

Anal.—Calc. for $C_{29}H_{41}N_5O_3$: C, 57.70; H, 6.85; N, 11.60. Found: C, 58.07; H, 7.37; N, 12.03.

17a-(2-Dimethylaminoethyl)-17a-aza-D-homo-5-androsten-3 β -ol (XIV)—*Method D*—Compound X (2.0 g.) was dissolved in 30 ml. of dioxane, a solution of 1.0 g. of lithium aluminum hydride in 300 ml. of dioxane was added, and the mixture was refluxed for 48 hr. Excess hydride was destroyed with water. The inorganic salts were filtered and washed with dioxane. The dioxane solution was evaporated to dryness, and the residue was crystallized from ethanol to give 1.8 g. (94%) of white crystals of XIV, m.p. 195–196°. The hydrobromide salt of XIV was prepared by passing HBr gas into its acetone solution and crystallizing from ethanol to give white needles, m.p. 309–310°.

Anal.—Calc. for $C_{23}H_{40}N_2O_2 \cdot HBr$: C, 52.88; H, 8.10; N, 5.36; Br, 30.60. Found: C, 52.45; H, 7.95; N, 5.09; Br, 31.22.

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Unexpected Formation of Thioacridone and Its Spectral Properties

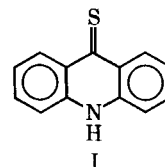
ANDRÉ DeLEENHEER*, Y. Y. SHUM, J. E. SINSHEIMER, and J. H. BURCKHALTER

Abstract □ The isolation of thioacridone as the major product in the literature synthesis of 9-(*p*-aminophenyl)acridine and from reaction of 9-aminoacridine with *n*-butylisothiocyanate is described. Chromatographic and spectral properties of thioacridone, useful in its identification, are reported.

Keyphrases □ Thioacridone—*isolation, characterization as a reaction product, spectral properties* □ 9-Aminoacridine and *n*-butylisothiocyanate—*isolation, characterization of thioacridone as a reaction product* □ 9-(*p*-Aminophenyl)acridine with acridine, aniline, and sulfur—*isolation, characterization of thioacridone as a reaction product*

Current interest in these laboratories in the use of acridine derivatives as fluorescent tagging agents has led to the isolation of thioacridone [9(10*H*)-acridinethione] (I) in two separate reactions. This article describes these isolations and reports spectral data of value in the characterization of thioacridone.

Chupakhin *et al.* (1) reported the synthesis of 9-(*p*-aminophenyl)acridine in a yield of 12–13% by heating acridine, aniline, and sulfur at 185°. This yield was confirmed under similar conditions in these laboratories, but thioacridone in 83% yield also was isolated from the same reaction mixture. The formation of the thioacridone is not surprising in light of its synthesis in 85%



yield by reaction of acridine and sulfur in a sealed tube at 190° (2) and the reported (3) high yield of 3,6-bis-(dimethylamino)-9(10*H*)-acridinethione from the fusion of 3,6-bis(dimethylamino)acridine and sulfur. It is interesting that Chupakhin *et al.* (1) were able to prepare 9-(*p*-aminophenyl)-10-methylacridinium iodide from 10-methylacridinium iodide and aniline in satisfactory yield (75%), apparently without appreciable thioacridone formation. This result is in agreement with Elsager's suggestion (3) that thioacridone formation in a sulfur fusion reaction proceeds through an *N*-sulfide intermediate.

The second unexpected isolation in these laboratories of thioacridone resulted from reactions involving 9-aminoacridine and *n*-butylisothiocyanate. The result is not readily explainable based upon prior reports in the literature. Formation of thioacridone under mild conditions in this reaction, together with no indication of isothiocyanate decomposition, speaks against involvement

by elemental sulfur. Also, there was no indication of SH^- arising from *n*-butylisothiocyanate under the reaction conditions. Direct attack by SH^- is the basis of several syntheses of thioacridones (4) and, indeed, an extension of such a process described by Cherntsov (5) was employed in the present investigation to obtain reference material. These syntheses, however, involve the facile replacement of chlorine in 9-chloroacridine.

The reaction may proceed by an attack of *n*-butylisothiocyanate, either through the nucleophilic sulfur upon the 9-position of aminoacridine or through an electro-positive isothiocyanate carbon attack at the 10-position of 9-aminoacridine. In the latter possibility, a nucleophilic sulfur could result and serve in an attack upon a second 9-aminoacridine molecule at the 9-position.

