[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

THE NUMBER OF STEREOISOMERIC AND NON-STEREOISOMERIC MONO-SUBSTITUTION PRODUCTS OF THE PARAFFINS

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Having successfully derived formulas of the (finite) recursion type permitting the calculation of the number of structurally isomeric alcohols of the methanol series,[1] as typical structurally isomeric mono-substitution products of the saturated aliphatic hydrocarbons, our attention was directed to an attempt to derive the number of stereoisomeric mono-substitution products. Very naturally, our initial efforts were to derive a relationship between the number of stereoisomers and the total number of asymmetric carbon atoms present among the structural isomers, or to determine the number of structural isomers containing one, two, three, etc., asymmetric carbon atoms per molecule. Solution of the problem by these methods seemed possible for it is now generally accepted that the presence of an asymmetric carbon atom in the molecule of an organic compound causes that substance to exist in two stereoisomeric modifications and if more than one asymmetric carbon atom is present the number of modifications possible may be computed by the expression 2^n, where n represents the number of asymmetric carbon atoms which are structurally distinct. If the asymmetric carbon atoms simultaneously present in a compound are not structurally distinct, the number of stereoisomers is actually less than that so calculated and hence the above expression requires modification. However, in addition to the problem of determining the numbers of structurally distinct asymmetric carbon atoms, pseudo-asymmetry presents a factor which requires consideration. It was soon found that any method, based upon the above schemes, which might permit the calculation of the number of stereoisomers for low carbon contents would be impossible of application at higher carbon contents. The problem was solved only by taking into account the fact that pseudo-asymmetry is related to structure and upon recognition of a method of forming the structural formulas, of the mono-substitution products, very similar to that previously utilized in calculating the number of structural isomers. This method involves the classification of the mono-substitution products into simple types, for each of which the number of stereoisomers may be computed. The types so chosen are those commonly recognized in derivatives of the paraffins, namely, primary, secondary and tertiary.

Primary.—The structural formulas of the primary mono-substitution products of the paraffins, $R-CH_2X$, of N total carbon atom content, may be

[1] Henze and Blair, THIS JOURNAL, **53**, 3042–3046 (1931).

formed from those of $N - 1$ carbon atoms, R–X, by removing the substituted group, X, from each and attaching the resulting alkyl radical, R–, to the $-CH_2X$ group. The number of stereoisomeric primary mono-substitution products that may be formed in this way will thus equal the total number of stereoisomeric mono-substitution products of all types containing $N - 1$ carbon atoms. This fact is readily seen for no additional asymmetric carbon atom has been created, through the addition of the $-CH_2X$ group, nor destroyed, since the substituted group X, which differs from any other group in the molecule, is replaced by $-CH_2X$ which also is different from any other group. For these same reasons the number of non-stereoisomeric primary mono-substitution products will equal the total number of non-stereoisomeric mono-substitution products of all types containing $N - 1$ carbon atoms. Therefore, the number of stereoisomeric and non-stereoisomeric primary mono-substitution products may be calculated by the following formulas[2]

$$Ps_N = As_{N-1} \qquad (I_s)$$
$$Pn_N = An_{N-1} \qquad (I_n)$$

where Ps_N is the number of stereoisomeric primary mono-substitution products of N carbon atoms, As_{N-1} is the total number of stereoisomeric mono-substitution products of all types containing $N - 1$ carbon atoms, Pn_N is the number of non-stereoisomeric primary mono-substitution products of N carbon atoms, and An_{N-1} is the total number of non-stereoisomeric mono-substitution products of all types containing $N - 1$ carbon atoms.

Secondary.—The structural formulas of the secondary mono-substitution products of the paraffins, RR′>CHX, of N total carbon atom content, may be formed from those of R–X and R′–X (the carbon content of R– plus R′– always equaling $N - 1$) by removing the X group from each and attaching the resulting alkyl radicals, R– and R′–, to the >CHX group. The total number of isomers that may be formed in this way will be conditioned by the number of possible cases of combining with the >CHX group complementary values of R– and R′–.[3] These possible cases are theoretically of two types: (a), in which the two alkyl radicals, R– and R′–, are of unequal carbon content; and (b), in which these are of equal carbon content. Type (b) is actually impossible with a mono-substitution product of an even number of carbon atoms since in this type $N - 1$ must be divisible by two.

