# A STUDY OF THE COMPOSITION OF VALIDOL OBTAINED FROM DIFFERENT TYPES OF RAW MATERIALS

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Validol, which exerts an influence on the central nervous system and possesses a reflex vasodilator action, is used in stenocardia, neuroses, and hysteria [1].

It is obtained by the esterification of menthol with isovaleric acid in the presence of small amounts of sulfuric acid. Until now it has been thought that Validol consists of a 20-30% solution of menthol in menthyl isovalerate [2].

By using gas-liquid chromatography (GLC), especially capillary chromatography, we have carefully examined the composition of Validol obtained both from natural and from synthetic menthol. When commercial samples of Validol obtained from *l*-menthol and industrial isovaleric acid (obtained by the oxidation of "fermentation isoamyl alcohol") were chromatographed, it was found that the Validol contained in addition to the two expected components (*l*-menthol and *l*-menthyl isovalerate), 2% of menthene hydrocarbons, consisting, in their turn, of two components, and also 23% of another component which, as we have shown, is 1-menthyl 2-methylbutyrate (see Fig. 1, a, e). The presence of 2-methylbutyric acid in the isovaleric acid was established by the GLC method.

Thus, it has been shown that the industrial isovaleric acid used for the synthesis of Validol consists of a mixture of ~ 80% of isovaleric acid and ~20% of 2-methylbutyric acid.

When *l*-menthol was esterified with synthetic isovaleric acid containing not more than ~2-3% of 2-methylbutyric acid, Validol was formed which, as was to be expected, contained a smaller amount of impurities and consisted of 54.7% of menthyl isovalerate, 1.9% of menthyl 2-methylbutyrate, 36.7% of menthol, and 6.7% of menthene hydrocarbons (Fig. 1b, f).

The synthetic menthol produced industrially and authorized for use in medicine consists of d,*l*-menthol and d,*l*-isomenthol, the amount of the latter in the commercial product being 25-30%. Consequently, the Validol obtained from synthetic menthol and industrial isovaleric acid has a more complex composition than the Validol from *l*-menthol and contains, according to capillary chromatography, menthene hydrocarbons (4.9%), isomenthol (3.6%), menthol (15.7%), and four esters – the menthyl and isomenthyl esters of 2-methylbutyric acid (12.9 and 4.5%, respectively) and the menthyl and isomenthyl esters of isovaleric acid (41.9 and 16.5%, respectively) (Fig. 1c, h).

The menthene hydrocarbons formed in the esterification of synthetic menthol consist of four components (Fig. 2a, b).

A component absent from the chromatogram of the hydrocarbon fraction of the Validol from natural *l*-menthol is apparently one of the isomenthenes (Fig. 2b).

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TABLE 1. Compositions of Various Samples of Validol

| Starting materials | | Products, wt. % | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | esters of 2-methyl butyric acid | | esters of isovaleric acid | |
| alcohol | acid | menthene hydrocarbons | menthol | isomenthol | isomenthyl | menthyl | isomenthyl | menthyl |
| Natural *l*-menthol | Industrial isovaleric | 2,0 | 22,0 | — | — | 23,0 | — | 53,0 |
| Natural *l*-menthol | Synthetic isovaleric | 6,7 | 36,7 | — | — | 1,9 | — | 54,7 |
| Synthetic d,*l*-menthol | Industrial isovaleric | 4,9 | 15,7 | 3,6 | 4,5 | 12,9 | 16,5 | 41,9 |
| Synthetic d,*l*-menthol | Synthetic isovaleric | 2,4 | 21,1 | 3,3 | 0,2 | 0,6 | 13,6 | 58,8 |

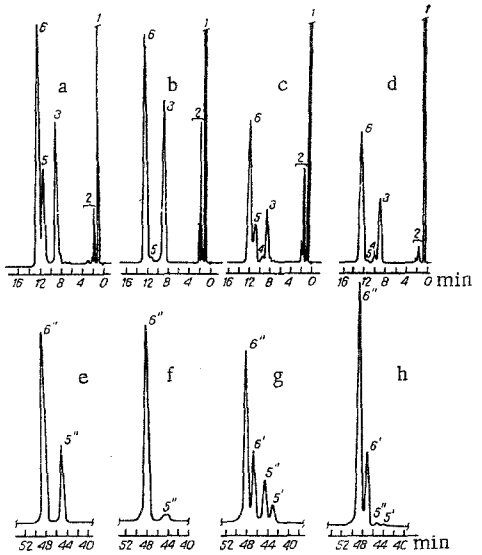


Fig. 1. Gas-chromatographic analysis of Validol on a packed column (a-d) and fragments of chromatograms of the stereoisomeric esters of Validol on a capillary column (e-h). 1) Hexane (solvent); 2) cyclohexene hydrocarbons; 3) menthol; 4) isomenthol; 5) isomenthyl 2-methylbutyrate: 5") menthyl 2-methylbutyrate; 5) combined peak of the esters 5' and 5"; 6') isomenthyl isovalerate; 6") menthyl isovalerate; 6) combined peak of the esters 6' and 6".

