PYRIMIDINES

XV. Substituted 2, 2'-Dioxo-6, 6'-spirobishexahydropyrimidines*

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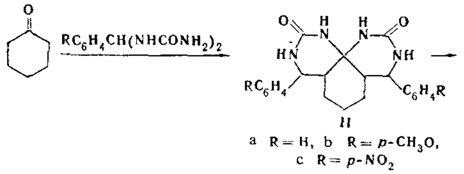
The reaction of cyclohexanone with arylidenebisureas (e.g. benzalbisurea) in an acid medium has given 4, 4'-diaryl-2, 2'-dioxo-5, 5'-trimethylene-6, 6'-spirobishexahydropyrimidines (II). The acid hydrolysis of IIa (aryl—C_6H_5) in the presence of 2, 4-dinitrophenylhydrazine leads to the 2, 4-dinitrophenylhydrazone of 2-hydroxy-8-oxo-4-phenyl-5, 6, 7, 8-tetrahydroquinazoline (IV). Compound IV was also obtained by the ozonization of 2-acetoxy-8-benzal-4-phenyl-5, 6, 7, 8-tetrahydroquinazoline (IX) and subsequent decomposition of the ozonide with a solution of 2, 4-dinitrophenylhydrazine. The structure of the compounds obtained was confirmed by means of their IR, UV, and PMR spectra. Corresponding 6, 6'-spirobishexahydropyrimidines have also been obtained from 2-methylcyclohexanone, acetone, and methyl ethyl ketone and benzalbisurea.

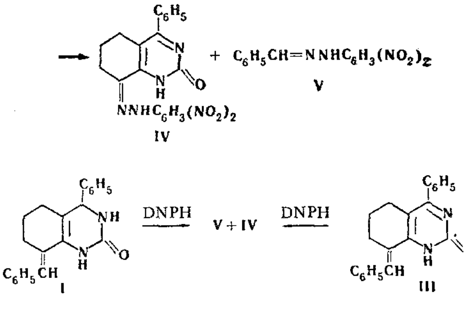
We have previously reported [2] that the condensation of cyclohexanone and benzalbisurea (BBU) gave two products: 8-benzal-2-hydroxy-4-phenyl-3, 4, 5, 6, 7, 8-hexahydroquinazoline (I) and a compound having the empirical formula $C_{22}H_{24}N_4O_2$ (IIa), the structure of which was not established. In order to establish the structure of this compound we have considered its spectral characteristics and have carried out the synthesis of a number of its analogs using other arylidenebisureas $RC_6H_4CH(NHCONH_2)_2$, where R = p-NO_2 and p-CH_3O. Compounds were obtained with the empirical formula $C_{22}H_{22}N_4O_2R_2$ (IIb, c) having properties similar to those of IIa.

Compounds II give negative qualitative reactions with dimethylaminobenzaldehyde (absence of a ureido group) and with 2, 4-dinitrophenylhydrazine (DNPH) (absence of a keto group) and do not decolorize solutions of bromine and potassium permanganate; IIa, b do not absorb hydrogen over 5% Pd/C at room temperature (absence of C=C and C=N bonds). The complete oxidation of IIa–c with potassium permanganate solution [3] gave the corresponding acids p-RC_6H_4COOH in an amount of 2 moles per mole of the initial II. The IR spectra of IIa–c have the absorption bands of NH, CH_2, $C{=}O_{amide}$ and p-C_6H_4R groups. The UV spectra of IIa and c exhibit the absorption only of the aryl substituents, and the extinction coefficients (ε) are double the extinction coefficients of the absorption of the corresponding p-substituted toluenes (see figure).



