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STEREOSPECIFIC HYDROGENOLYSIS OF BENZYL-TYPE ALCOHOLS

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Abstract—In order to obtain additional information regarding the stereospecificity of hydrogenolysis on Co and Cu as well as Ni and Pd, optically active methyl 3-hydroxy-3-phentybutyrate, 3-hydroxy-3-phenylvaleric acid, methyl 3-hydroxy-3-phenylvalerate and 3-phenylpentan-1,3-diol were hydrogenolysed. In the hydrogenolysis on Ni, Co and Cu, the configuration was retained whereas on Pd the inversion of configuration occurred as reported for other compounds.

In the hydrogenolysis of the benzyl–oxygen bond, it has been observed that the stereospecificity depends on the reaction conditions.[1–5]

The differences between Ni and Pd catalysts were investigated in detail showing that each metal has distinct features about several kinds of selectivity, for instance, the stereoselectivity on the hydrogenation of double bond[6] and the selectivity on the competitive hydrogenation of more than one functional groups[7] as well as the stereospecificity of hydrogenolysis.[8] Moreover, it was shown that the behaviour of Co and Cu catalysts was similar to that of Ni.[7a, 9] For example, (+)-2-phenylbutan-2-ol (I) was hydrogenolysed predominantly to (+)-2-phenylbutane (II) with retention of configuration over Raney Ni (R–Ni), Raney Co (R–Co) and Raney Cu (R–Cu) catalysts. In contrast, (+)-I was hydrogenolysed to (−)-II with Pd–C, $Pd(OH)_2$–C, Pd wire, Raney Pd (R–Pd) and Pt–C.[9] (+)-2-Phenyl-2-methoxybutane (methyl ether of I) was hydrogenolysed to (+)-II with retention of configuration on R–Ni and R–Co, and inversely to (−)-II on Pd–C, R–Pd and PtO_2.[9] As in these examples the products are hydrocarbons, in this paper so as to ascertain the generality of above results and to investigate the effects on the stereospecificity of substituents other than phenyl group in the hydrogenolysis of benzyl-type alcohols, optically active methyl 3-hydroxy-3-phenylbutyrate (III), 3-hydroxy-3-phenylvaleric acid (IV), methyl 3-hydroxy-3-phenylvalerate (V) and 3-phenylpentane-1,3-diol (VI) were hydrogenolysed to methyl 3-phenylbutyrate (VII), 3-phenyl-n-valeric acid (VIII) occasionally containing its ethyl ester (IX) formed from VIII with ethanol used as solvent, methyl 3-phenyl-n-valerate (X) and 3-phenylpentan-1-ol (XI), respectively.[10]

Optically active III,[11] IV, V and VI[12] were asymmetrically synthesized according to the literature. The absolute configurations of these compounds are known (Fig. 1): (+)-III,[11] (+)-IV, (+)-V and (−)-VI have the S configuration.[12] (−)-VII has the R configuration.[1c] Levene *et al.*[13] reported that (−)-VIII, (−)-IX, (−)-XI and S-(+)-II[14] have the same configuration. In the present paper, (−)-X was reduced to (−)-XI with LAH. Therefore, (−)-VIII, (−)-IX, (−)-X and (−)-XI all have the R configuration.

