sponding decomposition of *di-t*-butyl peroxide[6] and is an indication of the structure of the molecule as a perketal. Likewise, the observation that equations (1) and (2) are reversible—the pure peroxide can be hydrolyzed by acid to the original hydroperoxide and ketone—is pertinent.

(6) Raley, Rust and Vaughan, THIS JOURNAL, **70**, 1336 (1948).


## Summary

A series of new liquid peroxides derived from reaction of aldehydes and ketones with *t*-butyl hydroperoxide is presented together with methods of synthesis.


EMERYVILLE 8, CALIFORNIA RECEIVED[7] JANUARY 6, 1949

(7) Original manuscript received April 12, 1948.

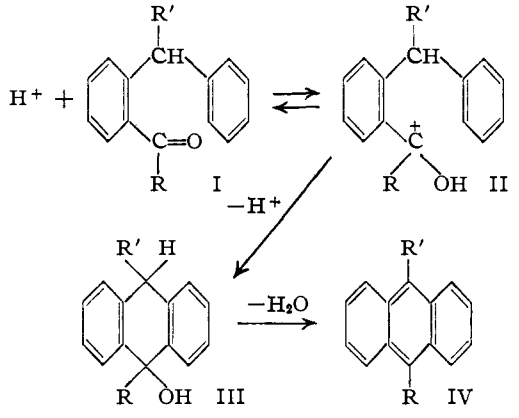
---

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

# Aromatic Cyclodehydration. XXII.[1] The Mechanism of the Cyclization of *o*-Benzylphenones. III

BY CHARLES K. BRADSHER AND FRANK A. VINGIELLO[2]

In acid media, *o*-benzylphenones (I) may be cyclized to yield anthracene hydrocarbons[3,4,5] (IV). Berliner[5] has found (where R′ = $CH_3$) that the




rate of cyclization decreases with increasing length of group R until *n*-butyl is reached, and remains approximately the same for *n*-pentyl and *n*-hexyl.

This was explained in terms of an increasing order of electron release with increase in size of the alkyl group[6] up to butyl, resulting in an increase in electron density on the positive central carbon atom, thus making the substitution reaction more difficult.

The present investigation was undertaken to determine (1) whether a similar difference in cyclization rates exists in the series in which R′ = H, (2) the effect on the cyclization rate when the inductive effect is varied, while steric factors are kept essentially constant and (3) the effect of varying R′ while R remains constant.

The procedure used in our rate studies differs from that employed by Berliner in that the reaction mixture was not refluxed, but heated in a thermostat in glass-stoppered tubes, and the weight of product isolated was corrected to allow for solubility in the cyclizing medium.[7]

TABLE I

RATES OF CYCLIZATION OF SOME *o*-BENZYLPHENONES (I)[a]

| R | $K$, (hr.$^{-1}$) × $10^{-2}$ |
|---|---|
| H | 540 |
| $CH_3$ | 70 |
| $C_2H_5$ | 30 |
| $C_6H_5CH_2$ | 23 |
| *p*-$CH_3C_6H_4$ | 4.2 |
| *p*-$BrC_6H_4$ | 4.2 |
| *p*-$ClC_6H_4$ | 4.1 |
| *p*-$FC_6H_4$ | 2.8 |
| $C_6H_5$ | 4.4 |
| $C_6H_5$ (R′ = $CH_3$) | 13 |
| $C_6H_5$ (R′ = $C_6H_5$) | 13 |

[a] R′ = H unless otherwise noted.

Like Berliner,[5] we have found the rate of cyclization to be of first order with respect to ketone concentration, and, as he has pointed out, the earlier statement by one of us and Smith that "the rate of cyclization of *o*-benzylphenones is roughly independent of the nature of the R group" is erroneous.[8]

In addition to the ketones mentioned, we have measured the rate of cyclization of *o*-benzylbenzaldehyde[9] (I, R = H; R′ = H). Under the conditions we have used, the rate of formation of anthracene was so great as to make accurate timing difficult.

The comparison of the rates shown by the *para*-substituted phenyl ketones (R′ = H; R = *p*-$XC_6H_4$) affords a test of the relative importance

(1) For the preceding communication of this series see *J. Org. Chem.*, **13**, 786 (1948).

