Pharmaceutical Chemistry Journal, Vol. 28, No. 2, 1994

METHODS OF SYNTHESIS OF DRUGS AND TECHNOLOGY OF THEIR PRODUCTION

SYNTHESIS OF BENZOFURAN AND INDOLE DERIVATIVES FROM ENAMINES OF 4-SUBSTITUTED CYCLOHEXANE-1,3-DIONES

V. M. Lyubchanskaya, L. M. Alekseeva, and V. G. Granik

UDC 547.728+547.752.2'567:541.124

We have previously found that the reaction of 4-benzoyl- and 4-ethoxycarbonylcyclohexane-1,3-diones (Ia, b) with amines proceeds selectively at the carbonyl group at the 1-position with the formation of the corresponding enamines (IIa, b) [1]. These enaminodicarbonyl compounds are of interest as starting materials for the synthesis of condensed benzofurans and indoles from them by carrying out the Nenitzescu reaction.

The present work is devoted to the study of the reaction of 3-morpholino-6-benzoyl- and 3-morpholino-6-ethoxycarbonylcylcohexen-2-ones (IIa, b) with p-benzoquinone (III) and the synthesis of derivatives of 6-hydroxydibenzofurans and 6-hydroxycarbazoles, which serve as multifunctional starting compounds for the search of physiologically active compounds based on them [2, 3].

The reaction of enamine IIa with quinone III in AcOH in the presence of Ac_2O leads smoothly to 2-benzoyl-8-hydroxy-1,2,3,4-tetrahydrodibenzofuran-1-one (IV). The structure of the latter follows from the ^1H NMR spectrum data, in which signals are observed at δ, ppm (d_6-DMSO): 2.16, 3.30 (m, 4H, 3,4-CH_2-groups), 5.03 (q, 1H, 2-CH, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.57, 8.05 (m, 5H, COPh), 7.20 (d, 1H, 9-CH, J = 2.5 Hz), 6.78 (q, 1H, 7-CH, J_1 = 8.8 Hz, J_2 = 2.5 Hz), 7.46 (d, 1H, 6-CH, J = 8.8 Hz), 9.47 (s, 1H, OH). The tricyclic compound IV readily enters into the Mannich reaction characteristic for 5-hydroxybenzofurans with the formation 9-aminomethyl derivatives (Va, b), isolated in the form of hydrochlorides. A detailed investigation of the structure of compound Va showed that complications are observed in its ^1H NMR spectrum due to the presence of an asymmetric carbon atom at the 2-position of the tricyclic ring. Thus, besides the signals (in d_6-DMSO) at δ: 1.62-2.56 (m, 4H, 3,4-CH_2 groups) 7.49-7.66 (m, 6H, COPh and 6-CH), 7.12 (d, 1H, 7-CH, J = 9 Hz) and 10.51 (s, 1H, OH) ppm, signals are observed in the spectrum of the CH_2 group of the dimethylaminomethylene fragment in the form of a quartet at 3.64 ppm (the nonequivalent protons are observed in the form of an AB-system, $J_{gem} \approx 14$ Hz), each component of which is split by a proton of the ^+NH group with various spin–spin coupling constants (J_1 = 6 Hz, J_2 = 4 Hz). The dimethylammonium group appears in the form of two doublets with different chemical shifts – at 2.67 and 2.70 ppm (J = 4.6 Hz).

The presence of the β-dicarbonyl fragment at the 1,2-positions of the tricyclic compound IV was utilized for closing the pyrazole ring by reacting compound IV with hydrazine hydrate. As a result 3-phenyl-9-hydroxy-4,5-dihydrobenzofuro[2,3-g]indazole (VI) was obtained. ^1H NMR spectrum of VI (d_6-DMSO), δ: 3.12 (m, 4H, 4,5-CH_2 groups), 7.66, 7.52 (m, 5H, C_6H_5) 6.72 (q, 1H, 8-CH, J_1 = 8.8 Hz, J_2 = 2.5 Hz), 7.22 (d, 1H, 10-CH), 7.36 (d, 1H, 7-CH), 9.23 (s, 1H, OH), 12.84 (s, 1H, NH) ppm.

