[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

β-Aroylacrylic Acids

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The quest for new antibiotic substances produced by microörganisms has stimulated investigations on comparatively simple synthetic compounds, particularly those having structural features common to several of the natural antibiotics. Geiger and Conn[2] have called attention to the structural feature, —CH=C(—)—C=O common to both penicillic acid and clavacin and have postulated that the antibacterial activity of both compounds is very likely closely associated with this grouping. The fact that both clavacin, penicillic acid and many α,β-unsaturated ketones[3] react with and are inactivated by sulfhydryl groups lends support to this hypothesis.

It has been reported that α,β-unsaturated ketones wherein the aromatic radical is adjacent to the carbonyl group show bacteriostatic activity.[2b] Acrylophenone and particularly the ortho halogen, hydroxy and alkyl derivatives[4] show substantial antibacterial activity.

Several years ago, we undertook an investigation of the antibacterial action of α,β-unsaturated keto acids and derivatives of the general formula

$$R-C(=O)-[CX=CH]n-COOH \quad \text{(I)}$$

(I) wherein R is aliphatic, aryl or heterocyclic, X is hydrogen or halogen and n = 1 or 2. In general, the β-aroylacrylic acids[5] have shown appreciable *in vitro* activity against a wide variety of gram negative organisms, as well as against several strains of *Staphylococcus aureus*. Several of the substituted acrylic acids also have shown a pronounced fungistatic activity *in vitro*.

In addition to the β-aroylacrylic acids of general formula I, α,β-unsaturated ketones of formula II, wherein R is aryl or heterocyclic and R′

$$R-CH=CH-C(=O)-R' \quad \text{(II)}$$

is a —CH_3 (III) or —COOH (IV) group, were prepared and tested for antibacterial and fungistatic activity. Although the compound (IV) differs from the β-aroylacrylic acids (I) only in the position of the keto group, they showed comparatively little activity. These findings are in agreement with those of Geiger,[4] who has reported the antibacterial and antifungal properties for several compounds of general formula II. A detailed account of the bacteriological data for the compounds herein reported will appear elsewhere.

The β-aroylacrylic acids reported in Table I were, for the most part, prepared by the Friedel–Crafts reaction of an aromatic nucleus with maleic anhydride. However, the presence of an excess of the aromatic compound as solvent led to the formation of β-aroyl-α-arylpropionic acids[6] (VI), the latter substances being formed by the addition of one mole of the aromatic compound across the double bond of the β-aroylacrylic acid (V). The propionic acids (VI) were isolated and identified

$$R-C(=O)-CH=CH-COOH + RH \longrightarrow$$

(V)

$$RC(=O)-CH_2-CH(R)-COOH$$

(VI)

in the reaction of toluene and phenol with maleic anhydride. It was found that by using one equivalent of the aromatic compound with either acetylene tetrachloride or nitrobenzene as solvent and the inverse or Perrier[7] modification of the Friedel–Crafts acylation reaction, the by-product propionic acids were eliminated; and substantially higher yields of the β-aroylacrylic acids were obtained.

Some time ago, Lutz and Taylor[8] successfully used the ester–acid chloride of dimethylfumaric acid in a Friedel–Crafts reaction for the preparation of *trans*-2-(2,4,6-trimethylbenzoyl)-1,2-dimethylacrylic acid. A modification of this procedure has been used in the present investigation; the solvent and reaction conditions paralleled those recently described.[9]

The requisite intermediate, ethyl hydrogen maleate, for the Friedel–Crafts synthesis was obtained in 80% yield by the partial saponification of the diethyl ester. Several exploratory experiments were made in an attempt to convert maleic anhydride to ethyl or methyl hydrogen maleate by reaction with the appropriate alcohol. However, a product of sufficient purity could not be obtained.[10] This is in sharp contrast to the ease of

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(2) (a) Conn and Geiger, *J. Bact.*, **47**, 422 (1944); (b) Geiger and Conn, THIS JOURNAL, **67**, 112 (1945).

(3) Posner, *Ber.*, **35**, 799 (1902); **37**, 502 (1904).

(4) Geiger, *Arch. Biochem.*, **16**, 423 (1948).

