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Condensation of 2-Alkylcyclohexane-1,3-diones with Cyclic Azomethines

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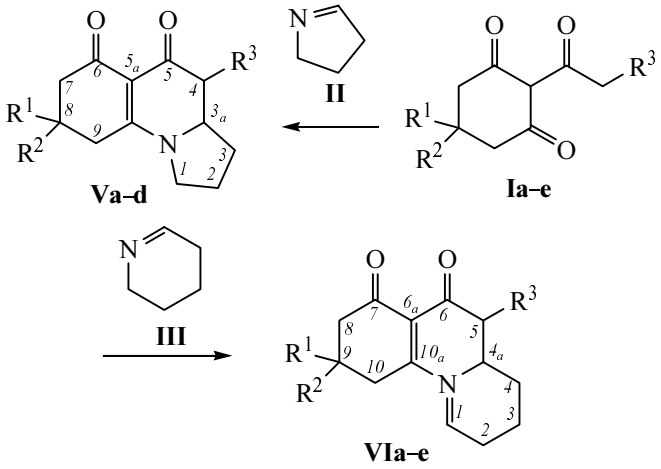
Abstract—Reaction of 2-acylcyclohexane-1,3-diones with 5- and 6-membered cyclic azomethines (3,4-dihydro-2*H*-pyrrole and 2,3,4,5-tetrahydropyridine) furnished derivatives of 2,3,3a,4,8,9-hexahydropyrrolo[1,2-*a*]quinoline-5,6(1H,5aH)-dione and 3,4,4a,5,9,10-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-6,7(2H,8H)-dione respectively. In reaction with 7-membered 3,4,5,6-tetrahydro-2*H*-azepine we failed to isolate polycyclic nitrogen-containing products.

2-Acylcyclohexane-1,3-diones (cyclic β-triketones) **I** are widely used in organic synthesis [1] and exhibit a versatile biological activity [2]. б-Methylene moiety in the side chain of the β-tricarbonyl fragment can be regioselectively involved into aldol-crotonic condensation with aromatic aldehydes; this reaction is applied, e.g., to the synthesis of naturally occurring compounds [2] and prostaglandin analogs [3]. In β-triketones fusion with 3,4-dihydroisoquinolines б-methylene group of the acyl chain also takes part. The latter reaction os often used in the synthesis of steroid heteroanalogs and of other polycyclic nitrogen-containing heterocycles [4–6].

We carried out an investigation of 2-acylcycloalkane-1,3-diones cyclocondensation with simple cyclic azomethines: 3,4-dihydro-2*H*-pyrrole (**II**), 2,3,4,5-tetrahydropyridine (**III**), and 3,4,5,6-tetrahydro-2*H*-azepine (**IV**).The azomethines were used as Schiff bases. These compounds in contrast to 3,4-dihydroisoquinoline derivatives are readily obtained from the corresponding N-containing heterocycles, but they are very unstable, easily polymerizable, and cannot be isolated in an individual state [7–8]. Therefore we brought into the condensation with the cyclohexane β-triketones **Ia–e** freshly prepared solutions of Schiff bases **II–IV**. Reactions of 2-acylcyclohexane-1,3-diones **Ia–d** with dihydropyrrole (**II**) gave rise to pyrroloquinolinediones **Va–d** in moderate yields (50–65%). In condensation of β-triketones **Ia–e** with tetrahydropyridine (**III**) pyridoquinolinedione derivatives **VIa–e** were obtained in lower yields (40–50%).



I, V, VI, $R^1 = R^2 = Me$, $R^3 = H$ (**a**); $R^1 = R^2 = R^3 = Me$ (**b**); $R^1 = R^2 = Me$, $R^3 = Ph$ (**c**); $R^1 = H$, $R^2 = Ph$, $R^3 = Me$ (**d**); **I, VI**, $R^1 = R^2 = Me$, $R^3 = Et$ (**e**).

The reaction proceeded in toluene for 2–3 days at room temperature or for 8–10 h at boiling. The condensation usually did not go to completion, and further addition of excess azomethine or longer heating resulted only in accumulation of side products (TLC monitoring). The cleaner course of the process was observed at room temperature. Reaction products were isolated by column chromatography on silica gel with subsequent crystallization.