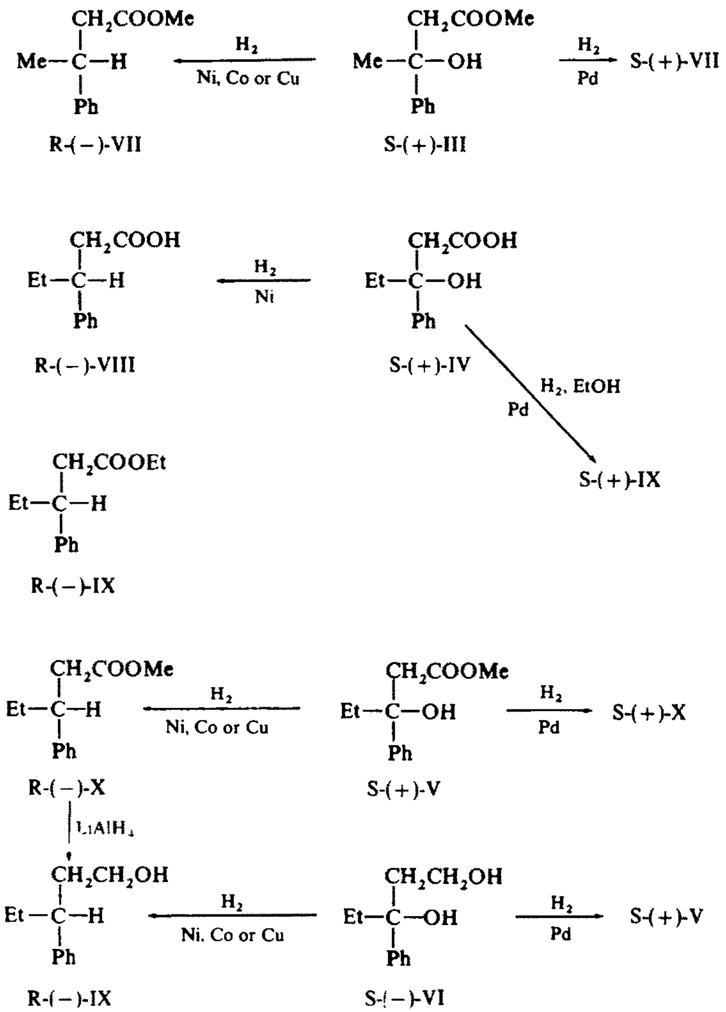

Fig. 1 Stereospecific hydrogenolysis of benzyl-type alcohols.

The hydrogenolysis on R–Ni and Pd catalysts were performed under ordinary pressure at room temperature. R–Co and R–Cu were used under about 60 atm and ± 160° in an autoclave. In all cases, ethanol was used as solvent. The results are given in Tables 1, 2 and 3. The expected products were produced except Exp. No. 6, in which it was observed that hydrogenolysis of S-(+)-IV was accompanied by esterification. If the esterification preceded the hydrogenolysis, Exp. No. 6 is essentially the same as No. 7 because both are hydrogenolysis of the ester. It was shown that the product formed from VI was not 3-phenylpentan-3-ol but 3-phenylpentan-1-ol (XI) (NMR spectrum). The spectrum has several peaks at 3·75 (δ-value, to be assigned to proton of 1-OH of XI), 3·29 (d, 1-CH_2), about 1·7 (m, 2- and 4-CH_2's), 2·50 (q, 3-CH) and 0·77 (t, 5-CH_3) and in the range of aromatic protons. Stereospecific hydrogenolysis

TABLE 1. HYDROGENOLYSIS ON R–Ni UNDER ORDINARY PRESSURE

Exp. No.	Substrate	Optical purity	Product	Optical purity	Stereo-specificity	Configuration
1	S-(+)-III	16·6	R-(−)-VII	16·4	94[1c] 98	retention
2*	S-(+)-IV	60·5	R-(−)-VIII	27·4	45	retention
3	S-(+)-V	69·4	R-(−)-X	69·4	100	retention
4	S-(−)-VI	85·0	R-(−)-XI	82·7	98	retention

* At 60–70°. In other cases at room temperature.

TABLE 2. HYDROGENOLYSIS ON Pd CATALYSTS UNDER ORDINARY PRESSURE

Exp. No.	Substrate	Optical purity	Cat.	Product	Optical purity	stereo-specificity	Configuration
5	S-(+)-III	83·5	Pd–C	S-(+)-VII	83·5	100[1c] 100	inversion
6	S-(+)-IV	89·2	Pd–C	S-(+)-IX	42·3	60	inversion
7	S-(+)-V	69·4	Pd–C	S-(+)-X	47·7	70	inversion
8*	S-(+)-V	75·9	Pd wire	S-(+)-X	43·2	57	inversion
9	S-(−)-VI	81·0	Pd–C	S-(+)-XI	74·3	88	inversion
10	S-(−)-VI	81·0	Pd wire	S-(+)-XI	53·5	66	inversion

* At 60–70°. In other cases at room temperature.

