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## Biochemorphic Aspects of Paraldehyde and Certain Acetals.*

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Paraldehyde has many features recommending it as a hypnotic agent. Conversations with Prof. C. W. Muehlberger and the late Prof. A. S. Loevenhart suggested a preliminary survey, at least, of the biochemorphology of paraldehyde and chemically related substances in the effort to determine whether or not there might be promise of finding a compound in the series with properties approaching more closely to those of an ideal clinical soporific. The compounds so far secured have been studied before,[1] but separately and not as a series. Acetal and methylal received clinical trial but were considered unsatisfactory.[2]

In Table I is a list of the compounds we investigated, with their structural formulae, certain physical characteristics, and toxicity data. The latter were obtained by administration to rabbits by stomach tube of dilute water emulsions of the respective substances. Table II is a summary of the comparative depressant action of these aldehyde derivatives as determined in 150 experiments on rabbits, in which observations were made and recorded by methods modified from those described by Magnus.[3]

These related compounds have equal rapidity and duration of action when given in doses of equal effectiveness. They are all excreted by the lungs in considerable amounts. Peripheral vasodilatation and increased heart rate are produced by all of them, but their effect on pupil size is inconstant. As may be seen from the summary data presented in Table II, none of these agents is particularly analgesic in action.

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[1] V. Cervello, *Arch. Exp. Pharmakol. u. Path.*, 1882, **16**, 265; V. Mering, *Berlin Klin. Wchnschr.*, 1882, **19**, 648; Langgard, A., *Therap. Monatsh.*, 1886, **24**; Personali, E., *J. de Pharm. et de Chim.*, 5th series, 1887, **15**, 33; Richardson, B. W., *Asclepiad*, 1888, **5**, 135; Dieballa, G., *Arch. Exp. Pharmakol. u. Path.*, 1894, **34**, 137.

[2] Peretti (of Andernach), *Der Irrenfreund*, 1883, **25**, 65.

[3] Magnus, R., *J. Pharm. Exp Therap.*, 1926, **29**, 35.

TABLE I.
Oral Toxicity of Paraldehyde and Certain Acetals in Rabbits.

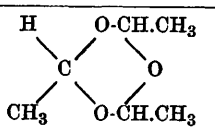
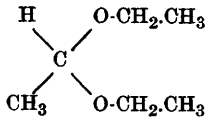
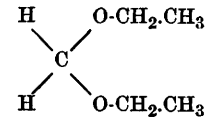
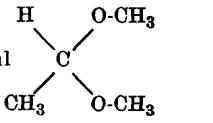
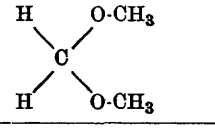
| Substance | Formula | Mol. Wt. | Sp. Gr. | Boiling Point | Vol. of $H_2O$ to dissolve one volume | Mortality Ratio millimols per kg. |
|---|---|---|---|---|---|---|
| Paraldehyde |  | 132 | 0.99 | 124°C. | 8 | 3/10 at 20<br>6/10 " 25 |
| Acetal |  | 118 | 0.82 | 104°C. | 18 | 0/8 " 25<br>2/5 " 28.5<br>5/8 " 30 |
| Ethylal |  | 104 | 0.85 | 85°C. | 11 | 0/5 " 15<br>2/8 " 20<br>4/8 " 25 |
| Dimethyl-acetal |  | 90 | 0.86 | 63°C. | 4 | 0/5 " 45<br>2/4 " 50<br>7/8 " 60 |
| Methylal |  | 76 | 0.86 | 41°C. | 3 | 1/5 " 60<br>4/7 " 75 |

TABLE II.
Summary of Certain Pharmacological Actions of Certain Paraldehyde Derivatives Administered in Dilute Water Emulsion by Stomach Tube to Rabbits.

| | Methylal | Dimethyl-acetal | Ethylal | Acetal | Paraldehyde |
|---|---|---|---|---|---|
| Average Lethal Dose ($LD_{50}$) in millimols per kg. | 75 | 50 | 25 | 30 | 25 |
| Average maximum percentage depression normal respiratory rate at ½ average lethal dose | 60 | 10 | 60 | 10 | 70 |
| % of average lethal dose causing complete loss of: | | | | | |
| 1. Posture | 80 | 120 | 80 | 100 | 50 |
| 2. Progression | 60 | 100 | 60 | 67 | 50 |
| 3. Righting reflex | 80 | 120 | 80 | 100 | 50 |
| 4. Response to various stimuli | 100 | 120 | 80 | 100 | 90 |
| 5. Corneal reflex | 100 | 120 | 100 | 100 | 75 |

Some conclusions can be drawn concerning the biochemorphic‡ aspects of these substances. Very striking is the difference in the effect of lengthening the carbon chain on the central, and on the terminal carbon atoms. The substitution of a methyl group on the central carbon atom reduces the effectiveness, whether the terminal groups be methyl or ethyl. The change is greater in the case of terminal methyl groups, as methylal and dimethylacetal differ more in effectiveness than do ethylal and acetal. With lengthening of the terminal carbon chain, the transition from methylal to ethylal is accompanied by a greater increase in toxicity than is the transition from dimethylacetal to acetal. However, the increase in hypnotic activity is not the same in the 2 cases, so that while acetal is more effective than dimethylacetal (in equal percentage of lethal dose), methylal and ethylal are about equally effective. The result of an ether linkage transforming acetal into paraldehyde is also striking. While there is an increase in toxicity of only about 20%, there is a much greater increase in hypnotic activity so that paraldehyde is about twice as effective as acetal. These considerations suggest that it would be desirable to investigate the hypnotic action of alpha-trioxymethylene, and the corresponding oxycyclic derivative of ethylal.

Though our findings indicate that none of the compounds studied here equals paraldehyde in value as a hypnotic, these observations may assist in the search for an improvement on it.

‡ The adjective "biochemorphic" has been coined to connote *that pertaining to the relationship between chemical constitution (including physical properties) and pharmacologicl (physiological or biological) action.* Such a term is badly needed especially when the restricted term "chemotherapy" (Ehrlich) is becoming loosely employed to cover this whole field (Dyson, G. M., The Chemistry of Chemotherapy, London, 1928). The noun indicating *the study of the relationship between chemical constitution and biological activity* would be "biochemorphology." The literal meaning of the term, *knowledge of living chemical structure,* really implies the fundamental objective of investigations on the relationships between chemical constitution and biological activity, so that there is no essential conflict with its technical meaning. "Pharmakomorphic" was also suggested for the use indicated (by Dr. T. E. Reynolds), but was not thought to be quite as satisfactory as "biochemorphic".