ATP at zero time and that isolated from the control sample.

A solution of PRPP, containing 1.45 μmoles of enzymatically active material was heated at 65° in 0.1 *M* acetate buffer, *p*H 4.0. After 10 and 40 minutes, respectively, 0.51 and 0.00 μmole of enzymatically active PRPP remained; 0.96 and 1.73 μmoles of reducing substance (referred to ribose) appeared. In another experiment involving a 30 min. heating period, the removal of 1.13 μmoles of PRPP was matched by the formation of 1.07 μmoles of reducing substance and 0.99 μmole of PP (determined by ion-exchange analysis); 0.30 μmole of inorganic orthophosphate was also produced.

These observations taken together with evidence, to be presented later, for the quantitative conversion of PRPP to A5P (equation (2)) or to U5P (equation (3)) lead us to propose a provisional structure of 5-phosphoribosylpyrophosphate for the activated ribose compound.

ADP did not replace ATP in equation (1) and ribose-1-phosphate (R1P) reacted at only 11% of the rate observed with R5P; this reactivity of R1P is likely due to its conversion to R5P by phosphoribomutase activity in the enzyme preparation. A sample presumed to contain ribose-1,5-diphosphate,[3] derived from glucose-1,6-diphosphate[4] and R1P by the action of phosphoglucomutase[5] and glucose-6-phosphate dehydrogenase, was inactive in place of PRPP in equation (3).

It is evident that PRPP may also prove to be the intermediate involved in the synthesis of ribotides of acylic purine precursors,[6] nicotinamide[7] and other nitrogenous compounds, and in the system for A5P synthesis described by Saffran and Scarano.[8] There is the further possibility that a 2-deoxyPRPP will prove to be the active condensing agent in the biosynthesis of deoxynucleotides.

(3) H. Klenow, *Arch. Biochem.*, **46**, 186 (1953).
(4) Kindly furnished by Dr. L. F. Leloir.
(5) Kindly furnished by Dr. D. H. Brown.
(6) G. R. Greenberg, *J. Biol. Chem.*, **190**, 611 (1951); W. J. Williams and J. M. Buchanan, *ibid.*, **203**, 583 (1953).
(7) I. G. Leder and P. Handler, *ibid.*, **189**, 889 (1951).
(8) M. Saffran and E. Scarano, *Nature*, **174**, 949 (1953).

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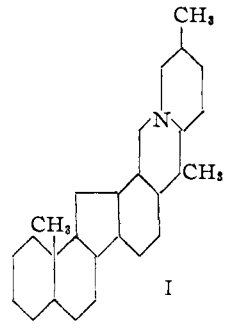
RECEIVED MARCH 5, 1954

THE VERATRINE ALKALOIDS. XXXVIII. THE RING SYSTEM OF THE TERTIARY POLYHYDROXY VERATRINE BASES. OXIDATIVE STUDIES WITH CEVANTHRIDINE AND VERANTHRIDINE

Sir:

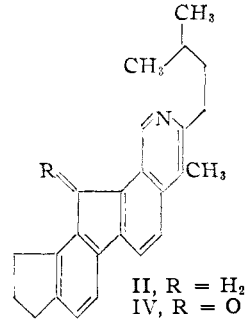
In a recent paper, a ring system (I) was suggested for veracevine,[1] cevine, germine and protoverine which was based on the chemical behavior and absorption spectra of several selenium dehydrogenation products of cevine.[2] The two largest basic fragments, cevanthridine,[3] $C_{25}H_{27}N$, and a



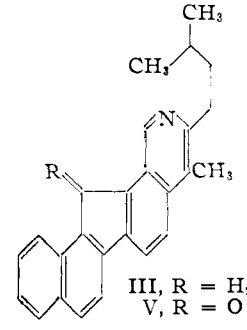
I

$C_{26}H_{25}N$ base[4] now named *veranthridine* were formulated as 1,2-cyclopentenofluorene and 1,2-benzofluorene derivatives, respectively, (II) and (III). We now wish to report a series of experiments with these degradation products which lend support to our earlier conclusions.

