Cincinnati. Mr. J. H. Lady, of this laboratory, performed the infrared analysis; Dr. D. O'Reilly, of Gulf Research Laboratories, performed the NMR analysis; Mr. E. Pantier, of this laboratory, performed some of the runs and distillations.

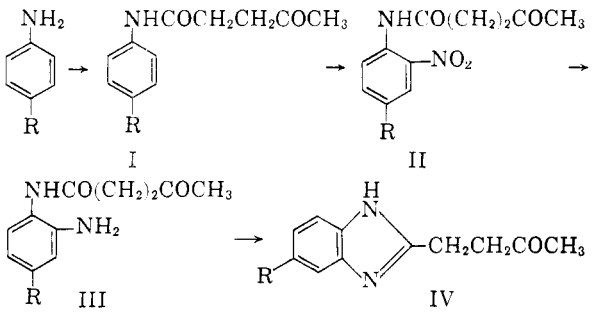
WESTINGHOUSE RESEARCH LABORATORIES
PITTSBURGH, PA.

Preparation of 5-Chloro- and 5-Bromo-2-(2-acetylethyl)benzimidazoles

TETSUO SUAMI[1] AND ALLAN R. DAY

Received February 6, 1959

In connection with other work on benzimidazoles, 2-acetylethylbenzimidazoles appeared to be of interest as potential antimetabolites and as starting materials for the preparation of other benzimidazole derivatives. The present paper describes the syntheses of two 2-acetylethylbenzimidazoles by the following route:



Six 4-substituted levulinanilides (I) were prepared by the acylation of 4-substituted anilines with γ-acetyoxy-γ-valerolactone (Table I). Lukes and Prelog[2] prepared levulinanilide and 4-methylevulinanilide by this method.

The oximes of the levulinanilide derivatives (Table II) were prepared by the usual method using hydroxylamine hydrochloride and 2*N* sodium hydroxide solution.

The levulinanilide derivatives, reported in Table I, were nitrated with a sulfuric acid–nitric acid mixture, at −10 to −20° (Table III). The oximes of the nitro compounds were prepared also (Table IV).

For the determination of the position of the nitro group, the nitrolevulinanilide derivatives were hydrolyzed with dilute hydrochloric acid to the corresponding nitroaniline derivatives. 4-Nitro-

TABLE I

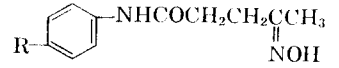
R	M.P., °C.	Yield, %	Formula	Analyses, %							
				Carbon		Hydrogen		Nitrogen		Chlorine		Bromine	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Cl	149–151[a]	58.7	$C_{11}H_{12}NClO_2$	58.54	58.58	5.36	5.36	6.21	6.22	15.71	15.56		
Br	157–158[b]	57.6	$C_{11}H_{12}NBrO_2$	48.91	48.99	4.48	4.63	5.19	5.22			29.58	29.40
COOH	214–216[c] (dec.)	48.5	$C_{12}H_{13}NO_4$	61.27	61.29	5.57	5.40	5.96	5.98				
$COOC_2H_5$	108–109[d]	28.8	$C_{14}H_{17}NO_4$	63.85	63.72	6.51	6.59	5.32	5.28				
$NHCOCH_3$	201–202[e] (dec.)	49.5	$C_{13}H_{16}N_2O_3$	62.89	62.75	6.50	6.65	11.29	11.23				
$NHCO(CH_2)_2COCH_3$	217–218[c]	37.8	$C_{16}H_{20}N_2O_4$	63.16	63.05	6.63	6.57	9.21	9.14				

[a] Recrystallized from 95% ethanol. [b] Recrystallized from methanol. [c] Recrystallized from water. [d] Recrystallized from ethyl acetate–ether. [e] Recrystallized from 1-butyl alcohol.

(1) Assistant Professor of Keio University (Tokyo, Japan). Postdoctoral Research Associate in the Department of Chemistry, University of Pennsylvania (1957–58).

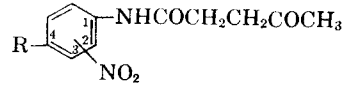
(2) R. Lukes and V. Prelog, *Collection Czechoslov. Chem. Communs.*, 1, 282 (1929).

