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# FORMATION OF ELECTRON-CAPTURING DERIVATIVES OF ALPRENOLOL BY TRANSBORONATION

## APPLICATION TO THE DETERMINATION OF ALPRENOLOL IN PLASMA*

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## SUMMARY

The reaction between 2,4-dichlorobenzeneboronic acid, 3,5-bis(trifluoromethyl)benzeneboronic acid or the 1,3-propanediamine derivatives of the boronic acids and the 3-isopropylaminopropan-2-ol side chain of the β-blocking drugs occurs essentially as an on-column thermal reaction in the gas phase. Derivatization of the side chain of the β-blocking drugs by transboronation is shown to be the method of choice for general application as it affects the detector background signal very little compared to the use of the boronic acid itself. The transboronation reaction can be used for the determination of alprenolol in plasma extracts with a detection limit of 2.5 ng $ml^{-1}$ using the electron-capture detector. The ultimate sensitivity of the method is limited by the detector background signal resulting from some column decomposition of the transboronation reagent.

## INTRODUCTION

Alprenolol (1-[2-allylphenoxy]-3-isopropylamino-propan-2-ol) is a β-adrenoceptor blocking drug effective in the control of hypertension[1]. As such, it is a member of a series of drugs (Table I) having in common either a 3-isopropylaminopropan-2-ol or 3-*tert.*-butylaminopropan-2-ol side chain[2]. Alprenolol has been determined in biological fluids by extraction into an organic solvent at high pH and formation of the bis(trifluoroacetyl) derivative for gas chromatography (GC) with an electron-capture detector (ECD)[3,4]. Formation of the perfluoroacyl derivatives (*e.g.* trifluoroacetyl, pentafluoropropionyl, heptafluorobutyryl) with electron-capture detection is the principal analytical method for the determination of the β-blocking drugs in general, although a few methods based on fluorescence, mass fragmentography, radioimmunoassay and high-performance liquid chromatography have also

* Determination of bifunctional compounds, Part VIII. For Part VI see ref. 11.
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been used. A disadvantage of the use of the perfluoroacyl derivatives for the analysis of biological fluids is that the non-selective nature of the derivatization reaction results in a multitude of detected peaks as well as the peak for the drug. Problems can arise due to a background peak overlapping with the substance of interest or from the appearance of background peaks having long retention times which add significantly to the dead time between injections. To remove the biological background contribution to the chromatogram often requires a lengthy sample clean-up procedure adding substantially to the analysis time.

The side chain of the $\beta$-blocking drugs contains a bifunctional group which can be selectively derivatized as its cyclic *n*-butane boronate[5–7]. Recently, boronic acids containing electron-capturing groups have been introduced for the selective trace analysis of bifunctional compounds[8–11]. The chemical specificity of the boronic acid reaction coupled to the selectivity and sensitivity of the ECD offers new possibilities for the selective trace analysis of bifunctional compounds in complex mixtures. The reaction between the 3-isopropylaminopropan-2-ol side chain of the $\beta$-blocking drugs and either 2,4-dichlorobenzeneboronic acid or 3,5-bis(trifluoromethyl)benzeneboronic acid was found to occur principally by on-column injection and not to a significant extent in solution. Co-injection of the drug with an excess of boronic acid necessary for its quantitative conversion to the derivative resulted in a complete masking of the response of the ECD to the drugs of interest. To circumvent this problem, a new reaction (transboronation) was developed in which co-injection of the $\beta$-blocking drug with the 2,4-dichlorobenzeneboronate of 1,3-propanediamine was employed to form the derivative of the 3-isopropylaminopropan-2-ol side chain (Fig. 1). The transborination reagent is very volatile and is eluted rapidly from the column so as to cause the minimum of detector disturbance at the point where the derivatives of the $\beta$-blocking drugs elute.

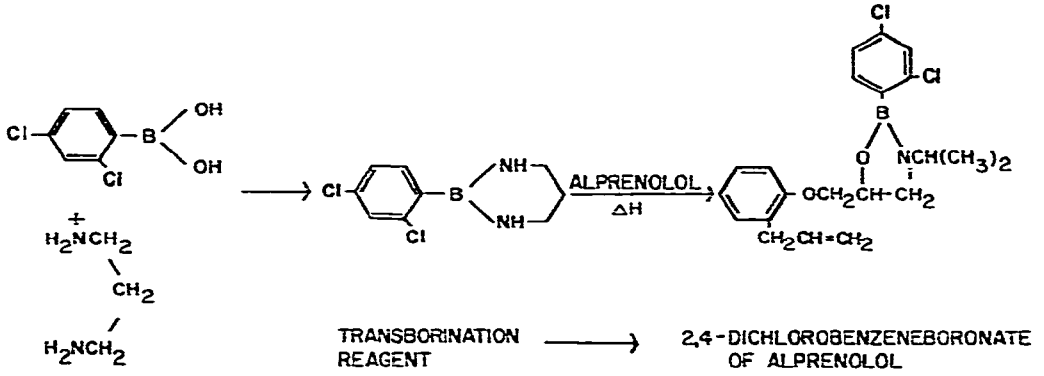



Fig. 1. Schematic illustration of the transboronation reaction for alprenolol.

