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# Unambiguous Synthesis of 1-(7-Indenyloxy)-3-isopropylamino-2-propanol Hydrochloride and Its 4-Indenyloxy Isomer, Potent β-Adrenergic Blocking Agents

1-(7-Indenyloxy)-3-isopropylamino-2-propanol hydrochloride (Ia) and its 4-indenyloxy isomer (IIa) were synthesized through the sequence of reactions in which possible isomerization of the indene nucleus was prevented by avoiding alkaline conditions. By referring to these standards, the preparation (YB-2) synthesized by the previously described method was found to be a 2: 1 mixture of Ia and IIa. *tert*-Butyl analogue of Ia and IIa (Ib, IIb) was also prepared similarly. Biological activities of Ia, IIa were compared with those of YB-2.

1-(7-Indenyloxy)-3-isopropylamino-2-propanol hydrochloride (YB-2) is a new potent β-adrenergic blocking agent[1,2] selected from a number of indene derivatives synthesized in these laboratories and is currently under clinical trials.

Generally, indenes are known to isomerize prototropically under basic conditions. Actually, we have observed a base-catalized isomerization of 7-acetoxyindene affording an equilibrium mixture of 7- and 4-acetoxyindene in a ratio of 2.2: 1.[1]

Since YB-2 was prepared by treating 7-indenol with epichlorhydrin in the presence of sodium hydroxide and further treating the reaction product with isopropylamine,[1] the compound was unavoidably exposed to basic conditions during its synthesis and the possibility that the preparation contained 4-indenyloxy isomer could not be ruled out. However, every attempt to detect and separate 4-indenyloxy isomer was not successful owing partly to the lack of authentic compounds with no structural ambiguity.

In this communication, we report the unambiguous synthesis of 1-(7-indenyloxy)-3-isopropylamino-2-propanol hydrochloride (Ia) and its 4-indenyloxy isomer (IIa) by new processes in which possible isomerization of indene nucleus was prevented by avoiding basic condition.

1-(1-Hydroxy-4-indanyloxy)-3-isopropylamino-2-propanol (Va, mp 149°) was prepared in a yield of 85% by the reaction of isopropylamine and 1-(1-hydroxy-4-indanyloxy)-2,3-epoxypropane (IV, mp 86°), which in its turn was prepared from 1-hydroxy-4-indanol (III)[1] and epichlorhydrin in 80% yield. Refluxing Va in 0.36N HCl in 70% aqueous ethanol for 16 hr effected dehydration producing Ia. The product was isolated conveniently from the reaction mixture, from which ethanol was removed, by extraction with chloroform after saturation with sodium chloride. The crude hydrochloride was purified by column chromatography on silica gel (eluant, iso-PrOH–Benzene–$H_2O$=8: 4: 1) affording isomer-free Ia (mp 142°, NMR (in $CDCl_3$) $\delta$: 6.46 (1H, d-t, $H_2$ of indene ring), 6.78 (1H, d-t, $H_3$ of indene ring), UV $\lambda_{max}^{H_2O}$ nm (log $\varepsilon$): 249 (3.93), 287 (3.05) 296 (2.98)) in 28% yield.

1) K. Murase, K. Niigata, T. Mase, and M. Murakami, *Yakugaku Zasshi*, **92**, 1358 (1972).
2) *a*) T. Takenaka and S. Tachikawa, *Arzneim. Forsch.*, **22**, 1864 (1972); *b*) T. Kimura, M. Endoh, N. Taira, and K. Hashimoto, *Experientia*, **28**, 813 (1972); *c*) K. Hashimoto, K. Kubota, S. Chiba, and N. Taira, *ibid.*, **28**, 822 (1972); *d*) F. Takenaka, T. Ishihara, M. Higuchi, I. Hiraki, T. Kawagoe, T. Umeda, M. Nozaki, and T. Takenaka, *Nippon Yakurigaku Zasshi*, **68**, 848 (1972); *e*) N. Takeya and T. Fujitani, *ibid.*, **68**, 270P (1972); *f*) S. Tachikawa and T. Takenaka, *Arch. Intern. Pharmacodyn.*, **202**, 79 (1973); *g*) H. Kato, Y. Noguchi, K. Nakao, and K. Takagi, *Japan. J. Pharmacol.*, **24**, 261 (1974); *h*) H. Kato, Y. Noguchi, and K. Takagi, *ibid.*, **24**, 589 (1974); *i*) K. Nakao, H. Kato, and K. Takagi, *ibid.*, **25**, 25 (1975); *j*) J. Sugimoto, M. Nagata, M. Sasa, M. Gamou, Y. Nishikubo, and H. Murakami, *J. Kansai Med. Univ.*, **26**, 391 (1974); *k*) H. Tatsuno, K. Shigenobu, and Y. Kasuya, *Arch. Intern. Pharmacodyn.*, in press.

