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Synthesis of *N*-Substituted Glutarimides

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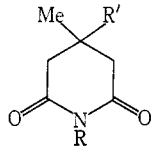
Abstract

A series of *N*-alkyl- and *N*-benzyl-glutarimides related to bemegride have been synthesized both by the Guareschi procedure and by *N*-alkylation.

It has been shown that a variety of small chemical modifications to the central nervous system (CNS) stimulant and analeptic drug 3-ethyl-3-methylglutarimide (bemegride, Megimide) leads to significant changes in pharmacological response in the mouse.[1–3] The modifications have involved each position of the glutarimide ring or one or both of the alkyl substituents. Of special interest in this context was the observation that *N*-ethylation and *N*-allylation of bemegride and of the related 3-butyl-3-methyl homologue, which has anticonvulsant and hypnotic action, produced, in each case, compounds with similar dual stimulant–depressant CNS action in the mouse.[2] This suggested that the responsive neuronal surface may have a limiting spatial dimension for accommodating such compounds.

This paper reports the synthesis of a further series of *N*-alkyl and *N*-benzyl derivatives of 3-ethyl-3-methyl- and of 3-butyl-3-methyl-glutarimide [(1) and (2)] for pharmacological investigation to provide further insight into the nature of the responsive neuronal mechanisms. The results of the latter will be published separately.



(1) R′ = Et
(2) R′ = Bu

Two complementary synthetic procedures were employed. The first involved the Guareschi procedure described previously.[4] This entailed reaction between the appropriate glutaric anhydride and amine to give the corresponding glutaramic acid followed by thermal dehydration. For systems where substituted benzylamines were not readily available the desired glutarimides were synthesized by *N*-alkylation of 3-ethyl-3-methylglutarimide by the appropriate benzyl bromide. Several compounds, including propyl, butyl, pentyl, hexyl, chloroethyl, hydroxyethyl, phenyl, substituted benzyl, phenethyl and thiazol-2-yl derivatives were synthesized by these two procedures.

[1] Laycock, G. M., and Shulman, A., *Nature* (*London*), 1963, **200**, 849.
[2] Shulman, A., *Proc. R. Aust. Chem. Inst.*, 1964, **31**, 41.
[3] Laycock, G. M., and Shulman, A., *Nature* (*London*), 1967, **213**, 995.
[4] Handley, G. J., Nelson, E. R., and Somers, T. C., *Aust. J. Chem.*, 1960, **13**, 129.

Experimental

Liquid products were purified by distillation. Solid products after distillation were recrystallized from benzene–petroleum, b.p. 60–80°. In a few cases further recrystallization from ethanol–water was necessary to achieve analytical purity. For the *N*-alkylglutarimides boiling points were measured from a sublimation apparatus and refer to block temperatures.

Unless otherwise stated infrared spectra contained imido carbonyl bands at 1720–1710 and 1670 cm^{-1}. Solid samples were measured as KBr discs and liquid samples as films. P.m.r. spectra were measured in $CDCl_3$ and were consistent with assigned structures. Chemical shifts of the glutarimide system, quoted on the δ scale from $SiMe_4$ as internal reference, ranged as follows: 0·79–0·91, t, CH_2CH_3; 0·88–1·12, s, 3-CH_3; 1·20–1·45, q, CH_2CH_3 or 1·20–1·35, m, $(CH_2)_3CH_3$; 2·28–2·60, s, $(H2)_2$, $(H4)_2$.

N-*Substituted Glutarimides from Amines*

The amine (0·05 mol) was added to 3-ethyl-3-methyl- or 3-butyl-3-methyl-glutaric anhydride[4] (0·05 mol) with considerable evolution of heat. The mixture was heated for 4 h at 170–190° and then distilled under reduced pressure. The yields of products were 80–90%.

The following *N*-substituted 3-ethyl-3-methylglutarimides were prepared in this way:

(i) *Propyl* (1; R = Pr), b.p. 75°/1 mm, n_D^{19} 1·4738 (Found: C, 67·0; H, 9·6; N, 7·2. $C_{11}H_{19}NO_2$ requires C, 67·0; H, 9·7; N, 7·1%).

