[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

Studies in the Anthracene Series. II. Alkyl Ketones Derived from 1,2,3,4-Tetrahydro-9,10-anthraquinone

BY EVERETTE L. MAY AND ERICH MOSETTIG

Recent malaria screening tests on tetrahydroanthracene derivatives prepared in this Laboratory[1] have shown that 1,2,3,4-tetrahydro-9,10-anthraquinone[2] and the corresponding 5-acetyl derivative exhibit some activity. This was of particular interest in view of the remarkable prophylactic properties of 1,4-naphthoquinone compounds, synthesized by Fieser and co-workers,[3] and it seemed desirable to attach higher acyl or alkyl groups to the benzenoid ring of tetrahydroanthraquinone.

The Friedel–Crafts reaction with tetrahydroanthracene and butyryl or heptanoyl chloride, using nitrobenzene as a solvent, gave readily the expected ketones in a yield of *ca.* 45%. The acyl groups had entered position 6, as shown by hypobromite oxidation to 1,2,3,4-tetrahydro-6-anthroic acid. No special efforts were made to isolate isomeric 5-derivatives, possibly formed in the reaction.

The ketones were oxidized, with chromic acid, to 6-butyryl- and 6-heptanoyl-1,2,3,4-tetrahydro-9,10-anthraquinones. Further, the 6-heptanoyltetrahydroanthracene was reduced to the carbinol with aluminum isopropoxide and to the hydrocarbon by the Clemmensen method. The hydrocarbon was oxidized with chromic acid to 6-heptyl-1,2,3,4-tetrahydro-9,10-anthraquinone.

None of the compounds tested showed any effectiveness against blood-inoculated or sporozoite-induced *gallinaceum* malaria.[4]

Experimental[5]

6-Heptanoyl-1,2,3,4-tetrahydroanthracene (NIH 2120).[6]—To a stirred mixture of 15 g. of aluminum chloride, 10 g. of heptanoyl chloride and 70 cc. of nitrobenzene, kept at 0 ± 5°, was added during ten minutes, 10 g. of tetrahydroanthracene[1] in 30 cc. of nitrobenzene. After stirring for one hour at 0°, the mixture was left at 0 to 5° overnight, poured into ice–hydrochloric acid, and the solvent steam-distilled. The remaining oil was dried in ether and distilled to give 10 g. of oil boiling at 212–217° (2 mm.). It crystallized from methanol in a yield of 7.1 g., m. p. 72–73°. From the methanolic filtrate an additional amount of ketone, melting at 72.5–73°, was obtained through the semicarbazone, making the total yield 7.4 g. (46%).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.7; H, 8.9. Found: C, 85.5; H, 8.6.

The semicarbazone crystallized from 95% ethanol in feathery leaflets, m. p. 197–198°.

Anal. Calcd. for $C_{22}H_{29}N_3O$: C, 75.2; H, 8.3. Found: C, 75.3; H, 8.3.

6-Butyryl-1,2,3,4-tetrahydroanthracene.—By a procedure similar to that above, 23 g. of aluminum chloride, 10 cc. of butyryl chloride, 100 cc. of nitrobenzene and 15 g. of tetrahydroanthracene gave 14 g. of an oil boiling at 165–195° (2 mm.) which crystallized from methanol in prisms (8 g.) of m. p. 67–70°. The filtrate yielded, through the semicarbazone, an additional 1.5 g. of ketone; total yield 45%. The analytical sample melted at 70–71°.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found: C, 85.8; H, 8.2.

The semicarbazone, crystallized as prisms from dioxane then from methanol, melted at 223–226° (dec.).

Anal. Calcd. for $C_{19}H_{23}N_3O$: C, 73.8; H, 7.5. Found: C, 73.8; H, 7.4.

Structure Proof.—A mixture of 0.9 g. of 6-heptanoyl-1,2,3,4-tetrahydroanthracene, 0.8 cc. of bromine in 10 cc. of 25% sodium hydroxide and 10 cc. of pyridine[7] was shaken for ten to fifteen hours and diluted with water. Filtration and acidification of the filtrate gave 0.3 g. (40%) of 1,2,3,4-tetrahydro-6-anthroic acid,[1] which crystallized from acetic acid in plates of m. p. 254–257°. Mixed with authentic material of m. p. 264–266° (cor.), 256–258° (uncor.), it showed no depression.

