compounds is due only to their low K^{Ca}_{CaL}-values or also to high K^{Co}_{CoL}-values.

The chelators show different patterns of effectiveness, that is, the differences in effectiveness are more pronounced in relation to the kidney than in other organs: EDTA, DTPA, TTHA, CyA are not able to reduce the retention of ^{60}Co by the kidney, whereas the other compounds were found to be markedly effective. The reasons for this discrepancy are not yet fully understood. Tentatively, different metabolic behaviour of particular chelates as well as the formation of ternary complexes in the kidneys (which are known to possess a high concentration of SH-groups[10]) can be assumed.

From the practical point of view the therapeutic use of BADS and BATE in cases of internal contamination with ^{60}Co is obvious. However, the highest significance must be attributed to D-dimethylcysteine (commonly known as penicillamine). Its high efficacy compares favourably with BADS and BATE. Our experimental data show that it can be administered orally without loss of effectiveness. Finally, its low toxicity must be stressed. More detailed studies on the effectiveness of these and other chelators, as influenced by several factors and, in particular, the time of their administration, are now under way and will be published elsewhere.

The generous supply of the polyamino-acids by J. R. Geigy AG., Basle, and of D-dimethylcysteine by Heyl and Co., Berlin, is gratefully acknowledged.

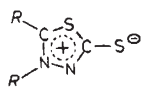
Du Khuong Lê

Institut für Strahlenbiologie,
Kernforschungszentrum,
Postfach 947,
Karlsruhe, Germany.

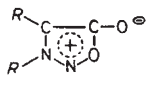
[1] Eybl, V., Sýkora, J., and Köcher, Z., *Arch. Exp. Path. Pharm.*, **236**, 13 (1959).
[2] Foreman, H., *Metal-Binding in Medicine* (J. B. Lippincott, Philadelphia and Montreal, 1960).
[3] Semenov, D. I., and Treguberko, I. P., *Trud. Inst. Biol., Akad. Nauk U.S.S.R., Ural. Filial.*, **9**, 20 (1957).
[4] Sivaramakrishnan, V. M., Sekhara Varma, T. N., Brahmanandam, S., and Nagarajan, B., *Proc. Soc. Exp. Biol. and Med.*, **11**, 817 (1962).
[5] Sivaramakrishnan, V. M., Sreenivasan, Sekhara Varma, T. N., and Brahmanandam, S., *Nature*, **193**, 1195 (1962).
[6] Rubanovskaya, A. A., *Mat. Toks. Radioact. Vech.*, **2**, 154 (1960).
[7] Anderegg, G., Nägeli, P., Müller, F., and Schwarzenbach, G., *Helv. Chim, Act.*, **42**, 827 (1959).
[8] Schwarzenbach, G., Gut, R., and Anderegg, G., *Helv. Chim. Act.*, **34**, 576 (1951).
[9] Catsch, A., *Radioactive Metal Mobilization in Medicine* (Ch. C. Thomas, Springfield, 1964).
[10] Ellman, G. E., *Arch. Biochem. Biophys.*, **82**, 70 (1959).

A New Class of Antimicrobial Agents

The mesoionic 1,3,4-thiadiazoles, I, were first reported by Busch[1], who assigned a bicyclic structure to the compounds.



(I)



(II)

Schoenberg[2] later re-examined the structure of Busch and offered a resonance hybrid structure, now accepted as being typical of a large group of heterocycles described as being mesoionic[3]. We became interested in the mesoionic 1,3,4-thiadiazoles as a natural extension of our interest in the pharmacology and pharmaceutical chemistry of the sydnones II[4–7]. It occurred to us that since the two ring systems are isoelectronic (that is, being mesoionic they both possess an aromatic, positively charged, 5-membered ring, and a balancing negative charge on an exocyclic atom) the possibility might exist that the two ring systems could also be bioisosteric. That is, the ring itself may behave as a pharmacologically active functional group and that this already expressde similarity between the ring systems may impart similar pharmacological activity. A more conservative speculation would be that perhaps the mesoionic 1,3,4-thiadiazole ring system would have some prominent pharmacological activity.

Accordingly, a number of these compounds were synthesized in our laboratory. The synthesis of the *C*-ethyl, *N*-phenyl derivative will be used as a typical procedure. Phenylhydrazine (32 g, 0·3 mole) was dissolved in 350 ml. of absolute ethanol and carbon disulphide (24 g, 0·3 mole) was added with stirring. A precipitate rapidly formed. This was not isolated but was treated directly with an ethanolic solution of potassium hydroxide (17 g in 120 ml., 0·3 moles). The precipitate dissolved and, after stirring, a precipitate of potassium phenyldithiocarbazinate formed in 85 per cent yield, m.p. 144°–46°. This acid salt (22 g, 0·1 mole) was suspended in 500 ml. of toluene and the slurry warmed to 60°. To this was added propionyl chloride (9·3 g, 0·1 mole) at a slow rate, maintaining the temperature at 60°. After the addition, the reaction mixture was cooled and the 4-phenyl-5-ethyl mesoionic 1,3,4-thiadiazole precipitate removed and recrystallized from ethanol to give a 5 per cent yield, m.p. 191°–192° (found: N, 53·84; S, 28·96). The nomenclature recommended by Katritzky for mesoionic compounds[8] becomes anhydro-4-phenyl-5-ethyl-2-thio-1-thia-3,4-diazolinium thiol.

In the course of a broad screening of these compounds for potential medicinal activity we assayed them for antibacterial activity by the standard disk method against *Staphylococcus aureus*, *Diplococcus pneumoniae* and *Escherichia coli*. Disks saturated with these compounds were incubated with brain heart infusion agar plates of the organisms and observed at 24- and 48-h intervals for zones of inhibition of growth. Penicillin was used as an antibacterial reference. Four of the 4-phenyl derivatives, namely, the 5-methyl, 5-ethyl, 5-isopropyl and the 5-propyl, were found to produce significant zones of growth inhibition of *S. aureus* and *D. pneumoniae*. The extent of inhibition was the same as that produced by the penicillin reference. The effect on the *E. coli* was minimal.

Preliminary pharmacological tests indicated a low order of acute intraperitoneal toxicity in mice. The acute median lethal dose was found to be greater than 500 mg/kg for the four compounds cited here.

These investigations indicate that these compounds might be safe antibacterial agents against at least some Gram-positive organisms.

Lemont B. Kier
Matthew C. Dodd
Paul Sapko

College of Pharmacy,
Ohio State University,
Columbus.

Thomas G. Stewart

College of Pharmacy,
University of Florida,
Gainesville.

[1] Busch, M., *Ber.*, **28**, 2635 (1895).
[2] Schoenberg, A., *J. Chem. Soc.*, 824 (1938).
[3] Baker, W., and Ollis, W. D., *Quart. Rev.*, **11**, 15 (1957).
[4] Kier, L. B., and Dhawan, D., *J. Pharm. Sci.*, **51**, 1058 (1962).
[5] Dhawan, D., and Kier, L. B., *J. Pharm. Sci.*, **53**, 83 (1964).
[6] Kier, L. B., Dhawan, D., and Fregly, M. J., *J. Pharm. Sci.*, **53**, 677 (1964).
[7] Fregly, M. J., Kier, L. B., and Dhawan, D., *Tox. and App. Pharmacol.*, **6**, 529 (1964).
[8] Katritzky, A. R., *Chem. and Indust.*, 521 (1955).

© 1964 Nature Publishing Group