ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 11, pp. 1715–1718. © Pleiades Publishing, Inc. 2006.
Original Russian Text © V.O. Koz'minykh, V.I. Goncharov, E.N. Koz'minykh, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 11, pp. 1727–1730.

Simple Procedure for Preparation of Quinoxalin-2(1*H*)-one 3-[Oxo(cyclo)alkyl(idene)] Derivatives

V. O. Koz'minykh[a], V. I. Goncharov[b], and E. N. Koz'minykh[a]

[a]*Perm State Pedagogical University, Perm, 614990 Russia*
e-mail: kvoncstu@yahoo.com
[b]*Stavropol State Medical Academy, Stavropol, Russia*

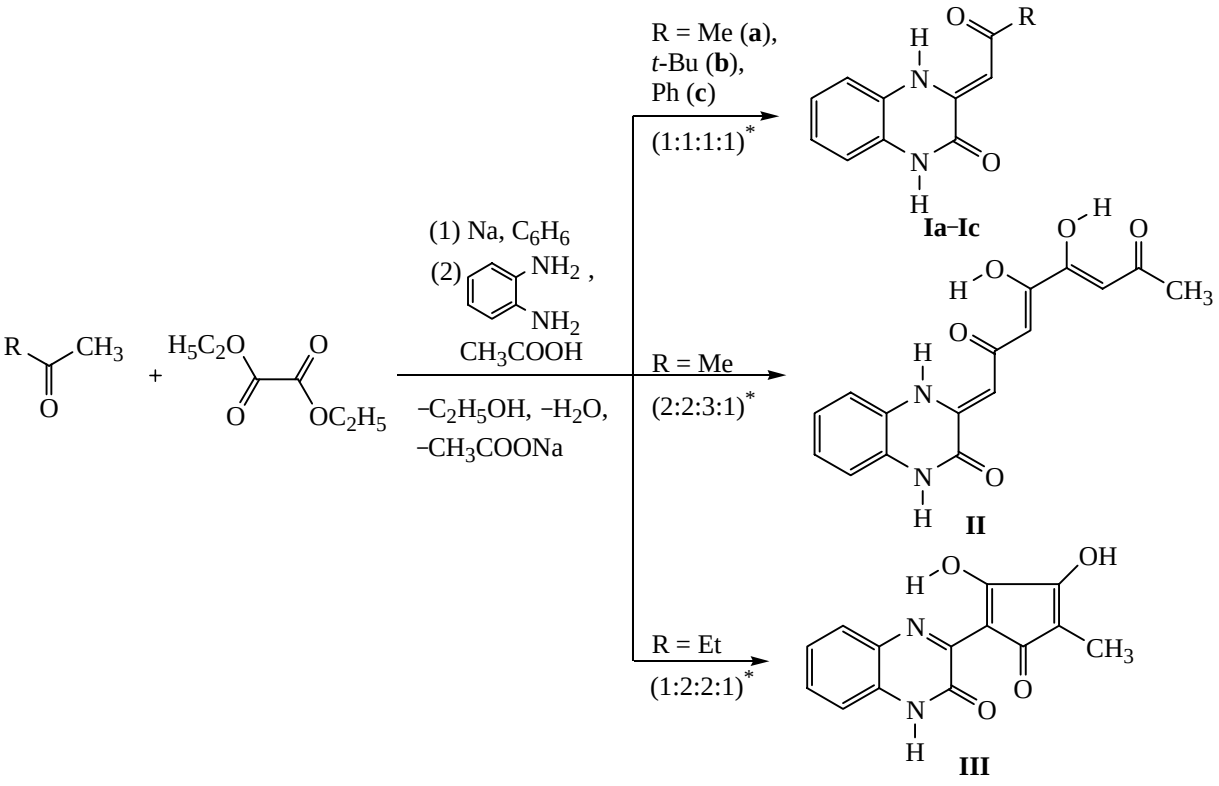
Received December 19, 2005

Abstract—A simple preparative procedure was developed for 3-(2-oxoalkylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones, 4,5-dihydroxy-1-[3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene]-3,5-octadiene-2,7-dione, and 3-(2,3-dihydroxy-4-methyl-5-oxo-1,3-cyclopentadien-1-yl)quinoxalin-2(1*H*)-one by reaction of methyl ketones first with diethyl oxalate in the presence of sodium, and then with *o*-phenylenediamine.

