and the resin was washed three times with dimethylformamide (20 ml). The combined filtrates were reduced under vacuum to approximately 50 ml and then ethyl acetate (400 ml) was added. The solution was left in the refrigerator for a few hours, then it was centrifuged. The resulting precipitate was washed with ethyl acetate and methanol (centrifuging after each wash) and finally it was suspended in ether (100 ml) and filtered. The precipitate was dried to give the protected nonapeptide (1.8 g) with m.p. = 234–238 °C $[\alpha]_D = -45$ ($c = 2$, dimethylformamide).

Purification of Oxytocin

The nonapeptide (0.5 g) was subjected to reduction with sodium and liquid ammonia, followed by oxidation at pH 7 (9) and the solution was freeze-dried. The product (0.6 g) was dissolved in 0.2 *N* acetic acid (10 ml) and was filtered through a Sephadex G.25 column, equilibrated with 0.2 *N* acetic acid and, using the same solvent as eluent, 5 ml fractions were collected and 0.1 ml samples used for the Folin–Lowry test. One major and several minor peptide peaks were observed. The contents of the tubes making up the fractions containing the major peak were lyophilized to give 0.4 g of white powder.

A Sephadex G.25 column was equilibrated with the aqueous phase of a mixture of 3.5% acetic acid (containing 1.5% pyridine): 1-butanol: benzene (2:1:1) and then the organic phase was run through. A solution of the partially purified oxytocin (100 mg) in the aqueous phase (2 ml) was added to the column, and then eluted with the organic phase. The fractions containing the major peptide peak (as determined by the Folin–Lowry reaction) were combined, diluted with twice their volume of water, and evaporated to a small volume. The solution was then freeze-dried to give a white powder (20 mg) having an activity of 508 u/mg.

Acknowledgments

The author would like to thank Dr. A. L. Tosoni for his interest and encouragement, and the Quality Control Department of the Connaught Laboratories for the biological assays.

Note added in proof—The author notes that M. Manning of McGill University has independently achieved the synthesis of oxytocin using the solid phase technique and has published the results in J. Am. Chem. Soc. **90**, 1348 (1968). (See also Takashima, du Vigneaud and Merrifield, J. Am. Chem. Soc. **90**, 1323 (1968) for the synthesis of deamino oxytocin.)

1. R. B. MERRIFIELD. J. Am. Chem. Soc. **85**, 2149 (1963).
2. R. B. MERRIFIELD. J. Am. Chem. Soc. **86**, 304 (1964).
3. M. BODANSZKY and J. T. SHEENAN. Chem. and Ind. 1597 (1966).
4. A. MARGLIN and R. B. MERRIFIELD. J. Am. Chem. Soc. **88**, 5051 (1966).
5. L. ZERVAS, D. BOROVAS, and E. GAZIS. J. Am. Chem. Soc. **85**, 3660 (1963).
6. D. F. ELLIOT and D. W. RUSSEL. Biochem. J. **66**, 49*P* (1957).
7. V. A. NAJJAR and R. B. MERRIFIELD. Biochemistry, **5**, 3765 (1966).
8. V. DU VIGNEAUD, C. RESSLER, J. M. SWAN. C. W. ROBERTS, P. G. KATSOYANNIS, and S. GORDON. J. Am. Chem. Soc. **75**, 4879 (1953).
9. V. DU VIGNEAUD and M. BODANSZKY. J. Am. Chem. Soc. **81**, 5688 (1959).
10. D. YAMASHIRO. Nature, 201, **76**, (1964).
11. M. H. HUBACHER. Org. Syntheses. Coll. Vol. II. John Wiley & Sons, Inc., New York. 1943. p. 455.

Synthesis of 5-methyl-8-hydroxy-1-tetralone

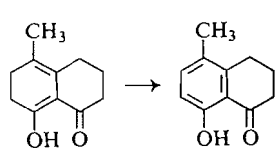
JOSEPH P. JOHN, R. K. NATARAJAN, S. SWAMINATHAN, AND P. S. VENKATARAMANI
Department of Organic Chemistry, University of Madras, Madras 25, India

Received September 19, 1967

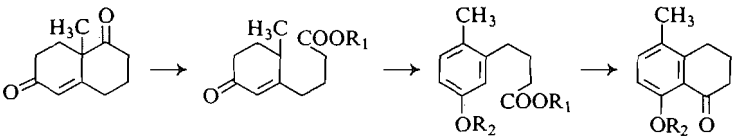
The tetralone **2***a* has been obtained in 45% overall conversion from the dione **3** by the sequence **3** → **4***a* → **4***b* → **5***b* → **5***a* → **2***a*.

Canadian Journal of Chemistry, 46, 2320 (1968)

The title compound (**2***a*) has been reported (1) as a liquid obtained in low yields by prolonged reflux of the enol ketone (**1**) in xylene. We have obtained it as a crystalline solid, m.p. 47–48.5 °C by the following method, which has been studied previously by Newman and Mekler (2).



