V	vapor-phase property
^	mixture component property
′	vapor pressure

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NEW COMPOUNDS

Reactions with (Arylmethylene)cycloalkanones. 2.[†] Synthesis of 10-(Arylmethylene)hexahydrocyclohepteno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-3-one Derivatives of Probable Anticancer Activity

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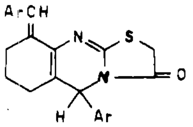
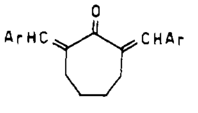
Cyclohepteno[1,2-*d*]pyrimidine-2-thiones (II) were prepared by heating 2,7-bis(arylmethylene)cycloheptanones with thiourea in ethanolic potassium hydroxide. Compounds II reacted with chloroacetic acid to yield the title compounds III. The 2,10-bis(arylmethylene) derivatives (VI) were prepared.

In part 1 (*1*) of this series 2,6-bis(arylmethylene)cyclohexanones were condensed with thiourea and then with chloroacetic acid to give (arylmethylene)thiazolo[2,3-*b*]quinazolin-3-one derivatives (A) (*1*).

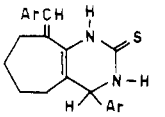


A

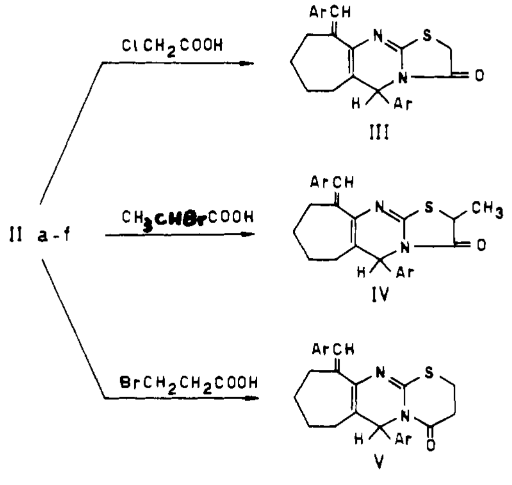
The previous sequence of reactions was applied to the cycloheptanone series. When 2,7-bis(arylmethylene)cycloheptanones were heated with thiourea in ethanolic potassium hydroxide, they yielded 4-aryl-9*H*-9-arylmethylene-1,2,3,4,5,6,7,8-octahydrocyclohepteno[1,2-*d*]pyrimidine-2-thione (II) (cf. ref 2 and references cited therein). The cyclohepteno[1,2-*d*]pyrimidine-2-thiones (II) were reacted with chloroacetic acid, 2-bromopropanoic acid, and 3-bromopropanoic acid in acetic acid–acetic anhydride, in the presence of anhydrous sodium acetate to give respectively 5-aryl-10-(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*,10*H*-cyclohepteno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-3-ones (III), their 2-methyl derivatives (IV), and 6-aryl-11-(arylmethylene)-2,3,6,7,8,9,10-heptahydro-4*H*,6*H*,11*H*-cyclohepteno[1,2-*d*]pyrimidino[2,1-*b*]1,3-thiazin-4-one (V).



I



II



III IV V

[†] For part 1, see ref 1.

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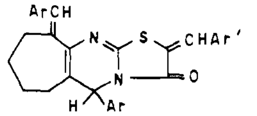
The 5-aryl-2,10-bis(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*,10*H*-cyclohepteno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-3-ones (VI) were prepared from II by the action of chloroacetic acid,


VI

a, Ar = C_6H_5; Ar′ = C_6H_5
b, Ar = C_6H_5; Ar′ = $C_6H_4OCH_3$-*p*
c, Ar = C_6H_5; Ar′ = C_6H_4Cl-*p*
d, Ar = C_6H_5; Ar′ = $C_6H_3O_2CH_2$-3,4
e, Ar = $C_6H_4OCH_3$-*p*; Ar′ = C_6H_5
f, Ar = $C_6H_4OCH_3$-*p*; Ar′ = $C_6H_4OCH_3$-*p*
g, Ar = $C_6H_4OCH_3$-*p*; Ar′ = C_6H_4Cl-*p*
h, Ar = $C_6H_4OCH_3$-*p*; Ar′ = $C_6H_3O_2CH_2$-3,4
i, Ar = C_6H_4Cl-*p*; Ar′ = C_6H_5
j, Ar = C_6H_4Cl-*p*; Ar′ = $C_6H_4OCH_3$-*p*
k, Ar = C_6H_4Cl-*p*; Ar′ = C_6H_4Cl-*p*
l, Ar = C_6H_4Cl-*p*; Ar′ = $C_6H_3O_2CH_2$-3,4
m, Ar = $C_6H_3O_2CH_2$-3,4; Ar′ = C_6H_5
n, Ar = $C_6H_3O_2CH_2$-3,4; Ar′ = $C_6H_4OCH_3$-*p*
o, Ar = $C_6H_3O_2CH_2$-3,4; Ar′ = C_6H_4Cl-*p*
p, Ar = $C_6H_3O_2CH_2$-3,4; Ar′ = $C_6H_3O_2CH_2$-3,4

