NEW COMPOUNDS

Reactions with (Arylmethylene)cycloalkanones. 3. Synthesis of 11-(Arylmethylene)octahydrocycloocta[*d*]thiazolo[3,2-*a*]pyrimidin-3-one Derivatives of Expected Biological Activity

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Cycloocta[*d*]pyrimidine-2-thiones (II) were prepared by heating 2,8-bis(arylmethylene)cyclooctanones with thiourea in ethanolic potassium hydroxide. Compounds II reacted with chloroacetic acid to yield the title compounds (III). The 2,11-bis(arylmethylene) derivatives IV were prepared.

There appears to be an increasing interest in the chemistry of 2,8-bis(arylmethylene)cyclooctanones and 2,8-bis(arylmethyl)cyclooctanones because of their biological activities (*3*, *5*). It was reported that they possess antifertility and hypocholesterolemic activities (*3*, *5*). In our previous work (*1*), it was found that a molecule containing a thiazolone ring fused to a cycloheptene system possesses anticancer activity (*1*). This induced the authors to prepare new derivatives from 2,8-bis(arylmethylene)cyclooctanones for the biological study.

2,8-Bis(arylmethylene)cyclooctanones (I) were prepared by the condensation of the aromatic aldehyde and cyclooctanone in the presence of pyridine–piperidine; then they were reacted with thiourea in ethanolic potassium hydroxide to yield 4-aryl-10-(arylmethylene)-1,2,3,4,5,6,7,8,9,10-decahydrocycloocta-[*d*]pyrimidine-2-thiones (II) (See Chart I). Compounds II reacted with chloroacetic acid and anhydrous sodium acetate in acetic acid–acetic anhydride to give 5-aryl-11-(arylmethylene)-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*]thiazolo[3,2-*a*]pyrimidin-3-ones (III). II also reacted with 3-bromopropionic acid to give 6-aryl-12-(arylmethylene)-2,3,7,8,9,10,11,12-octahydro-4*H*,6*H*-cycloocta[*d*]pyrimidine-[2,1-*b*]-1,3-thiazin-4-one (V).

5-Aryl-2,11-bis(arylmethylene)-2,3,6,7,8,9,10,11-octahydro-5*H*-cycloocta[*d*]thiazolo[3,2-*a*]pyrimidin-3-ones (IV) were prepared from II by the action of chloroacetic acid, the aromatic aldehyde, and anhydrous sodium acetate in acetic acid–acetic anhydride. Also, compounds IV could be obtained from III (see Chart II).

Compounds III showed carbonyl absorption at ~1725 cm^{-1} while the carbonyl group of IV appeared at ~1700 cm^{-1}. On the other hand, the CO group in V absorbed at 1685 cm^{-1}. The analogous six- and seven-membered heterocycles absorbed almost at the same frequency (*1*, *2*).

The UV spectrum of IIIA shows a maximum at λ230 nm (ε 18 400). The UV spectrum of compound IVe shows two maxima at λ230 (ε 29 550) and 375 nm (ε 20 000).

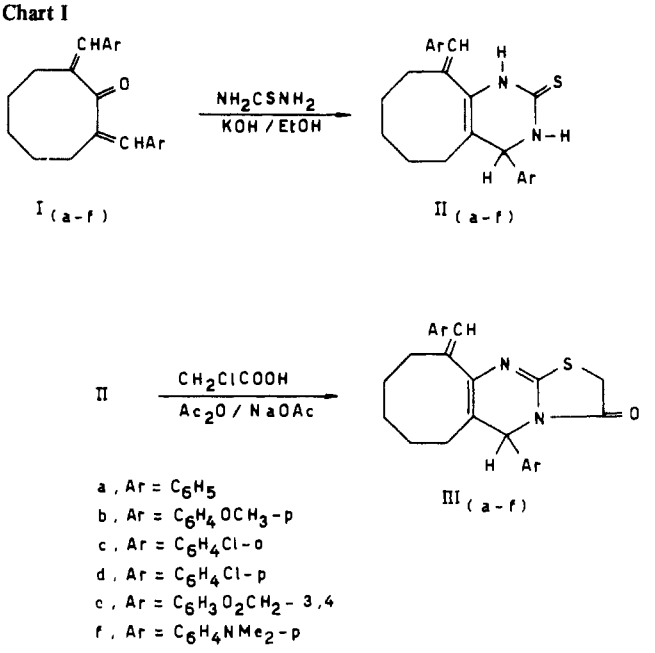
The ^1H NMR spectrum of compound IIa (in $CDCl_3$) showed the benzylic proton (a) as a sharp singlet at δ 6.60 and the methine proton (b) also as a singlet at δ 4.90. The aromatic protons gave multiplets (10 H) centered at δ 7.45, while the protons of the cyclooctene ring (10 H) appeared as a multiplet in the δ 1.20–2.70 region. The NH protons gave two broad singlets at δ 6.95 (1 H) and δ 7.70 (1 H).

The ^1H NMR spectrum of compound IVe (in $CDCl_3$) revealed the presence of two sharp singlets at δ 6.75 and 8.05 which are assigned for the benzylic protons, a and b, respectively. The aromatic protons (12 H) gave a multiplet centered at δ 7.40 while the methine proton (c) appeared as a singlet at δ 6.22. The protons of the cyclooctene ring appeared as a multiplet (10 H) in the δ 1.20–3.80 region.

