Synthesis of Some Aryl-Substituted Tetraoxopiperazines

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The synthesis of some para-substituted 1,4-diphenyl-2,3,5,6-tetraoxopiperazines is described. Nucleophilic ring opening occurs readily with glycols.

During our work, it became necessary to prepare some para-substituted 1,4-diphenyl-2,3,5,6-tetraoxopiperazines. We synthesized these compounds in a manner similar to that of Hearn and Medina-Castro (*3*) by refluxing the appropriate oxanilyl chloride in benzene containing triethylamine as shown in Figure 1. The structures of the halide precursors and cyclic products, all previously unreported, were confirmed by ir and elemental analyses. Table I summarizes the physical and spectral data.

The substituted tetraoxopiperazines were not readily soluble in most organic solvents but could be recrystallized from dimethyl sulfoxide. Although the carbethoxy derivative decomposed at its melting point, the methyl and bromo-substituted compounds sublimed unchanged. They all underwent nucleophilic attack on the heterocyclic ring by glycols to give symmetrical *p*-substituted diphenyl oxamides. Thus, II (R = $COOC_2H_5$) and triethylene glycol produced di(*p*-carbethoxyphenyl) oxamide, whereas II (R = CH_3) and ethylene glycol formed di(*p*-tolyl)oxamide. Forster and Saville (*2*) had noted a similar ring sensitivity when reacting 1,4-dimethyl-2,3,5,6-tetraoxopiperazine with aniline.

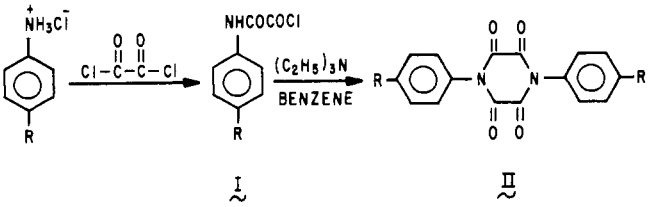
Experimental

Preparation of p-substituted oxanilyl chlorides. A mixture of 0.037 mole of *p*-substituted amine hydrochloride and 0.390 mole of oxalyl chloride was stirred and refluxed overnight. The resulting yellow solution was filtered under dry nitrogen, and the excess oxalyl chloride removed under vacuo. An oil remained that solidified upon cooling or when hexane was added. Recrystallization from benzene or benzene–hexane gave the product as fine yellow needles.

Preparation of p-substituted 1,4-diphenyl-2,3,5,6-tetraoxopiperazines. A mixture of 0.03 mole of *p*-substituted oxanilyl chloride, 4.5 ml of triethylamine, and 150 ml of dry benzene was stirred and refluxed 24 hr. The cooled mixture was filtered, and the solid washed successively with ethanol and water. It was then recrystallized from dimethyl sulfoxide.

Formation of di-(p-carbethoxyphenyl) oxamide from II (R = $COOC_2H_5$) and triethylene glycol. A mixture of 1.95 grams (4.46 mmol) of II (R = $COOC_2H_5$), 0.74 gram (4.91 mmol) of dry triethylene glycol, three drops of titanium isopropoxide, and 35 ml of dry dimethyl sulfoxide was refluxed under N_2 for 2 hr. Upon cooling, the solution deposited 1.35 grams (79%) of substituted oxamide. Recrystallization from dimethyl sulfoxide produced silky needles, mp, 287–287.5°C (lit. mp, 292–3°C) (*4*).

Formation of di-(p-tolyl) oxamide from II (R = CH_3) and ethylene glycol. A mixture of 0.08 gram (0.25 mmol) of II (R = CH_3) and 10 ml of dry ethylene glycol was refluxed under N_2 for 4 hr. Upon cooling, 0.06 gram (83%) of substituted oxamide was deposited. Following recrystallization from dimethyl sulfoxide, it melted at 268.5–269.5°C (lit. mp, 267–8°C) (*1*). An admixture with an authentic sample melted at 267–8°C, and ir's were super-



R = $COOC_2H_5$; CH_3; Br

Figure 1. Preparation of *p*-substituted 1,4-diphenyl-2,3,5,6-tetraoxopiperazines

Table I. Properties of Products[a]

Compound	Yield, %[b]	Mp, °C[c]	Ir bands, cm^{-1} [d]
I (R = $COOC_2H_5$)	92.5	123–4	3330 (NH stretch); 1705 (amide I); 1545 (amide II); 1785 (COCl); 855 (*p*-substituted aromatic)
I (R = CH_3)	85.0	93.5–4	3370 (NH stretch); 1725 (amide I); 1530 (amide II); 1770 (COCl); 820, 801 (*p*-substituted aromatic)
I (R = Br)	85.8	143–5	3270 (NH stretch); 1690 (amide I); 1536 (amide II); 1770, 1750 (COCl); 824 (*p*-substituted aromatic)
II (R = $COOC_2H_5$)	55.6	357–9 d	1710–40 (broad carbonyls); 1188, 1110, 1275 (carbonyl stretch); 850 (*p*-substituted aromatic)
II (R = CH_3)	26.2	270 subl.	1690, 1712 (carbonyls doublet); 812 (*p*-substituted aromatic)
II (R = Br)	64.6	370 subl.	1710–40 (broad carbonyls); 821 (*p*-substituted aromatic)

[a] Elemental analyses (C, H, N) in agreement with theoretical values were obtained and submitted for review. [b] Purified yield. [c] Melting points were determined on a Mel-Temp unit and are uncorrected. [d] Ir spectra were done on a Perkin-Elmer Model 21 recording spectrograph by use of KBr discs.

imposable. Ir (cm^{-1}): 1665 (amide I); 1530 (amide II); 3300 (NH stretch); 812,803 (*p*-substituted aromatic).