TABLE 3. HYDROGENOLYSIS ON Co AND Cu CATALYSTS

Exp. No.	Substrate	Optical purity	Cat.	Temp. (°C)	Press. (atm.)	Product	Optical purity	*	Configuration
11	S-(+)-III	82·7	R–Co	190	50	R-(−)-VII	82·6	99	retention
12	S-(+)-III	82·7	R–Cu	130–170	90	R-(−)-VII	66·7	81	retention
13	S-(+)-V	75·9	R–Co	155–165	55	R-(−)-X	58·1	76	retention
14	S-(+)-V	75·9	R–Cu	150–160	60	R-(−)-X	52·3	69	retention
15	S-(−)-VI	66·9	R–Co	155–160	50	R-(−)-XI	61·7	92	retention
16	S-(−)-VI	79·0	R–Cu	150–160	50	R-(−)-XI	79·0	100	retention

* Stereospecificity.

with retention of configuration should convert S-(+)-III, S-(+)-IV, S-(+)-V and S-(−)-VI to R-(−)-VII, R-(−)-VIII and/or R-(−)-IX, R-(−)-X and R-(−)-XI, respectively (Fig. 1). Tables 1 and 3 indicate that the direction of the stereospecific hydrogenolysis on R–Ni, R–Co and R–Cu are same and the configuration is retained. On the other hand, in Table 2, it is shown that in the hydrogenolysis on Pd catalysts the direction of the stereospecificity is converse to the above catalysts, therefore the inversion of configuration is observed as often reported in the case of other compounds.

Several mechanisms on the stereospecific hydrogenolysis of benzyl-type alcohols and their derivatives under moderate conditions have been reported. Khan *et al.*[15] mentioned the difference between Ni and Pd as follows: Both metals form metal alkyls and at the nickel–alkyl bond subsequent displacement is characterized by configurational retention, and since the hydrogen supply could be critical by rapid hydrogenolysis on Pd and since polarization of palladium-alkyl bond is alternative with nickel-alkyl bond, reaction with hydrogen proceeds as a type of nucleophilic substitution with inversion. Garbisch, Jr.[16] offered a mechanism containing two processes: One is that the substrate is first cleaved on the catalyst with retention of configuration, and then or after inversion on the catalysts, reacts with the adsorbed H atom; the other is the surface reaction which leads directly to a desorbed hydrogenolysed product with inversion and/or retention of configuration, but the detailed process and the reason for such direct substitution are not described.

Earlier, Mitsui[1-10] ascribed the stereospecificity to the adsorption state at the moment of cleavage which depends on the nature of catalyst metal. This adsorption state does not always mean the statically most stable state. Moreover, other fundamentals of his consideration are indicated as follows: (1) The reducing agents (an electron or electrons) nucleophilically attack the bottom of the substrate from the surface of catalyst like formation of carbon–metal bond under mild conditions. (2) If the displacing group is one of three adsorbed substituents, the reaction will proceed with retention of configuration (similar to S_Ni reaction in homogeneous substitution). If not, the reaction will proceed with inversion of configuration, corresponding to S_N2 reaction.

From this point of view, it is considered that the catalytic hydrogenolysis is competitive (Fig. 2) and that the stereospecificity reflects the difference of the apparent activation free energies of the two possible courses. In each case there would be adsorption of the substrate on the catalyst, a cleavage of C—O bond and a formation of carbon–metal bond (perhaps the rate-determining step of whole reaction), a hydrogenolysis of carbon–metal bond and a desorption of the product from the catalyst. This theory suggests that the retention of coconfiguration is observed in the hydrogenolysis on the catalyst having a large affinity for oxygen, and that the substrate would adsorb, at the moment of reaction, mainly with three substituents containing the OH group on R–Ni, R–Co and R–Cu, and mainly without the OH group on Pd catalysts. The stereospecificity, however, is not determined only by the affinity of the metal for oxygen, as mentioned at the beginning of this paper and explained in Fig. 2. Whether or not the configuration is retained may be determined by the difference of the free energy levels of the transition states (XII and XIII in Fig. 2) of hydrogenolysis, which depends on the affinity of substituents for the metal, the catalyst hindrance, the electronegativity of substituents and others. The low stereospecificity of Exp. No. 2 in Table 1 can be ascribed to the somewhat severe reaction condition required by the low activity of R–Ni often observed in the hydrogenolysis of acid. The lower stereospecificity of hydrogenolysis of V than III on Pd–C (Table 2) would be due to the larger catalyst hindrance at the transition state of the lower level (XIII, in this case) because the Et group of V would be larger than the Me group of III in comparison of steric bulkiness; namely, this catalyst hindrance would raise the energy level of XIII higher than the level of XII because XIII requires the adsorption of all substituents but the OH group, and would diminish the difference of the energy levels between XII and XIII. Similarly, the difference of the stereospecificity of the hydrogenolysis of V and VI (Tables 2 and 3) may be explained by the catalyst hindrance with an assumption that the —CH_2COOMe group is larger than the —CH_2CH_2OH group. Thus evidently there are some important

