Synthesis and Interconversion of 6-Aroyl-4-oxohexanoic Acids and 5-Aryl-2-furanpropionic Acids. Antiinflammatory Agents.

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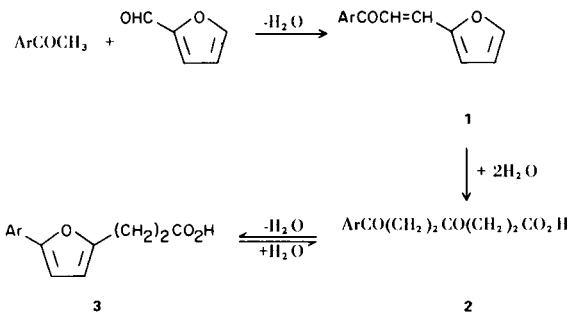
A series of 6-aroyl-4-oxohexanoic acids (**2**) was prepared for intermediate use by acid-catalyzed solvolysis of substituted 3-(2-furyl)acrylophenones (**1**). This reaction occasionally gave 5-aryl-2-furanpropionic acids (**3**) instead of, or in addition to, the desired diketones (**2**). Equilibrium between **2** and **3** was observed in the case where Ar is *m*-nitrophenyl. A rationalization for the formation of **3** is offered, and published reports with which our results differ are discussed. Diketones (**2**) were cyclized to furans (**3**) and antiinflammatory screening data are reported for the latter.

As intermediates in the synthesis of 1,5-diarylpyrrole-2-propionic acids having antiinflammatory and hypocholesterolemic activity (1), we prepared several 6-aroyl-4-oxohexanoic acids (**2**) by acid-catalyzed ethanolysis-hydrolysis of substituted 3-(2-furyl)acrylophenones (**1**). In some cases the desired 1,4-diketones (**2**) were unstable under the conditions of their formation from **1**. As a result, 5-aryl-2-furanpropionic acids (**3**) arising from acid-catalyzed cyclodehydration of **2** were obtained either alone or mixed with **2**. Since the furans (**3**) were of potential pharmacological interest, several additional



examples were then prepared by intentional cyclization of **2**. In this paper we report the synthesis and antiinflammatory activity of a series of **3**, and discuss our observations on the interconversion of **2** and **3** with particular reference to certain reports by other workers (2,3).

RESULTS

The furylacrylophenones (**1**) (Table I) were prepared by base-catalyzed condensation of 2-furaldehyde with acetophenones (4a). Catalytic amounts of sodium methoxide or sodium hydroxide in methanol or ethanol as solvent were generally used (Method **1**-A), but with the base-soluble hydroxyacetophenones an excess of sodium hydroxide in water or ethanol was used (Method **1**-B). The intermediate **1** were generally used without further purification, and in several cases were not isolated.

Conversions of **1** to diketones (**2**) (Table II) were effected by consecutive ethanolysis and hydrolysis catalyzed by hydrochloric acid (4b), either with, or more conveniently without, prior isolation of **1** (Methods **2**-A and **2**-B, respectively). Detailed study of the preparation of the *p*-methoxyphenyl compound (**2**-20) indicated no advantage in isolating the intermediate **1**. The *p*-(methylsulfonyl)phenyl compound (**2**-26) was prepared also by oxidation of the corresponding *p*-(methylthio)phenyl compound (**2**-25) with hydrogen peroxide in acetic acid (Method **2**-C). The intermediate **2** were usually cyclized to **3** without further purification.

In five cases using Methods **2**-A and **2**-B we failed to obtain the desired diketones (**2**). These were the *o*-fluoro- (**2**-2), *o*-chloro- (**2**-5), 2,5-dimethyl- (**2**-11), *o*-methoxy- (**2**-18) and 2,5-dimethoxyphenyl (**2**-21) compounds. Instead, the corresponding furans (**3**) were the only products isolated. In another three cases we obtained a mixture of **2** and **3**. These were the *m*-trifluoromethyl- (**2**-22), *m*-nitro- (**2**-23) and *p*-(methylsulfonyl)phenyl (**2**-26) compounds. In still another five cases, we obtained **2** containing very small amounts of **3**. These were the *m*- and *p*-fluoro- (**2**-3 and **2**-4), *m*- and *p*-chloro- (**2**-6 and **2**-7) and *m*-methoxyphenyl (**2**-19) compounds.

Most of the furans (**3**) (Table III) were prepared by cyclodehydration of **2** in refluxing toluene using *p*-toluenesulfonic acid as catalyst (Method **3**-A). We found

this procedure to be more convenient than the use of phosphorus pentoxide as described by Robinson and Todd (5). The progress of the reactions was followed by measurement of the water evolved, and most were complete in less than 4 hours. One run in benzene (3-6) required 8 hours. The products generally crystallized directly from the reaction solutions, and recrystallization was frequently unnecessary; in at least two cases (3-4 and 3-10) it seemed undesirable. Preparation of pure *o*-hydroxyphenyl compound (3-15) failed because of resistance of the diketone (2-15) to cyclodehydration and marked decomposition during prolonged reaction. Acetic acid was used as solvent in one case (Method 3-D).

As already indicated, five of the furans (3) were obtained as the sole product from the acidic solvolysis of furylacrylophenones (1), either with or without prior isolation of 1 (Methods 3-B and 3-C, respectively). These were 3-2, 3-5, 3-11, 3-18 and 3-21. Three of the furans (3) were obtained as coproducts with the corresponding diketones (2). These were 3-22, 3-23 and 3-26.

In the hope of gaining some further understanding of the conversion of 1 to 2 and 3, the *m*-nitro furan (3-23) and the corresponding diketone (2-23) (as 65% of a mixture with the furan) were subjected to the aqueous hydrolysis conditions used in methods 2-A and 2-B and 3-B and 3-C. Both gave an equilibrium mixture of roughly half furan and half diketone. A similar attempt to hydrolyze the *o*-chloro furan (3-5) did not generate the corresponding diketone (2-5).

The antiinflammatory activity of furans (3) was assessed by measuring their potency in delaying the appearance of uv light-induced erythema on the skin of depilated albino guinea pigs (6). The screening data are shown in Table III.

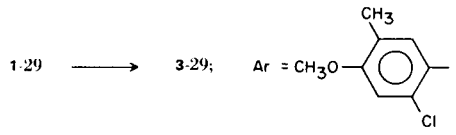
DISCUSSION

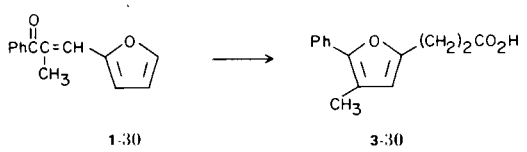
Dunlop and Peters (4c) have discussed the acid-catalyzed solvolytic cleavage of furans in general, and have commented specifically on the conversions $1 \rightarrow 2 \rightleftharpoons 3$. They regarded the solvolysis of 1, under reaction conditions typified by our methods 2-A and 2-B, as leading first to 2. The latter are then supposedly subject, under the reaction conditions, to cyclization to 3. Furans (3) in turn, may then be cleaved back to 2 to give an equilibrium mixture, the composition of which depends in part on the nature of the aromatic group.

