Reactions with (Arylmethylene)cycloalkanones. 1. 2,6-Bis(arylmethylene)cyclohexanones

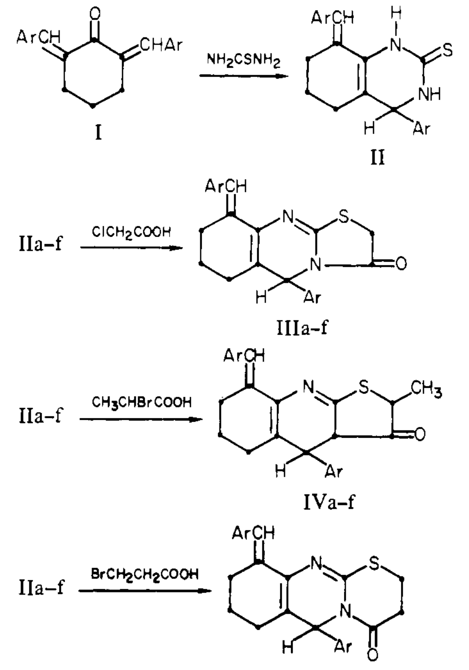
Mohamed Ibrahim Ali and Abou-Elfotooh G. Hammam*

Department of Chemistry, Faculty of Science, University of Cairo, Giza, A. R. Egypt, and National Research Centre, Dokki, Giza, A. R. Egypt

Bis(arylmethylene)cyclohexanones condensed with thiourea to give 8-(arylmethylene)octahydroquinazoline-2-thiones (II), which reacted with chloroacetic acid, with 2-bromopropanoic acid, and with 3-bromopropanoic acid to give, respectively, 5-aryl-9-(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*-thiazolo[2,3-*b*]quinazolin-3-ones (III), their 2-methyl derivatives IV, and 6-aryl-10-(arylmethylene)-2,3,7,8,9,10-hexahydro-4*H*,6*H*-1,3-thiazino[2,3-*b*]quinazolin-4-ones (V). Compounds III were transformed into 5-aryl-2,9-bis(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*-thiazolo[2,3-*b*]quinazolin-3-ones (VIII).

In previous papers (*1–3*), α,β-unsaturated ketones were transformed into thiopyrimidine derivatives and in turn into compounds containing the thiazolopyrimido moiety. The work in the present series deals with the application of the above sequence of reactions to α,α'-bis(arylmethylene)cycloalkanones. In this part, the 2,6-bis(arylmethylene)cyclohexanone derivatives are investigated.

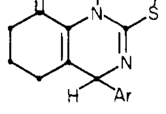
Thus when 2,6-bis(arylmethylene)cyclohexanones (I) were heated with thiourea in the presence of ethanolic potassium hydroxide, they gave 8-(arylmethylene)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones (II).

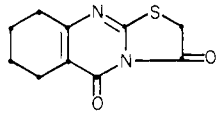


in formulas I through V
a, Ar = C_6H_5
b, Ar = $C_6H_4CH_3$-*p*
c, Ar = $C_6H_4OCH_3$-*p*
d, Ar = C_6H_4Cl-*o*
e, Ar = C_6H_4Cl-*p*
f, Ar = $C_6H_3O_2CH_2$-3,4

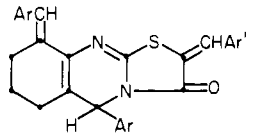
The quinazoline-2-thiones (II) were reacted with chloroacetic acid, 2-bromopropanic acid, and 3-bromopropanoic acid in acetic acid–acetic anhydride, in the presence of sodium acetate, to give, respectively, 5-aryl-9-(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*-thiazolo[2,3-*b*]quinazolin-3-ones (III), their 2-methyl derivatives IV, and 6-aryl-10-(arylmethylene)-2,3,7,8,9,10-hexahydro-4*H*,6*H*-1,3-thiazino[2,3-*b*]quinazolin-4-ones (V). These compounds do not dissolve in sodium hydroxide nor in sodium carbonate solutions. Compounds III and IV showed carbonyl absorption at ca. 1730 cm^{-1}, while the carbonyl group of V appeared at about 1690 cm^{-1}.

The formulation of compounds III, IV, and V as the linear structures rather than the angular isomers such as VI is in analogy to the formulation of 5*H*-thiazolo[2,3-*b*]quinazoline-3(2*H*),5-dione (VII) (*4*). Steric considerations are also in favor of this formulation (*1*).


VI


VII

Compounds III condensed with aromatic aldehydes in the presence of piperidine or in acetic acid–acetic anhydride solution, to give 5-aryl-2,9-bis(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*-thiazolo[2,3-*b*]quinazolin-3-ones (VIII). These compounds could also be obtained from II by the action of chloroacetic acid, the aromatic aldehyde in acetic acid–acetic anhydride. The carbonyl group in VIII absorbs around 1710 cm^{-1}, i.e., with a shift to lower frequency than in the starting III.