## EXPERIMENTAL

Hexane, dichloromethane and acetonitrile were "zur Analyse" grade (E. Merck, Darmstadt, G.F.R.) and 1,3-propanediamine was reagent grade (Labkemi AB, Stockholm, Sweden). The 2,4-dichlorobenzeneboronic acid and 3,5-bis(trifluoromethyl)benzeneboronic acid were obtained from Lancaster Synthesis (St. Leonard-

gate, Lancaster, Great Britain) and is available in the U.S.A. through the Alfa Products Division (Ventron, Danvers, MA, U.S.A.). Alprenolol hydrochloride, the *meta* analog of alprenolol hydrochloride, the *para* analog of alprenolol hydrochloride, metoprolol tartrate, practolol hydrochloride, pamatolol sulfate, H 87/07 and H 93/47 were obtained from AB Hässle (Mölndal, Sweden), oxprenolol hydrochloride from Ciba-Geigy (Basel, Switzerland), timolol maleate from Merck, Sharp & Dohme (Rahway, NJ, U.S.A.), propranolol hydrochloride and atenolol from ICI Pharmaceutical Division (Macclesfield, Great Britain). The 9,10-dibromoanthracene was a gift from Dr. K-E.Karlson (Department of Analytical Pharmaceutical Chemistry, Uppsala, Sweden).

A 5.5 $\mu M$ solution of 2,4-dichlorobenzeneboronic acid was prepared by dissolving 10.64 mg of the boronic acid in 10.0 ml of acetonitrile.

A 55.0 $\mu M$ solution of 1,3-propanediamine ($\varrho = 0.884$) was prepared by dissolving 23 $\mu$l of diamine in 477 $\mu$l of acetonitrile.

A solution of the transboronation reagent was prepared from 500 $\mu$l of the boronic acid solution, 50 $\mu$l of the propanediamine solution and 450 $\mu$l of acetonitrile. This solution was reprepared every few days.

Alprenolol hydrochloride (0.874 mmol $l^{-1}$) was prepared by dissolving 49.91 mg of the salt in 200 ml of 0.1 $M$ hydrochloric acid. For use with the ECD, 1.0 ml of the above solution was diluted to 10 ml with 0.1 $M$ hydrochloric acid. A solution of the internal standard, the *para* analogue of alprenolol (1.98 mmol $l^{-1}$) was prepared by dissolving 28.35 mg of the salt in 50 ml of 0.1 $M$ hydrochloric acid and diluting 1:10 with 0.1 $M$ hydrochloric acid prior to use. The alprenolol standard solutions were stable for several months when stored at 4 °C.

The internal standard 9,10-dibromoanthracene was prepared as a 1.0 mg $ml^{-1}$ solution in dichloromethane.

*Plasma samples*

Blood was collected from volunteers by means of vena puncture into stoppered heparin tubes and allowed to cool to room temperature before centrifuging at 3000 rpm for 10 min. The plasma was removed by disposable glass pipettes and stored in glass tubes with polyethylene stoppers at —20 °C until used.

*Extraction and derivatization*

Plasma samples spiked with a known amount of alprenolol were thawed at room temperature and a 2.0-ml aliquot added to a 13.0 × 1.5 cm I.D. Pyrex PTFE-lined screw-capped culture tube together with 25 $\mu$l of internal standard solution (*para* analogue of alprenolol), 0.3 ml of 0.1 $M$ sodium hydroxide and 5.0 ml of hexane–dichloromethane (4:1). The tubes were shaken mechanically in the horizontal position for 10 min and the phases separated by centrifuging at 3000 rpm for 5 min. A 4.0-ml volume of the organic phase in a conical-tipped culture tube was evaporated to a residue with a stream of nitrogen at about 40 °C. To the residue was added either 25 or 50 $\mu$l of the transboronation solution and after vigorous mixing 1.0 $\mu$l was taken for analysis.

*Gas chromatography and mass spectrometry*

A Varian 3700 gas chromatograph with flame-ionization detector (FID) and

pulse moduiated constant-current ECD was used for GC. Separations were carried out on a 1.5 m × 0.2 cm I.D. glass column packed with 3% OV-17 on Gas-Chrom Q (100–120 mesh) and a flow-rate of 40 ml $min^{-1}$ of nitrogen. Alprenolol in plasma was determined with a column temperature of 235 °C. The injector and detector block temperatures were 300 and 380 °C, respectively.

