ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 6, pp. 855–859. © Pleiades Publishing, Inc., 2006.
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Synthesis of Spirocyclic Benzo[*f*]quinoline Derivatives by Cascade Heterocyclization of Dimedone, 2-Naphthylamine, and Formaldehyde

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Received March 28, 2005

Abstract—The three-component condensation of dimedone, 2-naphthylamine, and formaldehyde in aliphatic alcohols under mild conditions gives in high yields the corresponding *N*-alkoxymethyl benzo[*f*]quinoline derivatives having a substituted 2-azaspiro[5.5]undecane fragment. The reaction involves formation of three new carbon–carbon bonds, two carbon–nitrogen bonds, and one carbon–oxygen bond, and the initial β-dicarbonyl system is conserved.

DOI: 10.1134/S1070428006060078

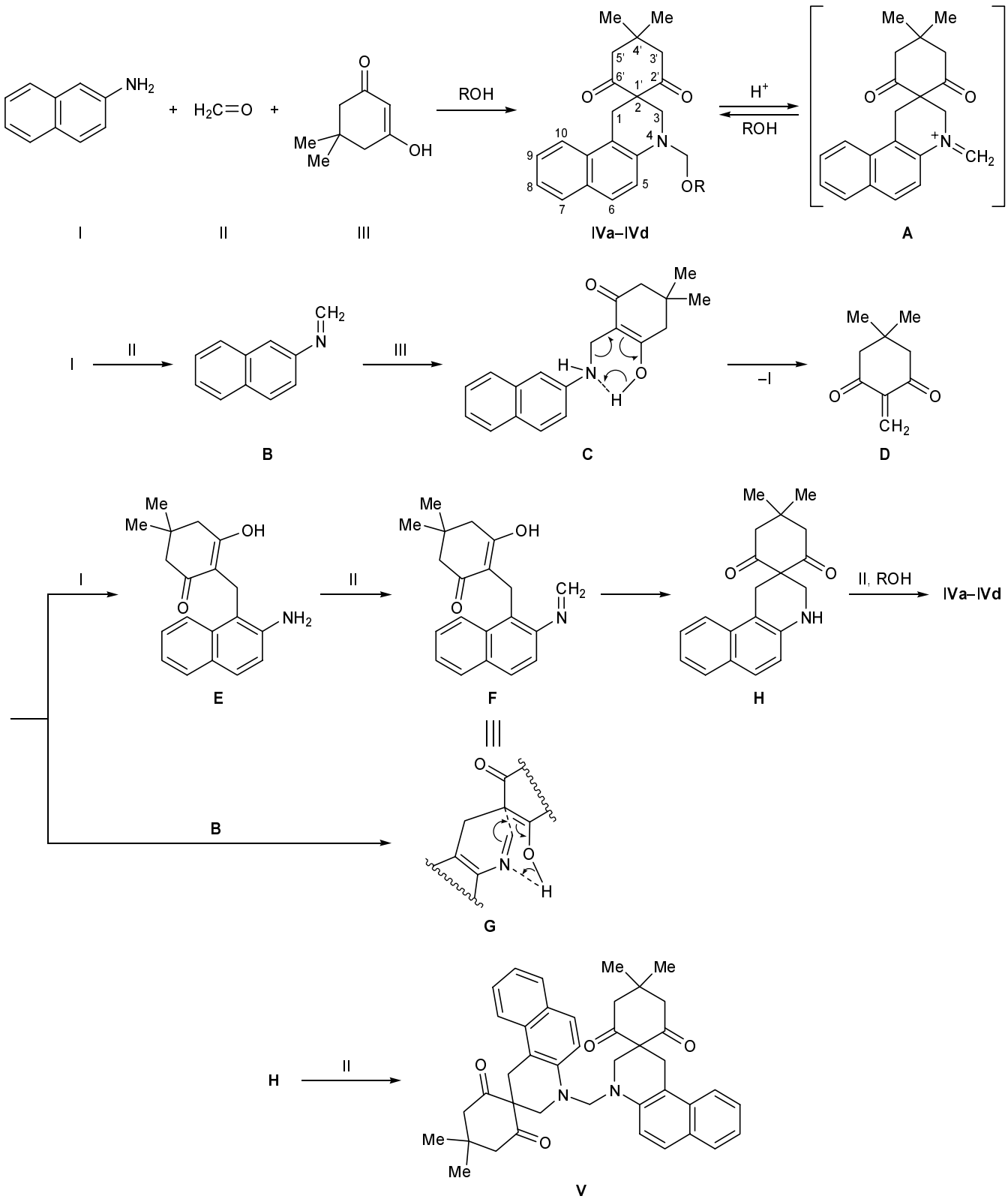
Three-component condensation of 2-naphthylamine, aromatic aldehydes, and cyclic β-dicarbonyl compounds provides a convenient synthetic route to various polynuclear heterocyclic compounds [1–3]. In particular, reactions of 5,5-dimethylcyclohexane-1,3-dione (dimedone) with 2-naphthylamine and aromatic aldehydes were used to obtain benzoacridine cytostatics [4] and analogs of natural alkaloids [5]. Various heterocyclic compounds were synthesized by triple condensation of amines, cyclic β-diketones, and formaldehyde [6–9]. The product structure was determined by the reaction conditions, structure of the initial reactants, and catalyst nature.