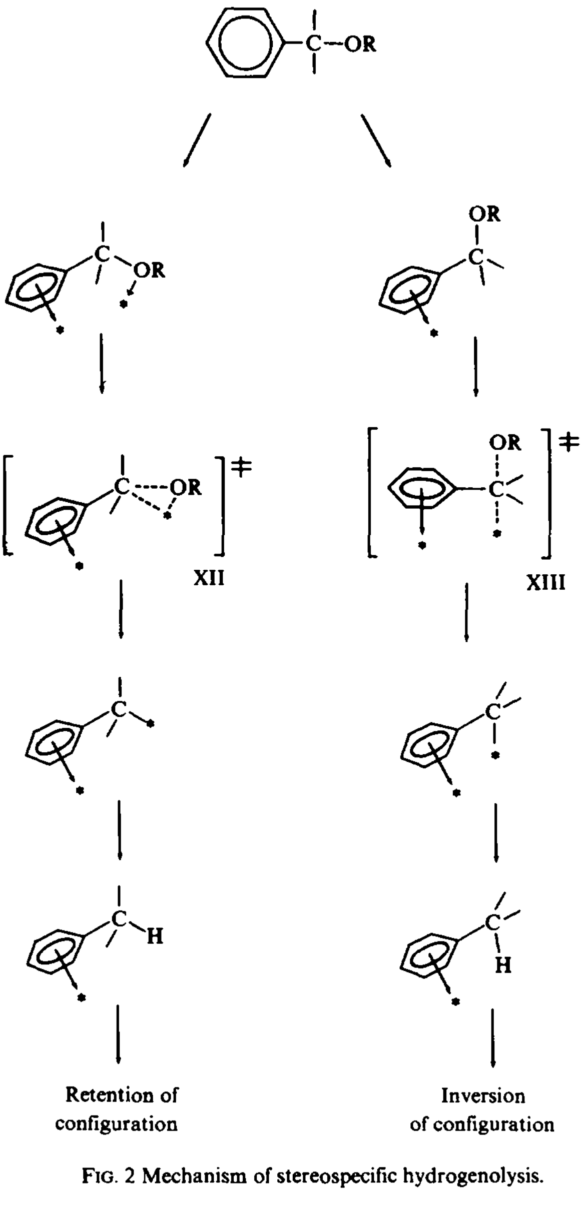

FIG. 2 Mechanism of stereospecific hydrogenolysis.

effects on the stereospecificity of the hydrogenolysis, e.g. the steric and electric effects of substituents as well as the affinity with catalyst metal. These facts were clearly observed in the hydrogenolysis of the derivatives of ethyl atrolactate.[17] Ethyl atrolactate itself was very stereospecifically hydrogenolysed with retention of configuration, while its acetate and propionate were predominantly inverted not only on Pd–C but also on R–Ni. These results would be due by the large steric bulkiness and electronegativity of the acyloxy groups; in other words, both factors would offer fewer disadvantages or more advantages to XIII than XII and would exceed the affinity with metal in effect, although the acyloxy groups could more strongly adsorb on R–Ni than the OH group. This consideration may explain not only various kinds of selective hydrogenation[1–10] but also a sharp contrast of reactivity in the hydrogenolysis of benzyl- and allyl-type alcohols on Ni and Pd.[18]

EXPERIMENTAL

S-(+)-3-*Methyl 3-hydroxy-3-phenylbutyrate* (III).[11] Acetophenone. 18 g (0·15 mol). was condensed with (−)-menthyl acetate, 40 g (0·2 mol), by means of diethylaminomagnesium bromide. The hydrolysis of the resulting (−)-menthyl ester was followed by esterification with diazomethane. Elimination of solvent and distilation afforded III, 42 g, $[\alpha]_D$ +9·50° (neat). Its IR spectrum and gaschromatography (PEG 4000) perfectly overlapped with the standard sample.