A somewhat different interpretation has been offered by Thewalt and Rudolph (7) who proposed that the initial aqueous ethanolic cleavage of 1 gives the ethyl ester of 3, a suggestion similar to one made earlier by Robinson (8). This intermediate is then supposedly converted to 2 on subsequent boiling with aqueous acid. Thewalt and Rudolph cited as support for their proposal the fact that they obtained the ethyl ester of 3-1 by distillation of the mixture resulting from aqueous ethanolysis of the corresponding 1. This observation had been reported earlier by Blicke and coworkers (9), but was interpreted by them as indicating cyclization of the ethyl ester of the corresponding diketone (2) during distillation. We regard the significance of the isolation of 3 ester by distillation as ambiguous if the material distilled still contained even catalytic amounts of acid since cyclization to 3 of any 2 present would be expected (4d,5).

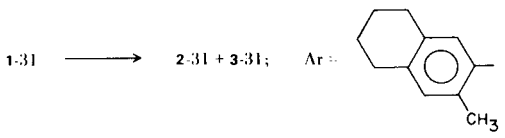
Our observation that both the *m*-nitro diketone (2-23) and the corresponding furan (3-23) give an equilibrium mixture of about equal amounts of each when refluxed in aqueous hydrochloric-acetic acid solution (see Experimental section) confirms the general proposal of Dunlop and Peters (4b) that such an equilibrium between 2 and 3 exists. Since the first crop of product mixture in the preparation of 2-23 and 3-23 by Method 3-B, isolated by crystallization from the hydrolysis mixture, contained about 80% of diketone (2-23) (see Experimental section) it might be concluded that 2 is the product first formed in the acid-catalyzed ethanolysis-hydrolysis of 1. This conclusion is seemingly supported by the fact that we observed in setting up the equilibration experiments that the furan (3-23) is less soluble in the hydrolysis medium (required more acetic acid to effect complete solution) than is the diketone (2-23), and should therefore crystallize more completely during isolation. This conclusion can be only tentative at best however, since the composition of the product mixture isolated is also dependent, among other things, upon the relative rates and degrees of solution of the components into the aqueous phase of the heterogeneous reaction mixture. In our discussion we have chosen to adopt the view of Dunlop and Peters, recognizing that it is equivocal.

Prior to our work, others had reported instances of the isolation of 3 from attempts to convert 1 to 2. Martin and Robinson (10) obtained 3-29 from 1-29 instead of the corresponding diketone (2). They reported failure of all attempts to reopen the furan ring, but mentioned specifically only a trial with methanolic hydrogen chloride. Turner (11) similarly obtained 3-30 from 1-30. Butenandt and coworkers (12) mentioned having obtained mixtures of furan (3-31) and the desired diketone (2-31) from 1-31, although they discussed and reported in detail only an experiment in which 2-31 was isolated.



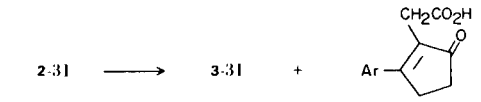


1-30 3-30



1-31 2-31 + 3-31; Ar =

A curious aspect of this last report deserves passing comment. Butenandt and coworkers reported that treatment of diketone (**2**-31) with aqueous alkali gave, in addition to the expected (8, 11) cyclic aldol addition product (**4**-31), varying amounts of the furan (**3**-31) as the major product. They argued that the furan arises because formation of **4**-31 is relatively more inhibited sterically by the *o*-methyl group. It should be noted however, that formation of furan (**3**-31) under conditions of aldol addition would result from nucleophilic attack on the aromatic ketone carbonyl in **2**-31 by oxygen rather than carbon of the aliphatic enolate anion. As has been shown for the simple case of acetaldehyde (13a, 14), this alternative reaction path is thermodynamically less favorable by about 20 kcal./mole. Since Butenandt and coworkers did not specify the purity of the diketone (**2**-31) which they subjected to the aldol cyclization, we feel that the possibility cannot be overlooked that the furan (**3**-31) isolated in variable amounts may have been present in the starting diketone.



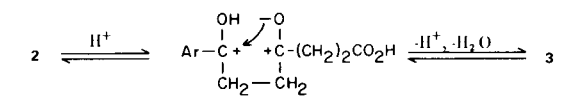
2-31 3-31 + Ar

4-31

After we had found that *ortho*-substituted diketones (**2**-2, **2**-5, **2**-11, **2**-18 and **2**-21) could not be synthesized by the traditional method of solvolysis of the corresponding furylacrylophenones (**1**), we were intrigued by the allegations of Brown and Chinn (2) that **2**-2, **2**-5 and **2**-18 (*o*-fluoro, -chloro, and -methoxy) are obtained by this procedure. Brown and Chinn did not, however, report melting points or other supporting data for the alleged diketones, or for other compounds supposedly prepared from them. In view of the proposal by Thewalt and Rudolph (7) that **3** might be intermediate in the conversion of **1** to **2**, we then subjected the *o*-chloro furan (**3**-5) to boiling aqueous hydrochloric-acetic acid for 24 hours (see Experimental section), but still did not detect diketone (**2**-5) in the material recovered. As mentioned above, Martin and Robinson (10) had already reported a similar experience. The equilibrium between **2**-5 and **3**-5 obviously overwhelmingly favors the latter in hot aqueous acid.

More recently, we were interested to note that Popp and coworkers (3) had also attempted to prepare the *m*-nitro diketone (**2**-23) by solvolysis of the corresponding acrylophenone (**1**). They reported detection only of furan (**3**-23) in the product, and mentioned further that attempts to hydrolyze **3**-23 in refluxing 5% sulfuric acid failed to give **2**-23. With reference to the general proposal of Dunlop and Peters (4b) that **2** and **3** are in equilibrium in hot aqueous medium, Popp and coworkers commented that such mixtures had not been observed by them or reported by others (but see Reference 12). This report contrasts with our own observations that both diketone (**2**-23) and furan (**3**-23) are obtained with the former as the predominant product, using the same reaction conditions as used by Popp and coworkers to solvolyze the corresponding **1**, and that both diketone and furan are converted to an equilibrium mixture of nearly equal amounts of the two in hot aqueous acid solution. Surprisingly, these workers reported using esterification with alcoholic hydrogen chloride as an alternative method of attempting to isolate various **2**, a procedure which would guarantee obtaining **3** at least partially even if **2** were initially present (4d,5).

