

FORMATION OF DIHYDRO-s-TETRAZINES BY THE
REACTION OF α -DIAZO KETONES WITH BASES

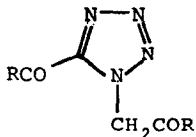
Peter Yates and Otto Meresz

Department of Chemistry

University of Toronto, Toronto 5, Canada

(Received 25 October 1966)

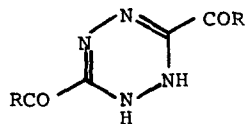
The reaction of 2-diazoacetophenone with potassium t-butoxide in t-butyl alcohol has previously been shown to give 5-benzoyl-2-phenacyltetrazole (I), a dimer of the diazo ketone, as the major product (1). Analogous reactions are observed in the case of 2-diazo-2',4',6'-trimethylacetophenone (II) (2) and 1-diazo-3,3-dimethyl-2-butanone (3), giving III and IV, respectively. However, when the diazo ketone II is treated with concentrated methanolic sodium methoxide at 0° an orange-red dimer* is formed in 60% yield (smaller amounts of this dimer are also obtained from the reaction of II with potassium t-butoxide in t-butyl alcohol).



I, R = C₆H₅

III, R = 2,4,6-(CH₃)₃C₆H₂

IV, R = (CH₃)₃C



V, R = 2,4,6-(CH₃)₃C₆H₂

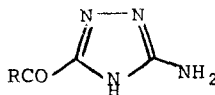
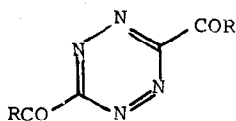
VIII, R = C₆H₅

X, R = p-CH₃OC₆H₄

XII, R = OH

* Satisfactory elemental analytical data have been obtained for all new compounds.

The orange-red dimer, m.p. 280° dec.(evac. cap.), is assigned structure V (or the corresponding 1,4-dihydro-s-tetrazine structure) on the basis of its spectroscopic properties [$\lambda_{\max}(\text{KBr})$ 5.99 μ , $\lambda_{\max}(\text{CH}_3\text{CN})$ 310 μ (ϵ 6,600), 412 μ (ϵ 240)] and its reactions. As a dihydrotetrazine derivative it undergoes characteristically (4) ready oxidation: treatment with activated manganese dioxide gives the s-tetrazine VI (24%), raspberry red needles, m.p. 194° dec.(evac. cap.), $\lambda_{\max}(\text{CHCl}_3)$ 5.87 μ , $\lambda_{\max}(\text{CH}_3\text{CN})$ 305 μ (ϵ 1500), 337 μ (ϵ 1400), 525 μ (ϵ 350), whose structure has been established by independent synthesis (vide infra). Hydrolysis of V with boiling methanolic potassium hydroxide gives 3-amino-5-mesityl-1,2,4-triazole (VII), mesitylformic acid, methyl mesitoate, and 2-mesityl-1-methoxyglyoxal 1-hydrazone; the formation of these products can readily be interpreted in terms of the assigned structure.



VI, R = 2,4,6-(CH₃)₃C₆H₂

VII, R = 2,4,6-(CH₃)₃C₆H₂

IX, R = C₆H₅

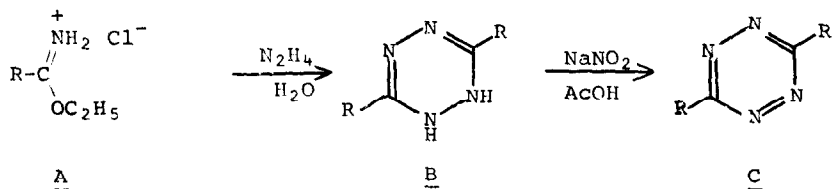
XI, R = p-CH₃OC₆H₄

Treatment of 2-diazoacetophenone with methanolic sodium methoxide gives a complex mixture of products, amongst which VIII, the analog of V, was not detected (1). However, reaction of 2-diazoacetophenone with powdered potassium hydroxide or the methylsulfinyl carbanion in dimethyl sulfoxide gives the dihydrotetrazine VIII in 30% yield. This was obtained as red-brown needles, m.p. 182-183°, $\lambda_{\max}(\text{KBr})$ 3.03, 6.06 μ , and could readily be oxidized with 5 N nitric acid to the tetrazine IX (90%), magenta platelets, m.p. 200-200.5°, $\lambda_{\max}(\text{KBr})$ 5.97 μ , $\lambda_{\max}(\text{CHCl}_3)$ 290 μ (sh, ϵ 15,800), 528 μ (ϵ 423). Both