1 **2***a*



3 4*a*, $R_1 = H$; 4*b*, $R_1 = CH_3$; 5*a*, $R_1 = H$; $R_2 = H$; 5*b*, $R_1 = CH_3$; $R_2 = H$; 5*c*, $R_1 = CH_3$; $R_2 = —Ac$; 5*d*, $R_1 = H$; $R_2 = —Ac$; 2*a*, $R_2 = H$; 2*b*, $R_2 = —Ac$

The above authors obtained the acetate ester (**5***c*) from the dione (**3**) by a sequence of steps involving cleavage of **3** to the acid (**4***a*), esterification, enol acetylation of **4***b*, bromination and dehydrobromination. We have obtained the desired acid (**5***a*) by saponification of the ester (**5***c*) but the overall yields were unsatisfactory. We find now that the ester (**4***b*) can be catalytically dehydrogenated to the phenolic ester (**5***b*) directly and then saponified to give 50% overall yield of **5***a* based on **3**. Several reagents were tried to effect the cyclization of the acid (**5***a*), and polyphosphoric acid proved singularly effective giving 85–90% yield of the tetralone (**2***a*) which had the expected spectral absorptions. The structure of **2***a* was also confirmed by a Wolff–Kishner reduction to the known 4-methyl-ar-1-tetralol (3). This gave excellent yields.

Experimental

γ-(3-Keto-6-methyl-1-cyclohexen-1-yl)butyric Acid (4a)

The following procedure for cleavage of the dione (**3**) to the acid (**4***a*) proved superior to the one described in the literature (2).

The dione (**3**) (40 g) (4) was mixed with a saturated solution of barium hydroxide (1500 ml) in an atmosphere of nitrogen, the mixture was kept overnight and then extracted with ether to remove any unreacted dione. The aqueous solution was acidified and extracted with ether. After usual work-up, an oil was obtained which soon solidified. It was triturated with ether and collected; yield, 40–41 g; m.p. 78–79 °C. (ether – petroleum ether).

The crude acid was converted to the methyl ester (**4***a*) as described in ref. 2.

Methyl-γ-(2-methyl-5-hydroxyphenyl) butyrate (5b)

The ester (**4***a*) (15g) was heated at 280–300 °C with a 10% Pd/C catalyst (1g) for 1h. After usual work-up, 11 g (94%) of the phenolic ester (**5***b*) was obtained; m.p. 80–81 °C (petroleum ether) and undepressed by a sample prepared according to Newman and Mekler (2). Below 280 °C, the above dehydrogenation was incomplete and gave a mixture **4***a* and **5***b*.

γ-(2-Methyl-5-hydroxyphenyl)butyric Acid (5a)

The ester (**5***b*) (30g) was saponified with 5% aqueous sodium hydroxide and after usual work-up yielded 22 g (50% yield based on the dione **3**) of crude acid (**5***a*), m.p. 90–93 °C. The analytical sample prepared by four crystallizations from ether – petroleum ether had m.p. 99–100 °C. λ_{max} ($CHCl_3$) 2.75 and 5.85 μ; λ_{max} (EtOH) 279 mμ (log ε 3.4).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 67.9; H, 7.4.

The same acid could be obtained by saponification of the ester (**5***c*) (2) but only in 30% yield based on the dione (**3**).

γ-(2-Methyl-5-acetoxyphenyl)butyric Acid (5d)

This was obtained in 60% yield by treatment of **5***a* with acetic anhydride and *p*-toluenesulfonic acid; m.p. 60–61.5 °C (petroleum ether); λ_{max} (EtOH) 216, 266, and 273 mμ (log ε 3.66, 2.70, 2.70); λ_{max} ($CHCl_3$) 5.71 and 5.85 μ nuclear magnetic resonance (CCl_4): τ −1.67 (s, —COOH), τ 7.73 and 7.8 (s, ar—CH_3 and —$OCOCH_3$) τ 2.92–3.33 (m, 3 aromatic protons) τ 7.37 to 7.63 (t, Ar—CH_2).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8. Found: C, 66.3; H, 6.9

The acetoxy acid (**5***d*) furnished a liquid acid chloride which was characterized as the amide m.p. 117–118 °C (ethylacetate). λ_{max} (KBr) 2.975, 3.125, 6.025, and 6.25μ.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.4; H, 7.8. Found: C, 68.3; H, 8.0.

5-Methyl-8-hydroxy-1-tetralone (2a)

A mixture of phosphorus pentoxide (30 g) and phosphoric acid (30 ml) was heated on a steam bath for 2 h. The acid (**5***a*) (8 g) was added and the resulting mixture was heated for an additional 1 h and poured onto crushed ice. The yellow product was collected, dried, and crystallized from petroleum ether after treatment with decolorizing charcoal. This method yielded 6.2 g (86%) of the tetralone **2***a* as pale-yellow needles; m.p. 45–47 °C. An analytically pure sample prepared by three more crystallizations had m.p. 47–48.5 °C; λ_{max} ($CHCl_3$) 6.15 (hydrogen bonded C=O) and 6.25μ (aromatic) and no absorption for —OH due to hydrogen bonding. λ_{max} (EtOH) 262, 345 mμ (log ε 4.0, 3.5) [cf.: with absorptions of 8-hydroxy-1-tetralone (5)] nuclear magnetic resonance ($CDCl_3$): τ – 2.4 (s, —OH), τ 2.70 and 3.25 (d, 2 adjacent aromatic protons), τ 7.1–7.5 (m, 2 benzylic protons and 2 protons α to carbonyl) τ 7.8 (s, Ar—CH_3) and τ 7.92 (m, 2 protons β to carbonyl).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 74.9; H, 7.2

The 2,4-dinitrophenylhydrazone had m.p. 285–286 °C (EtOAC—$CHCl_3$).