In order to rationalize the seemingly capricious appearance of furans (**3**) during the acid-catalyzed solvolytic conversion of **1** to **2**, we visualize the cyclodehydration of **2** to **3** as being initiated by protonation of the aromatic ketone carbonyl. Nucleophilic attack by oxygen of the aliphatic ketone carbonyl (or its enol) followed by elimination of a proton and the elements of water then complete the reaction (4e).



In those cases where **3** were not obtained in the conversion of **1** to **2**, apparently the susceptibility of the protonated aromatic ketone carbonyl in **2** to nucleophilic attack is reduced by delocalization of the positive charge into the aromatic ring, discouraging cyclization. In those cases where **3** were obtained, either partially or solely, apparently one or both of two effects inhibit this charge delocalization to varying degrees increasing the reactivity of the aromatic ketone and encouraging cyclization.

First, substitution *ortho* or *alpha* to the aromatic ketone carbonyl in **2** with sufficiently bulky groups sterically reduces the resonance interaction between the aromatic ring and ketone carbonyl necessary for charge delocalization, thus increasing the reactivity of the aromatic ketone. Second, ring substitution in any position in **2** by groups having a high electron-withdrawal capability reduces the capacity of the aromatic ring to delocalize the positive charge, again encouraging cyclization (13b).

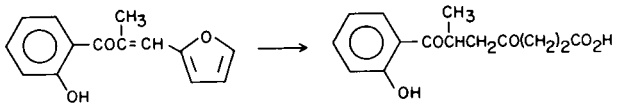
This view accommodates all of our results as well as those of others already cited (3,10-12). Thus, solvolysis of **1** containing a $+R$, $+I$ (15) methyl group *ortho* or *alpha* to the aromatic ketone carbonyl gave **3** exclusively or mixed with **2** (steric effect). With a $+R$, $-I$ fluoro, chloro or methoxy group in the *ortho* position, the reaction gave **3** exclusively (mostly or completely inductive effect). With fluoro or chloro in the *meta* or *para* position, or methoxy in the *meta* (but not *para*) position, the reaction gave principally **2**, but in addition very small amounts of **3** (inductive effect). Finally, solvolysis of **1** containing a $-R$, $-I$ trifluoromethyl, nitro or methylsulfonyl group in the *meta* or *para* position gave a mixture of **2** and **3** (resonance and inductive effects). The *meta*- and *para*-substituent effects observed correlate qualitatively with the appropriate σ values (16).

The failure of Popp and coworkers (3) to obtain pyridyl and quinolyl analogs of **2** is readily understandable since the nitrogen-containing rings, protonated under the reaction conditions and exerting strong electron withdrawal, would be expected to promote formation of **3**. This consideration, in fact, deterred us from attempting the preparation of pyridyl analogs even though we had succeeded in obtaining the heterocyclic thienyl diketone (**2**-27) without detecting furan (**3**-27) in the product.

The fact that the $+R$, $-I$ hydroxy group in the *ortho* position in **2**-15 did not promote cyclization to **3**-15 appears attributable to formation of a chelate ring with the aromatic ketone carbonyl (17). This inhibits protonation and holds the carbonyl group relatively coplanar

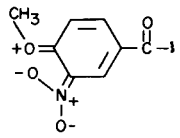
2-15

with the aromatic ring. The existence of chelation in **2**-15 is apparent from the relatively low frequency of its aromatic ketone carbonyl stretching vibration (Table II). That the role of the *o*-hydroxy group is not merely passive is suggested by the difficulty we experienced in forcing **2**-15 to cyclize by Method **3**-A (see Experimental section). Moreover, a clear manifestation of this effect is our observation that **1**-28 under the conditions of Method **2**-A gave only the diketone (**2**-28), *i.e.*, the stabilizing influence of the *o*-hydroxy group prevailed over the cyclization-promoting effect of the α-methyl group (11).



1-28 2-28

The fact that the corresponding furan (**3**) was not observed in the preparation of the 3-nitro-4-methoxy diketone (**2**-24) is also noteworthy. Inspection of molecular models indicates that the methoxy group need not sterically prevent the nitro group from being coplanar with the ring. The groups thus apparently interact primarily by resonance, and the electron thirst of the nitro group is quenched by the adjacent methoxy group to the extent that activation of the aromatic ketone and resultant furan formation are not observed. This effect is also evident in the relatively lower frequency of the aromatic ketone carbonyl stretching vibration in **2**-24 as compared with the *m*-nitro diketone (**2**-23) (Table II and Experimental section).



2-24

The 5-aryl-2-furanpropionic acids (**3**) were less potent as antiinflammatory agents in guinea pigs than the homologous furanacetic acids reported earlier from these laboratories by Kaltenbronn and Rhee (18). The best of the propionic acids, the *p*-chloro compound (**3**-7), was one-fourth as potent as the corresponding acetic acid (18). Some **3** showed toxic and even lethal effects at or below their minimum effective antiinflammatory doses.

EXPERIMENTAL

The ethanol used was 3A denatured, the petroleum ether was low boiling (distillation range about 30-60°). Melting points were observed in open capillary tubes in a calibrated Thomas-Hoover apparatus and the values were recorded without correction. Uv absorption spectra were recorded on a Cary Model 11 spectrophotometer, and ir absorption spectra on a Beckman IR5, -7 or -9 spectrophotometer.

TABLE I

Synthesis and Physical Properties of Substituted 3-(2-Furyl)acrylophenones (1)

Compound 1-	Ar	Synthesis			Purification		Ir (KBr), cm^{-1}		Molecular Formula	Elemental Analysis,	
		Method 1-	Yield, %	M.P., °C	Crystallization Solvent (a)	M.P., °C	Furan Ring	Ketone C=O		% Calcd., C	Found H
4	4′-FC_6H_4 (b)	A (c)	78	69.5-70			1555	1663	$C_{13}H_9FO_2$	72.2, 72.0	4.2, 4.2
8	4′-BrC_6H_4 (d)	A	83	79-80			1552	1657	$C_{13}H_9BrO_2$	56.3, 56.1	3.3, 3.4 (e)
15	2′-HOC_6H_4 (f)	B	70	106-108	B-PE	106-108	1557	1643	$C_{13}H_{10}O_3$	72.9, 72.6	4.7, 5.0
16	3′-HOC_6H_4	B (c)	98	145-148	M; E-W	149-151	1552	1645	$C_{13}H_{10}O_3$	72.9, 72.9	4.7, 4.6 (g)
17	4′-HOC_6H_4	B	77	140-150	M-W; EA-PE	160.5-162.5	1554	1649	$C_{13}H_{10}O_3$	72.9, 72.8	4.7, 4.8
25	4′-$CH_3SC_6H_4$	A	98	108-109	M	108.5-109.5	1551	1657	$C_{14}H_{12}O_2S$	68.8, 68.8	5.0, 5.1 (h)
26	4′-$CH_3SO_2C_6H_4$	A	89		EA; E	155.5-156.5	1554	1668	$C_{14}H_{12}O_4S$	60.9, 60.9	4.4, 4.7 (i)

(a) See Table III, footnote a. (b) Prepared by Brown and Chinn (2a) using sodium methoxide in methanol: yield not reported, m.p. approximately 70°. (c) Details are given in Experimental section. (d) Prepared by N. L. Drake and H. W. Gilbert, *J. Am. Chem. Soc.*, 52, 4965 (1930), using sodium hydroxide in aqueous ethanol: yield not reported, m.p. 80-81° (ethanol). (e) Br: 28.8, 28.6. (f) Prepared by Y. Otsuka, *J. Chem. Soc. Japan*, 65, 539 (1944); *Chem. Abstr.*, 41, 3797*g* (1947), using excess 50% aqueous sodium hydroxide in ethanol: 37% yield, m.p. 110°. (g) Found values are corrected for 0.75% ash. (h) S: 13.1, 13.4. (i) S: 11.6, 11.6.

