e]	$C_{24}H_{22}N_2O_2$	EtOAc	253–254	77.82	77.64	5.99	5.45	7.57	7.35
$CH_2CH_2NEt_2$	$CH_2CH_2NEt_2$					F	$C_{19}H_{32}N_4O{\cdot}2HClO_4$	MeOH	142–143	42.79	42.86	6.43	6.19	10.50	10.76
CH_2COOEt	CH_2COOEt					F	$C_{15}H_{18}N_2O_5$	EtOH	169–170	58.83	59.07	5.92	5.79	9.15	9.33

TABLE I (*Concluded*)

R_1	R_2	R_3	R_4	R_5	Method of prepn.	Formula	Recrystn. solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3COOH	CH_3COOH				[f]	$C_{11}H_{10}N_2O_5$	EtOH	291–292	52.80	52.60	4.03	4.42	11.20	11.29
$CH_3CH_2NEt_2$	$CH_3CH_2NEt_2$		*t*-C_4H_9		F	$C_{23}H_{40}N_4O\cdot 2HClO_4$	EtOH–H_2O	140	46.86	46.77	7.18	7.08	9.50	9.13
$CH_3CH_2NEt_2$	$CH_3CH_2NEt_2$	CH_3		CH_2	F	$C_{21}H_{36}N_4O\cdot 2HClO_4$	EtOH–H_2O	201–203	44.93	45.06	6.82	6.74	9.98	10.09
$CH_3CH(CH_3)NMe_2$	$CH_3CH(CH_3)NMe_2$				F	$C_{17}H_{28}N_4O\cdot 2HClO_4$	EtOH–H_2O	229–230	40.40	40.08	5.99	5.70	11.09	10.82
$CH_3CH_2NEt_2$	$CH_3CH_2NEt_2$		OCH_3		F	$C_{20}H_{34}N_4O_2\cdot 2HClO_4$	EtOH–H_2O	160–162	42.64	42.70	6.44	6.42	9.95	9.53
CH_3	CH_3		NO_2		F	$C_9H_9N_3O_2$	EtOAc	208–209	52.18	52.10	4.38	4.60	20.29	20.47
CH_3	CH_3		NH_2		C	$C_9H_{11}N_3O\cdot HCl\cdot 1/2$ H_2O	MeOH–Et_2O	310	48.55	48.26	5.89	6.20	18.88	18.83
CH_3	CH_3		$NHCONH_2$		F	$C_{10}H_{12}N_4O_2$	HOAc–H_2O	350	54.53	54.27	5.49	5.29	25.44	25.38
			–NHCONH–		[g]	$C_8H_8N_4O_2\cdot 1/2$ H_2O	EtOH	>340	48.24	48.00	3.54	3.49	28.13	28.10
		–CH=CHCH=CH–			A	$C_{11}H_8N_2O$	HCONMe$_2$–Et_2O	>345	71.73	71.36	4.38	4.58	15.22	15.81

[a] Catalytic hydrogenation of the 6-bromo compound using platinum oxide. [b] An acid solution of the amine was treated with potassium cyanate. [c] Benzimidazolone, benzoyl chloride and nitrobenzene were heated under reflux for four hours. [d] 1-Methylbenzimidazolone was refluxed with aqueous formaldehyde. See L. Monti and M. Venturi, *Gazz. chim. ital.*, **76**, 365 (1946). [e] Prepared from *t*-butylbenzimidazolone by the method of L. Monti, *Gazz. chim. ital.*, **72**, 515 (1942). [f] Obtained from the ester by hydrolysis. [g] Reduction of 5,6-dinitrobenzimidazolone and treatment of the diamine with phosgene.

D. Stannous Chloride Reduction of Nitro Groups.—This method can be illustrated by the procedure used for the preparation of 4-phenyl-1,2-phenylenediamine. To a well-stirred solution of 100 g. of stannous chloride hydrate in 180 ml. of concentrated hydrochloric acid was added portionwise 30 g. of 4-phenyl-2-nitroaniline. The temperature was maintained under 40° by cooling. The mixture became purplish in color and very thick. After two hours of stirring the mixture was allowed to stand overnight at room temperature. It was added slowly to a cold solution of 350 g. of sodium hydroxide in about 800 ml. of water, the temperature being held below 10°. After three hours 4-phenyl-1,2-phenylenediamine was removed by filtration and crystallized from a hot solution of it in 700 ml. of alcohol by the addition of water. The yield was 20 g. of m.p. 102–103°.

If the diamine is to be converted to the benzimidazolone the free diamine need not be isolated. The following procedure is an example of this. A suspension of 17.5 g. of 2-nitro-4 isopropylacetanilide in 125 ml. of concentrated hydrochloric acid was heated on the steam-bath for three hours to remove the acetyl group. The solution was cooled to 50° and a solution of 75 g. of stannous chloride hydrate in 30 ml. of water and 15 ml. of concentrated hydrochloric acid was added slowly with stirring. This solution was cooled to room temperature and decolorized with Darco. The resulting clear solution was treated directly with phosgene to give 5-isopropylbenzimidazolone.