TABLE II



R	M.P., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Bromine Calcd.	Bromine Found
H	144–145	$C_{11}H_{14}N_2O_2$	64.06	64.09	6.84	6.67	13.59	13.49				
CH_3	159–161	$C_{12}H_{16}N_2O_2$	65.43	65.62	7.32	7.09	12.72	12.68				
Cl	164–166	$C_{11}H_{13}N_2ClO_2$	54.89	54.74	5.44	5.35	11.64	11.53	14.77	14.55		
Br	178–180	$C_{11}H_{13}N_2BrO_2$	46.33	46.09	4.59	4.35	9.83	9.76			28.03	28.20
COOH	191–193 (dec.)	$C_{12}H_{14}N_2O_4$	57.59	57.51	5.64	5.68	11.20	11.21				
$COOC_2H_5$	178–179	$C_{14}H_{18}N_2O_4$	60.42	60.52	6.52	6.31	10.07	10.03				
$NHCOCH_3$	195–197 (dec.)	$C_{13}H_{17}N_3O_3$	59.30	59.16	6.51	6.75	15.96	15.94				
$NHCO(CH_2)_2COCH_3$	217–219 (dec.)	$C_{16}H_{22}N_4O_4$	57.47	57.42	6.63	6.45	16.76	16.78				

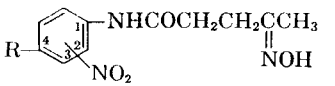
TABLE III



R	Position of Nitro Group	M.P., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Bromine Calcd.	Bromine Found
H	4	189–191[a]	49.6	$C_{11}H_{12}N_2O_4$	55.93	55.68	5.12	5.10	11.86	11.56				
CH_3	3	120–122[b]	24.0	$C_{12}H_{14}N_2O_4$	57.59	57.69	5.64	5.83	11.20	11.23				
Cl	2	82–84[c]	55.6	$C_{11}H_{11}N_2ClO_4$	48.81	48.90	4.10	4.30	10.35	10.27	13.10	13.21		
Br	2	91–92[c]	68.2	$C_{11}H_{11}N_2BrO_4$	41.92	42.13	3.52	3.65	8.89	8.84			25.36	25.28
COOH	2	178–180[d]	53.6	$C_{12}H_{12}N_2O_6$	51.43	51.63	4.38	4.38	10.00	9.89				
$COOC_2H_5$	2	105–106[e]	41.7	$C_{14}H_{16}N_2O_6$	54.54	54.53	5.23	5.12	9.09	8.96				
$NHCOCH_3$	2	163–164[f]	45.7	$C_{13}H_{15}N_3O_5$	53.24	53.13	5.16	5.26	14.33	14.35				
$NHCO(CH_2)_2COCH_3$	2 (3)	141–143[f]	58.9	$C_{16}H_{19}N_3O_6$	55.01	54.87	5.48	5.31	12.03	11.96				

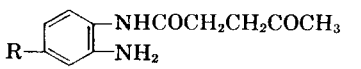
[a] Recrystallized from ethanol. [b] Recrystallized from ethanol and then from ethyl acetate. [c] Recrystallized from 75% methanol. [d] Recrystallized from ethanol-water. [e] Recrystallized from ethyl acetate. [f] Recrystallized from water.