DOI: 10.1134/S1070428006110194

3(2)-[Oxoalkyl(idene)] derivatives of quinoxalin-2(3)-ones are extensively used in organic synthesis and exhibit a biological action [1–5]. We developed a very simple and convenient preparative procedure for 3-(2-oxoalkylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones **Ia–Ic**, and also for 4,5-dihydroxy-1-[3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene]-3,5-octadiene-2,7-dione (**II**) and 3-(2,3-dihydroxy-4-methyl-5-oxo-1,3-cyclopentadien-1-yl)quin-

Scheme 1.



* Molar ratio ketone–diethyl oxalatet–Na–*o*-phenylenediamine.is given in parentheses.

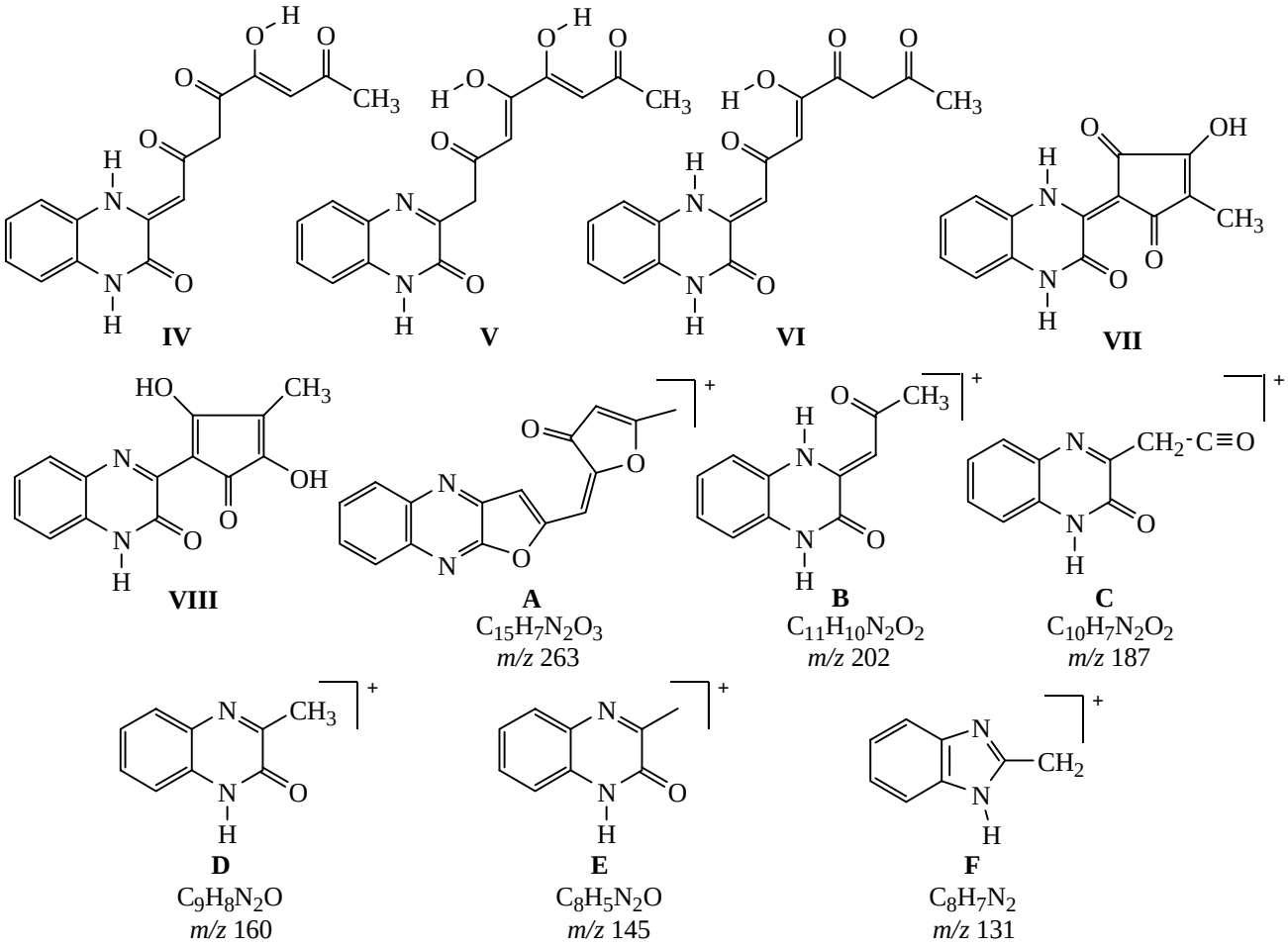
oxalin-2(1*H*)-one (**III**) by reaction of acetone, pinacolone, acetophenone or 2-butanone with diethyl oxalate in the presence of sodium at boiling in benzene followed by treating with acetic acid and *o*-phenylenediamine (Scheme 1).