Oxidation of cevanthridine (II) with chromium trioxide in acetic acid (75°, ten minutes) gave a complex mixture from which a ketobase (IV) (titrates against perchloric acid in acetic acid) was separated by chromatography over alumina. Crystallization from chloroform gave brilliant reddish-orange needles, m.p. 253–255° cor. Calcd. for $C_{25}H_{25}NO$: C, 84.47; H, 7.09. Found: C, 84.47; H, 7.12. ($\lambda_{max.}$: 277 mμ, log ε 4.90; 366 mμ, log ε 4.15 (EtOH). IV was also formed in almost quantitative yield by simply shaking a solution of II in hot ethanolic sodium ethoxide in air. Huang-Minlon reduction of IV regenerated cevanthridine, m.p. 211.5–213.5° cor., undepressed when admixed with an authentic specimen. Calcd. for $C_{25}H_{27}N$: C, 87.93; H, 7.97. Found: C, 87.91; H, 7.83. The ultraviolet spectrum was indistinguishable from that of authentic cevanthridine. A similar oxidation of veranthridine (III) proceeded smoothly to give a good yield of the corresponding ketobase



II, R = H_2
IV, R = O



III, R = H_2
V, R = O

(V) (titrates against perchloric acid in acetic acid), reddish-orange needles, m.p. 267–270° cor. Calcd. for $C_{26}H_{23}NO$: C, 85.45; H, 6.34. Found: C, 85.66; H, 6.34 ($\lambda_{max.}$ 265 mμ, log ε 4.60; 302 mμ, log ε 4.89; 342 mμ, log ε 4.08). This same substance was also isolated from the basic fraction of the selenium dehydrogenation mixture from cevine by chromatography over alumina; m.p. 266–269°. Calcd. for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83. Found: C, 85.37, 85.41; H, 6.37, 6.21; N, 3.82. The ultraviolet spectrum was identical with that of V prepared by chromic acid oxidation. The occurrence of V among the dehydrogenation products of cevine is due presumably to its ready formation

(1) S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **75**, 3248 (1953); S. M. Kupchan and D. Lavie, *ibid.*, **76**, 314 (1954).
(2) W. A. Jacobs and S. W. Pelletier, *J. Org. Chem.*, **18**, 765 (1953).
(3) B. K. Blount, *J. Chem. Soc.*, 122 (1935); 414 (1936); L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **139**, 293 (1941).
(4) L. C. Craig and W. A. Jacobs, *ibid.*, **139**, 263 (1941).

by air oxidation of III and provides a clue to the nature of veranthridine itself (*vide infra*). Huang-Minlon reduction of V regenerated veranthridine, m.p. 228–230°; mixed m.p. undepressed; ultraviolet spectrum identical with that of authentic III.

The facile oxidation of both cevanthridine and veranthridine under mild conditions to colored ketobases and the smooth reduction of the latter to the parent bases by the very specific method employed indicates that these red ketones are fluorenones and hence that cevanthridine and veranthridine are fluorene derivatives.[5] These results support our earlier conclusion that the nonnitrogenous portion of cevine (and the related polyhydroxy tertiary bases) *does not possess a normal steroid skeleton, but rather has the C-nor/D homo-steroid type of structure* which has been adopted for jervine and veratramine by Wintersteiner, *et al.*[6]

(5) *Cf.* the ease of oxidizing fluorene to fluorenone and of regenerating fluorene by the Wolff–Kishner reduction.

(6) For leading references see O. Wintersteiner and M. Moore, THIS JOURNAL, **75**, 4938 (1953).

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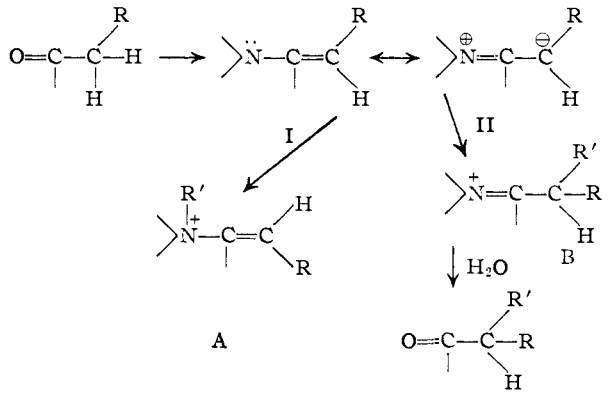
A NEW SYNTHESIS OF 2-ALKYL AND 2-ACYL KETONES

