

Biologically Active Compounds. II. The Synthesis of β -Carboxy- γ -butyrolactone Derivatives

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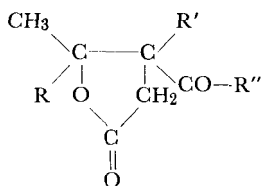
Amide derivatives of γ -substituted paraconic and aconic acids have been synthesized. Ultraviolet spectra of the aconic acid derivatives showed characteristic fine structure in the region of 245 to 280 $m\mu$.

For the purpose of studies designed to investigate biologically active substances, a number of the title new compounds were synthesized. Certain of the γ -lactone derivatives as are shown in Table I and II showed, to some extent, antibacterial, antifungal, and herbicidal activity.

In order to avoid the formation of pyrrolidone derivatives by the reaction of intramolecular ester group such as lactonic linkage with amines,¹⁾ the amides of γ -substituted paraconic and aconic acids (5 and 7)^{2), 3)} were prepared

by the reaction of equimolar amount of the chloride of the acids (5 and 7) with amines.⁴⁾ The general preparative ways of amides (6 and 8) are shown in Scheme I.

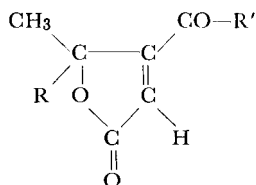
The infrared spectra of amides (6 and 8)⁵⁾ show an absorption band at 1750–1760 (for lactone carbonyl) and an absorption band at 1650–1680 (for amide carbonyl) as are shown in IR Charts I and IV. The ultraviolet spectra of aconic acids (5) exhibit characteristic bands in the region of 245 to 280 $m\mu$ as are shown in UV Charts.

Table I γ -Alkyl- γ -methylparaconic Acids and Their Anilides

R	R'	R''	Mp., °C	Yield, %	Formula	Calcd., %			Found, %		
						C	H	N	C	H	N
C ₂ H ₅	H	2, 4-Cl ₂ C ₆ H ₃ NH	135	40	C ₁₄ H ₁₅ Cl ₂ NO ₃	53.18	4.78	4.43	53.33	4.69	3.98
C ₂ H ₅	H	2, 5-Cl ₂ C ₆ H ₃ NH	120	37	C ₁₄ H ₁₅ Cl ₂ NO ₃	53.18	4.78	4.43	53.24	4.79	4.48
C ₂ H ₅	H	3, 4-Cl ₂ C ₆ H ₃ NH	157	72	C ₁₄ H ₁₅ Cl ₂ NO ₃	53.18	4.78	4.43	53.18	4.72	4.76
C ₂ H ₅	H	4-ClC ₆ H ₄ NH	128	61	C ₁₄ H ₁₆ ClNO ₃	59.68	5.72	...	59.69	5.79	...
<i>iso</i> -C ₄ H ₉	Br	OH	166	90	C ₁₀ H ₁₅ BrO ₄	43.02	5.43	...	43.27	5.63	...
<i>iso</i> -C ₄ H ₉	H	3, 4-Cl ₂ C ₆ H ₃ NH	195	66	C ₁₆ H ₁₉ Cl ₂ NO ₃	55.82	5.56	4.07	55.76	5.50	4.07
<i>iso</i> -C ₄ H ₉	H	2-ClC ₆ H ₄ NH	102	53	C ₁₆ H ₂₀ ClNO ₃	62.03	6.51	4.52	62.66	6.50	4.34
<i>iso</i> -C ₄ H ₉	H	4-ClC ₆ H ₄ NH	184	60	C ₁₆ H ₂₀ ClNO ₃	62.03	6.51	4.52	62.33	6.68	4.83