[2] It is to be noted that in using the formulas advanced in this treatment, for the calculation of the number of stereoisomeric and non-stereoisomeric mono-substitution products of any given carbon content, the number of stereoisomers and non-stereoisomers of each lesser carbon content must be known.

[3] The values of R– complementary to R′– satisfy the relationship that the total carbon content of R– plus R′– equal $N - 1$.

Type (a).—For each of the individual cases of this type the number of possibilities of combining the stereoisomeric and non-stereoisomeric values of both R– and R′– with the >CHX group may be expressed as follows: $As_i{\cdot}As_j + As_i{\cdot}An_j + An_i{\cdot}As_j + An_i{\cdot}An_j$ which when simplified yields $T_i{\cdot}T_j$ where i and j are the carbon contents of R– and R′–, respectively, $T_i = As_i + An_i$, and $T_j = As_j + An_j$. Since in these combinations each value of R– is different from each complementary value of R′–, the carbon atom of the >CHX group will become asymmetric and the number of stereoisomers of each case, for it is thus impossible to form a secondary mono-substitution product of this type which is non-stereoisomeric, will equal $2T_i{\cdot}T_j$. Hence, the total number of stereoisomeric mono-substitution products of this type will equal

$$2\,\Sigma\,T_i{\cdot}T_j \qquad \text{(IIa}_s\text{)}$$

where i and j are integers, distinct, and greater than zero, $i + j = N - 1$, and $i > j$.

The number of $T_i{\cdot}T_j$ terms included in this summation depends on whether N is even or odd.

Even: if N is even the number of terms of type (a) is $(N - 2)/2$

Odd: if N is odd the number of terms of type (a) is $(N - 3)/2$

Type (b).—The isomers of this type, in which the carbon contents of R– and R′– are the same, may be further classified into two groups: (1), in which R– and R′– are absolutely identical from the standpoint of both structural- and stereo-isomerism; and (2), in which R– and R′– are not identical.

Group (1).—The combinations of this group may be divided into those in which the identical values[4] are stereoisomeric and those in which the identical values are non-stereoisomeric. When identical stereoisomeric values are combined with the >CHX group, no asymmetric carbon atoms are created and hence the number of stereoisomers thus formed will equal the number of such possible combinations, or As_i. When identical non-stereoisomeric values are combined with the >CHX group, no asymmetric carbon atoms are created and since the alkyl radicals themselves contain no asymmetric carbon atoms no stereoisomers will result from such combinations.

Group (2).—The number of possibilities of combining non-identical complementary values, both stereoisomeric and non-stereoisomeric, of R– and R′– may be represented by the expression $As_i(As_i - 1)/2 + As_i{\cdot}An_i + An_i(An_i - 1)/2$. Since the carbon atom of the >CHX group becomes asymmetric with each of these combinations, the number of stereoisomers

[4] Combination of identical values signifies that each individual value, whether stereoisomeric or non-stereoisomeric, is combined through the >CHX group only with itself.

will be double the above expression, or $As_i(As_i - 1) + 2As_i \cdot An_i + An_i \cdot (An_i - 1)$.

A summation of the numbers in group (1) and group (2) of type (b) gives an expression for the total number of stereoisomers of this type, which, when simplified, yields

$$(T_i)^2 - An_i \qquad (\mathrm{IIb_s})$$

where i is an integer greater than zero and $2i = N - 1$.

The number of non-stereoisomers of type (b) will equal An_i.

$$An_i \qquad (\mathrm{IIb_n})$$

Tertiary.—The structural formulas of the tertiary mono-substitution products of the paraffins, RR′>C<XR″, of N total carbon atom content, may be formed from those of R–X, R′–X and R″–X (the carbon content of R– plus R′– plus R″– always equaling $N - 1$) by removing the X group from each and attaching the resulting alkyl radicals R–, R′– and R″– to the >C<X group. The total number of isomers that may be thus formed will be conditioned by the total number of possible cases of combining with the >C<X group complementary values of R–, R′– and R″–.[5] These possible cases are theoretically of two types: (a) in which the three alkyl radicals are of different carbon content; (b) in which two of the alkyl radicals are of the same carbon content and different from that of the third; and (c) in which the three radicals are of equal carbon content. Type (c) is actually possible only when $N - 1$ is divisible by three.

