Biologically Active Compounds. I. The Synthesis of 5-Substituted 4-Methyl-3-carboxy-3(or 4)-alkenamides

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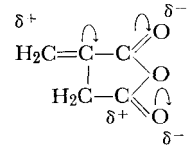
Monoamides of 5-substituted 4-methyl-3-carboxy-3(or 4)-alkenoic acids have been synthesized, starting with substituted itaconic anhydrides. The anhydride ring was opened by amines to afford N-aryl(or alkyl)-4-alkyl(or aryl)-3-carboxy-3(or 4)-alkenamides. The structure of the amide was elucidated by the comparison with the reference compound prepared from the corresponding Stobbe half-esters.

In connection with a study of compounds related to biologically active substances, a number of N-substituted 4-methyl-3-carboxy-3-(or 4)-alkenamides were prepared by the reaction of the corresponding succinic anhydrides with amines. All the new compounds listed in Table I and II were tested for antibacterial, antifungal, and herbicidal activity, but none of the tests were promising. The compounds 1, 2, 3, 4, 7, 8, 10, and 14 show activity as herbicides. The compounds 2, 3, 4, and 7 have antifungal activity and the compounds 6, 13, 15, 17, 18, 19, 20, and 23 show antibacterial activity.

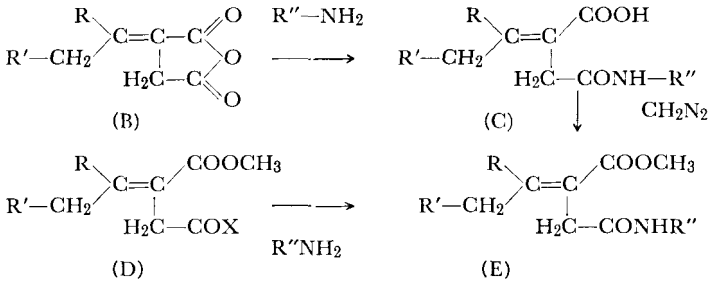
It has been considered[1] that in itaconic anhydride (A) the exclusive formation of the

(A)



ester or amide derivatives at the γ-position with respect to the methylene group, may be due to the conjugation of C=C bond of A to the nearby C=O group, which leads to lowering of the partial positive charge of the carbon atom of the carbonyl group, whereas the remote carbonyl group is not affected. Similarly, it may be assumed that in the reaction of the substituted itaconic anhydrides with amines, attack by a nucleophlic reagent will occur at the γ-carbonyl group with formation of C. Steric effects of the substituents at the α-position may favour the selective substitution at the γ-carbonyl. This assumption will be maintained if the amide (E) can be synthesized by an alternative route starting from Stobbe half-erter (D, X = OH) as is shown in Scheme I. However, difficulty in obtainning pure alkylidene type compound of the Stobbe half-ester was encountered, since the amide ester (E, R = R′ = CH_3 and R″ = p-Cl-C_6H_4) derived

SCHEME I



from D (R = R′ = CH_3 and X = Cl) showed ultraviolet absorption at λ_{max}^{EtOH} 249 mμ (ε 15000),

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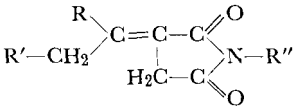
mp 83—84°, whereas the amide ester (E, R = R′ = CH_3 and R″ = *p*-Cl-C_6H_4) prepared from pure alkylidene type compound (B, R = R′ = CH_3) exhibited absorption at λ_{max}^{EtOH} 249 mμ (ε 21700), mp 83—84°. Thus, the former amide must be of about 70% purity. Although complete identification by the infrared spectra of both types of amide was missed, the absorption of the pure amide (E, R = R′ = CH_3 and R″ = *p*-Cl-C_6H_4) was well coincided with that of the former, as are shown in IR Charts III and IV.

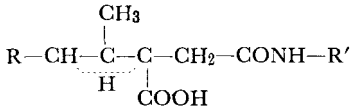
Esterification of the monoamides with a mixed solution of ethanol and benzene in the presence *p*-toluenesulfonic acid as a catalyst failed, but gave the corresponding imide derivatives (F).