The assumed structure of compounds **Va–d** and **VIa–e** was unambiguously confirmed by the sum of spectral data. In the IR spectra of all pyrroloquinolinediones **V**

and pyridoquinolinediones **VI** appeared in the region 1670–1690 cm^{-1} a strong absorption band characteristic of an *s-cis*-conjugated carbonyl group of an enaminodicarbonyl moiety [9], and a very strong band in the region 1540–1565 cm^{-1} corresponding to a conjugated olefin bond and an *s-trans*-conjugated carbonyl group. In the proton magnetic resonance spectra of tricyclic compounds **V** and **VI** the protons of the introduced cyclic fragments give rise to signals in appropriate regions and with expected multiplicity and integral intensity. Therewith only for pyrido-quinolinedione **VId** we observed under conditions of spectrum recording (in $CDCl_3$ solution) the presence of a diastereomers mixture. Mass spectra of compounds obtained contained molecular ion peaks, and the elemental analyses were consistent with the assumed structures.

The formation of condensation products from cyclohexane β-triketones with the seven-membered cyclic azomethine, tetrahydroazepine **IV**, was observed by means of TLC, but these compounds turned out to be very unstable under workup conditions, and we failed to characterize them.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 fromsamples in KBr pellets. ^1H NMR spectra were registered on spectrometer Bruker AT-200 from solutions in $CDCl_3$ with TMS as internal reference. Mass spectra were taken on MKh-1320 instrument. Melting points were measured on Boëtius heating block. The progress of reactions and purity of compounds was monitored by TLC on Silufol UV-254 plates (Merck), development under UV irradiation followed by spraying with alcoholic solution of iron(III) chloride. The column chromatography was carried out on silica gel 5/40 mesh (Merck , eluriated from dust).

3,4-Dihydro-2*H*-pyrrole (II) (methanol solution). To a solution of 0.1 mol of freshly distilled pyrrolidine in 100 ml of anhydrous ether at cooling to 0°C was added dropwise while stirring within 5–7 min 0.1 mol of *tert*-butyl hypochlorite in 20 ml of ether. The reaction mixture was stirred for 0.5 h at room temperature, then evaporated to 50 ml, and the solution was added dropwise to a solution of sodium methylate prepared by dissolving 2.4 g of sodium metal in 100 ml of anhydrous methanol. The reaction temperature was maintained at 0...5°C by cooling the flask with ice-salt mixture. The stirring was continued for 14–16 h at room temperature, the formed precipitate was filtered off, washed on the filter with a little methanol cooled to 0°C. The filtrate containing dihydropyrrole (**II**) was stored in a freezer and was used for condensation considering the yield of azomethine to be quantitative. Likewise were prepared methanol solutions of 2,3,4,5-tetrahydropyridine (**III**) and 3,4,5,6-tetrahydro-2*H*-azepine (**IV**) from piperidine and hexamethyleneamine respectively.

Condensation of 2-acylcyclohexane-1,3-diones Ia-e with azomethines II–IV. To a solution of 0.01 mol of triketone in 50 ml of toluene was added 20 ml of azomethine methanol solution prepared as described above. The reaction mixture was kept for 48–72 h at room temperature with addition after 24 h of 5 ml more of azomethine solution. Alternatively the reaction mixture was heated at boiling for 8–10 h adding every 2–2.5 h 5 ml of azomethine solution. The solvent was distilled off in a vacuum, the residue was dissolved in 100 ml of chloroform, the solution was once washed with 5% Na_2CO_3 solution, then with a small quantity (10 ml) of 1% hydrochloric acid, and dried on Na_2SO_4. Chloroform was removed on a rotary evaporator, and the reaction product was subjected to column chromatography on silica gel with gradient elution by ethyl acetate–ethanol mixture (gradient from 0 to 10%). The fractions giving red spots at spraying TLC plates with iron(III) chloride solution were collected. The combined fractions containing the target product were evaporated in a vacuum, and the residue was crystallized from chloroform–ethyl ether mixture.

