It is well known that bufadienolides are several times more potent than the cardenolide homologs[15]. This relationship is seen in guinea-pig atria in RP-values for bufalin and digitoxigenin, gamabufotalitoxin and digitoxigenin 3-suberoylarginine ester. The same relation, however, was not found in frog hearts. Since the sensitivity of frog hearts to digitoxigenin is about the same as that of guinea-pig atria, the RP's for the 4 bufadienolide-compounds are clearly larger in guinea-pig atria than in frog hearts. This suggests that the frog heart is less sensitive to bufadienolides, but not to cardenolides, than the mammalian heart.

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α- and β-activity of O-methylated derivatives of norepinephrine and epinephrine

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Summary. Metanephrine, iso-metanephrine, normetanephrine and isonormetanephrine were tested for α- and β-activity on various tissues obtained from rats, guinea-pigs and cats. It was found that methylation of the hydroxyl groups of norepinephrine or epinephrine in either the 3- or 4-position markedly reduces or abolishes α- and β-activity with the exception of the nictitating membrane of the cat. This receptor seems to show a tissue difference.

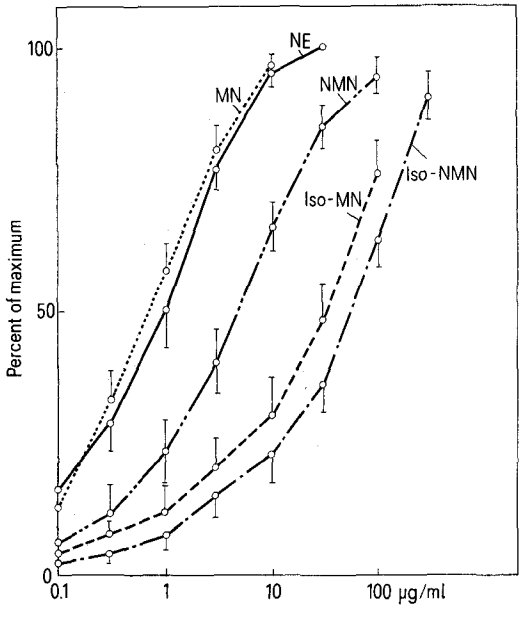
O-Methylation of norepinephrine or epinephrine is generally regarded as an inactivation process and the metabolites metanephrine and normetanephrine are thought to possess little or no activity on α- or β-receptors[2-4]. In contrast, Langer and Rubio[5] found recently that normetanephrine and metanephrine elicited responses of the cat's nictitating membrane equal to that of norepinephrine.

Since it is possible that this discrepancy is the result of a species and/or tissue difference, metanephrine and normetanephrine were tested on a variety of tissues obtained from rats, guinea-pigs and cats. In addition, the 2 isomers of metanephrine and normetanephrine, iso-metanephrine or 3-hydroxy-4-methoxy-N-methyl-phenylethanolamine and iso-normetanephrine or 3-hydroxy-4-methoxyphenylethanolamine, which had not been tested previously, were included in the experiments to obtain information on the importance of the methoxy-group in the 3- and 4-position.

Cats were anesthetized with ether to obtain the nictitating membrane or were sacrificed with an overdose of pentobarbital to obtain vas deferens and spleen. Rats and guinea-pigs were stunned with a blow to the head and quickly decapitated. The testing was performed with conventional methods and the experimental procedures have been described in detail[6-8]. Cumulative dose-response curves were obtained for auricles and nictitating membranes whereas all the other tests were performed by intermittent administration of the test compounds.

The figure shows the dose-response curves of the derivatives on the nictitating membrane of the cat. All compounds are active and the curves are practically parallel. Iso-metanephrine and iso-normetanephrine were less potent than the corresponding isomers.

The table shows a summary of the tissues tested. With the exception of the nictitating membrane, all other tissues did not respond or responded by less than 20% of the maximum response to norepinephrine even when the highest concentrations of the derivative were used.



Effect of O-methylated derivatives of norepinephrine and epinephrine on the nictitating membrane of the cat. The number of determinations was 6 in most instances. The curve for norepinephrine included for purposes of comparison is obtained from Trendelenburg et al.[7].