In a similar manner, 6-butyryl-1,2,3,4-tetrahydroanthracene gave 67% of the same acid.

The ethyl ester,[1] prepared from either sample melted at 109–110.5°, and the melting point was not depressed by authentic material.

6-Heptanoyl-1,2,3,4-tetrahydro-9,10-anthraquinone (NIH 2211).—To a stirred mixture of 5.0 g. of 6-heptanoyl-1,2,3,4-tetrahydroanthracene and 100 cc. of acetic acid was added during one-half hour, 4.8 g. of chromic acid in 10 cc. of water and 25 cc. of acetic acid. The temperature rose to 40°. After stirring for another hour the mixture was diluted with about 300 cc. of salt water and the whole extracted twice with ether. The ethereal solution was washed free of acid with dilute sodium carbonate, dried, and the ether evaporated. The yellow oil, in ethanol, was treated with Norit. By gradual cooling the filtrate deposited 1.8 g. (33%) of quinone of m. p. 57–63°; yellow rods from ethanol, m. p. 65.5–66.5°.

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.7; H, 7.5. Found: C, 77.8; H, 7.7.

6-Butyryl-1,2,3,4-tetrahydro-9,10-anthraquinone (NIH 2240).—Essentially as described above, this compound was obtained, from methanol, in a yield of 43%; yellow, feathery leaflets of m. p. 88–89°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.8; H, 6.6.

6-Heptyl-1,2,3,4-tetrahydro-9,10-anthraquinone (NIH 2177).—A mixture of 5.0 g. of 6-heptanoyl-1,2,3,4-tetrahydroanthracene, 18 g. of amalgamated zinc, 35 cc. of concentrated hydrochloric acid and 35 cc. of ethanol was refluxed for twenty-four hours. During this time a total of 35 cc. of concentrated hydrochloric acid and 35 cc. of ethanol was added in two portions. The alcohol was evaporated *in vacuo* and the remaining oil shaken into ether. The ether was dried, evaporated and the residue evaporatively distilled at 155° (0.05 mm.); yield 3.1 g., freezing point 14–16°. This material (5.4 g.) in 40 cc. of acetic acid was oxidized, as described above, with 5.5 g. of chromic acid in 5 cc. of water and 20 cc. of acetic acid. The yield of quinone, from ethanol, was 1.7 g. (29%),

(1) Garlock and Mosettig, THIS JOURNAL, **67**, 2255 (1945).

(2) Wiselogle, "Survey of Antimalarial Drugs 1941–1945," Vol. I, Edwards Brothers, Ann Arbor, Michigan, 1946, pp. 103, 153.

(3) *Ibid.*, Vol. I, p. 261 ff.; Vol. II, p. 1702 ff.

(4) Coatney and Cooper, unpublished results.

(5) All melting points given are uncorrected.

(6) Compounds tested are designated by an NIH number; results on these were obtained too late to be classified in the Survey monograph.

(7) The use of pyridine was suggested by the work of Schultz, Goldberg, Ordas and Carsch, *J. Org. Chem.*, **11**, 327, 330 (1946).

m. p. 58–60°. After two recrystallizations from ethanol it melted at 63–64°.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.3; H, 8.4. Found: C, 81.4; H, 8.6.

6-(1-Hydroxyheptyl)-1,2,3,4-tetrahydroanthracene (NIH 2192).—Seven grams of 6-heptanoyltetrahydroanthracene was reduced with 40 cc. of 1 *M* aluminum isopropoxide (one hour). Solvent was evaporated *in vacuo*, and the residue was partitioned between dilute hydrochloric acid and ether. Drying and evaporation of the ether gave an oil which crystallized from aqueous methanol in a yield of 6 g. (86%). After two recrystallizations from methanol it melted at 75.5–77°.

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.1; H, 9.5. Found: C, 85.0; H, 9.6.

Summary

6-Butyryl- and 6-heptanoyl-1,2,3,4-tetrahydroanthracenes have been synthesized and their structures proved by oxidation to the corresponding carboxylic acid.

6-Butyryl- and 6-heptanoyl-1,2,3,4-tetrahydro-9,10-anthraquinones are without value in *gallinaceum* malaria.