The ^1H NMR spectrum of compound Va showed the following assignments: a multiplet centered at δ 7.45 (11 H) for the aromatic protons and the benzylic proton (a); a singlet at δ 6.00 for the methine proton (b); a multiplet in the δ 0.9–3.20 region (14 H), for the 4 protons of the thiazine ring and the 10 protons of the cyclooctene ring.

The mass spectrum of IVe showed ion peaks at *m/e* 592 (M^+, 27%), 557 (M^+ – Cl, 100%), 481 (M^+ – C_6H_4Cl, 44%), and 453 (*m/e* 481 – CO, 5%).

Chart I



Experimental Section

2,8-Bis(arylmethylene)cyclooctanones (Ia–f). These bis(arylmethylenes) are found in the literature (*3–5*). In this work, these arylmethylene derivatives are prepared in ca. 75%

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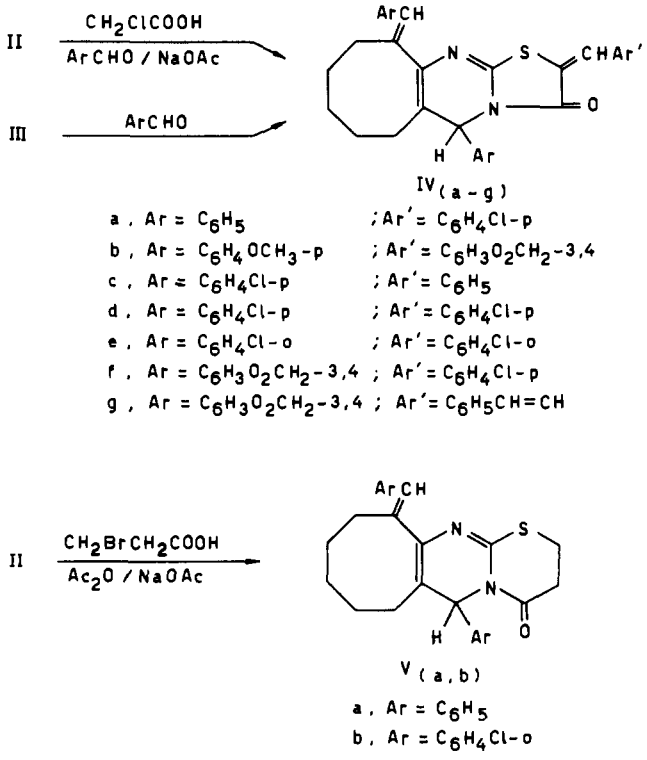
Chart II



yield as follows. A mixture of 6 g (0.05 mol) of cyclooctanone, 0.01 mol of the appropriate aldehyde in 10 mL of pyridine, and 0.5 mL of piperidine was refluxed in a water bath for 4 h, allowed to cool, and then poured into water. The solution was acidified with hydrochloric acid, and the bis(arylmethylene) derivatives were extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was pure enough to be used in the following step.

4-Aryl-10-(arylmethylene)-1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[d]pyrimidine-2-thiones (IIa-f). A mixture of 0.02 mol of I, 1.5 g of thiourea, and 2 g of potassium hydroxide in 100 mL of ethanol was refluxed for 3 h and left overnight. The ethanol was evaporated and the residue was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and then treated with petroleum ether (40/60) to give a pale yellow product (yield, ca. 80%) which was crystallized from the proper solvent (see Table I).

Tricyclic Heterocycles (III, V). A mixture of 0.005 mol of compound II, 1 g of chloroacetic acid or 1.5 g of 3-bromopropionic acid, and 2 g of fused sodium acetate in 10 mL of acetic acid and 4 mL of acetic anhydride was refluxed for 2.5 h, left to cool, and then poured into water. The solid obtained was filtered off, washed with water, and crystallized from the proper solvent (yield, ca. 65%, see Table I).

Table I

compd	mp, °C	yield, %	solvent	IR, cm^{-1} (CO)
IIa	230	80	E	
IIb	160	79	E	
IIc	200	79	E	
IId	205	80	E	
IIe	210	81	A	
IIf	241	79	D	
IIIa	140	65	E	1725
IIIb	165	65	E	1725
IIIc	150	65	E	
IIId	110	66	E	
IIIe	170	66	PE	
IIIf	190	65	A	
IVa	205	95	A	1700
IVb	115	95	M	1700
IVc	218	94	D	
IVd	210	96	B	
IVe	220	96	A	
IVf	220	95	A	
IVg	220	95	A	
Va	150	65	E	1685
Vb	160	65	E	1685

[a] Elemental analyses in agreement with theoretical values were obtained. [b] Solvent key: A = acetic acid, B = benzene, D = dioxane, E = ethanol, M = methanol, PE = petroleum ether 60/80.

5-Aryl-2,11-bis(arylmethylene)-2,3,6,7,8,9,10,11-octahydro-5H-cycloocta[d]thiazolo[3,2-a]pyrimidin-3-ones (IVa-g). (A) A mixture of 1 g of III, an equimolar amount of the appropriate aldehyde, and a few drops of piperidine was heated at 170 °C for 30 min and left to cool, and the product was crystallized. (B) A mixture of 1 g of III, an equimolar amount of the aldehyde in 10 mL of acetic acid, and 7 mL of acetic anhydride was refluxed for 1 h, left to cool, and poured into water. The product was collected and crystallized (see Table I). (C) A mixture of 2 g of II, 1 g of chloroacetic acid, an equimolar amount of the appropriate aldehyde, and 2 g of fused sodium acetate in 20 mL of acetic acid and 10 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. The yields of the three methods were ~95%.

Literature Cited

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