Compounds **I–III** obtained are crystalline substances colored from yellow to dark red, insoluble in water, sparingly soluble in the common organic solvents and soluble at heating in acetic acid, DMF, and DMSO.

The structure of compounds synthesized was confirmed by IR, ^{1}H NMR, and mass spectra. In the ^{1}H NMR spectrum of compound **II** registered in DMSO-d_6 appeared singlets from protons of three methine groups C^{6}H, C^{1}H, and C^{3}H at δ 6.05, 7.06, and 7.08 ppm; therewith two latter signals are located downfield and have nearly identical chemical shift; signals from the protons of N$^{4'}$H and N$^{1'}$H of the quinoxaline ring were observed at 11.84 and 12.93 ppm. The lack in the spectrum of possible signals of CH_2 groups protons indicates the enoliza-tion of the carbonyl groups in two β-dicarbonyl units of the polyketide chain, and the downfield shift of proton signals from methine groups C^{1}H, C^{3}H and from N$^{1'}$H confirms the presence of intramolecular hydrogen bonds in the chelate N$^{1'}$H-ring and conjugated OH-ring. In solution of compound **II** we did not find possible tautomers, in particular, forms **IV–VI** with nonenolized fragment $CH_2C{=}X$ (X = O, N–, Scheme 2) whose formation could not be *a priori* excluded (cf., for instance, [6]).

In the ^{1}H NMR spectrum of quinoxalinone **III** registered in DMSO-d_6 proton signals of N^{1}H group of heterocyclic amide unit (δ 11.68 ppm) and of hydroxy groups C$^{3'}$OH (δ 7.95 ppm) and C$^{2'}$OH (δ 14.10 ppm) of the cyclopentadiene fragment were present. The downfield shift of the latter signal indicated the hydrogen bond formation between the hydrogen of the C$^{2'}$OH hydroxy group and N^4 atom of the quinoxaline in a six-membered chelate ring. The possible tautomeric form **VII** did not appear in the spectrum of compound **III** for no signal from the proton at N^4 atom was observed

Scheme 2.



(Scheme 2). Nonetheless it is yet difficult to choose between two very close regioisomeric forms **III** and **VIII** distinguished by the reciprocal position of a hydroxy group and a methyl substituent at $C^{3'}$ and $C^{4'}$ atoms of the alicyclic unit.

In the mass spectrum of compound **II** the molecular ion peak is lacking, but characteristic peaks of fragment ions appear at *m/z* 263 **A**, 202 **B**, 187 **C**, 160 **D**, 145 **E**, and 131 **F** corresponding to the major fragmentation directions of this polyketide (Scheme 2) in full agreement with published data on analogous substances [6].

