 © 1988 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 61, 4427—4430 (1988)

Synthesis of γ-Butyrolactones, Quinoxalines, and Azauracils from 4-Aryl-2-oxobutanoic Acid Derivatives[1)]

G. H. Labib, M. Abdel Rahman, Y. El-Kilany, A. I. El-Massry, and E. S. H. El-Ashry*
Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt (A. R. E.)
(Received November 26, 1987)

4-Aralkyl-5-aryl-3-hydroxy-2(5*H*)-furanones (**2**) have been prepared from the corresponding 4-aryl-2-oxobutanoic acids (**1**). The anticipated products from the reaction of the furanones (**2**) with *o*-phenylenediamine (**3**) have not been isolated, but products resulting from the condensation followed by retro-aldol type of reaction are obtained and determined as 3-(2-arylethyl)-2(1*H*)-quinoxalinones (**4**). Compounds **4** could be readily obtained by the condensation of **3** with **1**. 4-Aryl-2-oxobutanoic acid thiosemicarbazones (**5**) have been cyclized to 5-(2-arylethyl)-6-azauracils (**6**).

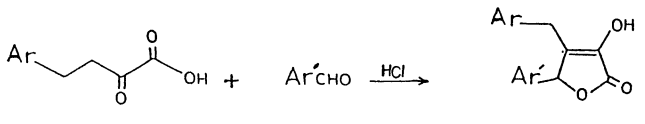
Butyrolactones are one of the integral building blocks of many natural products.[2)] Moreover, they exhibit a wide range of biological activities.[3)] The antitumour properties of lignans and the identification of a butyrolactone, with *m*-hydroxybenzyl residues in the urine of certain mammals have attracted much interest in their physiological activities and consequently, in their synthesis.[4)] In the present report, as a continuation of our work[5)] on lactones and vitamin C, we have prepared a number of unsaturated γ-butyrolactones possessing aralkyl residues. Having the above aspects in mind, the prepared lactones are of potential value as precursors for the synthesis of biologically important functionalized lactones. Moreover, their conversion into heterocyclic compounds of potential chemotherapeutic interest, such as quinoxalines and azauracils, have been investigated.

Results and Discussion

The 4-aryl-2-oxobutanoic acids (**1**) were prepared by the reductive rearrangement of the corresponding 4-aryl-2-oxo-3-butenoic acids; the preparation[6)] of which was carried out by the condensation of pyruvic acid with aromatic aldehydes in alkaline medium followed by acidification.

The condensation of the keto acids **1** with aromatic aldehydes in a solution of acetic acid and in the presence of hydrogen chloride afforded the corresponding butyrolactones **2**. The structures of **2** were deduced from the mode of their preparation[6)] as well as from their spectral data (Table 1). They exist exclusively in the enolic form in the solid state. This conclusion was based on the absence of carbonyl absorption bands in their IR spectra, whereas they showed absorptions indicating the presence of lactone carbonyl and hydroxyl groups at 1740—1755 and 3210—3350 cm^{-1}, respectively. The ^1H NMR spectrum of **2g** in a solution of $CDCl_3$ showed a broad singlet at δ 6.0 due to the hydroxyl group. The singlet appearing at δ 5.45 was due to H-5 and agreed with the enolic structure, otherwise it would be splitted by a neighboring proton if it existed in the keto form. The methylene protons appeared as two doublets at δ 3.68 and 2.82 (J=16 Hz) indicating their nonequivalence. This may be attributed to the difference in orientation of the two protons with respect to the anisotropic effect of the aromatic residue on position 5.

The reaction of α-keto lactones such as dehydroascorbic acid and its analogues with *o*-phenylenediamine **3** has been investigated extensively[5,7)] in our laboratory. The reaction products were usually of the 2(1*H*)-quinoxalinone type resulting from a direct condensation accompanied by a lactone ring opening. However, the attempted condensation of the lactones **2** with **3** did not similarly afford the anticipated 2(1*H*)-quinoxalinones or even fused furoquinoxaline derivatives. The reaction products were assigned to be the structures **4**. This was apparent from the elemental analysis which indicated the loss of the elements Ar'CHO. The infrared spectra of **4** showed the presence of bands in the carbonyl frequency region at 1665 cm^{-1} indicating the presence of OCN groups, thus, rejecting the structure having the fused heterocyclic ring in agreement with a structure having a quinoxalinone ring. The ^1H NMR spectrum (DMSO-d_6) of **4**, showed a singlet of four-proton intensity at δ=3.10 due to the ethylene group and a singlet of one proton intensity at δ=12.37 due to NH. The aromatic protons appeared as a multiplet at δ=7.0—8.0. Conclusive evidence for the structure to be 3-aralkyl-2(1*H*)-quinoxalinone was provided by their unequivocal synthesis by the reaction of the corresponding 4-aryl-2-



