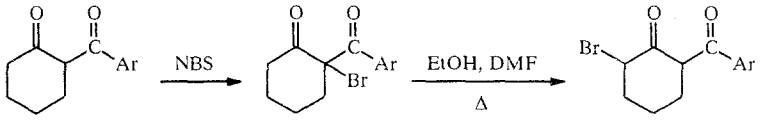
SYNTHESIS OF PHENYL-SUBSTITUTED DERIVATIVES OF DECAHYDRO-PHENANTHRIDINE-1,7-DIONE AND HEXAHYDRO-8-ISOQUINOLONE

Ya. Ya. Ozols, A. N. Pyrko,
B. A. Vigante, R. R. Dubure,
and G. Ya. Dubur

2-Bromo-2-aroylcyclohexan-1-ones were prepared by bromination of 2-aroylcyclohexan-1-ones with N-bromosucccinimide and were isomerized into 6-bromo-2-aroylcyclohexan-1-ones in attempted dehydrobromination by heating in organic solvents. The reaction of 2-benzoyldimedone with oxalyl chloride was investigated. The 2-benzoyl-3-chloro-5,5-dimethyl-2-cyclohexen-1-one obtained formed 2-benzoyl-5,5-dimethyl-2-cyclohexen-1-one in reduction with zinc activated with silver acetate. The cyclohexenone was reacted with some enaminocarbonyl compounds, yielding derivatives of decahydrophenanthridine-1,7-dione and hexahydro-8-isoquinolone.

2-Acetyl-2-cyclohexen-1-ones are used in synthesis of different oxygen- and nitrogen-containing heterocycles [1-3]. For this reason, it is useful to study the possibility of synthesizing their aromatic analogs, 2-aroyl-2-cyclohexen-1-ones in particular. Dehydrobromination of the corresponding 2-aroyl-2-bromocyclohexan-1-ones II and reduction of 2-benzoyl-3-chloro-2-cyclohexen-1-one (V) was attempted to develop a method for their preparation. 2-Bromo-2-aroylcyclohexan-1-ones II were prepared by bromination of β-diketones I with N-bromosuccinimide (N-BSI) in carbon tetrachloride. The structure of compound IIa, b was demonstrated by ESR, which unambiguously confirmed the presence of a bromine atom in the geminal position with the aroyl substituent (Table 1). The characteristic signals of enolated and nonenolated forms (compare with structure III [4]) are not present in compounds IIa, b (see Table 1). Signals of methylene group protons in positions 4 and 5 in the 1.7-2.1 ppm region appear in the spectra of compounds IIa, b. The signals were unambiguously assigned to protons in positions 3 and 6, manifested by absorption of the CH_2 group in position 3 in the 2.1-2.3 ppm region, while the methylene group next to the endocyclic oxo group produces signals in the form of a multiplet in the 2.7-33.3 ppm region. Compound IIc could not be isolated, since it is converted into known diketone IIIc during bromination or in the conditions of crystallization [4].



I-III a Ar = Ph; b Ar = *p*-ClC_6H_4; c Ar = *p*-$MeOC_6H_4$

Institute of Organic Synthesis, Latvian Academy of Sciences, Riga 226006; Institute of Bioorganic Chemistry, Belorussian Academy of Sciences, Minsk 220600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 631-635, May, 1992. Original article submitted April 1, 1991.

 0009-3122/92/2805-0530$12.50

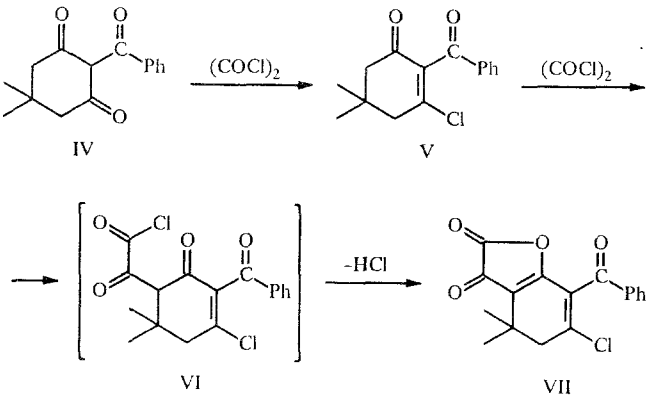
TABLE 1. ESR Spectra of Compounds IIa, b

Compound	Chemical shifts, δ, ppm (in $CDCl_3$)
IIa	1,7...2,3 (m 6H, 3,4,5-3CH_2); 2,7...3,3 (m, 2H, 6-CH_2); 7,2...8,0 (m, 5H, arom. protons)
IIb	1,7...2,3 (m 6H, 3,4,5-3CH_2); 2,7...3,3 (m, 2H, 6-CH_2); 7,2...8,0 (m, 4H, arom. protons)

In attempting dehydrobromination of compounds IIa, b by heating in ethanol or DMF with the method in [5], they were isomerized into known bromodiketones IIIa, b [4]. Analogous $\alpha \rightarrow \alpha'$ migration of the bromine atom has been observed in 2-bromo-2-acetylcyclohexan-1-one [6].

