COMMUNICATIONS TO THE EDITOR

THE REARRANGEMENT OF THE ISOMERIC 1,2-DIMETHYLAMINOCHLOROPROPANES. THE SYNTHESIS OF AMIDONE

Sir:

A recent note[1] describes the rearrangement and proof of structure of the new German analgesic drug Amidone, or No. 10820.[1]

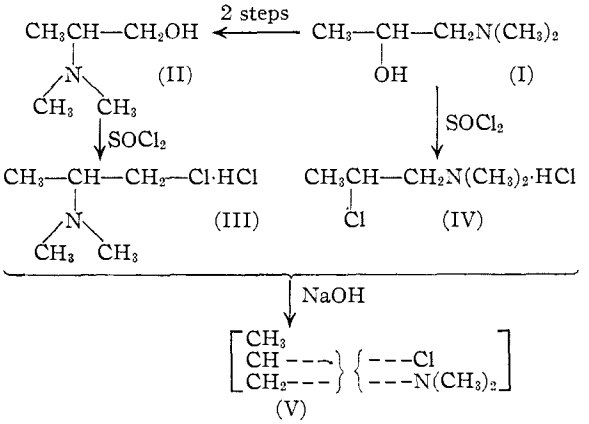
These investigators infer in their note that they have prepared 1-dimethylamino-2-chloropropane which on the sodamide condensation with diphenylacetonitrile rearranges through an ethyleneimmonium ion to give a mixture of 1-dimethylamino-2-methyl-3,3-diphenyl-butanenitrile and 2-dimethylamino-4,4-diphenylpentanenitrile.

Work in this laboratory confirms the physical constants for the two isomeric aminonitriles (low melting isomer m. p. 68.7–69°, high melting isomer 90.0–91.0° compared to 66–67° and 90–91°). Infrared absorption data collected on these two compounds also confirms the structures given by the above investigators.

The chlorination of 1-dimethylamino-2-propanol (I) (b. p. 124.0–124.5°) and 2-dimethylamino-1-propanol (II) (b. p. 145.0–145.5°) with thionyl chloride in anhydrous chloroform yields the corresponding dimethylaminochloropropane hydrochloride salts (III and IV). The latter salt (III) is much more soluble in chloroform than the former (IV). Both salts and a mixture of the two salts change crystalline form on heating and melt sharply 191.0–191.5° indicating that the two salts are isomeric and rearrange to the same compound under the influence of heat.

Isolation of the free bases from their salts gives dimethylaminochloropropanes (V) of identical boiling points (60–63° (110 mm.)) and identical infrared absorption curves confirming that the two products are identical. This product may be either of the two isomeric dimethylaminochloropropanes or an equilibrium mixture of the two. Thus, it appears that the isomeric 1,2-dimethylaminochloropropanes can rearrange, probably through the ethyleneimmonium ion, under the conditions used to isolate the free bases from their salts. The physical properties of this product indicate that it is in a non-polar form as contrasted to an ionic form since it is a liquid that may be distilled and on mixing with alcoholic silver nitrate gives a perfectly clear solution for a few seconds before depositing silver chloride.

The only product isolated from the reaction of the dimethylaminochloropropane (prepared from I) with moist silver oxide was the aminoalcohol II in very low yield (12%). The difficulty incurred in isolating products from this reaction mixture was such as not to preclude the possible presence of I also. These data show that I can be converted to II in low yields, but will not support the structure of the dimethylaminochloropropane, because of the apparent rearrangement possible during the chemical reaction.



Infrared absorption data for the dimethylaminochloropropane, the isomeric aminonitriles and Amidone will be presented later.

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RECEIVED FEBRUARY 7, 1947

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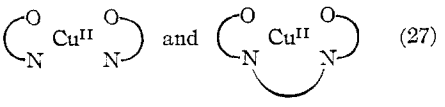
(1) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947).

STABILITY OF MULTIPLY-BONDED MOLECULAR ADDITION COMPOUNDS

Sir:

The marked increase in the stability of Werner complexes in which several coördinating groups are bound together into a "polydentate" structure has been emphasized recently by Calvin and Bailes,[1] who have compared copper chelates, for example, of the types:



(27)

It is pointed out that the precise source of this great increase in stability is as yet impossible to identify, although at least part of the answer may be the increase in entropy involved in the formation of the complex.

A more complete analysis of this entropy factor should provide a better understanding not only of Werner complexes, but also of other types of molecular complexes formed in colloid systems. Consideration of this entropy factor may be sim-

(1) M. Calvin and R. H. Bailes, THIS JOURNAL, **68**, 949–954 (1946).

plified by visualizing the mechanics of the structures involved. For example, where several coördinating groups are held together in a single molecule in such orientation that they can all simultaneously associate with a given metal atom (as in the second copper complex, above), it seems logical that the probability of complete dissociation of the complex is much less than where the coördinating groups are in separate molecules. Where all the groups are in a single molecule, it is necessary for all the coördinate linkages to be broken simultaneously. On the other hand, where the coördinate groups are in separate molecular units, the dissociation of each coördinate linkage can occur independently. This is the commonly accepted explanation for the great stability of polydentate complexes, *e. g.*, copper phthalocyanine.