II

a R = H, b R = p-CH_3O, c R = p-NO_2



IV

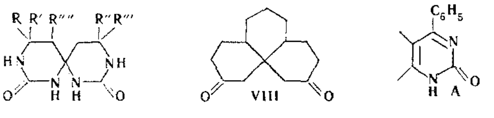
V

I

III

The PMR spectra (taken on a Varian 60 MHz instrument with CF_3COOH as solvent and $(CH_3)_4Si$ as standard) have three groups of signals: δ 1.0–2.0 (CH_2 and CH groups, multiplet), δ 4.5 (N—H, doublet), 7.0 ($C{-}H_{arom}$, singlet) with a ratio of the intensities of 10 : 2 : 10 (two N—H groups are protonated in CF_3COOH and their signals coincide with the signal of the solvent [4]). The results obtained permit the structure of 4, 4'-diaryl-2, 2'-dioxo-5, 5'-trimethylene-6, 6'-spirobishexahydropyrimidines to be ascribed to compounds IIa–c.

Spirobis compounds of the pyrimidine series are known. Thus, the condensation of acetone and urea has given 4, 4, 4', 4'-tetramethyl-2, 2'-dioxo-6, 6'-spirobishexahydropyrimidine (VI) [5, 6]. The synthesis of 4, 4-dimethyl-2, 2'-dioxo-4'-phenyl-6, 6'-spirobishexahydropyrimidine (VII) has been reported [7]. It must be mentioned that tricyclic systems of type VIII, similar in structure to II, are also known [8].



VI R = R^I = R^{II} = R^{III} = CH_3 R^{IV} = H
VII R = R^I = CH_3 R^{II} = C_6H_5 R^{III} = R^{IV} = H
XIII R = R^{II} = C_6H_5 R^I = R^{III} = R^{IV} = H
XIV R = R^{II} = C_6H_5 R^{IV} = CH_3 R^I = R^{III} = H

In a study of the properties of IIa, it was found that acid hydrolysis gave a complex mixture of products, and from this two substances were isolated by treatment with a solution of DNPH. One of them proved to be benzaldehyde 2, 4-dinitrophenylhydrazone (V), while the other substance had the empirical formula $C_{20}H_{16}N_6O_5$ (IV). The position and nature of the absorption band of the C=O group at 1660 cm^{-1} [2] permitted the assumption that this molecule contained a dehydrogenated pyrimidine ring (fragment A). It might be assumed that on the hydrolysis of IIa the splitting out of urea first took place with the formation of compounds I, which we have described previously [2]. In actual

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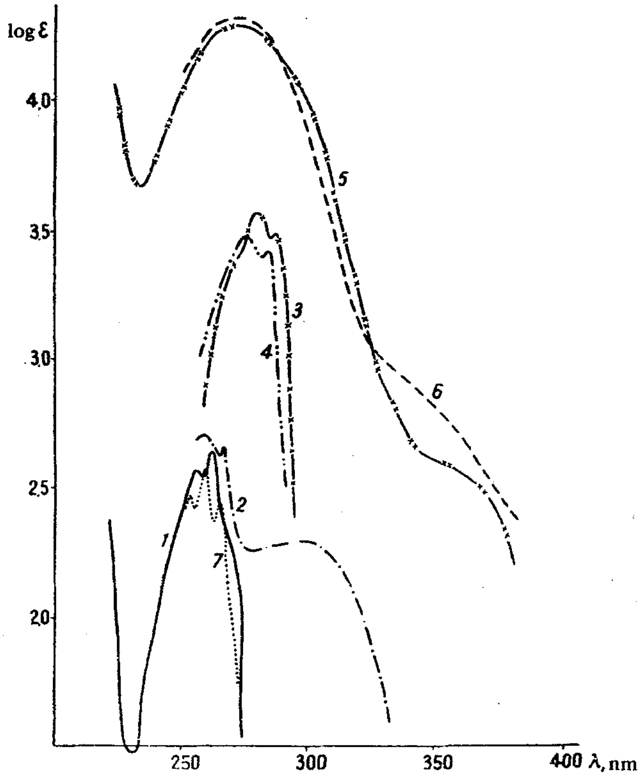
*For part XIV, see [1].