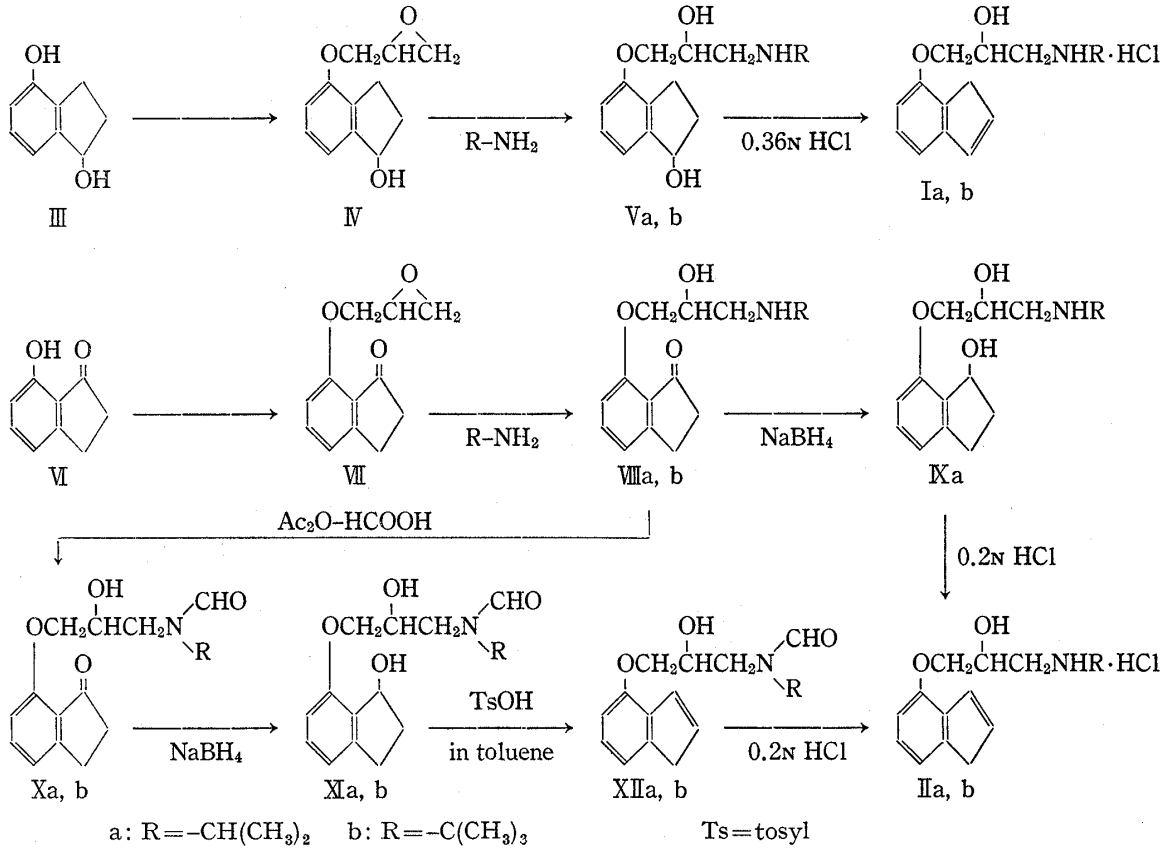


Chart 1

The synthesis of isomeric IIa involved the preparation of 1-(1-oxo-7-indanyloxy)-3-isopropylamino-2-propanol (VIIIa, mp 118°). This was prepared by the reaction of isopropylamine and 1-(1-oxo-7-indanyloxy)-2,3-epoxypropane (VII, an oil), the latter being obtained from 1-oxo-7-indanol (VI)[3] and epichlorhydrin. VIIIa was reduced to IXa with sodium borohydride and acid-catalyzed dehydration of IXa, carried out in the same manner as described for Va, led to IIa. However, column chromatographic purification of crude IIa obtained by this procedure was quite tedious and the following method of synthesis was found to be more satisfactory.