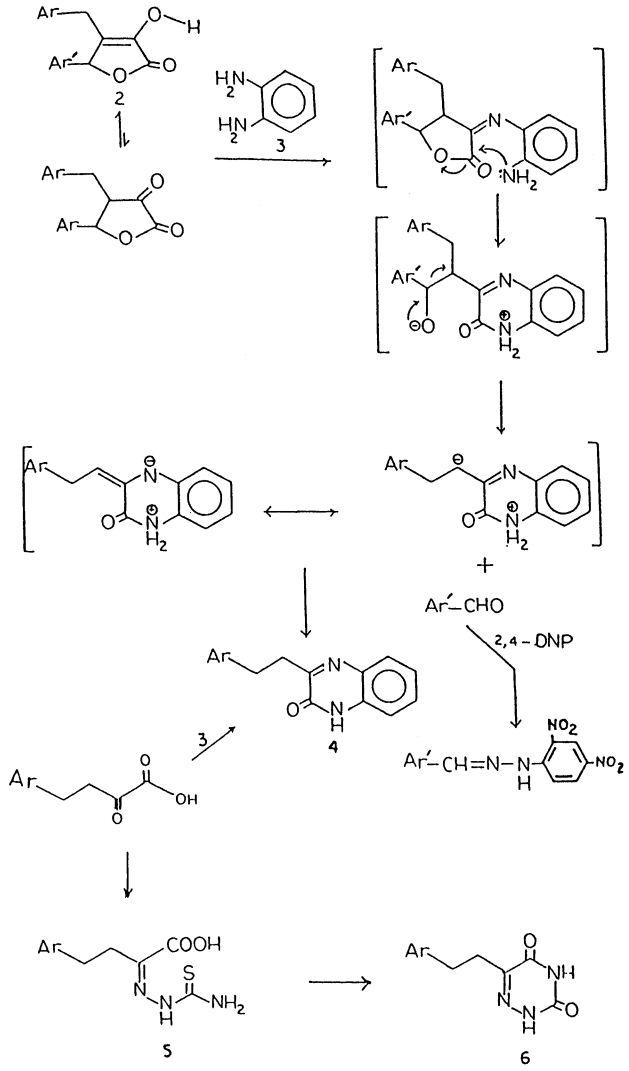
1 2

a) Ar=C_6H_5-, Ar'=CH_3-*p*-C_6H_4-
b) Ar=C_6H_5-, Ar'=CH_3O-*p*-C_6H_4-
c) Ar=CH_3-*p*-C_6H_4-, Ar'=C_6H_5-
d) Ar=CH_3-*p*-C_6H_4-, Ar'=CH_3-*p*-C_6H_4-
e) Ar=CH_3-*p*-C_6H_4-, Ar'=CH_3O-*p*-C_6H_4-
f) Ar=Cl-*p*-C_6H_4-, Ar'=C_6H_5-
g) Ar=Cl-*p*-C_6H_4-, Ar'=CH_3-*p*-C_6H_4-
h) Ar=Cl-*p*-C_6H_4-, Ar'=CH_3O-*p*-C_6H_4-
i) Ar=Cl-*p*-C_6H_4-, Ar'=NO_2-*p*-C_6H_4-

Scheme 1.

Table 1. ^{1}H NMR Spectral Data

Compd. No.	Solvent	Chemical shifts (δ) and assignments
2a	$CDCl_3$	7.00 (m, 9H, Ar), 6.00 (bs, 1H, OH is D_2O exchangeable), 5.45 (s, 1H, -CH-), 3.25 (dd, J=15 Hz, 2H, CH_2), 2.28 (s, 3H, CH_3)
2f	$CDCl_3$	7.10 (m, 10H, Ar, OH), 5.48 (s, 1H, -CH-), 3.43 (dd, J=15 Hz, 2H, CH_2)
2g	DMSO-d_6	10.27 (s, 1H,OH is D_2O exchangeable), 7.15 (m, 8H, Ar), 5.67 (s, 1H, -CH-), 3.40 (dd, J=15 Hz, 2H, CH_2), 2.30 (s, 3H, CH_2)
2h	DMSO-d_6	10.31 (s, 1H, OH is D_2O exchangeable), 7.10 (m, 8H, Ar), 5.70 (s, 1H, -CH-), 3.82 (s, 3H, OCH_3), 3.40 (dd, J=15 Hz, 2H, CH_2)
2i	DMSO-d_6	10.55 (s, 1H, OH is D_2O exchangeable), 7.21, 8.18 (m, d, 8H, Ar), 5.99 (s, 1H, -CH-), 3.43 (dd, J=15 Hz, 2H, CH_2)