2-Chloro-1,3-diketones are more stable in such a rearrangement [7, 8], but attempts to eliminate hydrogen chloride from the known 2-chloro-2-benzoylcyclohexan-1-one [4] in the presence of collidine [8] and other dehydrohalogenating agents did not produce positive results.

Since the methods of dehydrohalogenation described above did not lead to the formation of 2-aroyl-2-cyclohexen-1-ones, the reaction of direct hydrogenolysis of the C—Cl bond in chlorenedione V was studied. We investigated the reaction of 2-benzoyldimedone (IV) with oxalyl chloride to prepare V [9, 10]. It was found that the course of the reaction is a function of the ratio of the amounts of the starting triketone and oxalyl chloride. With a triketone—oxalyl chloride ratio of 1:2.5, chlorenedione V is the basic product of the reaction, and a significant amount of a product of further transformation is also formed with a 1:6 ratio: series VII hydrobenzofuran derivative. Compound VII is evidently formed as a result of oxalylation of chlorenedione V through intermediate dichlorotetraone VI.



IV V VI VII

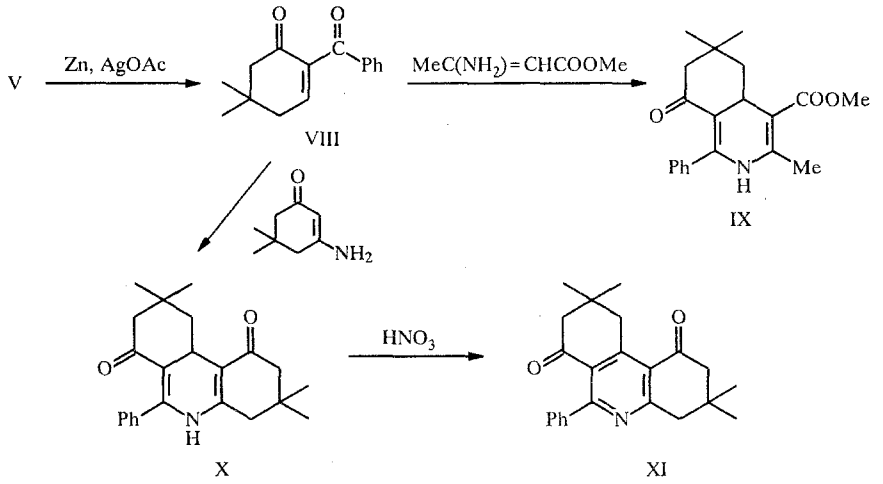
The IR spectrum of compound V contains absorption bands of endione (1630, 1672, and 1687) and aromatic (1585 and 1602 cm^{-1}) groups; there are molecular ion peaks (*m/z* 262, 264) in the mass spectrum.* Signals of methyl group protons at 1.22 (6H, s), methylene protons at 2.42 (2H, s) and 2.71 (2H, s), and aromatic protons in the 7.50-7.89 ppm (5H, m) region are observed in the ESR spectrum.

In addition to absorption at 1605, 1618, 1640, 1672, and 1695 cm^{-1}, there is an intense maximum at 1803 cm^{-1} in the IR spectrum of compound VII, characterizing a γ-lactone system. There are molecular ion peaks (*m/z* 316, 318) in the mass spectrum.† The ESR spectrum contains the signal of absorption of methylene group protons at 1.55 (6H, s), a methylene fragment at 2.68 (2H, s), and aromatic protons in the 7.39-7.81 ppm region (5H, m). All signals in the ^{13}C NMR spectrum could be assigned in accordance with structure VII (see Experimental).

*Elementary composition of the substance $C_{15}H_{15}ClO_2$ (mass spectrometry).

†Elementary composition $C_{17}H_{13}ClO_4$ (mass spectrometry).

