earliest kinetic examination by Daniels and Johnston[1] was a careful study over the temperature range 25 to 65°, and over this range a good estimate was made of the energy of activation. The primary object of this extension of the temperature range was to see how and if the energy of activation itself is a function of temperature.

Experimental

The apparatus used in this study was very nearly the same as that described by Johnston and Yost.[2] It consisted of a calibrated flowmeter system, U-shaped nitrogen pentoxide saturator, Hartridge and Roughton type of mixing chamber, stainless-steel stop gate, 30-cm. coil of glass tubing through heating bath to bring gases up to desired temperature, reaction cell 10 cm. long and 6 mm. internal diameter, bath of paraffin oil stirred and thermally regulated to ±0.3°, H-4 mercury arc filtered to give line at 436 mμ, electron multiplying photoelectric tube RCA 1P28, DuMont 208 oscilloscope, and 35 mm. camera. By means of thermocouples it was established that the temperature inside the reaction cell was identical with that of the bath at the flow rates used. The bath temperature was measured by a thermometer calibrated by the Bureau of Standards. Nitrogen pentoxide was prepared by the method and apparatus described by Mills and Johnston.[3] All studies were made with approximately 2 to 5 mm. of nitrogen pentoxide and at a total pressure of one atmosphere with nitrogen making up the difference. Reaction was followed colorimetrically by the appearance of nitrogen dioxide. The absorption coefficient expressed in units of length and concentration (not pressure) was constant from 25 to 125° and agreed with previously found and published values.[4]

Results

The reaction is

$$2N_2O_5 = 4NO_2 + O_2$$

and the first-order rate constant is defined as k in the expression

$$-(1/2)\, d(N_2O_5)/dt = k(N_2O_5)$$

At the concentrations of products encountered and in the temperature range 65 to 123° the correction for nitrogen tetroxide, N_2O_4, was negligible, greatly simplifying the computation of rate constants. By letting the reaction run for 20 or more half-lives, the initial concentration of nitrogen pentoxide could be computed as one-half the final concentration of nitrogen dioxide. The concentration of nitrogen pentoxide at any time was considered to be this initial value minus one-half the concentration of nitrogen dioxide. The plot of the logarithm of nitrogen pentoxide concentration against time gave a straight line (at least for the first half-life) whose slope times 2.303/2 gave the first-order rate constant. A summary of values of rate constants is given in Table I.

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE DECOMPOSITION OF NITROGEN PENTOXIDE AT HIGH TEMPERATURES

Temperature, °K.	Number of runs	Av. rate constant sec.$^{-1}$	Standard error of the mean sec.$^{-1}$
337.6	10	0.00256	0.00007
348.6	11	.00683	.00013
357.6	15	.0161	.0002
367.6	10	.0458	.0013
378.0	9	.122	.009
388.2	7	.258	.004
396.2	13	.525	.009

(1) F. Daniels and E. H. Johnston, THIS JOURNAL, **43**, 53 (1921).
(2) H. S. Johnston and D. M. Yost, *J. Chem. Phys.*, **17**, 386 (1949).
(3) R. L. Mills and H. S. Johnston, THIS JOURNAL, **73**, 938 (1951).
(4) H. H. Holmes and F. Daniels, *ibid.*, **56**, 630 (1934).

Discussion

The energy of activation is defined as E in the relation

$$d \ln k/dT = E/RT^2 \qquad (1)$$

By first assuming the energy of activation to be independent of temperature and by combining these data with those of Daniels and Johnston,[1] the energy of activation was computed by the method of least squares to give

$$k = 2.05 \times 10^{13}\, e^{-24650/RT}\ \text{sec.}^{-1} \qquad (2)$$

These results are in almost exact agreement with those obtained in the low temperature range alone.[1] To test the temperature dependence of the energy of activation itself, the same data were fitted to the usual three-parameter relation to give

$$k = 1.97 \times 10^{18}\, T^{-1.63}\, e^{-25790/RT}\ \text{sec.}^{-1} \qquad (3)$$

It has been said[5] with reference to the low temperature data alone that the results could equally well be expressed by Eq. (2) or by expressions like Eq. (3) wherein the absolute temperature is given a negative exponential value up to 14. These results cover a wide enough range of temperature to make that statement no longer true. The least-squares exponent of the absolute temperature in Eq. (2) is very nearly zero, and the energy of activation of this reaction is essentially constant from 25 to 123°.

(5) R. Fowler and E. A. Guggenheim, "Statistical Thermodynamics," University Press, Cambridge, 1949, p. 526.

