with a little water and dried at 100° *in vacuo*. There was obtained 1.5 g. of an orange-yellow solid. It gave a reddish blue color when tetrazotized and coupled with alkaline 2-naphthol-3,6-disulfonic acid (R-salt).

Acylation of 6,6'-Dichloro-4,4'-diaminostilbene-2,2'-disulfonic Acid.—The acylation of this compound with 2,4-dimethoxybenzoyl chloride and with *o*-ethoxybenzoyl chloride was done in same way as in the case of the 5,5'-dichloro analog.

2-Ethoxy-2'-chlorobenzanilide.—Mrs. Nancy Buckwalter prepared this compound for us by the Schotten–Baumann reaction and recrystallized it twice from alcohol; m.p. 75°.

Anal. Calcd. for $C_{15}H_{14}O_2NCl$: C, 65.3; H, 5.12; N, 5.08; Cl, 12.9. Found: C, 65.2; H, 5.13; N, 5.21; Cl, 12.8.

Ultraviolet Absorption Data. A. Nomenclature.—The spectra are plotted as $\log_{10}$ molar absorptivities *vs.* wave length in mμ.

B. **Preparation of Solutions.**—About 0.250 g. of each dye was weighed and dissolved in 400 ml. of distilled water by boiling for two minutes. The solution was then cooled to room temperature and diluted to 500 ml.. A 6.25-ml. aliquot was pipetted into a 250-ml. low actinic volumetric flask containing 200 ml. of water buffered to *p*H 9.0 ± 0.3. The solution was then diluted to the mark with distilled water. Benzanilide and its two derivatives were dissolved in and diluted with 95% ethanol in similar fashion.

All operations of dissolving and diluting the samples were performed in dim light and low actinic (red) flasks were used for making dilutions and storing. Extreme precaution was also used when filling the Beckman cells in order to minimize the light admitted to the sample. Direct sunlight and strong indirect lighting were avoided.

The spectra were determined on a Beckman Model DU quartz spectrophotometer over the range 210–400 mμ, in 1.000 ± 0.003 cm. cells, at 25–28°.

Acknowledgment.—The authors wish to thank Miss M. R. O'Rourke for the absorption data and other observations, Dr. S. M. Davis for valuable suggestions based on infrared observations, Miss Alice Kantor for certain preparations, and Mr. O. E. Sundberg and his associates for the microanalyses.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

The Synthesis of Substituted β-Thienyl- and β-Furylglutaric Acids

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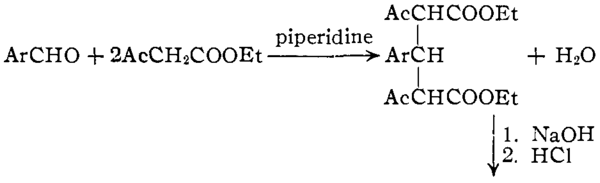
RECEIVED JANUARY 6, 1954

Heterocyclic aldehydes have been condensed with ethyl acetoacetate in the presence of piperidine to give ethyl bis-acetoacetates. These products were cleaved with alkali to give β-substituted glutaric acids. Eleven new ethyl bis-acetoacetates and ten new β-substituted glutaric acids are reported.

β-Alkylglutaric acids often have been prepared by treating the appropriate aldehyde with malonic acid,[2] malonic ester[2–4] or cyanoacetamide,[5,6] followed by hydrolysis and decarboxylation. This method usually affords good yields and is readily adapted to the preparation of various substituted glutaric acids but has the disadvantage of being rather long. A less versatile method is that employing the condensation of ethyl sodiomalonate[7–9] or ethyl sodiocyanoacetate,[10,11] with substituted ethyl crotonates, and ethyl sodiocyanoacetate has also been treated with ethyl β-hydroxybutyrate.[12] Other limited methods include the permanganate oxidation of 4-alkylcyclopentenes[13,14] and the hypochlorite oxidation of 5-alkyl-1,3-cyclohexanediones.[15]