S-(+)-3-*Hydroxy-3-phenylvaleric acid* (IV), S-(+)-*methyl 3-hydroxy-3-phenylvalerate* (V) *and* S-(−)-3-*phenyl-pentane*-1,3-*diol* (VI). What were described in our previous paper[12] were used.

Hydrogenolysis on R–Ni. The substrate was shaken with R–Ni in EtOH under H_2 and ordinary press.

III, 2·0 g, $[\alpha]_D^{15}$ +1·50° (neat), with R–Ni, 10 g (wet), was shaken during 3 hr. Work-up afforded R-(−)-methyl 3-phenylbutyrate (VII), b.p. 117–118°/14 mm, $[\alpha]_D^{15}$ −8·50° (neat), −6·82° (EtOH).

IV, 1·7 g (0·088 mol), $[\alpha]_D^{20}$ +1·33° (3·0 EtOH), was neutralized with NaOH—H_2O—EtOH and the resulting sodium salt of IV was shaken with R–Ni, 12·5 g (wet), during 55 hr at room temp and during additional 45 hr at 60–70°. After evaporation of solvent, the product was acidified with HCl and extracted with ether. The distillation afforded R-(−)-VIII, b.p. 119–120°/0·3 mm, 0·5 g, $[\alpha]_D^{20}$ −14·5° (18·0 benzene). Found: C, 73·84; H, 8·21. Calc. for $C_{11}H_{14}O_2$; C, 74·13, H, 7·92%.

V, b.p. 88°/0·1 mm, $[\alpha]_D^{20}$ +2·44° (27·0 EtOH), 2 g, was shaken with R–Ni, 6 g, during 108 hr. The product was (−)-X, b.p. 79–80°/0·1 mm, α_D^{18} −20·72° (neat), $[\alpha]_D^{18}$ −20·82° (EtOH), 1·5 g. Its IR spectrum agreed with that which was obtained by hydrogenolysis of V on Pd–C.

VI, m.p. 64–64·5°, $[\alpha]_D^{15}$ −45·5° (10·0 benzene), 2 g, with R–Ni, 3 g, was shaken during 263 hr. The product was R-(−)-XI, b.p. 90–91°/0·2 mm, α_D^{13} −14·13° (neat). Its IR spectrum superimposed with XI from VI with Pd–C. δ-values of its NMR spectrum were 3·75 (s, OH), 3·29 (d, 1-CH_2), about 1·7 (m, 2- and 4-CH_2's), 2·50 (q, 3-CH), 0·77 (t, 5-Me) and multiplet in the range of aromatic ring.

Hydrogenolysis on 5% Pd–C. The substrate was dissolved in EtOH, 5% Pd–C was added and the mixture was absorbed hydrogen at room temp under ordinary press.

III, $[\alpha]_D^{9}$ +9·60° (neat), 1·1 g with Pd–C, 2·5 g, was shaken during 100 hr. The product was S-(+)-VII, b.p. 71°/0·4 mm, $[\alpha]_D^{8}$ +34·8° (EtOH).

IV. $[\alpha]_D^{22}$ +19·6° (3·0 EtOH), 2 g, with Pd–C. 1 g, absorbed H_2. Work-up afforded mixture. The main product was S-(+)-IX, b.p. 96–98°/1 mm, α_D^{14} +10·86° (neat), $[\alpha]_D^{14}$ +11·6° (10·0 benzene), 1·2 g. Its IR spectrum has a peak at 1740 cm^{-1} (ester) and is transparent in the range of 4000–3200 cm^{-1}. In addition only one peak was detected in gas chromatography (PEG 4000). Found; C, 75·33; H, 8·82. Calc. for $C_{11}H_{14}O_2$ (VIII); C, 74·13; H, 7·92. Calc. for $C_{13}H_{18}O_2$ (IX, ethyl ester of VIII); C, 75·25; H, 8·69%. The minor product was liquid, b.p. 104–120°/1·5 mm, 0·1 g, contained needle crystals. The liquid had two peaks in gas chromatography; one of them agreed with that of the main product, and the other with that of VIII from IV with R–Ni. Its IR spectrum has peaks at 1740 cm^{-1} (ester) and 1720 cm^{-1} (acid).