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[CONTRIBUTION NO. 627 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Reaction of 2-Nitropropane with Acid Anhydrides[1,2]

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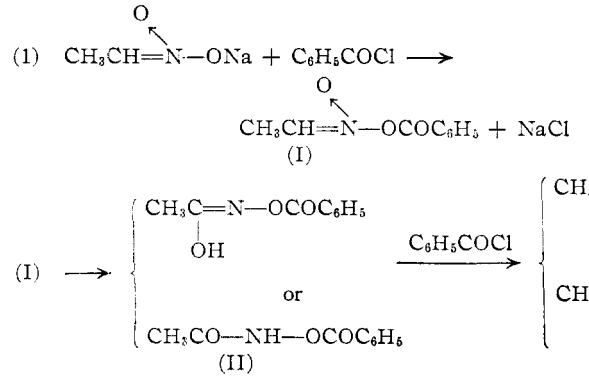
With the exception of a few which contain aromatic groups, no stable acyl derivative of the aci-nitroparaffins has been described. Thus, Nenitzescu and Isacescu[4] obtained acetyl aci-phenylnitromethane by the action of ketene with the aci-form of phenylnitromethane. These same investigators prepared acetyl and benzoyl aci-9-nitrofluorene by treatment of the potassium salt with the corresponding acid chlorides. Thurston and Shriner[5] obtained benzoyl aci-phenyl nitroacetonitrile by reaction of benzoyl chloride with both the sodium and silver salts of the nitro-compound.

The action of acetyl and benzoyl chlorides on simple primary nitroparaffins or their salts causes molecular rearrangements.[6] Jones,[7] for example, found the product of the action of benzoyl chloride on sodium aci-nitroethane to be dibenzoylacethydroxamic acid (III), probably by the following reactions.



The aci-benzoate (I) was not isolated, but was assumed to rearrange to (II), which on further reaction gave (III). That acylation may in certain instances occur on the carbon atom adjacent to the nitro group is evident from experiments by Gabriel,[8] who treated phthalic anhydride with sodium nitromethane and obtained, after acidification, small amounts of 2-nitroacetylbenzoic acid.

The present investigation reveals that a secondary nitroparaffin or its salt may give rise to a relatively stable aci-ester or mixed anhydride, $(CH_3)_2C{=}N{-}OCOR$ (IV), by reaction with aliphatic acid anhydrides. Acetyl and propionyl 2-aci-nitropropane were prepared by reaction of the acid anhydrides directly with 2-nitropropane in anhydrous toluene solution in the presence of potassium acetate, or with an ether suspension of sodium 2-nitropropane, both reactions being highly exothermic. In reactions with sodium 2-nitropropane cooling in an ice-bath was required. Yields were low, acetyl 2-aci-nitropropane being obtained in yields averaging 7.5% directly from the nitroparaffin and 17.3% from the sodium salt. Propionyl 2-aci-nitropropane was isolated in 9.5% yields from the nitroparaffin and 5.6% from its salt.

In every instance the reaction was accompanied by a slow and unexplained evolution of carbon dioxide and the development of a bright blue color, the latter possibly attributable to the monomolecular form of isopropyl pseudonitrole.[9,10] It distilled with the solvent and excess of reactants at the conclusion of the reaction, and could not be separated from them by distillation through a 38-cm. packed column. On prolonged standing the blue color disappeared, and after the ether or toluene solution had stood for a considerable time in contact with water a positive brown ring test

(1) Abstracted from a thesis submitted by Eugene P. Stefl in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Presented before the Organic Division of the American Chemical Society at the Atlantic City Meeting, April 17, 1947.

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(4) Nenitzescu and Isacescu, *Bull. soc. chim. Romania*, **14**, 53 (1932) (*C. A.*, **27**, 964 (1933)).

(5) Thurston and Shriner, *J. Org. Chem.*, **2**, 183 (1937).

(6) Gilman, "Organic Chemistry, an Advanced Treatise," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 626.

(7) Jones, *Am. Chem. J.*, **20**, 1 (1898).

(8) Gabriel, *Ber.*, **36**, 570 (1903).

(9) Scholl, *ibid.*, **21**, 508 (1888).

(10) Piloty and Stock, *ibid.*, **35**, 3093 (1902).