TABLE IV

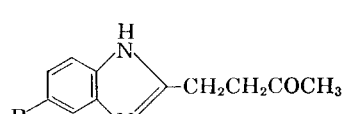


R	Position of Nitro Group	M.P., °C.	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Bromine Calcd.	Bromine Found
H	4	164–165	$C_{11}H_{13}N_3O_4$	52.59	52.43	5.21	5.02	16.73	16.72				
CH_3	3	143–144	$C_{12}H_{15}N_3O_4$	54.33	54.20	5.70	5.68	15.84	15.83				
Cl	2	127–130	$C_{11}H_{12}N_3ClO_4$	46.24	46.32	4.24	4.26	14.71	14.90	12.41	12.16		
Br	2	144–146	$C_{11}H_{12}N_3BrO_4$	40.01	39.97	3.67	3.89	12.73	12.77			24.21	24.38
COOH	2	189–190 (dec.)	$C_{12}H_{13}N_3O_6$	48.81	49.08	4.44	4.38	14.23	14.08				
$COOC_2H_5$	2	151–152	$C_{14}H_{17}N_3O_6$	52.01	51.93	5.30	5.18	13.00	12.96				
$NHCOCH_3$	3	164–166 (dec.)	$C_{13}H_{16}N_4O_5$	50.64	50.40	5.23	5.08	18.17	17.95				
$NHCO(CH_2)_2COCH_3$	2(3)	177–178 (dec.)	$C_{16}H_{21}N_5O_6$	50.26	50.33	5.54	5.57	18.32	18.37				

TABLE V



R	M.P., °C.	Yield, %	Formula	Analyses % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found	Bromine Calcd.	Bromine Found
Cl	151–153[a] (dec.)	32.3	$C_{11}H_{13}N_2ClO_2$	54.89	55.00	5.44	5.29	11.64	11.62	14.73	14.81		
Br	171–173[b] (dec.)	34.0	$C_{11}H_{13}N_2BrO_2$	46.33	46.15	4.59	4.62	9.83	9.98			28.03	27.77
$COOC_2H_5$	132–133[c]	23.0	$C_{14}H_{18}N_2O_4$	60.42	60.34	6.52	6.62	10.07	10.02				
$NHCOCH_3$	157–158[d] (dec.)	35.1	$C_{13}H_{17}N_3O_3$	59.30	59.29	6.51	6.57	15.96	15.95				



Cl	136–138	32.4	$C_{11}H_{11}N_2ClO$	59.33	59.34	4.98	4.98	12.58	12.55	15.92	16.17		
Br	146–147	14.2	$C_{11}H_{11}N_2BrO$	49.46	49.61	4.15	3.94	10.49	10.67			29.92	30.13

[a] Recrystallized from methanol-ether. [b] Recrystallized from ethanol-ether. [c] Recrystallized from methanol-water. [d] Recrystallized from ethanol.

aniline was obtained from nitrolevulinanilide. 4-Amino-2-nitrotoluene was obtained from nitro 4-methyllevulinanilide. From the hydrolysis of the other nitrolevulinanilides (R = Cl, Br, COOH, $COOC_2H_5$), 4-chloro-2-nitroaniline, 4-bromo-2-nitroaniline, 4-amino-3-nitrobenzoic acid, and ethyl 4-amino-3-nitrobenzoate, respectively, were obtained. 4-Acetamido-2-nitrolevulinanilide was hydrolyzed with barium hydroxide solution by the method of Bülow and Mann[3] to obtain 4-amino-3-nitroacetanilide.

Four of the compounds, in which the nitro groups were located in the 2 position, were reduced with iron powder and dilute hydrochloric acid in ethanol to form the corresponding amino derivatives.

Only two of the four amino compounds could be converted to benzimidazoles by Phillips procedure.[4] The amino compounds and 2-acetylethylbenzimidazoles are listed in Table V.

EXPERIMENTAL

General method for preparation of 4-substituted levulinanilides. The 4-substituted aniline (0.1 mole) was mixed with 0.1 mole of γ-acetoxy-γ-valerolactone[2] and 20–50 ml. of 50% aqueous ethanol. The mixture was allowed to stand for 3 to 4 days at room temperature with occasional shaking. The crystals, which separated, were removed and washed with 50% aqueous ethanol. The product was then recrystallized from a suitable solvent.

General method for preparation of nitro 4-substituted levulinanilides. The 4-substituted levulinanilide (0.04 mole) was added gradually to 50 ml. of concentrated sulfuric acid with cooling (−10 to −20°) and vigorous stirring. Then a mixture of 10 ml. of concentrated sulfuric acid and 3.2 ml. of concentrated nitric acid and a small amount of urea was added dropwise, with cooling and stirring. After 30 min., the mixture was poured onto cracked ice, at which point a yellow precipitate formed. After washing with cold water and drying, the product was recrystallized from a suitable solvent.