(5) In the recent literature, other investigators have reported antibacterial activity for β-benzoylacrylic acid,[4] its methyl and propyl ester (R. L. Worrall, *Med. World London*, (1946); *C. A.*, **41**, 6598 (1947)); as well as the 4-chloro, 2,4-dichloro and *p*-acetylamino derivatives (Rinderknecht, Ward, Bergel and Morrison, *Biochem. J.*, **41**, 463 (1947); British Patent 588,108).

(6) Compare Pummerer and Buchta, *Ber.*, **69**, 1010 (1936).

(7) Perrier, *ibid.*, **33**, 815 (1900); Mowry, Renoll and Huber, THIS JOURNAL, **68**, 1107 (1946).

(8) Lutz and Taylor, *ibid.*, **55**, 1598 (1933).

(9) Papa, Schwenk and Hankin, *ibid.*, **69**, 3018 (1947).

(10) Sudborough and Roberts, *J. Chem. Soc.*, **87**, 1844 (1905).

TABLE I

β-AROYLACRYLIC ACIDS, R—CO—CH=CH—COOH

R	Method	Yield,[a] %	M. p., °C.	Crystn. solvent	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
C_6H_5	I	91	98–99[b,c]	C_6H_6					
C_6H_5	II	80	98–99	C_6H_6					
4-ClC_6H_4[d]	I	62	154–155	C_6H_6	$C_{10}H_7O_3Cl$	57.14	57.42	3.33	3.65
2,4-$(Cl)_2C_6H_3$	III	17	190–191[e]	$CHCl_3$					
3,4-$(Cl)_2C_6H_3$[f]	I	56	142–143	C_6H_6	$C_{10}H_6O_3Cl_2$	48.98	49.06	2.44	2.45
4-BrC_6H_4[g]	I	90[h]	159–160[i]	C_2H_5OH					
4-IC_6H_4[j]	III	10	186–187	C_2H_5OH	$C_{10}H_7O_3I$	39.74	39.96	2.31	2.43
4-$CH_3C_6H_4$[k]	III	65	137.5–138.5[l]						
4-i-$C_3H_7C_6H_4$	III	55	103–103.5	C_6H_6	$C_{13}H_{14}O_3$	71.56	71.73	6.24	6.54
2,4-$(CH_3)_2C_6H_3$[m]	III	91	113–114[n]	$C_2H_5OH \cdot H_2O$					
2,5-$(CH_3)_2C_6H_3$	III	90	89–90	$C_2H_5OH \cdot H_2O$	$C_{12}H_{12}O_3$	70.58	70.36	5.88	6.12
2,5-$(t\text{-}C_4H_9)_2C_6H_3$[o]	III	48			$C_{19}H_{26}O_3$				
β-Tetralyl	III	50	147–148	$C_6H_5CH_3$	$C_{14}H_{14}O_3$	73.03	73.02	6.08	6.12
β-(1 and 2-naphthyl)[p]	II	70							
4-$C_6H_{11}\cdot C_6H_4$	III	68	141.5–143	C_6H_6	$C_{16}H_{18}O_3$	74.42	74.90	6.97	6.98
3CH_3-4-ClC_6H_3[q]	III	30	130–131	C_6H_6	$C_{11}H_9O_3Cl$	58.80	58.72	4.01	3.50
2Cl-5-$CH_3C_6H_3$[q]	III	39	135–136	$C_6H_5CH_3$	$C_{11}H_9O_3Cl$	58.80	58.31	4.01	3.97
4-OHC_6H_4[r]	III	4[s]	197–198	H_2O	$C_{10}H_8O_4$	62.50	62.24	4.16	4.33
4-$CH_3OC_6H_4$	III	70	138–139[t]	C_6H_6	$C_{11}H_{10}O_4$	64.08	63.98	4.85	5.02
4-$C_2H_5OC_6H_4$	II, III	76, 60	145.5–146.5[u]	H_2O					
2,4-$(CH_3O)_2C_6H_3$	II	68	189–190 dec.	CH_3OH	$C_{12}H_{12}O_5$	61.01	60.86	5.08	4.96
2,5-$(CH_3O)_2C_6H_3$	II, III	46, 11	151–152	C_6H_6	$C_{12}H_{12}O_5$	61.01	61.44	5.08	4.86
2-CH_3-4-OH-C_6H_3	III	25	162–163	C_6H_6	$C_{11}H_{10}O_4$	64.08	63.82	4.85	5.11
2-OH-5-CH_3-C_6H_3[v]	III	25	172.5–173	C_6H_6	$C_{11}H_{10}O_4$	64.08	64.57	4.85	4.88
2-CH_3-4-OH-5-iC_3H_7-C_6H_2	III	13	174–174.5	C_6H_6	$C_{14}H_{16}O_4$	67.74	67.86	6.45	6.70
3-$NO_2C_6H_4$	V	85	189–190[w]	C_2H_5OH					
3-NO_2-4-BrC_6H_3[x]	V	54	167–168	C_2H_5OH	$C_{10}H_6NO_5Br$	40.02	40.14	2.01	2.25
4-$CH_3OCNHC_6H_4$[y]	IV	85	242–244	C_2H_5OH	$C_{12}H_{11}O_4N$	61.79	62.02	4.76	4.93
2-Thienyl	III	34	152–153	H_2O	$C_8H_6O_3S$	52.74	52.61	3.29	3.34
5-Cl-2-Thienyl	III	53	165–166	C_6H_6	$C_8H_5O_3SCl$	44.44	44.54	2.31	2.54