Substituted 3-(2-Furyl)acrylophenones (1, Table I).

Method 1-A. 4′-Fluoro-3-(2-furyl)acrylophenone (1-4).

A mixture of 199 g. (1.44 moles) of 4′-fluoroacetophenone and 123 ml. (1.48 moles) of 2-furaldehyde was added dropwise with stirring over 45 minutes to a solution of 2.7 g. of sodium methoxide in 338 ml. of methanol, during which the temperature was kept below 30° by cooling. After an additional 4 hours, the precipitate obtained was collected, washed with methanol and dried; yield, 241 g.

In some cases ethanol was used as reaction solvent and the solution was refluxed for 1-2 hours (1-2, 1-3 and 1-14), 50% aqueous sodium hydroxide was used as catalyst (1-14, 1-25 and 1-26), and the furaldehyde was added alone to a mixture of the other materials (1-8).

The following unpurified 1 prepared by this method were less completely characterized than those listed in Table I. 2′-Fluoro-3-(2-furyl)acrylophenone (1-2): 29% yield; m.p. 31-32.5°; ir (liquid film) 1552 and 1666 cm^{-1}. 3′-Fluoro-3-(2-furyl)acrylophenone (1-3): sample isolated; m.p. 56-60°. 3-(2-Furyl)-4′-propylacrylophenone (1-14): sample isolated; liquid; ir (liquid film) 1553 and 1664 cm^{-1}.

Method 1-B. 3-(2-Furyl)-3′-hydroxyacrylophenone (1-16).

Over a period of 32 minutes, 90 ml. (1.7 moles) of 50% aqueous sodium hydroxide was added to a stirred mixture of 200 g. (1.47 moles) of 3′-hydroxyacetophenone and 122 ml. (1.47 moles) of 2-furaldehyde in 1 l. of water, during which the temperature rose to about 45°. The solution obtained was stirred for 1.5 hours in a warm water bath and acidified by the dropwise addition of 105 ml. (1.8 moles) of glacial acetic acid. The resulting precipitate was collected, washed with water and dried; yield, 307.7 g.

Ethanol was used as reaction solvent in the preparation of 1-15 and 1-28.

The following unpurified 1 prepared by this method was less completely characterized than those listed in Table I. 3-(2-Furyl)-2′-hydroxy-2-methylacrylophenone (1-28); 90% yield; liquid; ir (liquid film) 1553 (sh) and 1634 cm^{-1}.

6-Aroyl-4-oxohexanoic Acids (2, Table II).

Method 2-A. 6-(*p*-Fluorobenzoyl)-4-oxohexanoic Acid (2-4).

Over a period of 7 hours, 241 g. (1.11 moles) of 4-fluoro-3-(2-furyl)acrylophenone (1-4) was added to a refluxing solution of 500 ml. of concentrated hydrochloric acid in 1 l. of ethanol. The solution was refluxed an additional 16 hours and concentrated. The residual oil was refluxed for 3 hours with a solution of 500 ml. each of concentrated hydrochloric and glacial acetic acids in 2 l. of water, the slightly cooled aqueous layer was decanted from the insoluble oil over fluted filter paper and chilled, and the precipitate obtained was collected, washed with water and dried. A second similar hydrolytic extraction, and a third using the first filtrate, gave two more crops; total yield, 171.4 g.

In some cases all of the acrylophenone was combined initially with the acid and alcohol before heating (2-20 and 2-26), and acetic acid was not used in the hydrolytic extraction medium (2-15 and 2-17). It was necessary to concentrate the extracts to obtain 2-28, and an ether solution of the product was then dried over sodium sulfate and concentrated.

6-(*o*-Fluorobenzoyl)-4-oxohexanoic acid (2-2) could not be obtained by this method; corresponding furan (3-2) was the only observed product (see Table III and Method 3-B). 6-(*m*-Nitrobenzoyl)-4-oxohexanoic acid (2-23) was not obtained pure, but

TABLE II

Synthesis and Physical Properties of 6-Aroyl-4-oxohexanoic Acids (2)