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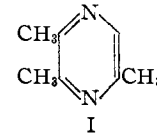
RECEIVED DECEMBER 4, 1950

The Action of Organolithium Compounds on 2,5-Dimethylpyrazine. II[1]

BY BERNARD KLEIN[2] AND PAUL E. SPOERRI

In an earlier communication,[3] it was reported that treatment of 2,5-dimethylpyrazine with methyllithium produced 2,5,6-trimethylpyrazine (I)



I

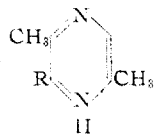
Similarly, with phenyllithium, the corresponding 2,5-dimethyl-6-phenylpyrazine was formed.

We wish to present additional evidence that this reaction is a general one for the direct alkylation in the pyrazine series. Thus, when 2,5-dimethylpyrazine was treated, in turn, with one equivalent of a series of alkyllithium compounds, the corresponding 2,5-dimethyl-6-alkylpyrazine was obtained (II), presumably by the 1,2 addition across the azomethine linkage. Evidently, the high electron

(1) From the Ph.D. thesis of Bernard Klein, Polytechnic Institute of Brooklyn, May, 1950. A major portion of the work was done in the laboratory of the Veterans Administration Hospital, Bronx, N. Y. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.
(2) Veterans Administration Hospital, Bronx 63, N. Y.
(3) B. Klein and P. E. Spoerri, THIS JOURNAL, **72**, 1844 (1950).

TABLE I

2,5-DIMETHYL-6-ALKYLPYRAZINES

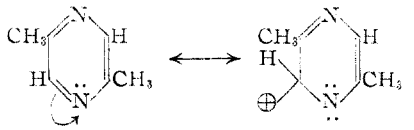


II

R	B.p. °C.	Mm.	n^tD	t	Yield, %	Empirical formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
CH_3	86–88.5	35	1.4968	25	44	$C_7H_{10}N_2$[a]	68.82	69.01	8.25	8.42		
C_2H_5	80–81	19[b]	1.4975	22	11.5	$C_8H_{12}N_2$		[c]				
C_4H_9	67	1	1.4926	23	22.4	$C_{10}H_{16}N_2$[d]	73.12	73.27	9.86	9.86	17.06	16.71
C_5H_{11}	96.5	7	1.4872	23	33.9	$C_{11}H_{18}N_2$[e]					15.72	15.42
C_6H_{13}	100.5–104	5.1	1.4853	29	23	$C_{12}H_{20}N_2$[f]					14.57	14.30
C_6H_5	124–126	1.4	1.5792		27	$C_{12}H_{12}N_2$[a]					15.21	15.11

[a] *Cf.* citation 4. [b] C. Stoehr, *J. prakt. Chem.*, [2] **55**, 69 (1897), gives the b.p. as 180–181°, n^{25}D 1.5014. [c] Analyzed as the *chloroplatinate*, calcd. for $C_{16}H_{24}N_4PtCl_6$: Pt, 28.65. Found: Pt, 29.03. [d] *Dipicrate*, m.p. 96.5–98°. Calcd. for $C_{28}H_{24}O_{14}N_8$: N, 16.72. Found: N, 16.57. [e] *Picrate*, m.p., 90–92.5°. Calcd. for $C_{17}H_{21}O_7N_5$: N, 17.2. Found: N, 17.1. [f] *Picrate*, m.p. 73–74°. Calcd. for $C_{18}H_{23}O_7N_5$: N, 16.72. Found: N, 16.52.

density of the ring nitrogen in pyrazine[4] produces a greater attraction for the metal of the organolithium compound in preference to replacement of the hydrogen of the lateral methyl group



These experiments are summarized in Table I.

When a small quantity of the parent heterocyclic hydrocarbon, pyrazine, became available to the authors, the possibility of direct introduction of side chain substituents onto the pyrazine nucleus by means of organolithium compounds in the manner described above appeared interesting and important. Accordingly, pyrazine was treated with one equivalent of phenyllithium under a variety of experimental conditions. In no case was it possible to isolate anything but polymeric material or starting compound (identified by mixed melting point and picrate).

Using butyllithium and conducting the reaction at −20°, however, it was possible to isolate 2-butylpyrazine in 10% yield and poor quality. Unfortunately not enough materials was available for redistillation, nor could the experiment be repeated because the limited supply of pyrazine had been exhausted. The picrate of 2-butylpyrazine proved to be a low melting solid (39–42°) and much loss occured on attempted recrystallization. The chloroplatinate gave a satisfactory analysis.

This procedure then, is a useful one for the direct introduction of substituents on the pyrazyl nucleus. Its limitations are primarily governed by the ease of preparation or availability of the particular organolithium compound.