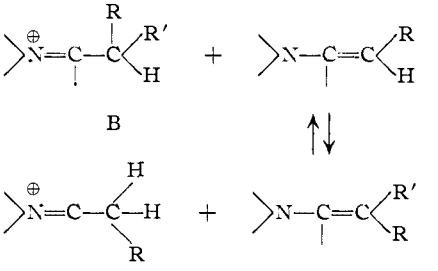
Sir:

We have discovered a new method for the alkylation and acylation of ketones. The condensation products of ketones and secondary amines are well known.[1,2] It is evident that these substances can undergo reaction with proper electron acceptors either at N or C according to path I or II:



We have found that the synthetically important path II is followed in a number of instances.[3] The pyrrolidine enamine from cyclohexanone reacts with methyl iodide in boiling methanol to yield a quaternary salt of type B, which is decomposed by water to produce about 70% of 2-methylcyclohexanone. Similar alkylation with benzyl chloride produces 2-benzylcyclohexanone. Functional groups may be present in the halide: *Ethyl bromoacetate leads to ethyl 2-oxo-cyclohexaneacetate in good yield.* It may be noted that the conventional synthesis of the latter compound requires five steps from cyclohexanone. The mildness of this new reaction lends itself to the alkylation of substances containing alkoxide labile groups: 4-hydroxycyclohexanone benzoate gives 2-methyl-4-hydroxycyclohexanone benzoate without loss of the benzoyl group in addition to the N-methiodide of the starting enamine (path I), isolated in 11% yield. The reaction may also be of interest, conversely, in cases where the halide contains base sensitive functions. The new reaction is not limited to alkyl halides: Acrylonitrile heated with the pyrrolidine enamine of cyclohexanone in dioxane solution *gives an 80% yield of 2-cyanoethylcyclohexanone,* a substance which is only obtained with difficulty by other methods. Methyl vinyl ketone gives directly, after treatment of the intermediate with water, $\Delta^{1,9}$-2-octalone in about 30–40% yield. Treatment of the enamine from cyclohexanone with benzoyl chloride gives 2-benzoylcyclohexanone and with ethyl chlorocarbonate in dioxane solution 2-carbethoxycyclohexanone is obtained.[4]

The monoalkylation obtained with alkyl halides is clearly the result of the much lower reactivity of the alkylated enamines since the salts of type B can produce alkylatable enamines by loss of a proton to the parent enamine



In agreement with this view, we have found that the pyrrolidine enamine from 2-methylcyclohexanone gives mostly recovered starting material under the conditions used with cyclohexanone itself.

This low reactivity of the fully substituted enamines is useful in certain cases, *e.g.*, the monomethylation of β-tetralones which is usually very difficult to achieve by direct methylation: Here again the reaction is easily applied in the presence of base sensitive groups: 5-phthalimido-2-tetralone produces the 1-methyl derivative in about 50–60% yield without interference from the imide function.[5]

The specially interesting case of the enamines

(1) C. Mannich and H. Davidson, *Ber.*, **69**, 2106 (1936).

(2) An especially convenient synthetic method has recently been described by F. E. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953).

(3) In a formal sense an electronic archetype for these reactions may well be the transformation of 1,3,3-trimethyl-2-methyleneindoline into 1,3,3-trimethyl-2-isopropylidene indoline on treatment with methyl iodide (C. Zatti and A. Ferratini, *Ber.*, **23**, 2302 (1890); G. Plancher, *ibid.*, **31**, 1488 (1898)).

(4) For a theoretically related reaction in the ketene acetal series see S. M. McElvain and R. V. Mullineaux, THIS JOURNAL, **74**, 1811 (1952).

(5) In this special case, the reaction recalls the monoalkylation of acetoacetic ester which may be effected with sufficiently reactive alkyl halides *via* dialkylaminocrotonic ester: R. Robinson, *J. Chem. Soc.*, **109**, 1038 (1916); W. M. Lauer and G. W. Lones, THIS JOURNAL, **59**, 232 (1937); G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3052 (1953).