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Synthesis of Tritium Labeled Isoxsuprine Hydrochloride

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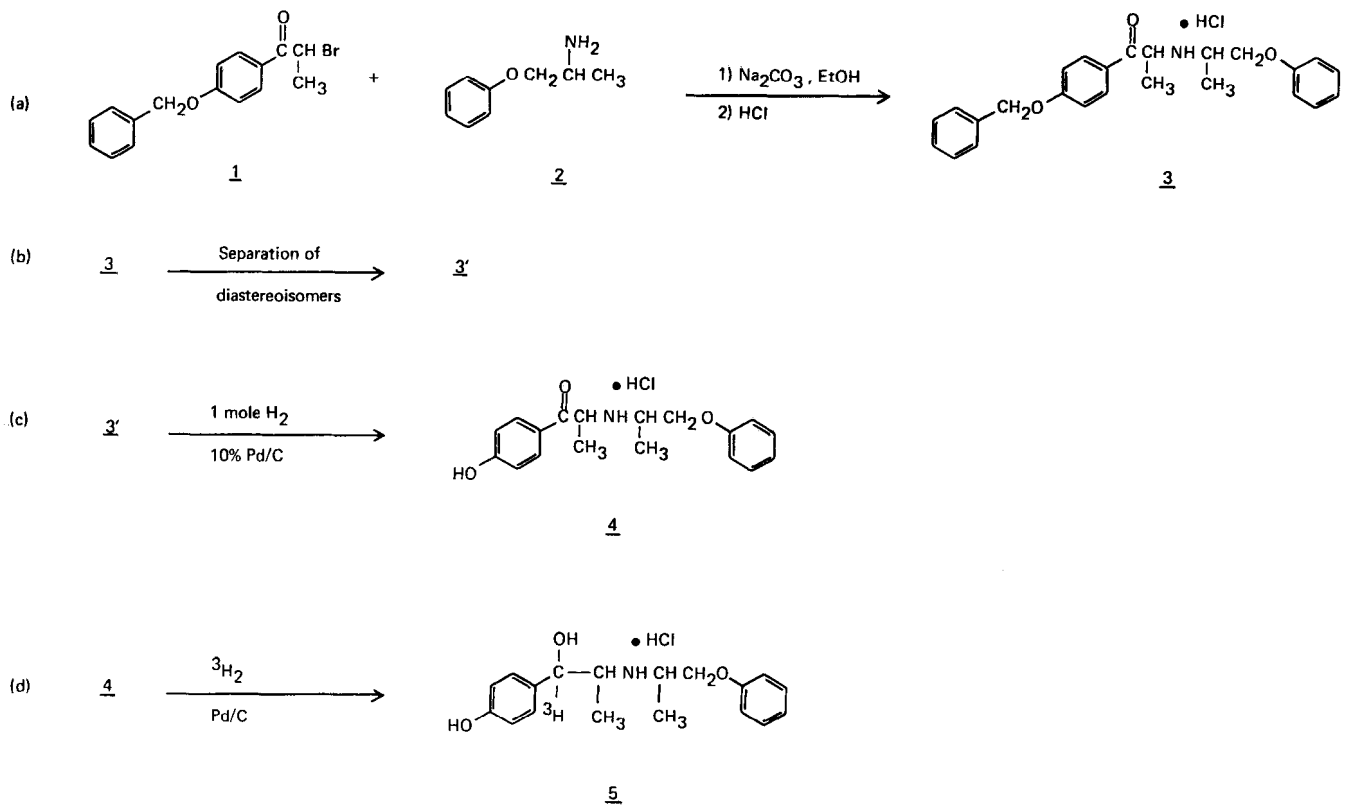
SUMMARY

Tritium labeled isoxsuprine hydrochloride was required for drug metabolism studies in these laboratories. This compound was prepared specifically labeled with tritium in the 1-position by the catalytic reduction of racemic β(R), γ(R)- and β(S), γ(S)-p-*hydroxy-α-(1-phenoxy-2-propylamino)-propiophenone hydrochloride with tritium.*

DISCUSSION.