By reaction of 2-naphthylamine (**I**) with a large excess of formaldehyde (**II**) and dimedone (**III**) in an aliphatic alcohol at room temperature in the absence of a catalyst we obtained *N*-alkoxymethyl-substituted spirocyclic benzo[*f*]quinoline derivatives **IV** in high yields (85–95%). When the reaction was carried out in ethanol, we also succeeded in isolating a small amount (less than 5%) of a more complex product, compound **V**, which contained two spirobenzoquinoline fragments linked through a methylene bridge (Scheme 1). Treatment of alcoholic solutions of compounds **IV** with a catalytic amount of hydrochloric acid resulted in almost quantitative exchange of the aliphatic residue (R). For example, addition of a few drops of hydrochloric acid to a solution of compound **IVd** in ethanol gave 90% of ethoxymethyl derivative **IVb**. Presumably, the exchange process involves reversible formation of iminium ion **A**.

Spiro compounds **IV** and **V** are likely to be formed following a cascade mechanism ("domino" reaction). In the first stage, 2-naphthylamine (**I**) reacts with formaldehyde (**II**) to give Schiff base **B** which takes up dimedone molecule **III** at the polarized double C=N bond. Reversible elimination of aromatic amine (**I**) from β-aminodiketone **C** via synchronous electron density redistribution produces α,β-unsaturated ketone **D** in which the double bond is strongly activated due to conjugation with two carbonyl groups. Ketone **D** reacts with 2-naphthylamine at the aromatic ring, yielding aminoketone **E**, and the latter undergoes condensation at the primary amino group with formaldehyde molecule to give Schiff base **F**. Intermediate **F** can also be formed directly from Schiff base **B** and α,β-unsaturated ketone **D**. Intramolecular cyclization of **F** (probably, through a six-membered transition state like **G**) leads to spirocyclic system **H**. *N*-Alkoxymethyl derivatives **IVa**–**IVd** and methylene-bridged derivative **V** are formed via subsequent functionalization of intermediate **H**, following a Mannich-type reaction pattern (amine + formaldehyde + alcohol [10] or amine + formaldehyde + amine [11]).