UV absorption spectra: 1) doubled adsorption spectrum of toluene [18] (in cyclohexane); 2) 2, 2'-dioxo-4, 4'-diphenyl-5, 5'-trimethylene-6, 6'-spirobishexahydropyrimidine (IIa) (in acetic acid); 3) doubled adsorption spectrum of p-methoxytoluene [19] (in ethanol); 4) 4, 4'-di-(p-methoxyphenyl)-2, 2'-dioxo-5, 5'-trimethylene-6, 6'-spirobishexahydropyrimidine (IIb) (in acetic acid); 5) doubled absorption spectrum of p-nitrotoluene [20] (in ethanol); 6) 4, 4'-di-(p-nitrophenyl)-2, 2'-dioxo-5, 5'-trimethylene-6, 6'-spirobishexahydropyrimidine (IIc) (in acetic acid); 7) 5-methyl-2, 2'-dioxo-4, 4'-diphenyl-5, 5'trimethylene-6, 6'-spirobishexahydropyrimidine (XII) (in acetic acid).

6, 6'-Spirobishexahydropyrimidines

Compound	Empirical formula	Mp*, °C	Found, %				Calculated, %				IR Spectra (υ cm^{-1}, in KBr)	Yield, %
			C	H	N	CH_3O	C	H	N	CH_3O		
IIa	$C_{22}H_{24}N_4O_2$	355 (decomp.)	70.5 70.5	6.54 6.62	14.7 14.9	—	70.2	6.38	14.9	—	3400, 3200 (N—H); 2860, 2920 (CH_2); 1680, 1665 (C=O); 700, 760 (C–H_{arom}).	85
IIb	$C_{24}H_{28}N_4O_4$	>350	66.6 66.3	6.50 6.68	12.9 12.9	13,8 13,5	66.1	6.42	12.8	14,2	3400, 3200 (N—H); 2870, 2340 (CH_2); 1690, 1680 (C=O) 1250 (C—O—C); 2840 (CH in CH_3O—), 780, 835 (C–H_{arom}).	70
IIc	$C_{22}H_{22}N_6O_6$	330 (decomp.)	56.4 56.3	5.22 4.88	18.6 18.5	—	56.6	4.72	18.0	—	3410, 3230 (N—H); 2860, 2940 (CH_2); 1660, 1680 (C=O); 1530, 1360, 860 (NO_2).	85
XII	$C_{23}H_{26}N_4O_2$	>350	—	—	14.2 14.3	—	—	—	14.4	—	3420, 3260 (N—H); 2950, 2875 (CH_2); 1690, 1675 (C=O); 710, 770 (C–H_{arom}).	15
XIII	$C_{19}H_{20}N_4O_2$	312—315	67.9 67.9	6.02 6.15	16.6 16.4	—	67.8	5.99	16.6	—	3400, 3235 (N—H); 1670 (C=O); 705, 707 (C–H_{arom}).	25
XIV	$C_{20}H_{22}N_4O_2$	298—301	—	—	15.5 15.3	—	—	—	15.9	—	3420, 3240 (N—H); 1670 (C=O); 700, 765 (C–H_{arom}).	56

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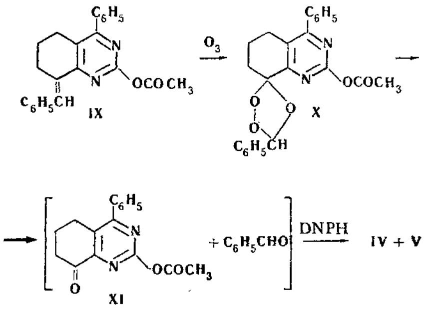
*Recrystallization from a mixture of acetic acid and ethanol.

fact, the acid hydrolysis of I when it was boiled with $CH_3COOH + HCl$ and the solution was then treated with DNPH led to a compound identical with product IV obtained from IIa. An intermediate in this reaction could be 8-benzal-2-hydroxy-4-phenyl-5, 6, 7, 8-tetrahydroquinazoline (III), since it is known [9] that in an acid medium compounds of type I are capable of disproportionation. In actual fact, when III was treated with a solution of DNPH, IV was again formed. The structure of IV was established by ozonizing IX,* obtained from III [2]. The ozonization method has been used previously in the pyrimidine series for the synthesis of aldehydes from styrylpyrimidines [10, 11].