V. $[\alpha]_D^{20}$ +2·44° (27·0 EtOH). 1 g. was hydrogenolysed on Pd–C. 1 g. with three drops of conc HCl during 108 hr. The product was S-(+)-X, b.p. 82–83°/0·15 mm, α_D^{18} +14·24° (neat), $[\alpha]_D^{18}$ +14·35° (3·97 EtOH). (Found: C, 74·54; H, 8·59. Calc. for $C_{12}H_{16}O_3$; C, 74·97; H, 8·39%.

VI, $[\alpha]_D^{15}$ −49·5° (10·0 benzene), 1·5 g with Pd–C, 0·5 g, absorbed H_2 during 188 hr to give S-(+)-XI, b.p. 88·5°/0·3 mm, α_D^{10} +13·05° (neat), $[\alpha]_D^{27}$ +12·2° (6·15 benzene). Found: C, 80·09; H, 9·68. Calc. for $C_{11}H_{16}O$; C, 80·44; H, 9·83%.

Hydrogenolysis on Pd-*wire*. V. α_D^{22} +14·92° (neat), $[\alpha]_D^{22}$ +2·68° (26·9 EtOH). 1·5 g. with Pd wire. 2·6 g, was shaken at 60–70° under ordinary press during 88 hr to give S-(+)-X, b.p. 97–98°/0·3 mm, $[\alpha]_D^{27}$ +13·0 (4·00 EtOH), 0·4 g.

VI, m.p. 63–64°, $[\alpha]_D^{27}$ −47·6° (10·0 benzene), 1·2 g, with Pd wire was shaken at room temp under ordinary press during 11 hr to give S-(+)-XI. b.p. 98–99°/0·3 mm. $[\alpha]_D^{27}$ +8·78° (6·15 benzene).

Hydrogenolysis on R-Co *and* R-Cu.* All hydrogenolyses were accomplished in EtOH in an autoclave.

III. $[\alpha]_D^{15}$ +9·50° (neat), 1·0 g, was hydrogenolyzed on R-Co, 2 g, under 50 atm at 190° during 14 hr to give R-(−)-VII, $[\alpha]_D^{13}$ −34·4° (EtOH). Hydrogenolysis of III, 1·0 g, on R-Cu (2 g), at 130–170° under 90 atm during 18 hr and addition of 1 g catalyst, at 160–180° under 90 atm during 10 hr yielded R-(−)-VII, $[\alpha]_D^{18}$ −27·8° (EtOH).

V, α_D^{22} +14·92° (neat), $[\alpha]_D^{22}$ +2·68 (26·9 EtOH), 1·5 g, was hydrogenolysed on R–Co, 1·2 g, at 155–165 under 55 atm during 48 hr to give R-(−)-X, b.p. 81°/0·2 mm, $[\alpha]_D^{25}$ −17·5° (4·00 EtOH). V, 1·0 g, was hydrogenolysed on R–Cu, 1·2 g, at 150–160° under 60 atm during 48 hr to give R-(−)-X, b.p. 82–83°/0·2 mm, $[\alpha]_D^{22}$ −16·8° (4·00 EtOH), 0·5 g.

VI, $[\alpha]_D^{20}$ −38·7° (10·0 benzene), 1·1 g, was hydrogenolysed on R–Co, 1·2 g, at 155–160° under 50 atm during 64 hr to give R-(−)-X, b.p. 97°/0·5 mm, $[\alpha]_D^{20}$ −10·01° (6·12 benzene). VI, m.p. 62–63°, $[\alpha]_D^{23}$ −46·0° (10·0 benzene), 1·2 g, was hydrogenolysed on R–Cu, 1 g, at 150–160° under 50 atm during 84 hr to give R-(−)-X, b.p. 100–101°/0·15 mm, $[\alpha]_D^{22}$ −13·1° (6·17 benzene), 0·6 g.

Reduction of (−)-*methyl* 3-*phenyl-n-valerate* (X). (−)-X, α_D^{18} −20·72° (neat), $[\alpha]_D^{18}$ −20·82° (3·98 EtOH), was reduced with LAH to yield R-(−)-XI, b.p. 138°/21 mm, $[\alpha]_D^{17}$ −14·5° (6·13 benzene).

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* The pressures described are the initial ones.