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REVIEW ARTICLE

Structural Analogs of Lysergic Acid

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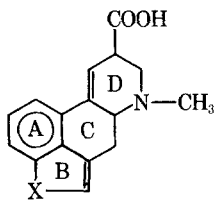
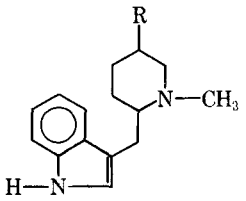
Keyphrases ☐ Lysergic acid structural analogs—literature review ☐ Structure–activity relationships—lysergic acid analogs ☐ Pharmacological activity—lysergic acid analogs

In the course of work on the preparation of the sulfur isosters (*Ia*) of lysergic acid (*Ib*), a literature search was made for other analogs of lysergic acid to see what types of molecular modification had already been applied to this structure. The following review of the published studies on analogs of lysergic acid is the result of this search. Most of these analogs consist of partial structures of lysergic acid or derivatives thereof, in which one or more of the rings have been opened or dissected away to discover the smallest fragment of the polycyclic system that might retain biological activity. The analogs are discussed in structural categories rather than by biological activity groups.

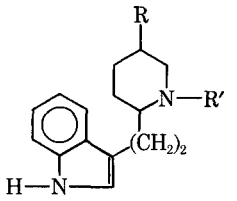


Ia: X = S
Ib: X = NH

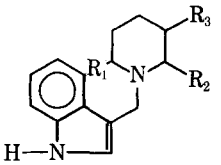
The analogs that probably bear the closest structural resemblance to the parent lysergic acid are indole derivatives of types II and III, in which only the C ring has been opened. The unsubstituted (R = H) and the ethyl-substituted (R = C_2H_5) derivatives of II showed high oxytocic activity *in vitro* on guinea pig uterus but



II



III

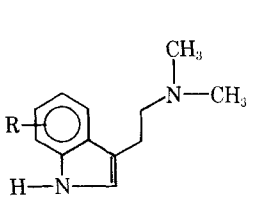


IV

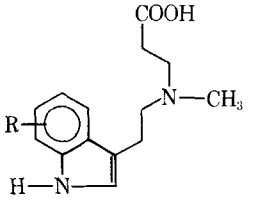
were not active *in vivo* (1, 2). Carboalkoxy substitution of II (R = COOR′) did not increase the activity (2). Castle and Whittle (3, 4) increased the distance between the indole and piperidine ring systems by one methylene group in a series of derivatives of type III. They prepared derivatives of III with both alkyl and carboxamido substituents for R but abandoned the series when the compounds failed to show any interesting activity in mouse behavior, oxytocic, and antimicrobial testing (4). Compounds of type IV (R_1, R_2 = H or CH_3, R_3 = H), although structurally less similar to lysergic acid, showed higher *in vivo* and *in vitro* oxytocic activity than those of type II (5, 6). When the indole system was replaced by naphthalene, the oxytocic dose caused blood pressure disturbances (6). Surprisingly, 3′-carboalkoxy substituents (IV, R_1, R_2 = H, R_3 = COOR) greatly reduced the oxytocic activity (6). When the amide group present in ergonovine was attached at the 3′-position [IV, R_1, R_2 = H, R_3 = CONHCH(CH_3)-

CH_2OH], the compound showed uterine inhibitory action (6).

Analogs of types V and VI (R = 4—Cl, 4—NO_2, 6—NO_2, 4—NH_2, 6—NH_2), in which both the C and D rings are open, have been prepared, but the testing results have not been reported (7).

