

Unexpected Synthesis and Crystal Structure of Ethyl 3-Benzoyl-2,6-bis(2-chlorophenyl)-1-cyano-4-hydroxy-4-phenylcyclohexane-1-carboxylate

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Abstract—Three-component condensation of dibenzoylmethane with *o*-chlorobenzaldehyde and cyanoacetamide in the presence of piperidine gave ethyl 3-benzoyl-2,6-bis(2-chlorophenyl)-1-cyano-4-hydroxy-4-phenylcyclohexane-1-carboxylate. The molecular and crystal structures of the product were studied by X-ray analysis.

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We previously showed that three-component condensation of dibenzoylmethane (**I**) with *o*-chlorobenzaldehyde (**II**) and cyanothioacetamide in ethanol at room temperature in the presence of amines leads to the formation of substituted ammonium 1,4,5,6-tetrahydropyridine-2-thiolates [1]. In continuation of our studies on the synthesis of pyridinechalcogenone derivatives by multicomponent condensation [2], in the present work we examined the reaction of dibenzoylmethane (**I**) with *o*-chlorobenzaldehyde (**II**) and cyanoacetamide (**III**). Surprisingly, the condensation product was ethyl 3-benzoyl-2,6-bis(2-chlorophenyl)-1-cyano-4-hydroxy-4-phenylcyclohexane-1-carboxylate (**IV**) (Scheme 1) instead of the expected ammonium tetrahydropyridin-2-olate analogous to the sulfur-containing compound obtained in the condensation with cyanothioacetamide.

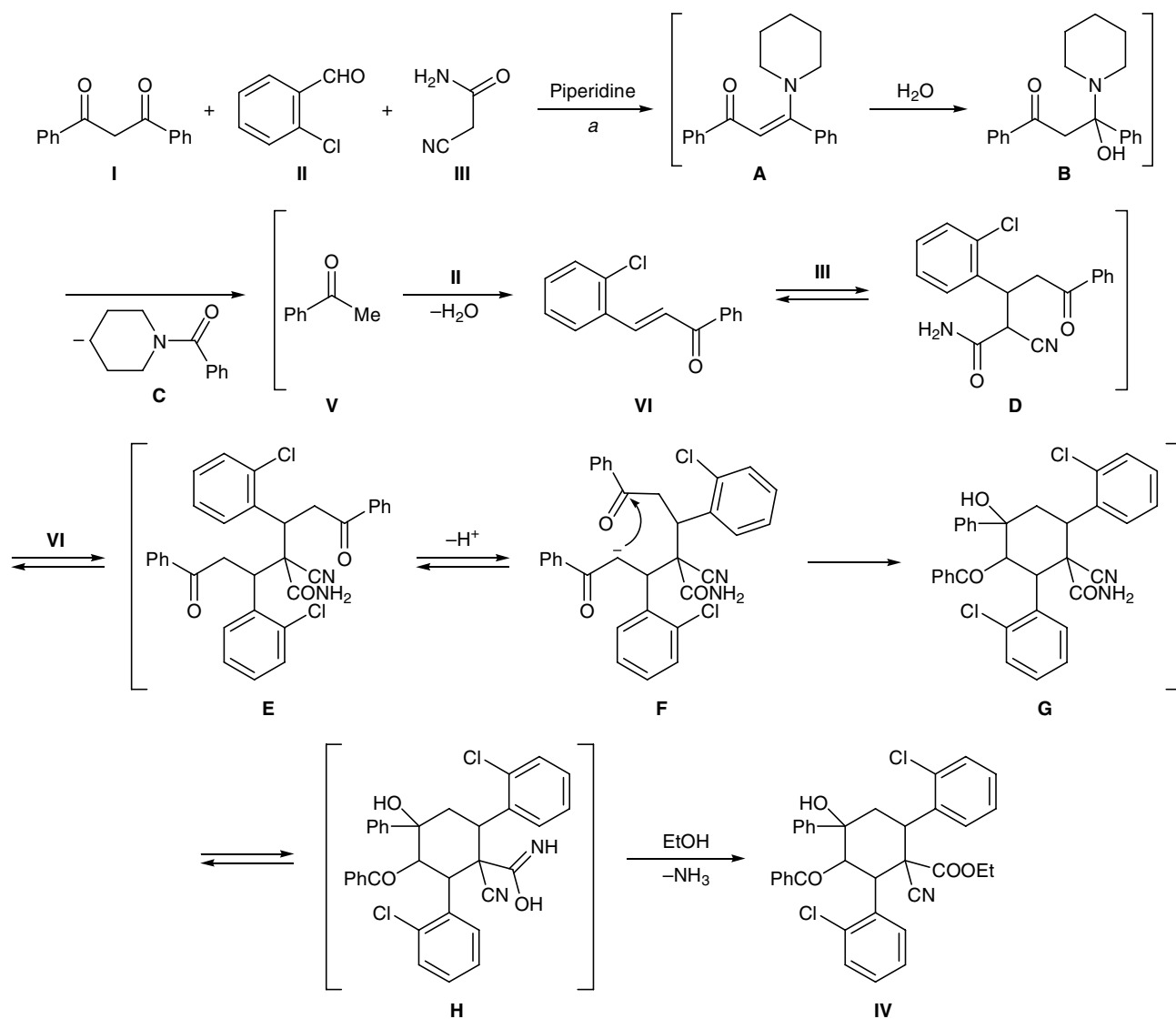
Presumably, the reaction scheme includes initial formation of enamino ketone **A** which undergoes hydrolysis to intermediate **B** rather than to initial dibenzoylmethane (**I**) and piperidine. Acyl cleavage [3] of intermediate **B** gives *N*-benzoylpiperidine **C** and acetophenone (**V**). Condensation of **V** with *o*-chlorobenzaldehyde (**II**) leads to chalcone **VI** which reacts with cyanoacetamide (**III**) according to Michael. Adduct **D** thus formed is a CH acid which in turn is capable of adding to chalcone **VI** with formation of Michael adduct **E**. The latter undergoes deprotonation to carbanion **F**, followed by intramolecular cyclization to