Hydrogenolysis of the C—Cl bond of chlorenedione V is executed by zinc activated with silver acetate according to the method described in [11]. The benzoylcyclohexenone VIII obtained was used in the reaction with β-aminocrotonic acid methyl ester and 3-amino-5,5-dimethyl-2-cyclohexen-1-one without preliminary isolation and identification. The structure of the hydrogenated derivatives of isoquinolone IX and phenanthridinedione X was in agreement with the data from physicochemical methods of analysis. In addition to two absorption bands (206, 252 and 202, 274 nm), the UV spectra of compounds IX and X have an absorption maximum characteristic of β-oxo-1,4-dihydropyridine systems at 401 and 408 nm, respectively. The mass spectra contain the peaks of molecular ions (*m/z* 325, 349) of substances IX and X.



In contrast to the reaction of acetylcyclohexenone and 3-amino-2-cyclohexen-1-one at −10°C [3], the reaction of the benzoyl analog was conducted in the present study with heating in acetic acid, and the intermediate products, 3,3,9,9-tetramethyl-6-phenyl-4*a*-hydroxy-1,2,3,4,4*a*,5,7,8,9,10,10*a*,10*b*-dodecaphenanthridine-1,7-dione, forexample,inallprobability undergo further transformations as a result.

Octahydrophenanthridinedione XI, whose structure is in agreement with the data from the spectral methods, was obtained by oxidation of decahydrophenanthridinedione X with nitric acid. The ESR spectrum contains two singlets of *gem*-dimethyl fragments (1.11 and 1.14 ppm), four singlets (2.55, 2.63, 3.13, 3.40 ppm) of methylene groups, two significantly shifted to the weak-field region (by ~1 ppm) in comparison to the signals of the corresponding protons of dehydrophenanthridine derivative (X) due to the effect of the heteroaromatic ring.

EXPERIMENTAL

The UV spectra were recorded on a Specord UV-vis spectrometer (in ethanol). The IR spectra were made on PE-580B and UR-20 instruments (in petrolatum). The mass spectra were obtained on AE1 MS-50 and Varian MAT-311 instruments with 70 eV ionizing electron energy, and the NMR spectra were recorded on Bruker WH/90 and WH/360 instruments with TMS as the internal standard. The individuality of the synthesized substances was monitored by TLC on Silufol UV-254 plates with chloroform—hexane—acetone solvent system, 9:7:2. Development was in UV light.

The data from elemental analysis for C, H, N, Cl, and Br agreed with the calculated values. The initial 2-aroylcyclohexan-1-ones were prepared by the methods in [4, 12-14], and 2-benzoyldimedone was prepared according to [15].

2-Bromo-2-benzoylcyclohexan-1-one (IIa, $C_{13}H_{13}BrO_2$). Here 4.05 g (20 mmole) of compound Ia was boiled with 4.60 g (25 mmole) of N-BSI in 20 ml of carbon tetrachloride for 2 h. Succinimide was separated, the filtrate was washed with water, dried with $MgSO_4$, and evaporated. The residue was crystallized from ethanol. Mp = 63°C. Yield of 2.8 g (50%).

2-Bromo-2-*p*-chlorobenzoylcyclohexan-1-one (IIb, $C_{13}H_{12}BrClO_2$) was prepared similar to compound IIa from 4.7 g (20 mmole) of substance Ib with a yield of 2.8 g (45%). Mp = 58°C (from a mixture of ether and heptane with cooling to −60°C).

Reaction of compound Ic with N-BSI. Here 2.5 g (40%) of the substance was obtained from 4.6 g (20 mmole) of compound Ic, and the analytical data corresponded to the characteristics of compound IIIc [4].

Isomerization of compound IIa into IIIa. Here 2.81 g (10 mmole) of compound IIa in 10 ml DMF was heated in a water bath for 2 h. The mixture was poured into water, and an oil which hardened at 0°C was obtained. Crystallization from ethanol yielded 1.6 g (58%) of a substance identical to known compound IIIa [4].

Compound IIb was analogously isomerized into IIIb [4].

