

[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 Laboratory¹ have shown that 1,2,3,4-tetrahydro-9,10-anthraquinone² 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-heptanoyl-tetrahydroanthracene 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

Experimental⁵

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 $0 \pm 5^\circ$, was added during ten minutes, 10 g. of tetrahydroanthracene¹ 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° .

(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.

Anal. Calcd. for $C_{22}H_{28}N_2O$: 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 $C_{15}H_{20}O$: 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 $C_{19}H_{24}N_2O$: 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 pyridine⁷ 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 $C_{21}H_{24}O_2$: 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 $C_{15}H_{18}O_2$: 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%),

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

