Reactions with (Arylmethylene)cycloalkanones. 4. Synthesis of Derivatives of Octahydrocycloocta[*d*]thiazolo[3,2-*a*]pyrimidin-3-one of Expected Biological Activity

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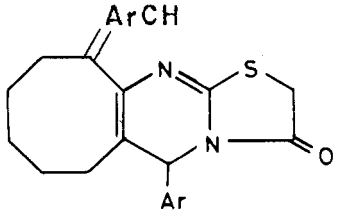
Cycloocta[*d*]pyrimidin-2-thiones (III) were prepared by heating 2-(arylmethylene)cyclooctanones with thiourea in ethanolic potassium hydroxide. Compounds III reacted with chloroacetic acid to yield 2-acetyl-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*]thiazolo[3,2-*a*]pyrimidin-3-ones (IV). The 2-arylmethylene derivatives (V) and the 2-arylhydrazono derivatives VI were prepared.

The literature (*6*, *8*) reveals that bis(arylmethylene)cyclooctanones and the mono(arylmethylene)cyclooctanones possess biological activity.

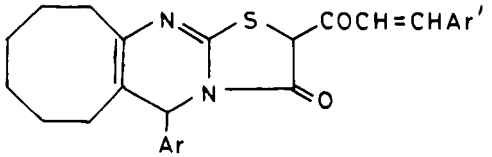
Now we have found that 2-(arylmethylene)cyclooctanones (II), by analogy with bis derivatives (*1-3*), react with thiourea in ethanolic potassium hydroxide to give 4-aryl-1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[*d*]pyrimidine-2-thione (III). (See Scheme I.)

Compounds III were reacted with chloroacetic acid in the presence of acetic acid–acetic anhydride (see Experimental Section) to give products which dissolve in cold aqueous sodium hydroxide and are precipitated by hydrochloric acid. They neither effervesce nor dissolve in aqueous sodium carbonate. The products give a deep violet color with ethanolic ferric chloride. This color reaction had not been observed in the compounds obtained from the bis(arylmethylene) derivatives studied previously (*1-3*). The elemental analysis and the mass spectrum proved that these compounds are 2-acetyl-5-aryl-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*]thiazolo[3,2-*a*]-pyrimidin-3-ones (IV) and not the expected compounds of formula A, analogous to previous work (*1-3*).



(A)

Compounds III reacted with chloroacetic acid and aromatic aldehydes to give 5-aryl-2-(arylmethylene)-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*]thiazolo[3,2-*a*]pyrimidin-3-ones (V) and not the 2-cinnamoyl derivatives B.



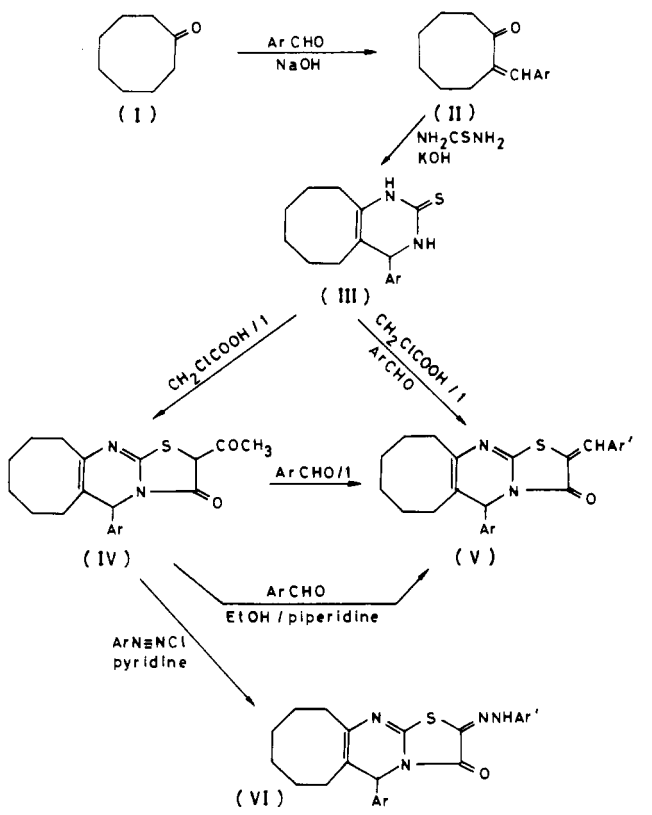
(B)

Compounds V also were prepared by the reaction of IV with aromatic aldehydes. No reaction took place in the absence of sodium acetate.