It is interesting to note that the ozonized X isolated proved to be a comparatively stable compound at room temperature. It was impossible to isolate 2-acetoxy-8-oxo-4-phenyl-5, 6, 7, 8-tetrahydroquinazoline (XI) in the pure form by hydrogenation of the ozonide over Pd/C. Compound XI was characterized in the form of a semicarbazone and a 2, 4-dinitrophenylhydrazone, the preparation of which was accompanied by the splitting off of the acetyl group. The 2, 4-dinitrophenylhydrazone proved to be identical with compound IV obtained in the hydrolysis of I, IIa, and III.



The structure of X was confirmed not only by the analytical data and the positive qualitative reaction with potassium iodide solution [12], but also by spectral data. Its IR spectrum has strong bands at 1020 and 1080 cm^{-1}, one of which can be ascribed to the absorption of the ozonide group —O—O— of the ozonide X [13, 14]. In the UV spectrum, the maximum of the absorption curve of compound X is displaced to the shortwave region in comparison with IX by 60 mμ, which is connected with a disturbance of the conjugation of the pyrimidine ring with the benzene ring. The formation of the spiro compound II from cyclohexanone is apparently connected with the presence in the latter of two active methylene groups in the α- and α'-positions at which condensation with BBU to form a diureido derivative can take place; the latter cyclizes to II.

With 2-methylcyclohexanone, which also has an α-CH_2 and an α'-CH group of similar reactivities, the reaction takes place analogously with the formation of 5-methyl-2, 2'-dioxo-4, 4'-diphenyl-5, 5'-trimethylene-6, 6'-spirobishexahydropyrimidine (XII).

This reaction has also been successfully extended to aliphatic ketones; acetone and methyl ethyl ketone gave 2, 2'-dioxo-4, 4'-diphenyl-6, 6'-spirobishexahydropyrimidine (XIII) and 5-methyl-2, 2'-dioxo-4, 4'-diphenyl-6, 6'-spirobishexahydropyrimidine (XIV), respectively. Compound XIII was identical with the compound obtained from dibenzalacetone and urea by the method of Zigeuner et al. [6]. It was impossible to obtain IIa under analogous conditions.

EXPERIMENTAL

The compounds were identified by an absence of the depression of the melting point of mixtures and by comparisons of IR spectra and of R_f values (thin-layer chromatography on silica gel).

Preparation of 6, 6'-spirobishexahydropyrimidines. A mixture of 20.0 mM of the ketone (80 mM for the aliphatic ketones), 40.0 mM of the arylidenebisurea, 25 ml of absolute ehtanol, and 20 drops of concentrated HCl was boiled with stirring for 4 hr. The gradual dissolution of the arylidenebisurea took place and then, after 40 min, a precipitate deposited which was filtered off and was carefully washed with ethanol and water. The corresponding 6, 6'-spirobishexahydropyrimidines were obtained (see table).

Acid hydrolysis of IIa. A mixture of 4.0 g (10.5 mM) of IIa, 60 ml of acetic acid and 12 ml of concentrated HCl was boiled for 1 hr 30 min and then the solvent was distilled off in vacuum. The residual oil was triturated with ether and dried; this gave 2.4 g of residue. The residue was dissolved in ethanol, and 2.0 g (10.0 mM) of DNPH in 60 ml of ethanol and 2 ml of concentrated H_2SO_4 were added; the mixture was boiled for 5 min. After some hours, a precipitate of V deposited; 1.0 g, mp 238–241°. The filtrate was neutralized with ethanolic KOH and the precipitate was filtered off and carefully washed with water to eliminate the inorganic salts. This gave 0.75 g of IV, mp 315–317° (from acetic acid). Found, %: C 57.0, 56.9; H 3.84, 3.74; N 20.2, 20.2. Calculated for $C_{20}H_{16}N_6O_5$, %: C 57.1; H 3.83; N 20.0. IR spectrum (ν, cm^{-1}) 1650 (C=O); 1630 (C=N); 1610, 1540, 1450 ($C=C_{arom}$); 1515, 1350, 840 (NO_2); 1440 (CH_2); 700, 750, 760, 790 ($C-H_{arom}$).