(F)

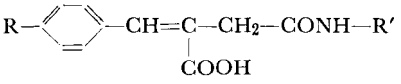
R = R′ = R″ = Alkyl and aryl

Table I N-Aryl(or alkyl)-4-methyl-3-carboxy-3(or 4)-alkenamides



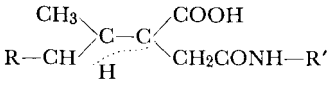
Compd., No.	R	R′	Mp, °C	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	H	2,3-Dichlorophenyl	143	75	$C_{13}H_{13}Cl_2NO_3$	51.67	4.34	4.63	51.60	4.42	4.75
2	H	2,5-Dichlorophenyl	157	70	$C_{13}H_{13}Cl_2NO_3$	51.67	4.34	4.63	52.06	4.40	4.45
3	H	3,4-Dichlorophenyl	160	82	$C_{13}H_{13}Cl_2NO_3$	51.67	4.34	4.63	51.51	4.40	···
4	H	*p*-Chlorophenyl	152	63	$C_{13}H_{14}ClNO_3$	58.25	5.27	5.23	58.23	5.27	5.14
5	H	α-Naphthyl	162	75	$C_{17}H_{17}NO_3$	72.06	6.05	4.94	71.70	6.00	4.88
6	CH_3	3,4-Dichlorophenyl	140	74	$C_{14}H_{15}Cl_2NO_3$	53.18	4.78	4.34	53.37	4.75	4.56
7	CH_3	*p*-Chlorophenyl	149	68	$C_{14}H_{16}ClNO_3$	59.68	5.72	4.97	59.87	5.77	4.62
8	CH_3	*o*-Chlorophenyl	104	70	$C_{14}H_{16}ClNO_3$	59.68	5.72	4.97	59.88	5.72	4.97
9	CH_3	*p*-Carboxyphenyl	171	63	$C_{15}H_{17}NO_5$	61.85	5.88	4.81	62.21	6.05	4.51
10	CH_3	Isobutyl	124	45	$C_{12}H_{21}NO_3$	63.41	9.31	···	63.38	9.32	···
11	CH_3	Phenyl	143	69	$C_{14}H_{17}NO_3$	67.99	6.93	5.66	67.60	6.88	5.28
12	Isopropyl	2,5-Dichlorophenyl	104	70	$C_{16}H_{19}Cl_2NO_3$	55.82	5.56	4.07	55.85	5.70	3.93
13	Isopropyl	3,4-Dichlorophenyl	137	68	$C_{16}H_{19}Cl_2NO_3$	55.82	5.56	4.07	56.00	5.65	4.00
14	Isopropyl	*p*-Chlorophenyl	155	68	$C_{16}H_{20}ClNO_3$	62.03	6.51	4.52	62.27	6.59	4.29
15	Isopropyl	*p*-Carboxyphenyl	160	45	$C_{17}H_{21}NO_5$	63.93	6.63	4.35	63.58	6.65	4.20
16	Isopropyl	Phenyl	113	65	$C_{16}H_{21}NO_3$	69.79	7.69	5.08	69.87	7.62	5.03

Table II N-Aryl-4-aryl-3-carboxy-3-butenamides



Compd., No.	R	R′	Mp, °C	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
17	H	2,4-Dichlorophenly	176	90	$C_{17}H_{13}Cl_2NO_3$	58.30	3.72	4.00	58.36	3.84	3.95
18	H	2,5-Dichlorophenyl	185	80	$C_{17}H_{13}Cl_2NO_3$	58.30	3.72	4.00	58.53	3.95	3.94
19	H	2,3-Dichlorophenyl	190	80	$C_{17}H_{13}Cl_2NO_3$	58.30	3.72	4.00	58.28	3.92	3.84
20	H	*p*-Chlorophenyl	193	85	$C_{17}H_{14}ClNO_3$	64.67	4.44	4.44	64.44	4.63	3.91
21	CH_3O	3,4-Dichlorophenyl	211	90	$C_{18}H_{15}Cl_2NO_4$	56.86	3.98	3.68	56.88	4.01	3.47
22	CH_3O	2,4-Dichlorophenyl	188	85	$C_{18}H_{15}Cl_2NO_4$	56.86	3.98	3.68	56.91	4.04	3.37
23	CH_3O	2,3-Dichlorophenyl	184	90	$C_{18}H_{15}Cl_2NO_4$	56.86	3.98	3.68	56.75	4.11	3.46
24	CH_3O	2,5-Dichlorophenyl	191	85	$C_{18}H_{15}Cl_2NO_4$	56.86	3.98	3.68	56.77	4.15	3.55
25	CH_3O	*p*-Chlorophenyl	196	85	$C_{18}H_{16}ClNO_4$	62.53	4.66	4.05	62.62	4.88	3.74

