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HETEROCYCLIC COMPOUNDS—II

N^--5 CYCLIZATION *VERSUS* O^--RING CLOSURES OF AN *o*-HYDROXYPHENYL-γ-CHLOROAMIDE. [THE SYNTHESIS AND SPECTRA OF N-(*o*-HYDROXYPHENYL)-PYRROLIDIN-2-ONE AND DERIVATIVES]

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Abstract—In the presence of alkali bases, *o*-hydroxyphenyl-γ-chloroamide (I) produces pyrrolidin-2-one (II) by an N^--5 cyclization, while other ω-chloroamides (I, n = 1, 2) only undergo O^--ring closures. The results emphasize the importance of the size of the resulting rings on the course of the cyclization of *o*-hydroxyphenyl-ω-haloamides (I, n = 1, 2, 3). The compound II was also obtained by two different routes and some derivatives are described. Intramolecular H-bonds in II and IV were suggested by NMR and IR spectral data.

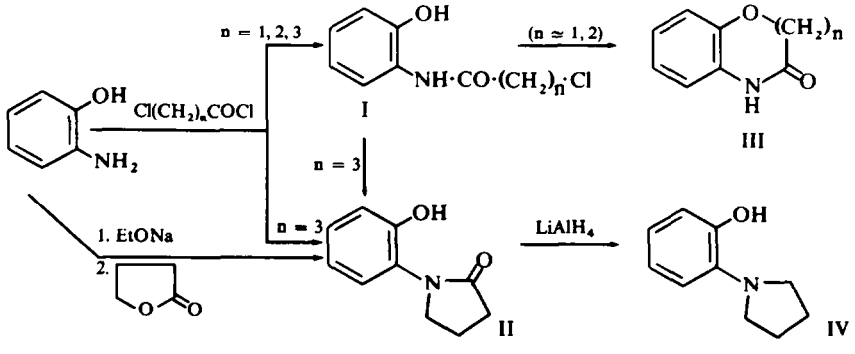
INTRODUCTION

IN a preliminary communication[1] it was shown that the sodium salt of 4-chloro-N-(*o*-hydroxyphenyl)-butyramide (I, n = 3) afforded N-(*o*-hydroxyphenyl)-pyrrolidin-2-one (II) by an N^--cyclization, although some related ω-chloroamides (I, n = 1, 2), under similar conditions, yielded the corresponding lactams III (n = 1,2) by O^--cyclization.[2–4] Now, we wish to report the experimental details concerning the synthesis of II and some derivatives, as well as the UV, IR and NMR spectra of the compounds obtained.

RESULTS AND DISCUSSIONS

Several attempts to obtain the 4-chloro-N-(*o*-hydroxyphenyl)butyramide (I, n = 3), from *o*-aminophenol and 4-chlorobutyryl chloride, failed, but in some instances a compound m.p. 133–135° was isolated from the reaction. This compound proved to

CHART 1

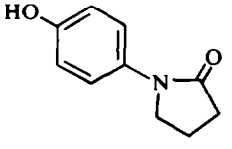


be N-(*o*-hydroxyphenyl)pyrrolidin-2-one (II) instead of the expected γ-chloroamide I (n = 3). In these experiments anhydrous benzene (or methylethylketone) was used as solvent and the reaction was carried out in the presence of (or without) triethylamine, the mixture being heated for several hours at the reflux temperature of the solvent. However, when the reaction was carried out under more mild conditions and in the presence of excess *o*-aminophenol, the expected γ-chloroamide I (n = 3) could be obtained in a moderate yield.

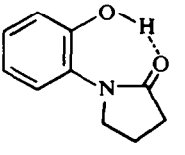
It was reported[2–4] that *o*-hydroxyphenyl-ω-chloroamides (I, n = 1, 2), in the presence of alkali bases, produce the corresponding cyclic amide III (n = 1, 2) by an O^--cyclization. However, the 4-chloro-N-(*o*-hydroxyphenyl)butyramide (I, n = 3) showed a different behaviour in the presence of the alkali bases and gave exclusively the product of N^--cyclization.* Thus, when a solution of the anhydrous sodium salt of I (n = 3) in DMF was heated under reflux for 3 hr, the N-(*o*-hydroxyphenyl)-pyrrolidin-2-one (II) was obtained in almost quantitative yield. The same compound II was obtained in high yield by heating the γ-chloroamide I (n = 3) in the presence of a concentrated sodium hydroxide solution.