Gilman and Spatz[5] have listed the general order of decreasing activity of interconversions by means of organolithium compounds as Metal–Metal > Halogen–Metal > Hydrogen–Metal. On this basis, since lateral metalation of the methyl group failed, it was thought possible to effect the metalation of halogenated pyrazine compounds by "exchange" with methyllithium, with the ultimate aim of introducing functional groups in the side chain. Both 2-chloropyrazine and 2,5-dimethyl-6-chloropyrazine failed to exchange with methyllithium in spite of the reactivity of the halogen.[6] This failure was not unexpected as Gilman and Spatz[5] were unable to demonstrate either X–M exchange, as they designated this reaction, or addition to the N=C linkage in the case of 2-chloroquinoline, where the reactivity of the halogen is also relatively high.

Experimental[7]

Preparation of Organolithium Compounds.—The organolithium compounds were prepared by the low temperature method of Gilman and his students.[8] When the reaction was complete the solution was pumped by dry nitrogen through a course, sintered glass filter into a dry, nitrogen flushed, graduated cylinder. The sediment in the reaction flask was thoroughly washed with several portions of dry ether, which was pumped over and added to the collecting cylinder. The combined contents of the cylinder were mixed, the volume noted and an aliquot taken for analysis either by acidimetric titration or the double titration of Gilman and Haubein.[9]

All the following experiments were conducted in a Grignard Type setup consisting of a 3-neck ground-joint flask of appropriate volume equipped with an addition funnel, Hershberg wire stirrer, and an efficient condenser suitably protected against moisture and carbon dioxide and in a dry, oxygen-free nitrogen atmosphere.

General Procedure for Alkylation of 2,5-Dimethylpyrazine.—A solution of dried, freshly distilled, 2,5-dimethylpyrazine in dry ether was added dropwise with good stirring, at 0°, to an equimolar solution of the alkyllithium compound. A reddish precipitate formed which was kept dispersed by vigorous stirring. After the addition was complete the mixture was stirred for an additional hour, permitting the temperature to rise to 15–20°. The reaction product was cautiously decomposed with ice-water, extracted with ether, the combined extracts dried, and the solvent removed. The residues were fractionally distilled through a jacketed helix-packed column.

2-Butylpyrazine.—To 15.1 g. (0.189 mole) of pyrazine dried *in vacuo* over P_2O_5, dissolved in 100 ml. of dry ether and cooled to −20°, 180 ml. of a cold solution of butyllithium (0.189 mole) was slowly added over 1 hour. A brown precipitate soon formed. When about three-fourths of the butyllithium was added, the mixture became pasty and solidified, making good stirring impossible. 50 ml. of

(4) I. J. Krems and P. E. Spoerri, *Chem. Rev.*, **40**, 328 (1947).

(5) H. Gilman and S. M. Spatz, THIS JOURNAL, **63**, 1553 (1941).

(6) A. E. Erickson and P. E. Spoerri, *ibid.*, **68**, 400 (1946).

(7) All melting points were taken on a Kofler micro hot stage and are corrected. Microanalyses by R. E. Schachat, H. Bilitch, Paotung-Huang and Dr. Francine Schwartzkopf, to whom we are deeply indebted.

(8) H. Gilman, J. A. Beal, C. G. Brannen, M. W. Bullock, G. E. Dennis and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

(9) H. Gilman and A. H. Haubein, *ibid.*, **66**, 1515 (1944).

dry ether was added to the reaction mixture and the addition was continued to the end. The mixture resolidified and was allowed to stand overnight under nitrogen, refluxed for 1 hour, cooled, decomposed cautiously with ice-water, and worked up. After removal of solvent (bath, 28°, pressure 25 mm.), the residue was distilled through a helix packed column. After a forerun of 0.9 g., 2.7 g. (10.4% based on pyrazine) of 2-butylpyrazine, b.p. 84° (19 mm.), $n^{26}D$ 1.4963 was obtained.

Anal. Calcd. for $C_8H_{12}N_2$: N, 20.57. Found: N, 19.07.

The **picrate** crystallized with extreme difficulty on long standing in the cold, m.p. 39–42°. Attempted recrystallization from ethanol produced great loss.

The **chloroplatinate** was a pale yellow microcrystalline powder.

Anal. Calcd. for $C_{16}H_{22}N_4PtCl_6$: Pt, 28.65. Found: Pt, 29.00.

2-Chloropyrazine.—An improved preparation of this compound from 2-hydroxypyrazine[10] was mentioned by Hort and Spoerri.[11] Details of this method are now given:

To 9.6 g. (0.1 mole) of 2-hydroxypyrazine in a 250-ml. 3-necked flask fitted with a stirrer and a reflux condenser bearing a drying tube, 30 ml. (0.3 mole) of freshly distilled $POCl_3$ was added. The mixture was warmed for a few minutes, refluxed for 40 minutes and cooled in an ice-water-bath. The cooled mixture was poured onto 300 g. chopped ice and stirred until all the excess $POCl_3$ was decomposed. The black solution was extracted with ether, the combined extracts dried over calcium chloride and the solvent evaporated. The residue was distilled through a jacketed modified Widmer column, collecting 8.1 g. (71%) of product, b.p. 62.5° (29 mm.), $n^{28}D$ 1.5340.