Table III Ultraviolet Spectra of Monoamides (C)



R	R′	λ_{max}^{EtOH} mμ	ε
CH_3	C_6H_5	241	15300
CH_3	*p*-Cl-C_6H_4	249	15300
CH_3	*o*-Cl-C_6H_4	242	13700
$(CH_3)_2CH$	C_6H_5	241	13800
$(CH_3)_2CH$	*p*-Cl-G_6H_4	249	13500
$(CH_3)_2CH$	*o*-Cl-C_6H_4	242	15700

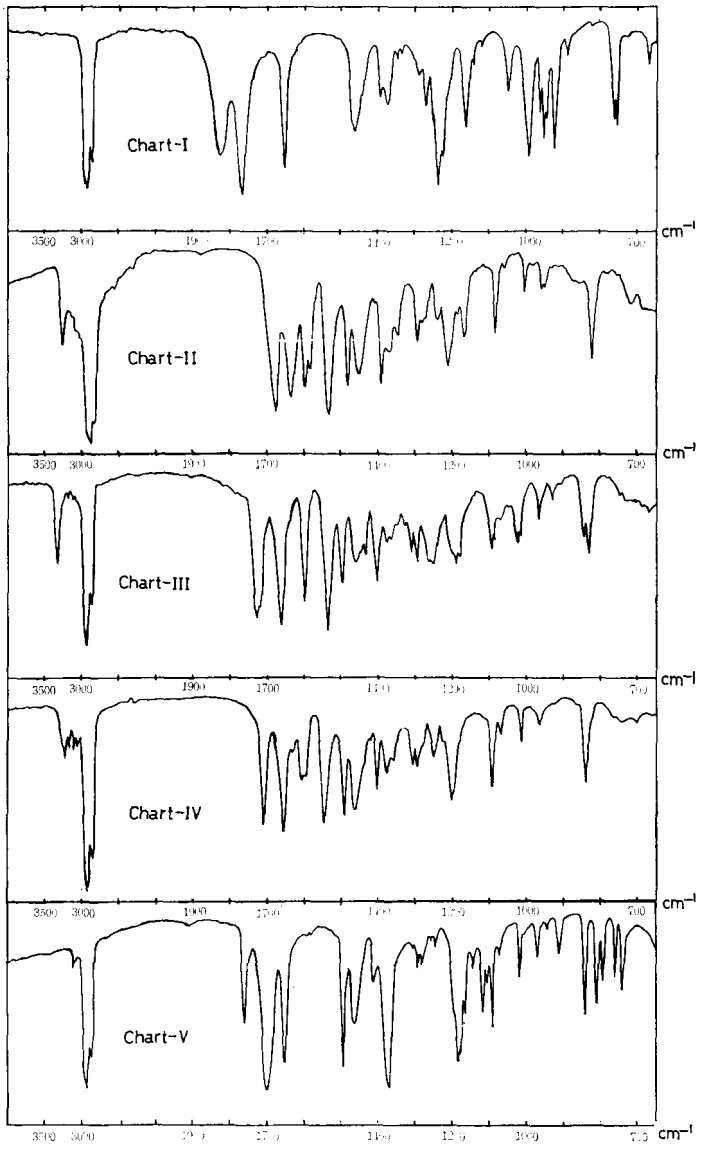
Experimental Section

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

α-Alkylidene(or alkenyl)succinic Anhydrides. — The anhydrides were prepared by the distillation[2] of the Stobbe half-esters obtained in the usual way.[3]

α-1-Methylpropylidene(or propenyl)succinic anhydride, thus prepared, boiled at 115—119° (2mm), n_D^{21} 1.4929.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.32; H,



IR Charts: I, α-1,3-dimethylbutylidenesuccinic anhydride; II, the compound C; III, the compound E from the path B; IV, the compound E from the path A; V, the compound F (R=R′=CH_3 and R″=*p*-ClC_6H_4, in nujol, respectively).