On heating compound IV with sodium methylate a C-debenzoylation takes place with the formation of 8-hydroxy-1,2,3,4-tetrahydrodibenzofuran-1-one (VII). Signals are observed in the ^1H NMR spectrum (d_6-DMSO) of the latter at δ: 2.13 (q, 2H, 3-CH_2, J = 6.2 Hz), 2.47 (t, 2H, 2-CH_2), 2.97 (t, 2H, 4-CH_2), 7.22 (d, 1H, 9-CH, J = 2.5 Hz), 7.36 (d, 1H, 6-CH, J = 8.8 Hz), 7.71 (q, 1H, 7-CH), 9.36 (s, 1H, OH) ppm.

Central Chemical Laboratory of Synthesis, All-Union Scientific-Research Chemical Pharmaceutical Institute, Moscow.
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 28, No. 2, pp. 36-39, February, 1994. Original article submitted December 29, 1991.

0091-150X/94/2802-0119$12.50

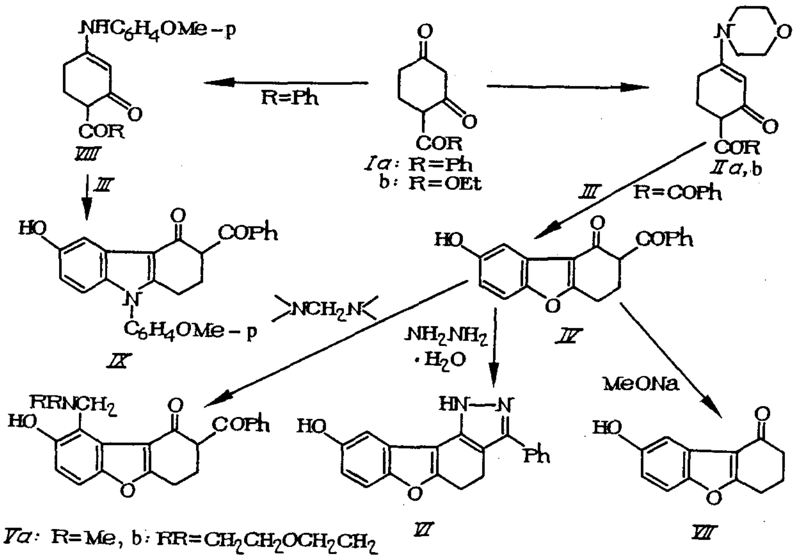
TABLE 1. Characteristics of Compounds IV, Va, b, VI, VII, IX-XI

Compound	mp, °C	Yield, %	Empirical formula	Mass, M^+
IV	220—3	61,2	$C_{19}H_{14}O_4$	306
Va	266—7 (dec)	50,0	$C_{22}H_{22}ClNO_4$	363
Vb	215—8 (dec)	31,7	$C_{24}H_{24}ClNO_5$	
VI	250—3	55,2	$C_{19}H_{14}N_2O_2 \cdot H_2O$	302
VII	239—40	74,3	$C_{12}H_{10}O_3$	202
IX	234—6	4,9	$C_{26}H_{21}NO_4$	411
X	174—5	11,0	$C_{15}H_{14}O_5$	274
XI	268—70 (dec)	6,8	$C_{17}H_{17}NO_5$	315

---

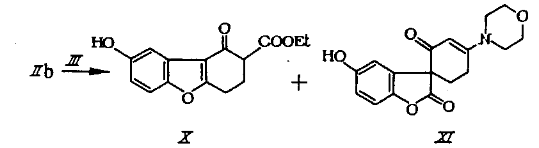
[*] Compounds IV, VII, X, XI were recrystallized from alcohol; VI) from aqueous dioxane; IX) from dichloroethane.