The mass spectra were recorded on a Varian Mat 44S quadrupole mass spectrometer and Mat 200 data handling system coupled to a Varian 3700 gas chromatograph via an open split capillary interface. All electron-impact mass spectra were recorded at 70 eV. The boronate derivatives were separated on a 1.5 m × 0.2 cm I.D. glass column of 3% OV-17 on Gas-Chrom Q (100–120 mesh) with helium as carrier gas at a flow-rate of 15.0 ml $min^{-1}$.

## RESULTS AND DISCUSSION

The reaction between excess *n*-butaneboronic acid and alprenolol was found to be a useful method for the identification of the parent drug and some of its metabolites (retaining the necessary bifunctional group in the side chain) in biological fluids by GC–mass spectrometry (MS)[5–7]. The reaction was employed for identification purposes and neither the reaction conditions nor the quantitative aspects of the reaction were discussed in detail. Following similar lines we tried to prepare the 2,4-dichlorobenzeneboronate and the 3,5-bis(trifluoromethyl)benzeneboronate of alprenolol for use with the ECD. In contrast to our previous experiences with these reagents and their reactions with other bifunctional compounds[9–12], we could not demonstrate the occurrence of any appreciable reaction in solution for alprenolol or the other $\beta$-blocking drugs given in Table I. The peak area for the 2,4-dichlorobenzeneboronate or the 3,5-bis(trifluoromethyl)benzeneboronate derivatives was dependent on the excess molar concentration of the boronic acid but was independent of the reaction time (0–8 h) and reaction temperature (20–120 °C) in the solution phase. From the above observations we concluded that the reaction between the 3-isopropylaminopropan-2-ol or the 3-*tert*.-butylaminopropan-2-ol side chain with either boronic acid occurred essentially entirely at the point of injection onto the column and that the reaction in solution was by comparison unimportant.

*Conditions for the formation of the 2,4-dichlorobenzeneboronate of alprenolol*

Using the FID and 9,10-dibromoanthracene as internal standard, it was established that an approximately thirty molar excess of 2,4-dichlorobenzeneboronic acid over alprenolol was required for the quantitative on-column derivatization of this drug (Fig. 2). With the ECD, the co-injection of such a large excess of boronic acid resulted in a complete over-loading of the detector in the analytical region of the chromatogram for alprenolol and no reliable data could be obtained. Masking of the detector was probably caused by a slow conversion of the boronic acid to its anhydride (a trimeric boroxine) which slowly elutes from the column over a long-time interval. A method was sought to convert the boronic acid to a volatile derivative which would elute rapidly from the column and also convert the 3-isopropylaminopropan-2-ol side chain of alprenolol to its 2,4-dichlorobenzeneboronate derivative. The reaction envisaged we have called transboronation in analogy to transesterification used for the conversion of one alkyl ester into another of different carbon number. The 2,4-dichlorobenzeneboronate derivative of 1,3-propanediamine was selected as

the transboronation reagent as the general stability of this derivative is moderate and it was considered that it would most likely react favorably with alprenolol under the conditions for derivatization. The reaction between the boronic acid and 1,3-propanediamine occurs quantitatively and instantaneously in solution[9]. It was found that an approximately 100 molar excess of the 2,4-dichlorobenzeneboronate of 1,3-propanediamine (DCBBPD) reagent was required for the complete conversion of the alprenolol side chain to its boronate derivative (Fig. 2). The optimum molar ratio of boronic acid to diamine was 1:1 and an excess of diamine over the boronic acid resulted in a lower yield of derivative (Fig. 3). The transboronation reaction was independent of injection port temperature above 250 °C (the peak for the alprenolol derivative tails at lower temperatures), the column temperature and the carrier gas flow-rate in the range of 30–100 ml $min^{-1}$. With the ECD, maximum response for the alprenolol derivative was obtained at a high detector temperature [dissociative mechanism of electron-capture[9,10]] and at low carrier gas flow-rates. For the latter, 30–40 $ml^{-1}$ was a convenient compromise between chromatographic performance and detector sensitivity. Under these conditions the 2,4-dichlorobenzeneboronate of alprenolol elutes as a symmetrical peak well removed from excess transboronation reagent (Fig. 4). Kováts indices for the 2,4-dichlorobenzeneboronate derivatives of the $\beta$-blocking drugs are given in Table I and in all cases the derivatives had good peak shape on GC.

