[Contribution from the Experimental Biology and Medicine Institute, National Institutes of Health, U. S. Public Health Service]

Studies in the Anthracene Series. VII. Reduction of Highly Hindered Ketones with Lithium Aluminum Hydride

By Everette L. May and Erich Mosettig

9-(3-Morpholino-1-hydroxypropyl)-anthracene, the dimethylamino analog and 9-(1-hydroxyethyl)-anthracene have been prepared by the lithium aluminum hydride reduction of the corresponding ketones. The dimethylamino compound was one-half as active and five times as toxic as quinine in avian malaria.

Recently[1] we reported that in the hydrogenation (platinum oxide, ethanol) of 9-(3-morpholino-1-oxopropyl)-anthracene (Ia) one of the terminal rings absorbs two moles of hydrogen, while the keto group is unaffected. Similar results were obtained with 9-acetyl- (Ic) and 9-propionyl-anthracenes.[2] In a somewhat earlier investigation Horeau and Jacques[3] had shown that hydrogenation of 9-benzoylanthracene with Raney nickel gives a mixture of 9,10-dihydro-9-anthracylphenylcarbinol and 9-benzoyl-1,2,3,4-tetrahydroanthracene in a ratio of 1:5.

By the use of lithium aluminum hydride Julian, *et al.*,[4] were able to reduce 9-benzoyl- and 9-benzoyl-10-phenylanthracenes to the corresponding carbinols in good yield. Therefore one might expect amino ketones Ia and Ib to yield similarly the 9-anthracyl alkamines IIa and IIb which were desired for biological tests. The carbinols IIa, IIb and IIc[5] were obtained in yields of 90, 45 and 80%, respectively.

The low yield of IIb can probably be ascribed to over-reduction. In this instance[6] little, or no, insoluble complex was obtained, whereas with Ia and Ic there was an immediate precipitation of a lithium aluminum hydride complex which prevented further reaction. The amino alcohols IIa and IIb were converted to their O-acetyl derivatives with acetic anhydride in pyridine.

The ultraviolet absorption curves (Figs. 1 and 2) of IIa and IIb are practically identical (with maxima occurring at about 256 mμ) but distinctly different from those of the 9,10-dihydroanthracene derivatives III and IV (reference 2) which give no peaks over the range measured. The curves of IIa and IIb also closely resemble the anthracylcarbinols described by Julian, *et al.*[4]

The morpholino alcohol (IIa) and the dimethylamino analog (IIb) were tested in blood-induced *gallinaceum* malaria (chicks).[7] IIa was ineffective at a maximum tolerated dose of 0.09 mg./g.,

R = (a) $—CH_2CH_2NC_4H_8O$, (b) $—CH_2CH_2NMe_2$, (c) $—CH_3$

while IIb had one-half the activity of quinine but was five times as toxic. This activity is comparable to that found for the corresponding phenanthrene derivative.[8,9]

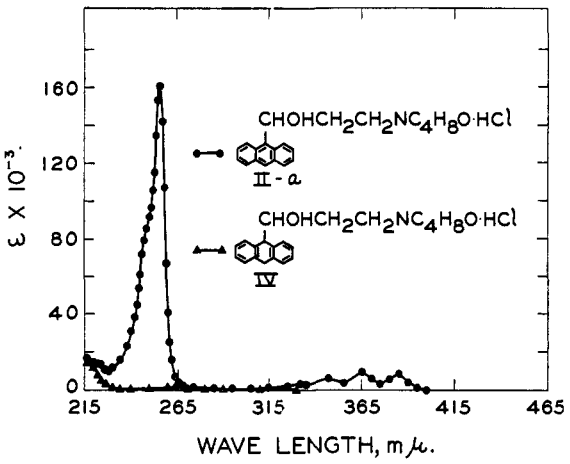

Fig. 1.—IIa, c (abs. ethanol) = 4.92×10^{-6} mole/l.; IV, c (abs. ethanol) = 4.87×10^{-5} mole/l.

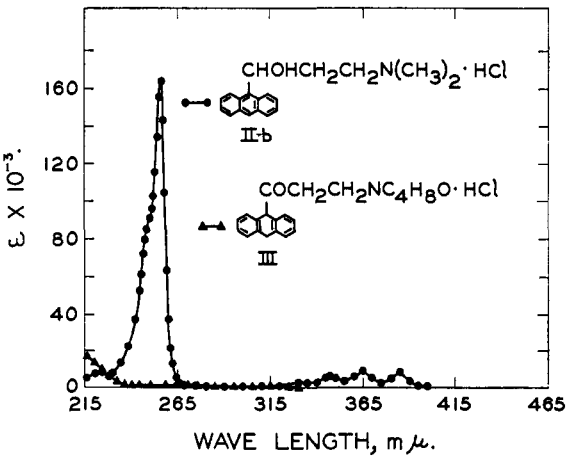

Fig. 2.—IIb, c (abs. ethanol) = 5.66×10^{-6} mole/l.; III, c (abs. ethanol) = 6.24×10^{-5} mole/l.