(ii) *Butyl* (1; R = Bu), b.p. 89°/1·1 mm, n_D^{19} 1·4731 (Found: C, 68·1; H, 10·1; N, 6·7. $C_{12}H_{21}NO_2$ requires C, 68·2; H, 10·0; N, 6·6%).

(iii) *Pentyl* (1; R = $(CH_2)_4Me$), b.p. 98°/0·8 mm, n_D^{19} 1·4723 (Found: C, 69·3; H, 10·3; N, 6·0. $C_{13}H_{23}NO_2$ requires C, 69·3; H, 10·3; N, 6·2%).

(iv) *Hexyl* (1; R = $(CH_2)_5Me$), b.p. 106°/0·8 mm, n_D^{19} 1·4720 (Found: C, 70·6; H, 10·7; N, 6·1. $C_{14}H_{25}NO_2$ requires C, 70·3; H, 10·5; N, 5·9%).

(v) *Hydroxyethyl* (1; R = CH_2CH_2OH), b.p. 119°/0·9 mm, n_D^{19} 1·4925 (Found: N, 6·9. $C_{10}H_{17}NO_3$ requires N, 7·0%).

(vi) *Chloroethyl* (1; R = CH_2CH_2Cl), b.p. 105°/1 mm, n_D^{19} 1·4944 (Found: C, 55·5; H, 7·5; N, 6·5. $C_{10}H_{16}ClNO_2$ requires C, 55·2; H, 7·4; N, 6·4%).

(vii) Phenyl (1; R = Ph), m.p. 127–128° (lit.[4] 128°).

(viii) Benzyl[4] (1; R = $PhCH_2$), m.p. −1°, b.p. 180°/0·1 mm (Found: C, 73·3; H, 7·9; N, 5·6. Calc. for $C_{15}H_{19}NO_2$: C, 73·4; H, 7·8; N, 5·7%).

(ix) *Phenethyl* (1; R = $PhCH_2CH_2$), b.p. 190°/0·1 mm (Found: C, 73·9; H, 8·2; N, 5·4. $C_{16}H_{21}NO_2$ requires C, 74·1; H, 8·2; N, 5·4%).

(x) p-*Methylbenzyl* (1; R = p-$MeC_6H_4CH_2$), m.p. 38–39° (Found: C, 73·9; H, 8·2; N, 5·3. $C_{16}H_{21}NO_2$ requires C, 74·1; H, 8·2; N, 5·4%).

(xi) p-*Methoxybenzyl* (1; R = p-$MeOC_6H_4CH_2$), m.p. 29–30° (Found: C, 69·4; H, 7·8; N, 4·9. $C_{16}H_{21}NO_3$ requires C, 69·8; H, 7·7; N, 5·1%).

The following *N*-substituted 3-butyl-3-methylglutarimides were prepared in this way:

(xii) *Propyl* (2; R = Pr), b.p. 100°/1 mm, n_D^{19} 1·4927 (Found: C, 69·3; H, 10·5; N, 6·2. $C_{13}H_{23}NO_2$ requires C, 69·3; H, 10·3; N, 6·2%).

(xiii) *Butyl* (2; R = Bu), b.p. 110°/0·8 mm, n_D^{19} 1·4729 (Found: C, 70·0; H, 10·1; N, 6·0. $C_{14}H_{25}NO_2$ requires C, 70·2; H, 10·5; N, 5·9%).

(xiv) *Pentyl* (2; R = $(CH_2)_4Me$), b.p. 116°/0·8 mm, n_D^{19} 1·4721 (Found: C, 70·9; H, 10·9; N, 5·9. $C_{15}H_{27}NO_2$ requires C, 71·1; H, 10·7; N, 5·5%).

(xv) *Hexyl* (2; R = $(CH_2)_5Me$), b.p. 122°/0·9 mm, n_D^{19} 1·4715 (Found: C, 71·8; H, 10·8; N, 5·6. $C_{16}H_{29}NO_2$ requires C, 71·9; H, 10·9; N, 5·2%).