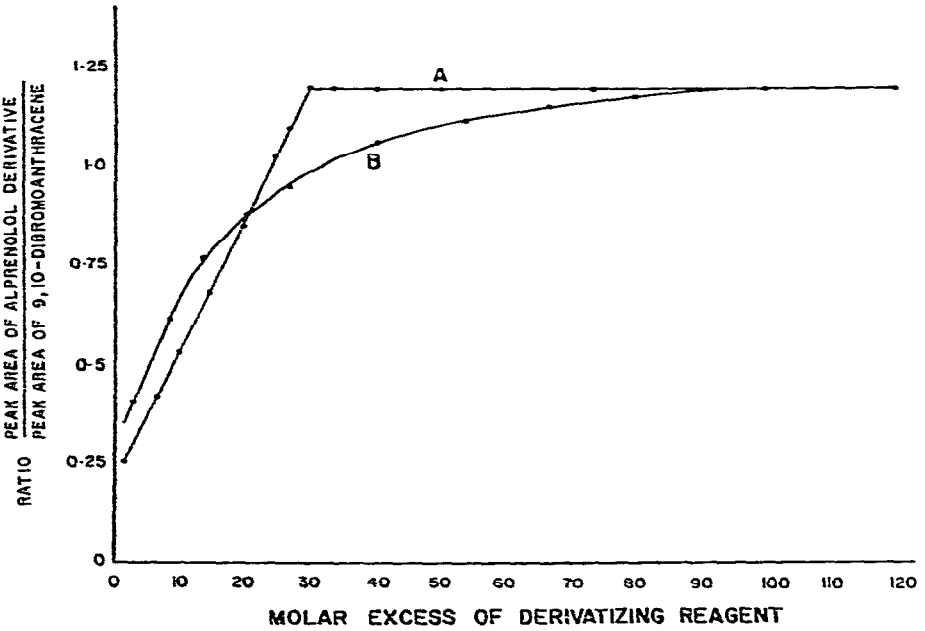


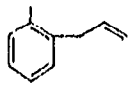
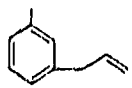
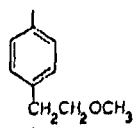
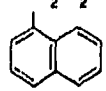
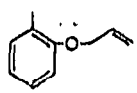

Fig. 2. Ratio of derivatizing reagent required for the quantitative reaction of alprenolol. A = 2,4-Dichlorobenzeneboronic acid, B = DCBBPD transboronation reagent.

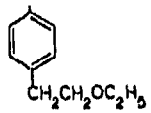
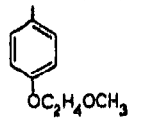
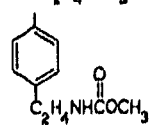
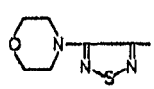
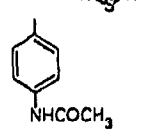
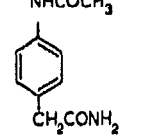
*Mass spectra of the 2,4-dichlorobenzeneboronates of alprenolol and related drugs*

GC–MS was used to confirm the constitution of the 2,4-dichlorobenzeneboronate of alprenolol (Fig. 5) and also for the other drugs studied (Table I). Molec-

TABLE I

STRUCTURE, RETENTION INDICES AND MASS SPECTRAL DATA FOR 2,4-DICHLOROBENZENEBORONATES OF THE β-BLOCKING DRUGS OF GENERAL FORMULA $R_1OCH_2CH(OH)CH_2NHCH(CH_3)_2$

| *Generic name* | $R_1$ | *Kováts index* | *Column temperature (°C)* | $[M]^+$ | $[M - CH_3]^+$ | *m/e* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *270* | *256* | *228* | *214* | *173* | *159* | *91* | *56* |
| Alprenolol |  | 3064 | 255 | 1.7 | 9.1 | 18.4 | 5.6 | 7.8 | 6.0 | 9.7 | 13.1 | 19.0 | 100.0 |
| *Meta* analog of alprenolol |  | 3121 | 255 | 4.9 | 32.1 | 7.8 | 6.6 | 5.0 | 6.5 | 9.7 | 8.9 | 15.9 | 100.0 |
| *Para* analog of alprenolol |  | 3186 | 255 | 4.0 | 19.2 | 6.1 | 5.4 | 5.4 | 6.1 | 10.1 | 11.0 | 16.6 | 100.0 |
| Metoprolol |  | 3346<br>3360 | 255<br>265 | 6.6 | 17.9 | 14.3 | 7.3 | 15.5 | 6.4 | 9.7 | 11.3 | 100.0 | 99.4 |
| Propranolol |  | 3535 | 255 | 6.6 | 3.7 | 13.0 | 14.0 | 20.2 | 3.3 | 7.4 | 12.8 | – | 100.0 |
| Oxprenolol |  | 3200 | 265 | 15.6 | 21.9 | 12.5 | 10.0 | 18.8 | 15.6 | 15.6 | 8.0 | 81.3 | 100.0 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H 93/47 |  | 3418 | 365 | 5.6 | 13.1 | 15.5 | 7.7 | 15.6 | 5.1 | 7.2 | 7.7 | 100.0 | 6.5 |
| H 87/07* |  | 3537 | 365 | 6.1 | 5.5 | 8.9 | 6.8 | 10.7 | 3.7 | 4.5 | 3.6 | — | 55.6 |
| Pamatolol** |  | 3568 | 265 | — | — | 5.1 | 6.3 | 7.0 | 5.5 | 6.3 | 11.7 | 24.2 | 100.0 |
| Timolol*** |  | 3660§ | 285 | 5.3 | 2.5 | 10.9 | — | 45.8 | 2.2 | 4.1 | 1.6 | — | 63.9 |
| Practolol |  | 3770§ | 285 | 6.2 | 17.9 | 15.4 | 7.9 | 14.8 | 5.7 | 7.9 | 7.8 | 72.9 | 100.0 |
| Atenolol§§ |  | 3870§ | 285 | — | — | 2.0 | 6.9 | 2.0 | 6.5 | 6.9 | 12.9 | 4.6 | 100.0 |