The presence of thioacridone accompanying the synthesis of 9-(*p*-aminophenyl)acridine was first assumed on the basis of the reaction conditions used in the presence of sulfur and was confirmed by comparison to reference material. In the case of the *n*-butylisothiocyanate reaction, the presence of thioacridone was deduced from IR, NMR, and mass spectral data and was confirmed by comparison with a reference sample.

EXPERIMENTAL¹

GLC was performed on a Hewlett-Packard model 5750 instrument, equipped with a 3.8% UCW-98 on 80/100 mesh Diatoport S in a glass column, 1.22 m., 0.64 cm. (4 ft., 0.25 in.). Thioacridone chromatographed at a retention time of 20 min. 24 sec., with helium as the carrier gas at 11 cm. sec.⁻¹. Operating temperatures were: injector, 227°; oven, 202°; and flame-ionization detector, 217°.

Isolation of Thioacridone during Synthesis of 9-(*p*-Aminophenyl)acridine—Aniline (10.08 g., 0.106 mole) was added to a mixture of 4.52 g. (0.025 mole) of acridine and 3.76 g. (0.014 mole) of sulfur and refluxed at 190° for 1.5 hr. The brown-red reaction mixture was washed three times with ether, and the ether solutions were discarded. 9-(*p*-Aminophenyl)acridine was recovered from the washed residue by extraction with 0.5 *N* HCl as previously described (1).

The acid-insoluble residue (5.37 g.) was dissolved in 100 ml. of acetone, the solution was filtered to remove sulfur, and an equal volume of water was added to deposit orange crystals. Two recrystallizations from acetone-water produced 3.75 g. (83%) of fine orange crystals, m.p. 262°. These crystals did not

depress the melting point of thioacridone, and they possessed the same GLC characteristics and IR spectra of a sample of thioacridone synthesized by the procedure of Cherntsov (5).

Thioacridone from 9-Aminoacridine and *n*-Butylisothiocyanate—9-Aminoacridine (0.5 g.) was refluxed in 10 ml. of *n*-butylisothiocyanate, which produced a red solution in 10 min. and was followed by the precipitation of red crystals. The mixture was refluxed for 1.5 hr. before excess reagent was removed *in vacuo* in a rotary evaporator. The crude compound was triturated with petroleum ether (30–60°), and the residue was recrystallized twice from acetone-pyridine to give 351 mg. (58%) of a product which chromatographed as a single compound by GLC and TLC: R_f 0.72 on silica gel G (250 μ) with a acetone, benzene, and ammonia system (74:74:2), and fluorometric detection.

The reaction product was deduced to be thioacridone on the basis of the following data: m.p. 265° [lit. (3) 266°]; IR (KBr) 3250 (NH), 3070 (aromatic CH), 1620, 1575, 1480, and 1455 (phenyl), 1292 and 1175 (NH), 1220 (C=S), 999 and 752 cm.⁻¹ (1,2-disubstituted phenyl); NMR (DMSO-*d*₆, tetramethylsilane) 8.61 (d, 2, $J = 8.0$ Hz., aromatic H), 8.17 (s, 1, D₂O shift, N—H), 7.0–7.7 (m, 6, aromatic H); mass spectrum (50 ev., 180°) *m/e* (relative intensity) 211 (80) M, 167 (21) M—CS, 105.5 (5) M/2, 83.5 (4) M—CS/2.

Identification was confirmed by comparison of GLC, mixed melting point, and identical IR spectrum with thioacridone synthesized by the procedure of Cherntsov (5).

Progress of this reaction at room temperature was also followed by GLC. In this manner, a yield of 5.2% of thioacridone was noted after 4 hr. and 10.2% after 48 hr. When a mixture of 9-aminoacridine (1.94 g.) and *n*-butylisothiocyanate (1.44 g.) was refluxed in 50 ml. of toluene, a 2% yield of thioacridone was detected by GLC after 30 min. and a 2.2% yield after 1 hr.

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¹ Melting points, observed by means of a Mel-Temp apparatus, are uncorrected. Spectrophotometers used were Perkin-Elmer model 337 IR, Varian A-60A NMR, and A.E.I. MS 902 mass spectrometer.