(2) Present address: Virginia Polytechnic Institute, Blacksburg Va.

(3) Bradsher, THIS JOURNAL, **62**, 486 (1940).

(4) Bradsher and Smith, *ibid.*, **65**, 451 (1943).

(5) Berliner, *ibid.*, **66**, 533 (1944).

(6) Berliner has been careful to emphasize that equally plausible explanations might be obtained from purely stereochemical considerations.

(7) While the solubility of the aryl anthracenes was small, that of the methyl- and ethylanthracenes was large enough to make errors in the solubility determination a significant source of error in the final rate.

(8) This statement, for which the senior author accepts full responsibility, was based upon only a few yields obtained under conditions which were not comparable.

(9) The cyclization of this compound was first observed by Bergmann, *J. Org. Chem.*, **4**, 1 (1939).

TABLE II

NEW KETONES (I) AND ANTHRACENE DERIVATIVES (IV) (R′=H)

| R | M. p., °C. | Formula | Analyses, % Calcd. | | Found | |
|---|---|---|---|---|---|---|
| | | I | | | | |
| 4-$FC_6H_4$ | 50–51[a] | $C_{20}H_{15}OF$ | F, 6.6 | | 6.6[b] | |
| 4-$CH_3C_6H_4$ | 68.5–69 | $C_{21}H_{18}O$ | C, 88.08 | H, 6.33 | 88.18 | 6.27[c] |
| $C_6H_5CH_2$ | B. p. (3 mm.) 209–211 | $C_{21}H_{18}O$ | C, 88.08 | H, 6.33 | 87.74 | 6.28[d] |
| | | IV | | | | |
| 4-$ClC_6H_4$ | 179–180 | $C_{20}H_{13}Cl$ | C, 83.19 | H, 4.53 | 82.72 | 4.53[c] |
| 4-$FC_6H_4$ | 168.5–169.5 | $C_{20}H_{13}F$ | F, 7.0 | | 7.0[b] | |
| 4-$CH_3C_6H_4$ | 145–145.5 | $C_{21}H_{16}$ | C, 93.99 | H, 6.01 | 93.98 | 6.33[c] |

[a] All solids were crystallized from ethanol except the fluoro ketone which was crystallized from petroleum ether. [b] Fluorine analyses by Mrs. A. R. Gilbert. [c] Analyses by Oakwold Laboratories. [d] Analysis by Micro-Tech. Laboratories.

of steric factors and of the electron-release of substituent groups, in that here the size of the groups may be considered as closely comparable. It is interesting to note that with the exception of the *p*-fluorophenyl ketone the *para*-substituted phenyl ketones, within the limits of probable experimental error, give the same rate as the parent phenyl ketone.

The significance of the lower rate shown by the fluorophenyl ketone is not clear, for the decreasing order of the electron release of the various substituent groups, as indicated by the ionization of the *para*-substituted benzoic acids[10] appears to be $CH_3 > H > F > Cl > Br$.

The similarity in cyclization rates shown by the other four phenyl ketones (I, R′ = H; R = *p*-$XC_6H_4$) should not lead to the conclusion that inductive effects are absent. It is probable that a decrease in the effective positive character of the central carbon atom of the conjugate acid (II) would lead to a lower rate of cyclization of that acid (II → IV).

The dependence of the rate of the over-all reaction (I → IV) upon hydrogen ion concentration[5] makes it clear that this rate depends upon the position of the equilibrium I ⇄ II. It seems probable that an increase in the electron density at the carbonyl group of the ketone (I) must increase the proportion of conjugate acid present at equilibrium,[11] and in this way act to *hasten* the over-all reaction. Since the relative magnitude of these two opposing effects cannot be determined, it is not possible to predict even the direction of the change in rate which would be expected for a given substitution.

The introduction of either a methyl[5] or phenyl group at R′ (R = $C_6H_5$) was found to lead to an increase in rate. In both cases this may be due to an increase in electron density at the *ortho* position at which cylization takes place, although it should be noted that where R′ = $C_6H_5$ there are four such positions with a corresponding increase in the probability of reaction.

(10) Watson, "Modern Theories of Organic Chemistry," Oxford, 1941, pp. 98–103.

