TABLE I

CARBOXYLATION OF *N*-WOOD ROSIN AND OLEIC ACID[a]

| Olefin | Weight, g. | $CH_3OH$, g. | $[Co(CO_4)]_2$, g. | Time, hr. | Wt. of Product, g. | Acid No. | Sapon. No. | Iodine No. | Conversion to Dibasic Esters, % |
|---|---|---|---|---|---|---|---|---|---|
| *N*-Wood rosin | Starting material | | | ... | ... | 167 | 172 | ... | ... |
| *N*-Wood rosin | 250 | 230 | 10 | 11.3 | 265 | 36 | 214 | ... | 60.5 |
| *N*-Wood rosin | 250 | 200 | 27 | 10.0 | 265 | 43 | 210 | ... | 56.0 |
| Oleic acid | 250 | 418 | 32 | 3.0 | 280 | 6 | 260 | Nil | 68.8 |
| Oleic acid | 200 | 400 | 29 | 1.0 | 261 | 17 | 276 | Nil | 79.3 |
| Oleic acid | Starting material | | | ... | ... | 199 | 200 | 90 | ... |

[a] Reactions were carried out at 220° and 6000 p.s.i.g. of CO.

and the aromatic dehydroabietic acid, as well as some of the neutrals, are, of course, unable to undergo reaction. Thus, a maximum conversion of about 75% can be expected. This is a second example of the preparation of difunctional derivatives from rosin using carbon monoxide.

The reaction of rosin with carbon monoxide and methanol is much slower than that with carbon monoxide and hydrogen (oxo reaction), taking about 10 hr. vs. 1 to 2 hr. for oxo reaction. The temperature of 220° was found to be optimum. At higher temperatures decomposition of the product occurred. Highest conversions were obtained using solid dicobalt octacarbonyl as the catalyst.

Under conditions similar to those for rosin, freshly distilled oleic acid (Darling and Company) reacts readily to give the methyl esters of dibasic acids in 60 to 80% yields. The reaction rate is much faster for oleic acid than for rosin (1 hour *vs.* 10 hr.). The remaining 20% of the product is probably methyl stearate since it contains no residual unsaturation or new functional groups, such as hydroxyl or carbonyl.

## EXPERIMENTAL

Some examples of typical experiments are shown in Table I. The experiments were all carried out as follows:

A 1000-ml. stainless steel pressure vessel was charged with 250 g. of *N*-wood rosin (Hercules Powder Company), 200 g. of absolute methanol (Merck and Company), and 27 g. of dicobalt octacarbonyl.[6] The pressure was raised to 2000 p.s.i.g. of carbon monoxide and the autoclave was heated to 220°. The pressure was maintained at 6000 to 5000 p.s.i.g. during the reaction. After no more gas was absorbed, the reactor was cooled, vented, and the product removed.

The catalyst was removed by diluting the product with ether and extracting the ether solution with 6*N* hydrochloric acid. The cobalt-free solution was washed until neutral, dried, and the solvent removed by distillation. The total product was analyzed for acid and ester in the usual manner.

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(6) I Wender, H. Greenfield, and M. Orchin, *J. Am. Chem. Soc.*, **73**, 2656 (1951).

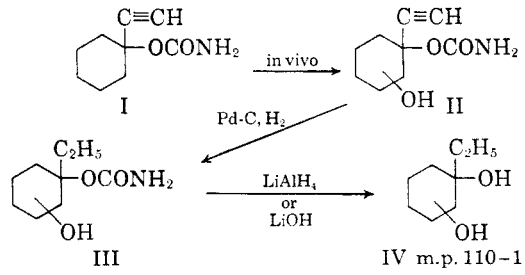
## *In Vivo* Hydroxylation of 1-Ethynylcyclohexyl Carbamate,[1] II. The Orientation of Hydroxylation

ROBERT E. MCMAHON

*Received July 9, 1959*

The human urinary metabolite of 1-ethynylcyclohexyl carbamate (I) has been shown to be 1-ethynyl-4-hydroxycyclohexyl carbamate by transformation to one of the isomers of 1-ethylcyclohexane-1,4-diol. The preparation and properties of the isomeric 1-ethynylcyclohexane-1,4-diols and 1-ethylcyclohexane-1,4-diols are reported.

In an earlier report[2] the metabolism of the central nervous system depressant, ethinamate [1-ethynylcyclohexyl carbamate, (I)], was described. In that study the major human metabolite was isolated in pure form and shown to be hydroxyethinamate (II). However, the ring position of the hydroxyl group in the metabolite was not established. Although biological hydroxylation at a saturated carbon atom in a carbocyclic ring is well known in the steroid field, the present case represents the first reported instance of enzymatic hydroxylation of a simple cyclohexane derivative.