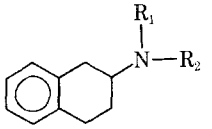


V

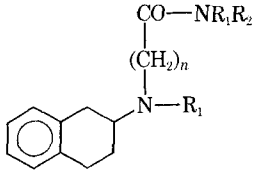


VI

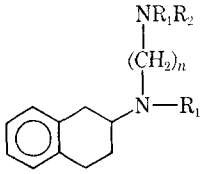
Dissection of the A and C rings from lysergic acid while keeping the amino group gives 1,2,3,4-tetrahydro-2-naphthylamine (VII, R_1, R_2 = H). Many derivatives



VII



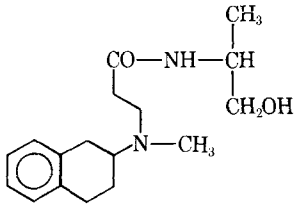
VIII



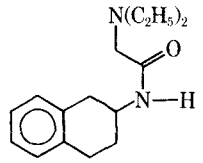
IX

of the basic structure of VII have been prepared as analogs of lysergic acid. The unsubstituted amine (VII, R_1, R_2 = H) exhibits both sympathomimetic and sympatholytic activity (8). Both the unsubstituted amine and the monomethyl derivative (VII, R_1 = H, R_2 = CH_3) showed pyretic and pressor activity in dogs (9). The pressor effect was not prevented by CNS destruction, indicating that it was not centrally mediated. The hyperthermic effect was, however, a central one (9). Ethyl substitution (VII, R_1 = H, R_2 = C_2H_5) or dimethyl substitution (VII, R_1, R_2 = CH_3) caused reduction in pressor activity, and the diethyl derivative (VII, R_1, R_2 = C_2H_5) showed hypotensive action (9).

Marini-Bettolo, Chiavarelli, Bovet, and their coworkers (10–20) prepared and tested over 200 derivatives of VII. The amides of type VIII and the diamines of type IX both showed sympatholytic activity, but only the amides were oxytocic (17). One of these amides, the ergonovine analog X, bore striking resemblance to the parent ergonovine in that it was a potent oxytocic with little vasomotor action (13). The tetrahydronaphthylamine derivative (XI) has been used clinically as an oxytocic (21). In this connection, it is surprising that the corresponding diethylaminoacetyl amide of tryptamine is less active (1/150 ergometrine) than 2-diethylaminoacetamidothiophene (1/100 ergometrine) (22). From their study of derivatives of VII, Marini-Bettolo *et al.* (10) concluded that the 1,2,3,4-tetrahydro-2-naphthylamine element in the structure of ergot al-



X

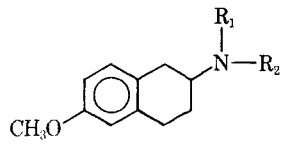


XI

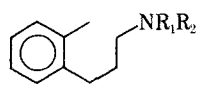
kaloids is essential for sympatholytic activity rather than the indole moiety.

Cymerman-Craig *et al.* (23, 24) also investigated derivatives of VII. As in the earlier work, the parent amine (VII, R_1, R_2 = H) and the lower alkyl derivatives showed pressor activity while the higher alkyl derivatives were hypotensive (25, 26). All of the derivatives showed effects upon body temperature and respiration. One of these (VII, R_1 = CH_3, R_2 = $CH_2CH_2CH_3$) was particularly interesting because it showed marked anti-5-hydroxytryptamine activity as well as optimum adrenolytic action and minimum respiratory depression. It was also hypothermic in rabbits, the opposite of the effect of the unsubstituted amine.

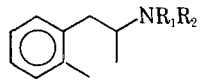
Kraushaar (27) studied a series of 6-methoxy-substituted derivatives (XII) and found them to have oxytocic activity. The parent amine (XII, R_1, R_2 = H) showed the strongest oxytocic action with the least side effects.



XII



XIII

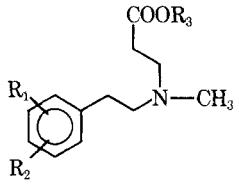


XIV

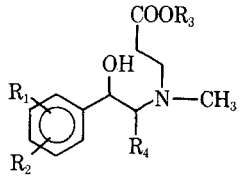
Cymerman-Craig *et al.* (28) prepared related compounds of types XIII and XIV, in which the saturated (C) ring was opened and where R_1 and R_2 were H or small alkyl groups. Work was suspended in this series when the derivatives were not found to be active.