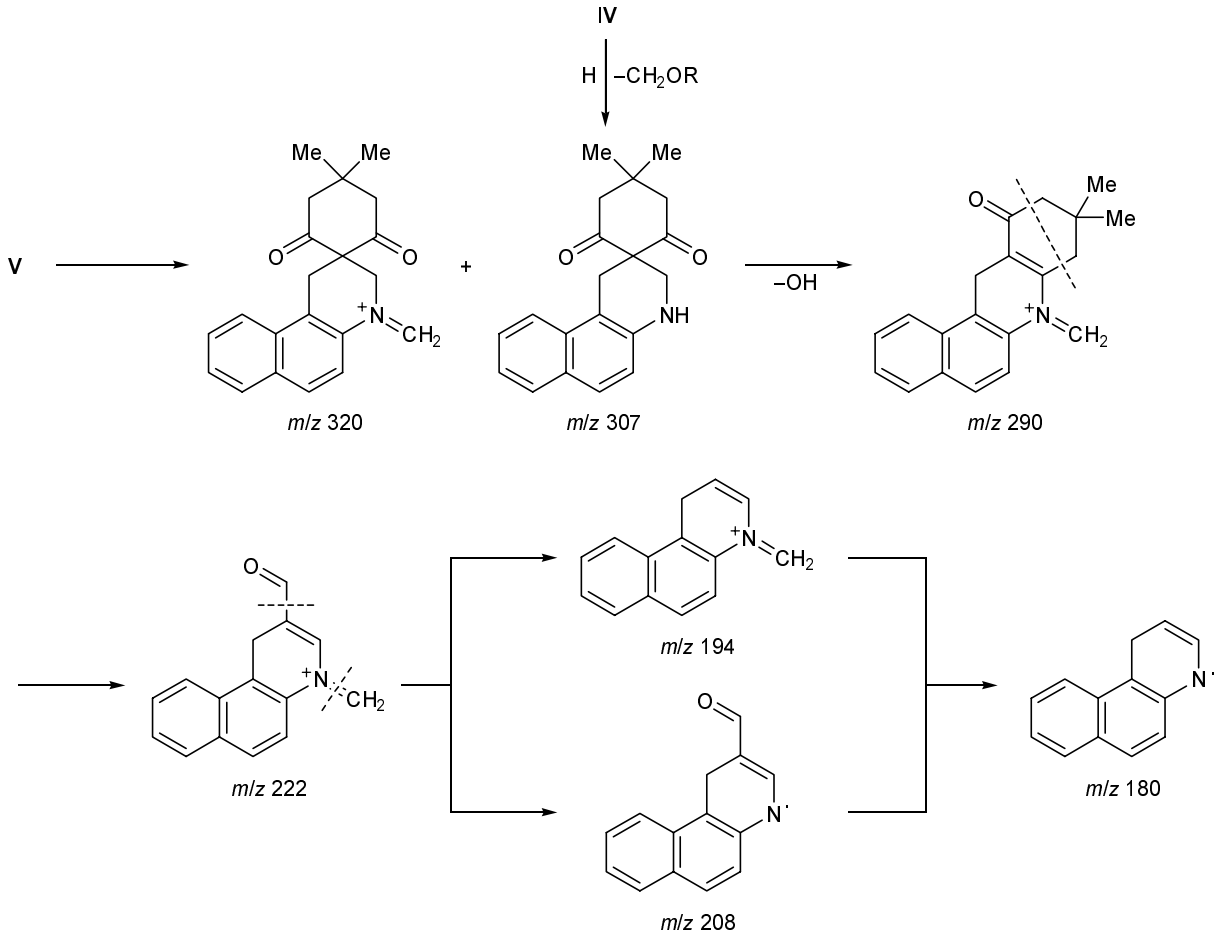
The structure of the products was determined on the basis of their IR, ^{1}H NMR, and mass spectra. The IR spectra of compounds **IVa**–**IVd** and **V** contained strong carbonyl absorption bands in the region 1725–

Scheme 1.



R = Me (**a**), Et (**b**), *i*-Pr (**c**), *n*-Bu (**d**).

Scheme 2.



1697 cm^{-1} and bands at 1095 cm^{-1} due to stretching vibrations of the ether moiety (C–O–C) (the latter band was absent in the spectrum of **V**). Stretching vibrations of the cycloaliphatic C–H bonds appeared in the region 3000–2800 cm^{-1}.