The products (V) of the reaction did not dissolve in aqueous sodium hydroxide or give the ferric chloride test. The elemental analysis and the mass spectrum of Vb agree with the structure.

Deacetylation of IV occurred also during coupling with arenediazonium salts in pyridine medium to give 5-aryl-2-arylhydrazono-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*]thiazolo[3,2-*a*]pyrimidin-3-ones (VI) (*4*). Compounds VI did not give the ferric chloride test.

Scheme I[a]



[a] 1 = Acetic anhydride and sodium acetate in acetic acid.

Experimental Section

2-(Arylmethylene)cyclooctanones (II). The 2-phenylmethylene derivative (IIa) is known in the literature (*5*, *7*). In this work, the arylmethylene derivatives are prepared in ~75% yield as follows. To a mixture of 6 g (0.05 mol) of cyclooctanone and 0.05 mol of the appropriate aldehyde was added aqueous sodium hydroxide (2 g of NaOH in 40 mL of H_2O). The mixture was refluxed for 5 h, allowed to cool, and then acidified with dilute HCl. The 2-arylmethylene derivatives were extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The crude pale yellow oil (~8 g) was used as such.

4-Aryl-1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[d]pyrimidine-2-thiones (IIIa-e) (Table I). A mixture of ca. 8 g of the crude 2-(arylmethylene)cyclooctanone, 3 g of thiourea, and 2.5 g of potassium hydroxide in 100 mL of ethanol was refluxed for 3 h. The ethanol was evaporated to half its volume

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Table I. 4-Aryl-1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[*d*]pyrimidine-2-thiones (III)[a]

compd	Ar	mp, °C	solvent[b]
IIIa	C_6H_5	230	A
b	$C_6H_4CH_3$-*p*	230	M
c	$C_6H_4OCH_3$-*p*	204	A
d	C_6H_4Cl-*p*	215	E
e	$C_6H_3O_2CH_2$-3,4	210	E

[a] Elemental analyses in agreement with theoretical values were obtained. [b] A = acetic acid; E = ethanol; D = dioxane; M = methanol.

Table II. 2-Acetyl-5-aryl-2,3,6,7,8,9,10,11-octahydro-5H-cycloocta[*d*] thiazolo[3,2-*a*] pyrimidin-3-ones (IV)[a]

compd	Ar	mp, °C	solvent
IVa	C_6H_5	230	M
b	$C_6H_4CH_3$-*p*	235	M
c	$C_6H_4OCH_3$-*p*	180	M
d	C_6H_4Cl-*p*	245	M
e	$C_6H_3O_2CH_2$-3,4	200	E

[a] See footnotes of Table I.

and the mixture was left overnight, whereas a white precipitate appeared. The mixture was treated with 50 mL of H_2O and shaken and filtered. The white precipitate was crystallized from the proper solvent. The infrared spectra of III show bands at 3270 (NH), 1285 (C=S), and 1640 (N—C=S) cm^{-1}. The mass spectrum of IIIa gave peaks at *m/e* 272, 30% (M^+), and at *m/e* 195 (base peak).

5-Aryl-2-acetyl-2,3,6,7,8,9,10,11-octahydro-5H-cycloocta[d]thiazolo[3,2-a]pyrimidin-3-ones (IVa–f) (Table II). A mixture of 1.5 g of compound III, 1 g of chloroacetic acid, and 4 g of fused anhydrous sodium acetate in 10 mL of acetic acid and 5 mL of acetic anhydride was refluxed for 3 h and left to cool. The reaction mixture was poured into water slowly with stirring. The solid obtained was filtered off, washed with water, and crystallized from the proper solvent (yield ca. 65%).

The infrared spectra of IV show bands at 1680 (CO) and 1613 (C=N) cm^{-1}. The UV of IVa shows peaks at λ = 240 (ϵ 10 769), 280 (ϵ 7692), and (ϵ 15 571) 360 nm. The mass spectrum of IVa showed molecular ion peak at *m/e* 354 (M^+) (90%), 326 (M^+ – 28) (90%), 311 (M^+ – 43) (95%), and 277 (M^+ – 77) (base peak).