Type (a).—For each of the individual cases of this type the number of possibilities of combining the stereoisomeric and non-stereoisomeric values of R–, R′– and R″– with the >C<X group may be expressed as follows: $T_i \cdot T_j \cdot T_k$. Since in this type the values of R–, R′– and R″– are different, the carbon of the >C<X group, to which these radicals are attached, is asymmetric and the number of stereoisomers of each case will equal $2T_i \cdot T_j \cdot T_k$. Hence, the total number of stereoisomeric mono-substitution products of this type will equal

$$2\,\Sigma\, T_i \cdot T_j \cdot T_k \qquad (\mathrm{IIIa_s})$$

where i, j and k are integers, distinct, and greater than zero, $i + j + k = N - 1$, and $i > j > k$.

The number of $T_i \cdot T_j \cdot T_k$ terms included in this summation depends on whether N is even or odd.

Even: if $N/6$ or $(N - 2)/6$ is an integer, the number of terms of type (a) is $(N - 2)(N - 6)/12$; and if $(N + 2)/6$ is an integer, the number of terms is $(N - 4)^2/12$.

Odd: if $(N + 1)/6$ or $(N + 3)/6$ is an integer, the number of terms is $(N - 3)(N - 5)/12$; and if $(N - 1)/6$ is an integer the number of terms is $[(N - 4)^2 + 3]/12$.

[5] The values of R– and R′– complementary to R″– satisfy the relationship that the total carbon content of R– plus R′– plus R″– equal $N - 1$.

Type (b).—The isomers of this type, in which the carbon content of R– and R′– are the same and different from that of R″–, may be further classified into two groups: (1), in which R– and R′– are absolutely identical from the standpoint of both structural- and stereo-isomerism; and (2), in which R– and R′– are not identical.

Group (1).—The combinations of this group may be divided into those in which the identical values are stereoisomeric and those in which the identical values are non-stereoisomeric. When identical stereoisomeric values for R– and R′– are combined through the $\geqslant$C–X group with the values, both stereoisomeric and non-stereoisomeric, of R″– no asymmetric carbon atoms are created and the number of stereoisomers thus formed will equal the number of such possible combinations or $As_i \cdot T_j$. Similarly, when identical non-stereoisomeric values for R– and R′– are combined through the $\geqslant$C–X group with stereoisomeric values for R″–, no asymmetric carbon atoms are created and the number of stereoisomers will equal $An_i \cdot As_j$. The remaining type of combination theoretically possible is that in which identical non-stereoisomeric values for R– and R′– are combined through the $\geqslant$C–X group with non-stereoisomeric values for R″–. Here, likewise, no asymmetric carbon atoms are created and, since the alkyl radicals contain no asymmetric carbon atoms, no stereoisomers will result.

Group (2).—The number of possibilities of combining with the $\geqslant$C–X group non-identical complementary values, both stereoisomeric and non-stereoisomeric, of R–, R′– and R″– may be represented by the expression $[As_i(As_i - 1)/2 + As_i \cdot An_i + An_i(An_i - 1)/2] \cdot T_j$. Since the carbon atom of the $\geqslant$C–X group becomes asymmetric with each of these combinations, the number of stereoisomers for each case will be double the above expression.

A summation of the numbers in group (1) and group (2) of type (b) gives an expression for the total number of stereoisomers of each case, which, when simplified, yields $[(T_i)^2 - An_i]T_j + An_i \cdot As_j$. Hence, the total number of stereoisomeric mono-substitution products of this type will equal

$$\Sigma[[(T_i)^2 - An_i] \cdot T_j + An_i \cdot As_j] \qquad \text{(IIIb}_s\text{)}$$

where i and j are integers, distinct, and greater than zero, and $2i + j = N - 1$.

The number of terms of type (b) also depends on whether N is even or odd.

Even: if $N/6$ or $(N - 2)/6$ is an integer, the number of terms of type (b) is $(N - 2)/2$; and if $(N + 2)/6$ is an integer, the number of terms is $(N - 4)/2$.