* Base peak *m/e* 49, α-cleavage of ether side chain.
** Highest ion in mass spectrum, *m/e* 417 (21.1) $[M - CH_3O_2]^+$.
*** β-Chain contains an $N\text{-}C(CH_3)_3$ substituent, main peaks *m/e* 199 (6.2), 187 (12.5), 154 (11.8), 112 (100.0), 96 (22.7), 70 (39.3), 57 (99.4).
§ Approximate value obtained by extrapolation.
§§ Highest ions in mass spectrum, *m/e* 403 (20.3) $[M - H_2O]^+$ and *m/e* 387 (30.4) $[M - H_2O - CH_3]^+$.

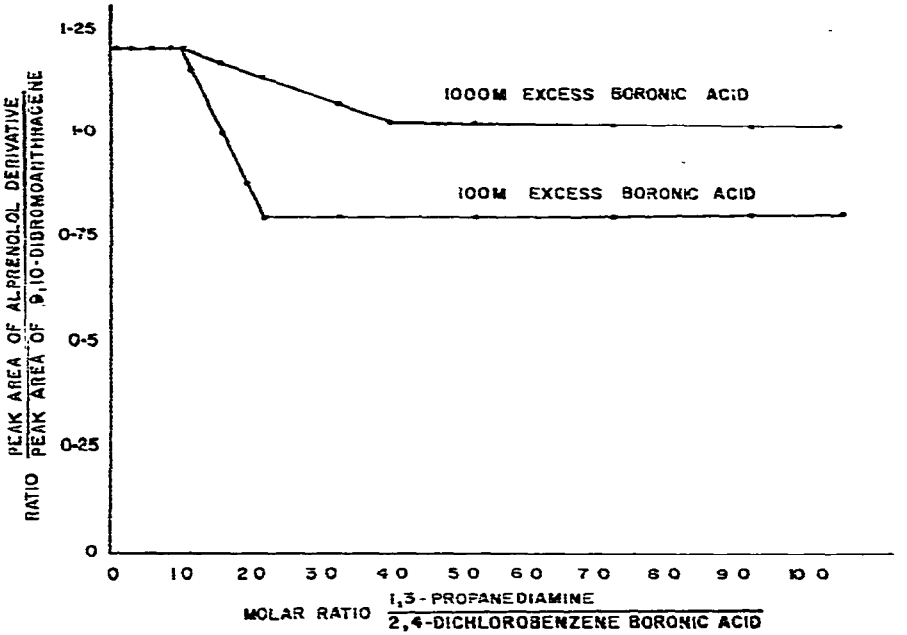
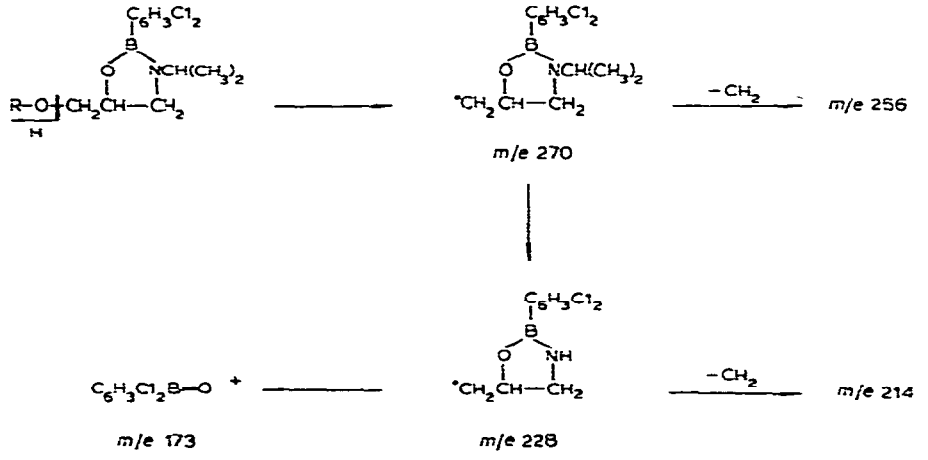



Fig. 3. The effect of excess 1,3-propanediamine on the formation of the 2,4-dichlorobenzeneboronate derivative of alprenolol by transboronation.

