Tetrahedron Letters No.19, pp. 1501-1504, 1969. Pergamon Press. Printed in Great Britain.

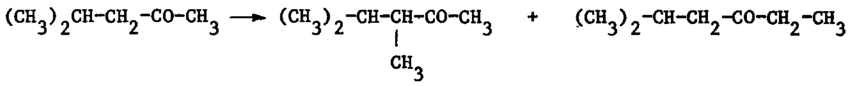
BASE-CATALYSED POLYALKYLATION OF ALIPHATIC KETONES.I.
GRAPH AND TOPOLOGICAL DESCRIPTION OF REACTION PATHWAYS.

Jacques-Emile Dubois and Annick Panaye

(Laboratoire de Chimie Organique Physique de la Faculté des Sciences de Paris,
Associé au C.N.R.S., 1, rue Guy de la Brosse, Paris 5° - France).

(Received in UK 7 March 1969; accepted for publication 20 March 1969)

It has been reported that the base-catalysed alkylation of alkylmethyl ketones is a directio-specific process under certain conditions (1), e.g. B is formed from A. However, recent work in this laboratory (2) and elsewhere (3,4) shows that both isomers may be obtained under a variety of other conditions, i.e. B and C from A.



$$(CH_3)_2CH\text{-}CH_2\text{-}CO\text{-}CH_3 \longrightarrow (CH_3)_2\text{-}CH\text{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{-}CO\text{-}CH_3 \quad + \quad (CH_3)_2\text{-}CH\text{-}CH_2\text{-}CO\text{-}CH_2\text{-}CH_3$$

A B C

This observation opens up the possibility of the synthesis of heavily substituted ketones from simpler ones by successive alkylations. In the course of our work on polyalkylation it became evident that optimization of the route to a given ketone presented certain serious problems as a result of the sensitivity of the orientation of consecutive steps to the experimental conditions. For example, for the preparation of an n-times alkylated ketone from acetone itself, there are in principle n ! routes, e.g. for the preparation of $R^1R^2CH\text{-}CO\text{-}CH_2R^3$ (n=3) n ! is 6, the substituents being introduced in the order $R^1R^2R^3$, $R^2R^3R^1$, $R^3R^2R^1$, $R^1R^3R^2$, $R^2R^1R^3$, or $R^3R^1R^2$ (where $R^1 \neq R^2 \neq R^3$). For six different substituents there could be 720 pathways.

In order to deal with these problems we were led to develop a method for studying polyalkylation which renders it possible to analyse both the orientation of each step and the alkylation sequence or reaction pathway in terms of the environments of α and α' sites and of the nature of alkylating groups.

Our approach, based on graph theory, leads to a diagram of the alkylation paths and to a topological description of the graphs which represent molecular structures, with particular attention to the environments of reactive sites.

The graph theory has been applied to isomerisation of trigonal bipyramidal phosphorus compounds (5,6) and carbonium ion rearrangements (7). As for the description of molecules, the graph theory has proved useful for the nomenclature of polycyclic aromatic hydrocarbons (8) and is incorporated in the DARC system of topological description (9). We will discuss briefly this latter system before progressing to reaction pathway descriptors.

All syntheses of a ketone through alkylation of a precursor ketone can be represented by an "alkylation graph" in which the ketones will conventionally be designated by a reduced form of the more general DARC description in order to arrive at a simple one-line numerical expression of the reaction pathway.

Topological description : In this system the ketone is described by an unique unambiguous descriptor DEL (10), which summarises the information concerning the atoms associated with a focus (>C-CO-C< for a ketone).

The α- and α'-substituents are depicted as shown (Figure 1)

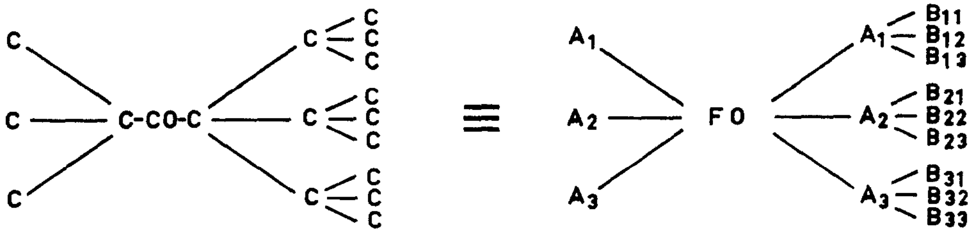
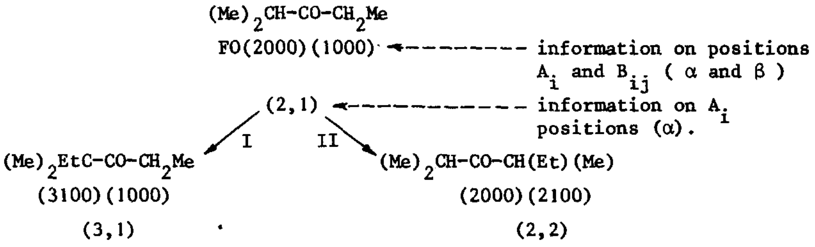


Figure 1

A_i and B_{ij} indicate positions which are (A_i or B_{ij} is assigned a value of unity) or are not (A_i or B_{ij} is assigned zero value) occupied by carbon atoms. The DEL is defined as : ΣA_i ΣB_{i1} ΣB_{i2} ΣB_{i3} . Thus the description of a ketone is reduced to FO (DEL)(DEL)' wherein the higher DEL is placed, by convention, first.