Compound 2-	Ar	Synthesis Method 2-	Yield, %	M.P., °C	Purification Crystallization Solvent (a)	Recovery, %	M.P., °C	Ir (KBr), cm^{-1}; C=O Aromatic Ketone	Carboxyl and Aliphatic Ketone (b)	Molecular Formula	Elemental Analysis, % Calcd., Found C	H
3	*m*-FC_6H_4	B (c)	50 (d)	105-109	EA-PE	53	113-114	1674	1716	$C_{13}H_{13}FO_4$	61.9, 61.7	5.2, 5.1
4	*p*-FC_6H_4(e)	A (c)	61	118-122	B	73	122-123	1679	1715,.1724	$C_{13}H_{13}FO_4$	61.9, 61.6	5.2, 5.2
		B	45 (d)	117-120				1682	1716, 1727		61.7	5.0
6	*m*-ClC_6H_4	B	33 (d)	74-84	E-W	43	84.5-88	1681	1698, 1713	$C_{13}H_{13}ClO_4$	58.1, 58.0	4.9, 5.2
7	*p*-ClC_6H_4	A	56 (d)	130-136	B	70	139-140	1685	1702	$C_{13}H_{13}ClO_4$	58.1, 58.3	4.9, 4.8
8	*p*-BrC_6H_4	A	58	135-141	B	87	141-143	1682	1695	$C_{13}H_{13}BrO_4$	49.9, 49.6	4.2, 4.4(f)
9	*m*-$CH_3C_6H_4$	B	30	80-88	EA-PE	58	88-90	1679	1708, 1718	$C_{14}H_{16}O_4$	67.7, 67.6	6.5, 6.4
10	*p*-$CH_3C_6H_4$ (g)	A	47	116-122	B	90	121-122	1672 (h)	1697, 1711	$C_{14}H_{16}O_4$	67.7, 67.9	6.5, 6.5
12	3,4-$(CH_3)_2C_6H_3$	B	40	99-102	CT	64	100-101	1673	1708	$C_{15}H_{18}O_4$	68.7, 68.4	6.9, 6.9
13	*p*-$C_2H_5C_6H_4$ (g)	B	44	95-104	AA-W	57	100.5-103	1671	1695, 1711	$C_{15}H_{18}O_4$	68.7, 68.5	6.9, 7.0
14	*p*-$CH_3(CH_2)_2C_6H_4$	B	24	85-90	B	68	88-90	1675	1701	$C_{16}H_{20}O_4$	69.5, 69.5	7.3, 7.4
15	*o*-HOC_6H_4	A	54	97.5-113	B	88	111.5-112.5	1648	1716	$C_{13}H_{14}O_5$	62.4, 62.2	5.6, 5.6
16	*m*-HOC_6H_4	A	38	138-143	EA-PE	76	147.5-149.5	1676	1699, 1714	$C_{13}H_{14}O_5$	62.4, 62.6	5.6, 6.0
17	*p*-HOC_6H_4	A	50	133-139	EA	50	142-144	1673 (h)	1710, 1725	$C_{13}H_{14}O_5$	62.4, 62.2	5.6, 5.8
19	*m*-$CH_3OC_6H_4$ (i)	B	37 (d)	82-88	EA-PE	55	86-88.5	1693	1700 (j)	$C_{14}H_{16}O_5$	(i)	
20	*p*-$CH_3OC_6H_4$ (k)	A	57	115.5-118.5				1670	1696, 1718	$C_{14}H_{16}O_5$	(k)	
		B	52	115-119.5	AA-W	25	119.5-120.5	1670	1695, 1718			
22	*m*-$CF_3C_6H_4$	B	3 (l)	64-69				1675	1695, 1700 (j)	$C_{14}H_{13}F_3O_4$	55.6, 55.9	4.3, 4.2(m)
24	3-NO_2-4-$CH_3OC_6H_4$	B	9	88-92	(n)		118.5-120.5	1681	1709, 1717 (o)	$C_{14}H_{15}NO_7$	54.4, 54.3	4.9, 4.9(p)
25	*p*-$CH_3SC_6H_4$	B	41	109-125	B	52	130-132	1673	1711, 1720	$C_{14}H_{16}O_4S$	60.0, 59.9	5.8, 5.7
26	*p*-$CH_3SO_2C_6H_4$	A	(q)		EA	(q)	149-150	1686 (r)	1708	$C_{14}H_{16}O_6S$	53.8, 53.9	5.2, 5.4
		B	(s)		EA	(s)	149-150	1686 (r)	1708			
		C (c)	66	147.5-150				1686 (r)	1708			
27	2-Thienyl	B	46	107-109	E-W	79	108-109.5	1672	1702, 1713	$C_{11}H_{12}O_4S$	55.0, 54.7	5.0, 5.1
28	(t)	A	17	liquid				1639	1715 (u)	$C_{14}H_{16}O_5$	63.6, 63.9	6.1, 6.3

(a) See Table III, footnote a. (b) The higher frequency band, where two were observed, is probably assignable to the ketone. Where only one band was observed, it was generally relatively broad. (c) Details are given in Experimental section. (d) Unpurified material contained a small amount of corresponding furan (**3**), as indicated by very weak ir absorption in the 1550-cm^{-1} region. In the case of **2**-6, furan was still detectable in the purified material. (e) Prepared by Brown and Chinn (2a) by Method **2**-A: yield not reported, m.p. approximately 123° (ethyl acetate). (f) Br: 25.5, 25.8. (g) Prepared by Turner (11) by Method **2**-A: **2**-10, 61% yield, m.p. 112-113° (sic) (benzene); **2**-13, 60% yield, m.p. 104-105° (carbon tetrachloride). (h) Split peak. Slightly weaker intensity absorption: **2**-10, at 1668; **2**-17, at 1678. (i) Prepared by Martin and Robinson(10) by Method **2**-A: yield not reported, m.p. 87-88° (acetic acid-water). (j) Shoulder. (k) Prepared by Robinson and Todd (5) by Method **2**-A: 50-55% yield (unpurified), m.p. 119° (water). (l) Furan **3**-22 was also obtained. See Table III, footnote k. (m) F: 18.9, 17.3. The low F analysis may indicate partial hydrolysis of the trifluoromethyl group. (n) Crystallization of the first crop, m.p. 90-92°, from acetic acid-water gave 60% recovery of material m.p. 90-115°. Recrystallization from ethyl acetate-petroleum ether then gave 70% recovery of the higher-melting dimorph. In chloroform solution the high- and low-melting materials gave identical ir spectra; in potassium bromide, the spectra were different. (o) Dimorph m.p. 90-92°: 1687 and 1713. In chloroform, both dimorphs: 1689 and 1714. (p) N: 4.5, 4.4. (q) Four hydrolytic extractions gave about 21% yield of a mixture of diketone (**2**-26) and furan (**3**-26), as indicated by ir absorption, m.p. 119-136°. Two recrystallizations from ethyl acetate of 0.7 g. of material, m.p. 129-136°, gave 0.1 g. of diketone. (r) Shoulder at 1693-1695. (s) Diketone (**2**-26) was obtained as a mixture with furan (**3**-26). See Experimental section under Method **3**-C. (t) Full structure is shown in text. (u) In chloroform.

TABLE III

Synthesis, and Physical and Antiinflammatory Properties of 5-Aryl-2-furanpropionic Acids (3)