VIIIa was first formylated with a mixture of acetic anhydride and formic acid giving 1-(1-oxo-7-indanyloxy)-3-(N-formyl-N-isopropylamino)-2-propanol (Xa, mp 125°) and then reduced with sodium borohydride to a corresponding alcohol (XIa, a gum). XIa was dehydrated by refluxing in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid and the crude product was purified by column chromatography to give 1-(4-indenyloxy)-3-(N-formyl-N-isopropylamino)-2-propanol (XIIa, mp 75°, yield 86%). Careful hydrolysis of XIIa by refluxing in 0.2N HCl in 80% aqueous methanol for 3 hr, followed by isolation and chromatographic purification similarly to Ia, afforded isomer-free IIa in a yield of 18% (mp 149°, NMR (in $CDCl_3$) $\delta$: 6.40 (1H, d-t, $H_2$ of indene ring), 7.0[4] (1H, $H_3$ of indene ring, overlap with aromatic protons). UV $\lambda_{max}^{H_2O}$ nm (log $\varepsilon$): 251 (4.05), 259 (3.93), 292 (3.35), 302 (3.29).

Examination of NMR, UV, GC[5] of Ia and IIa revealed that these two preparations are completely free from each other. It was further demonstrated that YB-2 obtained from

3) R.A. Barnes, E.R. Kraft, and L. Gordon, *J. Am. Chem. Soc.*, **71**, 3523 (1949).
4) Overlap of signals prevented accurate measurement.
5) The samples were trifluoroacetylated with a mixture of $CF_3COOH$ and EtOAc (1: 9) prior to GC-analysis (conditions: column: 3% OV-22 on Chromosorb W, AW, glass, 1.8 m × 1.8 mm i.d., temperature: column: 170°, inject.: 250°, detector: FID, 250°, He 25 ml/min).

Table I. Comparison of Pharmacological Properties of Ia, IIa and YB-2

| Compounds | β-Blocking activity[a] | | Local anesthetic activity[b] | ISA[c] |
|---|---|---|---|---|
| | Isolated atria $pA_2$ | Reserpinized rats $ED_{50}$ (μg/kg *i.v.*) | | |
| Ia | $8.35 \pm 0.022 (p > 0.05)$ | $63 \pm 8 (p > 0.05)$ | + | + |
| IIa | $8.53 \pm 0.047 (p < 0.05)$ | $35 \pm 1 (p < 0.05)$ | + | + |
| YB-2 | $8.38 \pm 0.030$ — | $45 \pm 4$ — | + | + |

a) mean ±S.E. from 6 experiments
b) surface anesthesia of guinea pig cornea
c) increase in heart rate in reserpinized rats

7-indenol by the previously reported method is actually an equilibrium mixture containing I and II in a ratio of 2:1.

As the synthetic method described previously[1] is the only one industrially feasible, we propose that the term YB-2 should be applied to a preparation consisting of a 2:1 equilibrium mixture of Ia and IIa.

N-*tert*-Butyl analogue of YB-2, another potent β-blocker in the same series reported previously,[1,6,7] was also found to be a mixture by referring to the similarly synthesized isomer-free compounds. Acidic dehydration of Vb (a gum) gave 1-(7-indenyloxy)-3-*tert*-butylamino-2-propanol hydrochloride (Ib, mp 145°) in 25% yield. The 4-indenyloxy isomer (IIb, mp 146°) was obtained from VIIIb (a gum) *via* intermediates Xb, (mp 135°), XIb (mp 89°) and XIIb (mp 73°). Both were found to be isomer-free on physicochemical measurements.

Biological activities of Ia and IIa were compared with those of YB-2. Ia showed the same potency as YB-2 in β-blocking and local anesthetic activity, whereas IIa was slightly more active than YB-2 in the former effect. Both Ia and IIa possessed the same degree of intrinsic sympathomimetic activity (ISA) as YB-2. When Ia and IIa were orally administered to rats and dogs and urine samples were examined for unchanged drug, it was found that these two compounds partially isomerized to each other in the body.

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