Enhancement of Steroid Absorption by Dialkylamides

Keyphrases ☐ Steroids—absorption ☐ Absorption, steroids—*N*,*N*-dialkylalkylamide effect ☐ Prednisone absorption enhancement—*N*,*N*-di-*n*-propylpropionamide

Sir:

Amides having two alkyl substituents on the nitrogen atom can interact in nonaqueous solvents with a number of organic nonelectrolytes to form molecular complexes (1). This suggests that the lipoid phase of biologic membranes might provide an environment conducive to complex formation between nitrogen-substituted amides and certain drugs. Pronounced drug–amide complex formation in the lipoid phase of biologic membranes might be expected to influence the rate of drug transfer across such membranes. The direction and magnitude of this effect would presumably depend on the partition coefficient and diffusion characteristics of the drug relative to those of the drug–amide complex in the membrane and on the extent of the drug–amide interaction.

The influence of nitrogen-substituted amides on drug absorption has not been investigated extensively. There is evidence, however, that *N*,*N*-dialkylalkylamides can influence the percutaneous absorption rate of certain drugs. Munro and Stoughton, for example, reported *N*,*N*-dimethylacetamide (DMA) and *N*,*N*-dimethylformamide to be superior to ethanol, benzene, and a cream base in promoting the penetration of hydrocortisone and griseofulvin into human skin (2). Reid and Brookes found that the percutaneous absorption of three corticosteroids was more rapid from an ointment base containing 25% DMA than from three other ointment bases (3). These observations are explainable on the basis of drug–amide complex formation, although a physical alteration of the cutaneous barrier may have occurred since amide concentrations of 25–100% were used.

We have studied the effect of relatively low *N*,*N*-dialkylalkylamide concentrations on steroid absorption from the rat small intestine. This preliminary communication describes one representative system: prednisone and *N*,*N*-di-*n*-propylpropionamide (DPP). Male Sprague-Dawley rats, starved 14–22 hr., were prepared as described by Doluisio *et al.* for studying drug absorption from solution by the *in situ* rat small intestine (4). Seven milliliters of drug solution was placed in the intestine, and 0.2-ml. samples were removed at 10-min. intervals for 1 hr. The volume of the luminal prednisone solution was maintained constant by adding solvent (isotonic saline) immediately prior to sample removal. About 4 ml. additional solvent was required for this purpose. The concentration of prednisone in the sample was determined by the colorimetric procedure of Porter and Silber (5). The initial prednisone and DPP concentrations in the luminal solution were 5×10^{-4} *M* and 2.8×10^{-2} *M* (0.5% v/v), respectively. Prednisone concentrations determined in the serial samples were corrected for previously removed drug.

Table I—Effect of 0.028 *M* *N*,*N*-di-*n*-Propylpropionamide (DPP) on the Absorption of Prednisone from the Rat Intestine

Percent Absorbed[a]					
10 min.		20 min.		60 min.	
Control	With DPP	Control	With DPP	Control	With DPP
26.0	56.1	37.5	72.3	61.6	90.4
26.4	46.6	42.3	64.0	70.3	86.5
23.6	47.1	36.2	63.3	58.5	88.1
23.2	49.0	37.8	65.4	62.0	87.4
		Mean			
24.8	49.7	38.4	66.2	63.1	88.1

[a] The effect of DPP was statistically significant ($p < 0.001$) at all times.

The results of the absorption experiments are summarized in Table I. The presence of amide enhanced significantly ($p < 0.001$) the absorption of the steroid. A detailed kinetic analysis of the entire data will be presented in a subsequent report. The nature of the prednisone–DPP interaction was studied in both water and isopropyl myristate (IPM) by equilibrium solubility and equilibrium partition methods. The results indicate that a molecular complex of stoichiometry other than 1:1 formed between prednisone and DPP. The interaction was more extensive in a nonpolar than in a polar medium. For example, 2% v/v DPP increased the solubility of prednisone in IPM by 137%, compared to a 27% increase obtained under similar conditions in water. In addition, the IPM–water partition coefficient was increased 110% when the IPM phase contained 2% v/v DPP. The IPM–water partition coefficient of DPP is about 4.

The integrity of the intestinal membranes did not appear to be affected by DPP in the concentration used in this study. The gross appearance of the gut did not change; the absorption rate of caffeine, a drug that does not appear to interact with DPP in a nonaqueous solvent (IPM), was the same in the presence and absence of the amide. (Caffeine and DPP may interact slightly in water; the aqueous solubility of caffeine is increased 15% by 2% v/v DPP.)