Thus, the use of tertiary enamine IIa in the Nenitzescu reaction made it possible to carry out a synthesis of benzofuran derivatives IV-VII, in which the position of the OH group is determined by the reaction mechanism [4, 5]. Contrary to this, when secondary enamines are introduced into the Nenitzescu reaction, both 5- and 6-hydroxyindoles can be formed [6]. In the present work we studied the reaction of 3-(p-methoxyphenylamino)-6-benzoylcyclohexen-2-one (VIII) with quinone III. As a result compound IX was isolated in a very low yield, which according to the ^1H NMR spectrum (d_6-DMSO) was found to be 2-benzoyl-5-(p-methoxyphenyl)-8-hydroxy-1,2,3,4-tetrahydrocarbazol-1-one. There are signals in the spectrum of this compound at 2.18, 3.16 (m, 4H, 3,4-CH_2 groups), 3.86 (s, 3H, OCH_3), 4.89 (q, 1H, 2-CH, $J_1 = 9.5$ Hz, $J_2 = 5$ Hz), 7.56-8.04 (m, 5H, Ph), 7.27 (m, 4H, C_6H_4), 6.94 (d, 1H, 6-CH), 6.68 (q, 1H, 7-CH, $J_1 = 8.6$ Hz, $J_2 = 2.5$ Hz), 7.42 (d, 1H, 9-CH), 9.18 (s, 1H, OH) ppm. Since there is a doublet in the weak field region (δ 7.42 ppm) with a very low splitting constant (J = 2 Hz), and not a doublet with a constant J = 8 Hz, it can be assumed that the OH group is present at the 8-position. This structure is also supported by comparison of the spectra of the above described benzofuran derivatives IV-VI with the spectrum of carbazole IX and the spectra of the substituted 5- and 6-hydroxyindoles described by us previously in [6, 7].

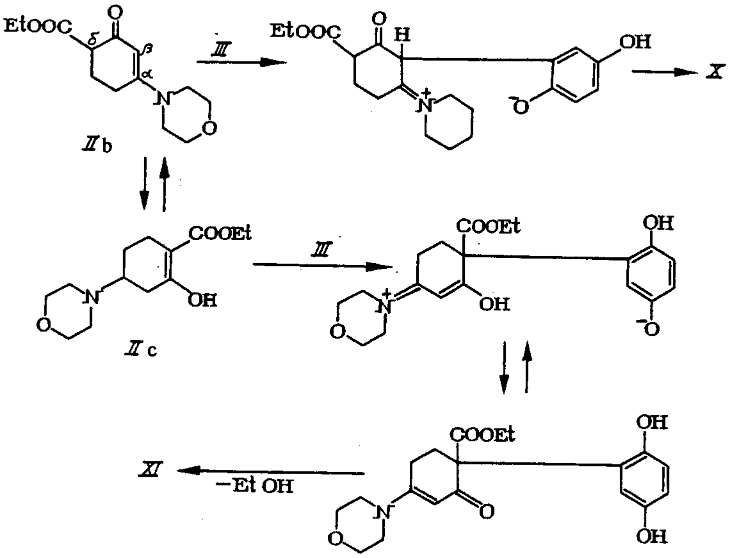


Entirely unexpected results were obtained in the study of the reaction of 3-morpholino-6-ethoxycarbonylcyclohexen-2-one (IIb) with quinone III. In contrast to enamine IIa, compound IIb undergoes the Nenitzescu reaction with the formation of two compounds. The first is the usual reaction product – 2-ethoxycarbonyl-8-hydroxy-1,2,3,4-tetrahydrodibenzofuran-1-one