No molecular ion peak was found in the mass spectra of **IVa**–**IVd** and **V**, indicating low stability of these compounds to electron impact. The fragmentation patterns of **IVa**–**IVd** and **V** differ only in the initial stages (Scheme 2). The mass spectrum of bisbenzoquinoline derivative **V** contained ion peaks with *m*/*z* 320 (I_{rel} 30%) and 307 (55%), which correspond to decomposition of its molecule without elimination of small fragments. Spiro compounds **IVa**–**IVd** give rise only to a fragment ion with *m*/*z* 307 (55%), which is formed via elimination of the $ROCH_2$ group and is stabilized by capture of a hydrogen atom. The subsequent fragmentation is common for all spiro derivatives **IV** and **V**. The ion peak with *m*/*z* 290 (I_{rel} 38–40%) corresponds to stabilized conjugated iminium ion formed by rearrangement of the ion with *m*/*z* 320 (with elimination of formaldehyde) or *m*/*z* 307 (with elimination of hydroxide ion). The most abundant ion (I_{rel} 100%) is that with *m*/*z* 222; it originates from decomposition of the ion with *m*/*z* 290, which involves cleavage of two carbon–carbon bonds adjacent to the conjugated O=C–C=C–N=C bond sequence (the stable conjugated iminium ion structure is retained). Elimination of CO and CH_2 from the ion with *m*/*z* 222 gives fragment ions with *m*/*z* 208 (16%), 194 (15%), and 180 (38–40%).

Compounds **IVa**–**IVd** showed in the ^1H NMR spectra signals typical of the aliphatic residue R and a set of signals in the region δ 7.15–8.0 ppm (6H) from the aromatic protons. Two diastereotopic methyl groups in the dimedone fragment give rise to two singlets (3H each) at δ 0.9–1.3 ppm. Two couples of protons on $C^{3'}$ and $C^{5'}$ are mutually enantiotopic, and each couple gives only one signal in the spectrum; however, the protons in each couple are diastereotopic; therefore, the signal is split due to geminal coupling (*AB* system). As a result, a typical doublet of doublets with a "roof"

effect is observed in the region δ 2.2–3.0 ppm (overall intensity 4H, J = 16 Hz). Protons on C^1 are enantiotopic, and they appear as a singlet at δ 3.4–3.6 ppm (2H). Likewise, the singlet at δ 3.5–3.8 ppm (2H) belongs to protons on C^3; downfield shift of that signal is induced by deshielding effect of the neighboring nitrogen atom. Enantiotopic protons in the NCH_2O group suffer from deshielding effects by the nitrogen and oxygen atom, and the corresponding signal is located even more downfield, at δ ~4.8 ppm (s, 2H).

The ^{1}H NMR spectrum of compound **V** resembles a double spectrum of compounds **IV**. Two singlets (6H each) at δ 0.94 and 1.02 ppm correspond to the two pairs of methyl groups, and two doublets in the region δ 2.2–3.0 ppm (8H, J = 16 Hz) belong to 3'-H and 5'-H. Protons on C^1 and C^3 appear as two singlets (4H each) at δ 3.55 and 3.65 ppm. A set of signals with an overall intensity of 12H in the region δ 7.10–8.0 ppm belongs to the aromatic protons, and protons in the methylene bridging group (NCH_2N) give a 2H-singlet at δ 4.81 ppm.

Spirocyclization products **IVa**–**IVd** and **V** contain a unique 2-azaspiro[5.5]undecane fragment which constitutes a structural basis of a number of alkaloids (sibirine, nitramine, nitrabirine, etc.), isolated from *Nitraria sibirica Pall.* [12–15] and related to neurotoxic alkaloids of the histrionicotoxin series [16]. Partially dehydrogenated 2-azaspiro[5.5]undecane system is also a structural fragment of a number of toxins isolated from some marine ostracean species [17].

To conclude, it should be noted that the described spirocyclization is general. Cyclic β-dicarbonyl compounds other than dimedone also react with 2-naphthylamine and a large excess of formaldehyde to produce structurally related spirocyclic benzo[*f*]quinoline derivatives [18].

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protege-460 Fourier spectrometer. The ^{1}H NMR spectra were measured on a Tesla BS-567 spectrometer (100 MHz) using $CDCl_3$ as solvent and TMS as internal reference. The mass spectra were obtained on a Hewlett–Packard HP 5890/5972 GC–MS system (electron impact, 70 eV; HP-5MS capillary column, 30 m × 0.25 mm × 0.25 μm, 5% of phenylmethylsilicone; vaporizer temperature 250°C).