Additional data, to be presented in a future report, indicate a relationship between the alkyl chain length of the nitrogen substituent and the absorption-enhancing effect of the dialkylpropionamides. These findings are significant because they may lead to a better understanding of intestinal absorption processes, particularly with respect to enhancing the absorption rate of certain poorly absorbed drugs.

(1) T. Higuchi and S. Chulkaratana, through T. Higuchi and K. A. Connors, in "Advances in Analytical Chemistry and Instrumentation," 4th ed., C. N. Reilley, Ed., Interscience, New York, N. Y., 1965, p. 117.
(2) D. P. Munro and R. B. Stoughton, *Arch. Dermatal.*, **92**, 585(1965).
(3) J. Reid and D. B. Brookes, *Brit. J. Dermatol.*, **80**, 328(1968).
(4) J. T. Doluisio, N. F. Billups, L. W. Dittert, E. T. Sugita, and J. V. Swintosky, *J. Pharm. Sci.*, **58**, 1196(1969).
(5) C. C. Porter and R. H. Silber, *J. Biol. Chem.*, **185**, 201(1950).

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Synthesis and Antibacterial Activity of 1-Styryl-3,4-dihydroisoquinolines

Keyphrases □ 1-Styryl-3,4-dihydroisoquinolines—synthesis □ Antibacterial activity—1-styryl-3,4-dihydroisoquinolines

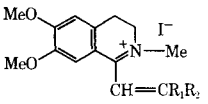
Sir:

So far, the synthesis of 1-styrylisoquinolines has been achieved either by the cyclization of the Schiff bases derived from cinnamaldehyde (1, 2) or by the condensation of 1-methylisoquinoline with aromatic aldehydes (3). In this communication, we wish to report a new procedure for the synthesis of 1-styryl-3,4-dihydroisoquinolines which were isolated as methiodide salts. The procedure involves the cyclodehydration of substituted β-phenethylamides to 3,4-dihydroisoquinolines through the Bischler-Napieralski reaction (4).

Details about the synthesis and characterization of 1-styryl-3,4-dihydroisoquinoline methiodides (Compounds 1–7) will be published (5).

The methiodide salts (Compounds 1–7) were subjected to *in vitro* screening for antimetabolites by a new method (6). In this method, the detection system utilizes the gram-positive *Bacillus subtilis* and gram-negative *Escherichia coli*. Both organisms were grown in two types of agar: nutrient agar and a completely synthetic medium with glucose as the only source of carbon.

Table I—Inhibition of *B. subtilis* Grown in Two Different Media[a]



Compound	R_1	R_2	Nutrient Agar	Synthetic Agar
1	Ph	Ph	24	35
2	Ph	*p*-Methylphenyl	25	36
3	*p*-Methylphenyl	*p*-Methylphenyl	29	35
4	*p*-Ethylphenyl	*p*-Ethylphenyl	36	39
5	*p*-Chlorophenyl	*p*-Chlorophenyl	28	35
6	Me	Ph	16	22
7	Me	Me	0	0

[a] The numbers in the body of the table are zones of growth inhibition in mm. around a 13-mm. paper disk.

These seven compounds were tested at concentrations of 1 mg./ml., and the results are presented in Table I.

The inhibition of test organism by Compounds 1–6 was stronger on synthetic agar than on nutrient agar. However, the difference was not large enough to suggest an antimetabolitelike mode of action (5). Compound 7 was essentially inactive against *B. subtilis*. None of the compounds inhibited the growth of *E. coli*. These results indicate that 1-styryl-3,4-dihydroisoquinoline methiodides possess some antibacterial activity.

A more extensive testing will be required before any structure–activity correlation can be drawn.

(1) E. C. Weinback and W. H. Hartung, *J. Org. Chem.*, **15**, 676(1950); W. M. Whaley and T. R. Govindachari, "Organic Reactions," vol. 6, Wiley, New York, N. Y., 1962, p. 151.
(2) W. H. Mills and J. L. B. Smith, *J. Chem. Soc.*, **121**, 2724(1922).
(3) T. Kametani, T. Terui, T. Ogino, and K. Fukumoto, *J. Chem. Soc. (C)*, **1969**, 874.
(4) F. Bergmann, M. Weizmann, E. Dimant, J. Patai, and J. Szmuskowica, *J. Amer. Chem. Soc.*, **70**, 1612(1948).
(5) R. E. Harmon, B. L. Jensen, S. K. Gupta, and J. Nelson, to be published.
(6) L. J. Hanka, "Abstracts," Fifth International Congress of Chemotherapy, Vienna, Austria, July 1967, B g/2, 351.

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