low point of circadian change of total white cells occurs at 0600 hours (Table 1) agrees with the other work.1

The qualitative changes in 4S and 5S RNA and the significance of their inverse change remain to be further elucidated. An analysis of higher molecular weight RNA is currently being performed in our laboratory using an agarose polyacrylamide system.

Recent technological advances in the electroencephalographic investigations of human sleep now provide a means for relating the consequences of different stages of sleep to cyclic variation of RNA. Implications for a possible anabolic role of sleep need to be considered. In view of the effect of chemo-therapeutic agents on nucleic acid and protein biosynthetic pathways, a circadian variation in RNA also has implications for drug therapy in infection and leukaemia.

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Table 1 White Cells per Cubic Millimetre of Supernatant

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Fig. 1 Typical histograms of twitch frequency of individual mice as a function of time elapsed after intraperitoneal injection of a, 20 mg/kg compound IIb.HCl; b, 40 mg/kg mescaline HCl; and c, 160 mg/kg compound IIa.HCl. The total number of twitches, integrated over the observation period, are a, 149; b, 353; c, 77.

Stereochemical Requirements of the Mescaline Receptor

This report describes some psychopharmacological properties of two conformationally restricted analogues of the psychotomimetic compound mescaline (I). The geometrical distinction between these cis (IIa) and trans (IIb) isomers of 2-(3,4,5-trimethoxyphenyl)-cyclopropylamine makes it possible to

![Chemical Structures](image)

examine possible stereochemical preferences of the receptor for mescaline and other hallucinogenic phenethylamines.

Mescaline possesses a number of rotational degrees of freedom as depicted by the arrows on its structural formula. If not for energy barriers which inhibit free rotation, the mescaline molecule can assume an infinite number of different conformations. The magnitude and location of existing energy barriers will vary to some extent according to the physical environment, and positive drug-receptor interactions might impose additional restrictions on the conformation of mescaline and related compounds.

Possible alternative orientations of the methoxy groups in mescaline have been considered in detail by Chothia and Pauling. These authors as well as others have made proposals concerning the conformation of the ethylamine side chain, which can rotate about the C1-C7, C7-C8, and C8-N bonds, and the relative orientation of the aromatic ring with respect to bond C7-C8. The proponents have selected among four principal alternatives which are the two in-plane conformations (C7-C8 coplanar with the aromatic ring) with C1-C7 and C8-N either cis (a) or trans (b), and the two out-of-plane conformations (C7-C8 normal to the aromatic ring) with C1-C8 and C8-N either cis (c) or trans (d). The various choices were made on the basis of their structural congruity with one or the other portion of the lysergic acid diethylamide (LSD) molecule (III), or with regard to energetic favourability or crystallographic data. Although Neville et al. and Bailey have provided nuclear magnetic resonance (NMR) data in support of trans conformations for some related phenethylamine-type drugs, there has been no direct pharmacological
comparison of receptor preferences among the proposed conformations for mescaline and its congeners.

We prepared compound IIb, which approximates transoid conformers β or δ, and found that, in rodents, it has behavioural effects resembling those due to mescaline. Subsequently, we synthesized compound IIA, which closely resembles cisoid conformers (either α or γ) of mescaline, with the objective of resolving part of the stereochemical controversy by pharmacological means.

The behavioural effects of compounds IIA (20 mg/kg), IIb (20 mg/kg) and of mescaline (40 mg/kg) were compared using mice and following our earlier procedure. We have found that the syndrome produced by mescaline, and consisting principally of hypoactivity associated with crouching and characteristic twitching of the hindquarters is reproducible, dose-dependent and relatively specific for phenethylamine-type hallucinogens. Fig. 1 shows the manually-recorded time distribution of twitch frequency for three of the animals treated with the respective subject compounds. Compound IIb is qualitatively indistinguishable from mescaline in this test (Fig. 1a and b respectively) although its potency is somewhat greater and its duration of action briefer than that of mescaline. By contrast, compound IIA is almost inactive in producing the mescaline syndrome in terms of twitch frequency at comparable dosages. When the dosage is increased eight-fold (160 mg/kg) over that of its geometric isomer IIb, a mescaline-like response is obtained (Fig. 1c).

The relative potencies of the two isomers were also examined in rats which had been trained on a schedule of differential reinforcement of low rate with a limited hold contingency (DRL15-LH5). This schedule has been useful for the assessment of psychotropic drugs such as amphetamine, mescaline and tetrahydrocannabinol. The results of primary interest are shown in Fig. 2, in which the "drug effect ratio" refers to schedule performance efficiency of the animals in the drug-treated and in the untreated condition. Since a value of less than 0.5 for this ratio indicates decreased efficiency as a result of drug administration, Fig. 2 shows that compound IIA reduces efficiency to a significant extent only at the 32 mg/kg dosage level whereas its geometric isomer IIb produces a significant decrease in efficiency at the 8 mg/kg level.