The racemic compound, α*(S)*, β*(R)*, γ*(R)*- and α*(R)*, β*(S)*, γ*(S)*-2-(1-phenoxy-2-propylamino)-1-(*p*-hydroxyphenyl)-1-propanol hydrochloride (**5**), or generically, isoxsuprine hydrochloride, has been reported as a peripheral vasodilator, uterine relaxant, and bronchodilator [1–4]. This compound with a non-labile tag was required for animal and clinical metabolism studies in these laboratories. The scheme used to prepare the tritiated material is reviewed in Scheme I. *p*-Benzyloxy-α-bromopropiophenone (**1**) and 1-phenoxy-2-propanamine (**2**) were prepared according to published procedures [1]. The condensation to the aminoketone was effected in ethanol with sodium carbonate; the diastereomeric product (**3**) was precipitated from an ether extract with 4 *N* hydrochloric acid. At this point, the desired racemate, β*(R)*, α*(R)*- and β*(S)*, γ*(S)*-*p*-benzyloxy-α-(1-phenoxy-2-propylamino)-propiophenone hydrochloride (**3'**), was isolated from the diastereomeric mixture by repeated recrystallization from 80 % ethanol. Selective debenzylation of **3'** to β*(R)*, γ*(R)*- and β*(S)*, γ*(S)*-*p*-hydroxy-α-(1-phenoxy-2-propylamino)-propiophenone hydrochloride (**4**) was achieved by limiting the palladium catalyzed uptake of hydrogen to one equivalent. This ketone (**4**) was catalytically reduced as the free base with tritium, and then it was converted to the hydrochloride (**5**) for isolation. The final product was purified and diluted to the

SCHEME 1.


(a)
1
2
1) Na2CO3, EtOH
2) HCl
3
(b)
3
Separation of
diastereoisomers
3'
(c)
3'
1 mole H2
10% Pd/C
4
(d)
4
3H2
Pd/C
5

desired activity by several recrystallizations with unlabeled isoxsuprine hydrochloride.

This synthetic scheme was chosen for several reasons. The tritium alpha to the aromatic ring should be reasonably stable chemically and biologically. The isomer separation could be accomplished early in the synthesis, and it has been shown that the reduction of the isomer-pure racemate (**3'**) is stereospecific and gives predominantly the *erythro* racemate (**5**) [2]. The debenzylation was very selective, and the tritium reduction could be done as the last step on the free base in an aprotic medium. Prior experiments had shown that tritium incorporation was inefficient when the debenzylation and reduction of the ketone were done simultaneously. Presumably, this was because the reduction was done on the hydrochloride which required a relatively large amount of protic solvent (acetic acid/water) for dissolution. Exchange with solvent and debenzylation both consumed tritium.

EXPERIMENTAL.

Diastereomeric p-*Benzyloxy-α-(1-phenoxy-2-propylamino)-propiophenone Hydrochloride* (**3**).

This compound was prepared by an adaptation of a procedure according to Moed and van Dijk [1]. A mixture of 31.9 g (0.100 mol) *p*-benzyloxy-α-bromopropiophenone (**1**), 15.9 g (0.105 mol) 1-phenoxy-2-propanamine (**2**), 5.6 g (0.053 mol) sodium carbonate and 175 ml abs ethanol was stirred under reflux for 3 hr. The solvent was distilled *in vacuo*, and 100 ml anh ether was added to the residue. The mixture was filtered, and the solid was washed with ether. The combined ethereal filtrates were shaken with 46 ml 4 *N* hydrochloric acid, and the resulting solid was filtered. It was washed, first with ether, and then water. Drying *in vacuo* at 60° gave 42.2 g of white solid, mp 180-193°, which represents a 99 % yield of the diastereomeric mixture.

β(R), *γ*(R)- and *β*(S), *γ*(S)-p-*Benzyloxy-α-(1-phenoxy-2-propylamino)-propiophenone Hydrochloride* (**3'**) *.

A mixture of the four possible stereoisomers as obtained above, 23.2 g, mp 180-193°, was dissolved in 325 ml hot 80 % ethanol. The solution was cooled slowly to 5°, and the resulting white solid was filtered and washed with 80 % ethanol. After air-drying, the solid weighed 12.9 g, mp 197.5-201°. The material was recrystallized from 125 ml 80 % ethanol, filtered, washed with 80 % ethanol and air-dried to give 7.9 g white crystalline material, mp 201.5-204.5°, literature mp ~ 205° [2].

* The stereochemistry of isoxsuprine is discussed by J. van Dijk, V. G. Keizer, J. F. Peelen and H. D. Moed [4].

Anal. Calcd for $C_{25}H_{28}ClNO_3$: C, 70.48; H, 6.63; N, 3.29. Found : C, 70.65; H, 6.56; N, 3.33.

β(R), γ(R)- and β(S), γ(S)-p-*Hydroxy-α-(1-phenoxy-2-propylamino)-propiophenone Hydrochloride* (**4**).