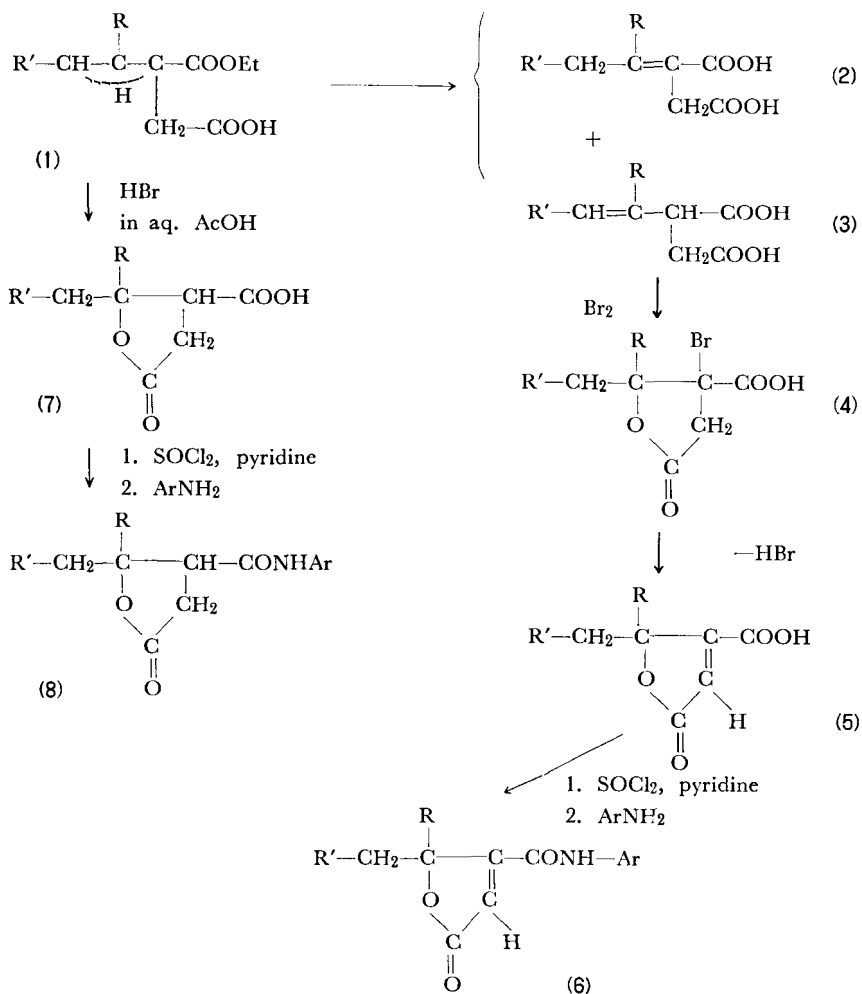
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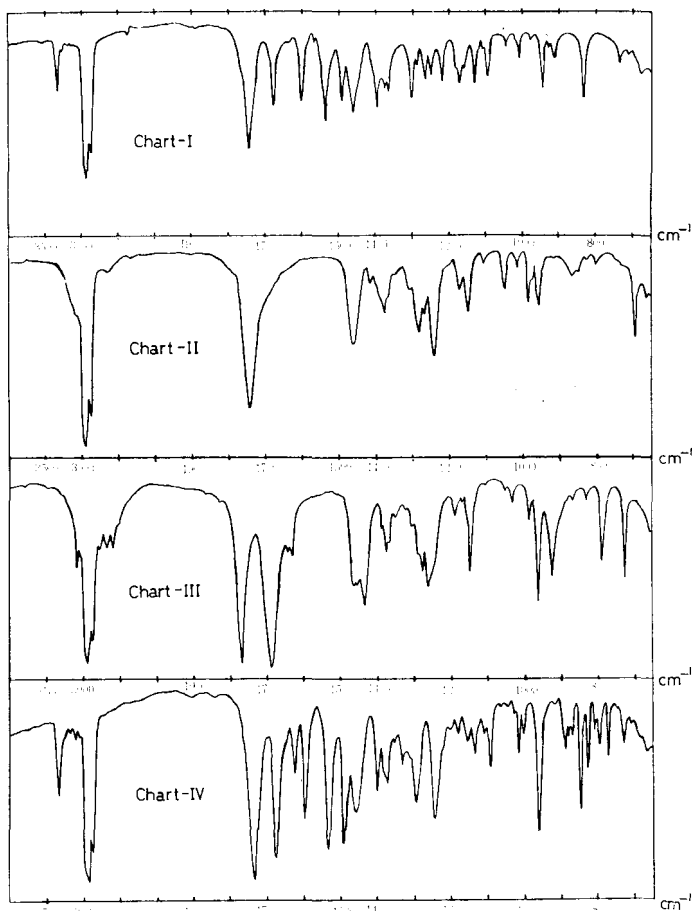
Table II 7-Alkyl-7-methyloaconic Acids and Their Anilides



R	R'	°C	%	Formula	Calcd., %			Found, %		
					C	H	N	C	H	N
C ₂ H ₅	4-ClC ₆ H ₄ NH	154	59	C ₁₄ H ₁₄ ClNO ₃	60.12	5.01	5.01	60.40	4.94	4.46
C ₂ H ₅	2,4-Cl ₂ C ₆ H ₃ NH	125	65	C ₁₄ H ₁₃ Cl ₂ NC ₃	53.52	4.14	4.46	53.57	4.16	4.25
C ₂ H ₅	3,4-Cl ₂ C ₆ H ₃ NH	190	44	C ₁₄ H ₁₃ Cl ₂ NO ₃	53.52	4.14	4.46	53.27	4.17	4.00
<i>iso</i> -C ₄ H ₉	OH	85.5	90	C ₁₀ H ₁₄ O ₄	60.54	7.12	...	60.60	7.20	...

Scheme I





IR Charts: I, *N*-(*p*-chlorophenyl)- γ -methyl- γ -isobutylparaconamide; II, γ -methyl- γ -isobutyl- β -bromoparaconic acid; III, γ -methyl- γ -isobutylaconic acid; IV, *N*-(*p*-chlorophenyl)- γ -methyl- γ -isobutylaconamide, nujol mull.

