Whether or not the azulene molecule has some such structure, can only be determined by further study, perhaps from its oxidation products. Its formation from the sesquiterpenes can aid but little in this direction, so long as their structure is so little known, but a synthesis from substances of known structure does not seem impossible. In this connection the formation of the blue oil by the dry distillation of calcium adipate, (Hentschel and Wislicenus),[1] is interesting. Such a synthesis would seem to give the greatest promise in indicating the structure of this remarkable substance, and would at the same time give additional evidence as to the structure of the sesquiterpenes to which it is related.

Two obvious typographical errors crept into the first article on azulene, in connection with the molecular weight determination (p. 169). This determination was made by Dr. Farnau of New York University, and the values found agreed well with those calculated for $C_{15}H_{18}$, 198.

BAYONNE, N. J.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN.]

THE CONSTITUTION OF THE SO-CALLED DITHIOURIMIDO-ACETYLACETONE.

BY WILLIAM J. HALE.

Received April 8, 1915.

The principal product resulting from the condensation of urea and acetylacetone has been called by Evans[2] acetylacetone-urea. The constitution of this substance, a 2-ketopyrimidine, has been thoroughly investigated by de Haan and others.[3] At the same time de Haan recognized in the reaction product the presence of two new distinct substances. One of these new compounds was found to be a 2-ketopyrimidine-urea and identical in all respects with the second product which Evans had obtained by the use of a slightly acid condensing medium, and to which he had assigned the structure corresponding to a diurimido-acetylacetone. In all cases it is to be assumed that, during these condensations, one molecule of acetylacetone and one molecule of urea proceed directly to the formation of a pyrimidine ring, and that afterwards another molecule of urea condenses with this pyrimidine ring to form either a simple ureide derivative or a second ring leading to a compound of the diureino type.

According to Evans, the principal product in the condensation of thiourea and acetylacetone is a 2-thiopyrimidine [II] (acetylacetone-thiourea). By use of a small amount of acid he further secured the product corresponding to his diurimido-acetylacetone, namely, dithiourimido-

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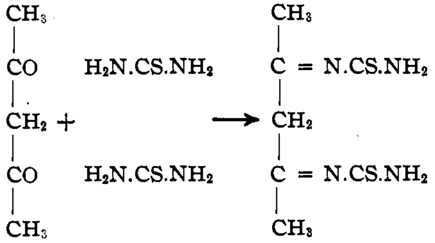
[1] *Ann.*, **275**, 312 (1893).

[2] *J. prakt. Chem.*, [2] **48**, 489 (1893).

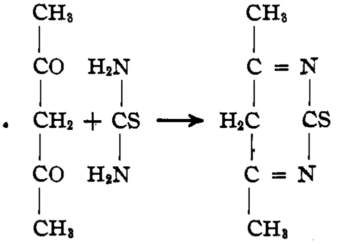
[3] *Rec. trav. chim.*, **27**, 162 (1908); THIS JOURNAL, **36**, 104 (1914).

acetylacetone (I). This 2-thiopyrimidine has lately[1] been shown to be possible of existence in a tautomeric form (III) but to a much less extent than that of the 2-ketopyrimidine. The dithiourimido product, however, received but little attention by Evans and has been known only in the form of a salt. It seemed more than likely that the products obtained from urea and acetylacetone might find their counterparts in the condensation mixtures from thiourea and this same ketone; consequently, a study of this condensation was undertaken to establish the exact constitution of Evans' dithiourimido-acetylacetone and at the same time to search for a third product of the diureino type (VI). The outlines of these condensations are given first as described by Evans in (I) and (II), and later as here to be interpreted in the light of previous work, especially that of de Haan[2] upon acetylacetone and the analogous substance urea.



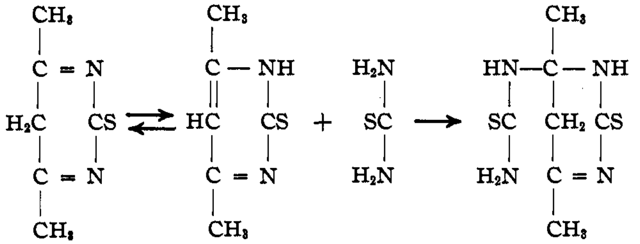
(I)

Dithiourimido-acetylacetone(Evans).



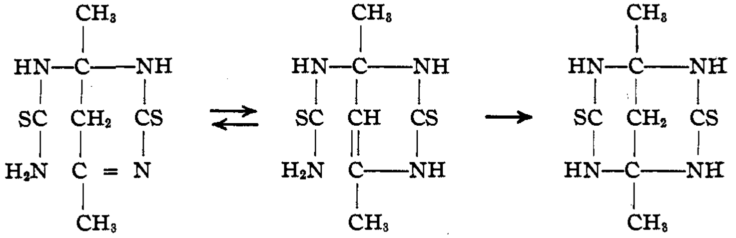
(II)

Acetylacetone-thiourea (Evans).