[a] The yields are calculated for recrystallized products. The majority of the yields reported are based on single experimental runs and do not represent the maximum obtainable. [b] Recrystallized from water gives the colorless hydrate, m. p. 60–62°, literature 64°; *Ber.*, **15**, 885 (1882). [c] Gabriel and Colman, *ibid.*, **32**, 398 (1899); Bogert and Ritter, THIS JOURNAL, **47**, 529 (1925). [d] Reference *e* reports m. p. 157–158° for this compound. Oxidation with alkaline permanganate gave *p*-chlorobenzoic acid, m. p. 242–243°, mixed m. p. with an authentic sample 242–244°. [e] Rinderknecht, Ward, Bergel and Morrison, *Biochem. J.*, **41**, 463 (1947). [f] Oxidation with alkaline permanganate gave 3,4-dichlorbenzoic acid, m. p. 206–207°, mixed m. p. 206–208°. [g] Calcd.: N. E., 257; Found: N. E. 256. Oxidation with alkaline permanganate gave *p*-bromobenzoic acid, m. p. and mixed m. p. 254–255°. [h] A 67% yield is obtained when the reaction mixture is heated on the steam-bath for four hours. [i] Kohler and Woodward, THIS JOURNAL, **58**, 1935 (1936), who prepared this compound from bromobenzene with aluminum bromide in tetrabromethane obtained a 73% yield. [j] Oxidation with alkaline permanganate yielded *p*-iodobenzoic acid which was converted to the *p*-nitrobenzyl ester, m. p. 140.5–141.5°; literature m. p. 141°, Shriner and Fuson, "Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 184. [k] Using method I, α(*p*-toluyl)β(*p*-toluyl)-propionic acid is the principal reaction product, m. p. 151–152°. *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.72; H, 6.45. Literature m. p. 151°, Pummerer and Buchta, *Ber.*, **69**, 1010 (1936). Oxidation of the substituted propionic acid with alkaline permanganate yielded terephthalic acid identified as the methyl ester, m. p. 140–141°; mixed m. p. with authentic sample 141–142°. [l] Pechmann, *Ber.*, **15**, 881 (1882). [m] The reaction was run at 0° and after stirring for one hour at 0°, the mixture was allowed to stand overnight. [n] Kozniewski and Marchlewski, *J. C. S. Abstr.*, II, 1190 (1906). [o] Obtained as the methyl ester, b. p. 181–184° (3 mm.); $n^{27}D$ 1.5347. *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.49; H, 4.63. Found: C, 75.78; H, 4.66. [p] The mixture of the two isomers was used for the bacteriostatic tests. Except for the use of acetylene tetrachloride in place of benzene, the compounds were obtained as described by Bogert and Ritter, THIS JOURNAL, **47**, 533 (1925). [q] Oxidation with alkaline permanganate yielded 4-chloroisophthalic acid, m. p. 294–295°, literature 294.5° (Ullmann and Uzbachian, *Ber.*, **36**, 1799 (1903)). [r] The "β-(*p*-hydroxybenzoyl)-acrylic acid" described by Bogert and Ritter, THIS JOURNAL, **47**, 532 (1925), m. p. 134.5°, was obtained by the published procedure. However, the Bogert and Ritter compound was shown to be α-(*p*-hydroxyphenyl)-β-(*p*-hydroxybenzoyl)-propionic acid. *Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.11; H, 4.92; N. E., 286. Found: C, 66.99; H, 5.08; N. E., 284.8. [s] Fieser, Gates and Kilmer, THIS JOURNAL, **62**, 2967 (1940), have reported a 5% yield of β-(*p*-hydroxybenzoyl)-propionic acid by the Friedel–Crafts reaction of phenol and succinic anhydride. [t] Rice, *ibid.*, **46**, 219 (1924). [u] Rice, *ibid.*, **46**, 2319 (1924). [v] Methylation with dimethyl sulfate in alkaline solution gave the 2-methyl ether which on esterification yielded the methyl-β-(2-methoxy-5-methylbenzoyl)-acrylate, b. p. 105–110° (4 mm.). *Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 5.51. Found: C, 66.65; H, 5.84. Oxidation of the ester with alkaline permanganate gave 4-methoxyisophthalic acid m. p. 259–261°, literature 261°; Jacobsen, *Ber.*, **11**, 898 (1878. [w] Bogert and Ritter, THIS JOURNAL, **47**, 532 (1925). [x] Oxidation with alkaline permanganate gave 3-nitro-4-bromobenzoic acid, m. p. 197–198°, literature 199°, Hübner and Ohly-Phillipp, *Ann.*, **143**, 251 (1867).