However, this phenomenon of the increased stability of complexes involving multiple bonds may also play a role in the formation of the less stable complexes involving hydrogen bonding. For example, in the case of proteins, as pointed out by Pauling,[2] the combined effect of a large number of hydrogen bonds between two adjacent close-fitting large molecules may result in a relatively stable association.

Another example of the effect of multiple bonds occurs in connection with tanning phenomena. Russell and Tebbens[3] have shown that the simple esters of gallic acid do not tan leather, but that polyesters, for example mannitol hexagallate, which contain a multiplicity of gallate groups, have the property of combining with hide substance.

This improbability of dissociation of a complex held together through several points of attachment must be directly reflected in the entropy factor involved in the association-dissociation equilibrium. The further elucidation of this effect to the point where the stability of complexes can be predicted quantitatively presents one of the most important objectives yet to be realized in physical and colloid chemistry.

(2) Linus Pauling, *Chem. Eng. News*, **24**, 1375–1377 (1946).

(3) Albert Russell and W. G. Tebbens, Jr., THIS JOURNAL, **64**, 2274–2276 (1942).

CLEVELAND, OHIO R. K. ILER

RECEIVED DECEMBER 12, 1946

5(4)-AMINO-4(5)-IMIDAZOLECARBOXAMIDE, A PRECURSOR OF PURINES

Sir:

An *inhibition analysis* of the effect of purines on the toxicity of sulfanilamide for certain bacteria showed that *p*-aminobenzoic acid functions in the biosynthesis of purines.[1] If sulfanilamide prevents *p*-aminobenzoic acid from functioning as a coenzyme, or from being converted to a coenzyme, involved in the biosynthesis of purines, the precursor preceding this "blocked" enzyme system might be expected to accumulate in the medium during sulfanilamide inhibition when biosynthesis of purines is the limiting factor for growth.

Stetten and Fox[2] isolated an amine formed by bacteria during sulfonamide bacteriostasis and on the basis of chemical studies proposed that the amine was 2-hydroxy-5,6-diaminopyrazine.

The correlation of certain other data suggested to us that 5(4)-amino-4(5)-imidazolecarboxamide, isomeric with 2-hydroxy-5,6-diaminopyrazine, might be a precursor of purines. Since a precursor of purines would be expected to accumulate in the medium under the conditions employed by Stetten and Fox,[2] the amine of Stetten and Fox[2] was isolated by their method for comparison with synthetic 5(4)-amino-4(5)-imidazolecarboxamide and found to be identical with that compound.

Synthesis of 5(4)-amino-4(5)-imidazolecarboxamide was effected by the method of Windaus and Langenbeck[3] except that the free amine instead of the picrate was isolated by hydrogenation of 5(4)-nitro-4(5)-imidazolecarboxamide in absolute ethanol and that Adams platinum catalyst was employed instead of a palladium catalyst. Evaporation of the solvent and recrystallization from absolute ethanol–benzene gave colorless needle-like prisms, m. p. 169.8–171.4° with decomposition when dried at 100° over phosphorus pentoxide. The picrate was prepared by addition of a small amount of alcoholic picric acid to the reduction product. Recrystallization from absolute ethanol gave bright yellow needle-like prisms, m. p. 239.6° with decomposition.

The amine which accumulated during sulfonamide bacteriostasis of *Escherichia coli* was isolated by the procedure of Stetten and Fox[2] as the picrate, bright yellow needle-like prisms, m. p. 239.4° with decomposition, which was converted by their procedure to the free amine, colorless needle-like prisms, m. p. 168.8–170.2° with decomposition when dried at 100° over phosphorus pentoxide.

A mixture of the isolated and synthetic picrates melted at 239.4° with decomposition. The melting points of each picrate and the mixture were determined in Pyrex melting point tubes by inserting the tubes in a bath a few degrees below the decomposition point. Contact with soft glass and time of heating of the picrate affect the decomposition point. A mixture of the isolated amine and synthetic 5(4)-amino-4(5)-imidazolecarboxamide melted at 169.2–170.6° with decomposition.

The results indicate that 5(4)-amino-4(5)-imidazolecarboxamide functions as a precursor of purine bases or is formed from a precursor of purines by the organism and that *p*-aminobenzoic acid or a compound synthesized by the organism from *p*-aminobenzoic acid functions as a coenzym:

(1) Shive and Roberts, *J. Biol. Chem.*, **62**, 463 (1946).

(2) Stetten and Fox, *J. Biol. Chem.*, **161**, 333 (1945).

(3) Windaus and Langenbeck, *Ber.*, **56**, 683 (1923).