

Studies Related to Pristane

VI. Synthesis of Digeranyl with some Remarks on the Physical Constants of Crocetane

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The aliphatic diterpene "Digeranyl" or 2,6,11,15-tetramethylhexadeca-tetra-2,6,10,14-ene, and its perhydro compound "Crocetane" were — as already mentioned in the first paper of this series ¹ — synthesised for the purpose of comparison of the latter with pristane. Digeranyl was synthesised by treating geranyl bromide with magnesium in the same manner as in the classical synthesis of squalene of Karrer and Helfenstein ². Although the synthesised diterpene and its perhydro compound had the correct composition, the physical constants of the latter cast doubt upon the homogeneity of these products. Crocetane had been synthesised twice before. Fischer and Löwenberg ³ used the Würtz synthesis from tetrahydrogeranyl bromide ³. Karrer and Golde ⁴ started from the carotenoid pigment crocetine. They converted its tetradecahydro compound into the ω,ω' -glycol by Bouveault-Blanc reduction. The ω,ω' -glycol, in turn was reduced, via its dibromide, to crocetane, with Zn-Cu in acetic acid at 150°. As will be seen from Table 1, these two syntheses of crocetane gave preparations that differed markedly in their physical constants. [All values recalculated to 20° according to Egloff: *Physical constants of hydrocarbons*. N. Y. 1939.]

Table 1. Physical constants of crocetane.

Author	d_4^{20}	n_D^{20}
From crude "Digeranyl"	0.8036	1.4480
Karrer and Golde	0.8025	1.4492
Fischer and Löwenberg	0.7887	1.4402
From citral ¹	0.7858	1.4405
From purified "Digeranyl"	0.7888	1.4410

Hydrogenation of our crude digeranyl gave a saturated hydrocarbon, $C_{20}H_{42}$, whose constants agree closely with those given by Karrer and Golde. (*cf.* first and second row of Table 1.)

In order to get some insight into the cause of these anomalies the same hydrocarbon was synthesised from citral in a manner similar to that used by Fischer and Löwenberg. Details of our method are given in the first communication of this series¹. As may be seen from the fourth row of Table 1 the physical constants of our product were very close to the ones given by Fischer and Löwenberg.

Using the conditions given by Karrer and Helfenstein² the digeranyl synthesis gave a forerun of over 35 % of aliphatic monoterpenes and a residue of about 10 % of higher terpenes which distilled at about 190° at 0.05 mm Hg; that is very close to the boiling point of the aliphatic triterpene, squalene. Establishment of these side reactions led to the possibility that they might have some influence on the diterpene fraction.

Since natural or synthetic squalene may be readily purified by the facile crystallisation of the hexahydrochloride, we attempted to isolate crystalline tetra derivatives from the diterpene of analogous structure: digeranyl. Dry hydrochloric acid in ether solution gave no crystalline addition compounds, at first, but on seeding the reaction mixture with squalene hexahydrochloride, ready crystallisation of a tetrahydro-chloride, m. p. 110°, occurred. The tetrahydrochloride which crystallises in thin leaflets, is apparently isomorphic with squalene hexahydrochloride. The yield in 4 preparations amounted to only 13 % of theory.

Treatment of this tetrahydrochloride with pyridine followed by warming to 150° with quinoline regenerated a digeranyl which was purified by chromatography on alumina and distillation at 95° C (air bath temperature) 10 mm Hg. The dispersion of this purified digeranyl is given in the experimental section. The digeranyl regenerated from the crystalline tetrahydrochloride has a lower density and refractive index than the crude starting material:

	d_4^{20}	n_D^{20}	R_D^{20}
crude "digeranyl"	0.8547	1.4884	92.59
digeranyl from hydrochloride	0.8347	1.48124	93.56

and a small exaltation in molecular refraction: R_D calc. 92.69.