VIIIa, Ar = Ar′ = C_6H_5
b, Ar = C_6H_5; Ar′ = $C_6H_5CH{=}CH$
c, Ar = C_6H_5; Ar′ = $C_6H_3O_2CH_2$-3,4
d, Ar = $C_6H_4CH_3$-*p*; Ar′ = C_6H_5
e, Ar = $C_6H_4CH_3$-*p*; Ar′ = C_6H_4Cl-*p*
f, Ar = $C_6H_4OCH_3$-*p*; Ar′ = C_6H_5
g, Ar = $C_6H_4OCH_3$-*p*; Ar′ = $C_6H_3O_2CH_2$-3,4
h, Ar = C_6H_4Cl-*p*; Ar′ = C_6H_5
i, Ar = C_6H_4Cl-*p*; Ar′ = $C_6H_5CH{=}CH$
j, Ar = C_6H_4Cl-*o*; Ar′ = C_6H_4Cl-*p*
k, Ar = C_6H_4Cl-*o*; Ar′ = $C_6H_3O_2CH_2$-3,4
l, Ar = $C_6H_3O_2CH_2$-3,4; Ar′ = C_6H_5
m, Ar = $C_6H_3O_2CH_2$-3,4; Ar′ = C_6H_4Cl-*p*

On the other hand, compounds V did not condense with aldehydes. This is similar to the behavior of the fused 1,3-thiazinone ring toward aldehydes (*5*, *6*).

Experimental Section

Bis(arylmethylene)cyclohexanones (Ia–f). The bis(arylmethylene)cyclohexanones are known in the literature (*7*). In this work, these arylmethylene derivatives were prepared in

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* To whom correspondence should be addressed at the University of Cairo.

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Table I. 8-(Arylmethylene)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones (II)

compd	mp, °C (solvent)	yield, %	formula (mol wt)
IIa	195 (MeOH)	85	$C_{21}H_{20}N_2S$ (332.5)
IIb	100 (pet.)[a]	75	$C_{23}H_{24}N_2S$ (360.5)
IIc	185 (MeOH)	80	$C_{23}H_{24}N_2O_2S$ (392.5)
IId	205 (MeOH)	85	$C_{21}H_{18}Cl_2N_2S$ (401.3)
IIe	220 (AcOH)	90	$C_{21}H_{18}Cl_2N_2S$ (401.3)
IIf	176 (MeOH)	95	$C_{23}H_{20}N_2O_4S$ (420.5)

[a] pet. = petroleum ether (bp 60–80 °C).

Table II. 5-Aryl-9-(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*-thiazolo[2,3-*b*]quinazolin-3-ones (III) and Their 2-Methyl Derivatives IV

compd	mp, °C (solvent)	yield, %	formula (mol wt)	IR, cm^{-1}
IIIa	185 (EtOH)	80	$C_{23}H_{20}N_2OS$ (372.5)	1725
IIIb	145 (MeOH)	98	$C_{25}H_{24}N_2OS$ (400.5)	1725
IIIc	130 (MeOH)	90	$C_{25}H_{24}N_2O_3S$ (432.5)	1730
IIId	110 (MeOH)	85	$C_{23}H_{18}Cl_2N_2OS$ (441.3)	1730
IIIe	190 (EtOH)	95	$C_{23}H_{18}Cl_2N_2OS$ (441.3)	1725
IIIf	146 (MeOH)	80	$C_{25}H_{20}N_2O_5S$ (460.5)	1730
IVa	194 (AcOH)	85	$C_{24}H_{22}N_2OS$ (386.5)	1730
IVb	145 (pet.)[a]	80	$C_{26}N_{26}N_2OS$ (414.5)	1720
IVc	165 (EtOH)	95	$C_{26}H_{26}N_2O_3S$ (446.5)	1730
IVd	130 (MeOH)	90	$C_{24}H_{20}Cl_2N_2OS$ (455.4)	1730
IVe	195 (AcOH)	98	$C_{24}H_{20}Cl_2N_2OS$ (455.4)	1730
IVf	142 (EtOH)	75	$C_{26}H_{22}N_2O_5S$ (474.5)	1725

[a] pet. = petroleum ether (bp 60–80 °C).