Quinoxalinones **Ia–Ic** and **II** result from *o*-phenylendiamine reaction with intermediate products of Claisen condensation of equimolar amounts of methyl ketones and diethyl oxalate: ethyl 2-hydroxy-4-oxo-2-alkenoates (acylpyruvates) **IX** [7, 8] and ethyl 2,6,7-trihydroxy-4,9-dioxo-2,5,7- decatrienoate (**X**) [9, 10] (Scheme 3). The primary product of 2-butanone condensation with diethyl oxalate (in a ratio 1:2), ethyl 2-hydroxy(3-hydroxy-4-methyl-2,5-dioxo-3-cyclopenten-2-ylidene)acetate (**XI**) [10, 11] (Scheme 3) also reacted with *o*-phenylendiamine yielding the target compound **III**.

Thus a simple and convenient preparative method was developed for 3-[oxo(cyclo)-alkyl(idene)]-substituted quinoxalin-2(1*H*)-ones that according to our data [12] was also suitable for the synthesis of other versatile acylmethyl (oxoylidene) derivatives of quinoxaline and 1,4-benzoxazine.

EXPERIMENTAL

IR spectra of quinoxalinones **II** and **III** were recorded on a spectrophotometer Specord M-80 from mulls in mineral oil. ^{1}H NMR spectra of compounds **II** and **III** were registered on a spectrometer Bruker DRX-500 (500.13 MHz) in DMSO-d_6, internal reference TMS. Mass spectra of compounds **II** and **III** were measured on Finnigan MAT INCOS-50 instrument in the mode of direct sample admission into the ion source (electron impact). The homogeneity of compounds **I–III** was confirmed by TLC on Silufol UV-254® plates in a system benzene–ethyl ether–acetone, 10:9:1, development in iodine vapor. Physical constants and spectral characteristics of the known 3-(2-oxoalkylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones **Ia–Ic** are reported in [3, 6, 13].

3-(2-Oxoalkylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones Ia–Ic. To a mixture of 20 mmol of acetone, pinacolone, or acetophenone, 2.8 ml (20 mmol) of diethyl oxalate, and 30 ml of benzene at stirring and cooling was added by small pieces 0.46 g (20 mmol) of sodium, and the reaction mixture was boiled for 2–3 h. The solvent was evaporated, the residue was thoroughly ground with 20–30 ml of ice water, then at stirring was added 10 ml of acetic acid and 2.16 g (20 mmol) of *o*-phenylendiamine. After 3–4 h the separated precipitate of compounds **Ia–Ic** was filtered off, dried, and recrystallized from acetic acid or DMF.

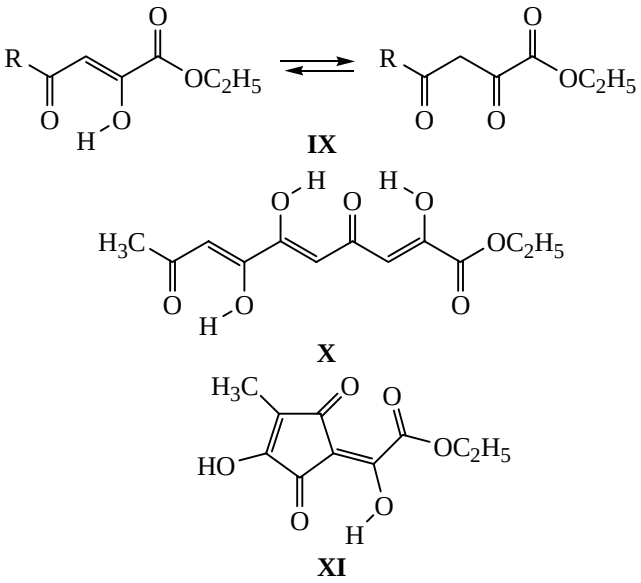
(**3-(2-Oxopropylidene)-3,4-dihydroquinoxalin-2(1*H*)-one (Ia).** Yield 3.0 g (74%), mp 267–268°C (decomp., DMF) (publ.: mp 256–257°C [13]).