2,5-Dimethyl-6-chloropyrazine.—Prepared from 2,5-dimethylpyrazine-1-oxide[12] as described above in 92% yield, b.p. 66–69° (8.6 mm.), $n^{25}D$ 1.5250. The *picrate* melted at 100–101°.

Acknowledgment.—We are indebted to Dr. B. S. Gordon, Chief, Laboratory Service, Veterans Administration Hospital, Bronx 63, New York, for his sustained interest and assistance during the course of this investigation.

(10) J. Weijlard, M. Tishler and A. E. Erickson, THIS JOURNAL, **67**, 805 (1945).

(11) E. Hort and P. E. Spoerri, *ibid.*, **70**, 1657 (1948).

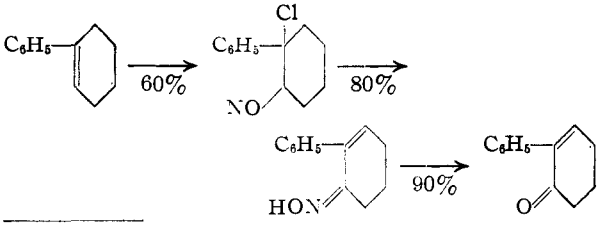
(12) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).

POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, 2, N. Y. RECEIVED DECEMBER 26, 1950

Use of 2-Phenylcyclohexenone in Experiments on the Synthesis of Morphine

BY C. F. KOELSCH

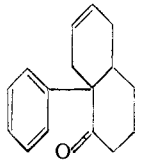
2-Phenyl-Δ^2-cyclohexenone and its reaction with ethyl malonate have been described recently, and it has been indicated that a promising route for synthesis of the morphine structure is thereby opened.[1,2] Certain aspects of that route were investigated in this Laboratory in 1944 with disappointing results, and it appears desirable to record these negative results now to prevent further duplication.



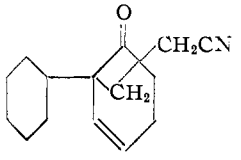
(1) W. E. Bachmann and L. B. Wick, THIS JOURNAL, **72**, 3388 (1950).

(2) W. E. Bachmann and E. J. Fornefeld, *ibid.*, **72**, 5529 (1950).

2-Phenylcyclohexenone was prepared by the reactions diagrammed, different from those used by Bachmann and Wick. The ketone could not be induced to react with butadiene, and a pure product was not obtained with acrylonitrile. Oxidation of the product expected from butadiene (I) to a diacetic acid, or Reformatzky reaction with the product expected from acrylonitrile (II)[3] would have given substances of considerable interest in syntheses of the morphine skeleton

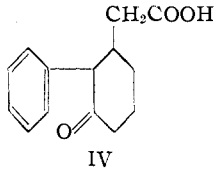


I

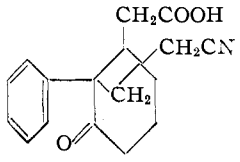


II

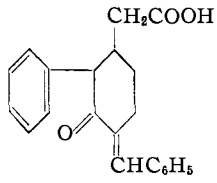
3-Oxo-2-phenylcyclohexaneacetic acid (IV) was obtained using the Michael reaction, a preparation differing only in detail from that used by Bachmann and Fornefeld. A pure product could not be obtained from the keto acid or its ester when reactions with acrylonitrile were attempted (expected formation of V), although a fair yield of benzal derivative (VI) was obtained from the keto acid and benzaldehyde in alkaline medium. This benzal derivative and its ester gave only resinous products when condensations with acrylonitrile were attempted.



IV

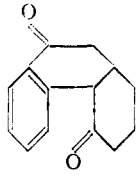


V



VI

The keto acid (IV) reacted with sulfuric acid to form 1,2,11,12-tetrahydrophenanthrene-4(3),9(10)-dione (VII). Possible uses of this substance were not investigated.



VII

Experimental

2-Phenyl-2-cyclohexenone.—A mixture of 48 g. of phenylcyclohexene, 100 ml. of acetic acid and 35 ml. of concentrated hydrochloric acid was cooled to 7° and treated dropwise with 35 g. of butyl nitrite in 30 ml. of acetic acid. The mixture was then stirred for 15 minutes while it was kept in a freezing mixture, and finally it was treated with 100 ml. of methanol. The precipitated product was removed, washed with two 25-ml. portions of methanol, then with water, and dried, giving 39 g. (57%) of nearly pure **phenylcyclohexene**

(3) H. A. Bruson and T. W. Riener, *ibid.*, **65**, 18 (1943).