TABLE II

R—C(=O)—C(X)=CH—COOH

R	X	M. p., °C.	Yield,[a] %	Crystn. solvent	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
C_6H_5	Br	109–110[b]		C_6H_6					
C_6H_5	Cl	114–115	37	H_2O	$C_{10}H_7O_3Cl$	57.00	3.37	56.88	3.46
4-Cl-C_6H_4	Br	152–153	40	C_6H_6	$C_{10}H_6O_3BrCl$	41.47	2.09	41.80	1.98
4-Cl-C_6H_4	Cl	148–149	48	C_6H_6	$C_{10}H_6O_3Cl_2$	48.98	2.47	49.30	2.72

[a] The yields do not represent the maximum obtainable since only single experimental runs have been made. [b] Bogert and Ritter, THIS JOURNAL, **47**, 530 (1925).

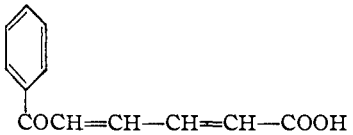
obtaining methyl hydrogen succinate from succinic anhydride and methyl alcohol.[11]

The reaction of ethyl hydrogen maleate with thionyl chloride gave very poor yields of the ester–acid chloride. However, with phosphorus trichloride, the ester–acid chloride was obtained in good yield and was used without distillation. Unlike the thionyl chloride method, the ester-acid chloride obtained by the phosphorus trichloride method was simply extracted from the reaction mixture with the appropriate solvent which was readily separable from the inorganic reaction product.

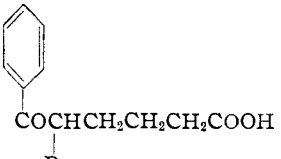
With benzene, the ester-acid chloride procedure gave an 80% yield of β-benzoylacrylic acid, this yield comparing favorably with those reported for the saturated ester-acid chloride reactions.[9] Resorcinol dimethyl ether yielded 68% of the expected β-(2,4-dimethoxybenzoyl)-acrylic acid, whereas with maleic anhydride, none of the acrylic acid was obtained. It has been reported[12] that resorcinol dimethyl ether and maleic anhydride give, in addition to a small quantity of the acrylic acid, 2,4-dimethoxyphenylsuccinic anhydride and 2,4-dimethoxyphenylsuccinic acid. Other phenyl alkyl ethers gave higher yields and purer products by the ester-acid chloride synthesis than obtained by the maleic anhydride reaction.

