REACTION OF 2-ACYLCYCLOHEXANE-1,3-DIONES WITH 6-HYDRAZINOPHENANTHRIDINE

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The reaction of cyclohexane β-triketones with 6-hydrazinophenanthridine gave enehydrazinodiketones, which were cyclized upon heating to give derivatives of 1-(phenanthridin-6'-yl)-4,5,6,7-tetrahydroindazole.

Cyclohexane β-triketones react with ammonia and primary amines to give enaminodicarbonyl derivatives [1] with an exocyclic enamino group. The reaction with hydroxylamine, hydrazine, or their O-alkyl, O-aryl, N-alkyl, and N-aryl derivatives does not stop at this step and the final products are isoxazoles [2] and pyrazoles [3]. Compounds with high biological activity have been found among such derivatives [4, 5]. The reaction of 2-acylcyclohexane-1,3-diones with nitrogen-containing α-heterylhydrazines has not been studied. In particular, interest was found in the reaction of β-triketones [6, 7] with hydrazinophenanthridine [8].

We studied the reaction of β-triketones Ia-Ig with hydrazine II. Enehydrazinodiketones IIIa-IIIg were obtained in high yield when the reaction was carried out at 20°C in methanol. According to Strakova et al. [3], analogous reactions carried out with hydrazine or phenylhydrazine gave tetrahydroindazole derivatives. The lack of cyclization products in our case is probably a result of the bulkiness of the phenanthridine fragment. The observed regioselectivity of the addition at the exocyclic carbonyl group is in accord with the results of previous work [1-3].

The formation of tetrahydroindazole derivatives IVa-IVc proceeds upon prolonged heating of IIIa, IIIc, and IIIe in methanol at reflux. The cyclization of asymmetric enehydrazinodiketones IIIb and IIId under the same conditions, as expected, leads to a mixture of isomers IV and V, which is readily seen in the PMR spectrum in the double set of signals. However, chromatographic separation of these regioisomers was not carried out. The characteristics of the compounds synthesized are given in Table 1 Product IVc was identified as its hydrochloride salt, while the others were identified as free bases.

TABLE 1. Characteristics of IIIa-IIIg and IVa-IVc

Compound	Chemical formula	mp, °C	Yield, %
IIIa	$C_{23}H_{23}N_3O_2$	198...200	89
IIIb	$C_{25}H_{25}N_3O_4$	104...106	88
IIIc	$C_{25}H_{27}N_3O_2$	175...177	91
IIId	$C_{27}H_{29}N_3O_4$	162...163	81
IIIe	$C_{27}H_{33}N_3O_2S$	99...100	79
IIIf	$C_{35}H_{45}N_3O_4$	102...103	78
IIIg	$C_{33}H_{33}N_3O_4$	205...206	80
IVa	$C_{23}H_{21}N_3O$	176...178	71
IVb	$C_{25}H_{25}N_3O$	154...156	76
IVc	$C_{15}H_{24}ClN_3OS$	115...116	65

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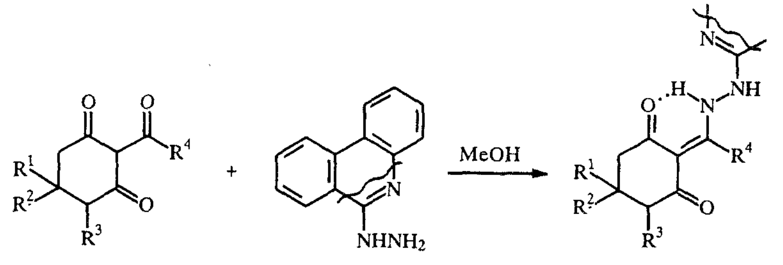
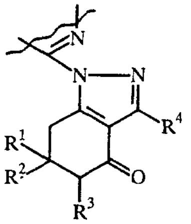
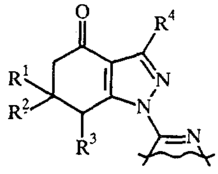