Hydrogenation of this regenerated digeranyl gave a saturated hydrocarbon whose physical constants are given in the last row of Table 1. These constants are identical within the limits of experimental error, with the earlier determinations of Fischer and Löwenberg³ and of our analogous preparation from citral.

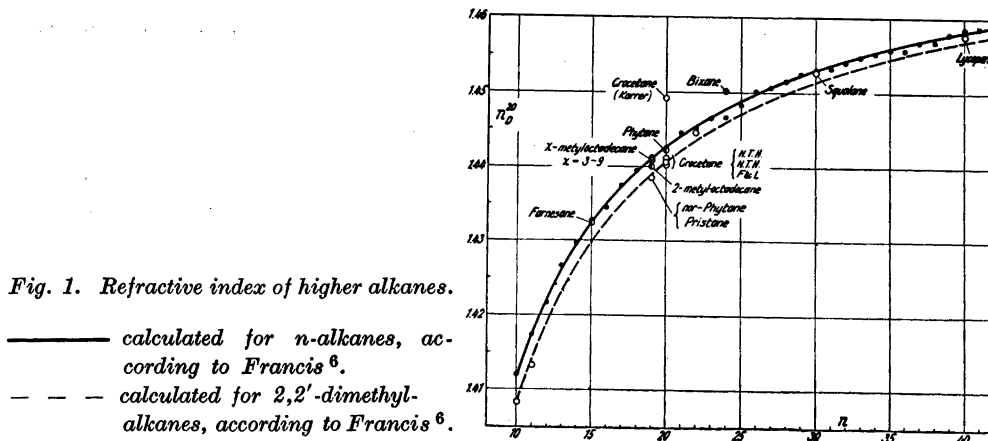


Fig. 1. Refractive index of higher alkanes.

— calculated for *n*-alkanes, according to Francis⁶.
 - - - calculated for 2,2'-dimethylalkanes, according to Francis⁶.

The identity of crocetane from purified "digeranyl" with that prepared according to Fischer and Löwenberg was put beyond any question of doubt by the infra-red measurements of Pliva and Sørensen given in the fourth communication of this series⁵.

Further proof for the correctness of the data given in the last three rows of Table 1 for crocetane may be deduced from Fig. 1 which gives the refractive indices of the higher alkanes.

The curves are drawn according to the equations of Francis⁶ for normal alkanes and for 2,2'-dimethylalkanes. The observed values are in good agreement with the calculated ones, the sole exception being Karrer's value for crocetane.

The empirical rules given by Francis for the refractive index of higher alkanes are simple. For normal alkanes Francis gives the general formula:

$$n_D^{20} = 1.4736 - \frac{0.62}{n}, \quad n > 10$$

Higher 2-methyl alkanes show depressions in density and refractive index of such an order that these constants coincide with those for the normal *n*-1 alkanes. 2,2'-dimethylalkanes exhibit still greater depressions and obey, according to Francis, the empirical relationship:

$$n_D^{20} = 1.4731 - \frac{0.65}{n}$$

Methyl groups removed by three carbon atoms or more from the end of the alkane chain cause small exaltations in n_D^{20} — of the order of + 0.0004 per methyl group. The excellence of these simple empirical rules for higher methyl substituted alkanes may be seen

from Table 2 which correlates some of the data determined in connection with the pristane problem with some data used by Francis.

Table 2. Refractive index of methyl-substituted higher alkanes.

Compound	Calculation	Refractive index = n_D^{20}	
		Calc.	Found
C ₁₈ 2-Methylheptadecane (= n -C ₁₇)		1.4371	1.4384
C ₁₉ 2-Methyloctadecane (= n -C ₁₈)		1.4392	1.4399
C ₁₉ 3 to 9-Methyloctadecane (= n -C ₁₉ + 1 side-Me)		1.4414	{ 1.4406 1.4413
C ₁₉ <i>Nor</i> -phytane (= 2,2'-dimethyl + 2 side-Me)		1.4397	1.4386
C ₂₀ Phytane (= n -C ₁₉ + 3 side-Me)		1.4422	1.4422
C ₂₀ Crocetane (2,2'-dimethyl + 2 side-Me)		1.4414	{ 1.4406 1.4411
C ₂₄ Bixane (= n -C ₂₄ + 4 side-Me)		1.4493	1.4502
C ₃₀ Squalane (= 2,2'-dimethyl + 4 side-Me)		1.4530	1.4528
C ₄₀ Lycopane (2,2'-dimethyl + 6 side-Me)		1.4592	1.4589