Scheme 2.

oxobutanoic acid **1** with *o*-phenylenediamine.

The formation of **4** from the lactone **2** may be explained as outlined in Scheme 2. The reaction may be started by a nucleophilic attack of the amino group on the α-carbonyl group in the keto form of **2** to give the Schiff base, which was not isolated, followed by the attack of the second amino group on the lactone carbonyl group which caused its ring opening. The final step of the reaction sequence is a retro-aldol condensation in which aldehyde is split off to give the product **4**. The generated aldehyde was trapped and isolated as its 2,4-dinitrophenylhydrazone.

When 4-aryl-2-oxobutanoic acids (**1**) were treated with thiosemicarbazide, they gave the corresponding thiosemicarbazones **5**, which upon boiling with methyl iodide in ethanol afforded colorless products whose elemental analyses and spectroscopic data agreed with the cyclized structures **6**. Their infrared spectra showed bands at 1685—1665 cm^{-1} due to the OCN groups and bands at 3240—3100 cm^{-1} due to NH groups. Their ^{1}H NMR spectra agreed with the assigned structures.

Experimental

Generals. Melting points were determined with Meltemp apparatus with a 76-mm immersion thermometer, and are uncorrected. Infrared spectra were recorded with a pye Unicam SP1025 spectrometer. ^{1}H NMR spectra were taken on a Varian EM-390 spectrometer. Chemical shifts are expressed in δ scale relative to tetramethylsilane as an internal standard. Elemental analyses were performed at Faculty of Science, Cairo University.

4-Aralkyl-5-aryl-3-hydroxy-2(5*H*)-furanone (2). A solution of **1** (5.6 mmol) and the aromatic aldehyde (5.6 mmol) in glacial acetic acid (6 ml) and 18% hydrochloric acid (6 ml) was heated on a water-bath for 4 h. The reaction mixture was poured onto crushed ice. The organic material was extracted with ether and the ether extract was washed with water, 5% sodium hydrogencarbonate solution to separate the unreacted acid, followed by 5% sodium hydroxide solution. The sodium hydroxide extract was cooled, acidified with cold concentrated hydrochloric acid and left overnight. The product was filtered, washed with water, dried, and recrystallized from the indicated solvent (Table 2).

3-(2-Phenylethyl)-2(1*H*)-quinoxalinone (4a). a) A solu-

Table 2. Microanalytical and Infrared Spectral Data of 4-Aralkyl-5-aryl-3-hydroxy-2(5*H*)-furanones (**2**)[a)]

Compd. No.	Ar	Ar′	Yield %	Mp °C	Molecular formula	Calcd (Found) (%) C	Calcd (Found) (%) H	ν_{max}^{KBr}/cm^{-1} CO	ν_{max}^{KBr}/cm^{-1} OH
2a	C_6H_5	CH_3-*p*-C_6H_4	19	147—148	$C_{18}H_{16}O_3$	77.1 (76.80)	5.7 (5.8)	1755	3250
2b	C_6H_5	CH_3O-*p*-C_6H_4	24	106	$C_{18}H_{16}O_4$	73.0 (73.1)	5.4 (5.6)	1750	3350
2c	CH_3-*p*-C_6H_4	C_6H_5	42	111—112	$C_{18}H_{16}O_3$	77.1 (76.9)	5.7 (5.5)	1740	3315
2d	CH_3-*p*-C_6H_4	CH_3-*p*-C_6H_4	27	155—156	$C_{19}H_{18}O_3$	77.6 (78.0)	6.1 (6.2)	1745	3300
2e	CH_3-*p*-C_6H_4	CH_3O-*p*-C_6H_4	19	102	$C_{19}H_{18}O_4$	73.6 (73.7)	5.8 (5.7)	1755	3300
2f	Cl-*p*-C_6H_4	C_6H_5	32	142—144	$C_{17}H_{13}ClO_3$	67.9 (67.9)	4.3 (4.5)	1745	3350
2g	Cl-*p*-C_6H_4	CH_3-*p*-C_6H_4	35	130—132	$C_{18}H_{15}ClO_3$	68.7 (69.0)	4.8 (4.5)	1755	3210
2h	Cl-*p*-C_6H_4	CH_3O-*p*-C_6H_4	32	118—120	$C_{18}H_{15}ClO_4$	65.6 (65.2)	4.5 (4.6)	1750	3340
2i	Cl-*p*-C_6H_4	NO_2-*p*-C_6H_4	41	156—158	$C_{17}H_{12}ClNO_5$	59.1 (59.1)	3.5 (3.7)	1755	3320