The structural assignment of the compound thus obtained was difficult on the basis of the elemental analysis and spectral data. Indeed, the NMR spectrum of the compound shows a pattern which might be in accord with both II and III structures but the sharp signal of the proton at 1·43 τ suggested an OH group. On the other hand, in the IR spectrum of II the amide I band appears at 1670 cm^{-1}, which is slightly lower than that observed for other N-substituted 2-pyrrolidinones.[6] Nevertheless, the presence of a broad absorption band in the 2600–3200 cm^{-1} region, and no absorption band for any non-bonded O—H stretching vibration, even in very diluted carbon tetrachloride solution, suggested that the amide carbonyl is involved in a H-bond, which explains the low value of the $\nu_{C=O}$ stretching frequency in II.

The intramolecular nature of the H-bond in II was proved by comparison of the IR spectra of II and of the related N-(*p*-hydroxyphenyl)pyrrolidin-2-one (V). As it was expected, in the IR spectrum of V (diluted solution in carbon tetrachloride) the ν_{OH} stretching band appeared at 3610 cm^{-1} (free OH) and the amide I band at 1705 cm^{-1}, a characteristic value for the $\nu_{C=O}$ frequency in N-substituted 2-pyrrolidinones.[6] In addition, the absorption of the amide I band near 1700 cm^{-1} in the spectrum of the O-acetyl derivative of II, gives further evidence of the chelated structure IIa of the parent compound II.



V



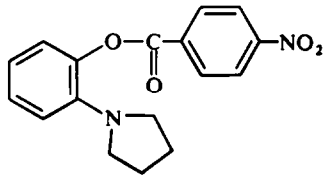
IIa

Additional evidence for the correctness of the structure assigned to II, was afforded by the preparation of the N-(*o*-hydroxyphenyl)pyrrolidin-2-one (II) by a different method, from sodium 2-aminophenoxide and γ-butyrolactone, under anhydrous conditions.

* The symbolism is that introduced by Scott *et al.*[5]

The chemical behaviour of II also agrees with the structure IIa assigned. Thus, while such cyclic amides as III easily undergo acid hydrolysis,[7, 8] the N-(*o*-hydroxyphenyl)pyrrolidin-2-one (II) remained unchanged, even after 10 hr of reflux with concentrated hydrochloric acid. It is obvious that the attack on the amide group is sterically hindered in IIa and this fact explains the remarkable resistance to acid hydrolysis of this compound as compared to III.

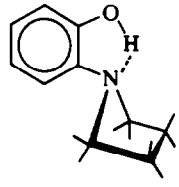
The reduction of II with LAH afforded the known N-(*o*-hydroxyphenyl)pyrrolidine



VI

(IV)[9–12] which was characterized as its *p*-nitrobenzoate (VI) and as hydrochloride (IV·HCl).[9]

It is appropriate here to observe that the IR and NMR spectra of the pyrrolidinophenol IV shows patterns which indicate an intramolecular H-bond of type O—H $\cdots$:N≡. Thus, the chemical shift of the phenol proton at 3·58 τ in the NMR spectrum of IV, and a broad absorption band in the 3300–2500 cm^{-1} region (and in



IVa

diluted solution in CCl_4 a broad band centered at 3350 cm^{-1}) agrees with the structure IVa. This type of intramolecular H-bond has been reported by Cameron *et al.*[13]

Table 1 records NMR and UV spectral data for the compounds studied.

Finally, it is appropriate to consider the unexpected course of the cyclization of I (n = 3) to II. It has been stated[14, 15] that alkylation of alkali salts of amides generally occurs on the N atom, and several studies[16–19] have shown that the cyclization of 4-halobutyramides, in the presence of alkali bases, occurs with N^--5 ring closure, exclusively. On the other hand, the cyclization of *o*-hydroxyphenyl-ω-haloamides (I, n = 1, 2) leads to the cyclic amides resulting from O^--6 or O^--7 ring closure, but with the γ-chloroamide I, the N^--5 ring closure is effective and leads to the N-substituted 2-pyrrolidinone (II). It is evident that in the *o*-hydroxyphenyl-ω-haloamides (which are nucleophiles possessing three sites of reaction) the attack by anionic oxygen nucleophile may compete with attack by the N atom and thus, in the series n = 1, 2, 3, the relative importance of N- and O-attack will be governed by the size of the resulting rings.