(II) (III) (IV)

(Formerly considered of structure (I))



(IV) (V) (VI)

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[1] THIS JOURNAL, 37, 594 (1915).

[2] *Loc. cit.*

The distinctive property of acetylacetone-thiourea in failing to release its sulfur atom, even by prolonged action of such desulfurizing agents as mercuric oxide and basic lead acetate, distinguishes this type of sulfur directly bound to the ring as markedly different from that form usually present in a side chain and so readily split off by these same agents; on the other hand, this property stamps it as closely similar to sulfur held within the ring itself. This inactivity of the sulfur atom is due to the presence of the strongly negative nitrogen atoms at either side of the carbon which holds it. When one of these nitrogen atoms carries an alkyl substituent[1] this property is lost and the sulfur can be completely removed. The action of chloroacetic acid,[2] however, is sufficient to remove this sulfur even in the firmly bound condition previously described. Prolonged boiling of an aqueous solution of acetylacetone-thiourea and chloroacetic acid yielded acetylacetone urea.[3]

The product prepared by Evans and called dithiourimido-acetylacetone (I) was obtained, as a hydrochloride, when just a few drops of conc. hydrochloric acid were added to an absolute alcoholic solution of the reacting components. The free base is most readily prepared by gently warming a concentrated aqueous solution of thiourea (2 mol) and acetylacetone (1 mol) at the temperature of the steam bath. This product is of a light yellow color and when converted into a hydrochloride by the action of hydrochloric acid affords a salt which corresponds exactly to the hydrochloride obtained by Evans, melting at 219°. The method employed by Evans leads to the formation of both this product just mentioned and the hydrochloride of acetylacetone-thiourea, hence it is not to be recommended. The free base prepared directly and in comparatively pure state is always yellow, but when allowed to form by a slow condensation, without the aid of heat and in the dark, possesses a much lighter yellow color. There is, however, no other point of difference between the products.

This so-called dithiourimido-acetylacetone readily gave up a part of its sulfur to mercuric oxide. In order to remove all of the sulfur the prolonged action of chloroacetic acid in aqueous solution was employed. From the reaction product was obtained a good yield of 2-ketopyrimidine-urea (VII) melting at 197° and in every respect identical with the product formerly known as diurimido-acetylacetone. Desulfurization must have proceeded as here shown.

The structure, therefore, is clearly indicated by this transformation into the well-known 2-ketopyrimidine-urea. In order to check this point there remained only to condense one molecule of thiourea with acetyl-

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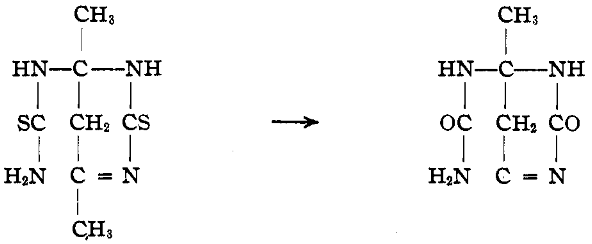
[1] Hale and Williams, This Journal, **37**, 599 (1915).

[2] Wheeler and Liddle, *Am. Chem. J.*, **40**, 549 (1908).

[3] Hale and Williams, This Journal, **37**, 598 (1915).

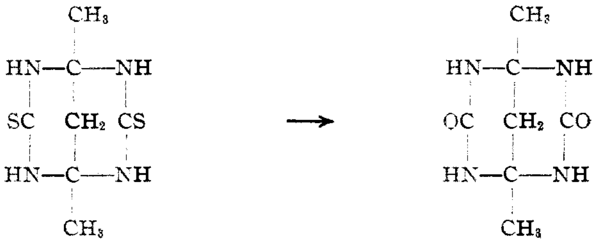


(IV) (VII)

acetone-thiourea and obtain the original product. This condensation proceeded well when these two substances were brought together in concentrated aqueous solution without the presence of condensing agent. The light yellow precipitate formed was identical in all respects with the so-called dithiourimido-acetylacetone, or 2-thiopyrimidine-thiourea, melting at 192°. There can be, therefore, no doubt as to the structure of the compound—that of a monothioureide of the base acetylacetone-thiourea. In the presence of strong acids in alcoholic solution, Evans obtained the more or less insoluble salts of acetylacetone-thiourea. When, however, acids are absent the aqueous, as well as alcoholic, solution of these reacting components favors the formation of the less soluble thiopyrimidine-thioureide. In the absence of alcohol, water and other condensing media, thiourea and acetylacetone yield both the thiopyrimidine and the thiopyrimidine-thioureide, but chiefly the latter, owing to its greater insolubility in acetylacetone itself.