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Effects of norepinephrine and 4 O-methylated derivatives on α- and β-receptors in various tissues

	Vas deferens			Spleen			Nictitating membrane	Auricle
	Guinea-pig	Rat	Cat	Guinea-pig	Rat	Cat	Cat	Guinea-pig
Norepinephrine	4.8 ± 0.12	4.9 ± 0.13	6.1 ± 0.22	5.1 ± 0.12	5.1 ± 0.1	5.2 ± 0.11	5.3 ± 0.2	6.3 ± 0.3
Metanephrine	< 3.7*	< 3.7	< 3.7	< 3.7	< 3.7	< 3.7	5.5 ± 0.1	< 5.0
Normetanephrine	< 3.7	< 3.7	< 3.7	< 3.7	< 3.7	< 3.7	4.7 ± 0.2	< 5.0
Iso-metanephrine	< 3.7	< 3.7	< 3.7	< 3.7	< 3.7	< 3.7	4.0 ± 0.2	< 5.0
Iso-normetanephrine	< 3.7	< 3.7	< 3.7	< 3.7	< 3.7	< 3.7	3.7 ± 0.2	< 5.0

Mean negative log molar E.D. 50 ± S.E. Values are derived from at least 4 but in most cases from 6 independent determinations. * No response or less than 20% of maximum obtained with norepinephrine.

The results of this study not only confirm but also extend previous findings and indicate that methylation of the hydroxyl-group in either the 3- or 4-position markedly reduces α- and β-activity of norepinephrine and epinephrine with the exception of the α-receptor of the nictitating membrane of the cat. On this organ all derivatives are active and metanephrine is perhaps slightly more potent than norepinephrine whereas normetanephrine looses some agonistic activity. The mild increase in potency of metanephrine seems to be due to the presence of the methoxy-group in the 3-position on the benzene-ring since methylation of the hydroxyl group in the 4-position decreases activity. Since this receptor is the only receptor found to respond to the methylated derivatives, it can be assumed that this presents a tissue rather than a species difference.

Etude du métabolisme de mescalines fluorées par Pieris brassicae (Insecte, Lépidoptère)

Metabolism of fluorinated mescalins by Pieris brassicae (Insect, Lepidoptera)

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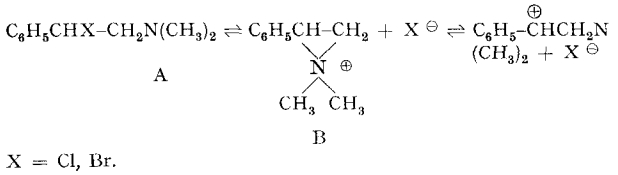
Summary. The action of α-fluorinated mescalins on induction of diapause in the cabbage butterfly, Pieris brassicae, has been studied. The introduction of fluorine into mescalin has no influence on this activity. This result suggests solvolysis of fluorine and in vivo formation of a common ethylimine intermediate. Activity decreases, however, with substitution of the nitrogen.

Il est couramment admis que l'introduction d'un atome de fluor dans une molécule organique biologiquement active en modifie les propriétés. Un exemple frappant est celui de l'acide monofluoroacétique qui s'inserre dans le cycle de Krebs[1]. Autrement dit, dans ce cas, le fluor a été intégré à divers composants du cycle avant de se retrouver et d'être identifié sous forme d'acide fluorocitrique.

Dans la stratégie de recherche que nous développons, il nous a paru intéressant de choisir une voie métabolique où, inversement, le site fluoré intervient dès le début. Notre choix s'est porté sur les dérivés de la phényléthylamine, dont un des représentants, la mescaline, est un psychodysleptique puissant[2]. Les travaux de W. et K. Block et Pazig[3] indiquent qu'une infime proportion de mescaline atteint le cerveau, la majeure partie étant stockée dans le foie. Ces résultats suggéraient que la mescaline est inactive et qu'elle réagirait in vivo pour donner naissance à un intermédiaire susceptible d'activité sur le système nerveux central[4].

Par ailleurs, les résultats de Chapman et Triggle[5], relatifs à la solvolyse d'halogéno-2 amines A antagoniste de l'adrénaline et la noradrénaline, indiquent que l'activité pharmacodynamique est liée à la formation intermédiaire du cycle éthyléneimine B



X = Cl, Br.

En admettant que la première étape du métabolisme traduisant l'action de la mescaline fluorée sur le système nerveux central corresponde à ce schéma, nous devons observer a priori une activité spécifique sensiblement identique, l'intermédiaire formé étant indépendant de la nature du substituant X éliminé. Cette activité sous entend la solvolyse du fluor qui s'est révélée particulièrement difficile en milieu neutre, à l'inverse des autres halogènes. On peut toutefois avancer un mécanisme caractérisé par la substitution interne du fluor par l'azote selon un schéma qui rappellerait la solvolyse acidocatalysée de fluoro-2 alcools aromatiques[6], conduisant ainsi à la formation in vivo d'une éthylèneimine.

Pour conduire et développer cette analyse, nous avons utilisé un test biologique basé sur un phénomène métabolique récemment mis en valeur. On sait qu'à la température de 20 °C une courte photophase de 9 h/24 h fournie pendant la durée de la vie larvaire conduit à la diapause nymphale d'un insecte Pieris brassicae. Le LSD et le sulfate de mescaline injectés à des doses bien définies pendant la période larvaire photosensible suppriment

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