8,8-Dimethyl-2,3,3a,4,8,9-hexahydropyrrolo-[1,2-*a*]quinoline-5,6(1*H*,5a*H*)-dione (Va). Yield 1.20 g (52%), mp 178–180°C. IR spectrum, ν, cm^{-1}: 1670, 1605, 1560, 1540. ^1H NMR spectrum, δ, ppm: 1.05 s, 1.10 s (6H, CH_3CCH_3), 1.60–2.00 m (2H, $NCH_2CH_2C\underline{H}_2$), 2.20–2.40 m (2H, $NCH_2C\underline{H}_2$), 2.24 s [2H, $COC\underline{H}_2C(CH_3)_2$], 2.36 d (1H, $COC\underline{H}_AH_B$, J 15.0 Hz), 2.46 s (2H, $CH_2C{=}C$), 2.58 d.d (1H, $COCH_A\underline{H}_B$, J_1 15.0, J_2 4.5 Hz), 3.5–3.9 m (3H, $C\underline{H}NC\underline{H}_2$). Found, %: C 72.15; H 8.31; N 6.12. $[M]^+$ 233. $C_{14}H_{19}NO_2$. Calculated, %: C 72.07; H 8.21; N 6.00.

4,8,8-Trimethyl-2,3,3a,4,8,9-hexahydropyrrolo-[1,2-*a*]quinoline-5,6(1*H*,5a*H*)-dione (Vb). Yield 1.30 g (53%), mp 174–175°C. IR spectrum, ν, cm^{-1}: 1685, 1610, 1560, 1545. ^1H NMR spectrum, δ, ppm: 1.05 s, 1.10 s (6H, CH_3CCH_3), 1.14 d (3H, CH_3, J 7.0 Hz), 1.60–2.00 m (2H, $NCH_2CH_2C\underline{H}_2$), 2.20 m (2H, $NCH_2C\underline{H}_2CH_2$), 2.24 s (2H, $COCH_2$), 2.30–2.45 m (1H, $COC\underline{H}CH_3$), 2.45 s (2H, $CH_2C{=}C$), 3.38 m (1H, NCH), 3.55–3.80 m (2H, NCH_2). Found, %: C 72.22; H 8.31; N 6.12. $[M]^+$ 247. $C_{15}H_{21}NO_2$. Calculated, %: C 72.84; H 8.56; N 5.66.

8,8-Dimethyl-4-phenyl-2,3,3a,4,8,9-hexahydropyrrolo[1,2-*a*]quinoline-5,6(1*H*,5a*H*)-dione (Vc). Yield 2.00 g (65%), mp 234–236°C. IR spectrum, ν, cm^{-1}: 1675, 1605, 1560, 1540. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 s, 1.18 s (6H, CH_3CCH_3), 1.54 m (1H, $NCH_2CH_2C\underline{H}_AH_B$), 1.85–2.15 m (3H, $NCH_2C\underline{H}_2CH_A\underline{H}_B$), 2.34 s, 2.55 s [4H, $C\underline{H}_2(CMe_2)C\underline{H}_2$], 3.43 m (1H, $NC\underline{H}_AH_B$), 3.58 d (1H, $COC\underline{H}Ph$, *J* 5.5 Hz), 3.72 m (1H, $NCH_A\underline{H}_B$), 4.15 m (1H, NCH), 7.00–7.30 m (5H, C_6H_5). Found, %: C 77.56; H 7.55; N 4.37. $[M]^+$ 309. $C_{20}H_{23}NO_2$. Calculated, %: C 77.64; H 7.49; N 4.53.

4-Methyl-8-phenyl-2,3,3a,4,8,9-hexahydropyrrolo[1,2-*a*]quinoline-5,6(1*H*,5a*H*)-dione (Vd). Yield 1.71 g (58%), mp 241–242°C. IR spectrum, ν, cm^{-1}: 1670, 1600, 1565, 1545. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.08 d (3H, CH_3, *J* 7.0 Hz), 1.60–2.0 m (4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.20 m (2H, $NC\underline{H}_2CH_2CH_2$), 2.38 m (1H, $COC\underline{H}CH_3$), 2.60–3.0 m [4H, $C\underline{H}_2(CHPh)C\underline{H}_2$], 3.20–3.46 m (3H, $C\underline{H}Ph$, $NC\underline{H}_2$), 3.64 m (1H, NCH), 7.20–7.40 m (5H, C_6H_5). Found, %: C 77.39; H 7.25; N 4.60. $[M]^+$ 295. $C_{19}H_{21}NO_2$. Calculated, %: C 77.26; H 7.17; N 4.74.