E. Acylation of the Nitrogen Atom in Benzimidazolone.—This was accomplished by heating the benzimidazolone with five times its weight of an acid anhydride under reflux for three hours. The cooled solution deposited the N,N′-diacyl derivative.

F. The alkylation of benzimidazolones can be illustrated by the preparation of 1,3-dimethylbenzimidazolone. A mixture of 152 g. (1.13 moles) of benzimidazolone and 365 g. (6.5 moles) of powdered potassium hydroxide in 2000 ml. of acetone was stirred and heated to gentle reflux. The external heat was removed and a solution of 432 g. (3.04 moles) of methyl iodide in 350 ml. of acetone was added dropwise, gentle reflux being maintained by the heat of reaction. Toward the end of the addition most of the solid material was in solution. This was heated for ten more minutes when the supernatant liquid was decanted. The pasty residue was extracted three times with more acetone. The combined extracts upon evaporation left a crystalline mass, weight 165 g., m.p. 103–108°. This was recrystallized from 450 ml. of hot benzene by the slow addition of 100 ml. of petroleum ether (b.p. 30 to 60°); yield 122 g. (66.5%), m.p. 111–112° (lit.[6] m.p. 113°). The addition of more petroleum ether to the mother liquor gave another 39 g. (21%), m.p. 109–112°. The reaction with allyl bromide took an hour of heating, but the yield was comparable. The reaction with benzyl chloride, β-phenylethyl bromide and ethyl iodide took much longer and the yields were lower.

G. Acylation of the benzene ring of benzimidazolone was performed by a Friedel–Crafts reaction in the usual manner. The method recently has been published by Vaughan and Blodinger.[4]

H. The hydrogenation of acylbenzimidazolones can be illustrated by the procedure for preparing 5-tetradecylbenzimidazolone. A suspension of 100 g. of 5-myristoylbenzimidazolone in 1500 ml. of ethanol was hydrogenated using 10 g. of copper chromite #8 as the catalyst at 225° for 3.5 hours. After removing the catalyst it was extracted several times with hot dioxane. The combined filtrates upon cooling gave 65 g. of 5-tetradecylbenzimidazolone. Recrystallization from 500 ml. of acetic acid yielded 54 g. of product melting at 226° with previous softening.

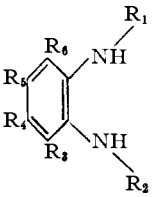
I. Nitrations of acylamino compounds were generally carried out in a manner similar to that used to prepare 3-nitro-4-acetylaminoacetophenone. To a stirred mixture of 47 g. of 4-acetylaminoacetophenone in 150 ml. of acetic acid and 50 ml. of acetic anhydride was added 23 ml. of fuming nitric acid at 40°. A clear solution resulted after about 18 ml. of nitric acid had been added. It was stirred for an additional hour and then poured into 1500 ml. of water. Forty-four grams of a *gummy* solid separated which was crystallized from 115 ml. of acetic acid to give 20 g. of 3-nitro-4-acetylaminoacetophenone melting at 135–137°. Recrystallization raised the melting point to 140–141°.

J. Deacylation of acylamines.—Acylamines were hydrolyzed to the amines either by heating with hydrochloric acid

(6) O. Fischer and E. Fussenegger, *Ber.*, **34**, 936 (1901).

TABLE II

1,2-PHENYLENEDIAMINES

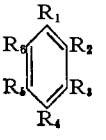


R_1	R_2	R_3	R_4	R_5	R_6	Method of prepn.	Formula	Recrystn. solvent	M.p., °C.	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
		CH_3				C	$C_7H_{10}N_2$		[a]				
		CH_3		CH_3		C	$C_8H_{12}N_2$		[b]				
			CH_3	CH_3		C	$C_8H_{12}N_2$		[c]				
		CH_3	CH_3	CH_3	CH_3	D	$C_{10}H_{16}N_2$		[d]				
			C_2H_5			C	$C_8H_{12}N_2 \cdot 2HCl$	EtOH–Et_2O	308[e]	45.94	46.13	6.75	7.10
		C_2H_5				C	$C_8H_{12}N_2 \cdot HCl$	EtOH	258	55.64	55.62	7.59	7.47
			n-C_3H_7			C	$C_9H_{14}N_2 \cdot 2HCl$	EtOH–Et_2O	206–210	48.44	48.79	7.23	7.50
			i-C_3H_7			C	$C_9H_{14}N_2 \cdot 2HCl$	Dil. EtOH	267	48.44	48.36	7.23	7.11
			n-C_4H_9			C	$C_{10}H_{16}N_2 \cdot 2HCl$	EtOH	235	50.63	50.52	7.65	7.80
			s-C_4H_9			C	$C_{10}H_{16}N_2 \cdot 2HCl$	EtOH–Et_2O	249–251	50.63	50.78	7.65	7.37
			t-C_4H_9			C	$C_{10}H_{16}N_2$		[f]				
			t-C_6H_{11}			D	$C_{11}H_{18}N_2$		[f]				
			s-C_5H_{11}			C	$C_{12}H_{18}N_2 \cdot 2HCl$	EtOH	214–217	52.59	52.49	8.03	8.02
			n-C_6H_{13}			C	$C_{12}H_{20}N_2$		[f]				
			C_6H_5			D	$C_{12}H_{12}N_2$	EtOH	102–103	78.21	78.29	6.57	6.77
			Ac			C	$C_8H_{10}N_2O \cdot HCl$	Dil. EtOH	280–287	51.50	52.06	5.96	6.38
			OH			D	$C_6H_8N_2$		[f]				
			OCH_3			C	$C_7H_{10}N_2O \cdot 2HCl$	EtOH–Et_2O	227	39.82	40.22	5.73	5.68
			OCH_3	OCH_3		C	$C_8H_{12}N_2O_2 \cdot HCl$	Dil. MeOH	230–250[g]	46.96	47.11	6.40	6.14
			OC_2H_5			C	$C_8H_{12}N_2O$		[h]				
			F			D	$C_6H_7N_2F$		[f]				
		i-C_3H_7		Br		D	$C_9H_{13}N_2Br$		[f]				
			Br			D	$C_6H_7N_2Br$		[f]				
		Cl		Cl		D	$C_6H_6N_2Cl_2$		[i]				
			Cl	Cl		C	$C_6H_6N_2Cl_2$		[j]				
		Cl	Cl	Cl			$C_6H_6N_2Cl_2$		[k]				
C_2H_5			CH_3			C	$C_9H_{14}N_2 \cdot 2HCl$	EtOH	178–180	48.44	49.03	7.23	7.33
C_6H_5						C	$C_{12}H_{12}N_2$		[l]				
CH_3			CH_3			D	$C_8H_{12}N_2$		[f]				
C_2H_5						C	$C_8H_{12}N_2 \cdot HCl$	EtOH–Et_2O	188–193[m]				
		–CH=CH–CH=CH–				C			[n]				