Odd: if $(N + 1)/6$ or $(N + 3)/6$ is an integer, the number of terms is $(N - 3)/2$; and if $(N - 1)/6$ is an integer, the number of terms is $(N - 5)/2$.

The number of non-stereoisomers of type (b) will equal

$$An_i \cdot An_j \qquad (IIIb_n)$$

Type (c).—The isomers of this type, in which the carbon contents of R–, R′–, and R″– are the same, are also classified into two groups: (1), in which at least two of the three alkyl radicals are absolutely identical from the standpoint of both structural- and stereo-isomerism; and (2), in which no two of the three alkyl radicals are absolutely identical.

Group (1).—The combinations of this group may be divided into those in which the identical values are stereoisomeric and those in which the identical values are non-stereoisomeric. When identical stereoisomeric values for R– and R′– are combined through the $\geqslant$C–X group with the values, both stereoisomeric and non-stereoisomeric, of R″–, no asymmetric carbon atoms are created and the number of stereoisomers thus formed will equal the number of such possible combinations or $As_i \cdot T_i$. Similarly, when identical non-stereoisomeric values for R– and R′– are combined through the $\geqslant$C–X group with stereoisomeric values for R″–, no asymmetric carbon atoms are created and the number of stereoisomers will equal $An_i \cdot As_i$. The remaining type of combination theoretically possible is that in which identical non-stereoisomeric values for R– and R′– are combined through the $\geqslant$C–X group with non-stereoisomeric values for R″–. Here, likewise, no asymmetric carbon atoms are created and, since the alkyl radicals contain no asymmetric carbon atoms, no stereoisomers will result.

Group (2).—The number of possibilities of combining non-identical complementary values, both stereoisomeric and non-stereoisomeric, of R–, R′–, and R″–, may be represented by the expression $As_i(As_i - 1)(As_i - 2)/6 + An_i \cdot As_i(As_i - 1)/2 + An_i \cdot As_i(An_i - 1)/2 + An_i(An_i - 1)(An_i - 2)/6$. Since the carbon atom of the $\geqslant$C–X group becomes asymmetric with each of these combinations, the number of stereoisomers will be double the above expression.

A summation of the numbers in group (1) and group (2) of type (c) gives an expression for the total number of stereoisomers, which, when simplified, yields

$$\frac{2\,T_i + (T_i)^3}{3} - (An_i)^2 \qquad (IIIc_s)$$

where i is an integer greater than zero, and $3i = N - 1$.

The number of non-stereoisomers of type (c) will equal

$$(An_i)^2 \qquad (IIIc_n)$$

The actual use of these formulas may be illustrated in the calculation of the number of stereoisomeric and non-stereoisomeric mono-substitution products of the carbon content of thirteen.

Primary.—Stereoisomers

$$Ps_{13} = As_{12} = 12{,}648$$

Non-stereoisomers

$$Pn_{13} = An_{13} = 184$$

Secondary.—Type (a), number of terms equals $(N - 3)/2 = 5$.

Stereoisomers

$$\begin{aligned}
2 \cdot T_1 \cdot T_{11} &= 2 \cdot 1 \cdot 4436 = 8872 \\
2 \cdot T_2 \cdot T_{10} &= 2 \cdot 1 \cdot 1553 = 3106 \\
2 \cdot T_3 \cdot T_9 &= 2 \cdot 2 \cdot 551 = 2204 \\
2 \cdot T_4 \cdot T_8 &= 2 \cdot 5 \cdot 199 = 1990 \\
2 \cdot T_5 \cdot T_7 &= 2 \cdot 11 \cdot 74 = 1628
\end{aligned}$$

Non-stereoisomers.—There can be no non-stereoisomers of this type.

Type (b), since the quotient of $(N - 1)/2$ is an integer, this term is present.

Stereoisomers

$$(T_6)^2 - An_6 = 28^2 - 8 = 776$$

Non-stereoisomers

$$An_6 = 8$$

Tertiary.—Type (a), number of terms (for $(N - 1)/6$ = an integer) equals $[(N - 4)^2 + 3]/12 = 7$.

