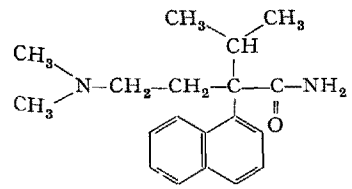
α-Isopropyl-α-(2-Dimethylaminoethyl)-1-Naphthylacetamide (DA 992), a New Anti-Inflammatory Agent

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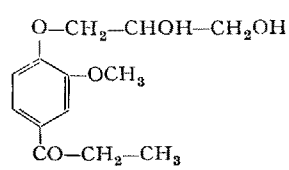
Influence on Central Nervous System of 3-(*p*-Propionyl-*o*-methoxy-phenoxy)-1,2-propanediol

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

the excitomotory picture induced by amphetamine, cocaine and caffeine, potentiates the hexobarbital induced sleep, and shows an anticonvulsant action against electroshock seizures, whereas it is ineffective against experimental seizures by pentylenetetrazol and strychnine. In the voluntary muscular activity of mice, DA 1128 orally displays an action rather similar to mephenesin in rota rod test, 50% in traction and in inclined screen tests, 25% in paralysing test. Like mephenesin, the new drug does not modify the corneal reflex, whereas it exhibits on pinna reflex an activity equivalent to one-half. It is interesting to note that ED_{50} calculated for traction test, anticonvulsant action and spontaneous activity in mice, both normal and pretreated with amphetamine, cocaine and caffeine, have been found to be, respectively, 20%, 41%, 33%, 25%, 28% and 27% of the paralysing ED_{50}.

DA 1128 is less toxic than mephenesin and mostly does not exhibit any haemolytic activity, either *in vivo* or *in vitro*. The LD_{50}, in mg/kg, have been recorded as follows: 458 intravenously, 674 intraperitoneally and 1056 orally in mice; 1637 orally in rats. Three months of oral treatment with 280 mg/kg daily of DA 1128 did not affect the blood picture and the body growth, and did not cause any pathological change in the chief organs.

Blood levels in rats and rabbits administered orally and intramuscularly with DA 1128 have shown the new drug to be quickly absorbed. DA 1128 displays in such animals a disappearance rate from blood circulation quite similar to mephenesin. It is excreted unchanged in small amounts; large amounts are found in urine of a metabolite which proved to be α-hydroxy-β-(4-propionyl-2-methoxyphenoxy)-propionic acid.

Zusammenfassung. Die hauptsächlichsten pharmakologischen Eigenschaften von 3-(*p*-Propionyl-*o*-methoxyphenoxy)-1, 2-propandiol (DA 1128) werden beschrieben. Wie Mephenesin zeigt DA 1128 eine beträchtliche depressorische Wirkung auf das Z.N.S. Das neue Arzneimittel jedoch zeigt – in Abweichung von Mephenesin – nur eine schwache paralytische Wirkung und eine geringe muskelrelaxierende Wirkung, ist weniger toxisch und besitzt keine hämolytische Wirkung. DA 1128 wird bei Versuchstieren rasch resorbiert.

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Incorporation of H^3-Progesterone Activity into 18-OH-Corticosterone and 18-OH-11-Desoxycorticosterone, Aldosterone and Corticosterone Following Treatment of Formaldehyde and Hydrocortisone, in Pregnant and New-Born Rats and Immediately *post partum*

It has been proved by several authors (PÉRON[1-3], WARD and BIRMINGHAM[4], ULICK[5], SÁNDOR et al.[6,7], KAHNT and NEHER[8]) that a significant quantity of 18-OH-corticosterone and 18-OH-11-deoxycorticosterone is produced by the adrenal of various species. The biological role of these steroids has not been clarified. It was, therefore, decided to study, under different physiological and pathological conditions, the incorporation of the radioactivity of H^3-progesterone into 18-OH-corticosterone and 18-OH-11-deoxycorticosterone. The investigations were carried out on the surviving adrenal slices of rats. An opportunity of examining the incorporated activity into aldosterone and corticosterone was also provided.

The present experiments were carried out on female rats of identical breed, as follows: 0.5 ml/100 g 2% formaldehyde was administered daily intramuscularly for 5 days; 5 mg hydrocortisone was given subcutaneously twice daily for 12 to 14 days. The investigations were carried out 24 h after the last treatment. The pregnant animals were in the last third of pregnancy; the new-born rats were 1 to 5 days old. Mother animals, deprived of their offspring, were used for the examination of the *post partum* condition.

The rats were killed by decapitation. The adrenals were removed, cleaned and cut in four, incubated in 10 ml/100 mg Krebs-Ringer-bicarbonate solution containing 200 mg % glycose, perfused with a mixture of 95% O_2 + 5% CO_2 at 38°C temperature. After a preliminary incubation of $^1/_2$ h, the medium was changed. The object of the examination consisted of a 4-h incubation. When changing the medium, 1 μg/mg H^3-progesterone dissolved in $^1/_{100}$ Vol ethanol and $^1/_{100}$ Vol propylene-glycol was added to the incubation mixture. (H^3-progesterone of random labelling according to Wilzbach's procedure, of 73 μC/mg spec. activity and 97% radiochemical purity was put at our disposal by the Isotope Institute of the National Atomic Energy Committee, Budapest.) 100 to 300 mg adrenal, taken from 4 to 10 rats, were incubated in each tube. The number of new-born animals was naturally much higher, that of pregnant rats was less; the adrenals of 2 to 3 rats were incubated together.

The incubation fluid was extracted with dichlormethane and chromatographed on Whatman No. 4 filter paper in a propylene-glycol-toluene system for 10 to 16 h. The steroids were localized by means of a UV lamp at 254 mμ and a fluorescence screen. Identification was done with aldosterone and corticosterone running simultaneously, i.e. by estimating the Rf. For the estimation of Rf, data of investigations carried out under similar conditions by WARD and BIRMINGHAM[4] and SHEPPARD et al.[9], were taken into consideration.

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