3-(3,3-Dimethyl-2-oxobutylidene)-3,4-dihydroquinoxalin-2(1*H*)-one (Ib). Yield 3.85 g (79%), mp 228–229°C (DMF) (publ.: mp 226–227 [13], 229–230°C [6]).

3-(2-Oxo-2-phenylethylidene)-3,4-dihydroquinoxalin-2(1*H*)-one (Ic). Yield 4.50 g (85%), mp 268–269°C (decomp., CH_3COOH) (publ.: mp 266–267 [3, 13], 264–265°C [6].

4,5-Dihydroxy-1-[3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene]-3,5-octadiene-2,7-dione (II). To a mixture of 1.4 ml (20 mmol) of acetone, 2.8 ml (20 mmol) of diethyl oxalate, and 30 ml of benzene at stirring and cooling was added by small pieces 0.69 g (30 mmol) of sodium, and the reaction mixture was boiled for 2.5 h. The solvent was evaporated, the residue was thoroughly ground with 30 ml of ice water, then at stirring was added 10 ml of acetic acid and 1.08 g (10 mmol) of

Scheme 2.



R = Me, *t*-Bu, Ph.

o-phenylendiamine. After 3–4 h the separated precipitate of compound **II** was filtered off, dried, and recrystallized from DMF. Yield 1.70 g (54%), mp 227–228°C (decomp.). From the residue after crystallization a small amount of compound **Ia** was isolated. Yield 0.3 g (15%), mp 267–268°C (decomp., DMF).

Compound **II**. IR spectrum, ν, cm^{-1}: 3170 ($N^{4'}H_{amide}$), 1667 ($C^{3'}=O_{amide}$), 1590–1620 ($=COH_{chelate}$). ^1H NMR spectrum, δ, ppm: 2.17 s (3H, CH_3), 6.05 s (1H, C^6H), 7.06 s (1H, C^1H), 7.08s (1H, C^3H), 7.06–7.35 m (4H, C_6H_4), 7.70 br.s (2H, C^4OH, C^5OH), 11.84 s (1H, $N^{4'}H$), 12.93 s (1H, $N^{1'}H$). Mass spectrum, *m/z* (I_{rel}, %) (ions with I_{rel} > 2% are reported): 263 (2) $[M–CH_3–2H_2O]^+$ **A**, 224 (2) $[C_{13}H_8N_2O_2]^+$, 202 (12) $[M–2CH_2CO–CO]^+$ **B**, 187 (11) $[M–CH_3CO–2CH_2CO]^+$ **C** , 160 (12) $[M–3CH_2CO–CO]^+$ **D**, 159 (7), 158 (4), 145 (2) $[M–CH_3CO–3CH_2CO]^+$ **E**, 132 (12) $[M–3CH_2CO–2 CO]^+$, 131 (16) $[M–3CH_2CO–2CO–H]^+$ **F**, 117 (3), 104 (4), 103 (3) $[C_7H_5N]^+$, 92 (3), 91 (3), 90 (6) $[C_6H_4N]^+$, 89 (3), 78 (3), 77 (8) $[C_6H_5]^+$, 76 (5), 75 (4), 65 (7), 64 (7), 63 (8), 52 (5), 51 (6), 50 (6), 45 (9), 44 (100), 43 (40), 42 (8), 41 (5), 40 (8), 39 (12), 38 (6). Found, %: C 61.47; H 4.30; N 9.23. $C_{16}H_{14}N_2O_5$. Calculated, %: C 61.14; H 4.49; N 8.91. *M* 314.