The mechanism of the reaction may be analogous to the one encountered by Zaugg

et al.[19] who pointed out that γ-haloamides undergo N^--5 cyclization by an irreversible second-order process in which the rate-limiting stage is the displacement of halide ion by amide anion. Accordingly, the preference for C—N bond formation in the cyclization of I (n = 3) may be an indication of the S_N2 character of the transition state.[14, 19]

TABLE 1. NMR AND UV SPECTRAL DATA

Compd.	Chemical shifts (τ values)					λ_{max} (nm)	1 g ε_{max}
	OH	Aromatic	$N—CH_2—C$	$CO—CH_2—C$	$C—CH_2—C$		
II	1·43 s	2·65–3·25 m	6·04 t	7·38 m[a]	7·69 m[a]	235 (sh)	3·60
						279	3·45
IV	3·58 s	2·83–3·45 m	6·67–7·33 m	—	7·72–8·23 m	246	3·41
						279·5	3·13
VI	—	2·72–3·30 m / 1·61 s[b]	6·57–6·85 m	—	8·00–8·30 m	254	4·31
						294	3·72

[a] There is a complex pattern between 7·10–8·10 τ.
[b] Four protons of the *p*-nitrobenzoyl group.

EXPERIMENTAL

All m.ps were determined in capillary tubes and are uncorrected. NMR spectra were taken in $CDCl_3$ soln containing TMS as internal standard, using a Varian A-60 spectrometer. Tests to locate OH protons were carried out for all compounds studied, by replacing the appropriate H atom by D.[20] IR spectra were recorded with a UR-10 Carl Zeiss–Jena double beam spectrophotometer and the UV spectra were recorded on a Unicam SP 800 spectrophotometer, in EtOH soln. Materials used in this work were purified prior to use. Unless otherwise stated, solns were dried over $MgSO_4$.

4-Chlorobutyryl chloride was obtained by the Reppe's procedure[21] from γ-butyrolactone and $SOCl_2$, in the presence of anhyd $ZnCl_2$, and it was twice distilled prior to use, (b.p. 176°).

4-Chloro-N(-o-hydroxyphenyl)butyramide, (I, n = 3)

To a warm soln of 43·6 g (0·04 moles) *o*-aminophenol (Fluka, *purtss.*) in 400 ml anhyd methylethylketone, a soln of 28·2 g (0·02 moles) 4-chlorobutyryl chloride in 100 ml methylethylketone was added dropwise with stirring, and the mixture heated for 1 hr on the water-bath. The mixture was then cooled, the solid material filtered off and the filtrate poured into 1000 ml dil HCl aq, with stirring. The organic layer was separated and dried and, to the dry soln, 100 ml xylene was added and then the soln was concentrated to a small volume, under reduced press. The soln afforded a crystalline product on cooling, the crystals were washed with xylene and dried. The crude 4-chloro-N-(*o*-hydroxyphenyl)butyramide melted at 99–100° and it was recrystallized from a n-hexane–n-propanol (8:1) to yield a pure product, m.p. 100–101°. (Found: N, 6·69; $C_{10}H_{12}ClNO_2$ requires: N, 6·57%); ν_{max}^{KBr}: 3620, 3374, 3255 (*b*), 2960, 2928, 2858, 1682, 1635, 1595, 1538, 1497, 1455, 1419, 1381, 1370, 1339, 1312, 1280, 1235, 1205, 1175, 1155, 1110, 1040, 989, 940, 770, 760, 652, 548, 472, 460 and 430 cm^{-1}.

