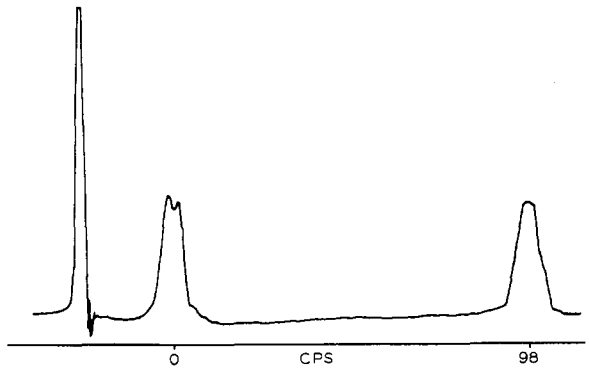

Fig. 1.—Proton nuclear magnetic resonance spectrum of 1.5 *M* dipotassium *threo*-3-deuterio-DL-malate in D_2O at 60 Mc. The magnetic field increases from left to right. The intense line on the left is due to H_2O in the D_2O.

configuration was assigned to I. In further work,[1] the high-resolution n.m.r. spectra of I, malic acid and their salts were examined in D_2O solution. The above assignment of configuration was accepted, and the results showed that either the relative magnitude of coupling constants of hydrogens on adjacent carbons were in the reverse order to those found by Lemieux, *et al.*[4] ($J_{trans} > J_{gauche}$), and recently confirmed,[5-9] or the two carboxyl groups of malic acid in solution were *gauche* to one another. As neither of these possibilities was attractive, it seemed more plausible that the original assignment[2] of configuration to I was incorrect, especially as the assumption was made that the two carboxyl groups of *crystalline* I were *trans*.[10]

We now report an unambiguous synthesis of *threo*-3-deuterio-DL-malic acid (II). This is shown *not* to be the DL-form of I. I must therefore have the *erythro* and not the *threo* configuration previously assigned.

Reduction of 3,4-epoxy-2,5-dimethoxytetrahydrofuran[11] with lithium aluminum deuteride gave 4-deuterio-3-hydroxy-2,5-dimethoxytetrahydrofuran (III), which had the same retention time on gas chromatography as undeuterated III.[11] Since $LiAlH_4$ is known to open epoxides in a *trans* fashion,[12] III should have the deuterium atom *trans* to the hydroxyl group.[13] Hydrolysis of III with 0.1*N* HCl and then oxidation with bromine in the presence of calcium carbonate gave II, initially isolated as the calcium salt, m.p. 125–126°, mixed m.p. with DL-malic acid, 125–126° [*Anal.* Calcd. for $C_4H_5DO_5$: C, 35.56; H and D, 5.22. Found: C 35.86, H and D (1 D assumed), 4.94].

The n.m.r. spectrum (60 Mc.) of the dipotassium salt of I in D_2O is shown in Fig. 1. It is different[14] from the spectrum[1] of the dipotassium salt of I. Hence I is the *erythro* isomer, and the addition of water to fumaric acid is *trans*, and not *cis*, as had been deduced previously.[2] The spectrum in Fig. 1 is that expected if the two carboxylate groups of the di-anion of II are *trans* and the coupling constants have their normal values.[4-9] Work is at present under way to synthesize the DL-form of I.

(4) R. U. Lemieux, R. K. Kullnig, H. G. Bernstein and W. G. Schneider, *ibid.*, **79**, 1005 (1957); **80**, 6098 (1958).

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(8) C. N. Banwell, A. D. Cohen, N. Sheppard and J. J. Turner, *Proc. Chem. Soc.*, 266 (1959).

(9) F. A. L. Anet, *ibid.*, 327 (1959).

(10) The *gauche* conformation cannot be ruled out because of the strong lattice forces present in the solid state.

(11) J. C. Sheehan and B. M. Bloom, THIS JOURNAL, **74**, 3825 (1952).

(12) E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Editor, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 61.

(13) The configuration at C_2 and C_5, which is immaterial for the present purpose, will be discussed in a future publication.

