

Bol. Inst. Quím. Univ. Nacl. Autón. Méx. 21, 259-262 (1969).

A CONVENIENT, INEXPENSIVE, LARGE-SCALE METHOD
FOR THE PREPARATION OF DEUTERATED-CARBINOL
DERIVATIVES

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Recibido, noviembre 12 de 1969.

RESUMEN

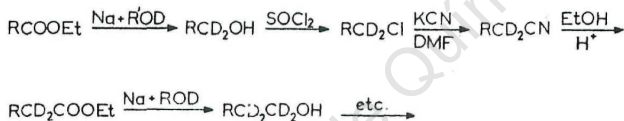
Se ha desarrollado un método barato y que sirve para preparar grandes cantidades de derivados de carbinoles deuterados, que no requiere del uso de deuteruro de litio y aluminio, y que permite obtener hasta el 100% de producto isotópico puro. Este método, que involucra el uso de óxido de deuterio comercial como fuente de materia prima isotópica, puede utilizarse, mediante una secuencia de pasos sencillos, en la obtención de derivados alfa deuterados.

The objective of this study was the attainment of an inexpensive, generally applicable method of preparing large quantities of deuterated carbinyl compounds such as alcohols, alkyl halides and other classes of substances which can be readily derivatized from such basic functionalities. Hitherto, the use of lithium aluminum deuteride (LAD) has been most widely applied for this purpose, but this

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procedure is clearly restricted by the obvious costliness of the LAD and the limited scale of safe, synthetic operation.

To illustrate our method, which represents a very convenient and inexpensive alternative to the approach currently in practice for preparing deuterated carbinols, let us consider the preparation of 20 grams of 2-deutero-2-propanol (DIP) which would cost more than Dlls. 200.00 purchased commercially (in the U.S.A.) and about half that much if prepared from LAD reaction with acetone. The scheme we have employed to prepare this amount of the desired product (see experimental section) is also readily adaptable to a safe, inexpensive laboratory scale preparation of as much as 6 to 10 times this amount using no larger than 3 liter flask equipment, (as follows):



It will be seen that virtually any primary alcohol ROH can be used for preparation of its borate ester.¹ The selection of ROH is simply based on the ease of separability (by distillation) of the deuterated alcohol product from the alcohol (produced) moiety of the original borate. In the case of DIP, amyl borate is very convenient.

The reaction of the borate ester with D₂O takes place in the same flask in which the ultimate reduction with sodium will occur. It is not necessary to separate the boric acid formed in step 1, since it does not interfere in step 2. Furthermore, the sodium reaction with the alcohol is easily controlled, initially by a cold water bath and finally by overnight stirring at ambient temperatures. To assure total deuteration of the product, (i.e., to exactly the same extent as the D₂O, which is the virtual starting material), the residual sodium is decomposed by addition of a small amount of excess D₂O when the rate of reduction has noticeably slowed. If H₂O is added instead at this point and any starting acetone still remains, the risk exists of forming the protio-alcohol as a contaminant. In the

example presented in the experimental section, addition of D_2O excess is omitted and the product is worked up after overnight stirring, by slow addition of 150 cc of H_2O , with the result that only 92% deuteration is achieved.

Our method can be applied advantageously, both directly and indirectly, to the preparation of the following deuterated-carbinol compound and derivatives:

1.—secondary alcohols, using the corresponding ketone as starting material,

2.—primary alcohols, using the corresponding esters as starting material,

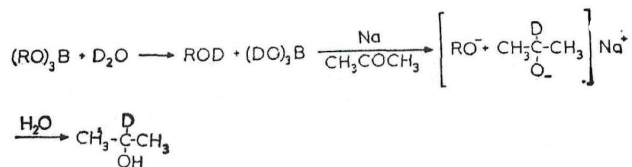
3.— α -deuterated, deuterated carbinol derivatives, using the following sequence of steps:

Finally, (what is often) the most important advantages of this method over the use of LAD, is the fact that one can readily attain an extent of deuteration approaching 100%, limited only by the purity of D_2O used (generally 99.7%). LAD is seldom obtainable in such purity and is much too readily (adventitiously) converted to protiated forms which result in extensive contamination of the products.

EXPERIMENTAL

Preparation of amyl borate. The procedure given in common laboratory manuals¹ is very satisfactory. The product boiled steadily at 110° (0.2 mm) through a 2 foot Vigreux column and was pure by vpc criteria.

Preparation of 2-deutero-2-propanol (DIP). Amyl borate (237 g, 0.87 M) was charged to a 500 ml 3 neck flask equipped with a strong mechanical stirrer, reflux condenser with drying tube and thermometer well. The D_2O (60 ml, 2.6 M) was added rapidly under vigorous stirring through the top of the condenser. Stirring was continued for 5 minutes to assure complete precipitation of boric acid before 23 g (0.4 M) of spectrograde acetone was added and the mixture cooled to *ca.* 10° . A total of 26 g (1.12 M) of metallic sodium in small pieces² were added during a period of 5 hrs. at $25-30^\circ$. The mixture was then allowed to reach room temperature under stirring overnight (12 hrs.).