Anal. Calcd. for $C_{17}H_{16}N_4O_5$: C, 57.3; H, 4.5. Found: C, 57.0; H, 4.2.

The tetralone (**2***a*) furnished 5-methyl-8-acetoxy-1-tetralone (**2***b*) on treatment with acetic anhydride and *p*-toluenesulfonic acid; m.p. 121.4–122.4 °C (benzene–petroleum ether); λ_{max} ($CHCl_3$) 5.70 (—OAC), 5.975 (ketone C=O), 6.3 (aromatic), and 6.85 μ.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5. Found: C, 71.8; H, 6.7.

Acknowledgments

The authors wish to thank Mr. R. Balasubramanian for analysis and infrared spectra and Dr. T. R. Govindachari for providing the nuclear magnetic resonance spectra. R. K. Natarajan is grateful to the Council of Scientific and Industrial Research, New Delhi for financial support. J. P. John and P. S. Venkataramani thank the University Grants Commission, New Delhi for the award of fellowships.

1. M. S. NEWMAN and A. B. MEKLER. J. Am. Chem. Soc. **82**, 4039 (1960).
2. M. S. NEWMAN and A. B. MEKLER. J. Org. Chem. **26**, 336 (1961).
3. R. B. WOODWARD and T. SINGH. J. Am. Chem. Soc. **72**, 500 (1950).
4. M. S. NEWMAN and S. RAMACHANDRAN. Org. Syntheses, **41**, 38 (1961).
5. F. A. HOCHSTEIN, C. R. STEPHENS, L. H. CANOVER, P. R. REGNA, R. PASTERNACK, P. N. GORDON, F. J. PILGRIM, K. J. BRUNINGS, and R. B. WOODWARD, J. Am. Chem. Soc. **75**, 5455 (1953).

Oxidative fragmentation of 3-pyrazolidinones to olefins

R. H. KENT AND J.-P. ANSELME[1]

Department of Chemistry, University of Massachusetts, Boston, Massachusetts 02116

Received January 22, 1968

The oxidation of 5-aryl-3-pyrazolidinones with mercuric oxide to the corresponding olefins is reported. Diethyl azodicarboxylate also converts 4,5-diphenyl-3-pyrazolidinone to *trans*-stilbene. The fragmentation of the intermediate cyclic α-carbonyl azo compounds is suggested to account for the observed products.

Canadian Journal of Chemistry, **46**, 2322 (1968)

The chemistry of l-pyrazolines has been the subject of increased investigation over the last few years (1). As part of our own interest in this general area, we have examined the oxidation of 3-pyrazolidinones (**1**) and we should like to report briefly our initial results.

When 5-phenyl-3-pyrazolidinone (**1**, Ar = C_6H_5, R = H) was oxidized with yellow mercuric oxide, the grayish color of mercury was observed along with vigorous evolution of gas. After removal of mercury and evaporation of the solvent, a thick greenish oil, having the odor of styrene, was obtained. Bromination of this oil gave a 42% yield of styrene dibromide, m.p. 71–73 °C. The oxidation of 4,5-diaryl-3-pyrazolidinones (**1**, R = Ar) gave the corresponding *trans*-stilbenes (**3**, R = Ar) in fair to good yields (see Table I). No attempts were made to obtain the highest possible yields.

In a recent review (2), Fahr and Lind have emphasized the extreme instability of cyclic α-carbonyl azo compounds. We believe that the initial step in our reaction is the oxidation of the 3-pyrazolidinones (**1**) to the corresponding α-carbonyl azo compounds (**2**). These highly reactive intermediates then undergo fragmentation (3) with the loss of carbon monoxide and nitrogen to give the olefins.[2] The formation of metallic mercury and a positive carbon monoxide test from the evolved gases, lend support to this view.

A related fragmentation has been previously observed by Rosenblum and his students (4). They reported the formation of *trans*-stilbene and tolan, from the oxidation of 5,6-diphenyltetrahydroöxadiazinone (**4**) and 5,6-diphenyl-1,2-dihydroöxadiazinone (**5**) with lead tetraacetate.

Presumably, similar azo compounds were formed and underwent fragmentation with loss of carbon dioxide and nitrogen. Although the

[1]To whom all correspondence should be addressed.

[2]Approximately nine months after our initial discovery of the oxidation of 3-pyrazolidinones with mercuric oxide, the lead tetraacetate oxidation of 4,5-diphenyl-3-pyrazolidinone to *trans*-stilbene was reported (12).