It is obvious that uncontrolled side reactions are also the cause of the deviations recorded for Karrer's crocetane, since there can be no doubt concerning the constitution of crocetin — the starting material in Karrer's and Golde's synthesis. Owing to the high cost of crocetin, Karrer and Golde were forced to repeat the Bouveault-Blanc reduction three times, side reactions at this stage are, however, improbable. We must, therefore, presume that the side reactions took place in the Zn-Cu reduction at the comparatively high temperature of 150° C. The four chlorine atoms were readily given off by the tetrahydrochloride of "digeranyl" on treatment under Rosemund-conditions. The resulting hydrocarbon was saturated but the refractive index of $n_D^{20} = 1.4695$ shows at once that these conditions must have caused cyclisation.

After our experimental work had been completed and partially published, there appeared three syntheses of digeranyl from geranyl chloride by Barnard and Bateman⁷ in connection with their studies on the reactions of allylic Grignard compounds. These authors obtained digeranyl I and isodigeranyl II as by-products in the reaction between the Grignard compound from geranyl chloride and carbon dioxide or ethyl chloroformate. They were also obtained in the reaction of the Grignard compound with silver bromide or with 1 mole geranyl chloride.

diterpene fraction are highly dependant upon the ratio of geranyl bromide to magnesium used under the conditions of Karrer and Helfenstein's squalene synthesis (see Table 3).

Table 3. Physical constants of whole diterpene fraction in relation to amount of magnesium present.

Geranyl bromide: Mg	n_D^{20}	d_D^{20}	R_D
2 : 1	1.4973	—	—
»	1.4967	—	—
»	1.4970	0.8824	90.96
1 : 1	1.4838	0.846	92.73
»	1.4884	0.8547	92.53
»	1.4889	0.8570	92.43
1 : 2	1.4846	0.8476	92.68

The yield of digeranyl-tetrahydrochloride, however, remained constant in all cases, at about 13 % of the diterpene fraction. These observations are in agreement with earlier statements^{9, 10} regarding the effect of small variations in reaction conditions upon the course of Grignard reactions.

It is highly probable that our diterpene fraction contains isomers other than I—III for the following reason. Digeranyl I from the tetrahydrochloride is perhydrogenated at a speed comparable to that of squalene. The crude diterpene fraction is hydrogenated at the same rate at the beginning but after about 2/3 of the theoretical amount of hydrogen has been taken up, the rate falls off and practically stops after 3/4 have been hydrogenated. The fact that this phenomenon, which is quite reproducible, is not due to the presence of poisoning impurities was clearly shown by the addition of squalene some hours later. The hydrogen consumption started again at the rate which is normal for this triterpene. Since I—III are devoid of hindered double bonds, one may presume the presence of other (cyclised) isomers.

EXPERIMENTAL

Geranyl bromide. Prepared from linalool by treatment with PBr_3 in pyridine solution in a manner analogous to that given by Karrer and Helfenstein² for the preparation of farnesyl bromide. B. p. 75–78°/1.6–1.8 mm $n_D^{20} = 1.5021$.