Experimental Section

All melting and boiling points are uncorrected. Microanalyses were performed by Miss Teruko Nisi of our department.

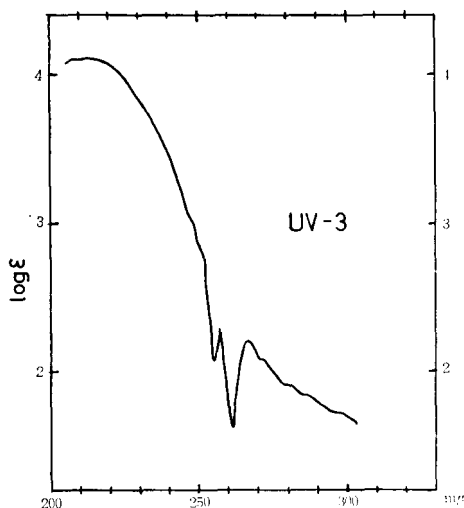
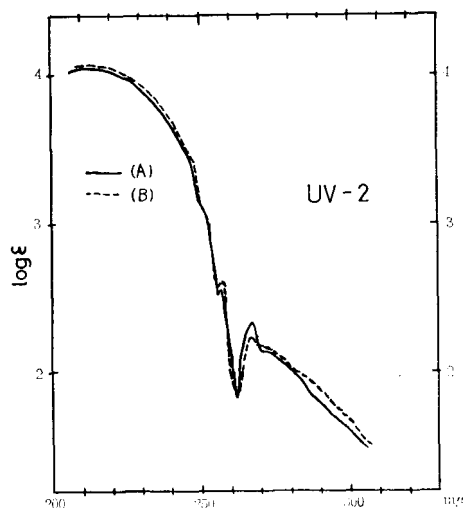
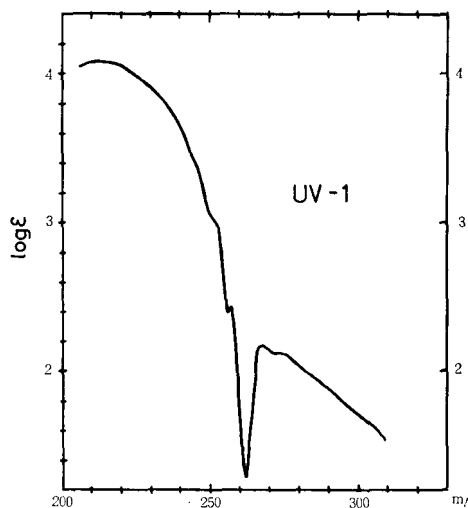
γ , γ -Dialkylparaconic Acids.²⁾— The acids were prepared by the lactonization of the Stobbe half-esters obtained in the usual way.⁶⁾

γ , γ -Dialkyl- β -bromoparaconic Acids.— The β -bromoparaconic acids were prepared by bromination of α -alkylidenesuccinic acids according to the procedure of Fittig and Kraencker.⁷⁾ γ -Methyl- γ -ethyl- β -bromoparaconic acid melted at 162–5° (lit.⁸⁾ mp 163°). The infrared spectrum of β -bromoparaconic acid (**4**, R = CH₃ and R' = (CH₃)₂CH), mp 166°, is shown in IR Chart II. These acids (**4**) were used for the preparation of aconic acids (**5**).³⁾

γ , γ -Dialkylaconic Acids.— γ , γ -Dialkyl- β -bromoparaconic acid (0.05 mole) in 200 ml

water was heated to 80–90° for 1 hr. Upon cooling to room temperature the oily material crystallized (from water or *n*-hexane). The physical and analytical data of aconic acid (**5**, R' = (CH₃)₂CHCH₂) are indicated in Table II. The infrared spectrum of **5** (R' = (CH₃)₂CHCH₂) is shown in IR Chart III. γ -Methyl- γ -ethylaconic acid melted at 118° (lit.⁸⁾ mp 117–119°).

General Procedure for Preparation of Anilides.— To a mixture of a γ , γ -substituted paraconic (or aconic) acid (0.02 mole), pyridine (2 ml), and thionyl chloride (1.4 ml) primary amine (0.03 mole) was added with stirring for 4–5 hr. The mixture was washed with water and taken up in ether. The ether solution was washed with sodium bicarbonate solution, with water, and dried (Na₂SO₄). Removal of the solvent afforded crude anilide. The resulting product was recrystallized from the appropriate solvent. The physical con-



UV Charts : UV-1, γ -methyl- γ -ethyloacetic acid; UV-2, (A) γ -pentylacetic acid, (B) γ -hexylacetic acid;³⁾ UV-3, acetic acid.

stants, yields, and analytical data are given in Tables I and II.

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