The β-aroyl-β-halogen acrylic acids, Table II, were prepared by the addition of halogen to the double bond of the acrylic acid and subsequent removal of hydrogen halide essentially as described by Bogert and Ritter.[13] The configuration of the β-halogen acids was not proven in this investigation. However, the identity of the β-benzoyl-β-bromoacrylic acid secured by Bogert and Ritter and that prepared by a bromomaleic anhydride Friedel–Crafts reaction by Rice[14] established the course of the dehydrohalogenation reaction. None of the β-aroyl-β-halogen acrylic acids showed antibacterial activity.

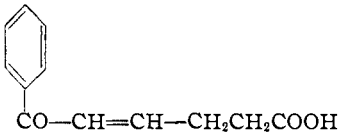
The preparation of the higher unsaturated acids (*n* equals 2 in formula I), 5-aroyl-2,4-pentadienoic acids, presented considerable difficulty. The requisite ester-acid chloride of muconic acid could not be prepared; and, therefore, resort to the polyanhydride synthesis[15] was necessary. Only 5-benzoyl-2,4-pentadienoic acid (VII) was prepared and then in very poor yield. In addition to the polyanhydride synthesis, an attempt to convert 5-benzoylvaleric acid by 2,4-dibromination and subsequent dehydrobromination yielded none of the pentadienoic acid (VII). The intermediate, 5-benzoyl-5-bromovaleric acid (VIII), however, was obtained in good yield and dehydrobromination with pyridine yielded the unsaturated keto acid, 5-benzoyl-4-pentenoic acid (IX).



VII



VIII



IX

The bacteriostatic action of the pentadienoic acid (VII) and the pentenoic acid (IX) was poor as compared to β-benzoylacrylic acid. However, IX, although not as active as β-benzoylacrylic acid, was considerably more active than VII.

The compounds of general formula II were secured by the condensation of pyruvic acid (R′ = COOH) or acetone (R′ = CH_3) with the appropriate aromatic aldehyde in alkaline solution in accordance with published methods.

Experimental

The synthesis of the following β-aroylacrylic acids will illustrate methods I–V in Table I. All melting points are corrected. The aluminum chloride used in the preparations was J. T. Baker granular anhydrous C. P. grade. Powdered anhydrous C. P. aluminum chloride

(11) Cason, THIS JOURNAL, **64**, 1107 (1942).
(12) Rice, *ibid.*, **53**, 3153 (1931).
(13) Bogert and Ritter, *ibid.*, **47**, 532 (1925).
(14) Rice, *ibid.*, **52**, 2095 (1930).
(15) Hill, *ibid.*, **54**, 4105 (1932).

was difficult to handle; and, in general, poorer yields were obtained.

Method I: β-Benzoylacrylic Acid.—To a mixture of 200 cc. of anhydrous, thiophene-free benzene and 49 g. (0.5 mole) of maleic anhydride at room temperature, there was added in small portions 132 g. (1.0 mole) of aluminum chloride. The temperature rose to 40–45° during the addition and the mixture was then heated on the steam-bath for two to three hours. The reaction mixture was decomposed with ice and 1:1 hydrochloric acid, the excess benzene steam-distilled; and, after cooling, the supernatant liquid was decanted from the semi-solid residue. The crude β-benzoylacrylic acid was dissolved in 5% sodium carbonate solution, filtered and acidified.

Method II: β-Benzoylacrylic Acid.—To 25 g. (0.17 mole) of freshly distilled ethyl hydrogen maleate,[16] there was added at about 5°, 12.4 g. of phosphorus trichloride.[17] The mixture was allowed to come to room temperature and then heated on the steam-bath for two hours. The mixture was extracted with 400 cc. of anhydrous benzene.[18] To the benzene extract, there was added slowly with cooling and stirring, 42 g. of anhydrous aluminum chloride. The reaction mixture was kept at room temperature for three hours and then decomposed with ice and 1:1 hydrochloric acid. The β-benzoylacrylic acid was isolated as described under I. The preparations of the alkoxy substituted aroylacrylic acids were carried out as described for the corresponding saturated compounds.[9]

Method III: β-(*p*-Toluyl)-acrylic Acid.—To a mixture of 200 cc. of anhydrous acetylene tetrachloride, 132 g. (1.0 mole) of aluminum chloride and 48 g. (0.5 mole) of maleic anhydride, there was added with stirring at room temperature 46 g. (0.5 mole) of toluene in the course of one to one and one-half hours. There was a copious evolution of hydrogen chloride and after stirring for four hours the reaction mixture was allowed to stand overnight. The β-(*p*-toluyl)-acrylic acid was isolated in the usual manner and recrystallized from benzene.