(1) E. L. May and E. Mosettig, This Journal, **70**, 686 (1948).

(2) Normal reduction of the keto group of the corresponding 9,10-dihydro derivatives can be effected either catalytically or with aluminum isopropoxide; *cf.* E. L. May and E. Mosettig, *ibid.*, **70**, 688 (1948).

(3) A. Horeau and J. Jacques, *Bull. soc. chim.*, 71 (1946).

(4) P. L. Julian, W. Cole, G. Diemer and J. G. Schafer, This Journal, **71**, 2058 (1949).

(5) L. F. Fieser and J. L. Hartwell, *ibid.*, **60**, 2555 (1938), prepared IIc by the reaction of 9-anthracenecarboxyaldehyde with methylmagnesium iodide.

(6) When only 1.3 equivalents of lithium aluminum hydride were used, a 50–60% yield of starting material could be recovered, and the yield of alcohol was very low. This appeared to be true also of the diamyl analog which was not thoroughly investigated.

(7) These compounds were tested by Dr. Joseph Greenberg of the National Institutes of Health.

(8) E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 105 (1946).

(9) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. II, J. W. Edwards, Ann Arbor, Michigan, 1946, p. 312.

Experimental[10]

9-(3-Dimethylamino-1-oxopropyl)-anthracene (Ib) Picrate.—The hydrochloride of Ib was reported by Fry.[11] It was converted to the picrate with alcoholic picric acid. The picrate crystallized from acetone–water in red crusts, m.p. 194–196°, or yellow short needles, m.p. 158–159°. The latter modification was analyzed.

Anal. Calcd. for $C_{25}H_{22}N_4O_8$: C, 59.3; H, 4.4. Found: C, 59.1; H, 4.5.

9-(3-Dimethylamino-1-hydroxypropyl)-anthracene (IIb).—The hydrochloride of Ib[11] (2.6 g.) was shaken with aqueous sodium carbonate and ether. Drying and evaporation of the ether left an oil which was dried in the vacuum desiccator overnight, stirred in 30 ml. of dry ether and treated during 10 minutes with 3.5 ml. (three equivalents)[6] of 1.8 *M* ethereal lithium aluminum hydride diluted with 7 ml. of dry ether. The mixture was decomposed by slow addition of 5 ml. of water. The clear ethereal solution was decanted, dried, evaporated to *ca.* 10 ml. and diluted with 3–4 ml. of ligroin (30–60°) to give 1.0 g. (45%) of IIb, m.p. 118–119°; prisms from ethanol.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.7; H, 7.6. Found: C, 81.7; H, 7.7.

The hydrochloride (NIH 4126) was prepared by addition of alcoholic hydrogen chloride (to congo red acidity) to an acetone solution of IIb and dilution with ether; yellowish prisms from ethanol–ether, m.p. 194–196° (dec.), $\lambda_{max.}^{absol.\ EtOH}$ 256 mμ (log ε 5.213).

Anal. Calcd. for $C_{19}H_{22}ClNO$: C, 72.3; H, 7.0. Found: C, 71.9; H, 7.2.

9-(3-Morpholino-1-hydroxypropyl)-anthracene (IIa) Hydrochloride (NIH 4127).—To a stirred suspension of 1.6 g. of Ia[1] and 30 ml. of dry ether was added 1.5 ml. of 1.8 *M* ethereal lithium aluminum hydride in 20 ml. of dry ether during 15 minutes. The mixture was stirred for an additional one-half hour, then 3 ml. of water was added slowly. Decantation, drying and acidification of the ether with alcoholic hydrogen chloride gave 1.6 g. (90%) of hydrochloride, m.p. 204–205° (dec.). It crystallized from ethanol in yellow-tinged needles, m.p. 209–210° (dec.), $\lambda_{max.}^{absol.\ EtOH}$ 256 mμ (log ε 5.206).

Anal. Calcd. for $C_{21}H_{24}ClNO_2$: C, 70.5; H, 6.8. Found: C, 70.7; H, 7.0.

The base, prepared from the hydrochloride with dilute, aqueous ammonia, crystallized from ethanol–water in rods of m.p. 124.5–126°.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.5; H, 7.2. Found: C, 78.6; H, 7.2.