Ia-g II IIIa-g



IVa-c



V

I, IIIa, b$R^1 = R^2 = R^4 =$ Me; a $R^3 =$ H, b$R^3 = CO_2Me$; c $R^1 = R^2 =$ Me, $R^3 =$ H, $R^4 =$ n-Pr; d $R^1 =$
$R^2 =$ Me, $R^3 = CO_2Me$, $R^4 =$ -Pr; e $R^1 =$ H, $R^2 = Me(C_2H_5S)CHCH_2$, $R^3 =$ H, $R^4 =$ n-Pr; IIIf $R^1 =$
$R^2 =$ Me, $R^3 = CO_2Me$, $R^4 = n\text{-}C_{11}H_{23}$; g $R^1 =$ H, $R^2 = 1,3,5\text{-}Me_3C_6H_2$, $R^3 = CO_2Me$, $R^4 =$ Et; IVa $R^1 =$
$R^2 =$ Me, $R^3 =$ H, $R^4 =$ Me; b $R^1 = R^2 =$ Me, $R^3 =$ H, $R^4 =$ n-Pr; c $R^1 =$ H, $R^2 = Me(C_2H_5S)CHCH_2$, $R^3 =$
H, $R^4 =$ n-Pr

The PMR spectra of enehydrazinodiketones IIIa-IIIg (Table 2) show downfield NH proton singlets at 8.26-8.85 and 16.12-16.40 ppm, which are shifted to lower field upon the addition of CF_3O_2H. These signals correspond to unassociated and chelated protons. The IR spectra of these compounds have bands for the C=C double bond at 1605 cm^{-1}, broad carbonyl bands at 1555-1565 cm^{-1}, and broad NH bands at 3180-3290 cm^{-1}, which also indicates the formation of an intramolecular chelate. These data indicate that IIIa-IIIg exist mainly in the enehydrazinodiketone form stabilized by intramolecular hydrogen bonding. In the case of asymmetrical enehydrazines IIIb, IIId, IIIf, and IIIg, there are structural preconditions for the existence of these compounds in two forms. Analysis of the PMR spectra and thin-layer chromatographic data indicate the existence of only one form but do not permit a selection of a specific form.

The IR spectra of IIIa-IIIg also have bands for a free carbonyl group at 1635-1640 cm^{-1} and CO_2Me groups at 1730-1745 cm^{-1} (esters IIIb, IIId, IIIf, IIIg) and also a free NH group at 3410-2450 cm^{-1}.

The PMR spectra of indazolones IVa-IVc (Table 2), in contrast to the spectra of the corresponding starting enehydrazinoketones IIIa, IIIc, and IIIe, lack NH group signals. The IR spectra of these compounds have a free carbonyl band at 1670 cm^{-1}. The CO_2Me group is retained in the formation of the mixture of products IV and V from IIIb and IIId (1740 cm^{-1}).

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for 0.01 M solutions in $CHCl_3$. The PMR spectra were taken on a WH-90 spectrometer at 90 MHz in $CDCl_3$ with HMDS as the internal standard. The chromatography was carried out on Silufol UV-254 plates using 1:3:6 acetone—ethanol—chloroform as the eluent. Bromine vapor was used for development.

The elemental analysis data for C, H, N, and Cl corresponded to the calculated values.

Starting ketones Ia-Ig were obtained according to procedures described in our previous work [6, 7].

N-(Phenanthridin-6′-yl)-N′-[R^4-(5-R^1-4-R^2-1,3-dioxo-4-R^3-cyclohexylidene-2)-methyl]hydrazines (IIIa-IIIg). A sample of 0.21 g (1 mmole) II was added to a solution of 1 mole triketone Ia-Ig in 20 ml methanol and stirred for 18 h at 20°C with monitoring by thin-layer chromatography. The solvent was removed in vacuum. The residue was filtered off, dried, and recrystallized.