ular ions were observed in most cases if relatively weak. The ion $[M-CH_3]^+$ was generally more prominent than the molecular ion. The combined presence of the isotope peaks for boron ($^{10}B$:$^{11}B$ = 1:4.2) and chlorine result in extensive splitting of the principal fragment ions as can be seen in the mass spectrum of the alprenolol derivative (Fig. 5). The prominent ion *m/e* 368 $[M-Cl]^+$ and the greater relative abundance of the ion *m/e* 268 compared to *m/e* 270 in the mass spectrum of the alprenolol derivative are not typical of the boronate derivatives studied. The base peak in most mass spectra, *m/e* 56, could have the composition $C_3H_6N$ or $C_3H_4O$



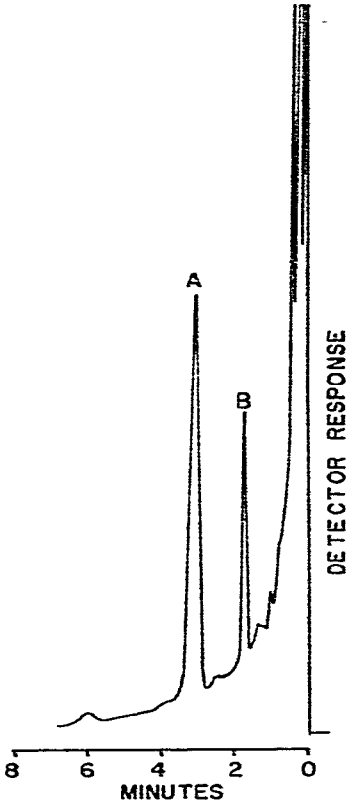



Fig. 4. GC–ECD chromatogram for approximately 50 ng of the 2,4-dichlorobenzeneboronate derivative of alprenolol (A) formed by transboronation. The internal standard is 9,10-dibromoanthracene (B) and the column temperature 250°C.

and most likely arises from the derivatized side chain. Those derivatives with an alkyl group attached directly to the benzene ring in the non-derivatized side chain have an abundant ion at *m/e* 91, which is presumably the tropylium ion (also observed in practolol). The principal ions characteristic of the derivatized side chain are summarized in Table I and arise by further fragmentation of the ion *m/e* 270 (formed by $\alpha$-cleavage with proton transfer) as shown below.

*Conditions for the formation of the 3,5-bis(trifluoromethyl)benzeneboronate of alprenolol*

Either 3,5-bis(trifluoromethyl)benzeneboronic acid or the 1,3-propanediamine derivative of 3,5-bis(trifluoromethyl)benzeneboronic acid (transboronation reagent) reacts in a similar manner to that described for 2,4-dichlorobenzeneboronic acid and its transboronation reagent with the 3-isopropylaminopropan-2-ol side chain of the $\beta$-blocking drugs. The molar ratio of reagent for quantitative derivatization of the drug side chain is different. The 3,5-bis(trifluoromethyl)benzeneboronate of alprenolol is formed quantitatively with a five molar excess of the 3,5-bis(trifluoromethyl)benzeneboronic acid or a ten molar excess of the 1,3-propanediamine boronate

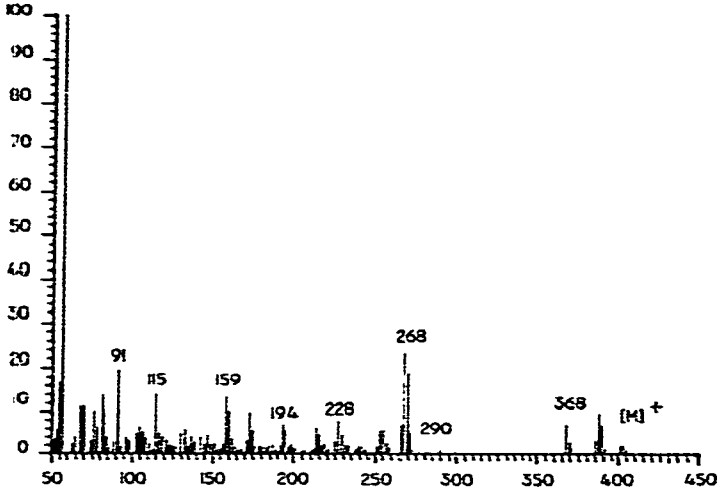



Fig. 5. The mass spectrum of the 2,4-dichlorobenzeneboronate derivative of alprenolol.

transboronation reagent. The transboronation reaction could not be used with the ECD due to interference between the derivative of alprenolol and by-products produced by the transboronation reagent itself (see later, under determination of alprenolol in plasma for further details). The transboronation reaction can be applied to the determination of the less volatile $\beta$-blocking drugs such as metoprolol and propranolol as their 3,5-bis(trifluoromethyl)benzeneboronate derivatives are easily separated on the GC column from the reagent generated by-products. Compared to the 2,4-dichlorobenzeneboronate derivatives of the $\beta$-blocking drugs, the 3,5-bis-(trifluoromethyl)benzeneboronates can be analyzed with a column temperature 20–30 °C lower and with maximum response to the ECD at the lowest practical detector temperature.