Compound 3-	Ar	Synthesis Method 3-	Yield, %	M.P., °C	Purification Crystallization Solvent (a)	Recovery, %	M.P., °C	Ir (KBr), cm^{-1} Furan Ring	Carboxyl C=O	Molecular Formula	Elemental Analysis, % Calcd., Found C	H	Minimum Effective Antiflammatory Dose, mg./kg. (b)
1	C_6H_5 (c)	A	77	90-116	M-W	93	117-117.5	1549	1696	$C_{13}H_{12}O_3$	72.2, 72.0	5.6, 5.8	100 (d)
2	o-FC_6H_4	B (e)	2	113-115				1543	1695	$C_{13}H_{11}FO_3$	66.7, 66.4	4.7, 4.9 (f)	(g)
4	p-FC_6H_4	A (e)	97	133-133.5	M-W	91	131-132.5	1557	1698	$C_{13}H_{11}FO_3$	66.7, 66.4	4.7, 4.7 (f)	100
5	o-ClC_6H_4	C (e)	27	85-103	T	62	103-104	1547	1713	$C_{13}H_{11}ClO_3$	62.3, 62.5	4.4, 4.2 (h)	200
6	m-ClC_6H_4	A	94	104-106	B-PE	72	105-106	1547	1702	$C_{13}H_{11}ClO_3$	62.3, 62.5	4.4, 4.6 (h)	100
7	p-ClC_6H_4	A	92	141-143	EA-PE	63	142-143	1548	1696	$C_{13}H_{11}ClO_3$	62.3, 62.5	4.4, 4.5 (h)	12.5
8	p-BrC_6H_4	A	91	147-148.5				1546	1694	$C_{13}H_{11}BrO_3$	52.9, 53.2	3.8, 3.9 (i)	25
9	m-$CH_3C_6H_4$	A	59	105.5-106.5				1547	1704	$C_{14}H_{14}O_3$	73.0, 72.8	6.1, 6.0	100
10	p-$CH_3C_6H_4$	A	92	120-121	B	91	119.5-121	1558	1693	$C_{14}H_{14}O_3$	73.0, 73.0,	6.1, 6.3	100
12	3,4-$(CH_3)_2C_6H_3$	A	94	129-130				1548	1708	$C_{15}H_{16}O_3$	73.8, 73.4	6.6, 6.6	>100
13	p-$C_2H_5C_6H_4$	A	84	113.5-114.5				1551	1702	$C_{15}H_{16}O_3$	73.8, 73.7	6.6, 6.6	100
14	p-$CH_3(CH_2)_2C_6H_4$	A	70	99-100.5				1553	1691	$C_{16}H_{18}O_3$	74.4, 74.3	7.0, 7.2	>100
17	p-HOC_6H_4	D (e)	56	194-196	M	37	196-197.5	1557	1695	$C_{13}H_{12}O_4$	67.2, 67.0	5.2, 5.3	> 50 (d)
18	o-$CH_3OC_6H_4$	C	4	118.5-120.5	E-W	64	120-121.5	1544	1716	$C_{14}H_{14}O_4$	68.3, 68.2	5.7, 5.9	100
19	m-$CH_3OC_6H_4$	A	76	110.5-111.5				1549	1704	$C_{14}H_{14}O_4$	68.3, 68.0	5.7, 5.9	>100 (j)
20	p-$CH_3OC_6H_4$ (c)	A	59	140-142.5	E	42	141.5-142.5	1557	1698	$C_{14}H_{14}O_4$	68.3, 68.4	5.7, 5.7	50 (d)
21	2,5-$(CH_3O)_2C_6H_3$	C	3	141-146	E-W; B	94; 68	147.5-148.5	1548	1717	$C_{15}H_{16}O_5$	65.2, 65.4	5.8, 6.0	100
22	m-$CF_3C_6H_4$	C	9 (k)	66-72				1551	1720	$C_{14}H_{11}F_3O_3$	59.2, 59.1	3.9, 4.1 (l)	(g)
23	m-$NO_2C_6H_4$ (m)	B (e)	(n)		B	(n)	122-124	1552	1707	$C_{13}H_{11}NO_5$	59.8, 59.9	4.2, 4.4 (o)	
		A	81 (p)	122-124				1552	1706		59.7	4.2 (o)	100
26	p-$CH_3SO_2C_6H_4$	A	100	158-160	AA-W (q)	86	160-162.5	1548	1700	$C_{14}H_{14}O_5S$	57.1, 57.2	4.8, 4.8 (r)	>100
		C (e)	(n)	153-156	E	63	158-160	1548	1696				
27	2-Thienyl	A	87	89.5-90.5	CH	64	90.5-93.5	1566	1723	$C_{11}H_{10}O_3S$	59.4, 59.7	4.5, 4.8 (s)	>100

(a) AA, acetic acid; B, benzene; CH, cyclohexane; CT, carbon tetrachloride; E, ethanol; EA, ethyl acetate; M, methanol; PE, petroleum ether; T, toluene; W, water. (b) Test method is described in Reference 6. Compounds were administered as an aqueous solution or partial suspension of the sodium salt, except for 3-23 which was administered as the acid suspended in aqueous acacia. These data are preliminary screening estimates. In order of increasing potency, the minimum effective doses of some reference agents, calculated from the results of formal quantitative bioassays, are: aspirin 28, mefenamic acid 10, phenylbutazone 5.3, flufenamic acid 3.3, indomethacin 1.7 and meclofenamic acid 0.4 mg./kg. (c) Prepared by Robinson and Todd (5) using phosphorus pentoxide in benzene: 3-1, 88% yield (unpurified), m.p. 116° (toluene); 3-20, 70-75% yield (unpurified), m.p. 141° (benzene). (d) Lethal at this dose. (e) Details are given in Experimental section. (f) F: 8.1, 3-2 8.1, 3-4 7.9. (g) Not tested. (h) Cl: 14.1, 3-5 14.3, 3-6 14.4, 3-7 14.4. (i) Br: 27.1, 26.5. (j) Toxic at this dose. (k) The initial hydrolytic extract on concentration gave about 3% yield of diketone (2-22) and a subsequent extract gave furan (3-22). (l) Insufficient sample for F analysis (see Table II, footnote m). (m) Prepared by Popp, Schleigh, and Katz (3) by Method 3-B: yield not reported, m.p. 119-120° (benzene). (n) See Experimental section. (o) N: 5.4, 3-B 5.3, 3-A 5.2. (p) Starting diketone (2-23) contained about 35% of furan (3-23). See Experimental section. (q) An initial recrystallization from methanol-water caused partial conversion to the methyl ester, and the acid was regenerated using potassium hydroxide in ethanol. (r) S: 10.9, 10.9. (s) S: 14.4,14.2.

was observed as the major component of a mixture with furan (3-23) (see Table III and Method 3-B).

Method 2-B. 6-(*m*-Fluorobenzoyl)-4-oxohexanoic Acid (2-3).

A mixture of 100.0 g. (0.724 mole) of 3′-fluoroacetophenone and 60.0 ml. (0.724 mole) of 2-furaldehyde was added dropwise with stirring over 1 hour to a solution of 1.0 g. of sodium methoxide in 100 ml. of ethanol, during which the temperature rose to 38°. The resulting solution was stirred and refluxed for 2 hours. [A chilled sample of the solution gave a precipitate of the intermediate acrylophenone (1-3)]. After addition of 200 ml. of concentrated hydrochloric acid and an additional 500 ml. of ethanol, the solution was refluxed for 16 hours and concentrated. The residual oil was refluxed for 4 hours with a solution of 375 ml. each of concentrated hydrochloric and glacial acetic acids in 1.5 l. of water, the slightly cooled aqueous layer was decanted from the insoluble oil over fluted filter paper and chilled, and the precipitate obtained was collected, washed with water and dried. A second similar hydrolytic extraction, and two further extractions using the first two filtrates alternately, gave three more crops; total yield, 89.9 g.

In some cases 50% aqueous sodium hydroxide was used as basic catalyst (2-4, 2-6, 2-9 and 2-26), the furaldehyde was added alone to a mixture of the other materials (2-4, 2-6, 2-9, 2-18, 2-19, 2-20, 2-24 and 2-25) and the acrylophenone solution was not refluxed (2-4, 2-6, 2-9, 2-12, 2-13, 2-19, 2-20, 2-22, 2-26 and 2-27). In the case of 2-27, acetic acid was not used in the hydrolytic extraction medium.