(14) After correction for the fact that the spectrum given in ref. (1) was taken at 40 Mc. The n.m.r. spectra of the L and DL forms of the same diastereoisomer would be expected to be identical in solution. The spectrum in Fig. 1 is exactly that predicted for the *erythro* isomer on the basis of the (incorrect) assignments of ref. 1, both as regards chemical shifts and coupling constants. The assignments in ref. 1 become correct if, in the terminology used in that paper, H_b and H_c are interchanged.

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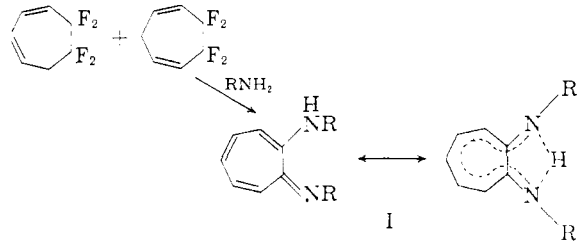
RECEIVED DECEMBER 31, 1959

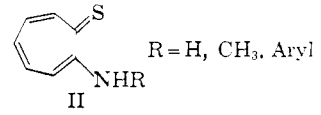
NOVEL ANALOGS OF TROPOLONE

Sir:

An attractive synthesis of tropolone by hydrolysis of the tetrafluorocycloheptadienes accessible from cyclopentadiene and tetrafluoroethylene was reported recently from this Laboratory.[1] It has now been found that the tetrafluorocycloheptadienes also serve as intermediates to the little-studied 1-amino-7-imino-1,3,5-cycloheptatrienes I, the nitrogen analogs of tropolone.

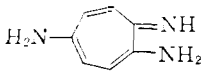


The N,N′-dialkyl and -diaryl derivatives are stable, highly colored compounds that exhibit aromatic-like reactivity similar to that of tropolone. Furthermore, the aminoimines I are convertible by reaction with hydrogen sulfide to the previously unreported 1-amino-7-thioxo-1,3,5-cycloheptatrienes II.

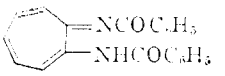


Reported examples of 1-amino-7-imino-1,3,5-cycloheptatrienes include the compounds III and IV.

(1) J. J. Drysdale, W. W. Gilbert, H. K. Sinclair and W. H. Sharkey, THIS JOURNAL, **80**, 3672 (1958).



III



IV

The 5-amino derivative III was obtained by nitrosation of tropolone and then oximation and reduction.[2] Very recently the dibenzoyl derivative IV of 1-amino-7-imino-1,3,5-cycloheptatriene was prepared from 1,3-diazaazulene by reaction with benzoyl chloride.[3] Attempted hydrolysis of IV yielded 2-phenyl-1,3-diazaazulene with either acidic or basic catalysts.

The aminoimines I were obtained in 30–80% yield by reaction of the tetrafluorocycloheptadienes with primary amines and with ammonia.

I (R = H): (hemihydrate), 30% yield of yellow crystals from ether, m.p. 112–113°. *Anal.* Calcd. for $C_7H_8N_2 \cdot 1/2H_2O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.01; H, 6.93; N, 21.54.

I (R = H): CF_3COOH salt. *Anal.* Calcd. for $C_7H_8N_2 \cdot CF_3COOH$: N, 11.96. Found: N, 11.92.

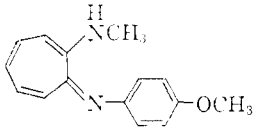
I (R = CH_3): 75% yield of yellow crystals from methanol, m.p. 66.5–67°. *Anal.* Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.91. Found: C, 73.05; H, 8.26; N, 18.92.

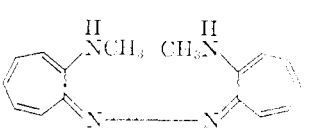
I (R = *p*-ClC_6H_4): 70% yield of red crystals, m.p. 168–170°. *Anal.* Calcd. for $C_{19}H_{14}N_2Cl_2$: C, 66.87; H, 4.13; N, 8.21. Found: C, 66.71 H, 4.22; N, 8.13.