Fig. 3 shows randomly selected daily records of the performance of two animals given 32 mg/kg of either IIA or IIb compared with their pre-drug day and post-drug day performance. These records indicate that whereas the overall response rates are little affected by drug treatment, compound IIA, and more particularly IIb, decreases the rate of reinforced responding, as has already been reflected by the data of Fig. 2. Although the temporal-spaced response deficit was evident at all effective dose levels, very few of these records showed the prolonged periods of cessation of responding previously reported due to mescaline. But visual examination of the rats during the sessions, and independent observation of these sessions presented in random order on videotape, showed that rats treated with compound IIb (16 and 32 mg/kg) exhibited mescaline-like changes in gross motor behaviour resembling those seen in mice, whereas rats which had received compound IIA could not be distinguished from the saline controls.

The pronounced differences in the psychopharmacological properties of compounds IIA and IIb are of dual interest. First, it has been shown that such quantitative differences are absent in the parent, nuclear-unsubstituted cis and trans-2-phenylcyclopropylamines in their activity as monoamine oxidase inhibitors either in vitro or in vivo. The introduction of nuclear methoxy substituents, as in the pair, IIA and IIb, is therefore responsible not only for qualitative distinctions between the pharmacology of trans-2-phenylcyclopropylamine and IIb, but also for quantitative differences between the potency ratios of these closely related pairs of geometric isomers. Second, if we assume that the more intense mescaline-like action of isomer IIb is consequent to its superior effect at the site of action (rather than to its resistance to metabolic degradation, an alternative possibility), we are encouraged to support the concept of a transoid conformation for mescaline at the receptor level.

This work was supported by grants from the National Research Council of Canada, the Ontario Mental Health Foundation and the Government of Canada Department of...
Keratoblast and Keratocyte, not Keratinocyte

Cells of both the reproductive and functional compartments of oral and cutaneous epithelia are at present indiscriminately called "keratinocytes". The two types of cells, however, differ markedly in function and fate, and it is therefore logical, as well as useful, to distinguish them by different terms. It is therefore proposed to introduce the term "keratoblast" to denote a cell in the reproductive compartment of these tissues, and thus to distinguish dividing cells from those that produce keratin.

The principal cellular components of oral and cutaneous epithelia fall conveniently into two compartments, namely a proliferative or reproductive compartment and a functional or mature compartment. The cells of the proliferative compartment, found chiefly in the basal cell layer, are reproductive and end by mitotic division. The cells of the functional compartment, found chiefly in the spinous, granular and cornified cell layers, produce keratin and later die and desquamate. The proliferative compartment, having retained its reproductive capacity, constitutes the germinative population for the functional compartment.

The difference between these two types of cells is important enough to warrant a separate name for each, and there are precedents for a semantic distinction between mature and immature cells—for example, chondroblast and chondrocyte, fibroblast and fibrocyte, osteoblast and osteocyte.

"Keratoblast" is the logical name for a reproductive cell of oral and cutaneous epithelia. It connotes "progenitor of keratocyte" and is preferred to "keratinoblast", which is not a well formed word. The Greek word from which these words are derived is "keratos", meaning "horn", and the stem is "kerato-", not "keratino-".1

The term "keratinocyte", unfortunately, is not accurate. The proper form, as explained in the preceding paragraph, is "keratocyte". There is an analogy here with the closely related melanin-producing cells which are correctly termed "melanocytes" rather than "melaninocytes". It should be mentioned also that "keratinize" and its derivatives, "keratinised" and "keratinization" are not correct, the proper forms being "keratize", "keratinized" and "keratinization" respectively.

None of the "keratinocyte" nor the other words improperly formed with "keratino-" have yet been included in either Nomina Anatomica or Nomina Histologica; therefore it is to be hoped that "keratocyte" and the other words properly formed with "kerato-" will be generally accepted as the preferred terms.

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Effect of PABA on Chloroquine Resistance in Plasmodium berghei yoelii

In mice1 paraaminobenzoic acid (PABA) in the diet of the host is necessary for the growth of blood infections of Plasmodium berghei. The area of the parasite metabolism in which PABA is involved is believed to be closely associated with the point of action of certain antimalarial drugs including pyrimethamine, proguanil and the sulphonamides. Several drugs of this group are antagonized by PABA.2 The effect of PABA on the antimalarial action of chloroquine has received little attention as chloroquine does not seem to act directly on the pathways of PABA metabolism. Kirakosyan,3 however, has shown that chloroquine is more effective against a sensitive strain of P. berghei berghei in mice when PABA is absent from the diet of the host.

I have examined the effect of different dietary concentrations of PABA on the degree of chloroquine resistance of strains of P. berghei yoelii. All strains of P. berghei yoelii show resistance to the drug*, but results from different laboratories on the degree of resistance are sometimes inconsistent. The present results provide a probable explanation for these discrepancies.

Fig. 1 The effect of different dietary concentrations of PABA on the response to chloroquine of blood infections of P. berghei yoelii (strain 33X). Each point represents the average parasitaemia of five mice. 0, 5 x 10⁻³ g PABA per 100 ml in drinking water; ■, 2.5 x 10⁻³ g PABA per 100 ml in drinking water; ▲, 1.25 x 10⁻³ g PABA per 100 ml in drinking water; □, 0.4 mg chloroquine per kg mouse weight administered; △, 40 mg chloroquine per kg distilled water administered; †, time at which chloroquine or distilled water was administered.

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