PREPARATION OF BRASSYLIC ACID FROM 5,6,7,8,9,10,11,12,13,14-DECAHYDROCYCLODODECA[1,2-d]PYRIMIDINE(1H,3H)-2,4-DIONE OBTAINED BY THE CONDENSATION OF CYCLODODECANONE AND UREA OR BIURET

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A simple method is proposed for the preparation of brassylic acid by the alkaline hydrolysis of 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)dione-2,4, which is the product of the condensation of cyclododecanone with urea or biuret. The condensation of the cyclododecanone with thiourea proceeds differently, leading to 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)spirocyclododecane-2-thione-4.

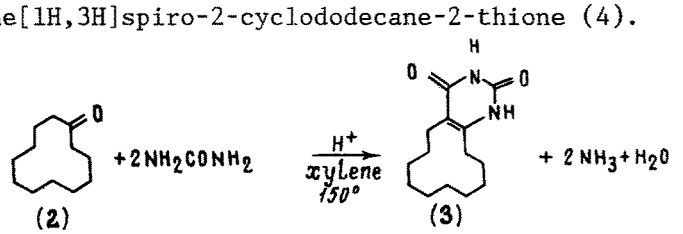
Keywords: brassylic acid, cyclododecanone, 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)dione-2,4, 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[1,2-d]pyrimidinespirocyclododecane-2-thione-4, et, me-urea, biuret, methoxycarbonylcyclododecanone, phenylamide of cyclododecanone-carboxylic acid.

Brassylic acid 1 is used in the perfume industry for the preparation of a valuable fragrance, ethylenebrassylate, which has a musk odor. The synthetic methods for the preparation of brassylic acid are rather complex and it is produced on an industrial scale by a microbiological procedure or ozonolysis of rapeseed oil [1]. Bischoff and Herma [2] found that acid hydrolysis of the product of the condensation of cyclohexanone with urea gives cyclohexanone and the amide of 2-cyclohexanonecarboxylic acid.

In previous work [3], we showed that the amide of 2-cyclododecanonecarboxylic acid smoothly undergoes alkaline cleavage to give brassylic acid . The structure of the product of the condensation of cyclohexanone with urea formed at 150°C in o-xylene was first incorrectly determined by McKay et al. [4] and then identified by Zigeuner [5] as 5,6,7,8-tetrahydrospiro[cyclohexane-1,2'(1H)-quinazoline]-4'(3'H)-one. Apparently, the product of the condensation of cyclohexanone with thiourea obtained by McKay et al. [4] should have an analogous structure.

Bischoff et al. [6] subsequently showed that the condensation of cyclododecanone 2 with urea at 280°C in the presence of p-toluenesulfonic acid, i.e., under conditions different from those in previous work [2, 4], gives 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)dione-2,4 (3) and not the analog of the product of the condensation of cyclohexanone with urea.

We have found that the condensation of ketone 2 with urea and thiourea under conditions analogous to those in previous work [2, 4], i.e., at 150°C in xylene or in xylene—DMF, proceeds differently, while the condensation of cyclohexanone with urea and thiourea proceeds through the same mechanism. The condensation of ketone 2 with urea leads to pyrimidine-2,4-dione (3) and the condensation with thiourea leads to 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[1,2-d]pyrimidine[1H,3H]spiro-2-cyclododecane-2-thione (4).



(2) (3) (1)

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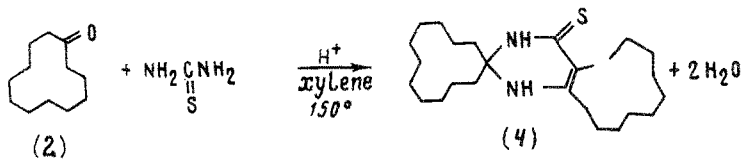
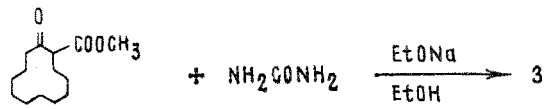


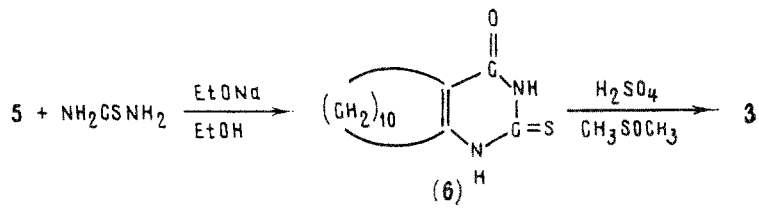
(2) (4) (2)

The structure of pyrimidine 3 was supported by an independent synthesis from 2-methoxycarbonylcyclododecanone 5 and urea in the presence of EtONa in absolute ethanol.