A micro-hydrogenation apparatus equipped with a magnetic stirrer and a rubber septum for the introduction of materials by injection was charged with 0.5 g 10 % Pd/C. The flask was evacuated and then purged with hydrogen, and then 5 ml methanol was injected. The mixture was vigorously stirred until hydrogen uptake ceased. The stirrer was stopped, and a solution of 2.0 g (4.7 mmol) *β(R), γ(R)*- and *β(S), γ(S)-p*-benzyloxy-α-(*1*-phenoxy-*2*-propylamino)-propiophenone hydrochloride (**3'**) in 30 ml warm methanol was injected. The mixture was stirred vigorously under hydrogen, and in 10 min 5.08 mmol hydrogen (108% of theory) had been absorbed. The flask was evacuated immediately, and the catalyst was filtered and rinsed with methanol. The filtrate was evaporated to dryness, and the residue was recrystallized from water and dried *in vacuo* to give 1.18 g (74.5% yield) white crystalline solid, mp 200-202.5°.

Anal. : Calcd for $C_{18}H_{22}ClNO_3$: C, 64.35; H, 6.60; Cl, 10.55; N, 4.17. Found : C, 64.58; H, 6.58; Cl, 10.64; N, 4.20.

α(S), β(R), γ(R)- and *α(R), β(S), γ(S)-1-*^{3}*H-2-(*1-*Phenoxy-2-propylamino)-1-(p-hydroxyphenyl)-1-propanol Hydrochloride* (**5**) *.

A mixture of 250 mg (0.745 mmole) *β(R), γ(R)*- and *β(S), γ(S)-p*-hydroxy-α-(1-phenoxy-2-propylamino)-propiophenone hydrochloride (**4**), 75.2 mg (0.745 mmole) triethylamine, 125 mg 10 % Pd/C and 11.0 ml ethyl acetate was stirred under 50 Ci tritium until 102 % of the theoretical amount of tritium was absorbed. The mixture was filtered, and the residue was thoroughly rinsed with methanol. The combined filtrates were treated with excess methanolic HCl and evaporated *in vacuo*; the residue was dissolved in 10 ml methanol **. The solvent was evaporated *in vacuo*. The residue was dissolved in 60 ml hot water with 4.972 isoxsuprine hydrochloride, filtered hot and cooled slowly to 5° C; the resulting crystalline solid was filtered and air-dried to give 4.193 g material. It was recrystallized in like manner from 50 ml water to give 3.667 g crystalline solid, fraction **A**. The mother liquors of the two recrystallizations were combined and concentrated *in vacuo* to about 50 ml, and 0.5 g sodium bicarbonate was added. The mixture was extracted with

* Generic name isoxsuprine hydrochloride.

** The tritium reduction was performed at New England Nuclear Corporation.

chloroform (3 × 50 ml). The combined extracts were treated with 5 ml 3.5 *N* methanolic HCl and evaporated to dryness *in vacuo*. The residue was recrystallized from 25 ml water in the manner described above to give 1.192 g crystalline solid, fraction **B**. Fractions **A** and **B** were combined with 18.237 g isoxsuprine hydrochloride by recrystallization of the whole from 250 ml water. The white crystalline solid had a specific activity of 45.2 μCi/mg *. This material was further diluted with 13.460 g isoxsuprine hydrochloride by recrystallization from 340 ml water to give 29.681 g material of specific activity 28.4 μCi/mg, mp 206-206.5°, mixed mp 204-206°, literature mp 202-203° [1]. Paper radiochromatographic analysis showed no impurities *.

Anal. : Calcd for $C_{18}H_{24}ClNO_3$: C, 63.99; H, 7.16; N, 4.15. Found : C, 63.83; H, 6.99; N, 4.03.

* The activity determinations and paper radiochromatographic analyses were done by Dr. J. A. LaBudde and his group. Activities were determined in a Packard Tri-Carb liquid scintillation spectrometer. For the chromatographic work, the compound was dissolved in water and spotted on Whatman No. 1 paper. The compound was found to be homogeneous in two solvent systems : (1) n-butanol/acetic acid/water (3/1/1), (2) 20 % chloroform in ethanol. The chromatograms were scanned in a Vanguard "Autoscanner 880" for detection of radioactivity. In solvent system (1), the compound gave a single peak with R_f 0.82 (authentic sample R_f 0.78). In solvent system (2) the compound gave a single peak with R_f 0.76 (authentic sample R_f 0.71).

REFERENCES

1. MOED, H. D. and van DIJK, J. — *Rec. Trav. Chim. Pays-Bas*, **75** : 1215 (1956).
2. VAN DIJK, J. and MOED, H. D. — *Ibid.*, **78** : 22 (1959).
3. VAN DIJK, J. and MOED, H. D. — *Ibid.*, **80** : 873 (1961).
4. VAN DIJK, J., KEIZER, V. G., PEELEN, J. F. and MOED, H. D. — *Ibid.*, **84** : 521 (1965).