the aromatic aldehyde, and anhydrous sodium acetate in the presence of acetic acid–acetic anhydride. The following assignments apply in structures I–V: a, Ar = C_6H_5; b, Ar = $C_6H_4OCH_3$-*p*; c, Ar = $C_6H_5CH{=}CH$; d, Ar = C_6H_4Cl-*p*; e, Ar = $C_6H_3O_2CH_2$-3,4; f, Ar = $C_6H_4NMe_2$-*p*.

Experimental Section

***Bis(arylmethylene)cycloheptanones* (*Ia–f*).** The bis(arylmethylene)cycloheptanones are known in the literature (*3*, *4*).

In this work, these arylmethylene derivatives were prepared in 70% yield as follows.

A mixture of 6 g (0.05 mol) of cycloheptanone, 0.10 mol of the appropriate aromatic aldehyde, and 50 mL of MeOH was stirred and treated with 50 mL of 6% sodium methoxide during 30 min, stirring was stopped, and the reaction mixture was refluxed for 1 h. Then the alcohol was evaporated, the residue was dissolved in ether and dried over anhydrous sodium sulfate, and then the ethereal solution was treated with petroleum ether (40–60 °C) to give pale yellow crystals; the melting points agreed with those in the literature.

***4-Aryl-9H-9-(arylmethylene)-1,2,3,4,5,6,7,8-octahydrocyclohepteno[1,2-d]pyrimidine-2-thione* (*IIa-f*).** A mixture of (0.04 mol) of II, 3 g of thiourea, and 4 g of potassium hydroxide in 200 mL of ethanol was heated on a water bath for 3 h, and then the ethanol was evaporated to half its volume and left overnight. The products were filtered off and washed with water. See Table I.

***Tricyclic Heterocycles* (*III*, *IV*, *V*).** A mixture of 5 g of compound II, 3 g of chloroacetic acid, 2-bromopropanoic acid, or 3-bromopropanoic acid, and 6 g of fused sodium acetate in 10 mL of acetic acid and 2 mL of acetic anhydride was refluxed for 2 h and left to cool. The solution was filtered from insoluble material and then poured gradually into cold water. The solid obtained was filtered off, washed with water, and crystallized from the proper solvent. See Table I.

Table I[a]

compd	mp, °C (solvent)[b]	yield, %	IR, cm^{-1} (CO)
IIa	204 (E)	92	
IIb	194 (A)	87	
IIc	245 (D)	78	
IId	220 (M)	82	
IIe	190 (n)	90	
IIf	181 (D)	82	
IIIa	180 (D)	72	1730
IIIb	168 (n)	70	1728
IIIc	183 (M)	68	
IIId	168 (M)	75	
IIIe	176 (D)	82	
IIIf	152 (M)	78	
IVa	156 (E)	65	1730
IVb	135 (n)	60	1725
IVc	143 (M)	85	
IVd	155 (D)	80	
IVe	176 (M)	75	
Va	110 (A)	82	1690
Vb	167 (E)	75	1685
Vc	104 (D)	80	1680
Vd	156 (n)	85	
Ve	206 (E)	78	
VIa	192 (D)	65	1715
VIb	155 (n)	72	1712
VIc	214 (A)	85	
VId	210 (n)	67	
VIe	177 (n)	65	
VIf	155 (A)	68	
VIg	195 (E)	65	
VIh	180 (D)	72	
VIi	180 (E)	92	
VIj	202 (M)	90	
VIk	151 (D)	75	
VIl	210 (A)	85	
VIm	230 (E)	80	
VIn	205 (D)	72	
VIo	199 (D)	82	
VIp	256 (n)	90	

[a] Satisfactory elemental analyses were found. [b] Key: A = acetic acid, E = ethanol, M = methanol, D = dioxane, n = *n*-hexane.

***5-Aryl-2,10-bis(arylmethylene)-2,3,6,7,8,9-hexahydro-5H,10H-cyclohepteno[1,2-d]thiazolo[3,2-a]*pyrimidin*-3-ones* (*VIa–p*).** A mixture of 0.005 mol of II, 1 g of chloroacetic acid, 2 g of fused sodium acetate, an equimolar amount of the appropriate aldehyde in 10 mL of acetic acid, and 4 mL of acetic anhydride was refluxed for 2 h and left overnight. The yellow crystals were filtered off, washed with water, and crystallized from the proper solvent. See Table I.

***Anticancer Activity*.** Compounds Ic,d, IIa,b,f, and IIIa,b,d,e,f showed anticancer activity and low toxicity. The results of these tests will be published elsewhere.

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