*The determination of alprenolol in plasma as its 2,4-dichlorobenzeneboronate*

For the analysis of alprenolol in plasma, 9,10-dibromoanthracene was not a good internal standard as it elutes too close to the solvent front. The *para* substituted allyl analog of alprenolol (1-[4-allylphenoxy]-3-isopropylaminopropan-2-ol) is easily separated from alprenolol GC and was selected as internal standard. Alprenolol and the para analog of alprenolol can be extracted from plasma adjusted to pH 14.0 with a mixture of hexane–dichloromethane (4:1) in greater than 98% yield with one extraction[13]. Using an extraction solvent of low polarity is important as it minimizes the number of potential interfering compounds extracted from the plasma and also reduces the amount of water co-extracted. Both traces of water and in particular residues of sodium hydroxide (readily observed as the sodium salt of the boronic acid which is insoluble in acetonitrile) reduce the precision of the analysis. The hexane–dichloromethane extract is essentially moisture free and the residue obtained by evaporation can be dissolved directly in the transboronation reagent for analysis. A calibration curve (Fig. 6) was prepared by adding known amounts of alprenolol to plasma which was processed as described in the experimental section. The calibration curve was linear over the range 0.2 ng (detection limit) to

about 75.0 ng (this corresponds to approximately a 100 *M* excess of transboronation reagent to alprenolol). For alprenolol hydrochloride at the 1.0, 10.0 and 60.0 ng level on-column, the recovered amounts were 0.98 ng ± 8.1% ($n = 5$), 10.28 ng ± 2.2% ($n = 7$) and 61.4 ng ± 2.4% ($n = 5$), respectively. For a 2.0-ml plasma sample and injection of 1.0 μl from 25 μl of reagent mixture, the detection limit for alprenolol hydrochloride corresponds to 2.5 ng $ml^{-1}$ of plasma. This is adequate for the detection of this drug in biological fluids and for all but the most demanding pharmacological studies where a detection limit of about 0.5 ng $ml^{-1}$ may be necessary.

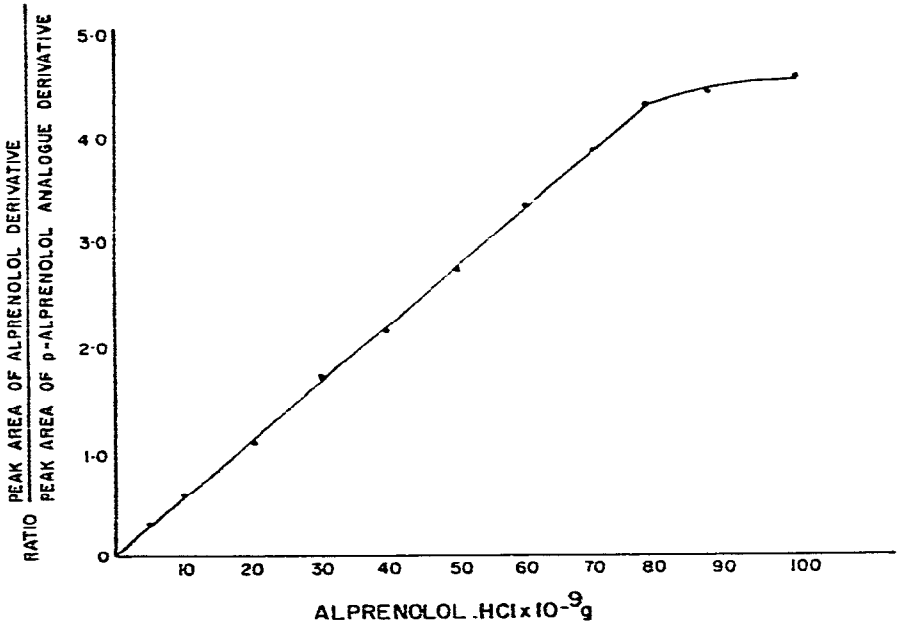



Fig. 6. Calibration curve for alprenolol hydrochloride extracted from plasma.