5-Aryl-2-(arylmethylene)-2,3,6,7,8,9,10,11-octahydro-5H-cycloocta[d]thiazolo[3,2-a]pyrimidin-3-ones (Va–o) (Table III). General Method. (a) A mixture of 0.5 g of III, 1 g of chloroacetic acid, 0.3 g of the aromatic aldehyde, and 2 g of fused sodium acetate in 10 mL of acetic acid and 6 mL of acetic anhydride was refluxed for 2.5 h. The reaction mixture was poured into cold water, and the solid formed was collected and crystallized. (b) To a mixture of 0.5 g of IVa and 0.3 g of piperonaldehyde in 15 mL of methanol was added a few drops of piperidine, and the whole mixture was refluxed for 3 h and left overnight. The solid formed was collected and crystallized. (c) A mixture of 0.5 g of IVa and 0.3 g of piperonaldehyde in 10 mL of ethanol containing 0.1 g of NaOH was refluxed for 2 h and left overnight; 2 mL of acetic acid were added and the solid formed was collected and crystallized. (d) A mixture of 1 g of IVa, 0.5 g of piperonaldehyde, and 3 g of anhydrous sodium acetate in 7 mL of acetic anhydride was refluxed for 2 h, cooled, and poured into cold water. The solid formed (Vc) was collected and crystallized.

The yields in methods a and b were ~90%. Compound Vc prepared by the different methods a–d has the same melting point and mixed melting point. The infrared spectra of V showed CO absorption at ca. 1700 cm^{-1} and C=N at 1613 cm^{-1}. The UV spectrum of Vb shows two maxima at λ = 240 nm (ϵ 15 862) and λ = 390 nm (ϵ 24 827). The mass spectrum of Vb shows a molecular ion peak at *m/e* 414 (M^+) (50%), 386 (M^+ – 28) (50%), and 337 (M^+ – 77) (base peak).

Table III. 5-Aryl-2-(arylmethylene)-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*]thiazolo[3,2-*a*]-pyrimidin-3-ones (V)[a]

compd	Ar	Ar′	mp, °C	solvent
Va	C_6H_5	C_6H_5	215	E
b	C_6H_5	$C_6H_4CH_3$-*p*	210	A
c	C_6H_5	$C_6H_3O_2CH_2$-3,4	220	A
d	$C_6H_4CH_3$-*p*	C_6H_5	210	E
e	$C_6H_4CH_3$-*p*	$C_6H_4CH_3$-*p*	235	E
f	$C_6H_4CH_3$-*p*	$C_6H_4OCH_3$-*p*	200	E
g	$C_6H_4OCH_3$-*p*	C_6H_5	180	E
h	$C_6H_4OCH_3$-*p*	$C_6H_3O_2CH_2$-3,4	215	A
i	$C_6H_4OCH_3$-*p*	$C_6H_3(OMe)_2$-3,4	180	E
j	C_6H_4Cl-*p*	C_6H_5	212	E
k	C_6H_4Cl-*p*	C_6H_4Cl-*p*	220	D
l	C_6H_4Cl-*p*	$C_6H_4(OMe)_2$-3,4	220	A
m	$C_6H_3O_2CH_2$-3,4	C_6H_5	185	M
n	$C_6H_3O_2CH_2$-3,4	$C_6H_4OCH_3$-*p*	205	A
o	$C_6H_3O_2CH_2$-3,4	$C_6H_3O_2CH_2$-3,4	237	D

[a] See footnotes of Table I.

Table IV. 5-Aryl-2-(arylhydrazono)-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*] thiazolo[3,2-*a*] pyrimidin-3-ones (VI)[a]

compd	Ar	Ar′	mp, °C	solvent
VIa	C_6H_5	C_6H_5	155	E
b	C_6H_5	$C_6H_4CH_3$-*p*	235	D
c	$C_6H_4CH_3$-*p*	C_6H_5	135	E
d	$C_6H_4CH_3$-*p*	$C_6H_4CH_3$-*p*	220	E
e	$C_6H_4OCH_3$-*p*	C_6H_5	435	E
f	$C_6H_4OCH_3$-*p*	$C_6H_4CH_3$-*p*	235	E

[a] See footnotes of Table I.

5-Aryl-2-(arylhydrazono)-2,3,6,7,8,9,10,11-octahydro-5H-cycloocta[d]thiazolo[3,2-a]pyrimidin-3-ones (VI) (Table IV). A cold diazonium salt solution (prepared in the usual way from 0.6 g of the amine) was gradually added with stirring to a cooled solution of 1.5 g of IV in 10 mL of pyridine. The reaction mixture was cooled for 0.5 h and poured into 100 mL of water. The precipitate formed was collected and crystallized. The infrared spectra of VI show CO absorption at ca. 1730 cm^{-1} and C=N at ca. 1625 cm^{-1}. The UV spectrum of VIa shows two maxima at λ = 240 nm (ϵ 15 000) and λ = 390 nm (ϵ 21 000).

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