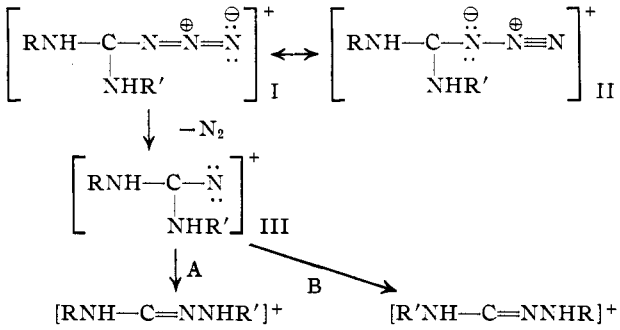
MIGRATION OF NITROGEN IN THE SCHMIDT REACTION

Sir:

From a consideration of the mechanism proposed for the isomerization of substituted 5-aminotetrazoles[1,2] together with a study of the products formed by the acid induced degradation of 5-substituted tetrazoles,[3] we have concluded that guanyl azides can undergo a Curtius or Schmidt type reaction.



Under the conditions used the carbodiimides hydrolyze to carbon dioxide, an amine and a hydrazine. The rearrangement of III involves an interchange in which the electrons are transported to the electronically deficient nitrogen by a nitrogen atom rather than a carbon atom. This has not been previously observed and affords another opportunity for studying the competitive migration aptitudes of groups. The degradation of 5-hydrazinotetrazole[4] in concentrated hydrochloric acid at 170° is an example. Opening of the tetrazole ring[2] yields a guanyl azide where R = NH_2 and R′ = H. Since ammonia is absent in the products, the rearrangement must occur almost exclusively by route A; *i.e.*, the amino group migrates in preference to the hydrazino group. We have found that 5-phenylaminotetrazole (IV) degrades largely to aniline and hydrazine (route A, where R = C_6H_5 and R′ = H): A solution of 0.5 g. of IV in 10 ml. of 85% phosphoric acid was heated at 190–200° for 2.5 hours, cooled, diluted with 10 ml. of water, refluxed for 1.5 hours, re-cooled, partially neutralized, and treated with benzaldehyde. Benzalazine (0.51 g. 79%; m.p. 92–93°) was removed and the solution was made alkaline. Benzalaniline (0.38 g., 68%; m.p. 46–49°) was recovered.

The Schmidt reaction should be capable of extension to the ammonocarbonic acids[5] provided that one of the contributing forms is a carbonium ion. With guanidine the product should be aminoguanidine and experimentally the latter has been recovered in about 1% yield. Ten grams of sodium azide was added portionwise during 2 hours to an agitated slurry of 10.8 g. of guanidine sulfate, 35 ml. of 96% sulfuric acid and 150 ml. of benzene at 25–28°. The temperature was next raised to and held at 40–50° for 4 hours. After the benzene layer was decanted, the acid layer was diluted with water, partially neutralized, shaken with benzaldehyde, neutralized to *p*H 9, and cooled to 5°. The hydrazone was removed, washed with water, extracted with petroleum ether until free of benzalazine, and converted to a picrate (0.3 g., 1%) which alone and in admixture with an authentic sample of benzalaminoguanidine picrate melted at 252–254°. X-Ray powder patterns were identical. Under similar conditions hydrazine and guanidine sulfates do not react to give aminoguanidine.

This extension of the Schmidt reaction will be fully explored.

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(1) W. G. Finnegan, R. A. Henry and E. Lieber, submitted to *J. Org. Chem.*

(2) R. A. Henry, W. G. Finnegan and E. Lieber, accepted for presentation at the 123 National Meeting of the American Chemical Society, Los Angeles, California.

(3) F. R. Benson, *Chem. Revs.*, **41**, 55 (1947).

(4) J. Thiele and H. Ingle, *Ann.*, **287**, 233 (1895).

(5) E. C. Franklin, "Nitrogen System of Compounds," Reinhold Publ. Corp., New York, N. Y., 1935, p. 86.

THE CYCLIZATION OF SQUALENE IN CHOLESTEROL SYNTHESIS

Sir:

The hypothesis that the triterpenoid hydrocarbon squalene is an intermediate in the biological synthesis of cholesterol (I) has recently received direct experimental support.[1,2] It has further been shown[3] that acetic acid, the principal carbon source in cholesterol synthesis, is a precursor also for squalene. The squalene hypothesis can be harmonized with the hitherto known distribution of acetate carbon in cholesterol[4] if one assumes that (a) each isoprene unit of the hydrocarbon contains 3 methyl and 2 carboxyl carbons of acetate, arranged as shown: 

(o = acetate methyl, x = acetate carboxyl); and (b) that in the transformation to sterol, squalene cyclizes as suggested by Robinson[5] (*cf.* Fig. 1, A).

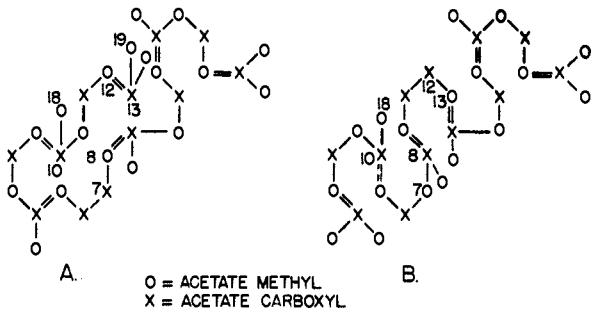

Fig. 1.

We now wish to propose the alternative mechanism shown in Fig. 1 B, as a more likely one to be involved in this transformation. Robinson's scheme provides for a conversion without rearrangement of the carbon skeleton of squalene. In mechanism B, on the other hand, one or more methyl migrations is necessary at some stage for the construction of the quaternary center at C_{13}. As is clear from Fig. 1, cyclization of squalene ac-

(1) R. G. Langdon and K. Bloch, THIS JOURNAL, **74**, 1869 (1952).

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(4) J. Würsch, R. L. Huang and K. Bloch, *ibid.*, **195**, 439 (1952).

(5) R. Robinson, *J. Soc. Chem. Ind.*, **53**, 1062 (1934).