Stereoisomers

$$\begin{aligned}
2 \cdot T_9 \cdot T_2 \cdot T_1 &= 2 \cdot 551 \cdot 1 \cdot 1 = 1102 \\
2 \cdot T_8 \cdot T_3 \cdot T_1 &= 2 \cdot 199 \cdot 2 \cdot 1 = 796 \\
2 \cdot T_7 \cdot T_4 \cdot T_1 &= 2 \cdot 74 \cdot 5 \cdot 1 = 740 \\
2 \cdot T_7 \cdot T_3 \cdot T_2 &= 2 \cdot 74 \cdot 2 \cdot 1 = 296 \\
2 \cdot T_6 \cdot T_5 \cdot T_1 &= 2 \cdot 28 \cdot 11 \cdot 1 = 616 \\
2 \cdot T_6 \cdot T_4 \cdot T_2 &= 2 \cdot 28 \cdot 5 \cdot 1 = 280 \\
2 \cdot T_5 \cdot T_4 \cdot T_3 &= 2 \cdot 11 \cdot 5 \cdot 2 = 220
\end{aligned}$$

Non-stereoisomers.—There can be no non-stereoisomers of this type.

Type (b), number of terms (for $(N - 1)/6$ = an integer) equals $(N - 5)/2 = 4$.

Stereoisomers

$$\begin{aligned}
[(T_1)^2 - An_1]T_{10} + An_1 \cdot As_{10} &= (1^2 - 1) \cdot 1553 + 1 \cdot 1488 = 1488 \\
[(T_2)^2 - An_2]T_8 + An_2 \cdot As_8 &= (1^2 - 1) \cdot 199 + 1 \cdot 176 = 176 \\
[(T_3)^2 - An_3]T_6 + An_3 \cdot As_6 &= (2^2 - 2) \cdot 28 + 2 \cdot 20 = 96 \\
[(T_5)^2 - An_5]T_2 + An_5 \cdot As_2 &= (11^2 - 5) \cdot 1 + 5 \cdot 0 = 116
\end{aligned}$$

Non-stereoisomers

$$\begin{aligned}
An_1 \cdot An_{10} &= 1 \cdot 65 = 65 \\
An_2 \cdot An_8 &= 1 \cdot 23 = 23 \\
An_3 \cdot An_6 &= 2 \cdot 8 = 16 \\
An_5 \cdot An_2 &= 5 \cdot 1 = 5
\end{aligned}$$

Type (c), since the quotient of $(N - 1)/3$ is an integer, this term is present.

Stereoisomers

$$[2\cdot T_4 + (T_4)^3]/3 - (An_4)^2 = (2\cdot 5 + 5^3)/3 - 3^2 = 36$$

Non-stereoisomers

$$(An_4)^2 = 3^2 = 9$$

$$As_{13} = Ps_{13} + Ss_{13} + Ts_{13} = 12{,}648 + 18{,}576 + 5{,}962 = 37{,}186$$
$$An_{13} = Pn_{13} + Sn_{13} + Tn_{13} = 184 + 8 + 118 = 310$$
$$T_{13} = As_{13} + An_{13} = 37{,}186 + 310 = 37{,}496$$

The following table indicates the number of stereoisomeric and non-stereoisomeric mono-substitution products of the paraffins as calculated by the use of the recursion formulas.[6]