(11) F. O. Rice, "The Mechanism of Homogeneous Organic Reactions," The Chemical Catalog Company, Reinhold Publ. Corp., New York, N. Y., 1928, p. 52.

In conclusion, it might be said that, for similar experimental conditions, the rate of cyclization of *o*-benzylphenones depends upon several factors, the most important of which appear to be: (1) the steric nature of R and perhaps also of R′, (2) the position of the equilibrium between ketone and conjugated acid (I ⇄ II), (3) the effective positive character of the central carbon atom of the conjugate acid, (4) the electron density at the *ortho* position of the benzene ring into which cyclization takes place and (5) the number of such positions available.

## Experimental

**Apparatus.**—The constant temperature unit consisted of a large upright metal cylinder insulated with asbestos and provided with a reflux condenser. Attached to the upper plate of the cylinder, and extending downward within it were several heating wells made of metal pipe, about 21 mm. in internal diameter and 29 cm. in length, sealed at the lower end. When *n*-butyl alcohol was refluxed in the cylinder, a constant temperature of 117.5° was maintained in the wells.

The reaction tubes consisted of Pyrex test-tubes of about 18 mm. internal diameter and about 40 ml. capacity. Each had at the upper end, a 24/40 joint provided with two glass hooks and was closed with a glass stopper similarly equipped. The reaction tubes fitted closely in the heating wells which contained mineral oil for more effective transfer of heat.

**Materials.**—The liquid ketones used in the rate studies were carefully fractionated and showed a boiling range of one degree or less. The solid ketones were carefully recrystallized to constant melting point and dried under reduced pressure.

The acid cyclizing medium was prepared as a stock solution by adding 166.4 ml. of 48% hydrobromic acid to 43.6 ml. of distilled water and 700 ml. of glacial acetic acid.

**Cyclization Procedure.**—Into a reaction tube were placed 200–500 mg. of the ketone and 20 or 30 ml.[12] of the stock cyclizing reagent. The time was recorded and the tube heated over a free flame with shaking for about forty-five seconds, during which time the ketone dissolved, and the solution came to a slow boil. The tube was quickly stoppered (secured by means of rubber bands) and inserted into one of the wells of the constant temperature cylinder kept at 117.5°. At the end of an appropriate period,[13] the mixture was cooled, crystallization induced, and the mixture allowed to stand for five hours at approximately 15°. At the end of this period, the crystals were transferred quantitatively to a weighed sintered glass funnel,

(12) The larger volume was used when the more insoluble ketones were being cyclized.

(13) At least four and frequently five or six different time intervals were used for each compound.

washed with 10 ml. of cold water, and dried to constant weight in a vacuum desiccator. The product was weighed and, in each instance, the melting point was determined.

The solubility of each of the anthracene derivatives was determined by putting a weighed quantity through the same procedure used in the cyclization, and determining the dissolved portion by difference. The solubilities varied from 195 mg. (20 ml.) for 9-ethylanthracene to 2 mg. (30 ml.) for 9,10-diphenylanthracene.

**Preparation of Ketones.**—All but three of the ketones employed in this study have been described previously. These three were prepared from *o*-benzylbenzonitrile[9,3] by the action of the following Grignard reagents in the following yields: *p*-fluorophenylmagnesium bromide (77%); *p*-tolylmagnesium bromide (38%); benzylmagnesium chloride (72%). Further details concerning these ketones and the new anthracene derivatives can be found in Table II.

## Summary

The rates of cyclization of ten ketones and one aldehyde have been measured at 117.5°. The data suggest that steric factors as well as electronic effects may play an important part in determining the rate of cyclization.