Water³ (ca. 150 ml) was now added slowly while stirring was continued until no more hydrogen evolution could be noted by means of an exit H₂SO₄ bubbler. The reaction mixture was now transferred to a separatory funnel and the upper layer retained. The lower aqueous layer was "salted out" by addition of K₂CO₃ to the point of turbidity and then extracted 3 times with 50 ml portions of ether. The ether extracts were combined with the (upper) alcohol layer and the total was twice washed with 20 ml portions of saturated K₂CO₃ solution, then dried over solid K₂CO₃ and distilled using a 75 cm Vigreux column. The fraction distilling at 75-95° was collected and redistilled in a spinning band column. Six fractions of ca. 3 gram each were collected boiling about 81° (by uncalibrated thermocouple), proved to be 95% pure DIP containing 92% deuterium by NMR estimation.

ABSTRACT

A method has been developed for preparing deuterated carbinol derivatives, cheaply and in large quantities, which does not entail the use of lithium aluminum deuteride and assures the attainment of nearly 100% isotopically pure product. This method, involving only the use of commercial D₂O as the source of isotopic raw material, can be applied in a sequence of simple steps for alpha deuteration as well.

NOTES

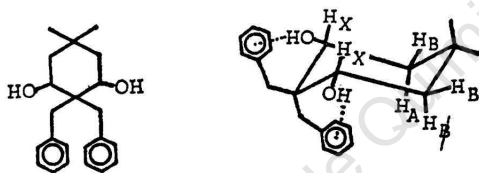
1. A. I. Vogel, "Practical Organic Chemistry", John Wiley and Sons, Inc., New York, p. 305 (1948).
2. More rapid and complete reaction can be achieved through the use of finely divided sodium prepared by the technique of K. Hafner and H. Kaiser, *Org. Syn.* 44, 94 (1964) and F. Elsinger, *ibid.*, 45, 7 (1965) and added slowly through a solids addition funnel under a nitrogen atmosphere.
3. At this point addition of ca. 10 ml D₂O and continued stirring until cessation of gas evolution will assure complete deuteration of the product.

ERRATA, CORRIGENDA, ADENDA.

Página

- 102 7) Para que el H de la base del OH muestre constante/ de acoplamiento de uno de los anillos aromáticos;⁶ cuando se determina el IR en /s
/i
- 106 hexan/6. El espectro de masas (Fig. 29), muestra M^+ 306 (que corresponde a la /-5-ona /M
108 irradiar en 1.75 (H_d), cambia la señal de la base del alcohol a /A

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- 125 Se sintetizó el 3,3-dimetil-6,6-dibencil-biciclo-[3,3,0]-hexano 13. Su /1
- 128 dimetil-3-[1',1'-dibencilmetilen]-ciclopentano-3-ona 14, cuya rnm (Fig. /4
- 132 1,1-Dimetil-3-[1',1'-dibencilmetilen]-ciclopentano-3-ona 14. La parte /4
- 172 2. M. C. Rock, F. Walls y H. Kwart, *Ibid.* 21, / (1969). /102
- 175 C_4 y C_6 . Centrada en 1.96 está la señal múltiple de los hidrógenos de C_5 . /d
- 178 alílicos aparece como /os señales dobles centradas a 2.4 y 2.1 y el resto de /d
- 179 y Kwart,⁴ han reportado una /iferencia de 0.58 ppm en la posición de las se- /d
- 181 Figura 12.—La señal doble de doble, centrada en 5.06 se debe al hidrógeno en la base del mesilato, con $J_{ax} = 10$ y $J_{bx} = 6$ Hz. Estas constantes de acoplamiento hacen suponer que el grupo mesilo está en posición ecuatorial. La señal en 3.0 se debe a los hidrógenos del mesilo y la múltiple cen-

{ $J_{ax} = J_{bx} = 4$ Hz. Ya que la molécula se mueve libremente podemos suponer que estas constantes son el promedio de las dos conformaciones.

- 213 dos influencias tienden a cancelarse mutuamente, lo cual /a

225 butirolactones (1, 2 y 3) y dos dioles (4 y 5) que no estaban des- /a

227 ~~La primera fracción (55%) (p. e. 54° a 1 mm) se identificó~~
como una mezcla de dimetil nonatrienos, que ya ha sido descrita
en la literatura² y que no se separó en sus componentes.

La primera fracción (55%) (p. e. 54° a 1 mm) se identificó
La otra fracción (40%) (p. e. 68° a 1 mm), se identificó como

255 sa del látex de *Hevía brasiliensis*. La presencia de esta enzima junto /e

259 The obje~~t~~ive of this study was the attainment of an inexpensive, /c

262 Water~~y~~ (ca. 150 ml) was now added slowly while stirring was con- /^{3, 4}

3. At this point addition of ca. 10 ml D₂O and continued stirring until cessation of gas evolution will assure complete deuteration of the product.

4. The carbinol carbon of secondary alcohols is nearly quantitatively deuterated using this procedure. However, the molecule also becomes partially deuterated by exchange reaction occurring simultaneously at carbons α to the (former) carbonyl group. This method of preparing carbinol deuterated alcohols is therefore only applicable where deuteration of positions adjacent to the carbinol group is of no consequence, or are required also to be fully deuterated.