Reaction of 2-benzoyldimedone (IV) with oxalyl chloride. A. Here 4.88 g (20 mmole) of compound IV in 35 ml of dry chloroform was treated with 10 ml (120 mmole) of oxalyl chloride and boiled for 4 h. It was poured into 200 ml of water, the organic part was extracted with 200 ml of chloroform, washed with an aqueous solution of sodium bicarbonate and water, and dried with $MgSO_4$. The solvent was evaporated, the residue was treated with ether—hexane mixture, and yellow substance VII ($C_{17}H_{13}ClO_4$) with mp = 158-160°C (from ethanol) was obtained. ^{13}C NMR spectrum ($CDCl_3$): 192.75 (COC_6H_5); 188.74 ($C_{(3)}$); 161.84 ($C_{(6)}$); 156.30 ($C_{(2)}$); 151.96 ($C_{(7a)}$); 136.02 ($C_{(7')}$); 134.53 ($C_{(4')}$); 129.34; 128.87 ($C_{(2')}$ and $C_{(3')}$); 122.28 ($C_{(1')}$); 118.88 ($C_{(3a)}$); 52.10 ($C_{(5)}$); 35.19 ($C_{(4)}$); 27.05 ppm ($2CH_3$). Yield of 1.5 g (24%).

After separation of compound VII, the filtrate was left overnight at 0°C, and colorless substance V ($C_{15}H_{15}ClO_2$) with mp = 104-106°C (from ethanol) was isolated. Yield of 1.8 g (35%).

B. Similarly, 3.80 g (71%) of substance V was obtained from 4.88 g (20 mmole) of 2-benzoyldimedone and 4.3 ml (50 mmole) of oxalyl chloride.

1-Phenyl-3,6,6-trimethyl-6-methoxycarbonyl-2,4*a*,5,6,7,8-hexahydro-8-isoquinolone (IX, $C_{20}H_{23}NO_3$). Here 1 g of chlorovinyldione V in 5 ml of methanol was added to 2.1 g of zinc activated with silver acetate according to [11]. In 3 h, 0.4 g of β-aminocrotonic acid methyl ether was added and left for 15 h. The residue was separated, the solvent was evaporated, and the sediment was boiled for 1 h in 6 ml of acetic acid. The mixture was filtered, the sediment was extracted with 25 ml of ethanol after elimination of the solvent, concentrated to 5-10 ml, and repeatedly chromatographed in three stages on preparative glass plates (220 × 280 mm) on a loose layer of Silasorb 600 (LC), 30 μm in chloroform—hexane—acetone system 9:9:1. The yellow bands were collected from the plates, eluted with a mixture of 30 ml of acetone and 30 ml of ethanol, filtered, and evaporated. The sediment was treated with ether and a yellow substance with mp of 110-112°C was obtained. IR spectrum: 1595, 1670, 1695, 1730, 3270 cm^{-1}. Yield of compound IX of 0.1 g (8%). It turned dark when stored in air due to decomposition. Other products of the reaction were not isolated.

3,3,9,9-Tetramethyl-6-phenyl-1,2,3,4,5,7,8,9,10,10*a*-decahydrophenanthridine-1,7-dione (X, $C_{23}H_{27}NO_2$). Here 1 g of chorovinyldione V in 4 ml of methanol was added to 2.1 g of zinc activated with silver acetate according to [11]. After 3 h, 0.53 g of 3-amino-5,5-dimethyl-2-cyclohexen-1-one was added and held for 15 h while shaking gently. The solution was filtered off from the sediment, the methanol was evaporated, and the residue was boiled for 1 h in 10 ml of acetic acid. After evaporation of the acetic acid and separation in a chromatographic column (silica gel L 100/160, eluent: ether—hexane mixture 1:2, 1:1, 2:1), 0.40 g (30%) of compound X was obtained, mp 199-201°C (from ether). IR spectrum (KBr): 1480, 1605, 1633, 1680, 3250 cm^{-1}. IR spectrum ($CDCl_3$): 0.99, 1.05, 1.06, 1.08 (12H, s, 4Me); 1.53 (111, t, J = 12 Hz, C^{10}—H ax.); 2.05-2.33 (611, m, $3 \cdot H_2$); 2.42 (1H, d.d. J_1 = 12 Hz, C^{10}—H eq.); 3.88 (1H, d.d, J_1 = 3.5 Hz, J_2 = 12 Hz, C^{10a}—H); 5.84 (NH), 7.27 (2H, m. arom.), 7.38 ppm (3H, m, arom.). Mass spectrum (*m/z*): 349 (M^+).