substituted cyclohexane **G**. Alcoholysis of the amide group in **G** through tautomeric transformation into imidic acid **H** leads to the formation of compound **IV** as final product. Substituted cyclohexanecarboxylate **IV** can also be obtained by condensation of chalcone **VI** with ethyl cyanoacetate in ethanol in the presence of piperidine (Scheme 2). In this case, the process is likely to involve double Michael addition with formation of intermediates **J** and **K**, respectively.

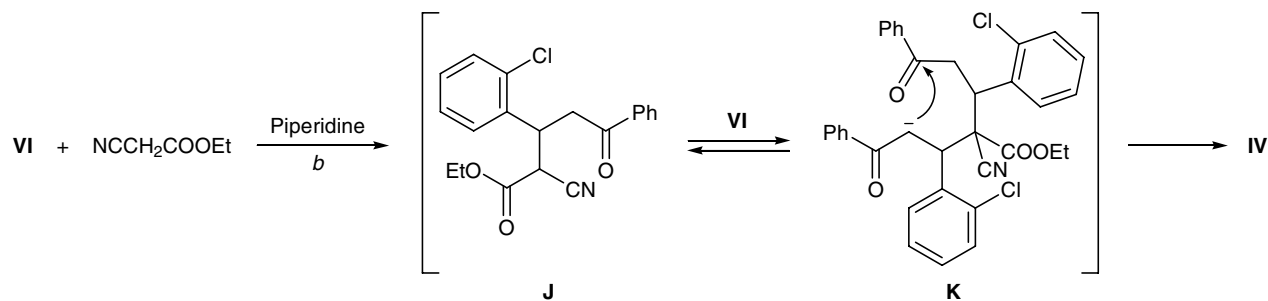
The reaction of 1,3-diphenylprop-2-en-1-one with malononitrile in basic medium is known to give 3-benzoyl-4-hydroxy-2,4,6-triphenylcyclohexane-1,1-dicarbonitrile [4] which is isostructural to **IV**.

The structure of product **IV** was unambiguously proved by the X-ray diffraction data (Fig. 1). Despite heavy substitution, the central cyclohexane ring adopts an almost undistorted *chair* conformation: the torsion angles in the ring vary within a fairly narrow range, from 52.3 to 60.7° (average 56.9°). Due to steric conditions, the four benzene rings C⁷–C¹², C¹⁷–C²², C²⁴–C²⁹, and C³⁰–C³⁵ are arranged propeller-like with respect to the cyclohexane ring: the first benzene ring with the second and forth benzene rings forms dihedral angles of 61.6 and 65.9°, respectively; the dihedral angle between the second and third benzene rings is 77.8°; and the third benzene ring is turned through a dihedral angle of 46.9° relative to the forth plane. The bond lengths and bond lengths in molecule **IV** do

Scheme 1.



Scheme 2.



not differ from standard values [5]. Molecules **IV** in crystal (Fig. 2) are linked to form centrosymmetric dimers through intermolecular hydrogen bonds $\text{O}^4\cdots\text{H}^4\cdots\text{O}^3$ with the following parameters: $\text{O}^3\cdots\text{O}^4$ 2.931(4), $\text{O}^3\cdots\text{H}^4$ 2.21(4) Å; $\angle\text{O}^3\text{H}^4\text{O}^4$ 162(2)°.