[a] S. Gabriel and A. Thieme, *Ber.*, **52**, 1080 (1919). [b] O. Jacobsen, *ibid.*, **21**, 2826 (1888). [c] E. Noelting, A. Braun and G. Thesmar, *ibid.*, **34**, 2252 (1901). [d] L. I. Smith and L. R. Hac, THIS JOURNAL, **56**, 477 (1934). [e] H. Paucksch, *Ber.*, **17**, 770 (1884), gives m.p. 45–47° for free base. [f] No isolation. Solutions of these compounds were immediately treated with phosgene to give the benzimidazolones. [g] W. Heinisch, *Monatsh.*, **15**, 233 (1894); no m.p. given. [h] Autenrieth and Hinsberg, "Beilstein," Vol. 13, p. 564. [i] O. N. Witt, *Ber.*, **7**, 1604 (1874). [j] R. Nielzki and A. Konwaldt, *ibid.*, **37**, 3893 (1904). [k] Obtained from Dr. G. Stein of these laboratories. [l] M. Schöpff, *Ber.*, **22**, 3287 (1889). [m] A. Hempel, *J. prakt. Chem.*, [2] **39**, 199 (1889), gives b.p. of free base as 248–249°. [n] E. Lellmann and A. Remy, *Ber.*, **19**, 803 (1886).

TABLE III

BENZENE DERIVATIVES



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				Et	J			[a]				
NH_2	NO_2		n-C_3H_7			J	$C_9H_{12}N_2O_2$	H_2O–EtOH	59–60	59.98	59.95	6.71	6.51
NH_2	NO_2		i-C_3H_7			J			[a]				
NH_2	NO_2		n-C_4H_9			J			[b]				
NH_2	NO_2		t-C_4H_9			J			[c]				
NH_2	NO_2		s-C_4H_9			J			[b]				
NH_2	NO_2		s-C_5H_{11}			J			[b]				
NH_2	NO_2		t-C_5H_{11}			J			[b]				
NH_2	NO_2		n-C_6H_{13}			J			[b]				
NH_2	NO_2		Ac			J			[d]				
NH_2	NO_2		OH			J			[e]				
NO_2	NO_2		OCH_3	OCH_3					[f]				

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			l	$C_{11}H_{14}N_2O_3$	EtOH–H_2O	135	59.44	59.62	6.35	6.17
NHAc	NO_2		*i*-C_3H_7			l	$C_{11}H_{14}N_2O_3$	EtOH–H_2O	81–82	59.44	59.30	6.35	6.32
NHAc	NO_2		*s*-C_4H_9			I			*c*				
NHAc	NO_2		*s*-C_5H_{11}			I			*b*				
NHAc	NO_2		*t*-C_5H_{11}			I	$C_{13}H_{18}N_2O_3$	Petr. eth.	53–54	62.39	62.53	7.25	7.09
NHAc	NO_2		*n*-C_6H_{13}			I	$C_{14}H_{20}N_2O_3$	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		l	$C_{11}H_{13}N_2O_3Br$	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	$C_{16}H_{21}NO$	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. Heusler, *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).

Acknowledgment.—The authors wish to thank Dr. L. H. Sarett for his encouragement and guidance in this investigation.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

Synthesis of Some Substituted Benzoxazolones

BY ROBERT L. CLARK AND ARSENIO A. PESSOLANO

RECEIVED NOVEMBER 2, 1957

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).