Derivatives similar to XIII and XIV, in which the amino nitrogen bears more complex substituents, have, however, shown activity. Baltzly and his coworkers (29, 30) found that esters of types XV and XVI exhibited oxytocic action when the rings contained methoxy substituents (R_1, R_2 = OCH_3). The compounds without ring substituents were inactive, and the disubstituted derivatives were approximately 10 times as potent as the monosubstituted ones (29). The disubstituted derivatives had only 5–10% of the oxytocic activity of ergonovine. In the series containing hydroxyl substituents and chain branching (XVI), the addition of the hydroxyl appeared to increase the oxytocic action (30).

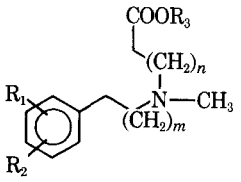
The effects of varying the distance between the nitrogen and the ring and that between the nitrogen and the carbonyl were studied in compounds of type XVII (31). Compounds of type XVII, where m = 1 and n = 0,



XV



XVI



XVII

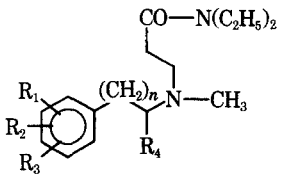
were inactive, indicating that at least two carbons must separate the amine and ester functions. Compounds with more than two carbons between the nitrogen and the carbonyl were also active, however. Lack of appropriate compounds limited the study of the distance between the nitrogen and the ring, but benzyl derivatives (XVII, $m = 0$) were inactive. In all cases, the ester substituent (R_3) did not appear to be critical.

Compounds of general structure XVIII were evaluated as cholinesterase inhibitors (32). Compounds with none, one, two, and three methoxy ring substituents (R_1, R_2, R_3), where R_4 = H or CH_3 and $n = 0$ or 1, were tested; although all were found to have some activity, none was as active as LSD.

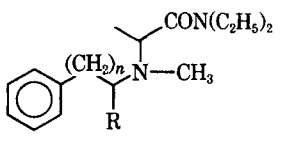
Compounds of type XIX as well as simple derivatives of type XX were also tested for cholinesterase inhibition (33). In the series of type XIX, the distance between the nitrogen and the ring appeared to be important since XIX (R = H, $n = 1$) was 10 times as active as XIX (R = H, $n = 0$). Although the simple derivatives of type XX were active, both series showed activity on the order of one one-thousandth that of LSD.

Plieninger (34) tested compounds of types XXI, XXII, and XXIII. All of these showed oxytocic activity, but the series with the double bond in the nitrogen-bearing ring (XXIII) had markedly higher potency.

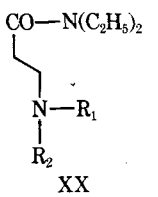
Compounds of general structure XXIV, which can be viewed as lysergic acid analogs, in which the indole system has been replaced by pyridine and where rings C and D are open, were found to have no anti-5-hydroxytryptamine activity (35). Two of these did, however, show a slight but significant 5-hydroxytryptamine potentiating action (XXIV, R_1 = H, R_2 = OEt, NEt_2).