Method IV: β-(*p*-Acetaminobenzoyl)-acrylic Acid.[19]—To a cooled (0°) mixture of 200 cc. of carbon disulfide and 185 g. of aluminum chloride, there was added in one portion a ground mixture of 50 g. of acetanilide and 38 g. of maleic anhydride. The temperature rose to 35° and the reaction mixture became deep yellow. After adding an additional 100 cc. of carbon disulfide, the reaction mixture was left at room temperature for forty-eight hours. After decomposing the reaction mixture with ice and hydrochloric acid, the carbon disulfide was removed by heating the mixture on the steam-bath. The resulting yellow suspension was filtered and recrystallized from aqueous alcohol.

Method V: β-(3-Nitro-4-bromobenzoyl)-acrylic Acid.—To 60 cc. of fuming nitric acid, 19 g. of *p*-bromobenzoylacrylic acid was added slowly in small portions with constant stirring, maintaining the temperature between 0–3°. Stirring was continued for ten minutes and the mixture was filtered quickly through glass wool into an ice and water mixture. The nitro compound, which precipitated immediately, was filtered and recrystallized from ethanol.

Preparation of β-(*p*-Chlorobenzoyl)-β-chloroacrylic Acid.—Chlorine was passed into a suspension of 21 g. (0.1 mole) of β-(*p*-chlorobenzoyl)-acrylic acid until an increase in weight of 14 g. was obtained. After standing at room temperature for two hours, the solvent was removed. To the residue, petroleum ether was added and the mixture set aside to crystallize.

A mixture of 17 g. of the crude trichloro compound, 6 g. of freshly fused sodium acetate and 50 cc. of acetic acid was heated on the steam-bath for one hour. The mixture was then poured into water and extracted twice with ether. The ether extracts were washed with water, dried, and, after removing the ether, the residue was recrystallized.

β-Benzoyl-β-chloroacrylic acid was prepared as described for the *p*-chloro compound using β-benzoylacrylic acid. The β-benzoyl-β-bromoacrylic acid was prepared as described by Bogert and Ritter.[13]

The β-(*p*-chlorobenzoyl)-β-bromoacrylic acid was secured by the dibromination of β-(*p*-chlorobenzoyl)-acrylic acid in the conventional manner and the removal of hydrogen bromide with sodium acetate in acetic acid.

Preparation of 5-Benzoyl-4-pentenoic Acid.—To 41.2 g. (0.2 mole) of 5-benzoylvaleric acid dissolved in 500 cc. of chloroform, there was added dropwise with stirring 35.2 g. (0.22 mole) of bromine. The bromine reacted slowly and after warming to 40–50° the reaction proceeded rapidly. After heating for one hour at this temperature, the solvent was removed and the residue was taken up in benzene. The benzene solution was treated with Norit and the bromo compound precipitated with petroleum ether; yield, 52 g. (91%), m. p. 90–92°. Recrystallized from benzene–petroleum ether, m. p. 111–111.5°. Calcd. for $C_{13}H_{13}O_3Br$: Br, 28.6. Found: Br, 28.7.

A mixture of 29.7 g. (0.1 mole) of the bromo compound and 50 cc. of anhydrous pyridine was allowed to stand overnight and then heated on the steam-bath for two hours. The mixture was poured into 2 *N* hydrochloric acid, the resulting solution extracted with ether; and, after washing with water and drying over sodium sulfate, the ether extract was evaporated. The dark brown residue was recrystallized from benzene; yield 1.5 g., m. p. 159–159.5°. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88. Found: C, 70.40; H, 5.51. The dehydrobromination experiment was repeated using 59.4 g. (0.2 mole) of the bromo compound and 3.6 g. of purified pentenoic acid was obtained.