9,9-Dimethyl-3,4,4a,5,9,10-hexahydro-1*H*-pyrido-[1,2-*a*]quinoline-6,7(2*H*,8*H*)-dione (VIa). Yield 1.04 g (42%), mp 184–185°C. IR spectrum, ν, cm^{-1}: 1680, 1620, 1535, 1510 (R = H). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 s, 1.08 s (6H, CH_3CCH_3), 1.50–1.65 m (2H, $NCH_2CH_2C\underline{H}_2$), 1.75–1.80 m (4H, $NCH_2C\underline{H}_2CH_2C\underline{H}_2$), 2.25 s, 2.42 s [4H, $C\underline{H}_2C(CH_3)_2C\underline{H}_2$], 2.36 d.d (1H, $COC\underline{H}_ACH$, J_1 15.5, J_2 6.5 Hz), 2.80 d.d (1H, $COCH_B$, J_1 15.5, J_2 6.5 Hz), 3.09 t.d (1H, $NC\underline{H}_AH_B$, J_1 13.0, J_2 3.0 Hz), 3.58 m (1H, $NCH_A\underline{H}_B$), 4.17 br.d (1H, NCH, *J* 13.0 Hz). Found, %: C 72.79; H 8.65; N 5.60. $[M]^+$ 247. $C_{15}H_{21}NO_2$. Calculated, %: C 72.84; H 8.56; N 5.66.

5,9,9-Trimethyl-3,4,4a,5,9,10-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-6,7(2*H*,8*H*)-dione (VIb). Yield 1.18 g (45%), mp 135–136°C. IR spectrum, ν, cm^{-1}: 1690, 1620, 1540, 1525 (R=CH_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 s, 1.10 s (6H, $\underline{CH}_3C\underline{CH}_3$), 1.18 d (3H, $\underline{CH}_3CH$, *J* 7.5 Hz), 1.5–2.0 m [(6H, $NCH_2(\underline{CH}_2)_3$], 2.2–2.3m (1H, $CO\underline{CH}CH_3$), 2.27 C, 2.40 br.s [4H, $\underline{CH}_2(CH_3)_2\underline{CH}_2$], 3.13 t.d (1H, $N\underline{CH}_ACH_B$, J_1 13.0, J_2 2.0 Hz), 3.27 d.t (1H, NCH, J_1 11.0, J_2 3.0 Hz), 4.17 br.d (1H, $NCH_A\underline{CH}_B$, *J* 13.0 Hz). Found, %: C 73.77; H 8.95; N 5.55. $[M]^+$ 261. $C_{16}H_{23}NO_2$. Calculated, %: C 73.53; H 8.87; N 5.36.

(4a*R*,5*R*)-9,9-Dimethyl-5-phenyl-3,4,4a,5,9,10-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-6,7(2*H*,8*H*)-dione (VIc). Yield 1.62 g (50%), mp 179–180°C. IR spectrum, ν, cm^{-1}: 1695, 1610, 1540, 1505. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 s, 1.09 s (6H, CH_3CCH_3), 1.52–2.04 m [(6H, $NCH_2(C\underline{H}_2)_3$], 2.25 s, 2.40 s [4H, $C\underline{H}_2(CMe_2)C\underline{H}_2$], 3.23 m (1H, $NC\underline{H}_AH_B$), 3.45 d (1H, $COC\underline{H}Ph$, *J* 2.0 Hz), 3.85 d.t (1H, NCH, J_1 11.0, J_2 2.0 Hz), 4.20 m (1H, $NCH_A\underline{H}_B$), 7.18–7.30 m (5H, C_6H_5). Found, %: C 78.11; H 7.73; N 4.01. $[M]^+$ 323. $C_{21}H_{25}NO_2$. Calculated, %: C 77.98; H 7.79; N 4.33.

