A NEW SERIES OF SUBSTITUTED 1,5-DIPHENYL-PYRAZOLINE-3-CARBOXYLIC ACIDS AND THEIR ESTERS

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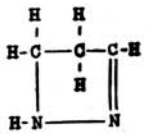
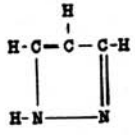
The synthesis of pyrazole and pyrazoline compounds has been carried out in the laboratory of Carthage College and their pharmacology has been studied in certain medical and pharmaceutical laboratories.

A serious problem in the synthesis of pyrazoline compounds is the determination of the ring structure in the final product. In many pyrazoline compounds the ring is not very stable. It tends to go to the more stable pyrazole structure.



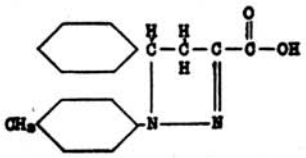
PYRAZOLINE



PYRAZOLE

Because of this tendency it is very important to be able to determine which of the two ring structures is present in the compound under consideration. The elementary analysis of the compound is not adequate as the difference in composition is only two hydrogen atoms. The Knorr[1] test for pyrazolines (intense colorations with ferric chloride, chromates, etc.) is very sensitive and will give the test even when only traces of the pyrazoline compound is present. As a result pyrazole compounds are often considered to be pyrazolines due to traces of pyrazolines as impurities.

One of the series of compounds which is being studied in our laboratory, and which is considered in this paper is the substituted 1,5-diphenylpyrazoline-3-carboxylic acid, in which a methyl group is present in the ortho, meta, or para positions in the 1-phenyl group.



p-Methyl-1,5-diphenylpyrazoline-3-carboxylic acid

These compounds are quite stable. By careful oxidation with permanganate they give the corresponding 1,5-diphenylpyrazole-3-carboxylic acids with distinctly different melting points. These pyrazole acids on reduction with sodium-amalgam[2] and alcohol give the original pyrazoline acids.

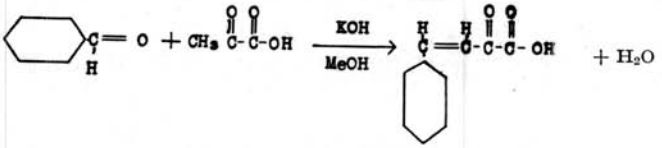
1,5-diphenylpyrazoline-3-carboxylic acid m.p. 196° $\underset{[H]}{\overset{[O]}{\rightleftharpoons}}$

1,5-diphenylpyrazole-3-carboxylic acid m.p. 185°

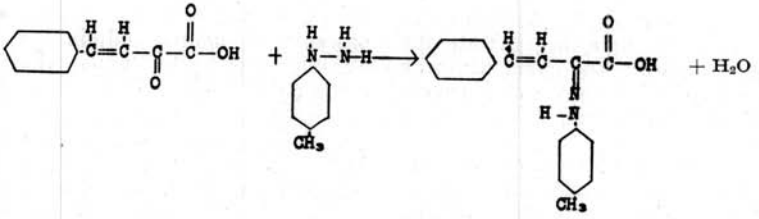
The compounds of this series show marked antipyretic and mild analgesic properties.

The synthesis of the 1-tolyl-5-phenylpyrazoline-3-carboxylic acids is as follows:

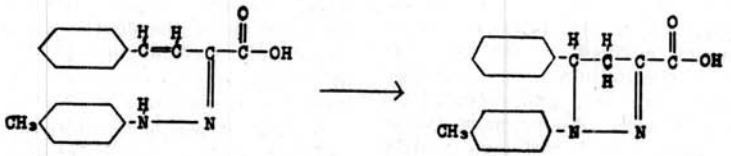
1. Benzaldehyde is condensed with pyruvic acid to form benzalpyruvic acid.[3]



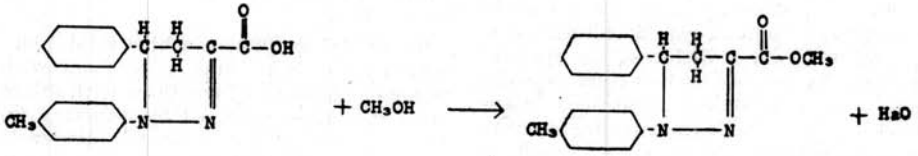
2. Benzalpyruvic acid is treated with o-, m-, or p-tolylhydrazine in glacial acetic acid to form the corresponding tolylhydrazone.



3. Refluxing the tolylhydrazone of benzalpyruvic acid in glacial acetic solution will cause the tolylhydrazone to rearrange forming the pyrazoline ring.[4]



The methyl and ethyl esters of these acids were prepared by two procedures:
1. The treatment of the acid with absolute methyl or ethyl alcohol in the presence of dry HCl as a catalyst.



2. The benzalpyruvic acid was esterified[5] by the same method and this ester was used in the preparation of the tolylhydrazone which was rearranged to the pyrazoline compound. The esters prepared by each method were identical.

The following are the compounds of this series which we have prepared and identified: 1-(o-tolyl)-5-phenylpyrazoline-3-carboxylic acid, m.p. 187-189°; methyl ester, m.p. 114-115°, ethyl ester m.p. ....; 1-(m-tolyl)-5-phenylpyrazoline-3-carboxylic acid, m.p. 185-186°, methyl ester, m.p. 121.5-122.5°, ethyl ester, m.p. 73-74°; 1-(p-tolyl)-5-phenylpyrazoline-3-carboxylic Acid, m.p. 178°, methyl ester, m.p. 113-114°, ethyl ester, m.p. 91-92°.

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5. Reimer, M. J. Am. Chem. Soc. 46, 783 (1924).