(xvi) *Hydroxyethyl* (2; R = CH_2CH_2OH), b.p. 130°/0·9 mm, n_D^{19} 1·4881 (Found: C, 62·9; H, 9·3; N, 6·2. $C_{12}H_{21}NO_3$ requires C, 63·4; H, 9·3; N, 6·2%).

(xvii) *Phenyl* (2; R = Ph), m.p. 75–76° (Found: C, 74·0; H, 8·1; N, 5·4. $C_{16}H_{21}NO_2$ requires C, 74·1; H, 8·2; N, 5·4%).

(xviii) *Benzyl* (2; R = $PhCH_2$), b.p. 190°/0·1 mm (Found: C, 74·5; H, 8·5; N, 5·2. $C_{17}H_{23}NO_2$ requires C, 74·7; H, 8·5; N, 5·1%).

(xix) *Phenethyl* (2; R = $PhCH_2CH_2$), b.p. 200°/0·1 mm (Found: C, 75·0; H, 8·8; N, 5·1. $C_{18}H_{25}NO_2$ requires C, 75·2; H, 8·8; N, 4·9%).

3-Ethyl-3-methyl-N-(*thiazol-2-yl*)*glutarimide*

A mixture of 2-aminothiazole (1·46 g) and 3-ethyl-3-methylglutaric anhydride[4] (12 g) in tetrahydrofuran (250 cm^3) was boiled for 5 h. Evaporation to dryness and crystallization from chloroform–petroleum gave the glutaramic acid (10·8 g, m.p. 155–157°). This was boiled in acetic anhydride for 4 h. Evaporation to dryness and crystallization from toluene–petroleum gave *3-ethyl-3-methyl*-N-(*thiazol-2-yl*)*glutarimide* (7·6 g), colourless crystals, m.p. 101–102·5° (Found: C, 55·4; H, 5·9; N, 11·8. $C_{11}H_{14}N_2O_2S$ requires C, 55·4; H, 5·9; N, 11·8%). ν_{max} 1730, 1685 cm^{-1}. δ 0·90, 3H, t; 1·10, 3H, s; 1·45, 2H, q; 2·60, 4H, s; 7·38, 7·67, 2H, ABq, J 4 Hz.

N-*Substituted Glutarimides from Bromides*

To a solution of potassium hydroxide (2·80 g) in water (20 cm^3) was added 3-ethyl-3-methylglutarimide[4] (7·75 g) in ethanol (125 cm^3) followed immediately by the benzyl bromide (0·05 mol) in ethanol (125 cm^3). The mixture was boiled for 1 h, a precipitate of potassium bromide beginning to form after 30 min. The solution was then poured into water (500 cm^3) and extracted with ether. The extract was dried and solvent evaporated. The yield of product after distillation or recrystallization was 80–90%.

The following *N*-substituted 3-ethyl-3-methylglutarimides were prepared in this way:

(i) p-*Nitrobenzyl* (1; R = *p*-$O_2NC_6H_4CH_2$), m.p. 102–103° (Found: C, 62·0; H, 6·3; N, 9·6. $C_{15}H_{18}N_2O_4$ requires C, 62·0; H, 6·3; N, 9·6%).

(ii) p-*Aminobenzyl* (1; R = *p*-$H_2NC_6H_4CH_2$), prepared by catalytic hydrogenation of (1; R = *p*-$O_2NC_6H_4CH_2$), m.p. 159–160° (Found: C, 69·1; H, 7·8; N, 10·7. $C_{15}H_{20}N_2O_2$ requires C, 69·2; H, 7·7; N, 10·8%).

(iii) m-*Nitrobenzyl* (1; R = *m*-$O_2NC_6H_4CH_2$), m.p. 83–84° (Found: C, 62·3; H, 6·3; N, 9·4. $C_{15}H_{18}N_2O_4$ requires C, 62·0; H, 6·3; N, 9·6%).

(iv) p-*Chlorobenzyl* (1; R = *p*-$ClC_6H_4CH_2$), m.p. 74–75° (Found: C, 64·6; H, 6·6; N, 5·0. $C_{15}H_{18}ClNO_2$ requires C, 64·6; N, 6·5; N, 5·0%).

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