Table III. 6-Aryl-10-(arylmethylene)-2,3,7,8,9,10-hexahydro-4*H*,6*H*-1,3-thiazino[2,3-*b*]quinazolin-4-ones (V)

compd	mp, °C (solvent)	yield, %	formula (mol wt)	IR, cm^{-1}
Va	130 (pet. 3)[a]	85	$C_{24}H_{22}N_2OS$ (386.5)	1685
Vb	130 (pet. 1)[a]	80	$C_{26}H_{26}N_2OS$ (414.5)	1690
Vc	133 (MeOH)	90	$C_{26}H_{26}N_2O_3S$ (446.5)	1695
Vd	120 (pet. 2)[a]	75	$C_{24}H_{20}Cl_2N_2OS$ (455.4)	1670
Ve	200 (AcOH)	95	$C_{24}H_{20}Cl_2N_2OS$ (455.4)	1670
Vf	167 (EtOH)	93	$C_{26}H_{22}N_2O_5S$ (474.5)	1690

[a] pet. 1 = petroleum ether, bp 40–60 °C. pet. 2 = petroleum ether, bp 60–80 °C. pet. 3 = petroleum ether, bp 80–100 °C.

Table IV. 5-Aryl-2,9-bis(arylmethylene)-2,3,6,7,8,9-hexahydro-5*H*-thiazolo[2,3-*b*]quinazolin-3-ones (VIII)

compd	mp, °C (solvent)	yield, %	formula (mol wt)	IR, cm^{-1}
VIIIa	230 (benzene)	98	$C_{30}H_{24}N_2OS$ (460.6)	1710
VIIIb	185 (AcOH)	85	$C_{32}H_{26}N_2OS$ (486.6)	1710
VIIIc	215 (B/A)[a]	95	$C_{31}H_{24}N_2O_3S$ (504.6)	1712
VIIId	205 (AcOH)	98	$C_{32}H_{28}N_2OS$ (488.6)	1705
VIIIe	130 (MeOH)	80	$C_{32}H_{27}ClN_2OS$ (523.1)	1705
VIIIf	225 (B/A)[a]	96	$C_{32}H_{28}N_2O_3S$ (520.6)	1710
VIIIg	195 (AcOH)	90	$C_{33}H_{28}N_2O_5S$ (564.6)	1712
VIIIh	230 (B/P)[b]	95	$C_{30}H_{22}Cl_2N_2OS$ (529.5)	1695
VIIIi	190 (AcOH)	98	$C_{32}H_{24}Cl_2N_2OS$ (555.5)	1705
VIIIj	200 (AcOH)	95	$C_{30}H_{21}Cl_3N_2OS$ (563.9)	1715
VIIIk	155 (EtOH)	90	$C_{31}H_{22}Cl_2N_2O_3S$ (573.5)	1715
VIIIl	240 (AcOH)	98	$C_{32}H_{24}N_2O_5S$ (548.6)	1705
VIIIm	210 (AcOH)	85	$C_{32}H_{23}ClN_2O_5S$ (583.0)	1705

[a] B/A = benzene/acetic acid. [b] B/P = benzene/petroleum ether.

almost quantitative yield (ca. 95%) as follows. A mixture of 4.9 g (0.05 mol) of cyclohexanone, 0.10 mol of the appropriate aromatic aldehyde, and 50 mL of methanol was stirred vigorously and treated with 50 mL of 6% sodium methoxide for 15 min. Stirring was continued for 2 h, and the yellow product that separated was collected and crystallized; the melting points agreed with those in the literature.

8-(Arylmethylene)-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thiones (IIa–f). A mixture of 0.02 mol of I, 1.5 g of thiourea, and 100 mL of ethanol containing 2 g of potassium hydroxide was heated on a water bath for 3 h, and then the alcohol was evaporated. The residue was dissolved in acetic acid then poured into cold water with stirring. The product formed was filtered off and crystallized. See Table I.

The Tricyclic Heterocycles (III, IV, V). A mixture of 1.7 g of II, 1 g of chloroacetic acid or 2-bromopropanoic acid or 3-bromopropanoic acid, and 2 g of fused sodium acetate in 10 mL of acetic acid and 4 mL of acetic anhydride was refluxed for 2 h, allowed to cool, and then poured into cold water with stirring. The solid that separated was collected and crystallized. See Tables II and III.

The products do not dissolve in sodium carbonate nor in sodium hydroxide solutions.

5-Aryl-2,9-bis(arylmethylene)-2,3,6,7,8,9-hexahydro-5H-thiazolo[2,3-b]quinazolin-3-ones (VIII). Method A. A mixture of 2 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 crystallized from the proper solvent.

Method B. A mixture of 2 g of III, an equimolar amount of the appropriate aldehyde in 10 mL of acetic acid, and 5 mL of acetic anhydride was heated on a sand bath for 1 h and poured into cold water. The solid that separated was collected.

Method C. A mixture of 2 g of II, 1 g of chloroacetic acid, an equimolar amount of the appropriate aldehyde in 20 mL of acetic acid and 10 mL of acetic anhydride was refluxed for 3 h. The reaction mixture was poured into cold water and the precipitate formed was collected and crystallized.

These methods gave nearly the same yield. See Table IV. Satisfactory elemental analyses were found and agreed with calculated values within the expected limits.

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Received for review March 1, 1978. Accepted June 23, 1978.