For this reason, it was of importance to establish the position of hydroxylation. The proof of structure is described in this paper.

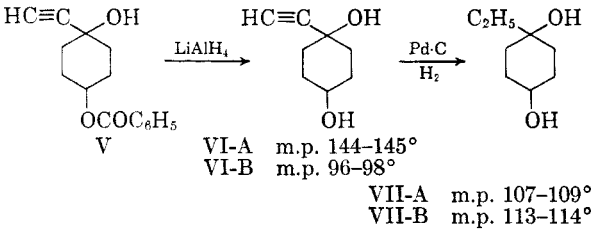
Direct conversion of II to the corresponding 1-ethynylcyclohexanediol by hydrolytic procedures

(1) Eli Lilly and Company Trademark, VALMID®, ethinamate, Lilly.

(2) R. E. McMahon, *J. Am. Chem. Soc.*, **80**, 411 (1958).

failed to produce a pure, isolable product. However, after catalytic reduction of the metabolite to its saturated analog (III), the carbamate grouping was easily removable. Degradation of III either by warming with aqueous lithium hydroxide or by refluxing with lithium aluminum hydride in benzene yielded the diol (IV). This diol was a white crystalline product, m.p. 110–112°, which was easily purified by vacuum sublimation at 65°. The infrared spectrum was quite consistent with the expected structure, *i.e.* a 1-ethylcyclohexanediol (IV).

The position of the second hydroxyl group in IV was established by synthesis. Since II had been found to be optically inactive,[2] it was tentatively assumed that hydroxylation had occurred in the four position. Synthetic efforts were therefore undertaken in this direction. The preparation of the pure *cis* and *trans* isomers of 1-ethylcyclohexane-1,4-diol (VII) was achieved through synthesis of the corresponding 1-ethylnylcyclohexyl-1,4-diols (VI).




Jones and Sondheimer[3] have reported the preparation of 1-ethynyl-4-benzoyloxycyclohexanol (V) and its conversion to 1-ethynylcyclohexane-1,4-diol (VI). However, both of these materials were a mixture of the *cis* and *trans* isomers and were not separated. In the present work V was prepared by the method of Jones[3] and was converted to a mixture of the diols (VI-A and VI-B) by reduction with lithium aluminum hydride. The mixture so obtained was then separated into the pure isomers. One isomer (VI-A, m.p. 144–145°) was obtained directly by crystallization from benzene solution. Chromatography of the mother liquors on alumina yielded the second isomer (VI-B, m.p. 96–98°) by elution with a 4:1 benzene-ether mixture. By elution with a more polar solvent (99:1 ether-methanol) more of isomer A was obtained. The ratio in yields of isomer A to isomer B was about 4:1. The relative geometrical configuration of VI-A and of VI-B have not as yet been established.[4]

The desired 1-ethylcyclohexane-1,4-diols (VII-A and VII-B) were obtained readily from the acetylenic analogs by catalytic hydrogenation. Reduction of VI-A yielded the corresponding saturated diol VII-A, m.p. 107–109°, while VI-B yielded VII-B, m.p. 113–114°.

By a comparison of physical properties, the ethylcyclohexanediol (IV), obtained through transformation of the human metabolite (II), was shown to be identical with VII-B, the higher melting isomer of 1-ethylcyclohexane-1,4-diol. The metabolite II is thus shown to be 1-ethynyl-4-hydroxycyclohexyl carbamate. In this simple case, therefore, enzymatic hydroxylation has occurred at the position in the ring furthest removed from steric interference. These results have led to a study of the effect of ring substitution upon the pharmacological properties of ethinamate analogs.

*Acknowledgment.* The author is grateful to Warren Miller for valuable technical assistance and to Ann Van Camp and Donald Woolf for physical data.

## EXPERIMENTAL[5]

*1-Ethynylcyclohexane-1,4-diols. Isomer* VI-A. Fifty-six g. of 4-benzoyloxycyclohexanone[6] was converted to 1-ethynyl-4-benzoyloxycyclohexanol by the method of Jones and Sondheimer.[3] The crude product, which was a red oil, was obtained in 76% (48 g.) yield. This was not distilled but was converted directly to the mixed 1-ethynylcyclohexane-1,4-diols by dissolving in 500 ml. of ether and adding dropwise to a stirred suspension of 8.5 g. of lithium aluminum hydride in a mixture of 400 ml. of ether and 300 ml. of benzene. When addition was complete, 1*N* NaOH was added dropwise until the precipitate became granular and settled. The solution was then filtered, and the filtrate was evaporated to dryness. The residue was taken up in warm benzene. Upon cooling 6.4 g. (23.2% yield) of crystalline 1-ethynylcyclohexane-1,4-diol (VI-A) separated. After recrystallization from benzene–petroleum ether the product melted at 144–145°.

*Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.80.

The 3,5-dinitrobenzoate was prepared by the method of Brewster and Ciotti,[7] m.p. 197–199°.

*Anal.* Calcd. for $C_{22}H_{16}O_{12}N_4$: N, 10.60. Found: N, 10.67.

*Isomer VI-B.* Isomer B was obtained by alumina chromatography of the filtrate after removal of isomer A. From the fractions eluted with 4:1 benzene-ether was obtained 3.5 g. (12.7% yield) of VI-B, m.p. 96–98°.

*Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.40; H, 8.66.

The 3,5-dinitrobenzoate of isomer B melted at 213–215°.

*Anal.* Calcd. for $C_{22}H_{16}O_{12}N_4$: N, 10.60. Found: N, 10.32.

From the fractions eluted with ether and 99:1 ether-methanol was obtained an additional 2.4 g. of VI-A bringing the total yield of this isomer to 8.8 g. (32%).

*1-Ethylcyclohexane-1,4-diol. Isomer VII-A.* One-half gram of 1-ethynylcyclohexane-1,4-diol (VI-A) was converted quantitatively to the corresponding 1-ethylcyclohexane-1,4-diol by hydrogenation at atmospheric pressure using palladium on calcium carbonate as a catalyst. The product was purified by sublimation at 65° (0.1 mm.), m.p. 107–109°.

*Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.90; H, 11.06.

*Isomer* VII-B. 1-Ethynylcyclohexane-1,4-diol (VI-B) was reduced to the corresponding saturated diol in the same

(3) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

(4) It would seem reasonable, however, to suppose that of the two isomers, the *cis* would be the more firmly bound on the alumina. Consequently, VI-A would be *cis*-1-ethynylcyclohexane-1,4-diol and VI-B would be the *trans* isomer.

(5) All melting points are corrected.

(6) D. A. V. Denny and D. A. H. Taylor, *J. Chem. Soc.*, 1922 (1957).

(7) J. H. Brewster and C. J. Ciotti, Jr., *J. Am. Chem. Soc.*, **77**, 6214 (1955).

manner. After sublimation the product melted at 113–114°

*Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.45; H, 11.29.

*Degradation of hydroxyethylcyclohexyl carbamate* (III) *to 1-ethylcyclohexane-1,4-diol* (VII-B). This conversion was carried out by two different methods, refluxing for 1 hr. with excess lithium aluminum hydride in benzene and by basic hydrolysis with lithium hydroxide. The identical product was obtained in each case. The latter procedure is described here:

Ten milligrams of hydroxyethylcyclohexylcarbamate (III), prepared from the human metabolite as described previously,[2] was refluxed for 10 min. with 1*N* lithium hydroxide. After cooling, the reaction mixture was extracted with ether, and the ether extract was evaporated to dryness. Sublimation of the residue at 65° (0.1 mm.) gave a crystalline solid, m.p. 110–112°. When mixed with 1-ethylcyclohexane-1,4-diol (VII-A), the melting point was depressed to 76–81°. Upon admixture with VII-B, however, the melting point was not depressed (112–113°). The X-ray crystallographic pattern and infrared spectrum were identical to that of 1-ethylcyclohexane-1,4-diol (isomer VII-B).

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## Some Reactions of 1-Methoxypyridinium Salts and a Color Test for *N*-Oxides