9-(1-Hydroxyethyl)-anthracene (IIc).—One gram of 9-acetylanthracene[1] was reduced as described for Ia. The decomposed mixture was shaken with 10% hydrochloric acid. Drying and evaporation of the ether left a solid which crystallized from methanol in needles, m.p. 117–121°; yield 0.8 g. (80%). Recrystallized from ether–ligroin (30–60°) the IIc melted at 124–125° alone or in mixture with material prepared from 9-anthracenecarboxaldehyde.[5]

9-(3-Morpholino-1-acetoxypropyl)-anthracene Hydrochloride.—A mixture of 0.15 g. of IIa hydrochloride, 0.1 ml. of acetic anhydride and 2 ml. of dry pyridine was shaken for 7 hours and evaporated to dryness *in vacuo*. The residue was washed with acetone and recrystallized from ethanol; yield 80%, oblong plates, m.p. 214–215° (dec.). Analysis indicated one mole of solvate ethanol which was indeterminate by weight loss.

Anal. Calcd. for $C_{23}H_{26}ClNO_3 \cdot C_2H_5OH$: C, 67.3; H, 7.2; Cl, 8.0. Found: C, 67.5; H, 7.3; Cl, 8.2.

Crystallization of the product from methanol gave a solvate-free hydrochloride; prisms.

Anal. Calcd. for $C_{23}H_{26}ClNO_3$: C, 69.1; H, 6.6. Found: C, 68.6; H, 6.7.

9-(3-Dimethylamino-1-acetoxypropyl)-anthracene Hydrochloride.—The hydrochloride of IIb was acetylated as described for that of IIa; dense, yellow-tinged prisms,[12] m.p. 211–212° (dec.), from acetone.

Anal. Calcd. for $C_{21}H_{24}ClNO_2 \cdot H_2O$: C, 67.0; H, 7.0. Found: C, 66.9; H, 7.0.

On refluxing this hydrated hydrochloride with methanolic alkali IIb was regenerated.

(10) Melting points, observed in a capillary, are uncorrected. The absorption measurements and microanalyses are from the Institutes service analytical laboratory under the direction of Mr. William C. Alford.

(11) E. M. Fry, *J. Org. Chem.*, **10**, 259 (1945).

(12) The compound first crystallized as white, thin prisms which gradually changed to the more dense, tinged ones.

RECEIVED OCTOBER 6, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

The Oxidation of Isoborneol with Chromic Acid[1]

BY WILLIAM A. MOSHER AND ESLEY O. LANGERAK[2]

Isoborneol on oxidation with chromic anhydride in aqueous acetic acid yields 96% camphor, 2% α-campholenic acid and 2% 1,2,2-trimethylcyclopentanol-3-acetic acid. These two acids have not been previously isolated from isoborneol oxidation and the latter is a new terpene-derived hydroxy-acid.

These products are accounted for through the deficient oxygen intermediate. The results with isoborneol are significant because the alcohol and acid functions are obtained in the same molecule as a result of the splitting reaction.

Mosher and Langerak[3] have previously shown that cleavage of secondary aliphatic alcohols to aldehydes and alcohols of lower molecular weight is a general reaction, although only trace yields of the cleavage products are obtained unless one group attached to the carbinol carbon is tertiary such as is the case with methyl-*t*-amylcarbinol (I). A 7% yield of *t*-amyl alcohol is formed when this secondary alcohol is oxidized with chromic anhydride in aqueous acetic acid.[4] The similarity in group relationships between this aliphatic alcohol (I) and isoborneol (II) is at once apparent, and suggests this terpene alcohol for oxidative study.

Because of its relation to camphor synthesis, the oxidation of isoborneol has received considerable study. This literature is well reviewed by Simonsen[5] but special attention should be called to the work of Acharya and co-workers[6] who reported yields of camphor as high as 96% using nitric acid in sulfuric acid solution; the highest yield reported by those workers with chromic acid is 70%.

Our oxidation of isoborneol with chromic anhy-

(1) Presented before the Division of Organic Chemistry, American Chemical Society, Philadelphia, April, 1950.

(2) F. G. Cottrell Research Fellow in Chemistry 1946–1949. From a thesis presented in partial fulfillment of the requirements for the Ph.D. degree, 1949.

(3) Mosher and Langerak, THIS JOURNAL, **71**, 286 (1949).

(4) Mosher and Whitmore, *ibid.*, **70**, 2544 (1948).

(5) Simonsen, "The Terpenes," 2nd Edition, Vol. II, Cambridge University Press, 1949.

(6) Acharya and co-workers, *J. Univ. Bombay*, **11A**, pt. 5, 113 (1943); *C. A.*, **37**, 5952 (1943).