The following 2 could not be obtained by this method; corresponding furans (3) were the only observed products (see Table III and Method 3-C): 6-(*o*-chlorobenzoyl)-4-oxohexanoic acid (2-5), 6-(2,5-dimethylbenzoyl)-4-oxohexanoic acid (2-11), 6-(*o*-anisoyl)-4-oxohexanoic acid (2-18), and 6-(2,5-dimethoxybenzoyl)-4-oxohexanoic acid (2-21).

Method 2-C. 6-[*p*-(Methylsulfonyl)benzoyl]-4-oxohexanoic Acid (2-26).

A stirred solution of 13.0 g. (0.046 mole) of 6-[*p*-(methylthio)benzoyl]-4-oxohexanoic acid (2-25) in 100 ml. of glacial acetic acid at 55° was treated dropwise with 18.0 ml. (0.176 mole) of 30% aqueous hydrogen peroxide, keeping the temperature at 50-60° with a cold water bath. The solution was then heated at 70-85° for 4 hours, cooled to room temperature, diluted with an equal volume of water and chilled. The precipitate obtained was collected, washed with acetic acid-water (1:1) and dried; yield, 9.5 g.

5-Aryl-2-furanpropionic Acids (3, Table III).

Method 3-A. 5-(*p*-Fluorophenyl)-2-furanpropionic Acid (3-4).

A solution of 12.6 g. (0.05 mole) of 6-(*p*-fluorobenzoyl)-4-oxohexanoic acid (2-4) and 0.1 g. of *p*-toluenesulfonic acid monohydrate in 50 ml. of toluene was refluxed using a Barrett receiver until water evolution (calcd. and observed, 0.9 ml.) appeared complete (2.25 hours). The thick slurry obtained after 3 hours at room temperature was diluted with about 40 ml. of petroleum ether, the precipitate was collected, washed with petroleum ether and dried; yield, 11.3 g.

The reaction times varied from 1 to 4 hours except for 3-27 which was run for 22 hours, and 3-6 which was run in benzene and required 8 hours. An attempt to prepare 3-23 in boiling benzene in an open flask for 40 minutes did not give complete cyclization. In the case of 3-26 complete solution was never achieved but the nature of the suspended solid changed during reaction. In some cases, the reaction solution was not diluted with petroleum ether before filtration. Recrystallization of the products was frequently not only unnecessary, but even undesirable since in some cases it resulted in discoloration and lowered m.p. A trial attempt to prepare 3-1 without the acid catalyst gave little if any cyclization in 1.5 hours.

5-(*o*-Hydroxyphenyl)-2-furanpropionic acid (3-15) was not obtained pure by this method. Material isolated in about 58% yield, m.p. 117-124°, after reaction time of 3.75 hours still contained about 15% of diketone (2-15) as indicated by ir absorption [(potassium bromide) 1549 (furan ring) and 1712 cm^{-1} (carboxyl C=O)] and C analysis [$C_{13}H_{12}O_4$ (calcd./found) C, 67.2/66.5]. Attempts at recrystallization were unsuccessful. Extending reaction time to 7 hours resulted in marked decomposition.

Method 3-B. 5-(*o*-Fluorophenyl)-2-furanpropionic Acid (3-2).

A solution of 5.0 g. (0.023 mole) of 2′-fluoro-3-(2-furyl)-acrylophenone (1-2) and 5 ml. of concentrated hydrochloric acid in 20 ml. of ethanol was refluxed for 3 hours and concentrated. The residual oil was refluxed for 1.5 hours with a solution of 10 ml. of concentrated hydrochloric acid in 50 ml. of water, and after cooling, the aqueous layer was decanted from the insoluble oil over fluted filter paper. Only a trace of solid separated when the decantate was chilled. The oil was then refluxed for 2 hours with a solution of 10 ml. of concentrated hydrochloric acid and 25 ml. of glacial acetic acid in 50 ml. of water, and the chilled decantate gave a precipitate which was collected, washed with water and dried; yield, *ca.* 0.1 g. Another hydrolytic extraction with the previous mother liquor did not give more product.

Method 3-B. 5-(*m*-Nitrophenyl)-2-furanpropionic Acid (3-23) and 6-(*m*-Nitrobenzoyl)-4-oxohexanoic Acid (2-23).

Over a period of 7 hours, 123.6 g. (0.508 mole) of 3-(2-furyl)-3′-nitroacrylophenone (11) was added to a refluxing solution of 250 ml. of concentrated hydrochloric acid in 750 ml. of 95% ethanol. The solution was refluxed an additional 16 hours and concentrated. The residual oil was refluxed for 17 hours with a solution of 250 ml. of each of concentrated hydrochloric and glacial acetic acids in 1 l. of water. After cooling slightly, the aqueous layer was decanted from the insoluble oil over fluted filter paper and chilled. The precipitate obtained was collected, washed with water and dried, giving 19.0 g. of a mixture of about 80% diketone (2-23) and 20% furan (3-23), as indicated by ir and uv absorption, m.p. 97-105°. A second similar hydrolytic extraction gave a second crop of 19.1 g., m.p. 99-105°. Two additional extractions using the first and second filtrates successively gave a third crop of 13.7 g., m.p. 97-105°, and a fourth crop of 2.2 g., m.p. 99-105°.

Recrystallization of the fourth crop from 100 ml. of benzene gave 1.7 g. of furan (3-23), m.p. 122-124°. The fact that the recovery of furan from this recrystallization (77%) was greater than the equilibrium concentration of furan in the hydrolysis medium (about 57%; see below) suggests that partial cyclization of diketone occurred during heating in benzene.

Attempts to obtain pure diketone (2-23) by fractional recrystallization of the earlier crops were not successful. The purest sample observed resulted from recrystallization of the second crop from 175 ml. of toluene and then from 100 ml. of ethanol-175 ml. of water to give 10.6 g. of material which still contained about 15% of furan (3-23) as indicated by uv and ir absorption [(chloroform) 1700 (aromatic ketone C=O) and 1715 cm^{-1} (carboxyl and aliphatic ketone C=O)] and C analysis [$C_{13}H_{13}NO_6$ (calcd./found) C, 55.9/56.8].

Method 3-C. 5-(*o*-Chlorophenyl)-2-furanpropionic Acid (3-5).

