Confrontation of the above-mentioned results[9] with the present experiments seems to lend further support to the hypothesis that within the preoptic region two different autonomic systems overlap which might be represented on one side by catecholamine and, on the other side, by tryptamine receptor sites. It is suggested that melatonin, among other factors, may also play a neurohumoral role in modulating the state of wakefulness and sleep[10].

Zusammenfassung. An nicht narkotisierten Katzen wurde die Wirkung einer direkten lokalen chemischen Reizung subkortikaler Strukturen durch Melatonin untersucht. Diese Substanz, appliziert im Bereich der Area praeoptica, löste trophotropische Effekte und Schlaf aus.

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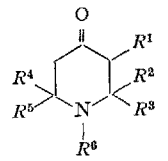
Ketal Formation in 4-Piperidones

Acid-catalysed hemiketal and ketal formation in alcoholic solutions of homocyclic ketones has recently been demonstrated by physical methods[1,2]. We and others find that certain heterocyclic ketones, in the presence of ethanol and acid, give either ketone or ethylketal salts (see Table). Ketal formation, where it occurs, is induced by merely treating the basic ketone with a slight excess of ethanolic hydrogen chloride at room temperature and allowing the hydrochloride salt to separate. The results of the Table may be interpreted in terms of (a) ring size and (b) generation of new 1,2-*cis* or 1,3-diaxial interactions, i.e. by the same factors that influence hemiketal formation in homocyclic ketones[2].

The results with the 4-piperidones (Ia–d) and the five and seven ring ketones (VII–X) are consistent with Brown's I-strain concept[3]. Carbonyl addition in 4-piperidones relieves strain inherent in a six membered ring containing one trigonal carbon atom and leads to an ideally staggered conformation, not attainable in the five and seven ring analogues (VII–X). If the 4-piperidone be substituted in the α-position (axial or equatorial), or the β-position (axial), ketal formation results in unfavourable

Action of ethanol-acid on some 4-piperidones and related ketones



Compound	R^1	R^2	R^3	R^4	R^5	R^6	Product isolated	Reference
I a	H	H	H	H	H	H	ketal HCl	7
b	H	H	H	H	H	*n*-Bu	ketal HCl	8
c	H	H	H	H	H	Bz	ketal HCl	8
d	H	H	H	H	H	$(CH_2)_2Ph$	ketal HCl	9
II a	Me	H	H	H	H	Me	ketone HCl	10
b	Me	H	H	H	H	$(CH_2)_2Ph$	ketone picrate	9
c	Et	H	H	H	H	$(CH_2)_2Ph$	ketone picrate	9
d	*n*-Pr	H	H	H	H	$(CH_2)_2Ph$	ketone picrate	9
III	H	Me	H	H	H	$(CH_2)_2Ph$	ketal HCl	5
IV	H	Me	H	Me	H	$(CH_2)_2Ph$	ketal HCl	5,11
V	H	Me	H	Me	H	H	ketal HCl	5
VI	H	Me	Me	Me	Me	H	ketone HCl	11
VII	N-benzylazacycloheptan-4-one						ketone HCl	12
VIII	N-(2-phenethyl)azacycloheptan-4-one						ketone HCl	12
IX	N-benzyl-3-pyrrolidone						ketone HCl	12
X	N-(2-phenethyl)-3-pyrrolidone						ketone HCl	12

non-bonded interactions that are not produced in β-equatorially substituted compounds. Hence the results for compounds IIa–d and III. The ketone (V) is known to be *cis*[4], thus ketal formation does not introduce unfavourable 1,3-interactions. The ketone (IV) is a *cis-trans* mixture in which the latter form predominates (from results of the isomeric composition of derived 4-phenyl-4-piperidinols)[5] and the ketal, isolated in small yield, most likely derives from the *cis*-component. Ketal formation with the ketone (VI) necessarily introduces new 1,3-diaxial interactions and is thus unfavoured. Facile acid-catalysed ketal formation in 4-piperidones is probably a result of carbonyl carbon being activated towards nucleophilic attack by the electronic influence of the protonated nitrogen atom. This influence is reflected in the lower carbonyl absorption frequencies of 4-piperidones in comparison with those of their salts [e.g. 1-(2-phenethyl)-4-piperidone base, 1717 cm^{-1}; HCl salt, 1736 cm^{-1}][12].

The related phenomenon of hydrate formation in 1-methyl-4-piperidone has been reported by LYLE, ADEL, and LYLE[6].

Zusammenfassung. Die Reaktion gewisser heterocyclischer Ketone mit Äthanol in Gegenwart von Säure ist abhängig von der Ringgrösse und wird plötzlich durch die Wechselwirkung von 1,2-*cis*- oder 1,3-diaxalen Substituenten beeinflusst.

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Inhibitory Activity of Benzoyl Hydrazides and Hydrazine on the Growth of Influenza Virus in Chick Embryo Lung Tissue Culture[1]

Hydrazine and its derivatives have occasionally been found to be effective chemotherapeutic agents against various microbial agents[2–8], but with the exception of the inhibition of Theiler's virus in tissue culture by 1-hydrazinophthalazine (Apresoline)[9], there is no report of effective viral antagonism by hydrazine derivatives.

In the course of testing the antiviral properties of analogs of amino acids and amino acid precursors[10,11], anthranilic acid hydrazide was found to inhibit the growth of influenza virus in chick embryo lung tissue culture. This report deals with the study of the antiviral characteristics of hydrazides, particularly anthranilic acid hydrazide.

Materials and methods. Hydrazine was purchased from the Eastman Kodak Co., Rochester, N.Y., and the five effective hydrazide compounds were kindly supplied by Hoffmann-La Roche, Nutley, N.J. The technique of the use of chick embryo lung tissue culture in the testing of the inhibition of growth of the influenza virus by drugs was described previously[10]. Briefly, influenza A virus, WS strain, aliquots of the drug, and finely dispersed embryonic chick lung were put in rubber-stoppered tubes. After incubation at 36°C for 44 h in a roller drum, the tubes were examined under 100× magnification for drug toxicity to the chick cells. Tubes showing normal tissue growth were tested for the growth of virus by means of the hemagglutination technique. The criterion for positive inhibition of virus by a compound was an eightfold or greater reduction of the hemagglutination end point.

Results. In the course of testing some 900 metabolically active compounds[11], anthranilic acid hydrazide, benzoic acid hydrazide, 2-methoxybenzoic acid hydrazide, *m*-nitrobenzoic acid hydrazide, salicylic acid hydrazide, as well as hydrazine itself, were found to inhibit effectively the growth of influenza virus in tissue culture (Table), while 16 other hydrazine derivatives were found to be ineffective or only partially effective.

In order to determine the effect of anthranilic acid hydrazide upon the growth of virus chick embryo lung tissue culture tubes were inoculated with 10^3 EID_{50}[12] of influenza virus. An inoculum of 0.25 mg of anthranilic acid hydrazide per ml of medium was subsequently added to tubes at intervals from 0 to 8 h after virus administration. The virus titer in these tubes was determined after 24 h of incubation. In addition the virus titers in the tube receiving the compound at zero h and

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