DURHAM, N. C. RECEIVED NOVEMBER 1, 1948

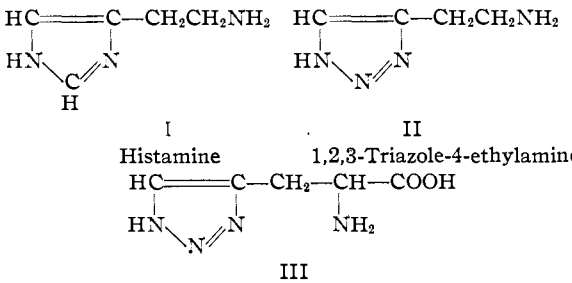
---

[MASSACHUSETTS INSTITUTE OF TECHNOLOGY, DEPARTMENT OF CHEMISTRY]

# The Synthesis of Triazole Analogs of Histamine and Related Compounds

BY JOHN C. SHEEHAN AND CHARLES A. ROBINSON[1]

The concept of metabolite antagonism[2] has proved to be an especially profitable starting point for the synthesis of biologically active compounds. It is generally believed that close structural similarity is desirable in fashioning molecules as possible metabolite antagonists. Many of the powerful known antagonists differ only slightly in structure; for example, riboflavin and chloroflavin, thiamine and pyrithiamine, and adenine and benzimidazole. For this reason it seemed strange that in the case of antagonists to histamine, compounds with close structural similarity have been generally neglected in the wide search for antihistaminics. Since the triazole ring has been shown to be antagonistic to the imidazole ring in the cases of the triazole analogs of adenine and guanine,[3] the triazole analogs of histamine and histidine were synthesized.



I Histamine

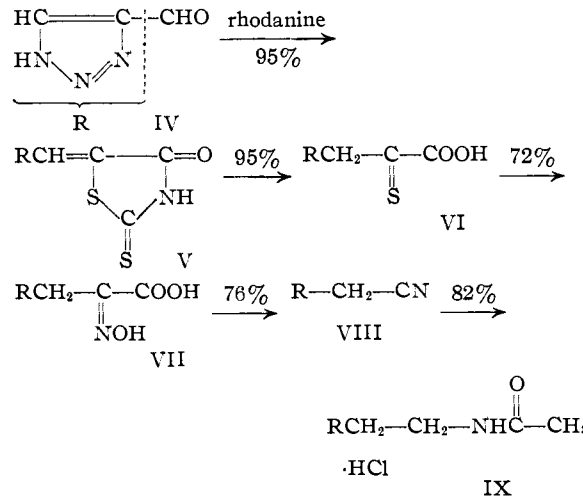
II 1,2,3-Triazole-4-ethylamine

III

α-Amino-1,2,3-triazole-4-propionic acid

The starting compound for the syntheses was 1,2,3-triazole-4-carboxaldehyde (IV), previously prepared by Hüttel[4] from propiolaldehyde and hydrazoic acid. Although the preparation of propiolaldehyde diethyl acetal from acrolein has been reported previously,[5] considerable difficulty was encountered until the modified procedure described in the Experimental Section was used. Extraction of the propiolaldehyde diethyl acetal with chloroform avoids the difficult separation of the azeotrope of this product and ethanol since chloroform does not extract ethanol from the aqueous solution. With this and other improvements a markedly higher over-all yield (50%) was obtained. The diethyl acetal was hydrolyzed and converted into 1,2,3-triazole-4-carboxaldehyde in 50% yield without isolation of the propiolaldehyde.

The synthesis of the nitrile (VIII) was accomplished by the rhodanine method,[6] analogous to the excellent procedure of Julian and Sturgis.[7]



R IV

V

VI

VII

VIII

IX

(1) Bristol Laboratories Fellow, 1947–1948.

(2) For reviews of metabolite antagonism, see R. O. Roblin, Jr., *Chem. Rev.*, **38**, 255 (1946), and D. W. Woolley, "Currents in Biochemical Research," edited by D. E. Green, Interscience Publishers, Inc., New York, N. Y., 1946, p. 357.

(3) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

(4) R. Hüttel, *Ber.*, **74B**, 1680 (1941). Hüttel represented the triazole aldehyde as a 2,1,3-triazole. In order to show its relationship to histamine more clearly, we have chosen to use the tautomeric 1,2,3-triazole structure as in formula IV.

(5) L. Claisen, *Ber.*, **31**, 1010 (1898); **31**, 1021 (1898); **36**, 3664 (1903); **40**, 3907 (1907); F. Reitzenstein and G. Bönitsch, *J. prakt. Chem.*, **86**, 34 (1912); M. Grard, *Ann. chim.*, **13**, 337 (1930).

(6) C. Granacher, *et al.*, *Helv. Chim. Acta*, **5**, 610 (1922); **6**, 458 (1923).

(7) P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).