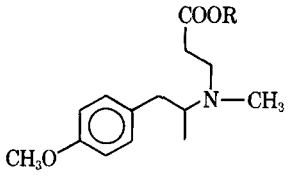
XVIII



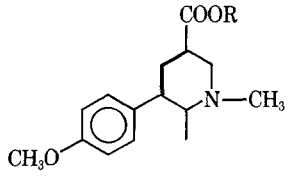
XIX



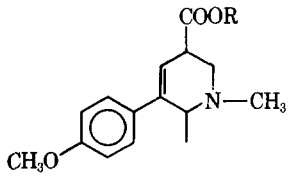
XX



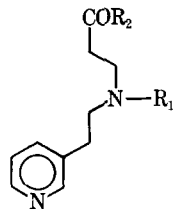
XXI



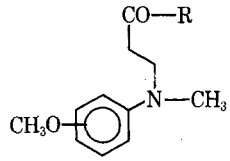
XXII



XXIII



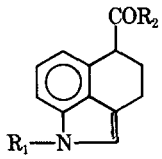
XXIV



XXV

In all of the series considered up to this point, the amino nitrogen was separated from the aromatic ring by a carbon chain. A series of compounds (XXV) has been tested in which the nitrogen is attached directly to the aromatic ring (36). The ethyl ester, amide, and diethylamide of XXV, with both *meta*- and *para*-methoxy substituents, were tested for anti-5-hydroxytryptamine activity. All except the amides in the *para*-series were found to be active but were weak compared to LSD. In addition, the ester in the *meta*-series showed anticholinergic action.

A series of compounds (XXVI) which contain the A, B, and C rings of lysergic acid was prepared, presumably for pharmacological evaluation, but testing results were not reported (37). The compounds were derived from intermediates of a new synthesis of lysergic acid recently reported (38).

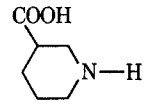


R_1 = H, CH_3CO
R_2 = OH, OCH_3, $N(C_2H_5)_2$

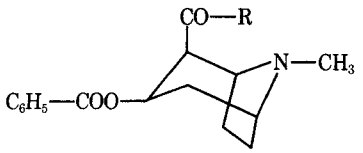
XXVI

The D ring of lysergic acid can be viewed as a piperidine-3-carboxylic acid (XXVII) derivative. Many derivatives of XXVII have been prepared and evaluated for biological activity, and these could be considered analogs of lysergic acid. Among the first such compounds to be tested were derivatives of the alkaloid cocaine (XXVIII, R = OCH_3). The diethylamide (XXVIII, R = NEt_2) was compared with cocaine and found to be a longer acting local anesthetic but was four times as toxic to mice as cocaine (39). The diethylamide specifically inhibited the effects of 5-hydroxytryptamine on rat uterus, whereas cocaine inhibited both 5-hydroxytryptamine and oxytocin in the same system.

Lasslo *et al.* (40, 41) prepared a series of piperidinecarboxylic acid derivatives of types XXIX, XXX, XXXI,

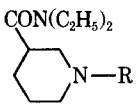


XXVII

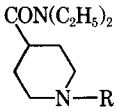


XXVIII

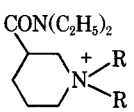
and XXXII, including some of types XXIX and XXX with ring unsaturation. The activities, if any, of these compounds were not reported, however.



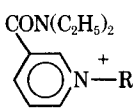
XXIX



XXX



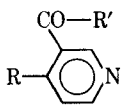
XXXI



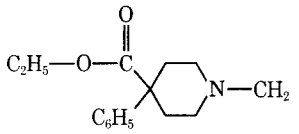
XXXII

Quintana and Schrader (42) extended this series with some additional derivatives like XXIX and XXX. These included some with different amide substituents and some dimeric compounds, but again no testing results were reported.

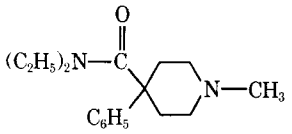
Lehrfeld (43) prepared a series of 6-substituted nicotinic acid derivatives (XXXIII) as analogs of lysergic acid, but no additional information has been published on these compounds.



XXXIII



XXXIV



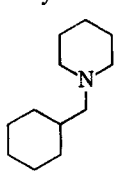
XXXV

The occurrence of psychic side reactions with meperidine (XXXIV) led Lasslo and Waller (44) to prepare the diethylamide derivative XXXV. In preliminary testing, both XXXIV and XXXV were found to have CNS effects.