For the preparation of β-aryl glutaric acids, a convenient method was used by Knoevenagel[16] and later developed by Smith and Kort.[17] This method involved the piperidine-catalyzed condensation of an aromatic aldehyde with two moles of ethyl acetoacetate to give an ethyl benzal-bis-acetoacetate, which upon hydrolysis with concentrated alkali solution and subsequent acidification gave the corresponding β-arylglutaric acid.



$$\mathrm{ArCHO} + 2\mathrm{AcCH_2COOEt} \xrightarrow{\text{piperidine}} \mathrm{ArCH(AcCHCOOEt)_2} + \mathrm{H_2O} \xrightarrow{\text{1. NaOH; 2. HCl}} 2\mathrm{HOAc} + 2\mathrm{EtOH} + \mathrm{ArCH(CH_2COOH)_2}$$

It was the purpose of the present work to determine whether this synthetic method could be extended to include the preparation of glutaric acids having heterocyclic residues in the β-position.

Twelve heterocyclic aldehydes were successfully condensed with ethyl acetoacetate to give the corresponding ethyl bis-acetoacetates in yields of 24–77%. The data for these products are summarized in Table I. Condensation attempts with 2-quinolinecarboxaldehyde, 3-indolecarboxaldehyde, 3-thianaphthenecarboxaldehyde and 5-nitro-2-furaldehyde were unsuccessful.

Hydrolysis of the bis-esters with concentrated alkali resulted in the formation of ten new β-substituted glutaric acids in yields of 52–73%. These

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TABLE I

BIS-ESTERS DERIVED FROM ETHYL ACETOACETATE

Aldehyde	Yield, %[a]	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
5-Methyl-2-furaldehyde	45	99–100	61.35	61.20	6.87	6.73
5-Chloro-2-furaldehyde	46	95–96	54.77	54.64	5.68	5.65
5-Bromo-2-furaldehyde	77	101–103	48.93	48.85	5.07	5.18
2-Thiophenecarboxaldehyde	51	107–108	57.61	57.32	6.26	6.31
5-Methyl-2-thiophenecarboxaldehyde	67	114–116	58.68	58.17	6.57	6.48
2,5-Dimethyl-3-thiophenecarboxaldehyde	68	116–117	59.66	59.43	6.85	6.90
5-Ethyl-2-thiophenecarboxaldehyde	34	99–100	59.66	59.39	6.85	6.71
5-Propyl-2-thiophenecarboxaldehyde	24	96–97	60.58	60.45	7.12	6.82
5-Chloro-2-thiophenecarboxaldehyde	70	136–137	52.51	52.27	5.44	5.28
2-Pyrrolecarboxaldehyde	54	159–160	60.52	60.55	6.87	6.80
Nicotinaldehyde	60	144–145	61.88	61.95	6.64	6.75
Piperonal[b]	51	150–151	...	...	..	..

[a] These figures represent the yield from the first crystal crop only; upon standing, the mother liquor deposited a second crop, and sometimes a third crop. [b] Previously reported by E. Knoevenagel and H. Hoffmann, *Ann.*, **303**, 228 (1898).

data are given in Table II. No acids could be obtained from the bis-esters of nicotinaldehyde and 2-pyrrolecarboxaldehyde.

TABLE II

β-SUBSTITUTED GLUTARIC ACIDS

Substituent	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
5-Methyl-2-furyl	62	134–136	56.60	56.57	5.70	5.73
5-Chloro-2-furyl	73	121–122	46.47	46.55	3.90	4.12
5-Bromo-2-furyl	59	93 dec.	39.01	39.27	3.27	3.39
2-Thienyl	59	121–122	50.46	50.38	4.71	4.68
5-Methyl-2-thienyl	58	134–135	52.62	52.62	5.30	5.47
2,5-Dimethyl-3-thienyl	62	148–149	54.53	54.41	5.82	6.09
5-Ethyl-2-thienyl	60	95–96	54.53	54.36	5.82	5.94
5-Propyl-2-thienyl	69	73–74	56.23	46.08	6.29	6.18
5-Chloro-2-thienyl	52	119–120	43.47	43.22	3.65	3.72
3,4-Methylenedioxyphenyl	68	175–176	57.14	56.91	4.80	4.79

The optimum reflux time for hydrolysis of the bis-ester was determined for ethyl piperonylidene-bis-acetoacetate, and was found to be one hour. It is interesting to note, however, that the yield obtained after refluxing for only ten minutes was 82% of that obtained by a one-hour reflux period.