A mixture of 100.0 g. (0.648 mole) of 2′-chloroacetophenone and 54 ml. (0.65 mole) of 2-furaldehyde was added dropwise with stirring over 1.2 hours to 150 ml. of ethanol containing 1.5 g. of sodium methoxide, during which the temperature rose to about 40°. After an additional 3 hours, 600 ml. of 95% ethanol and 250 ml. of concentrated hydrochloric acid were added, the solution was refluxed for 18 hours and concentrated. The oily residue was refluxed for 2 hours with a solution of 250 ml. of concentrated hydrochloric acid and 100 ml. of glacial acetic acid in 1 l. of water, the cooled aqueous layer was decanted from the insoluble oil over fluted filter paper and chilled, and the precipitate obtained was collected, washed with water and dried. The hydrolytic extraction was then repeated using a solution of 375 ml. of each of concentrated hydrochloric and glacial acetic acids in 1.5 l. of water. Using the preceding two aqueous filtrates alternately, with occasional addition of more acetic acid and water, the extraction process was continued until nine crops of product had been collected; yield, 44.8 g.

Samples recrystallized from ethanol-water and from cyclohexane gave slightly low C analyses, suggesting the possible presence of some diketone (**2**-5), although the latter was not detectable in the ir spectrum. A solution of 27.2 g. of the crude product and 100 mg. of *p*-toluenesulfonic acid monohydrate in 150 ml. of toluene was refluxed for 3.5 hours as in Method **3**-A, but no detectable water was evolved. Analytically pure product (16.8 g.) crystallized from the filtered (charcoal) and cooled toluene solution.

Method **3**-C. 5-[*p*-(Methylsulfonyl)phenyl]-2-furanpropionic Acid (**3**-26) and 6-[*p*-(Methylsulfonyl)benzoyl]-4-oxohexanoic Acid (**2**-26).

A mixture of 125.0 g. (0.630 mole) of *p*-(methylsulfonyl)-acetophenone, 53.0 ml. (0.639 mole) of 2-furaldehyde and 2 ml. of 50% aqueous sodium hydroxide in 1.5 l. of ethanol was stirred for 5 hours. After addition of 500 ml. of concentrated hydrochloric acid, the mixture was stirred and refluxed for 16 hours and concentrated. The residual oil was refluxed for 2 hours with a solution of 250 ml. each of concentrated hydrochloric and glacial acetic acids in 1 l. of water. After cooling slightly, the aqueous layer was decanted from the insoluble oil over fluted filter paper and chilled. The precipitate obtained was collected, washed with water and dried giving 34.5 g. of a mixture of about half diketone (**2**-26) and half furan (**3**-26), as indicated by ir absorption, m.p. 120-136°. A second similar hydrolytic extraction gave a second crop of 41.3 g., m.p. 120-136°. A final extraction using the combined first and second filtrates gave a third crop of 11.6 g., m.p. 125-138°.

A solution of 22.5 g. of product mixture in 500 ml. of 5% aqueous potassium carbonate was chilled and the resulting precipitate was collected and dissolved in water. Acidification of this solution gave 3.5 g. of furan (**3**-26), m.p. 153-156°. Crystallization from 25 ml. of ethanol gave 2.2 g., m.p. 158-160°.

Two recrystallizations of 20.0 g. of product mixture from ethyl acetate (200 and 150 ml.) gave 2.0 g. of diketone (**2**-26), m.p. 149-150°.

In the case of **3**-11, **3**-18, and **3**-21, the initial reaction solution was refluxed for 3-6 hours to assure complete formation of the intermediate acrylophenone.

5-(2,5-Xylyl)-2-furanpropionic acid (**3**-11) was not obtained pure by this method. Material isolated from two extractions in about 1% yield, m.p. 120-131°, showed a slight inflection in the ir spectrum (potassium bromide) at 1682 cm^{-1} suggestive of the possible presence of some diketone (**2**-11). Crystallization of 0.7 g. of material, m.p. 129-131°, from ethyl acetate-petroleum ether gave 0.2 g., m.p. 137-139°; the C analysis was low [$C_{15}H_{16}O_3$ (calcd./found) C, 73.8/72.7], but the ir spectrum [(potassium bromide) 1540 (furan ring) and 1699 cm^{-1} (carboxyl C=O)] showed no evidence for diketone.

Method **3**-D. 5-(*p*-Hydroxyphenyl)-2-furanpropionic Acid (**3**-17).

A solution of 30.0 g. (0.120 mole) of 6-(*p*-hydroxybenzoyl)-4-oxohexanoic acid (**2**-17) and 0.1 g. of *p*-toluenesulfonic acid monohydrate in 150 ml. of glacial acetic acid was refluxed for 64 hours and diluted hot with 300 ml. of hot water. The crystalline precipitate obtained on chilling was collected and dried; yield, 15.6 g.

Interconversion of 6-(*m*-Nitrobenzoyl)-4-oxohexanoic Acid (**2**-23) and 5-(*m*-Nitrophenyl)-2-furanpropionic Acid (**3**-23) under Acid Hydrolysis Conditions.

In the following experiments, the composition of the mixtures obtained was calculated from their uv absorption (19) in ethanol, and confirmed qualitatively by their ir absorption. Since a pure sample of ketone (**2**-23) was not at hand, the absorption maximum of 3′-nitroacetophenone at 225 mμ (ε, 22,800) was used as a basis for calculation. For furan **3**-23, its maximum at 292 mμ (ε, 20,500) was used.

A solution of 1.0 g. of a mixture of 65% diketone and 35% furan [uv maximum 292 (E_1^1 281) and 225 mμ (654); obtained from the experiment described under Method **3**-B] in 10 ml. of water containing 5 ml. of each of concentrated hydrochloric and glacial acetic acids was refluxed. A sample (2 ml.) was withdrawn at the indicated intervals and concentrated to dryness under reduced pressure. The residue was scraped from the flask, ground in a mortar and its uv and ir spectra determined. The product compositions were: at 1 hour, 51% diketone and 49% furan [uv max 292 (E_1^1 384) and 225 mμ (557)]; at 5 hours, 49% diketone and 51% furan [uv max 292 (E_1^1 410) and 225 mμ (553)].

A similar experiment was done starting with 1.0 g. of pure furan, with the exception that an additional 5 ml. of glacial acetic acid was needed to effect complete solution at reflux. The product compositions were: at 5 hours, 41% diketone and 59% furan [uv max 292 (E_1^1 470) and 225 mμ (508)]; at 24 hours, 43% diketone and 57% furan [uv max 292 (E_1^1 435) and 225 mμ (504)].

Attempt to Convert 5-(*o*-Chlorophenyl)-2-furanpropionic Acid (**3**-5) to 6-(*o*-Chlorobenzoyl)-4-oxohexanoic Acid (**2**-5) by Acid Hydrolysis.

A suspension of 1.0 g. of furan (**3**-5) in 10 ml. of water containing 5 ml. each of concentrated hydrochloric and glacial acetic acids was refluxed and sufficient additional glacial acetic acid (two 5-ml. portions) was added to effect complete solution. Samples withdrawn after 2 and 24 hours and worked up as described in the preceding experiments showed no evidence (ir and uv) for formation of diketone (**2**-5).

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