Acknowledgment

The author is grateful to Lois Kamarowski for the ir spectra.

Literature Cited

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(3) Hearn, W. R., Medina-Castro, J., *J. Org. Chem.*, **33**, 3980 (1968).
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Preparation of 2-Hydroxy-2-methylpropyl Acetate and 2-Hydroxy-2-methylbutyl Acetate

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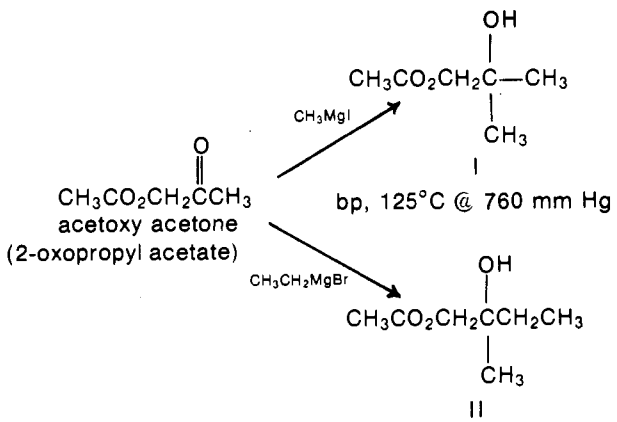
2-Hydroxy-2-methylpropyl acetate (I) and 2-hydroxy-2-methylbutyl acetate (II) were prepared by the (peracetic acid-induced) free-radical hydroxylation of isobutyl acetate and 2-methylbutyl acetate, respectively. Both I and II were identified on the basis of nuclear magnetic resonance (nmr), infrared, mass spectroscopic, and elemental analysis data.

In 1903 Kling (2) reported the preparation of 2-hydroxy-2-methylpropyl acetate (I) and 2-hydroxy-2-methylbutyl acetate (II) by the following reactions:



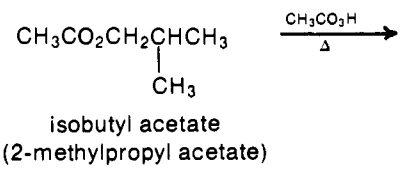
I
bp, 125°C @ 760 mm Hg

II
bp, 152–158°C @ 10 mm Hg

In 1914 Menge (3) prepared II by the reaction of "freshly fused potassium acetate and methylethylglycol chlorhydrin," but reported a boiling point of 94–94.5°C at 16 mm Hg. Menge's synthesis of II was supported by elemental analysis and cryoscopic molecular weight data.

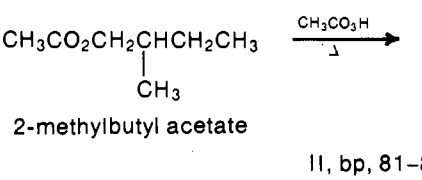
Recently, Van Sickle (4) prepared I by the reaction of sodium acetate and 1,2-epoxy-2-methylpropane but reported only nmr data to identify I.

We prepared both I and II by means of the (peracetic acid-induced) free-radical hydroxylation (1) of isobutyl acetate and 2-methylbutyl acetate, respectively. These esters were allowed to react with peracetic acid at approximately 100°C, thereby effecting hydroxylation at the tertiary carbon atoms.



isobutyl acetate
(2-methylpropyl acetate)

I, bp, 72–73°C @ 15 mm Hg



2-methylbutyl acetate

II, bp, 81–82.5°C @ 8 mm Hg

Both I and II are clear, colorless liquids with distinctly ethereal odors; infrared, nmr, mass spectroscopic, and elemental analysis data were consistent with the structural assignments.

On the basis of our results, neither I nor II appears to have been prepared by Kling; the data reported by Menge are consistent with our identification of II, and the nmr spectrum reported by Van Sickle is equivalent to our spectrum for I.

Experimental

Gas-liquid chromatography (glc) was conducted with a F/M Model 720 chromatograph by use of 60 ml/min of helium as the carrier gas. For analytical purposes a 12-ft × 1/4-in. column containing 10% Si-550 on Chromosorb W (not acid washed) was operated at 150°C; preparative glc was carried out at 130°C with a 10-ft × 1/4-in. column containing 20% SE-30 on Chromosorb S, 60–80 mesh. Elemental analyses (C, H) in agreement with theoretical values were obtained and submitted for review.

2-Hydroxy-2-methylpropyl acetate (I). A 250-ml round-bottomed flask was equipped with a thermometer, magnetic stirring bar, nitrogen purge tube, dropping funnel, and a distillation head. The flask was loaded with 58.1 grams (0.5 mole) of isobutyl acetate (99.8% pure by glc)