Synthesis of 3,3-Disubstituted Glutarimides

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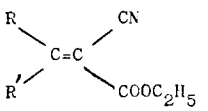
The following 3,3-disubstituted glutarimides have been synthesized, and their intermediate compounds prepared: 3-*p*-methylmercaptophenyl-3-methylglutarimide, 3-*p*-nitrophenyl-3-methyl glutarimide, 3-cyclohexyl-3-methylglutarimide, 3-*p*-fluorophenyl-3-ethylglutarimide, and 3-*m*-trifluoromethylphenyl-3-ethylglutarimide. 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 6.0μ due to carbonyl groups. The characteristic skeletal absorption is two strong bands at 11.5 and 11.6μ. Imide group absorption is a strong band near 7.8μ. The infrared spectra of deuterated glutarimides do not show appreciable shifts of imide absorption.

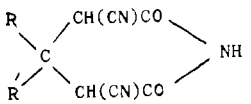
Table I. Ethyl Alkylidenecyonoacetates



R	R′	B.P., °C. (Mm. of Hg)	Yield, %	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
p-$CH_3SC_6H_4$	CH_3	210(2.2)	57	64.36	64.55	5.74	5.90
p-$NO_2C_6H_4$	CH_3[a]		78	59.77	60.20	4.98	4.81
C_6H_{11}	CH_3	154(4.6)	88	70.58	70.30	8.59	8.35
p-FC_6H_4	C_2H_5	156(2.5)	64	68.01	68.26	5.66	5.78
m-$CF_3C_6H_4$	C_2H_5	167(5.5)	67	60.60	60.34	4.71	4.50

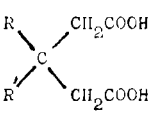
[a] M.P. 156° C.

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



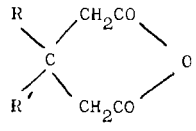
R	R′	B.P., °C.	Yield, %	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
p-$CH_3SC_6H_4$	CH_3	262	80	60.20	59.98	4.34	4.30
p-$NO_2C_6H_4$	CH_3	290–3	70	56.38	56.18	3.38	3.46
C_6H_{11}	CH_3	270	65	64.86	65.22	6.56	6.60
p-FC_6H_4	C_2H_5	234–5	99	63.15	63.10	4.21	4.02
m-$CF_3C_6H_4$	C_2H_5	282	69	57.31	57.12	3.58	3.43

Table III. 3,3-Disubstituted Glutaric Acids



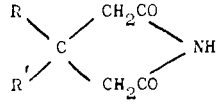
R	R′	M.P., °C.	Yield, %	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
p-$CH_3SC_6H_4$	CH_3	110	15	58.20	58.66	5.97	5.59
p-$NO_2C_6H_4$	CH_3	148	48	53.93	53.85	4.86	4.92
C_6H_{11}	CH_3	156	45	63.15	63.08	8.77	8.72
p-FC_6H_4	C_2H_5	122–4	35	61.41	61.42	5.90	5.64
m-$CF_3C_6H_4$	C_2H_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, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
p-$CH_3SC_6H_4$	CH_3	96–100	Quant.	62.40	62.34	5.60	5.80
p-$NO_2C_6H_4$	CH_3	161–2	Quant.	57.83	57.25	4.41	4.35
C_6H_{11}	CH_3	50	Quant.	68.57	68.45	8.57	8.48
p-FC_6H_4	C_2H_5	78	Quant.	66.10	66.29	5.50	5.12
m-$CF_3C_6H_4$	C_2H_5	69	Quant.	58.74	58.90	4.54	4.78

Table V. 3,3-Disubstituted Glutarimides



R	R′	M.P., °C.	Yield, %	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	IR, $\lambda_{Max.}$KBr, μ[a] C=O	IR, $\lambda_{Max.}$KBr, μ[a] NH	IR, $\lambda_{Max.}$KBr, μ[a] Skeletal	NMR, τ[a] NH
p-$CH_3SC_6H_4$	CH_3	189–90	40	62.65	62.44	6.02	6.06	5.8,6.0	7.8	11.55	1.5
p-$NO_2C_6H_4$	CH_3	189–90	45	58.06	58.23	4.83	5.09	5.8,5.95	7.9	11.65	1.5
C_6H_{11}	CH_3	186	52	68.89	70.21	9.09	9.58	5.8,5.95	7.8	11.70	1.65
m-FC_6H_4	C_2H_5	156–9	62	66.38	68.33	5.95	6.09	5.8,5.95	7.85	11.55	1.45
m-$CF_3C_6H_4$	C_2H_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 $CDCl_3$ 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 D_2O to samples dissolved in $CDCl_3$. 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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