

Synthesis of 3,3-Disubstituted Glutarimides

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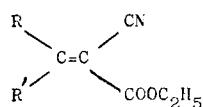
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The following 3,3-disubstituted glutarimides have been synthesized, and their intermediate compounds prepared: 3-*p*-methylmercaptophenyl-3-methylglutarimide, 3-*p*-nitrophenyl-3-methyl glutarimide, 3-cyclohexyl-3-methylglutarimide, 3-*p*-fluorophenyl-3-ethylglutarimide, and 3-*m*-trifluoromethylphenyl-3-ethylglutarimide. The infrared and NMR spectra of 3,3-disubstituted glutarimides were recorded and assignments have been given.

TO STUDY their pharmacological effects, several 3,3-disubstituted glutarimides, summarized in Table V, were prepared. 3,3-Disubstituted glutaric acids (Table III) were synthesized by the method of McElvain and coworkers (1). Alkylidene derivatives (Table I) were obtained by treating appropriate ketones with ethyl cyanoacetate, which, after reaction with cyanoacetamide in sodium ethoxide solution gave corresponding dicyanoglutarimides (Table II), which were hydrolyzed to 3,3-disubstituted glutaric acids (Table III).

These acids, when boiled with acetic anhydride, gave 3,3-disubstituted glutaric anhydrides (Table IV). Related glutarimides were prepared by reaction of glutaric anhydrides with urea (Table V). The infrared spectra of glutarimides, recorded on a Leitz Model III Spectrograph (KBr wafer), include two strong bands at 5.9 and 6.0 μ due to carbonyl groups. The characteristic skeletal absorption is two strong bands at 11.5 and 11.6 μ . Imide group absorption is a strong band near 7.8 μ . The infrared spectra of deuterated glutarimides do not show appreciable shifts of imide absorption.

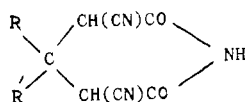
Table I. Ethyl Alkylidenecyanoacetates



R	R'	B.P., °C. (Mm. of Hg)	Yield, %	Analyses			
				Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
<i>p</i> -CH ₃ SC ₆ H ₄	CH ₃	210(2.2)	57	64.36	64.55	5.74	5.90
<i>p</i> -NO ₂ C ₆ H ₄	CH ₃		78	59.77	60.20	4.98	4.81
C ₆ H ₁₁	CH ₃	154(4.6)	88	70.58	70.30	8.59	8.35
<i>p</i> -FC ₆ H ₄	C ₂ H ₅	156(2.5)	64	68.01	68.26	5.66	5.78
<i>m</i> -CF ₃ C ₆ H ₄	C ₂ H ₅	167(5.5)	67	60.60	60.34	4.71	4.50

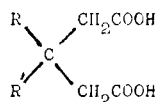
^a M.P. 156°C.

Table II. 3,3-Disubstituted 2,4-Dicyanoglutarimides



R	R'	B.P., °C.	Yield, %	Analyses			
				Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
<i>p</i> -CH ₃ SC ₆ H ₄	CH ₃	262	80	60.20	59.98	4.34	4.30
<i>p</i> -NO ₂ C ₆ H ₄	CH ₃	290-3	70	56.38	56.18	3.38	3.46
C ₆ H ₁₁	CH ₃	270	65	64.86	65.22	6.56	6.60
<i>p</i> -FC ₆ H ₄	C ₂ H ₅	234-5	99	63.15	63.10	4.21	4.02
<i>m</i> -CF ₃ C ₆ H ₄	C ₂ H ₅	282	69	57.31	57.12	3.58	3.43

Table III. 3,3-Disubstituted Glutaric Acids



R	R'	M.P., °C.	Yield, %	Analyses			
				Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
<i>p</i> -CH ₃ SC ₆ H ₄	CH ₃	110	15	58.20	58.66	5.97	5.59
<i>p</i> -NO ₂ C ₆ H ₄	CH ₃	148	48	53.93	53.85	4.86	4.92
C ₆ H ₁₁	CH ₃	156	45	63.15	63.08	8.77	8.72
<i>p</i> -FC ₆ H ₄	C ₂ H ₅	122-4	35	61.41	61.42	5.90	5.64
<i>m</i> -CF ₃ C ₆ H ₄	C ₂ H ₅	160-1	30	55.26	55.16	4.93	4.96

Table IV. 3,3-Disubstituted Glutaric Anhydrides

R	R'	M.P., ° C.	Yield, %	Analyses			
				Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
<i>p</i> -CH ₃ SC ₆ H ₄	CH ₃	96-100	Quant.	62.40	62.34	5.60	5.80
<i>p</i> -NO ₂ C ₆ H ₄	CH ₃	161-2	Quant.	57.83	57.25	4.41	4.35
C ₆ H ₁₁	CH ₃	50	Quant.	68.57	68.45	8.57	8.48
<i>p</i> -FC ₆ H ₄	C ₂ H ₅	78	Quant.	66.10	66.29	5.50	5.12
<i>m</i> -CF ₃ C ₆ H ₄	C ₂ H ₅	69	Quant.	58.74	58.90	4.54	4.78

Table V. 3,3-Disubstituted Glutarimides

R	R'	M.P., ° C.	Yield, %	Analyses				IR, λ _{Max} .KBr, μ ^a			NMR, τ ^a NH
				Carbon, %		Hydrogen, %		C=O			
				Calcd.	Found	Calcd.	Found		NH	Skeletal	
<i>p</i> -CH ₃ SC ₆ H ₄	CH ₃	189-90	40	62.65	62.44	6.02	6.06	5.8,6.0	7.8	11.55	1.5
<i>p</i> -NO ₂ C ₆ H ₄	CH ₃	189-90	45	58.06	58.23	4.83	5.09	5.8,5.95	7.9	11.65	1.5
C ₆ H ₁₁	CH ₃	186	52	68.89	70.21	9.09	9.58	5.8,5.95	7.8	11.70	1.65
<i>m</i> -FC ₆ H ₄	C ₂ H ₅	156-9	62	66.38	68.33	5.95	6.09	5.8,5.95	7.85	11.55	1.45
<i>m</i> -CF ₃ C ₆ H ₄	C ₂ H ₅	148-9	50	58.94	60.64	4.91	5.42	5.8,5.90	7.9	11.60	1.58

^a Refer to the text for details on IR and NMR.

The NMR spectra of glutarimides in CDCl₃ solution were recorded on a Varian A60A Spectrometer using TMS as internal standard. The NH proton absorption of the imide group, for which not many examples can be found in literature, was studied carefully. Deuteration was accomplished by adding D₂O to samples dissolved in CDCl₃. The imide proton absorption disappeared rapidly. After evaporation of solvent, pure deuterated glutarimides were obtained. The NH proton absorption in all cases, including the case of

3,3-methylethylglutarimide, is a very broad band at τ 1.45-1.65.

LITERATURE CITED

- (1) McElvain, S.M., Clemens, D.H., *J. Am. Chem. Soc.* **80**, 3915 (1958).

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