The Validol obtained from synthetic d,*l*-menthol and synthetic isovaleric acid [3] has a simpler composition and contains only small amounts of menthyl and isomenthyl 2-methylbutyrates (Fig. 1d, h).

The absence of other impurities from the Validol obtained from synthetic d,*l*-menthol was shown by the chromatography with the addition of neomenthol, neomenthyl isovalerate, isovaleric acid, and thymol.

The compositions of all the Validols studied are given in Table 1.

## EXPERIMENTAL

Preparation of Validol. A mixture of 177 g of natural *l*-menthol or synthetic d,*l*-menthol, 105 g of industrial valeric acid of "ch" ["pure"] grade or synthetic isovaleric acid, and 2.3 ml of concentrated sulfuric acid was stirred at 80-82°C for 12 h and was then kept at this temperature for another 12 h without stirring. After cooling, the reaction mixture was washed with water, twice with 2% caustic potash solution, and again with water until the washwaters were neutral and was then distilled in vacuum. The yield of Validol was 180 g; bp 60-136°C (10-14 mm), $d_4^{20}$ 0.894-0.907, $n_D^{20}$ 1.4485-1.4510.

Gas-Liquid Chromatographic Analysis. All the Validol samples and the menthene hydrocarbons were analyzed on a KhV-1 chromatograph of the Topchiev Institute of Petrochemical Synthesis of the Academy of Sciences of the USSR (the detector being a katharometer) under the following conditions: sorbent 15% of Lac-1-R-296 [poly(ethylene adipate)] on Celite 545 with a grain size of 60-80 mesh, column 3 m long and 6 mm in diameter, temperature 165°C, rate of flow of carrier gas (helium) 80 ml/min, amount of sample 1 μl. The quantitative calculation of the components present in the Validol was performed by the normalization method (reduction to 100%) without taking correction factors into account. The areas of the peaks were selected as the parameter for calculation. In this case, initially a mixture of menthyl and isomenthyl 2-methylbutyrates issued as one peak and then a mixture of menthyl and isomenthyl isovalerates as another (Fig. 1 c, peaks 5 and 6).

We obtained the following values of the relative retention volumes (with respect to hexane): menthene hydrocarbons (last peak) 1.2; neomenthol 3.79; isovaleric and 2-methylbutyric acids 3.86; menthol 4.35;

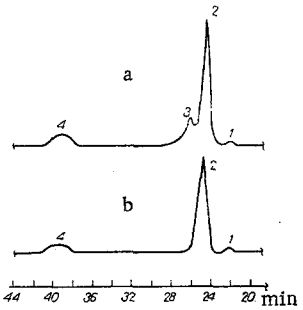


Fig. 2. Gas-chromatographic analysis of the cyclohexene hydrocarbon impurities in Validol from synthetic d,*l*-menthol (a) and from natural *l*-menthol (b). A mixture of isovaleric and 2-methylbutyric acid was used for esterification. The time is shown from the moment of issuance of the hexane.

isomenthol 4.86; menthyl and isomenthyl 2-methylbutyrates 5.53; menthyl and isomenthyl isovalerates 6.05; 2-isopropyl-3-methylphenol ("ordinary" thymol) 22.4; thymol 25.7).

The quantitative compositions of the samples of Validol were found by means of a "Khrom-2" chromatograph fitted with a copper capillary column (100 m long and 0.35 mm in internal diameter) coated with Tween 85, which was deposited by forcing through 10 ml of a 10% solution in ethyl acetate; the rate of flow of hydrogen was 28 ml/min and of the carrier gas (helium) 5 ml/min; temperature 140°C.

Under these conditions the following values of the relative retention volumes (referred to hexane) were obtained: menthene hydrocarbons (four) 1.27, 1.29, 1.32, and 1.41; 2-methylbutyric and isovaleric acids 3.91 and 4.07, respectively; isomenthyl 2-methylbutyrate 5.86; menthyl 2-methylbutyrate 6.05; isomenthyl isovalerate 6.30; menthyl isovalerate 6.49; menthol 6.98; isomenthol 8.33.

In order to achieve a better separation of the menthene hydrocarbons the analysis was performed at a temperature of 60°C (instead of 140°C) with all the other working parameters of the capillary column unchanged. In this way it was possible to improve the separation of the peaks of the menthene hydrocarbons considerably (see Fig. 2a, b).

## LITERATURE CITED

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