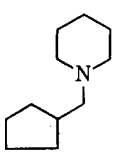
The work on analogs of lysergic acid has led to smaller and smaller fragments that show biological activity. Such simple derivatives as the *N*-substituted piperidines XXXVI, XXXVII, and XXXVIII show oxytocic activity of the order of one-tenth that of methylergonovine (45). Other simple compounds that show oxytocic activity are the tetrasubstituted glycinamides (XXXIX). An extensive series of these were tested; those with ethyl, propyl, and butyl substituents were found to be the most active (46).

Some completely open-chain analogs of lysergic acid (XL, R = OEt, NEt_2) were reported, but no testing results were given (47).

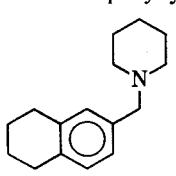
Comparatively lesser attention has been directed toward synthesis of the more complex and polycyclic



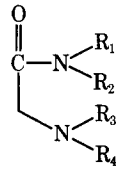
XXXVI



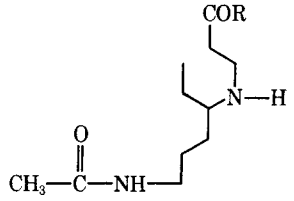
XXXVII



XXXVIII



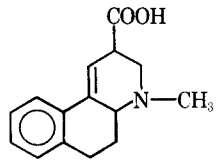
XXXIX



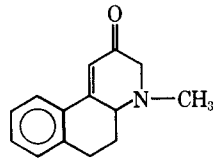
XL

analogs of lysergic acid, but recent developments and some as yet uncompleted efforts in this area deserve mention. An interesting analog of lysergic acid would be 2-carboxy-4-methyl-1,2,3,4,4*a*,5,6-hexahydrobenzo-[*f*]quinoline (XLI), lacking only the pyrrole nucleus; naturally, this molecule has attracted the attention of several groups of workers.

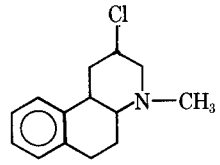
The crucial hexahydrobenzo[*f*]quinoline (XLII) necessary for the synthesis of XLI was assembled independently by Leemann and Fabbri (48) and Cymerman-Craig *et al.* (49), using a reaction scheme reminiscent of the original synthesis of lysergic acid by Kornfeld *et al.* (50). The ketone, XLII, has been reduced and converted



XLI



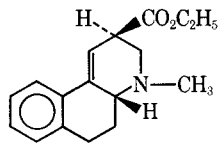
XLII



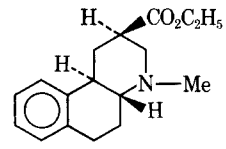
XLIII

to halide XLIII, but all attempts to displace the halogen in order to attach the carboxyl have been unsuccessful[1]. However, the desired acid XLI was obtained by Horii *et al.* (51), utilizing an entirely different synthetic approach, and was found to possess marked oxytocic activity. These workers claimed XLI and its derivatives as uterine-contracting agents in several patents (52).

These workers have prepared all stereoisomers of XLI and its 10,10*a*-dihydro derivative (53) and also their diethyl, *n*-butyl, and 2-hydroxyisopropylamide derivatives (54). The most potent oxytocics that have



XLIV



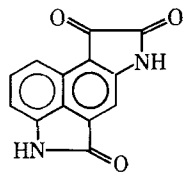
XLV

appeared from this work are XLIV and XLV, which show one-sixteenth and one-fifteenth the activity of ergometrine (51).

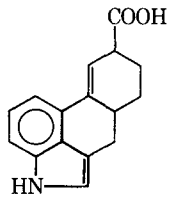
Godshall (55) attempted to synthesize compounds of a steroid nature incorporating features of the lysergic

[1] J. Cymerman-Craig, personal communication, September 1968.

acid structure. It is hoped that this "marriage" of the lysergic acid structure and the steroids might yield compounds that cross the blood–brain barrier more easily than do the normal steroids. Thus far, XLVI is the only related compound reported, and no testing results in this area are yet available[2].