a) Recrystallized from petroleum ether except **a** from carbon tetrachloride-petroleum ether; **b**, **d**, and **h** from benzene-petroleum ether; **i** from carbon tetrachloride.

tion of **2a** (1.12 g, 4 mmol), *o*-phenylenediamine (0.43 g, 4 mmol) and drops of acetic acid in ethanol (25 ml) was heated on a water-bath for 4 h. It was then concentrated and the product (yield 0.4 g, 40%) was crystallized from ethanol as colorless needles, mp 207—209 °C; ν_{max}^{KBr} 1665 (OCN) and 3140 (NH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=3.10 (s, 4H, $2CH_2$), 7.33, 7.74 (m, d, 9H, Ar), 12.37 (s, 1H, NH is D_2O exchangeable).

Found: C, 77.1; H, 5.7; N, 11.1%. Calcd, for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6; N, 11.2%.

The *p*-methylbenzaldehyde which splitted out from the reaction was trapped as *p*-methylbenzaldehyde 2,4-dinitrophenylhydrazone.

b) A solution of **1a** (0.78 g, 4.4 mmol), and *o*-phenylenediamine (0.47 g, 4.4 mmol) in ethanol (20 ml) was heated under reflux on a water-bath for 1 h, and the product (yield 0.3 g, 27%) was found to be identical with the one obtained by method a.

3-[2-(*p*-Chlorophenyl)ethyl]-2(1*H*)-quinoxalinone (4g). a) A solution of **2g** (0.6 g, 1.9 mmol), *o*-phenylenediamine (0.2 g, 1.9 mmol) and drops of acetic acid in ethanol (18 ml) was processed as above to give the title compound (yield 0.35 g, 65%) as pale yellow needles; mp 218—220 °C; ν_{max}^{KBr} 1665 (OCN) and 3140 (NH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=3.10 (s, 4H, $2CH_2$), 7.33, 7.76 (m, d, 8H, Ar), 12.36 (s, 1H, NH is D_2O exchangeable).

Found: C, 67.3; H, 4.9; N, 9.8%. Calcd for $C_{16}H_{13}Cl\,N_2O$: C, 67.5; H, 4.6; N, 9.8%.

The *p*-methylbenzaldehyde which splitted out from the reaction was trapped as *p*-methylbenzaldehyde 2,4-dinitrophenylhydrazone.

b) A solution of 4-(*p*-chlorophenyl)-2-oxobutanoic acid (**1f**, 0.12 g, 0.6 mmol), and *o*-phenylenediamine (0.06 g, 0.6 mmol) in ethanol (10 ml) was processed as before to give a product (yield 0.1 g, 63%) identical with that obtained by method a.

4-(*p*-Methylphenyl)-2-oxobutanoic Acid Thiosemicarbazone (5c). A solution of **1c** (1.92 g, 10 mmol) and thiosemicarbazide (0.91 g, 10 mmol) in ethanol (50 ml) was heated under reflux on a water-bath for 1 h. The product was crystallized from water as colorless crystals; mp 174—175 °C; ν_{max}^{KBr} 1680 (COOH), 3200, 3280, 3440 (NH, NH_2, OH) cm^{-1}.

Found: C, 54.6; H, 5.9; N, 15.8%. Calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.3; H, 5.7; N, 15.9%.

4-(*p*-Chlorophenyl)-2-oxobutanoic Acid Thiosemicarbazone (5f). A solution of **1f** (1.06 g, 5 mmol) and thiosemicarbazide (0.45 g, 5 mmol) in ethanol (25 ml) was processed as above to give the title compound (yield 0.8 g, 56%) as colorless crystals; mp 178—179 °C; ν_{max}^{KBr} 1687 (COOH), 3200, 3290, 3470 (NH, NH2, OH) cm^{-1}.