Preparation of 5-Benzoyl-2,4-pentadienoic Acid.—The requisite intermediate, muconic acid, was prepared by the dehydrobromination of ethyl α,α′-dibromoadipate. From 500 g. of adipic acid, 985 g. (90%) of ethyl α,α′-dibromoadipate, b. p. 165–170° (5 mm.), was obtained.[20] To refluxing 6 *N* potassium hydroxide in absolute methanol, there was added slowly 332 g. (1.0 mole) of the dibromo ester. The orange-yellow mixture was refluxed for one-half hour, cooled and then filtered. The precipitate was washed with methanol, decomposed with dilute hydrochloric acid and the precipitated muconic acid, after standing overnight, was filtered, yield 32.5 g. (23%), m. p. 306–307°, literature[21] 307–308°. The dehydrobromination of two moles of the dibromo ester gave 67.5 g. of muconic acid.

A mixture of 14.2 g. (0.1 mole) of muconic acid and 150 cc. of acetic anhydride was refluxed for four hours. The acetic acid and excess acetic anhydride were removed *in vacuo* and to the residual black tarry mass, 300 cc. of benzene was added. After refluxing for fifteen minutes, the benzene mixture was cooled and 21 g. of aluminum chloride added. The reaction mixture was heated on the steam-bath for two hours and then decomposed. The benzene layer was extracted several times with 5% sodium carbonate solution, and, on acidification, 1.2 g. of a yellow solid was obtained. Recrystallized from benzene, m. p. 165–166°. *Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.95. Found: C, 71.59, 71.48; H, 5.35, 5.30. The residual benzene solution yielded 1.7 g. of 1,4-dibenzoylbutadiene, which, after recrystallization

(16) Shields, *J. Chem. Soc.*, **59**, 740 (1891).

(17) In two preliminary experiments, ethyl hydrogen maleate was treated with 1.5 moles of freshly distilled thionyl chloride (Fieser, "Experiments in Organic Chemistry," 2nd ed., 1941, D. C. Heath and Co., New York, N. Y., p. 381); and, after heating at 40° for two hours, the excess thionyl chloride was removed *in vacuo*. To the residue, there was added 100 cc. of anhydrous benzene, the benzene removed *in vacuo*, and the ester-acid chloride taken up in 250 cc. of anhydrous benzene. The Friedel-Crafts reaction was carried out as usual and 20 and 28% yields of β-benzoylacrylic acid were obtained.

(18) Benzene was used as extraction solvent for the preparation of β-benzoylacrylic acid. For the preparation of other β-aroylacrylic acids by this reaction, acetylene tetrachloride was used for extraction.

(19) Compare English, Clapp, Cole and Krapcho, THIS JOURNAL, **67**, 2264 (1945).

(20) Stephen and Weizmann, *J. Chem. Soc.*, **103**, 271 (1913).

(21) Ingold, *ibid.*, **119**, 962 (1921).

from benzene, melted at 194.5–195°. *Anal.* Calcd. for $C_{18}H_{14}O_2$: C, 82.44; H, 5.34. Found: C, 82.40; H, 5.55.

Salicylacetone.—Prepared from salicylaldehyde and acetone in 10% sodium hydroxide essentially as described,[22] yield 65%, m. p. 140.5–141.5°, literature 139°.

***p*-Hydroxybenzalacetone.**—To 25 g. of *p*-hydroxybenzaldehyde dissolved in 70 cc. of 10% sodium hydroxide, there was added at 25° 50 g. of acetone, followed by 100 cc. of 10% sodium hydroxide. The resulting mixture was diluted to 2000 cc. and allowed to stand at room temperature for seventy-two hours. The deep red solution was then acidified and the crude *p*-hydroxybenzalacetone recrystallized from benzene, yield 22 g., m. p. 107–108°, literature[23] 102–103°.

3-Bromo-2-hydroxybenzalacetone: Procedure was as described for *p*-hydroxybenzalacetone using 3-bromo-2-hydroxybenzaldehyde. The substituted benzalacetone was obtained in a yield of 56%, and, after recrystallization from ethyl alcohol, melted at 155–156°. *Anal.* Calcd. for $C_{10}H_9O_2Br$: C, 49.81; H, 3.76. Found: C, 49.87; H, 3.88.