(4a*S*,5*S*)-5-Methyl-9-phenyl-3,4,4a,5,9,10-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-6,7(2*H*,8*H*)-dione (VId). Yield 1.33 g (43%), mp 166–168°C. IR spectrum, ν, cm^{-1}: 1690, 1620, 1525. Diastereomers mixture. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 d, 1.26 d (1:2, 3H, $COCHCH_3$, *J* 7.0 Hz), 1.40–2.00 m [6H, $NCH_2(C\underline{H}_2)_3$], 2.44–2.70 m (3H, $COC\underline{H}_2$, $CO\underline{CH}$), 2.86–3.00 m (2H, $C\underline{H}_2CHPh$), 3.10–3.40 m (3H, $C\underline{H}Ph$, NCH_2), 4.10 br.t (1H, NCH, *J* 11.0 Hz), 7.20–7.40 m (5H, C_6H_5). Found, %: C 77.71; H 7.45; N 4.67. $[M]^+$ 309. $C_{20}H_{23}NO_2$. Calculated, %: C 77.64; H 7.49; N 4.53.

9,9-Dimethyl-5-ethyl-3,4,4a,5,9,10-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-6,7(2*H*,8*H*)-dione (VIe). Yield 1.13 g (41%), mp 162–163°C. IR spectrum, ν, cm^{-1}: 1685, 1620, 1545, 1525 (R = C_2H_5). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.95 t (3H, $\underline{CH}_3CH_2$), 1.06 s, 1.10 s (6H, $\underline{CH}_3C\underline{CH}_3$), 1.4–2.0 m [8H,$CH_3\underline{CH}_2$, $NCH_2(\underline{CH}_2)_3$], 2.04 br.t (1H, $CO\underline{CH}CH_2$, *J* 7.5 Hz), 2.26 s, 2.37 br.s [4H, $\underline{CH}_2(CH_3)_2\underline{CH}_2$], 3.16 t.d (1H, $N\underline{CH}_ACH_B$, J_1 13.5, J_2 2.0 Hz), 3.42 br.d (1H, NCH, *J* 11.0 Hz), 4.14 d.d (1H, $NCH_A\underline{CH}_B$, J_1 13.5, J_2 2.0 Hz). Found, %: C 74.30; H 9.11; N 5.17. $[M]^+$ 275. $C_{17}H_{25}NO_2$. Calculated, %: C 74.14; H 9.15; N 5.09.

REFERENCES

1. Rubinov, D.B., Rubinova, I.L., and Akhrem, A.A., *Chem. Rev*., 1999, vol. 99, p. 1047.
2. Rubinov, D.B., Rubinova, I.L., and Akhrem, A.A., *Khim. Polim. Soed*., 1995, p. 635.
3. Lakhvich, F.A., Pashkovskii, F.S., and Lis, L.G., *Zh. Org. Khim*., 1992, vol. 28, p. 1626.
4. Gulyakevich, O.V., Mikhal'chuk, A.L., Verenich, A.I., Rubinov, D.B., Zenyuk, A.A., and Akhrem, A.A., *Enaminy v organicheskom sinteze* (Enamines in Organic Synthesis), Ural. Otd. Akad Nauk, 1996, p. 111.
5. Budnikova, M.V., Rubinov, D.B., Lis, L.G., and Mikhal'chuk, A.L., *Mendeleev Commun*., 1999, p. 208.
6. Budnikova, M.V., Zheldakova, T.A., Rubinov, D.B., and Mikhal'chuk, A.L., *Zh. Obshch. Khim*., 2002, vol. 72, p. 1053.
7. Quick, J. and Oterson, R., *Synthesis*, 1976, p. 745.
8. Bachmann, W.E., Cava, M.P., and Dreiding, A.S., *J. Am. Chem. Soc.,* 1954, vol. 76, p. 5554.
9. Lakhvich, F.A., Lis, L.G., Rubinov, D.B., Rubinova, I.L., Kurbako, V.Z., and Bykhovets, A.I., *Vestsi Akad. Nauk BSSR, Ser. Khim.,* 1989, no. 1, p. 51.