3,3,9,9-tetramethyl-6-phenyl-1,2,3,4,7,8,9,10-octahydrophenanthridine-1,7-dione (XI, $C_{23}H_{25}NO_2$). Here 0.75 ml of conc. HNO_3 was added to 250 mg of compound X in 5 ml of ethanol and the mixture was held at 20°C for 2 days. The solvent was evaporated and the sediment was treated with a saturated solution of $NaHCO_3$ and 100 ml of ether. The ether extract was dried with $MgSO_4$. After evaporation of the solvent, 0.18 g (75%) of compound XI was obtained. Mp = 170-172°C (from ether). PMR spectrum ($CDCl_3$): 1.11 and 1.14 (12H, s, 4Me): 2.55, 2.63, 3.13, 3.40 (8H, s, $4CH_2$); 7.42 ppm (511, m, arom.). Mass spectrum (*m/z*): 347 (M^+).

LITERATURE CITED

1. B. B. Snider, Tetrahedron Lett., **21**, 1133 (1980).
2. A. N. Pyrko, V International Conf. on Chem. and Biotechn. of Biol. Active Nat. Prod. Book Abstr., Vol. 3, Varna (1989), p. 235.
3. Ya. Ya. Ozole, A. N. Pyrko, F. A. Lakhvich, B. A. Vigante, R. R. Dubure, G. Ya. Dubur, and A. A. Akhrem, Khim. Geterotsikl. Soedin., No. 1, 66 (1990).
4. Ya. Ya. Ozols, V. Ya. Vigante, E. E. Liepin'sh, and A. K. Aren, Zh. Org. Khim., **9**, 1194 (1973).

5. R. P. Bokaldere, A. Ya. Liepinya, E. V. Lozha, D. O. Lolya, and Ya. F. Fremanis, Zh. Org. Khim., **17**, 2371 (1981).
6. A. A. Akhrem and A. M. Moiseenkov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1345 (1968).
7. A. A. Akhrem, A. M. Moiseenkov, and F. A. Lakhvich, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 407 (1972).
8. M. E. McEntee and A. R. Pinder, J. Chem. Soc., No. 11, 4419 (1957).
9. A. A. Akhrem, A. M. Moiseenkov, and F. A. Lakhvich, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2786 (1971).
10. F. A. Lakhvich, T. S. Khlebnikova, and A. A. Akhrem, Zh. Org. Khim., **25**, 2541 (1989).
11. A. A. Akhrem, F. A. Lakhvich, and A. N. Pyrko, Zh. Org. Khim., **19**, 2322 (1983).
12. S. Hünig, E. Benzing, and E. Lücke, Chem. Ber., **90**, 2833 (1957).
13. S. Hünig and W. Lendle, Chem. Ber., **93**, 909 (1960).
14. R. Campbell and H. Gilow, J. Am. Chem. Soc., **84**, 1440 (1962).
15. A. A. Akhrem, F. A. Lakhvich, S. J. Budai, T. S. Khlebnicova, and J. J. Petrusevich, Synthesis, No. 12, 925 (1978).

4-HYDROXY-2-QUINOLONES. 3.* SYNTHESIS AND PHYSICOCHEMICAL PROPERTIES OF 1-R-3-CARBETHOXY-4-HYDROXY-2-QUINOLONES

I. V. Ukrainets, P. A. Bezuglyi,
V. I. Treskach, A. V. Turov,
and S. V. Slobodzyan

1-R-3-Carbethoxy-4-hydroxy-2-quinolones were synthesized by intramolecular cyclization of N-R-2-carbalkoxymalonanilic acids by the Dieckmann reaction. The possibility and advantages of conducting this reaction in aqueous medium were demonstrated. The mutually perpendicular orientation of the heterocyclic and aryl fragments was demonstrated for the 1-phenyl derivative by ESR spectroscopy.

There are now several versions of synthesis of 4-hydroxy-2-quinone-3-carboxylic acids and their derivatives, used to create many antimalarials [2-4]. 3-Carbethoxy-4-hydroxy-2-quinolone (Ia) was first prepared by heating methyl anthranilate with malonic ester in the presence of sodium ethylate in 1927 [5]. Compounds of this class were later synthesized by reducing cyclization of 2-nitrobenzoylmalonic esters [6] and by the reaction of cyanoacetic ester with an excess of anthranilic acid in dry pyridine [7].

Acylation of esters of the corresponding anthranilic acids with ethoxymalonyl chloride with subsequent intramolecular condensation of anilides (II) formed by the Dieckmann reaction, which takes place in the presence of basic catalysts in

*See [1] for Communication 2.

Khar'kov Pharmaceutical Institute, Khar'kov 310002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 636-639, May, 1992. Original article submitted March 16, 1990; revision submitted February 5, 1991.

0009-3122/92/2805-0534$12.50