(X), mass spectrum $M^{+\cdot}$ 274, ^{1}H NMR spectrum (d_6-DMSO), δ: 2.2-3.2 (m, 4H, 3,4-CH_2 groups), 3.55 (q, 1H, 2-CH, J_1 = 8.7 Hz, J_2 = 4.9 Hz), 1.27 (t) and 4.22 (q) (COOEt), 7.47 (d, 1H, 9-CH, J = 2.6 Hz), 6.82 (q, 1H, 7-CH, J_1 = 2.6 Hz, J_2 = 9 Hz), 7.31 (d, 1H, 6-CH, J = 9 Hz), 8.64 (s, 1H, OH) ppm. The structure of the second compound (XI) was established by means of the spectral data. Absorption bands are observed in the IR spectrum of compound XI in mineral oil at 1585, 1790 and 3160 cm^{-1}, which can be attributed to the carbonyl groups of the enamino-ketone, the five-membered lactone and the hydroxy group, respectively. A peak of the molecular ion $M^{+\cdot}$ 315 is observed in the mass spectrum. Lastly, signals are observed in the ^{1}H NMR spectrum belonging to the CH_2 groups of the cyclohexene and morpholine rings, trisubstituted benzene ring, while the signals of the COOEt group are absent. ^{1}H NMR spectrum of compound XI (d_6-DMSO), δ: 2.0-4.0 (m, 4H, 5^1,6^1-CH_2 groups), 3.46 (m, 4H, NCH_2), 3.67 (t, 4H, OCH_2), 5.22 (s, 1H, 3^1-CH), 6.99 (d, 1H, 4-CH), 7.03 (m, 2H, 6,7-CH), 9.38 (s, 1H, OH), ppm. These data combined with the results of the elemental analysis made it possible to propose for compound XI the structure of 3-spiro-(2'-oxo-4'-morpholinocyclohexen-3'-yl)-5-hydroxybenzofuran-2-one.



As far as we know [5], this is the first case of the occurrence of reactions of quinone III in two alternative paths – with the participation of enamine and β-dicarbonyl fragments. Since the possibility of the Nenitzescu reaction with dienamines was realized in [8], it can be assumed that the formation of the spiro compound XI is due to the addition of quinone according to Michael to the tautomeric enol IIc, which, being a dienamine, has a high electron density at the δ-position with respect to the morpholine residue. Thus, the addition of quinone III to β- and δ-positions of compound IIb determines the above indicated paths of this unexpected reaction.



It should be noted that the δ-position of the tautomer IIc is enriched with electrons not only because of conjugation with the morpholine N-atom, but also because of the electron-donor influence of the hydroxy group. This combined effect, together with the possible stabilization of the transition state involving the formation of an intramolecular hydrogen bond between the CO (COOEt) and OH groups (arising during the tautomerization of the quinone fragment) determines the unusual process of formation of the spiro compound XI discussed above.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a "Varian XL-200" spectrometer in d_6-DMSO, using TMS as internal standard. The mass spectra were obtained on a "Varian" chromato-mass spectrometer (GFR) with direct introduction of the sample into the ionic sources. The course of the reactions and the purity of the compounds was monitored chromatographically on Silufol UV-254 plates in a benzene–methanol (9:1) system, with development in UV light. The characteristics of the compounds are given in Table 1. The essential analysis data correspond to the calculated values.

2-Benzoyl-8-hydroxy-1,2,3,4-tetrahydrodibenzofuran-1-one (IV). A 1.33 g portion (12 mmoles) of p-benzoquinone was added with stirring at 20°C to a solution of 3.5 g (12 mmoles) of enamine IIa in a mixture 20 ml of AcOH acid and 2.0 ml of Ac_2O and the mixture was stirred for 20 h. The precipitate that separated out was filtered off, washed with AcOH and water, and dried. Yield, 2.3 g of compound IV.