4-Alkoxymethyl-4',4'-dimethyl-1,2,3,4-tetrahydrospiro[benzo(*f*)quinoline-2,1'-cyclohexane]-2',6'-diones IVa–IVd (*general procedure*). A mixture of 1.43 g (0.01 mol) of 2-naphthylamine and 2.10 g (0.07 mol) of paraformaldehyde in 15 ml of the corresponding alcohol was stirred for 40 min at room temperature. A solution of 1.40 g (0.01 mol) of dimedone in 15 ml of the same alcohol was added to the mixture over a period of 30 min, and the mixture was stirred for 1 h and left overnight. The precipitate was filtered off, the filtrate was left to stand on exposure to air until most part of the solvent vaporized, and the second portion of the product was filtered off. To obtain an analytical sample, the crude product was recrystallized from the corresponding alcohol.

4-Methoxymethyl-4',4'-dimethyl-1,2,3,4-tetrahydrospiro[benzo(*f*)quinoline-2,1'-cyclohexane]-2',6'-dione (IVa). Yield 91%, mp 168°C. IR spectrum, ν, cm^{-1}: 1095 (C–O–C); 1700, 1725 (C=O); 2800–2960 ($C–H_{aliph}$). ^{1}H NMR spectrum, δ, ppm: 1.05 s (3H, CH_3), 1.25 s (3H, CH_3), 2.67 and 2.95 d (2H each, 3'-H, 5'-H, J = 16 Hz), 3.40 s (3H, OCH_3), 3.57 s (2H, 1-H), 3.78 s (2H, 3-H), 4.90 s (2H, NCH_2O), 7.25–8.07 m (6H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 307 (55), 290 (39), 222 (100), 208 (16), 194 (15), 180 (39), 168 (22), 167 (22), 152 (31), 83 (23), 55 (22), 41 (20). Found, %: C 75.07; H 7.14; N 4.03. $C_{22}H_{25}NO_3$. Calculated, %: C 75.19; H 7.17; N 3.99.

4-Ethoxymethyl-4',4'-dimethyl-1,2,3,4-tetrahydrospiro[benzo(*f*)quinoline-2,1'-cyclohexane]-2',6'-dione (IVb). Yield 86%, mp 137°C. IR spectrum, ν, cm^{-1}: 1095 (C–O–C); 1700, 1725 (C=O); 2800–2960 ($C–H_{aliph}$). ^{1}H NMR spectrum, δ, ppm: 0.85–1.2 m (9H, CH_3, $CH_2C\mathbf{H}_3$), 2.42 d and 2.70 d (2H each, 3'-H, 5'-H, J = 16 Hz), 3.32–3.67 m (6H, 1-H, 3-H, $OC\mathbf{H}_2CH_3$), 4.80 s (2H, NCH_2O), 7.05–8.0 m (6H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 307 (55), 290 (38), 222 (100), 208 (16), 194 (15), 180 (39), 168 (22), 167 (22), 152 (31), 83 (23), 55 (22), 41 (20). Found, %: C 75.53; H 7.44; N 3.80. $C_{23}H_{27}NO_3$. Calculated, %: C 75.59; H 7.45; N 3.83.

4-Isopropyloxymethyl-4',4'-dimethyl-1,2,3,4-tetrahydrospiro[benzo(*f*)quinoline-2,1'-cyclohexane]-2',6'-dione (IVc). Yield 95%, mp 145°C. IR spectrum, ν, cm^{-1}: 1095 (C–O–C); 1700, 1725 (C=O); 2800–2960 ($C–H_{aliph}$). ^{1}H NMR spectrum, δ, ppm: 0.80–1.07 m [6H, $CH(C\mathbf{H}_3)_2$], 1.18 s (3H, CH_3), 1.25 s (3H, CH_3), 2.56 d and 2.87 d (2H each, 3'-H, 5'-H, J = 16 Hz), 3.32–3.67 m [5H, 1-H, 3-H, $C\mathbf{H}(CH_3)_2$], 4.86 s (2H, NCH_2O), 7.12–8.00 m (6H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 307 (55), 290 (38), 222 (100), 208 (15), 194 (15), 180 (40), 168 (20), 167 (27), 152 (33),

83 (19), 55 (22), 41 (20). Found, %: C 75.92; H 7.70; N 3.70. $C_{24}H_{29}NO_3$. Calculated, %: C 75.96; H 7.70; N 3.69.