Crude digeranyl. Geranyl bromide was treated with varying relative quantities of magnesium (turnings) in anhydrous ether in a manner analogous to the squalene synthesis of Karrer and Helfenstein (*ibid.*), and the reaction product fractionated. A halogen free liquid fraction, which amounted to about 1/3 of the material and distilled at 65°/12 mm

was collected. $n_D^{20} = 1.4629$ (myrcene 1.4716, dihydromyrcene, n_D^{20} 1.4514). The diterpene fraction, which amounted to about 55 % of theory, distilled at 118–121°/0.5 mm (147–149°/2.6–3 mm). The rest gave a fraction amounting to 8–10 % which boiled at 190°/0.05 mm; squalene boiling at 195° at the same pressure. The physical constants of the diterpene fraction, as a function of the quantity of magnesium used, are given in Table 2.

$C_{20}H_{34}$ (274.5)	Calc.	C 87.50	H 12.50
	Found	» 87.2, 87.6	» 12.10, 12.84

Digeranyl tetrahydrochloride. A solution of 38 g crude digeranyl in anhydrous ether was saturated with dry hydrogen chloride at -10°C . The solution turned dark but no crystallisation ensued. On seeding the solution with a few crystals of squalene hexahydrochloride immediate crystallisation occurred. m. p. was 110° after two recrystallisations from ether. The yields from four different preparations of digeranyl were 17, 12.4, 11.4 and 13.1 % of theory.

$C_{20}H_{38}Cl_4$ (420.3)	Calc.	C 57.14	H 9.11
	Found	» 57.07	» 9.22

Digeranyl from the tetrahydrochloride. 4.8 g of digeranyl tetrahydrochloride was refluxed in pyridine in an atmosphere of CO_2 for 14 hours in a manner analogous to the procedure given by Heilbron, Kamm and Owens¹¹ for the regeneration of squalene from its hexahydrochloride. Since this treatment proved to be insufficient the material was heated for further 4 hours at 150° in quinoline. The hydrocarbon was isolated in the usual way and distilled at 95–100°/10⁻⁴ mm (air bath temperature).

$C_{20}H_{34}$ (274.5)	Calc.	C 87.50	H 12.50
	Found	» 87.1	» 12.6

Table 4. Dispersion of digeranyl from tetrahydrochloride.

$$d_4^{20} = 0.8347 \quad R_\lambda \text{ calc.} = \frac{90.725 \cdot \lambda^2}{\lambda^2 - 1.0554 \cdot 10^6} \quad \lambda_0 = 1027 \text{ \AA}$$

λ	n_λ^{20}	$R_\lambda, \text{ obs.}$	$R_\lambda, \text{ calc.}$
6678.1	1.47732	92.91	92.92
5895.9	1.48124	93.56	93.57
5875.7	1.48132	93.57	93.58
5015.6	1.48814	94.70	94.70
4921.9	1.48914	94.87	94.86
4713.1	1.49154	95.26	95.25
4471.5	1.49476	95.79	95.78

Crocetane. 0.87 g digeranyl regenerated from the tetrahydrochloride was hydrogenated with 17 % PtO_2 on silica without solvent at 90°C , filtered and distilled at 95°/0.001 mm. The dispersion of this distillate — cf. Table 5 — gave the correct value for

the dispersional constant λ_0 for saturated hydrocarbons. In agreement with this result further purification with 100 % sulphuric acid followed by distillation over metallic sodium had no effect on the dispersional data.

Table 5. Dispersion of crocetane from digeranyl tetrahydrochloride.

$$d_4^{20} = 0.7888, R_{\lambda, \text{calc.}} = \frac{92.383 \cdot \lambda^2}{\lambda^2 - 0.7866 \cdot 10^6} \lambda_0 = 886.9 \text{ \AA}$$

λ	n_{λ}^{20}	R_{λ} obs.	R_{λ} calc.
6678.1	1.43834	94.02	94.04
5895.9	1.44100	94.52	94.52
5875.7	1.44108	94.53	94.53
5015.6	1.44561	95.38	95.37
4921.9	1.44624	95.49	95.48
4713.1	1.44782	95.79	95.77
4471.5	1.44982	96.16	96.16

Perhydro squalene. Squalene is hydrogenated slowly. The most suitable conditions are those used by Heilbron, Hilditch and Kamm¹² and by Chapman¹³, that is, in the absence of solvent and at a high temperature (150 to 200° C). Using platinum catalysts, at ordinary temperature the hydrogen uptake in most solvents is very slow and incomplete. In acetic acid or mixtures of solvents in which acetic acid is the major component, hydrogenation is rapid and complete. To test the reproducibility of the dispersional data for higher alkanes, 3 preparative hydrogenations in acetic acid with PtO₂/SiO₂ catalysts and one without solvent using Ni at 100° and 150 atm., were carried out.