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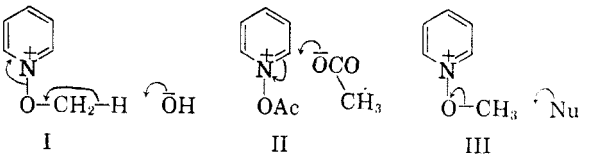
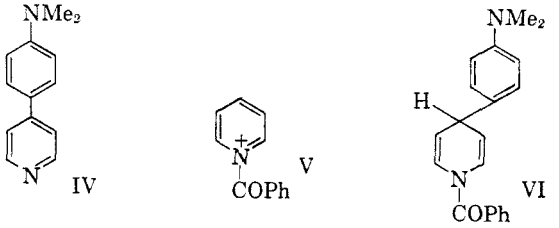
1-Alkyloxypyridinium salts react (*cf.* structure I) with hydroxide ion to give pyridine and an aldehyde,[1–3] but many reactions are known in which pyridine 1-oxide derivatives are attacked in the $\alpha$- or $\gamma$- positions of the ring by nucleophilic reagents,[4] as in *e.g.*, structure II. In an attempt to effect a reaction of this type, 1-methoxypyridinium toluene-*p*-sulfonate was treated with a series of nucleophilic reagents.* Sodium ethoxide and sodium phenoxide gave pyridine in good and poor yield, respectively. Sodium acetate, benzyl mercaptan, morpholine, aniline, hydroxylamine, semicarbazide, and phenyl magnesium bromide gave pyridine 1-oxide in 15–56% yield. The 1-methoxypyridinium ion acts here as a methylating agent (structure III) and *N*-methylaniline was isolated as the toluene-*p*-sulfonamide from the reactions with aniline. This appears to be the first time that 1-alkoxylpyridinium salts have been dealkylated without concomitant loss of the *N*-oxide oxygen atom.



I II III

Treatment of pyridine with benzoyl chloride and dimethylaniline yields 4-(*p*-dimethylaminophenyl) pyridine (IV),[5] probably by addition of dimethylaniline to V followed by aromatization of VI. It appeared that an analogous reaction could occur with pyridine 1-oxide; however, this compound behaved as an oxidizing agent and gave crystal violet probably admixed with methyl violet by releasing formaldehyde or its equivalent from dimethylaniline which then combined with further molecules of dimethylaniline. When pyridine 1-oxide hydrochloride and dimethylaniline were heated together, the same blue color was formed.



IV V VI

The production of a blue color on gently heating with dimethylaniline and hydrochloric acid was found to be a convenient color test for *N*-oxides and also for nitro compounds. Crystal violet is formed from dimethylaniline, *via* an oxidative dealkylation to formaldehyde, by many inorganic oxidizing agents,[6–8] *e.g.*, $KClO_3$, $Mn_3O_4$, $Cu(NO_3)_2$, $H_2O_2$. Of organic compounds, benzene sulfonyl chlorides react slowly.[9] Peroxides give colors with dimethylaniline.[10] Nitro compounds, and especially polynitrocompounds, form yellow or orange-red charge transfer complexes with dimethylaniline.[11,12]

Methyl ketones give a violet coloration with *m*-dinitrobenzene and methanolic alkali[13]; this reaction is also given by $\alpha$-methyl-chromones and -pyrones.[14] Neither 2-, 3-, or 4-methylpyridines nor their 1-oxides gave a similar coloration under these conditions; however, 1,2- (VII) and 1,4-, but not 1,3-dimethylpyridinium ions and 1-methoxy-2- (VIII) and 1-methoxy-4-methylpyridinium ions showed a positive reaction.

(1) E. Ochiai, M. Katada, and T. Naito, *J. Pharm. Soc. Japan*, **64**, 210 (1944); *Chem. Abstr.*, **45**, 5154 (1951).
(2) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).
(3) W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).
(4) A. R. Katritzky, *Quart. Rev.*, **10**, 395 (1956).
* Note added in proof: Reactions of this type between 1-methoxypyridinium salts and cyanide ions leading to 2- and 4-cyanopyridines have recently been described by T. O. Kamoto and H. Tani, *Chem. and Pharm. Bulletin (Japan)*, **7**, 130 (1959); and by W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959).
(5) E. Koenigs and E. Ruppelt, *Ann.*, **509**, 142 (1934).
(6) Beilstein, Hauptwerk, XII, 153.
(7) A. W. Hofmann, *Ber.*, **6**, 352 (1873).
(8) F. T. Naylor and B. C. Saunders, *J. Chem. Soc.*, 3519 (1950).
(9) L. Horner and H. Nickel, *Ann.*, **597**, 20 (1955).
(10) I. de Paoline, *Gazz. Chim. Ital.*, **60**, 859 (1930).
(11) J. Walter, *Zeit. für Fabenindustrie*, **10**, 49; *Chem. Zentr.*, **1**, 1411 (1911).
(12) B. Dale, R. Foster, and D. L. Hammick, *J. Chem. Soc.*, 3986 (1954).
(13) B. von Bitto, *Ann.*, **269**, 377 (1892).
(14) A. Schönberg and M. M. Sidky, *J. Org. Chem.*, **21**, 476 (1956).