EXPERIMENTAL

The IR spectrum of **IV** was recorded on an IKS-40 spectrometer from a sample dispersed in mineral oil. The ^1H NMR spectrum was measured on a Varian

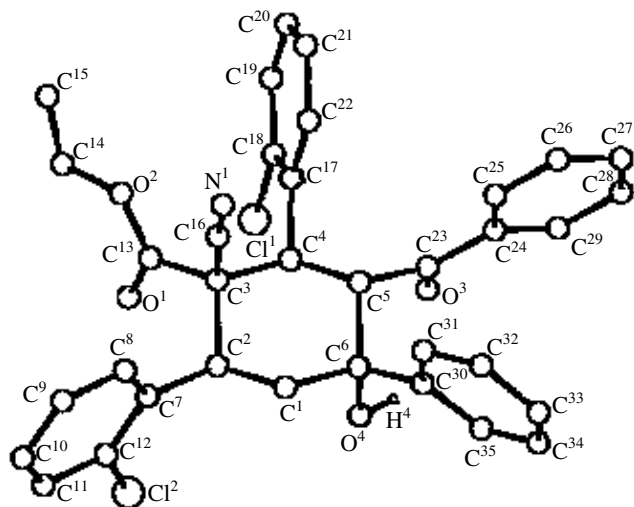


Fig. 1. Structure of the molecule of ethyl 3-benzoyl-2,6-bis(2-chlorophenyl)-1-cyano-4-hydroxy-4-phenylcyclohexane-1-carboxylate (**IV**) according to the X-ray diffraction data.

Gemini-200 instrument (199.975 MHz) from a solution in DMSO- d_6 . The melting point was determined on a Kofler hot stage. The progress of the reaction was monitored, and the purity of product **IV** was checked, by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; development with iodine vapor and UV light.

The X-ray diffraction data for compound **IV** were obtained on an Enraf–Nonius CAD-4 automatic four-circle diffractometer ($\text{CuK}\alpha$ irradiation, scan rate ratio $2\theta/\omega = 1.2$, $\theta_{\max} = 60^\circ$, spherical segment $0 \leq h \leq 11$, $-13 \leq k \leq 13$, $-14 \leq l \leq 14$) from a $0.16 \times 0.28 \times 0.40$ -mm single crystal at room temperature. Total of 4442 reflections were measured, 4168 of which were symmetry-independent ($R_{\text{int}} = 0.031$). Triclinic crystals

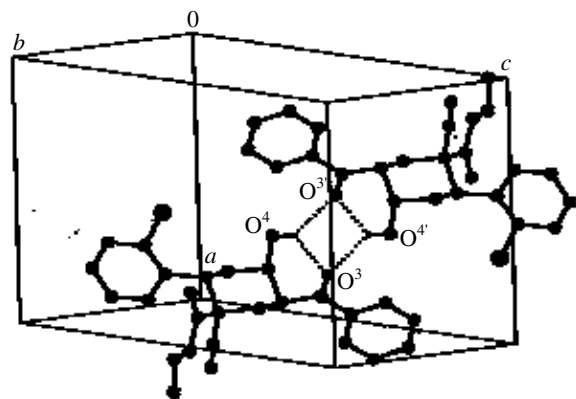


Fig. 2. Packing of ethyl 3-benzoyl-2,6-bis(2-chlorophenyl)-1-cyano-4-hydroxy-4-phenylcyclohexane-1-carboxylate (**IV**) molecules in crystal. Hydrogen bonds $\text{O}-\text{H}\cdots\text{O}$ are shown with dotted lines.

with the following unit cell parameters: $a = 10.886(3)$, $b = 12.141(7)$, $c = 12.555(3)$ Å; $\alpha = 102.99(3)^\circ$, $\beta = 90.45(2)^\circ$, $\gamma = 108.89(4)^\circ$; $V = 1524(1)\text{Å}^3$; M 598.5; $Z = 2$; $d_{\text{calc}} = 1.30$ g/cm 3 ; $\mu = 22.5$ cm $^{-1}$; $F(000) = 627.0$; space group $P2_1/c$ (no. 2). The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using CRYSTALS software package [6]; 3059 reflections with $I > 2\sigma(I)$ were used in the refinement (383 refined parameters, 8.0 reflections per parameter). All hydrogen atoms were visualized from the difference synthesis of electron density and were included in the calculation with fixed positional and thermal parameters (only the H^4 atom was refined in isotropic approximation). Absorption by the crystal was taken into account using the azimuthal scanning technique [7]. Chebyshev's weight scheme [8] with the following parameters was applied: 1.01, -0.83 , 0.17, -0.77 . The final divergence factors were $R = 0.061$, $R_w = 0.066$; GOF 1.154. The complete set of crystallographic data was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 176736).

