

Simple Methylation of Amides

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Summary Reaction of amides with chloromethyl methyl sulphide in strong acid, followed by treatment with Raney nickel yields the methylamides; the preparation and activity of *N*²-methyl-tetracycline are reported.

ALKYLATION of amides is rarely performed since it is usual to hydrolyse the amide to the acid, which then gives the substituted amide *via* activation of the carboxy-group. In the tetracycline field the primary amide group has been converted into the *N*-*t*-butyl derivative *via* a Ritter reaction on the nitrile,¹ but no other amides have been reported since the free acid has not been obtained without concomitant complete decomposition of the antibiotic. Since the *N*-*t*-butyl derivative of 6-demethyl-6-deoxy-tetracycline still shows antimicrobial activity, albeit limited to Gram positive organisms¹, the preparation of the less bulky methyl derivative seemed appropriate to assess the importance of the amide group to biological activity. We have developed a simple procedure for the monomethylation of amides, which does not require strongly basic conditions.²

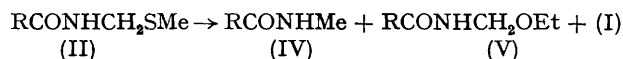
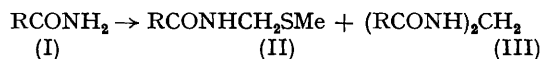
ClCH_2SMe (10 ml) was added to a solution of PhCONH_2 (6.06 g) in MeSO_3H (32.5 ml) at 0 °C. After 24 h, and again after 48 h, at 0 °C further ClCH_2SMe (10 ml) was added, and after a total of 76 h the mixture was poured on ice and extracted with EtOAc. Chromatography on silica gel (C_6H_6 -EtOAc as eluant) of the residue after evaporation of EtOAc gave $\text{PhCON}(\text{CH}_2\text{SMe})_2$ (2.5%, oil), compound (II; R = Ph) (83%), compound (III; R = Ph) (8%), and original PhCONH_2 (6%). The amide (II; R = Ph) (2.72 g) was added to a suspension of Raney nickel (50 g) in boiling 90% ethanol (130 ml), and after 1.5 h the solution was cooled, filtered, and evaporated to dryness. The residue, after chromatography on silica gel (C_6H_6 -EtOAc) gave (V; R = Ph) (5%, oil), (IV; R = Ph) (80%), and PhCONH_2 (10%). This sequence was performed on minocycline† to give

TABLE

Amide (I)	Conditions ^a	M.p./°C	(II) ^b Yield/% ^c	M.p./°C	(III) ^b Yield/% ^c	M.p./°C	(IV) ^b Yield/% ^c
Nicotinamide	(A)	95	90	—	—	105	74
Isonicotinamide	(A)	90	90	—	—	115	75
Benzamide	(A)	105	15	218	80	80	80
	(B)	..	83	..	8	..	80
Pivalamide	(A)	55	18	155	80	90	85
	(B)	..	15 ^d	..	30 ^d	..	85

^a (A): $\text{CF}_3\text{CO}_2\text{H}$, 25 °C for 16 h; (B): MeSO_3H , 0 °C for 76 h. ^b All compounds gave satisfactory analytical and spectral data. The methylamides were identified by comparison with authentic samples. ^c Yields are based on isolated product. ^d About 50% of (I) was recovered unchanged.

Treatment of amides (I) (Table) with ClCH_2SMe in $\text{CF}_3\text{CO}_2\text{H}$ or MeSO_3H yields (II) and variable amounts of (III). When (II) is refluxed in 90% EtOH in the presence of a large excess of Raney nickel, the methylamides are formed in good yields, together with minor amounts of (I) and (V). The following example is indicative of the operating conditions.



† Minocycline³ was chosen as a model because in the absence of a deactivating substituent, alkylation of the aromatic ring occurs preferentially.⁴

‡ N.m.r. spectrum (internal salt); δ 2.47 (6H, s, 4-NMe₂), 2.59 (6H, s, 7-NMe₂), 3.00 (3H, d, *J* 5.2 Hz, CONHMe), and 6.84 and 7.34 (2H, dd, *J* 9 Hz, 8- and 9-H).

¹ C. R. Stephens, J. J. Beereboom, H. H. Rennhard, P. N. Gordon, K. Muray, R. K. Blackwood, and S. von Wittenau, *J. Amer. Chem. Soc.*, 1963, **85**, 2643.

² A. W. Titherley, *J. Chem. Soc.*, 1901, **79**, 393, 403.

³ M. J. Martell and J. H. Boothe, *J. Medicin. Chem.*, 1967, **10**, 44.

⁴ L. Bernardi, R. de Castiglione, P. Masi, and U. Scarponi, *I Farmaco*, in the press.

*N*²-methyl-7-dimethylamino-6-deoxytetracycline,‡ whose antibacterial activity was found§ to be lower, but still comparable with, that of the parent compound, particularly on Gram positive and tetracycline resistant strains.

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