6.54. Found: C, 62.19; H, 6.66.

The ultraviolet measurement[4] showed that the anhydride, λ_{max}^{EtOH} 235 mμ (ε 8700), contained 73% of an alkylidene compound. Upon standing for several months, pure α-1-methylpropylidenesuccinic anhydride solidified, λ_{max}^{EtOH} 235 mμ (ε 12000).

Similarly, α-1,3-dimethylbutylidene(or butenyl)succinic anhydride boiled at 162—165° (11 mm), n_D^{21} 1.4841, mp 80—81° (from *n*-hexane), λ_{max}^{EtOH} 238 mμ (ε 12400) (all alkylidene type compound). The infrared spectrum is shown in IR Chart I.

Anal. Calcd for $C_{10}H_{14}O_3$: C. 65.91; H, 7.74. Found: C, 66.10; H, 7.88.

α-Benzylidenesuccinic Anhydrides. — The α-benzylidenesuccinic acids were dehydrated with $SOCl_2$ as described by El-Abbady.[5]

Preparation of Amides (Table I and II). General Method. — To a mixture of α-substituted succinic anhydride (0.01 mole) in 30 ml of chloroform a solution of a primary amine (0.01 mole) in 10 ml of chloroform was added at room temperature. Then, the mixture was stirred for 5 hr on water bath at 50°. When the mixture had cooled completely and set solid, it was collected on a filter and washed several times with benzene. The material obtained by this procedure was then recrystallized from a mixed solvent of ethanol-benzene without any special precautions: IR (cm^{-1}) 1670—1690 (amide C=O), and 1645—1660 and 1530—1560 (amide NH). The infrared spectrum of an amide (C, R = R′ = CH_3 and R″ = *p*-ClC_6H_4) is shown in IR Chart II. The ultraviolet absorptions of the monoamides are shwon in Table III.

N-(*p*-Chlorophenyl)-3-carbomethoxy-3(or 4)-hexenamides (E). Path A. — To a suspension of 2.0 g of N-(*p*-chlorophenyl)-4-methyl-3-carboxy-3-hexenamide, prepared by the reaction of *p*-chloroaniline with α-1-methylpropylidenesuccinic anhydride, λ_{max}^{EtOH} 235 mμ (ε 12000), in 2 ml of ether excess amount of an ethereal solution of diazomethane was added at 0—5°. After standing for 3 hr, removal of the solvent gave N-(*p*-chlorophenyl)-4-methyl-3-carbomethoxy-3-hexenamide in quantitative yield, mp 83—84°, λ_{max}^{EtOH} 249 mμ (ε 21700). The infrared spectrum is shown in IR Chart IV.

Anal. Calcd. for $C_{15}H_{18}ClNO_3$: C, 60.92; H, 6.14; N, 4.74. Found: C, 60.88; H, 6.50; N, 4.83.

Path B. — To a mixture of 4-methyl-3-carbomethoxy-3(or 4)-hexenoic acid (0.011 mole) prepared by the Stobbe condensation of methyl ethyl ketone with dimethyl succinate, 1 ml of pyridine and 0.7 ml of thionyl chloride *p*-chloroaniline (0.015 mole) in 2 ml of benzene was added with stirring for 2 hr. The mixture was hydrolyzed with water and taken up in ether. The extracts were washed with water and dried over anhydrous sodium sulfate. On removal of the solvent, there was obtained 1.8 g (ca. 60%) of N-(*p*-chlorophenyl)-4-methyl-3-carbomethoxy-3(or 4)-hexenamide, mp 83—84°, λ_{max}^{EtOH} 249 mμ (ε 15000). The infrared spectrum is indicated in IR Chart III. Microanalyses of III gave correct result for carbon and hydrogen.

N-(*p*-Chlorophenyl)-α-1-methylpropylidenesuccinimide (F, R = R′ = CH_3 and R″ = *p*-ClC_6H_4). —Refluxing of 2.8 g of N-(*p*-chlorophenyl)-3-carboxy-3(or 4)-hexenamide (C, R = R′ = CH_3 and R″ = ClC_6H_4) with 30 ml of benzene and 10 ml of ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate gave N-(*p*-chlorophenyl-α-1-methylpropylidenesuccinimide (F) in quantitative yield, mp 120—121° (from *n*-hexane). The infrared spectrum of F is shown in IR Chart V.

Anal. Calcd. for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.74; H, 5.34; N, 5.18.

References

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