Ozonization of 2-acetoxy-8-benzal-4-phenyl-5, 6, 7, 8-tetrahydroquinazoline (IX) [2]. Ozone was passed through a solution of 1.0 g (2.8 mM) of IX in 40 ml of CCl_4 at 5–10° for 1 hr 30 min. Then the resulting solution was purged with nitrogen in order to eliminate the excess of ozone and the solvent was distilled off in vacuum. The residue was triturated with ether, and the precipitate was filtered off, giving 0.82 g (77%) of the ozonide X, mp 139–141° (from ethanol). Found, %: C 68.3, 68.5; H 5.23, 5.11; N 7.20, 7.04. Calculated for $C_{23}H_{20}N_2O_5$, %: C 68.3; H 4.98; N 6.92. IR spectrum (ν, cm^{-1}): 1795 (C=O); 1195 (C–O–C); 2870, 2950 (CH_2); 1620, 1510 ($C=C_{arom}$); 1020 and 1080 (–O–O–); 700, 760 ($C-H_{arom}$). UV spectrum (in C_2H_5OH): λ_{max}, nm 284 (log ε 4.04).

Decomposition of the ozonide X. a) A hot ethanolic solution of 0.19 g (1.0 mM) of DNPH containing 10 drops of concentrated H_2SO_4 was added to a hot saturated solution of 0.20 g (0.5 mM) of X in ethanol [15]. The precipitate that deposited was filtered off and was then boiled twice successively with ethanol (40–50 ml). The evaporation of the ethanolic filtrate gave V, mp 239–240°. The residue insoluble in ethanol amounted to 0.2 g and this was recrystallized from acetic acid to give IV, mp 315–317°.

b) A mixture of 0.50 g (1.24 mM) of the ozonide X in 10 ml of ethanol, 0.30 g (2.7 mM) of semicarbazide hydrochloride in 7 ml of ethanol, and 0.22 g (2.7 mM) of sodium acetate in 3 ml of water was boiled for 3 hr. The precipitate was filtered off, giving 0.25 g of 2-hydroxy-8-oxo-4-phenyl-5, 6, 7, 8-tetrahydroquinazoline semicarbazone, mp 276–279° (from acetic acid). Found, %: C 60.3, 60.3; H 5.33, 5.41; N 23.2, 23.4. Calculated for $C_{15}H_{15}N_5O_2$, %: C 60.6; H 5.08; N 23.6.

2, 2'-Dioxo-4, 4'-diphenyl-6, 6'-spirobishexahydropyrimidine (XIII). A mixture of 2.3 g (10.0 mM) of dibenzalacetone [16] and 2.7 g (45.0 mM) of urea in 10 ml of ethanol containing 0.5 ml of concentrated HCl was boiled for 9 hr. The precipitate was washed

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*Compound IX was selected because its solubility was better than that of III and because of the possibility of the easy elimination of the acetoxy group.

with ethanol and ether, giving 1.2 g (35%) of **XIII**, mp 305–310° (from acetic acid and ethanol.)

8-Benzal-2-hydroxy-4-phenyl-3,4,5,6,7,8-hexahydroquinazoline (I). A mixture of 2.0 g (7.3 mM) of dibenzalcyclohexanone [17], 0.9 g (14.6 mM) of urea, 10 ml of ethanol, and 0.5 ml of concentrated HCl was boiled for 8 hr. The precipitate was carefully washed with ether to eliminate dibenzalcyclohexanone. This gave 0.1 g (4%) of I, mp 198–203°, identical with the I obtained previously [2].

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