Since the structure of dithiourimido-acetylacetone found its counterpart in the structure of 2-ketopyrimidine-urea, there seemed a possibility that a third product might be expected to accord with a 2,4-dithioureinopentane, Formula VI. The analogous keto derivative was found to be present in very small quantities in the reaction product obtained by heating urea and acetylacetone upon a water bath. It remained always as the portion insoluble in alcohol. de Haan obtained small portions of this substance, decomposing at 290°, when urea and acetylacetone were allowed to condense in aqueous solution. Thiourea and acetylacetone were heated together under many conditions of temperature and pressure and scarcely a trace of a portion insoluble in alcohol could be procured. Several months' standing of absolute alcoholic solutions of thiourea and acetylacetone did yield a product practically insoluble in alcohol. This substance decomposed at 265° and refused to release its sulfur to mercuric oxide or basic lead acetate. Prolonged action of chloroacetic acid removed all of the sulfur and converted it into the 2,4-diureinopentane (VIII) of de Haan, decomposing at 290°.

The third possibility, therefore, in the condensation of thiourea and acetylacetone is fulfilled and a two-ring compound produced. The



(VI) (VIII)

great difficulty in producing any appreciable amount of this dithioureine would seem to rest upon the increased difficulty for the 2-thiopyrimidine-thiourea (IV) to undergo further transformation to yield another imino nitrogen (V), a necessary step preliminary to the second ring formation (V) to (VI). As previously reported[1] the stable form of 2-thiopyrimidine itself is undoubtedly quinoid in structure, and this transformation of the ring to produce a second imino form would be attended with greater and greater difficulty.

Experimental Part.

When concentrated sulfuric acid is added to an alcoholic solution of acetylacetone and thiourea, crystals of acetylacetone-thiourea hydrosulfate soon make their appearance. The constitution and properties of the free base, liberated by the action of barium carbonate upon this salt, have previously been described.[1] On the other hand, when only a very small quantity of acid is used as the condensing agent in this reaction there results, according to Evans, a salt of dithiourimido-acetylacetone. This latter will now be described as a thiopyrimidine-thioureide.

6-Thioureido-4,6-dimethyl-2-thio-1,2,5,6-tetrahydropyrimidine (IV).—The condensation of thiourea and acetylacetone, upon the addition of a few drops of concentrated hydrochloric acid to the absolute alcoholic solution, resulted in the slow formation of a hydrochloride melting at 219°. Three days were required for the completion of the reaction as described by Evans. Under these conditions, however, a variable amount of acetylacetone-thiourea hydrochloride is always formed and naturally constitutes a part of the crystalline product. Many crystallizations are necessary to remove the last traces of this latter salt. As the free base from the former salt was not isolated by Evans, it seemed advisable to attempt its preparation by a condensation in the absence of acids. Accordingly thiourea and acetylacetone were brought together in an alcoholic as well as in an aqueous solution and in each case, after a few days, small, yellow crystals of the free base appeared. The slight solubility of thiourea in absolute alcohol materially lessened the quantity of condensation product formed, but with water as the medium a relatively large yield was obtained. Dur-

Loc. cit.

ing this condensation in aqueous solution a considerable portion of colorless crystals of thiourea separate, but with the gradual increase in amount of thioureide precipitated a further solution of thiourea and subsequent condensation proceeds. After several weeks' standing in the dark an excellent yield of light lemon-yellow monoclinic prisms was removed. Gently warming the reaction mixture to effect complete solution from time to time, secures a more rapid conversion of thiourea into the final product; consequently, the following procedure was adopted as giving the best results.

Three grams (2 mol) of thiourea were dissolved by warming in 5 cc. of water and 2.5 g. (excess of 1 mol) of acetylacetone added. The test tube containing the mixture was then sealed and placed in a steam bath (98°) from 10 to 12 hours. Upon cooling the reaction mixture, 3.3 g. of yellow condensation product separated and from the mother liquor an additional 0.6 g. was collected, bringing the percentage of yield to 91% of the theoretical. The color of this product was of a more decided yellow than that possessed by the free base resulting through a slow condensation in the dark. Repeated crystallizations under varying conditions failed to reduce materially this yellow color of the product, whereas with the light lemon-yellow colored product, repeated crystallizations rendered it almost, but never quite, colorless. These two products are, however, identical in crystalline form and in all other respects. The melting point of this thiopyrimidine-thioureide is 192°. 4,6-Dimethyl-2-thiopyrimidine-thiourea is fairly soluble in water or alcohol, crystallizing from either, but better from the latter, in monoclinic prisms. It is only slightly soluble in acetone and practically insoluble in chloroform, ethyl acetate, benzene, ether or ligroin.