N-(o-Hydroxyphenyl)pyrrolidin-2-one (II)

(a) *By 4-chloro-N-(o-hydroxyphenyl)butyramide cyclization.* To a soln of NaOEt (obtained from 0·23 g Na and 20 ml EtOH), 2·14 g (0·01 mole) finely powdered 4-chloro-N-(*o*-hydroxyphenyl)butyramide was added and then the solvent removed *in vacuo*. To the solid residue, 50 ml DMF was added and the mixture heated at the reflux of the solvent for 3 hr and, then, DMF removed at reduced press. The residue was

treated with 30 ml water, the mixture extracted with chloroform (3 × 30 ml), the extract washed with water, dried, and the solvent evaporated to yield 1·6 g (90%) of almost pure II, m.p. 134–135°.

Alternatively, 2·14 g of I and 10 ml 20% NaOH aq were heated for 3 hr on a water-bath and the reaction mixture worked up to give 1·5 g (85%) of II, m.p. 133–134·5°.

An analytical sample of II was obtained by recrystallization of the crude product from 35% aqueous EtOH (charcoal) and subsequent vacuum sublimation. The pure II, white crystals, melted at 135·5–136·0°. (Found: C, 67·75; H, 6·09; N, 8·36; $C_{10}H_{11}NO_2$ requires: C, 67·77; H, 6·26; N, 7·90%); (*a*) ν_{max}^{KBr}: 3200–2400 (*b*), 1670, 1651, 1591, 1525, 1472, 1454, 1411, 1311, 1285, 1238, 1210, 1162, 1131, 1116, 1085, 1048, 935, 872, 862, 755, 745, 661, 642, 590, 577, 547, 511 and 470 cm^{-1} and (*b*) in 0·01% CCl_4 soln, the amide CO band appeared at 1680 cm^{-1} and in the 3000 cm^{-1} region the spectrum shows the following pattern: 3170 w, 3097 s, 3062 ms, 2997 s, 2970 ms and 2895 ms (cm^{-1}).

(b) *From sodium o-aminophenoxide and γ-butyrolactone.* A rapid stream of N_2 was passed for 20 min through a suspension of 109·2 g (1 mole) *o*-aminophenol (Fluka, *puriss.*) in 500 ml EtOH, and then, under N_2 atmosphere, a soln of NaOEt (obtained from 4·6 g Na and 100 ml abs EtOH) was added to the above suspension. The solvent was removed by distillation on the water-bath under reduced press and the solid residue was treated with 129 g (1·5 moles) freshly vacuum-distilled γ-butyrolactone. The mixture was heated until about 7 ml water (Karl–Fischer method) distilled off and the temp of the mixture reached 200°. After 15 min at this temp, the excess γ-butyrolactone was removed by distillation under reduced press and the mixture was cooled to the room temp. The solid product was dissolved in 500 ml warm water, the soln cooled to 10–12° and the crystalline ppt filtered off, washed with cold water and dried to yield 31 g of II, m.p. 133·5–135°. The mother liquor was extracted with chloroform, the extract was cooled at −5° and the soln filtered to give 25·5 g of II, m.p. 132–134°. The total yield of II was 56·5 g (32%). The mother liquor was treated with conc HCl aq to give a brown coloured oil which was not characterized.

(c) *From o-aminophenol and 4-chlorobutyryl chloride. o*-Aminophenol (0·2 moles) in 250 ml anhyd benzene was treated with a soln of 28·2 g 4-chlorobutyryl chloride in 250 ml benzene. The mixture was refluxed for 5 hr and then it was washed with water and dried. The soln was distilled on the water-bath to remove the solvent and then vacuum-distilled to yield an oil (b.p. 155–165°/7 mmHg) which was dissolved in MeOH–benzene and cooled. The soln afforded 2·9 g crystals, m.p. 134–135°, and the mixture m.p. of this product with II showed no depression, and also the spectra of this product and of II are identical.

Attempted hydrolysis of II

A mixture of 1 g of II and 15 ml conc HCl aq was heated on water-bath for 10 hr and then the mixture worked up. The starting amide II was recovered unchanged.