TABLE I

NUMBER OF STEREOISOMERIC AND NON-STEREOISOMERIC MONO-SUBSTITUTION PRODUCTS OF THE PARAFFINS

	Primary		Secondary		Tertiary		Totals		
Carbon content	Stereo-isomers	Non-stereo-isomers	Stereo-isomers	Non-stereo-isomers	Stereo-isomers	Non-stereo-isomers	Stereo-isomers	Non-stereo-isomers	Total isomers
1	0	1	0	0	0	0	0	1	1
2	0	1	0	0	0	0	0	1	1
3	0	1	0	1	0	0	0	2	2
4	0	2	2	0	0	1	2	3	5
5	2	3	4	1	0	1	6	5	11
6	6	5	14	0	0	3	20	8	28
7	20	8	34	2	6	4	60	14	74
8	60	14	98	0	18	9	176	23	199
9	176	23	270	3	66	13	512	39	551
10	512	39	768	0	208	26	1,488	65	1,553
11	1,488	65	2,192	5	646	40	4,326	110	4,436
12	4,326	110	6,360	0	1,962	74	12,648	184	12,832
13	12,648	184	18,576	8	5,962	118	37,186	310	37,496
14	37,186	310	54,780	0	18,014	210	109,980	520	110,500
15	109,980	520	162,658	14	54,578	342	327,216	876	328,092
16	327,216	876	486,154	0	165,650	595	979,020	1,471	980,491
17	979,020	1,471	1,461,174	23	504,220	981	2,944,414	2,475	2,946,889
18	2,944,414	2,475	4,413,988	0	1,539,330	1,684	8,897,732	4,159	8,901,891
19	8,897,732	4,159	13,393,816	39	4,712,742	2,798	27,004,290	6,996	27,011,286
20	27,004,290	6,996	40,807,290	0	14,475,936	4,763	82,287,516	11,759	82,299,275

Summary

1. No direct or simple relationship appears to exist between the number of stereoisomeric and non-stereoisomeric mono-substitution products of the paraffins and their carbon contents.

[6] The structural formulas of the mono-substitution products of the paraffins, inclusive of a carbon content of ten, were written in connection with the derivation of these recursion formulas. The total number of stereoisomers and non-stereoisomers as indicated by inspection of the above-mentioned structural formulas agreed exactly with the numbers obtained by use of the recursion formulas.

2. Formulas of the (finite) recursion type are advanced which permit the calculation from their carbon content of the number of stereoisomeric and non-stereoisomeric primary, secondary and tertiary mono-substitution products of the paraffins. In using these recursion formulas to calculate the total number of such isomers of any given carbon content, the total number of isomers, both stereoisomeric and non-stereoisomeric, of every lesser carbon content must be known.

3. The total number of isomeric mono-substitution products so obtained agrees exactly through those of the decanes with the numbers required by theory as tested by actually writing the structural formulas and counting the number of stereoisomers and non-stereoisomers.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

RESEARCHES ON PYRIMIDINES. CXXV. THE EFFECT OF DILUTE ACIDS AND OF LIGHT ENERGY ON THYMINE GLYCOL. SYNTHESIS OF ACETYLMETHYLDIALURIC ACID

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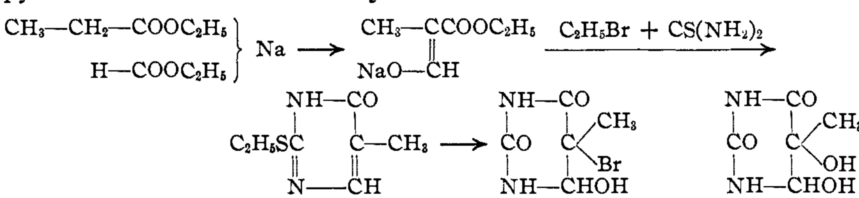
The method of preparing thymine glycol,[1] first described by Baudisch and Davidson, was modified by converting 2-ethylmercapto-5-methyl-6-oxypyrimidine I directly into bromoxyhydrothymine II by the action of bromine and then removing the bromine by the usual procedure to obtain the glycol derivative III. For the preparation of the ethyl mercaptopyrimidine I the method of Johnson and Schmidt-Nickels[2] was used.



I II III

Method of Preparation.—Three and one-half grams of 2-ethylmercapto-5-methyl-6-oxypyrimidine I was suspended in 57 cc. of water, and with continuous stirring and gentle warming 5 cc. of bromine was gradually added. A pasty red mass was first formed which, however, on further warming went quickly into solution. The solution, colored with the excess of bromine, was filtered, concentrated *in vacuo*, and the precipitated bromoxyhydrothymine II purified by crystallization from hot water. In later preparations, instead of using silver oxide to replace the bromine in II by hydroxyl as practiced by Baudisch and Davidson, an equivalent amount of silver carbonate was used in order to avoid an alkaline reaction during the change.

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[1] Baudisch and Davidson, *Ber.*, **58**, 1680 (1925).

[2] Johnson and Schmidt-Nickels, THIS JOURNAL, **52**, 4511 (1930).