Experimental

Ethyl Bis-acetoacetates.—The preparation of these compounds is illustrated by the following preparation of ethyl 2,5-dimethyl-3-thenylidene-bis-acetoacetate.

2,5-Dimethyl-3-thiophenecarboxaldehyde (14.0 g.) (0.10 mole) and ethyl acetoacetate 26.0 g. (0.20 mole) were mixed and 1.0 ml. of piperidine was added. Thirty-six hours later the mixture was clouded with water droplets, but there was no solid material. It was then placed in the refrigerator for several hours, whereupon it became very tacky, and vigorous scratching with a stirring rod produced, almost instantly, a solid mass of crystals. The cake was then broken up and transferred to a büchner funnel, where a few drops of liquor were pressed out. The solid was dissolved in 20 ml. of alcohol by warming, and after an hour or two the material was filtered off and carefully washed with 5 ml. of alcohol. The product weighed 26.1 g. (68%) and was light yellow in color. This material is sufficiently pure for use in preparing the corresponding glutaric acid. A portion was recrystallized from a mixture of $^{1}/_{3}$ benzene and $^{2}/_{3}$ ligroin, washed with more of the same, and dried *in vacuo*. This product was white and melted at 116–117°.

The time required for solid to form in the bis-ester mixtures varied from a half-day to a half-week. It should be noted, however, that these mixtures exhibit a marked tendency to remain in a viscous liquid state, and in the absence of scratching may deposit no crystalline material for several days or weeks. After the first crop of crystals is removed the filtrate usually deposits one or more additional crops. Thus in the reaction of 5-ethyl-2-thiophenecarboxaldehyde with ethyl acetoacetate, the solid which formed was accompanied by a large proportion of sirupy liquid, and two days standing seemed to produce no more precipitate. The solid was filtered off, and after washing with a little alcohol, weighed 16.1 g. (34%). The mother liquor and wash were combined, and after a few hours a second crop formed which weighed 3.7 g. Additional crops amounting to 12.7 g. raised the yield to 68%.

β-Substituted Glutaric Acids.—The ethyl bis-acetoacetate, 7.0 g., was dissolved in 50 ml. of alcohol, and 50% alkali solution (50 g. of sodium hydroxide in 50 ml. of water) was added. This mixture was refluxed for one hour, whereupon it was transferred to a 600-ml. beaker with the aid of 20 ml. of water, approximately 40 ml. of alcohol was boiled off on a hot-plate, and 45 ml. more of water was added and the mixture was cooled in ice. One hundred milliliters of concentrated hydrochloric acid was added while the mixture was stirred in an ice-bath to maintain the temperature below 50°. The mixture was then made acidic to congo red with some additional acid (about 5 ml.) and after chilling was filtered. The solid was recrystallized from water (15–100 ml.).

It was found that if a hydrolysis mixture containing β-(5-methyl-2-furyl)-glutaric acid was adjusted to *p*H 5 and extracted with ether, the amount of the organic acid removed by the ether was only 20% of that removed at *p*H 4. This particular acid, however, is decomposed at very low *p*H values, and a *p*H of 4 is recommended for its precipitation.

The substituted glutaric acids are fairly soluble in water, but are insoluble in the saturated sodium chloride solution of the hydrolysis mixture, and so may be removed by filtration. Ether extraction also may be used to remove the acids, but the material obtained by evaporation of the ether is contaminated with tar and 5-substituted-3-methyl-4-carbethoxycyclohexenone (arising from cyclization and monodecarboxylation of the bis-ester), and subsequent purification of the acid results in a lesser yield than that obtained by simply filtering off the solid. These acids, like the bis-esters, exhibit a marked tendency to form supersaturated solutions; chilling and scratching with a stirring rod are often necessary to initiate crystallization.

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