o-N-Diisopropylaminoethoxy-Butyrophenone, a New Local Anaesthetic Drug

The wide spectrum of biological activities of N-substituted β-phenoxyethylamines[1], some of which were also described recently for their spasmolytic action[2,3], prompted us to examine these substances for a possible local anaesthetic activity and in fact pilot experiments showed that acylation was effective in conferring this activity on phenoxyethylamines. A systematic research into *ortho*, *meta* and *para* isomers of acyl-phenoxyethylamines enabled us to establish the superiority of the *ortho* isomers, the optimal length of the basic chain and of the acyl group as well as the best type of N-substituent. The most promising compound is the *ortho*-N-diisopropylaminoethoxy-butyrophenone since modifications of this structure, such as the introduction of other substituents into the benzene ring, e.g. alkyls, halogens, amino and nitro groups, or the transformation of the acyl radical into alcohol, alkyl and carboxylethyl radicals, greatly reduced the anaesthetic activity.

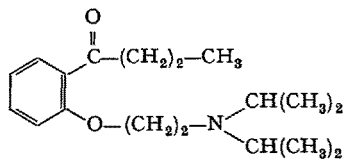

Table I shows the surface, infiltration and troncular anaesthetic activity of *ortho*-N-diisopropylaminoethoxy-butyrophenone hydrochloride (Rec 7-0518) compared with the activity of cocaine and of procaine. Table II gives the intraperitoneal and subcutaneous LD_{50}'s of the three substances.

On comparing the activities and the toxicities of these compounds, it will be seen that Rec 7-0518 shows higher therapeutic indices than cocaine, a model for surface anaesthetic activity, and than procaine, a model for infiltration anaesthetic activity. The results obtained in clinical experiments agree with these pharmacological findings.

The *ortho*-N-diisopropylaminoethoxy-butyrophenone was prepared by condensing the *o*-hydroxy-butyrophenone with the β-N-diisopropylamino-ethylchloride hydrochloride in an alcoholic medium and in the presence of a base. The resulting product is a colourless oil with a b.p. of 183–185°C/6–7 Torr. Analysis: calc. for $C_{18}H_{29}NO_2$ C 74.19%, H 10.05%, N 4.81%. Found C 74.45%, H 9.90%, N 4.52%.

The hydrochloride of the *ortho*-N-diisopropylaminoethoxy-butyrophenone (Rec 7-0518) is obtained as a white and bitter crystalline powder, with a m.p. of 129–130°C. Analysis: calc. for $C_{18}H_{30}ClNO_2$ C 65.93%, H 9.22%, Cl 10.81%, N 4.28%. Found C 65.89%, H 9.20%, Cl 10.86%, N 4.25%.

Table I. Effective concentrations in 50% of the animals (EC_{50}'s) calculated according to LITCHFIELD and WILCOXON[4]

Type of anaesthesia	Rec 7-0518 mg/ml	Cocaine mg/ml	Procaine mg/ml
Surface[5] (rabbit eye)	0.75 (0.61–0.92)	2.8 (2.3–3.4)	21 (18–26)
Infiltration[6] (mouse tail)	0.38 (0.27–0.54)	0.38 (0.30–0.47)	3.6 (2.7–4.9)
Troncular[7] (rat ischiatic nerve)	2.1 (1.7–2.6)	0.90 (0.78–1.1)	6.0 (5.1–7.0)

The values in brackets represent the $P = 0.05$ fiducial limits of the EC_{50}'s.

Table II. Intraperitoneal and subcutaneous LD_{50}'s

Route	Rec 7-0518 mg/kg	Cocaine mg/kg	Procaine mg/kg
i.p.	102 (96–108)	79 (75–83)	173 (156–192)
s.c.	217 (187–252)	81 (57–115)	830 (703–979)

The values in brackets represent the $P = 0.05$ fiducial limits of the LD_{50}'s.

Riassunto. Da una serie di β-fenossietilamine acilate è stata selezionata una nuova sostanza e cioè l'*o*-N-diisopropylaminoetossibutirrofenone, che possiede elevate proprietà anestetiche locali di superficie, per infiltrazione e tronculari. Si sono comparate le attività anestetiche e la tossicità del nuovo composto con quelle della cocaina e della procaina.

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Gewinnung von Chloroplasten ohne Verwendung von Flüssigkeiten

Bei allen bekannten Methoden, einzelne Zell- und Gewebebestandteile in grösseren Mengen zu gewinnen (Zell- und Gewebetrennung, isolation of subcellular components)[1–4], werden zur Trennung Flüssigkeiten benutzt. Durch diese treten bei den zu isolierenden Komponenten unkontrollierbare Veränderungen auf (Extraktion und Verlagerung von Substanzen, Schädigung von Fermenten usw.). Es wurden daher Versuche unternommen, eine Trennung ohne Verwendung von Flüssigkeiten zu erzielen. Als Ausgangsmaterial dienten dabei Pulver gefriergetrockneter pflanzlicher und tierischer Gewebe.