General method for preparation of amino 4-substituted levulinanilides. The nitro compound (0.04 mole), 12 g. of reduced iron powder, and 4.5 ml. of 2*N* hydrochloric acid was added to 40 ml. of ethanol and the mixture heated for 8 hr. on a steam bath. The reaction mixture was neutralized with 2*N* sodium hydroxide solution. The hot solution was filtered and the filtrate evaporated under reduced pressure. The crude product, so obtained, was recrystallized from a suitable solvent.

General method for preparation of 2-acetylethylbenzimidazoles. One g. of the 2-aminolevulinanilide derivative was dissolved in 10 ml. of 4*N* hydrochloric acid and the solution was refluxed for 2 hr. The solution was neutralized with ammonium hydroxide. A gummy precipitate was formed. The mixture was allowed to remain in the refrigerator (2–3 hr.) until the gummy product became solid. The crude product was then recrystallized from hot water with the aid of decolorizing carbon. The products are soluble in 1*N* hydrochloric acid and in 2*N* sodium hydroxide solution.

General method for determining the position of the nitro group. One g. of the 4-substituted nitrolevulinanilide was dissolved in 5 ml. of 95% ethyl alcohol and 5 ml. of 2*N* hydrochloric acid. The solution was refluxed for 1 hr. and cooled to yield crystals of the corresponding nitroaniline. The products were purified by recrystallization from hot water. They were identified by melting point and mixed melting point determinations.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA.

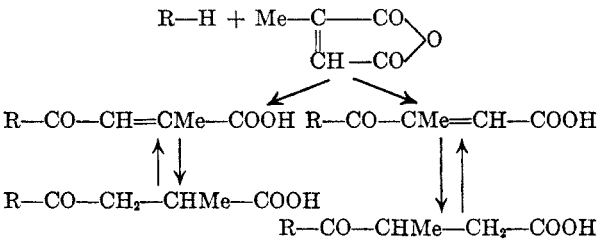
(3) C. Bülow and E. Mann, *Ber.*, **30**, 980 (1897).
(4) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

Syntheses of Some β-Aroyl-α- and β-methylacrylic Acids

ABDALLAH M. FLEIFEL

Received February 6, 1959

The condensation of citraconic anhydride with anisole, *p*-cresyl methyl ether, diphenyl, and fluorene has been studied. Powdered anhydrous aluminum chloride (2 equiv.) was added portionwise to the mixture of citraconic anhydride (1 equiv.) and the aromatic compound (1 equiv.) in *s*-tetrachloroethane or nitrobenzene as solvent. In each case, the reaction product was a mixture of two isomeric acids: R—CO—CH=CMe—COOH (type A) and R—CO—CMe=CH—COOH (type B). The structure of both acids is established by one of the following methods: (i) Reduction of the obtained β-aroylacrylic acids (A or B) with hydrogen in palladium chloride solution and activated charcoal to the corresponding β-aroylpropionic acids.[1] These have been found to be identical with authentic specimens prepared by the action of methylsuccinic anhydride on the corresponding aromatic compound.[2–4] (2) The synthesis of β-aroylacrylic acids (A or B) by bromination of the corresponding β-aroylpropionic esters followed by dehydrobromination and hydrolysis.[5] This is illustrated in the following scheme:



Acids of type A were predominant and less soluble (*cf.* ref. 4), those of type B were more soluble and hence comparatively difficult to purify.

(1) F. Mayer and G. Stamm, *Ber.*, **56**, 1424 (1923).
(2) F. G. Baddar, H. A. Fahim, and A. M. Fleifel, *J. Chem. Soc.*, 3302 (1955).
(3) B. L. Bhatt and K. S. Nargund, *J. Univ. Bombay*, **11**, Pt. 3, 131 (1942).
(4) F. G. Baddar, H. A. Fahim and A. M. Fleifel, *J. Chem. Soc.*, 2199 (1955).
(5) E. P. Kohler and H. Engelbrecht, *J. Am. Chem. Soc.*, **41**, 768 (1919).