3,5-Dibromo-4-hydroxybenzalacetone was secured from 3,5-dibromo-4-hydroxybenzaldehyde as described for the 2-isomer, yield 48%, m. p. 150.5–151° after recrystallization from acetone–water. *Anal.* Calcd. for $C_{10}H_8O_2Br_2$: C, 37.52; H, 2.52. Found: C, 37.75; H, 2.94.

The following substituted pyruvic acids were prepared essentially as described in the literature: benzalpyruvic acid, yield 80%, m. p. 60–61°, literature[24] 61–62°; *p*-methoxybenzalpyruvic acid yield 60%, m. p. 130.5–131°, literature[25] 131°; furfural pyruvic acid, yield 68%, m. p. 112–113°, literature[26] 112°; and piperonylidene-acetic acid, yield 82%, m. p. 163–164°, literature[27] 162–163°.

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Summary

1. β-Aroylacrylic acids have been obtained by the Friedel–Crafts reaction using maleic anhydride and/or the corresponding ester-acid chloride with the appropriate aromatic compound.

2. Two higher unsaturated acids were prepared, but their antibacterial activity was not comparable to the β-aroylacrylic acids.

3. Several benzalpyruvic acids and benzalacetones are described. However, these compounds show poor antibacterial action.

4. It will be reported elsewhere that β-aroylacrylic acids have *in vitro* bacteriostatic activity against a variety of gram negative organisms as well as against several strains of *Staphylococcus aureus*. Several of the compounds also show fungistatic activity.

(22) Harries, *Ber.*, **24**, 3180 (1891).
(23) Zincke and Muhlhausen, *Ber.*, **36**, 134 (1903).
(24) Reimer, THIS JOURNAL, **53**, 3148 (1931).
(25) Reimer, *ibid.*, **48**, 2458 (1926).
(26) Friedmann, *Helv. Chim. Acta*, **14**, 790 (1931).
(27) *C. A.*, **35**, 5875 (1941); R. Nath Sen and B. Kumar Sen, *J. Indian Chem. Soc.*, **11**, 411 (1934).

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The Synthesis of Acyl-2-thenoylmethanes by the Alkali Amides[1]

BY SAMUEL R. HARRIS[2] AND ROBERT LEVINE

A convenient method for preparing β-diketones of the type $RCOCH_2COR'$ is to condense a methyl ketone with an ester in the presence of a basic condensing agent such as sodium,[3] sodium ethoxide,[3] sodium triphenylmethide,[4] sodium amide[4,5] or lithium amide.[6] The following equation indicates the reaction which takes place.

$$CH_3COR + R'CO_2C_2H_5 \xrightarrow[\text{agent}]{\text{basic condensing}} RCOCH_2COR' + C_2H_5OH$$

Apparently no β-diketones containing the thiophene nucleus have been prepared previously. In the present investigation a series of such β-diketones has been synthesized by condensing 2-acetylthiophene with appropriate esters in the presence of sodium amide or lithium amide. Two methods of synthesis have been used. Either two equivalents of the alkali amide are allowed to react with one of the ketone and two of the ester (Method A)[4,5] or two equivalents each of base and ketone are allowed to react with one of the ester (Method B).[4,5]

The results are summarized in Table I. It will be observed that when sodium amide or lithium amide is used in Method A the yield of product using the former is much higher. This may be due to the fact that the lithio derivative of the ketone is probably less soluble in ether than the corresponding sodio derivative and hence does not react as completely with the acylating ester. It may also be seen that when Method B is employed using sodium amide as the base, the yields of the β-diketones are much lower than those obtained with the same base employing Method A. It may also be observed that when benzoyl-2-thenoylmethane is prepared using sodium amide in Method B, the yield of product is 16% when the

(1) Paper II in a series on condensations effected by the alkali amides. For Paper I see Zellars and Levine, *J. Org. Chem.*, **13**, 160 (1948).
(2) This work is based on a thesis submitted by Samuel R. Harris in partial fulfillment of the requirements for the degree of Master of Science at the University of Pittsburgh.
(3) Sprague, Beckham and Adkins, THIS JOURNAL, **56**, 2665 (1934).
(4) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945).
(5) Adams and Hauser, *ibid.*, **66**, 1220 (1944).
(6) Zellars and Levine, *J. Org. Chem.*, **13**, 160 (1948).