(5)

The reaction of ketone 5 with thiourea in the presence of EtONa gives the thioanalog of 3, namely, 5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)-2-thione-4-one (6), which is converted to pyrimidine 3 upon treatment with sulfuric acid in DMSO according to Mikolajczyk and Luczak [7].



(6)

Pyrimidine 3, which we obtained by three pathways, was identical to a sample prepared according to the procedure of Bischoff [6]. The structure of spiro compound 4 was established by elemental analysis and mass spectral data. We propose that the difference in the pathways in the reaction of ketone 2 with urea and thiourea is a consequence of the ready conversion of urea into biuret with the loss of ammonia, while biuret condenses with ketone 2 to give pyrimidine 3. Indeed, we found that heating ketone 2 with biuret in xylene–DMF gives pyrimidine 3 in good yield.

$$2 + NH_2CONHCONH_2 \xrightarrow[\text{xylene, DMF}]{150^\circ} 3 + NH_3\uparrow + H_2O.$$

Apparently, the condensation of urea with 2-alkylcyclohexanone and cyclooctanone at 280°C, leading to substituted pyrimidine-2,4-diones [6] also proceeds through the conversion of urea to biuret, which then condenses with the ketone.

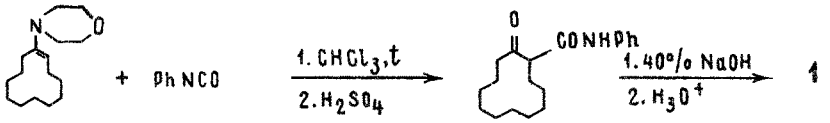
We have shown that pyrimidine 3 upon heating with aqueous KOH at 250-280°C undergoes hydrolytic cleavage with the formation of brassylic acid 1:

$$3 + KOH + H_2O \xrightarrow[2.\ H_3O^+]{1.\ 250-280^\circ} HOOC(CH_2)_{11}COOH$$

1

A different reaction pathway is observed to a slight extent along with this course for the cleavage of pyrimidine 3, which leads to starting ketone 2.

We studied another method for the preparation of brassylic acid 1 from ketone 2: the reaction of 1-morpholinocyclododecene 7 with phenyl isocyanate gives, by analogy to the work of Ried and Kappeler [8], the N-phenylamide of 2-cyclododecanonecarboxylic acid 8, which upon heating in aqueous NaOH gives acid 1 in high yield.



(7) (8)

EXPERIMENTAL

The mass spectra were taken on a Kratos MS-890 mass spectrometer.

5,6,7,8,9,10,11,12,13,14-Decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)dione-2,4 (3). a. A mixture of 9 g (0.05 mole) ketone 2 and 6 g (0.1 mole) NH_2CONH_2 was heated at reflux in a mixture of 20 ml DMF and 5 ml o-oxylene with a Dean–Stark trap for 8 h. The mixture was cooled and 100 ml water was added. The organic layer was separated. The aqueous layer was filtered to remove the insoluble precipitate, which was washed with ether on the filter to give 6 g (50%) 3, mp 310°C (from ethanol). Mass spectrum, (M^+) 250. Found, %: C 66.87; H 8.55; N 11.44. $C_{14}H_{22}N_2O_2$. Calculated, %: C 67.20; H 8.80; N 11.20.

b. A mixture of 4.5 g (0.025 mole) ketone 2 and 5 g (0.05 mole) $NH_2CONHCONH_2$ in a mixture of 20 ml DMF and 5 ml o-xylene was heated for 7 h with a Dean–Stark trap. Analogous work-up gave 3.6 g (60%) 3, mp 310°C (from toluene). Found, %: C 66.78; H 8.81; N 11.13. $C_{14}H_{22}N_2O_2$. Calculated, %: C 67.20; H 8.80; N 11.20.

c. A sample of 2 g ketoester 5 and 0.6 g NH_2CONH_2 were added to a solution of NaOEt obtained from 0.5 g sodium and 25 ml absolute ethanol. The mixture was heated at reflux for 3 h. Excess ethanol was distilled off in vacuum. The residue was poured into water. The precipitate was filtered off and washed on the filter with hexane. The aqueous layer was acidified with hydrochloric acid. The precipitate formed was filtered off and washed with hexane. Both precipitates after crystallization had mp 308-310°C (from ethanol).