The infrared and ultraviolet spectral data are interpreted as being consistent with the proposed structures. Furthermore, nuclear magnetic resonance studies indicated that the nitrogen atoms of the dimethylaminoimine I (R = CH_3) are identical. Thus, either the hydrogen atom is shared equally between the two nitrogen atoms or there is rapid exchange of hydrogen between the atoms.[4]

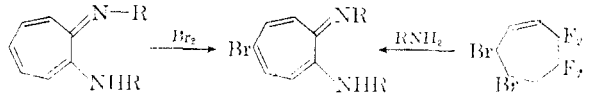
The adjacency of the nitrogen atoms was further established by formation of stable chelates with Ni^{++}, Co^{++}, and Cu^{++} ions, and by conversion of the aminoimines to tropolone.

Although stable to strong aqueous acids or bases, the dimethylaminoimine I (R = CH_3) reacted with amines in dioxane containing a catalytic amount of acetic acid to yield new aminoimines derived by displacement of the methylamino group.





Ring substitution has been effected by various electrophilic reagents. In contrast to tropolone, which gives a mixture of mono-, di- and tribromo derivatives, reaction of I (R = *p*-ClC_6H_4) with one mole of bromine gave a single isomer in 90% yield, red crystals, m.p. 181–182°. It was established indirectly that substitution had occurred at the 4-position by condensation of 3,4-dibromo-6,6,7,7-tetrafluorocycloheptene with *p*-chloroaniline to obtain a monobromoaminoimine identical with the product obtained from the bromination reaction.



The 1-amino-7-thioxo-1,3,5-cycloheptatrienes II were obtained by action of hydrogen sulfide on the aminoimines I. The N-substituted derivatives are stable compounds, soluble in dilute acids and insoluble in strong bases. Nuclear magnetic resonance studies of the nitrogen atom indicate that there is little, if any, contribution to the structure by the iminothiol tautomer.[4] Chelate derivatives were formed with Cu^{++}, Ni^{++} and Co^{++} ions.

II (R = H), 60% yield of yellow crystals from methanol, m.p. 137–138.5°. *Anal.* Calcd. for C_7H_7NS: C, 61.27; H, 5.15; N, 10.21; S, 23.37; mol. wt., 137.2. Found: C, 61.20; H, 5.15; N, 9.94; S, 23.40; mol. wt., 122.

The corresponding N-methyl and N-*p*-tolyl derivatives have been synthesized and the observed analytical data are in accord with the proposed structures.

These and other reactions of the aminoimines I and the aminothioxocycloheptatrienes II will be fully reported shortly.

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RECEIVED JANUARY 9, 1960

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(3) I. Murata, *Bull. Chem. Soc. Japan*, **32**, 841 (1959).

(4) We are indebted to Drs. W. D. Phillips and D. B. Chesnut for this determination and interpretation.

QUANTITATIVE ASPECTS OF NUCLEATION IN CALCIUM PHOSPHATE PRECIPITATION[1]

Sir:

After many many years of a single-minded view, prompted primarily by the theories of Robison,[2] a new and different approach to the problem of biologically induced calcification has developed. Currently, it is almost universally recognized that collagen fibers possess the unique property of inducing crystals of calcium phosphate to form.[3,4] This change in viewpoint resulted primarily from a clarification of the solubility properties of bone mineral itself.[5,6] It is now clear that normal serum is highly supersaturated with respect to bone mineral *if solid phase is present* as it always is in the living animal. Bone mineral prototypes (hydroxyapatites) and dead bone powders evince widely varying dissolution products (Ca × P inorganic) which are strongly dependent upon experimental conditions, but rarely if ever are products greater than 10 (Ca × P_i in (mg.%)^2) encountered. Living bone in culture, however, will support higher products[7,8] approaching the physiological (*ca.* 20).

(1) This paper is based on work performed under contract with the United States Atomic Energy Commission at The University of Rochester Atomic Energy Project, Rochester, New York.

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(3) W. F. Neuman and M. Neuman, "The Chemical Dynamics of Bone Mineral," The University of Chicago Press, Chicago, Ill., 1958.

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(7) B. E. C. Nordin, *J. Biol. Chem.*, **227**, 551 (1957).

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