3-R^4-4-Oxo-6-R^1-6-R^2-1-(phenanthridin-6′-yl)-4,5,6,7-tetrahydroindazoles (IVa-IVc). A sample of 0.21 g (1 mmole) II was added to a solution of 1 mmole triketone Ia, Ic, or Ie in 20 ml methanol. The reaction mixture was heated

TABLE 2. PMR Spectra of Bases IIIa-IIIg and IVa-IVc, δ, ppm

Compound	4(5)-CH s	5(6)-2CH_3,	6(7)-CH_2	NH, s	N^1H, s	Ar, m	R^4	Other signals
IIIa	2,40 s (2H)	1,06	2,40 s (2H)	16,40	8,68	7,10...8,56	2,90 s (CH_3)	—
IIIb	3,41 s	1,16	2,38 d (6-CH_A) 2,84 d (6-CH_B)	16,30	8,30	7,14...8,20	2,90 s (CH_3)	3,76 s (OCH_3)
IIIc	2,44 s (2H)	1,06	2,44 s (2H)	16,36	8,69	7,18...8,54	1,08 t (CH_3) 1,76 m ($C\underline{H}_2CH_3$) 3,42 t (CH_2—C=)	—
IIId	3,36 s	1,08	2,38 d (6-CH_A) 2,84 d (6-CH_B)	16,26	8,32	7,18...8,60	1,08 t (CH3) 1,78 m ($C\underline{H}_2CH_3$) 3,40 t (CH_2—C=)	3,76 s (OCH_3)
IIIe	2,44 m	—	2,10...2,30 m (1H, 6-CH_A)	16,12	8,85	7,10...8,60	1,06 t (CH3) 1,76 m ($C\underline{H}_2CH_3$) 3,40 t (CH_2—C=)	1,18 t ($SCH_2C\underline{H}_3$) 1,26 d ($SCHC\underline{H}_3$) 2,55 q ($CH_3C\underline{H}_2S$) 2,88 m (SCH) 2,44...2,78 m (5-CH,6-CH_B, 4-CH_2)
IIIf	3,40 s	1,14	2,38 d (6-CH_A) 2,82 d (6-CH_B)	16,15	8,84	7,12...8,80	0,88 t (CH_3); 1,12...1,80 m $(CH_2)_9$; 3,40 t (CH_2-C=)	3,76 s (OCH_3)
IIIg	4,12 m	—	2,68 m (6-CH_A); 3,14 m (6-CH_B)	16,20	8,26	7,18...8,60; 6,80 br. c, 2H-Ph	1,36 t (CH_3); 3,44 q (CH_2)	2,40 s (3-CH_3Ph); 2,50 s (1,5-2CH_3Ph);3,58 s (OCH_3); 4,40...4,44 m (5-CH)
IVa	2,48 s	1,12	2,96 s	—	—	7,70...8,80	2,62 s (CH_3)	—
IVb	2,46 s	1,10	2,92 s (7-CH_2)	—	—	7,66...8,86	1,03 m (CH_3); 1,82 m ($C\underline{H}_2CH_3$); 3,02 t (CH_2C=N)	—
IVc	2,50 m	—	2,34 m (1H,6-CH_A)	—	—	7,70...8,78	1,04 t (CH_3CH_2); 1,80 m (CH_2CH_3); 3,10 m (CH_2C=N)	1,16 t (SCH_2CH_3) 1,28 d ($SCHCH_3$) 2,46 q (CH_3CH_2S) 2,90 m (SCH) 2,50...3,10 m (6-CH, 7-CH_B, 5-CH_2)

at reflux for 56 h. Hydrazines IIIa, IIIc, and IIIe formed at the onset of the reaction gradually converted to the corresponding indazolones IVa-IVc as monitored by thin-layer chromatography. At the end of the reaction, the solvent was removed in vacuum. The residue was filtered off, dried and recrystallized. Base IVc was dissolved in ethyl acetate and the hydrochloride salt was obtained by introducing dry HCl gas. The salt was filtered off, dried, and recrystallized.

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