All hydrogenation products were purified with 100 % H₂SO₄, washed carefully with sodium hydroxide solution and with water and distilled over liquid sodium. As may be seen from Table 6 the reproducibility of the dispersional constants is good. Refractive index figures vary by some 3 units in the fourth decimal place; our values being intermediate between those of Tsujimoto¹⁴, $n_D^{20} = 1.4525$, and those of Chapman¹³, $n_D^{20} = 1.4532$.

Table 6. Dispersion of Squalane. I—III Pt, IV Ni-Catalyst.

$$R_D, \text{theory} = 140.74, R_{\lambda=\infty}, \text{theory} = 137.51, \lambda_0 \text{theory} = 885.2 \text{ \AA}$$

$$I \ d_4^{20} = 0.81078 \ \lambda_0 = 889.6 \ R_{\lambda=\infty} = 137.58 \quad II \ d_4^{20} = 0.81026 \ \lambda_0 = 887.2 \ R_{\lambda=\infty} = 137.67$$

λ	n_{λ}^{20}	R_{λ} , obs.	R_{λ} , calc.	n_{λ}^{20}	R_{λ} , obs.	R_{λ} , calc.
6678.1	1.45009	140.06	140.07	1.45001	140.13	140.14
5892.9	1.45277	140.78	140.79	1.45267	140.84	140.86
5875.7	1.45289	140.81	140.81	1.45277	140.87	140.88
5015.6	1.45755	142.06	142.05	1.45745	142.13	142.11
4921.9	1.45823	142.24	142.23	1.45812	142.31	142.29
4713.1	1.45986	142.68	142.67	1.45976	142.75	142.72
4471.5	1.46187	143.22	143.25	1.46179	143.29	143.31

III $d_4^{20} = 0.81061$, $\lambda_0 = 886.8$, $R_{\lambda=\infty} = 137.58$ IV $d_4^{20} = 0.81072$, $\lambda_0 = 885.9$, $R_{\lambda=\infty} = 137.63$

λ	n_{λ}^{20}	R_{λ} , obs.	R_{λ} , calc.	n_{λ}^{20}	R_{λ} , obs.	R_{λ} , calc.
6678.1	1.44989	140.04	140.05	1.45017	140.09	140.10
5892.9	1.45257	140.76	140.77	1.45287	140.82	140.81
5875.7	1.45265	140.78	140.79	1.45297	140.84	140.83
5460.7	—	—	—	1.45483	141.34	141.35
5015.6	1.45732	142.03	142.02	1.45764	142.10	142.07
4921.9	1.45801	142.22	142.19	—	—	—
4713.1	1.45959	142.64	142.63	—	—	—
4471.5	1.46167	143.20	143.21	1.46195	143.25	143.26
4358.3	—	—	—	1.46302	143.54	143.56

SUMMARY

One of the components of the diterpene mixture that ensues when geranyl bromide is coupled with magnesium has been isolated as its crystalline tetrahydrochloride. The hydrocarbon which is regenerated from this tetrahydrochloride is digeranyl (I), since on hydrogenation a hydrocarbon $C_{20}H_{42}$, which is identical with crocetane — 2,6,11,15-tetramethylhexadecane, is formed. The physical constants of this hydrocarbon are in accordance with those recorded by Fischer and Löwenberg in 1929. It is demonstrated that these are the correct values for crocetane — the data in the literature for this hydrocarbon being somewhat conflicting.

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