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Condensation Products of Camphor with Barbituric and Thiobarbituric Acids

Kâfurun Barbitürik ve Tiyobarbitürik Asidlerle Kondensasyon Ürünleri

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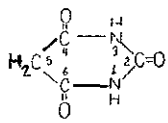
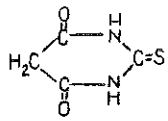
Barbituric acid is a cyclic ureid, derived from malonic acid. It can be prepared by condensing urea with the malonic acid dichloride, or better with ethylmalonate in the presence of sodium ethoxide(1). The numbering pattern of the barbituric acid ring follows the pyrimidine pattern, and is as follows:



According to this structure, barbituric acid is 2,4,6-trioxohexahydropyrimidine.

When thiourea is used instead of urea in the above mentioned synthesis, thiobarbituric acid, having a >C=S group instead of >C=O at C_2 position, is obtained. Thiobarbituric acid is 2-thio-4,6-dioxopyrimidine.



The presence of the —NH—CO—NH— (or —NH—CS—NH—) group enables the molecule to produce resonance hybrid ions. As a

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result, barbituric and thiobarbituric acids have acidic properties. On comparison, they are stronger acids than acetic acid, and their aqueous solutions are strongly acid to pH indicators. They combine with one equivalent of alkali to produce their alkali salts.

The active hydrogen at C_5 position brings forth the second important characteristic of these particular substances. While barbituric and thiobarbituric acids have no distinct pharmacological activity, their C_5 substituted derivatives act as hypnotics, provided that the substitution contains at least four carbon atoms(2). For example, 5,5′-dimethyl barbituric acid, having a total substitution of two carbon atoms on C_5, is not a hypnotic drug. The C_5 hydrogens, having a position between two carbonyl groups, are activated, and therefore they can react very easily with metalic sodium, this being an intermediate step in the preperation of the C_5 substituted derivatives. These hydrogens can also react with active carbonyl compounds to give condensation derivatives containing an ethylenic group (—C=C—) (3). The focus of our studies has been on the latter of these reactions, and the subject of this paper is a study on the reactions of barbituric and thiobarbituric acids with camphor, which has an active carbonyl group.

EXPERIMENTAL

2,2-bis-(5,5′-bibarbituryl) camphan (I): 2.6 g (0.02 mol) barbituric acid, 0.76 g (0.005 mol) camphor, 20 ml acetic acid anhydride and 10 ml glacial acetic acid are refluxed at 140 - 160° for 4 - 5 hours. A dark yellow precipitate is formed on cooling. It is filtered and washed first with ehter, then with alcohol. A dark yellow substance is obtained with a yield of 72%. Another method of purification is the crystallisation of the product from ethanol. This, however, is less desirable when compared with the former method, because it gives a poorer yield due to the fact that the product is slightly soluble in ethanol. The resulting substance which is purified according to either of these methods is a yellow powder, mp. 290° (decomp.). It is sparingly soluble in ethanol, ether, and acetone and practically insoluble in water. Its solutions in alkali hydroxides exhibit a dark green precipitate with pyridine and cupric sulphate. (Zwikker reaction).

Chromatography: The substance shows only one spot on the thin

layer chromatography when Methanol-Acetic acid combination (10:1) is used as solvent. Adsorbent is Silica Gel $HF_{254-366}$.

UV Spectrum (VSU 1-Model Spectrophotometer) : $\lambda_{max.}^{EtOH}$ 275 mμ (ε 60,229).

IR Spectrum (KBr, Perkin-Elmer, Model 137) : 3300 cm^{-1} NH or OH (enol); 1739 cm^{-1}, 1786 cm^{-1} and 1695 cm^{-1} CO; 1639 cm^{-1} and 1515 cm^{-1} C=C; 1471 cm^{-1} CH_2 bending bond; 825 cm^{-1} olefinic CH bending bond.

Anal. Calcd. for $C_{26}H_{26}O_{10}N_8 . 3H_2O$: C, 46.98; H, 3.91; N, 16.56. Found C, 46.43; H, 4.01; N, 16.55.

2,2-bis-(5,5'-bithiobarbituryl) camphan (II): 2.88 g (0.02 mol) thiobarbituric acid, 0.76 g (0.002 mol) camphor, 20 ml. acetic acid anhydride and 10 ml glacial acetic acid are refluxed at 140 - 160° for 4 - 5 hours. A brownish precipitate is formed on cooling, which is then filtered and washed first with water, then with ether and alcohol. The resulting product is a brownish-orange substance with a yield of 56 %, showing a melting point of 278° (decomp.).

2,2-bis-(5,5'bithiobarbituryl) camphan is sparingly soluble in ethanol, ether, and acetone, and is practically insoluble in water. It is, however, soluble in alkali hydroxides, and its solution in sodium hydroxide exhibits a yellowish-green precipitate with pyridine and cupric sulphate.

Chromatography : The substance shows only one spot on the thin layer chromatography when Ethanol-Acetic acid (9 : 1) is used as solvent and Silica Gel $HF_{544-366}$ is used as the adsorbent.

UV Spectrum (VSU 1-Model Spectrophotometer) : $\lambda_{max.}^{EtOH}$ 264 mμ (ε 57,631).

IR Spectrum (KBr, Perkin-Elmer, Model 137) : 3448 cm^{-1} NH or OH (enol); 3077 cm^{-1} CH stretching; 1538 cm^{-1} C=C; 1266 cm^{-1} CH_2; 1156 cm^{-1} CH_2; 795 cm^{-1} C=C.