An aqueous solution of this substance readily blackens mercuric oxide or basic lead acetate—a point distinguishing it at once from acetylacetone-thiourea, and indicating the presence of a free thioureide group.[1]

The formation of this thiopyrimidine-thiourea presupposes the intermediate formation of a thiopyrimidine in the reaction mixture and the subsequent condensation of this product and a second molecule of thiourea. The thiopyrimidine that must be formed, *i. e.*, acetylacetone-thiourea, is very soluble in chloroform and hence may readily be removed from mixtures of these substances when present. Under the conditions of the reactions here given the final crystalline products, by extraction with chloroform, failed to show the presence of any acetylacetone-thiourea. The presence therefore of water alone (and alcohol as well) as condensing medium, may be looked upon as facilitating the production of this thiopyrimidine-thiourea at the expense of the thiopyrimidine in process of formation.

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[1] *Loc. cit.*

When a solution of 1 part of thiourea in 10 parts of acetylacetone alone is heated to boiling under a reflux condenser for 5 or 6 hours and then allowed to stand several days, these same yellow crystals of the thiopyrimidine-thioureide make their appearance. With less decomposition the same end is accomplished by warming the two ingredients in a sealed test-tube for 24 hours at about 98° (steam bath). The yellow prisms begin to separate during the heating, and upon cooling they are precipitated in an excellent state of purity. Washing with cold water removed no trace of thiourea. One gram of thiourea and 10 g. of acetylacetone yielded thus 1 g. of the thioureide crystals. When the red mother-liquor was evaporated to dryness upon a steam bath and the residue digested with chloroform, about 0.6 g. of the intermediate acetylacetone-thiourea was dissolved out. The portion insoluble in the chloroform (0.2 g.) consisted of the thioureide alone and increased its production in this case to 1.2 g. We may conclude, therefore, that the absence of water in the condensing medium makes possible the formation of both products: acetylacetone-thiourea and thiopyrimidine-thioureide, and that the favored formation of the latter, even in the presence of so large an excess of acetylacetone, is undoubtedly due to its slight solubility in this medium.

Preparation of 2-Thiopyrimidinethiourea from Acetylacetonethiourea.—When conc. aqueous solution of thiourea (1 mol) and acetylacetone (1 mol) are brought together at room temperature, prisms of thiopyrimidine-thiourea soon separate. These crystals when purified melt at 192° and are identical with the product obtained by condensing 2 molecules of thiourea and 1 molecule of acetylacetone in aqueous solution. The possibility of a molecular type of compound between these two component parts was at once dismissed. Many crystallizations from various solvents as well as many extractions with chloroform (in order to withdraw the readily soluble acetylacetone-thiourea portion) proved futile. The product is without water of crystallization.

0.1346 g. subst. gave 0.1912 g. CO_2 and 0.0686 g. H_2O.

Calc. for $C_7H_{12}N_4S_2$: C, 38.85%; H, 5.59%. Found: C, 38.75%; H, 5.70%.

In order to identify the hydrochloride obtained by Evans according to his mode of condensation, a portion of thiopyrimidine-thiourea was dissolved in water and treated with a little concentrated hydrochloric acid. The hydrochloride thus prepared crystallized from alcohol in irregular yellow prisms melting at 219°, checking exactly the observations reported by Evans. An analysis also accorded with the same result. There can be no doubt, therefore, as to the identity of the two products as hydrochlorides and hence, also, as free bases.

0.2220 g. HCl salt gave 0.1252 g. AgCl.

Calc. for $C_7H_{12}N_4S_2.HCl$: HCl, 14.42%. Found: HCl, 14.35% (Evans, 14.06%).

Replacement of Sulfur by Oxygen.—When 1 g. of thiopyrimidine-thiourea is boiled with 1.5 g. of chloroacetic acid in 15 cc. of water for five hours under reflux condenser, the sulfur atom of the thioureide side chain, as well as that directly united to the pyrimidine nucleus, is replaced by oxygen. The reaction mixture, evaporated to dryness, was extracted with absolute alcohol and the residue almost neutralized with potassium hydroxide solution, when it was again evaporated to dryness over the steam bath and the final residue extracted with benzene. Colorless crystals melting at 197° were obtained upon removal of the benzene. This substance proved to be identical with the 2-ketopyrimidine-urea (VII) of de Haan. Mixtures of the two showed this constant melting point and their solubilities also exactly accorded. de Haan[1] proved that urea and acetylacetone-urea condensed in alcoholic solution to produce this product melting at 197° and thus further proof of the constitution of the analogous thiopyrimidine-thiourea is established.