Ethyl 3-benzoyl-2,6-bis(2-chlorophenyl)-1-cyano-4-hydroxy-4-phenylcyclohexane-1-carboxylate (IV). *a.* A mixture of 2.24 g (10 mmol) of dibenzoylmethane (**I**), 1.41 g (10 mmol) of *o*-chlorobenzaldehyde (**II**), 0.84 g (10 mmol) of cyanoacetamide (**III**), and 1 ml (10 mmol) of piperidine in 25 ml of anhydrous ethanol was stirred for 2 h at 18°C and was then left to stand for 48 h. The precipitate was filtered off and washed with ethanol and hexane. Yield 2.51 g (47%), colorless crystals, mp $202\text{--}204^\circ\text{C}$ (from EtOH). IR spectrum, ν , cm^{-1} : 3455 (OH), 2250 ($\text{C}\equiv\text{N}$), 1722 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 0.87 t (3H, Me, $J = 7.14$ Hz), 2.05 d.d (1H, 5-H, $J = 14.38$, 2.76 Hz), 2.79 t (1H, 6-H, $J = 13.90$ Hz), 3.83 q (2H, CH_2Me , $J = 7.14$ Hz), 4.78 d (1H, 2-H, $J = 11.90$ Hz), 4.93 d.d (1H, 5'-H, $J = 12.38$, 2.76 Hz), 5.13 d (1H, 3-H, $J = 11.90$ Hz), 5.52 br.s (1H, OH), 6.92–7.42 m (14H, H_{arom}), 7.51 d (2H, H_{arom} , $J = 7.36$ Hz), 7.92 m (1H, H_{arom}), 7.96 d.d (1H, H_{arom} , $J = 7.48$, 1.52 Hz). Found, %: C 70.05; H 4.60; N 2.12. $\text{C}_{35}\text{H}_{29}\text{Cl}_2\text{NO}_4$. Calculated, %: C 70.24; H 4.88; N 2.34.

b. A mixture of 2.43 g (10 mmol) of compound **VI**, 0.53 ml (5 mmol) of ethyl cyanoacetate, and 1 ml (10 mmol) of piperidine in 20 ml of anhydrous ethanol was stirred for 2 h at room temperature and was then left to stand for 24 h at that temperature. The precipitate was filtered off, washed with ethanol and hexane, and recrystallized from ethanol. The product was iden-

tical in the melting point, IR spectrum, and chromatographic data to a sample obtained according to the procedure described above in *a*.

REFERENCES

1. Krivokolysko, S.G., Dyachenko, V.D., Chernega, A.N., and Litvinov, V.P., *Khim. Geterotsikl. Soedin.*, 2001, p. 790.
2. Dyachenko, V.D., *Materialy I Mezhdunarodnoi konferentsii "Khimiya i biologicheskaya aktivnost' azotistyykh geterotsiklov i alkaloidov"* (Proc. Ist Int. Conf. "Chemistry and Biological Activity of Nitrogen-Containing Heterocycles and Alkaloids"), Moscow: Iridium, 2001, vol. 2, p. 101; Dyachenko, V.D., Krivokolysko, S.G., and Litvinov, V.P., *Khim. Geterotsikl. Soedin.*, 1996, p. 1099; Dyachenko, V.D., Krivokolysko, S.G., and Litvinov, V.P., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1997, p. 2016; Dyachenko, V.D., *Russ. J. Gen. Chem.*, 2005, vol. 75, p. 447.
3. March, J., *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, New York: Wiley, 1985.
- Translated under the title *Organicheskaya khimiya. Reaktsii, mekhanizmy i struktura*, Moscow: Mir, 1987, vol. 2, p. 473.
4. Al-Arab, M.M., Tabbal, H.D., Ghanem, B.S., and Olmstead, M.M., *Synthesis*, 1990, p. 1157; Victory, P., Berrell, J.I., Vidal-Ferran, A., Seoane, C., and Soto, J.L., *Tetrahedron Lett.*, 1991, vol. 32, p. 5375; Mishriky, N., Asaad, F.M., Girgis, A.S., and Ibrahim, Y.A., Abstracts of Papers, *4th Ibn Sina Int. Symp. Pure and Applied Heterocyclic Chemistry*, Cairo, 1992, p. 34; *Ref. Zh., Khim.*, 1993, no. 15Zh303.
5. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Taylor, R., *J. Chem. Soc., Perkin Trans. 2*, 1987, p. S1.
6. Watkin, D.J., Prout, C.K., Carruthers, J.R., and Betteridge, P.W., *CRYSTALS, Issue 10*, Chemical Crystallography Laboratory, Univ. of Oxford, 1996.
7. North, A.C.T., Phillips, D.C., Scott, F., and Mathews, F.S., *Acta Crystallogr., Sect. A*, 1968, vol. 24, p. 351.
8. Carruthers, J.R. and Watkin, D.J., *Acta Crystallogr., Sect. A*, 1979, vol. 35, p. 698.