Simple Methylation of Amides

By LUIGI BERNARDI,* ROBERTO DE CASTIGLIONE, and UGO SCARPONI
(*Farmitalia, Laboratori di Milano, Via dei Gracchi, 35-Milano, Italy*)

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 organisms[1], 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 $PhCON(CH_2SMe)_2$ (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]	(II)[b] M.p./°C	(II)[b] Yield/%[c]	(III)[b] M.p./°C	(III)[b] Yield/%[c]	(IV)[b] 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): CF_3CO_2H, 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 CF_3CO_2H 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.

$$\underset{(I)}{RCONH_2} \rightarrow \underset{(II)}{RCONHCH_2SMe} + \underset{(III)}{(RCONH)_2CH_2}$$

$$\underset{(II)}{RCONHCH_2SMe} \rightarrow \underset{(IV)}{RCONHMe} + \underset{(V)}{RCONHCH_2OEt} + (I)$$

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.

(*Received*, 11*th February* 1975; *Com.* 164.)

† Minocycline[3] 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-NMe_2), 2·59 (6H, s, 7-NMe_2), 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.