VIII and IX were identified by their spectra and by independent synthesis (vide infra). Similar treatment of 2-diazo-4'-methoxyacetophenone with potassium hydroxide gives X (28%), as a brown microcrystalline powder, m.p. 262-262.5° dec., $\lambda_{\max}(\text{KBr})$ 3.00, 6.06 μ , which on oxidation gives XI, deep red platelets, m.p. 178-179° dec., $\lambda_{\max}(\text{KBr})$ 6.02 μ , $\lambda_{\max}(\text{CHCl}_3)$, 310 $m\mu$ (ϵ 30,000), 529 $m\mu$ (ϵ 400).

The formation of the dihydrotetrazines V, VIII and X, by the action of bases on α -diazo ketones is analogous to the formation of the dihydrotetrazinedicarboxylic acid XII by the action of potassium hydroxide on diazoacetic esters, which has long been known (5). However, the formation of dihydrotetrazine derivatives from diazo ketones has not previously been observed, nor, indeed, does there appear to have been a previous report of the preparation of a C-acyldihydro-s-tetrazine by any route.

In order to develop a practicable method for the independent synthesis of the tetrazines VI, IX, and XI, we have modified the general method of Pinner (6): imino ether hydrochlorides (A) were treated with 85% hydrazine hydrate for 12 hours at 20-30° and the resulting dihydrotetrazines (B), which separated, were oxidized to the tetrazines (C) with sodium nitrite in aqueous acetic acid. The results, shown in Table



1, were gratifying in that s-tetrazines have usually been prepared previously in only very poor or undisclosed yields (4) [Pinner (7) failed to obtain the tetrazine XVI, of prime interest in the present investigation].

Oxidation of the diols XVI, XVII, and XVIII with dimethyl sulfoxide and acetic anhydride (vol. ratio 1:1) at room temperature for 3 days gave the diaroylettrazines IX(60%), XI(59%), and VI(72%), respectively. Reduction of IX with aqueous sodium bisulfite in acetic acid gave the dihydrotetrazine VIII(70%). The identity of these products with those obtained from the diazo ketones was established by spectroscopic comparisons and mixture melting point determinations.

TABLE 1

Synthesis of Tetrazines (C) from
Imino Ether Hydrochlorides (A)

Compound <u>C</u>	M.p.	Yield(%) ¹
XIII, R = C ₆ H ₅	191-192° [lit.(6) 192°]	84
XIV, R = C ₆ H ₅ CH ₂	71.5-72° [lit.(6) 74°]	66
XV, R = p-CH ₃ OC ₆ H ₅	244-245°	81
XVI, R = C ₆ H ₅ CHOH ²	174-175.5°	78
XVII, R = p-CH ₃ OC ₆ H ₄ CHOH ²	206-207°	72
XVIII, R = 2,4,6-(CH ₃) ₃ C ₆ H ₂ CHOH ²	228-229°	6

¹Overall yields from A; in the case of XV and XVI the intermediates (B) were isolated in yields of 87 and 97%, respectively ²These products consist of mixtures of diastereomers, formed in the yields quoted; the m.p.'s are those of samples obtained by fractional crystallization, which appear to be single diastereomers

Acknowledgment is made to the National Research Council of Canada, and to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

REFERENCES

1. P. Yates and D. G. Farnum, Tetrahedron Letters, No. 17, .
22 (1960).
2. H. A. Morrison, Ph.D. Thesis, Harvard University
3. P. Yates and A. G. Crowther, unpublished results.
4. J. G. Erickson, P. F. Wiley, and V. P. Wystrach,
"The 1,2,3- and 1,2,4-Triazines, Tetrazines and
Pentazines," in "The Chemistry of Heterocyclic Compounds,"
A. Weissberger, ed., Interscience Publishers, Inc.,
New York, 1956, p. 179.
5. T. Curtius, A. Darapsky, and E. Muller, Ber. 41, 3161
(1908).
6. A. Pinner, Ann. 297, 221 (1897); A. Pinner, C. Goebel,
J. Colman, A. Salomon, and F. Gradenwitz, Ann., 298,
1 (1897).
7. A. Pinner, Ber. 30, 1871 (1897).