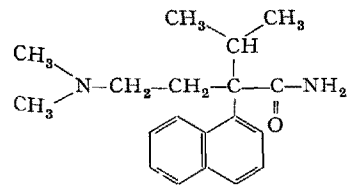
## α-Isopropyl-α-(2-Dimethylaminoethyl)-1-Naphthylacetamide (DA 992), a New Anti-Inflammatory Agent

In recent years some hundreds of naphthalene derivatives have been prepared in our laboratories to compare their pharmacological properties with those of corresponding benzene derivatives[1-6]. During these studies we have been able to point out the interesting properties of α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (DA 992), properties which we wish to report briefly in this paper. DA 992 is a colourless substance soluble in alcohols and insoluble in water, which gives with organic and inorganic acids water-soluble salts.



M. W. : 298.418
M. P. : 133–134°C

Against oedemas induced by subplantar injection of kaolin, dextran, serotonin, formalin and carrageenin, in formalin peritonitis, in chronic experimental inflammations such as agar granuloma and croton oil granuloma pouch, DA 992 shows in rats, administered both orally and intraperitoneally, an anti-inflammatory action rather similar to phenylbutazone (PBZ). The new substance exhibits also, in rats, an antipyretic activity on brewer's yeast fever which, for intensity and duration, corresponds to PBZ, and an analgesic action in the hot-plate test and an analgesic-anti-inflammatory action slightly lower than PBZ. DA 992 displays intraperitoneally an anti-hyaluronidase activity quite similar to PBZ and an activity on serotonin-induced diarrhoea in mice, which at 12.5 mg/kg is slightly higher than 4.4 mg/kg of cyproheptadine. Contrary to other antiphlogistic drugs, DA 992 exhibits a light diuretic action: 50 mg/kg orally administered gives rise to a diuresis which is equivalent to 6.25 mg/kg of hydrochlorothiazide, the urinary excretion of $Na^+$ and $Cl^-$ appearing remarkably increased in relation to that of control animals. Furthermore, after repeated treatment, DA 992 does not cause any gastric lesion in normal animals, nor make worse lesions in ulcer-sensitized animals, nor produce leukopenia. Subacute oral toxicity in adrenalectomized rats is remarkably lower than PBZ: 14% and 28% death rate against 100% of corresponding doses of PBZ (100 and 200 mg/kg, daily for 6 days).

Acute toxicity is relatively low, the $LD_{50}$ giving, in mg/kg, the following results: 269 intraperitoneally and 1446 orally in rats; 72 intravenously, 264 intraperitoneally and 1086 orally in mice. Chronic toxicity, carried out in rats by oral administration of 260 mg/kg daily for 8 weeks, and of 55 mg/kg daily for 9 months, confirm the good tolerance of DA 992: weight gain plots, haematologic and hystological examinations did not exhibit, in fact, any pathological change due to the drug.

Preliminary investigations have shown DA 992 to be well absorbed in rats and rabbits, after both oral and intramuscular administration. Similar results have been found during preliminary trials in human subjects: in fact, blood levels of 2–4 mg/100 ml were attained in man in the first hours following oral administration of a single 400 mg dose. In human subjects, about 50% DA 992 is excreted unchanged.

*Zusammenfassung.* Die pharmakologischen Eigenschaften von α-Isopropyl-α-(2-dimethylaminoäthyl)-1-naphthylacetamide (DA 992) werden beschrieben. Dieser neue synthetische Stoff entwickelt eine entzündungshemmende und antipyretische Aktivität, gleich wie Phenylbutazon, eine gute analgetische und analgetisch-entzündungshemmende Wirkung sowie eine intensive Antiserotoninwirkung *in vivo*. Die Vorversuche haben gezeigt, dass DA 992 von Versuchstieren und Mensch gut und verträglich absorbiert wird.

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*Research Laboratories of Istituto De Angeli S.p.A., Milano (Italy), May 4, 1964.*

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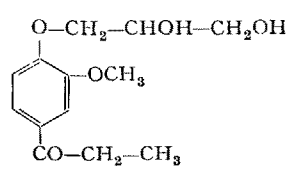
## Influence on Central Nervous System of 3-(*p*-Propionyl-*o*-methoxy-phenoxy)-1,2-propanediol

By inserting in the same base structure both ketonic and α-glycerol radicals, which are known to be able to confer muscle-relaxing and sedative properties on molecules, we obtained a series of acylphenol glycerol ethers, which exhibit, as a general feature, a depressant action on C.N.S. 3-(*p*-Propionyl-*o*-methoxy-phenoxy)-1,2-propanediol (DA 1128) proved to be the most interesting among the compounds studied, from a chemical, pharmacological and toxicological point of view. DA 1128 is a colourless substance, freely soluble in water and alcohols.

DA 1128 displays a marked depressant action on C.N.S. but, contrary to mephenesin, to which it is to some extent structurally related, it shows only a weak paralysing action and a lower muscle-relaxing activity. The new substance significantly inhibits, both orally and intraperitoneally, spontaneous activity in mice and antagonizes



M. W. : 254.274
M. P. : 69–70° C