XLVI



XLVII

The authors' efforts toward the sulfur analog (I*a*) of lysergic acid have progressed to the three-ring stage (56), but attempts to add the D ring have not yet been successful. The synthesis of nor-7-deazalysergic acid (XLVII) was recently described, along with the 10,10*a*-dihydro derivative (57), but again no biological activity studies on these compounds or derivatives are yet available.

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RESEARCH ARTICLES

Investigation of Semisolid Lipophilic Preparations by Small Strain and Continuous Shear Viscometry and Their Application to Texture Profile

B. W. BARRY and A. J. GRACE

Abstract □ The effects of grade variation of white soft paraffin on the rheological properties of paraffin ointment BP, simple ointment BP, and some nonpharmacopoeial paraffinic and emulsion preparations were investigated by continuous shear and creep viscometry. The creep curves were analyzed to determine discrete and continuous spectra of retardation times and transformed mathematically to determine dynamic parameters such as storage and loss compliances. The elastic properties of the white soft paraffins influenced the properties of preparations made with these paraffins. There was no general correlation between viscosity data for the preparations, possibly due to some specific interaction such as that described for hard paraffin and liquid paraffin. Dilution of white soft paraffin with liquid paraffin shortened the retardation times but did not significantly alter the type of retardation spectrum involved (bimodal), while emulsification radically altered the retardation mechanisms. The utility of the types of viscometry and various analyses of the creep curves is discussed in terms of correlation with sensory data for texture profile evaluation. It is concluded that small strain experiments are important in texture profile evaluation.

Keyphrases □ Ointments—paraffin effect on rheological properties □ Paraffin, soft—rheological effect, ointments □ Rheology—ointments, emulsions, soft paraffin □ Viscometry—continuous shear, creep, oscillatory □ Viscoelasticity—ointments, soft paraffin, emulsions

Manufacturers of therapeutic and cosmetic semisolid preparations must be able to reproduce the consistency of their products and to ensure that new products are of a consistency acceptable to the consumer. By correlating sensory data with rheological data, a texture profile may be determined, an important concept which has been developed in recent years in the food industry. Many of the parameters, such as viscosity, elasticity, and ductility, which contribute to a subjective assessment of consistency may be measured rheologically. Sherman (1) recently discussed the textural profile and evaluation of pharmaceutical products for external application, and he reviewed the published data correlating instrumental and sensory evaluations of textural properties.

Many rheological techniques are available for evaluation of pharmaceutical materials. Continuous shear viscometry has been a popular approach (2–4); in particular, the Ferranti–Shirley cone and plate viscometer with an automatic flow curve recorder unit and X-Y plotter has been used (5–9). However, the information derived from continuous shear experiments is of limited use in characterizing complex rheological properties such as viscoelasticity, because the high rates of shear involved often cause breakdown of the viscoelastic structure of the sample. To examine a viscoelastic material in its ground state, approximating to zero shear conditions, it is usual to employ small strain experiments such as creep (10) and oscillatory (11) methods.

It was shown that the rheological properties of white soft paraffin BP may vary considerably from grade to grade (10), and a brief discussion of the effect of such variation on the industrial use of the materials was given. The properties of a sample depend on the source of the crude petroleum, the type and degree of refining, blending processes, and the mechanical and thermal history of the material (12–14). Such variation in the properties of white soft paraffin is reflected in the properties of formulations containing significant amounts of this material. The purposes of the present work are: (*a*) to investigate the effects of grade variation of white soft paraffin on the rheological properties of selected lipophilic formulations, and (*b*) to indicate various rheological techniques and methods of experimental data treatment that are available and may be of use in texture profile studies of pharmaceutical preparations.