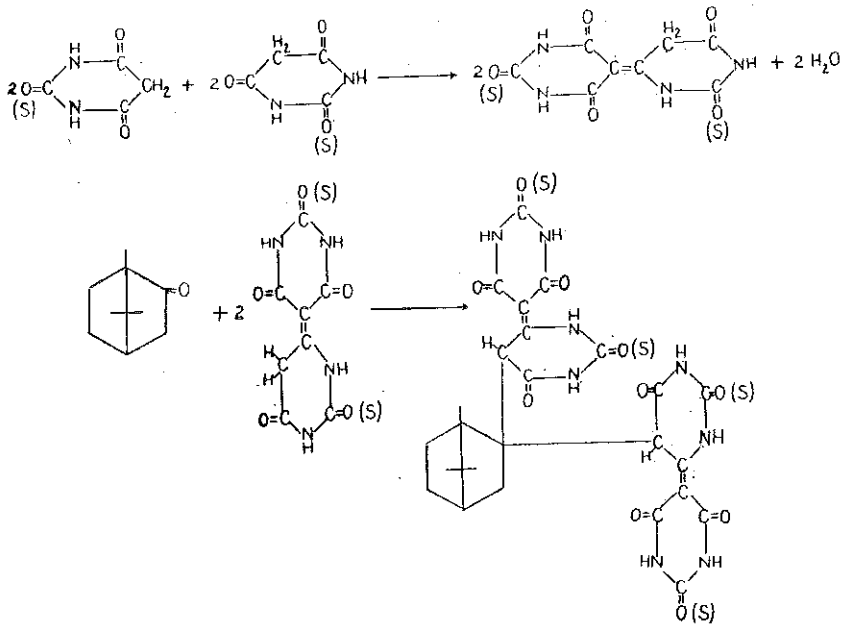
Anal. Calcd. for $C_{26}H_{26}O_6N_8S_4 . 3H_2O$: C, 42.47; H, 3.37; N, 15.3; S, 1695. Found C, 42.8; H, 3.57; N, 15.38; S, 17.57.

DISCUSSION

Barbituric and thiobarbituric acids can easily give condensation products with the carbonyl groups if this group is an aldehyde;

however, the reaction is rather difficult when it is a keton (especially if it is a cyclic keton). As a matter of fact, the uneffectiveness of either hydrochloric acid or pyridine in the condensation of the barbituric and thiobarbituric acids with a keton has been pointed out previously(4).

In this study the first attempt was to condense the barbituric acid and thiobarbituric acid with camphor in the presence of dried sodium acetate; however, the reaction failed to proceed. Then the reaction conditions were altered by taking four mols. of barbituric acid for each mol of camphor, and using glacial acetic acid and acetic acid anhydride as the condensation agents. The reaction proceeded as shown below, and 62% (I) and 56% (II) were obtained.



(O = Barbituric acid derivative) (I)

(S = Thiobarbituric acid derivative) (II)

Theoretically, one mol. of camphor should have reacted with one mol barbituric or thiobarbituric acid, the active acid hydrogens and the oxygen of the carbonyl group giving rise to one mol of water, and therefore an ethylenic bond being formed between these substances. However, the reaction proceeded quite contrarily.

In the first step of the reaction, two molecules of barbituric or thiobarbituric acid interacted to produce bibarbituric or bithiobarbituric acid by the elimination of a molecule of water, which is formed from the C_5 hydrogens of one molecule and C_4 oxygen of the other molecule.

Formation of bibarbituric acid is previously recorded in literature. Baeyer has shown that this particular product could be obtained by heating barbituric acid(5).

As the reaction proceeded, two molecules of the previously formed bibarbituric acid reacted with one molecule of camphor within the reaction mixture to give the final product. This was a satisfactory explanation of the reason why four molecules of barbituric acid were needed for every molecule of camphor. The three molecules of water which were eliminated during the total process were bounded by the resulting substance as crystal water.

The elemental analysis, the UV and IR spectra confirmed our view about the molecular structure of the final products.

SUMMARY

Barbituric and thiobarbituric acids were condensed with camphor in an acetic acid medium, the resulting substances being 2,2-bis-(5,5′-bibarbituryl)camphan and 2,2-bis-(5,5′-bithiobarbituryl)camphan. The molecular structures of the final products were determined by using UV and IR spectra, some chemical reactions as well as the elemental analysis.

ÖZET

Bu çalışmada barbitürik ve tiyobarbitürik asidlerin aktif bir keton karbonili taşıyan kâfur ile kondensasyon reaksiyonları incelenmiş ve literatürde barbitürik asidlerle karbonil bileşikleri arasındaki reaksiyon için uygulanan metod kullanıldığı halde, elde edilen ürünler beklenenden farklı olmuştur. Karbonil (—C=O) oksijeni ile barbitürik ve tiyobarbitürik asidlerin C_5 deki aktif iki hidrojeni arasında su çıkışı ile bir kondansasyon reaksiyonu olmamış, buna karşılık önce iki molekül barbitürik ve tiyobarbitürik asidler arasında su çıkışı ile yürüyen bir reaksiyon sonucunda bibarbitürik ve bitiyobarbitürik asidler meydana gelmiş ve bu asidlerin iki molekülü ile kâfur reak-

siyona girerek 2,2-bis-(5,5′-bibarbitüril)kamfan ve 2,2-bis-(5,5′-bitiyobarbitüril)kamfan teşekkül etmiştir. Elde edilen maddelerin yapısı bazı kimyasal reaksiyonlar, eleman analizi, UV ve IR spektrumları yardımı ile aydınlatılmıştır.

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