2-Benzoyl-8-hydroxy-9-dimethylaminoethyl-1,2,3,4-tetrahydrodibenzofuran-1-one hydrochloride (Va). A solution of 1.5 g (5 mmoles) of compound IV and 0.51 g (5 mmoles) of bisdimethylaminoethane in 50 ml of dioxane was boiled for 6 h. The solution was diluted with 250 ml of water. The crystals that separated out were filtered off, washed with water, dried and dissolved in 100 ml of acetone. The solution was filtered and the filtrate was acidified with conc. HCl to pH 3. The precipitate was filtered off, washed with acetone, and dried. Yield, 1.0 g of compound Va. Compound Vb was obtained in a similar way.

3-Phenyl-9-hydroxy-4,5-dihydrobenzofuro[2,3-g]indazole (VI). A solution of 3.6 g (12 mmoles) of compound IV and 1.8 ml (36 mmoles) of hydrazine hydrate in 180 ml of alcohol was boiled for 5 h, and then cooled to 20°C. The precipitate was filtered off, washed with alcohol, water, and dried. Yield 2.0 g of compound VI.

6-Hydroxy-1,2,3,4-tetrahydrodibenzofuran-1-one (VII). A 2.0 ml portion of sodium methylate (containing 6 mmoles of Na) was added to a solution of 0.92 g (3 mmoles) of compound IV in 30 ml of isopropanol, and the mixture was boiled for 4 h. The reaction mixture was diluted with 150 ml of water, the solution was filtered off, and the filtrate was acidified with conc. HCl to pH 5. The precipitate that separated out was filtered off, washed with water, and dried. Yield 0.45 g of compound VII.

2-Benzoyl-5-(p-methoxyphenyl)-8-hydroxy-1,2,3,4-tetrahydrocarbazol-1-one (IX). A 0.54 g portion (5 mmoles) of p-benzoquinone was added with stirring at 20°C to a solution of 1.6 g (5 mmoles) of enamine VIII in a mixture of 5 ml of AcOH and 0.5 ml of Ac_2O, and the mixture was stirred for 24 h. The precipitate was separated out was filtered off, washed with AcOH, water, dried, and recrystallized from dichloroethane. Yield 0.1 g of compound IX.

2-Ethoxycarbonyl-8-hydroxy-1,2,3,4-tetrahydrodibenzofuran-1-one (X); 3-spiro-(2^1-oxo-4^1-morpholinocyclohexen-3^1-yl)-5-hydroxybenzofuran-2-one (XI). A 0.65 g portion (6 mmoles) of p-benzoquinone was added with stirring at 20°C to a solution of 1.52 g (6 mmoles) of enamine IIb in a mixture of 10 ml of AcOH and 1.0 ml of Ac_2O. The mixture was stirred for 24 h, the precipitate was filtered off, washed with AcOH, water, and dried at 110°C. Yield 0.15 g of compound XI. The molar liquor was diluted with 100 ml of water, and the precipitate that separated out was filtered off, washed with water, and dried. Yield, 0.2 g of compound X.

REFERENCES

1. V. M. Lyubchanskaya, L. S. Sarkisova, L. M. Alekseeva, and V. G. Granik, Khim.-farm. Zh., No. 4, 35 (1991).
2. M. D. Mashkovskii, Drugs [in Russian], Vol. 1, Moscow (1977), p. 418.
3. International Patent WO 90/08135, Publ. July 26, 1990.
4. G. R. Allen, Organic Reactions, Vol. 20, Ed. J. Wiley and Sons, New York–London (1973), p. 337.
5. V. G. Granik, V. M. Lyubchanskaya, and T. I. Mukhanova, Khim.-farm. Zh., No. 6, 37 (1993).

6. V. M. Lyubchanskaya, L. S. Sarkisova, L. M. Alekseeva, L. M. Kuleshova, Yu. N. Sheinker, and V. G. Granik, Khim.-farm. Zh., No. 9-10, 108 (1992).
7. V. M. Lyubchanskaya, L. M. Alekseeva, and V. G. Granik, Khim. Geterotsikl. Soedin., No. 1, 40 (1992).
8. U. Kuklander and H. Toberich, Chem. Ber., **116**, No. 1, 152 (1983).