4-Butoxymethyl-4',4'-dimethyl-1,2,3,4-tetrahydrospiro[benzo(*f*)quinoline-2,1'-cyclohexane]-2',6'-dione (IVd). Yield 89%, mp 101°C. IR spectrum, ν, cm^{-1}: 1095 (C–O–C); 1700, 1725 (C=O); 2800–2960 (C–H_{aliph}). ^1H NMR spectrum, δ, ppm: 0.80–1.07 m (6H, CH_2CH_3, CH_3), 1.20 s (3H, CH_3), 1.25–1.67 m (4H, $CH_2CH_2CH_3$), 2.58 d and 2.90 d (2H each, 3'-H, 5'-H, J = 16 Hz), 3.38–3.65 m (4H, OCH_2CH_2, 1-H), 3.70 s (2H, 3-H), 4.88 s (2H, NCH_2O), 7.15–8.00 m (6H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 307 (55), 290 (40), 222 (100), 208 (16), 194 (15), 180 (38), 168 (25), 167 (25), 152 (35), 83 (22), 55 (23), 41 (19). Found, %: C 76.27; H 7.92; N 3.56. $C_{25}H_{31}NO_3$. Calculated, %: C 76.30; H 7.94; N 3.56.

4-{2',6'-Dioxo-(4',4'-dimethyl-1,2,3,4-tetrahydrospiro[benzo(*f*)quinoline-2,1'-cyclohexan]-4-ylmethyl}-4',4'-dimethyl-1,2,3,4-tetrahydrospiro-[benzo(*f*)quinoline-2,1'-cyclohexane]-2',6'-dione (V). A mixture of 1.43 g (0.01 mol) of 2-naphthylamine and 2.10 g (0.07 mol) of paraformaldehyde in 15 ml of ethanol was stirred for 40 min at room temperature. A solution of 1.40 g (0.01 mol) of dimedone in 15 ml of ethanol was added over a period of 30 min, and the mixture was stirred for 1 h and left overnight. The precipitate was filtered off and treated with 20 ml of boiling acetone, and the undissolved material was filtered off. Yield 0.15 g (~4%), mp 254°C (decomp.). IR spectrum, ν, cm^{-1}: 1700, 1725 (C=O); 2800–2960 (C–H_{aliph}). ^1H NMR spectrum, δ, ppm: 0.94 s (6H, CH_3), 1.02 s (6H, CH_3), 2.42 d and 2.83 d (4H each, 3'-H, 5'-H, J = 16 Hz), 3.55 s (4H, 1-H), 3.65 s (4H, 3-H), 4.81 s (2H, NCH_2N), 7.05–8.02 m (12H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 320 (30), 307 (55), 290 (39), 222 (100), 208 (15), 194 (15), 180 (38), 168 (25), 167 (22), 152 (35), 83 (20), 55 (24), 41 (20). Found, %: C 78.44; H 6.79; N 4.50. $C_{41}H_{42}N_2O_4$. Calculated, %: C 78.57; H 6.75; N 4.47.

Exchange of substituent R between compounds IVd and IVb. Compound **IVd**, 1 g, was dissolved in 10 ml of ethanol on stirring and slight heating, two drops of concentrated hydrochloric acid was added to the solution, and the mixture was stirred for 30 min at room temperature and heated to the boiling point. After cooling, the precipitate was filtered off, the filtrate was left to stand on exposure to air until most part of the solvent vaporized, and the second portion of the product was filtered off. Overall yield of compound **IVb** 0.84 g (90%).

This study was performed under financial support by the Belarussian–Russian Foundation for Basic Research (project no. Kh04R-017).

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