Reaction Pathways and graph representation : The DEL can be reduced to a more abreviated form for specific problems. Here, ketones will be indexed simply as (ΣA_i, $\Sigma A_i'$) corresponding to the number of α- and α'-substituents. Thus, (Me)$_2$CH-CO-CH$_2$-Me (DEL=FO(2000)(1000)) becomes (2,1). Ethylation may lead first to (Me)$_2$EtC-CO-CH$_2$-Me (3,1) or (Me)$_2$CH-CO-CH(Et)(Me) (2,2). Subsequent ethylation of these products could give (Me)$_2$EtC-CO-CH(Et)(Me) (3,2) and (Me)$_2$CH-CO-C(Me)(Et)$_2$ (2,3) which are not identical but are α-substituted to the same extent.



Schema : Coding of alkylation by DEL
and the reduced description

Development of such a reaction scheme leads to the "alkylation graph" in which the nodes are the ketones and the intervals correspond to the conversion of one ketone to another by alkylation and where only the order of the introduction of the substituents into the "left-" and "right-" hand branches is considered. These elementary graphs summarise the reaction pathway types (Figures 2,3,4).

Conia's directio-specific alkylations (1) are then represented by Figure 2. If no step in the synthesis of $R^1R^2R^2C\text{-}CO\text{-}CR^2R^2R^2$ from $R^1CH_2\text{-}CO\text{-}CH_3$ were specific, the entire graph would be traced out (Figure 3). For the polyethylation of neohexylmethyl ketone (11), the graph (Figure 4) lies between these two extremes.

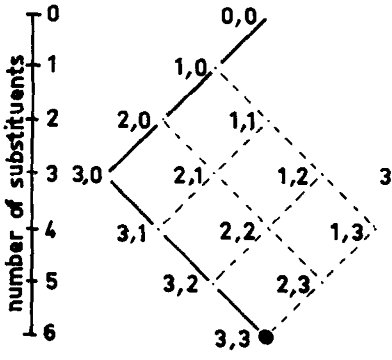


Figure 2

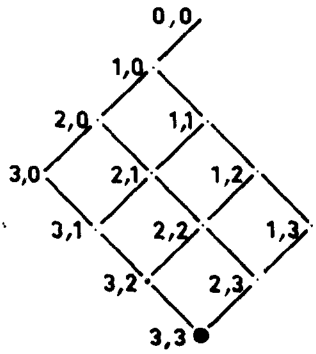


Figure 3

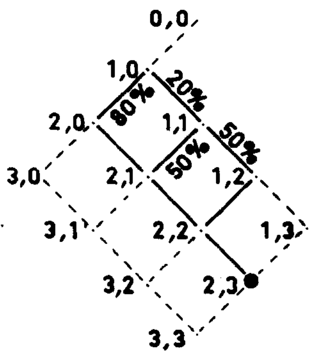
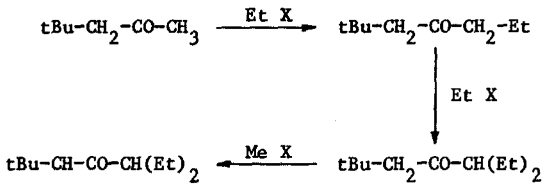


Figure 4

One-line description of reaction pathways : The description of the alkylating agent RX is reduced, like that of the ketone, to a DEL and a focus, in this case -X, which can however be ignored since only the alkyl group enters into the product. Alkylation in the "left-" and "right-"hand branches is denoted by I and II respectively(see schema). For example, the sequence of alkylations



becomes : [FO(1111)(0000)] II(1100)II(1100)I(1000) → (2111)(2200)≡FO(2200)(2111). The DEL of the end product is obtained very simply by summing the DEL's of the original ketone and those of the radicals appropriate to the alkylations in the "left-" and "right-"hand sides.

The reaction pathway method, leading to the numerical one-line description of a pathway, described in this paper, can be applied to multi-step syntheses involving different reactions and where optimization is very important.

REFERENCES

(1) J.M. CONIA, *Record of Chem.Progress*, **24**, 42 (1963).

(2) J.E. DUBOIS, M. CHASTRETTE and A. PANAYE, *C.R.Acad.Sci.*, **267C**, 1413 (1968).

(3) H.O. HOUSE and V. KRAMAR, *J.Org.Chem.*, **28**, 3362 (1963).

(4) D. CAINE, *J.Org.Chem.*, **29**, 1868 (1964).

(5) J.D. DUNITZ and V. PRELOG, *Angew.Chem.Internat.Edn.*, 725, (1968).

(6) P. LANTEBUR and F. RAMIREZ, *J.Amer.Chem.Soc.*, **90**, 6722 (1968).

(7) A.T. BALABAN, D. FARCASIU and R. BANICA, *Rev.Roumaine Chim.*, **11**, 1205 (1966).

(8) A.T. BALABAN and F. HARARY, *Tetrahedron*, **24**, 2505 (1968).

(9) J.E. DUBOIS and H. VIELLARD, *Bull.Soc.chim.Fr.*, 900,905 and 913 (1968).

(10) DEL = Descriptor obtained by propagation of an Environment Limited to two ranks of atoms A_i and B_{ij}.

(11) A. PANAYE, Diplôme d'Etudes Supérieures, Faculté des Sciences de Paris (1968).