Found: C, 46.6; H, 4.3; N, 14.5%. Calcd for $C_{11}H_{12}ClN_3O_2S$: C, 46.2; H, 4.2; N, 14.7%.

5-[2-(*p*-Methylphenyl)ethyl]-6-azauracil (6c). A solution of **5c** (0.27 g, 1 mmol) in ethanol (5 ml) was treated with methyl iodide (0.15 ml) and the reaction mixture was heated under reflux on a water bath for 3 h. The product (yield 0.15 g, 65%) was crystallized from ethanol as colorless crystals; mp 207—208 °C; ν_{max}^{KBr} 1685 (OCN) and 3240 (NH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.17 (s, 3H, CH_3), 2.67 (s, 4H, $2CH_2$), 6.90 (m, 4H, Ar), 11.80 (s, 2H, 2NH are D_2O exchangeable).

Found: C, 62.0; H, 5.6; N, 18.4%. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.6; N, 18.2%.

5-[2-(*p*-Chlorophenyl)ethyl]-6-azauracil (6f). A solution of **5f** (0.29 g, 1 mmol) in ethanol (10 ml) was treated with methyl iodide (0.15 ml) and the reaction mixture was processed as above to give the product (yield 0.17 g, 68%); mp 229—230 °C; ν_{max}^{KBr} 1665 (OCN) and 3100 (NH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.81 (s, 4H, $2CH_2$), 7.22 (m, 4H, Ar), 11.93 (s, 2H, 2NH are D_2O exchangeable).

Found: C, 52.4; H, 4.0; N, 16.6%. Calcd. for $C_{11}H_{10}ClN_3O_2$: C, 52.5; H, 4.0; N, 16.7%.

References

1) Ketoacids and lactones, Part 2. For part 1, see E. S. H. El Ashry, A. Amer, G. Labib, A. Abdel Rahman, and A. El Massry, *J. Heterocycl. Chem.*, **24**, 63 (1987). A part in the series "Scope of the Reactions of Hydrazines and Hydrazones," Abstracted from the M. Sc. (1981) and Ph. D. (1984) Theseses of A. El Massry.

2) Y. S. Rao, *Chem. Rev.*, **76**, 625 (1976); R. McCrindle and E. Nakamura, *Can. J. Chem.*, **52**, 2029 (1974); L. J. Haynes and J. R. Plimmer, *Quart. Rev. Chem. Soc.*, **14**, 292 (1960); T. C. McMorris and A. W. Barksdales, *Nature (London)*, **215**, 5098 (1967); H. M. R. Hoffman and J. Rape, *Angew. Chem., Int. Ed. Engl.*, **214**, 94 (1985); N. Petragnani, H. M. C. Ferraz, and G. V. J. Silva, *Synthesis*, **1986**, 157.

3) L. J. Haynes, *Quart. Rev. London*, **2**, 46 (1948); F. Dickens, *Brit. Med. Bull.*, **20**, 96 (1964); J. H. Hartwell, *Cancer Treat. Rep.*, **60**, 1031 (1976); A. H. Barclay and R. E. Perdue, Jr., *Cancer Treat. Rep.*, **60**, 1081 (1976).

4) G. Cooley, R. D. Farrant, D. N. Kirk, and S. Wynn, *Tetrahedron Lett.*, **22**, 349 (1981); A. Pelter, P. Satyanarayana, and R. S. Ward, *Tetrahedron Lett.*, **22**, 1549 (1981).

5) E. S. H. El Ashry, *Advan. Chem. Ser. (ACS)*, **200**, 179 (1982).

6) P. Cordier and S. Jung, *C. R. Acad. Sci.*, **252**, 3199 (1960); P. Cordier and A. Haberzettl, *C. R. Acad. Sci., Ser. C*, **254**, 699 (1962).

7) E. S. H. El Ashry, M. A. Abdel Rahman, Y. El. Kilany, and N. Rashed, *Carbohydr. Res.*, **153**, 146 (1986); E. S. H. El Ashry, Y. El Kilany, N. El Shimy, and T. N. Huckerby, *Sci. Pharm.*, **54**, 121 (1986); E. S. H. El Ashry, Y. El Kilany, and H. Abdel Hamid, *Gazz. Chim. Ital.*, **116**, 721 (1986); H. Zimmer and A. Amer, *J. Heterocycl. Chem.*, **20**, 359 (1983).