There are no interferents co-extracted from plasma which effect the analysis of alprenolol (Fig. 7). The other major peaks in the chromatogram (A→D) are present in the DCBBPD reagent and are not due to the plasma extract. These peaks do not interfere with the determination of alprenolol but would cause problems with the analysis of some of the other β-blocking drugs. The baseline of the chromatogram is many times more stable when the DCBBPD reagent is used in place of the boronic acid. However, some shift of the baseline occurs upon each injection, most probably due to partial thermal decomposition of the reagent along the length of the column leaving a residue of the boronic acid/anhydride which contributes a background signal to the detector. This limits the amount of signal amplification which can be employed and therefore the ultimate sensitivity of the method. An increase in sensitivity of at least one order of magnitude should be obtainable with a stable baseline. Between injections the baseline can be returned to its original position by heating the column to 310 °C for 5.0 min. This also enables those peaks eluting after the internal standard to be removed rapidly once the baseline has been established for

measuring its area. This rapid change of temperature and the presence of boronic acid residues on the column has not significantly effected its performance in over five months continuous use. An equally effective, although less convenient method of baseline correction is to inject 2.0 $\mu$l of a 10% (v/v) solution of 1,2-ethanediol in dichloromethane at the column operating temperature used for the alprenolol analysis. In this case the column residues of boronic acid/anhydride are probably eluted from the column as the volatile 1,2-ethanediol boronate derivative.

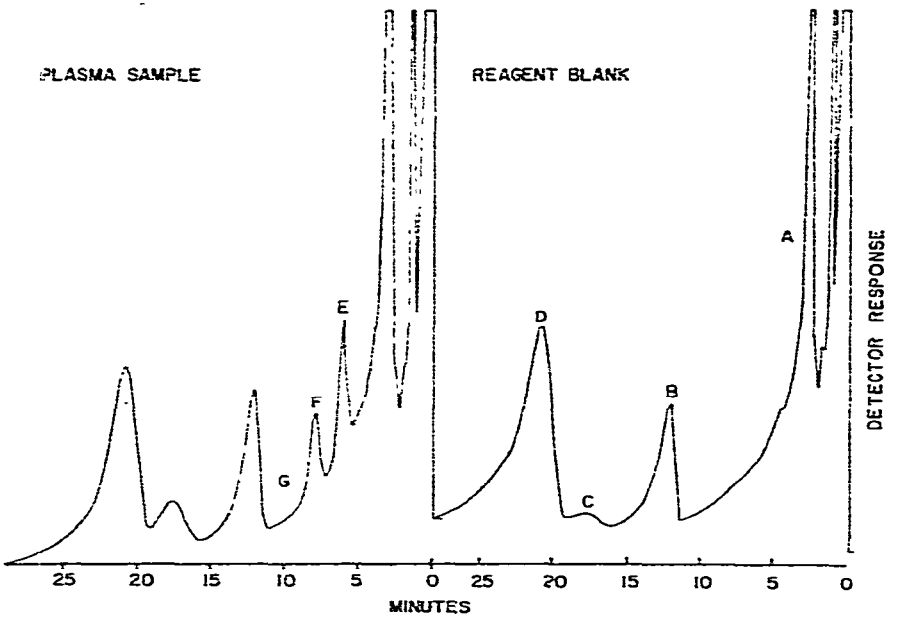



Fig. 7. GC–ECD chromatograms for plasma extract. A to D are reagent-generated products independent of the plasma extract, E corresponds to approximately 10.0 ng of alprenolol derivative and F is the derivative of the *p*-alprenolol analog used as internal standard. G is the point where temperature programming is started for routine analysis.

## CONCLUSIONS

The reaction between 2,4-dichlorobenzenenenboronic acid or 3,5-bis(trifluoromethyl)benzeneboronic acid and the 3-isopropylaminopropan-2-ol side chain of the $\beta$-blocking drugs is essentially an on-column thermal reaction occurring in the gas phase. A more convenient method for the formation of derivatives of the side chain of the $\beta$-blocking drugs is the transboronation reaction using the 1,3-propanediamine derivative of the boronic acid as the transboronation reagent. This method of derivatization is methodologically simple and compared to the use of the boronic acid itself, has the advantage of preventing a build-up of reagent on the column which interferes with the detector background signal of the FID and ECD and provides a much cleaner background spectrum when GC–MS is employed for derivative identification. For general purposes, the transboronation reaction is a more convenient and reliable method of derivatization of the side chain in the $\beta$-blocking drugs studied than reaction with the boronic acids themselves.

Compared to other methods for the determination of the β-blocking drugs, the proposed method for alprenolol has the advantage of speed and selectivity with adequate sensitivity for most applications to its determination in biological fluids. The selectivity of the derivatization reaction/detector combination gives a clean background chromatogram for plasma extracts with the exception of a few reagent generated products. These products do not interfere in the determination of alprenolol when the 2,4-dichlorobenzeneboronate of 1,3-propanediamine is used as the transboronation reagent but would interfere in the determination of some of the other β-blocking drugs. The reagent generated products have not been identified but only interfere in the use of the ECD as they are present at trace levels and are not normally observed with the FID. With the ECD, the ultimate sensitivity of the method for the detection of alprenolol is limited by the detector background signal due to some decomposition of the transboronation reagent on the GC column.

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