N-(o-*Hydroxyphenyl*)*pyrrolidine* (IV)

To a soln of 5 g LAH in 400 ml anhyd ethyl ether, 10 g N-(*o*-hydroxyphenyl)pyrrolidin-2-one was added portion-wise. The mixture was refluxed for 5 hr and then treated with 5 ml water, 5 ml 15% NaOH aq and finally with 20 ml water. The mixture was filtered, the ethereal soln was washed with water and dried, the ether removed and the residue extracted with warm light petroleum. After the evaporation of the solvent, 5·9 g of IV was obtained as a pink crystalline powder, m.p. 104–106°. An almost colourless analytical sample was obtained by further purification, m.p. 109°, (lit.[11] 111°); $\nu_{max}^{CCl_4}$: 3350 (*b*), 3045, 2936, 2880, 2835, 1590, 1497, 1362, 1282, 1253 cm^{-1}.

N-(o-*Hydroxyphenyl*)*pyrrolidine hydrochloride* (IV HCl)

A rapid stream of anhyd HCl was passed through a soln of 0·1 g of IV in 20 ml anhyd benzene. The hydrochloride of IV precipitated as almost colourless crystals, m.p. 185–186° (lit.[9] m.p. 187–188°).

Alternatively, the hydrochloride was obtained by heating 0·3 g of IV with 2 ml HCl aq, evaporation to dryness and the solid recrystallized from abs EtOH to yield a product melting at 182°.

N-(o-*Hydroxyphenyl*)*pyrrolidine* p-*nitrobenzoate* (VI)

The *p*-nitrobenzoyl derivative of IV was obtained from IV and *p*-nitrobenzoyl chloride in the presence of anhyd Et_3N (benzene solns). The crude product (m.p. 112–116°) was purified by chromatography (silica-gel, benzene) and recrystallized from abs EtOH to yield an analytical sample of VI, red needles, m.p. 120·5°. (Found: C, 65·25; H, 5·20. $C_{17}H_{16}N_2O_4$ requires: C, 65·31; H, 5·13%); ν_{max}^{KBr}: 1735, 1610, 1529, 1508, 1485, 1455, 1351, 1324, 1274, 1252, 1182, 1165, 1150, 1104, 1089, 1020, 966, 879, 856, 830, 755, 718, 511 and 479 cm^{-1}.

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REFERENCES

[1] I. I. Badilescu, *Tetrahedron Letters* 3599 (1968)
[2] O. Aschan, *Berichte Dtsch. Chem. Ges.* **20**, 1524 (1887)
[3] J. Hill and G. R. Ramage, *J. Chem. Soc.* 3709 (1964)
[4] G. S. Sidhu, G. Thyagarajan and U. T. Bhalerao, *Indian J. Chem.* **2**, 211 (1967)
[5] F. L. Scott, R. E. Glick and S. Winstein, *Experientia* **13**, 183 (1957)
[6] R. Mecke, R. Mecke and A. Lüttringhaus, *Chem. Ber.* **90**, 975 (1957)
[7] D. Huckle, I. M. Lockhart and M. Wright, *J. Chem. Soc.* 1137 (1965)
[8] D. Evans and I. M. Lockhart, *Ibid.* 4806 (1965)
[9] L. Birkofer and G. Daum, *Chem. Ber.* **95**, 183 (1962)
[10] L. Birkofer and G. Daum, *Angew. Chem.* **72**, 707 (1960)
[11] A. H. Sommers, *J. Am. Chem. Soc.* **78**, 2439 (1956)
[12] S. Danishefsky and R. Cavanaugh, *Chem. & Ind.* 2171 (1967)
[13] D. W. Cameron, P. M. Scott and A. Todd, *J. Chem. Soc.* 42 (1964)
[14] N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Am. Chem. Soc.* **77**, 6269 (1955)
[15] L. I. Smith and J. Nichols, *J. Org. Chem.* **6**, 502 (1941)
[16] H. W. Heine, P. Love and J. L. Bove, *J. Am. Chem. Soc.* **77**, 5420 (1955)
[17] C. J. M. Stirling, *J. Chem. Soc.* 255 (1960)
[18] B. A. Cunningham and G. L. Schmir, *J. Org. Chem.* **31**, 3751 (1966)
[19] H. E. Zuagg, R. J. Michaels, A. D. Schaefer, A. M. Wenthe and W. H. Washburn, *Tetrahedron* **22**, 1257 (1966)
[20] L. M. Jackman, *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, p. 71. Pergamon Press, Oxford (1966)
[21] W. Reppe, *Liebigs Ann.* **596**, 194 (1955)