5,6,7,8,9,10,11,12,13,14-Decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)spirocyclododecane-2-thione-4 (4). A mixture of 9 g ketone 2 and 7.6 g NH_2CSNH_2 was heated at reflux for 10 h in a mixture of 20 ml DMF and 5 ml o-oxylene with a Dean–Stark trap. The mixture was treated by analogy to the experiment with urea to give 10.6 g (51%) 4, mp 234-238°C (from ethanol). Found, %: C 74.64; H 10.99; N 6.89; S 8.18. $C_{26}H_{46}N_2S$. Calculated, %: C 74.64; H 11.00; N 6.69; S 7.65. Mass spectrum: M^+ 418.

5,6,7,8,9,10,11,12,13,14-Decahydrocyclododeca[1,2-d]pyrimidine(1H,3H)-2-thione-4-one (6). A sample of 5 g 5 and 1.6 g NH_2CSNH_2 was added to a solution of EtONa obtained from 1 g sodium and 25 ml ethanol. The mixture was stirred at reflux for 3 h. Excess ethanol was distilled off in vacuum and the residue was poured into water. The precipitate was filtered off and washed on the filter with hexane to give 4 g (73%) 6, mp 272-275°C (from toluene). Found, %: C 62.72; H 8.34; N 10.48; S 12.02. $C_{14}H_{22}N_2OS$. Calculated, %: C 63.16; H 8.27; N 10.52; S 12.03. Mass spectrum: M^+ 266.

Oxidation of 6 to Give 3. A mixture of 0.5 g 6 in 10 ml DMSO and 1 ml H_2SO_4 was stirred for 1 h at 80-100°C. CH_3SCH_3 liberated during the reaction was absorbed by a solution of $HgCl_2$ in ethanol. The mixture was cooled and 10 ml water was added. Then, the mixture was neutralized by the addition of aqueous ammonia. The precipitate was filtered off and washed on the filter with water to give 0.4 g (85%) 3, mp 312°C (from ethanol).

Brassylic Acid (1). A sample of 6 g 3 and 40 ml 50% aqueous KOH was heated in an autoclave at 250-300°C for 7 h. The reaction mass was poured from the autoclave and the residue was washed with hot water. The suspension obtained was extracted with toluene and ether. The organic layer was separated, washed with water, and dried over Na_2SO_4. Distillation of the solvent gave 1 g cyclododecanone. The alkaline solution was acidified by the addition of hydrochloric acid and the acid separated was filtered off to give 3 g (67%) acid 1, mp 112-114°C (mp 114°C [9]).

Phenylamide of Cyclododecanonecarboxylic Acid. A mixture of 5 g (0.02 mole) morpholinocyclododecene 7 and 2.4 g (0.02 mole) phenyl isocyanate in 30 ml dry chloroform was heated at reflux for 3 h. The solvent was distilled off in vacuum. The mixture was cooled to 0°C and 20 ml 70% H_2SO_4 was added with stirring and left for 12 h in a refrigerator. The reaction mass was then poured into ice water and extracted with benzene. The organic layer was separated off, washed with water, and dried over Na_2SO_4. The solvent was distilled off and the residue was diluted with heptane. The precipitate formed was filtered off and crystallized from ethanol–water to give 5.5 g (58%) amide 8, mp 135-136°C. IR spectrum (ν, cm^{-1}): 1640 (CO), 3350 (NH). Found, %: C 75.64; H 8.97, N 4.70. $C_{19}H_{27}O_2N$. Calculated, %: C 75.80; H 8.96; N 4.66.

Brassylic Acid (1). A sample of 3.6 g (0.012 mole) amide 8 was added to a solution of 5 g NaOH in 6.5 g ethanol and 1 ml water. The mixture was heated at reflux for 12 h. Excess

ethanol was distilled off in vacuum. The residue was diluted with water and extracted with ether. The aqueous solution was acidified by the addition of hydrochloric acid. The precipitated acid was filtered off to give 2.5 g (86%) 1, mp 112-114°C (from toluene).

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