2,4-Dithioureinopentane (VI).—In repeating the work of earlier investigators de Haan showed that when urea and acetylacetone were heated together a very small quantity of a substance insoluble in alcohol could be obtained. The formula he assigned to this product is that of a 2,4-diureinopentane (VIII) and resulted upon the further intramolecular condensation of 2-ketopyrimidine-urea. In working upon thiourea and acetylacetone alone, no appreciable amount of a similar substance could be prepared. This type of compound, however, was isolated in three or four instances where thiourea and acetylacetone in absolute alcoholic solution had been allowed to stand in stoppered tubes over the summer months, more or less exposed to the sunlight. The dark yellow crystalline mass was powdered and extracted with boiling absolute alcohol. The alcohol removed the thiopyrimidine-thiourea, but left undissolved a colorless crystalline product insoluble in practically all reagents. It is only slightly soluble in acetone or water, but of course soluble in acids. It may be crystallized from acetylacetone in which it is fairly soluble. The decomposition point is about 265°.

0.1142 g. subst. gave 27.3 cc. N_2 (25.5° and 746.6 mm. over H_2O).
Calc. for $C_7H_{12}N_4S_2$: N_2, 25.91%. Found: 26.08%.

As this substance does not blacken mercuric oxide, we may consider that its two sulfur atoms are in two separate positions similar to that one already indicated for 2-thiopyrimidine. By the action of chloroacetic acid, however, the compound is freed of all sulfur. The aqueous chloroacetic acid solution, after five hours' boiling with this product, was evaporated to dryness, extracted with absolute alcohol and the residue treated with moist silver oxide and again evaporated. Extraction of the final

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[1] *Rec. trav. chim.*, **27**, 175 (1908).

product with water gave a colorless substance, identical with that compound decomposing at 290° and obtained by de Haan as stated above.

It is exceedingly difficult to procure any appreciable quantity of this dithioureinopentane. The greater ease by which the diureinopentane may be procured is, in one respect at least due to the practical insolubility of this latter product in acetylacetone.

For the kind assistance of Mr. Frank C. Vibrans upon the analytical data in this paper the author desires to express his indebtedness.

ANN ARBOR, MICHIGAN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF COLUMBIA UNIVERSITY AND THE HARRIMAN RESEARCH LABORATORY. NO. 249.]

INOSITE AND PINITE AND SOME OF THEIR DERIVATIVES.

BY EDWARD G. GRIFFIN AND J. M. NELSON.

Received April 12, 1915.

Inosite and its derivatives possess considerable interest. The sugar itself is interesting, due to its wide occurrence in nature and possible important physiological functions, and also due to its close relationship in chemical constitution to the hexoses and some hydroaromatic compounds. The synthesis of the derivatives of inosite, when compared to the synthesis of the analogous derivatives of a substance like glucose, affords a comparison of the effect on the properties of a hexose in which the carbons are arranged in the form of a closed ring instead of an open chain. The derivatives might also prove valuable in the study and synthesis of many complex substances like phytin and some of the tannins, which yield, on decomposition, inosite or closely related products like phloroglucin and quinic acid, $C_6H_7(OH)_4COOH$.

Derivatives of inosite mentioned in literature prior to this investigation are: the hexacetate, hexabenzoate,[1] hexa- and trinitrates,[2] monobromopentacetate, two isomeric dibromotetraacetates, and mono- and dibromohydrins.[3] While this work was in progress, Müller published a second article describing a triacetate, three isomeric chlorohydrinpentacetates, a chlorohydrintriacetate, a chlorohydrin, two new isomeric inosites, which he called iso and ψ; and an iso-inosite hexacetate and tetrabenzoate.[4]

By the action of acetyl bromide on inosite the following products were obtained: Bromopentacetylcyclohexanpentol, $C_6H_6Br(OCOCH_3)_5$;[5] two

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[1] Maquenne, *Compt. rend.*, **104**, 297 (1887).

[2] Vohl, *Ann.*, **101**, 55 (1857).

[3] Müller, *J. Chem. Soc.*, **91**, 1780 (1907).

[4] *J. Chem. Soc.*, **101**, 2383 (1912).

[5] The names ascribed to the esters and derivatives of inosite mentioned in literature are sometimes not satisfactory, and for that reason the Geneva system of nomenclature has been adopted.