3-(2,3-Dihydroxy-4-methyl-5-oxo-1,3-cyclopentadien-1-yl)quinoxalin-2(1*H*)-one (III). To a mixture of 0.9 ml (10 mmol) of 2-butanone, 2.8 ml (20 mmol) of diethyl oxalate, and 20 ml of benzene at stirring and cooling was added by small pieces 0.46 g (20 mmol) of sodium, and the reaction mixture was boiled for 3 h. The solvent was evaporated, the residue was thoroughly ground with 20 ml of ice water, then at stirring was added 10 ml of acetic acid and 1.08 g (10 mmol) of *o*-phenylendiamine. After 3 h the separated precipitate of compound **III** was filtered off, dried, and recrystallized from DMF. Yield 1.95 g (72%), mp 298–300°C (decomp., DMF). IR spectrum, ν, cm^{-1}: 3240–3195 (OH), 3185 (N^1H_{amide}), 1678 ($C^2=O_{amide}$), 1665 ($C^{5'}=O$). ^1H NMR spectrum, δ, ppm: 1.87 s (3H, CH_3), 7.14 t (1H, C^6H, *J* 8.0 Hz), 7.32 t (1H, C^7H, *J* 8.4 Hz), 7.40 d (1H, C^8H, *J* 8.8 Hz), 7.95 s (1H, $C^{3'}OH$), 8.05 d (1H, C^5H, *J* 9.0 Hz), 11.68 br.s (1H, N^1H), 14.10 br.s (1H, $C^{2'}OH$). Mass spectrum, *m/z* (I_{rel}, %) (ions with I_{rel} > 5% are reported): 270 (22) $[M]^+$, 226 (9), 225 (11), 224 (22) $[M–CO–H_2O]^+ = [C_{13}H_8N_2O_2]^+$, 223 (9), 198 (10), 197 (12), 169 (22), 168 (31) $[M – C_7H_4N]^+$, 167 (5), 153 (5), 140 (5), 129 (5), 114 (5), 112 (7), 103 (5), 102 (8) $[C_7H_4N]^+$, 84 (12), 77 (15) $[C_6H_5]^+$, 76 (10), 75 (5), 73 (32), 70 (7), 63 (8), 52 (7), 51 (11), 50 (11), 45 (8), 44 (100), 42 (22), 41 (13), 40 (10), 39 (18), 38 (5). Found, %: C 61.97; H 3.50; N 10.56. $C_{14}H_{10}N_2O_4$. Calculated, %: C 62.22; H 3.73; N 10.37. *M* 270.

REFERENCES

1. *Heterocyclic Compounds*, Elderfield, R.C., Ed., New York: Wiley, 1957.
2. Cheeseman, G.W.H. and Werstiuk, E.S.G., *Adv. Heterocycl. Chem.*, 1978, vol. 22, p. 367.
3. Pitirimova, S.G., *Cand. Sci. (Chem.) Dissertation*, Perm, 1979, 139 p.
4. Koz'minykh, V.O., Igidov, N.M., Koz'minykh, E.N., and Berezina, E.S., *Azotistye geterotsikly i alkaloidy* (Nitrogen Heterocycles and Alkaloids), Kartsev, V.G. and Tolstikov, G.A., Moscow: IRIDIUM PRESS, 2001, vol. 1, p. 345.
5. Koz'minykh, V.O. and Koz'minykh, E.N., *Izbrannye metody sinteza i modifikatsii geterotsiklov* (Selected Methods of Synthesis and Modification of Heterocycles), Kartsev, V.G., Ed., Moscow: IBS PRESS, 2003, vol. 1, p. 255.
6. Sof'ina, O.A., Igidov, N.M., Koz'minykh, E.N., Trapeznikova, N.N., Kasatkina, Yu.S., Koz'minykh, V.O., *Zh. Org. Khim.*, 2001, vol. 37, p. 1067.
7. Perevalov, S.G., Burgart, Ya.V., Saloutin, V.I., and Chupakhin, O.N., *Usp. Khim.*, 2001, vol. 70, p. 1039.