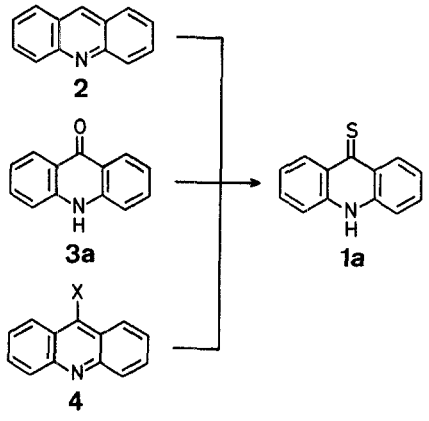
Thiations with Tetraphosphorus Decasulfide in Hexamethylphosphoric Triamide; Synthesis of Thioacronycine and Acridanethiones

R. R. SMOLDERS*, J. HANUISE, R. COOMANS, V. PROIETTO, N. VOGLET, A. WAEFELAER

Institut des Industries de Fermentation – Institut Meurice Chimie, Service de Chimie Organique, 1 Avenue E. Gryzon, B-1070 Bruxelles, Belgique

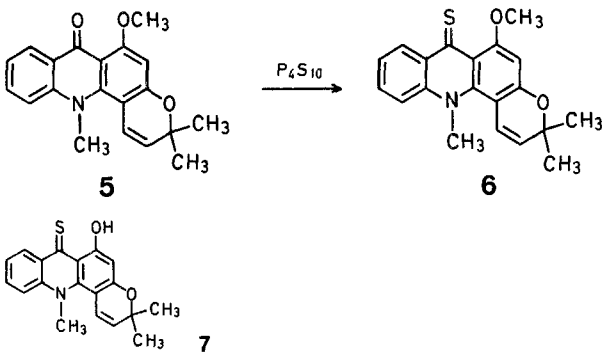
There are mainly three preparative routes to 9-acridanethiones **(1)**:

- reaction of acridine **(2)** with sulfur at high temperatures[1] (this method has also been applied to the 3,6-bis[dimethylamino][2] and 3,6-bis[diethylamino][3] derivatives);
- O/S exchange in 9-acridanone[4] **(3)** (and its 10-methyl[5] and 10-phenyl derivatives[6]) with tetraphosphorus decasulfide, or in 10-methylacridanone with boron sulfide or, better, silicon disulfide;
- reaction of 9-haloacridine **(4)** or its derivatives with sodium sulfide, calcium polysulfide, potassium *O*-alkyl dithiocarbonates (potassium xanthates), or thiourea[8]. This method is the most frequently used route to 9-acridanethiones.



In view of synthesizing 9-acridanethiones of possible pharmacological activity, we have now investigated the conversion of 9-acridanones **(3)** into 9-acridanethiones **(1)** using tetraphosphorus decasulfide. This reagent has hitherto been used for the conversion of other types of carbonyl compounds into the thioxo derivatives[9]. We performed the reaction in hexamethylphosphoric triamide (HMPT) and obtained the desired 9-acridanethiones **(1)** in high yields. For comparison, we attempted the same O/S exchange reaction with sulfur[22] and with 2,4-bis[4-methoxyphenyl]-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson reagent)[23]. Whereas the yields obtained using sulfur were lower in our experiments than the yields obtained using tetraphosphorus decasulfide (our procedure), no conversion could be achieved using Lawesson reagent.

The conditions used by us proved to be particularly useful for the conversion of acronycine **(5)** into thioacronycine **(6)**. This already earlier attempted[10] conversion is accompanied by *O*-demethylation to **7** as an undesired side reaction when tetraphosphorus decasulfide in benzene is used. Under our experimental conditions, this side reaction is completely suppressed.



Conversion of 9-Acridanones (3) into 9-Acridanethiones (1); General Procedure:

The 9-acridanone (**3**; 10 mmol) is added to a stirred solution of tetraphosphorus decasulfide (2.22 g, 5 mmol) in hexamethylphosphoric triamide (30 ml) which is protected for moisture. Stirring is continued (temperature and time, see Table) until no more 9-acridanone can be detected by T.L.C. analysis (silica gel, chloroform/methanol 8/2). The mixture is poured into diluted aqueous ammonia (250 ml). The solid product which separates is isolated by filtration, washed several times with water, and air-dried. The residue is recrystallized from methanol.

Thioacronycine (6):

Acronycine[21] (**5**; 1.929 g, 6 mmol) is added to a stirred solution of tetraphosphorus decasulfide (1.33 g, 3 mmol) in HMPT (18 ml) which is protected from moisture. Stirring is continued for 1 h at 140 °C. The mixture is then diluted with water (100 ml) and extracted with ether (10 × 50 ml). The organic extract is washed with water (200 ml), dried with magnesium sulfate, and evaporated. The residue (1.9 g, m.p. 170–181 °C) is recrystallized twice from ethanol; yield: 0.93 g (45%); m.p. 186–187 °C.

$C_{20}H_{19}NO_2S$	calc.	C 71.18	H 5.67	N 4.15	O 9.48	S 9.50
(337.4)	found	71.11	5.74	4.03	9.57	9.45

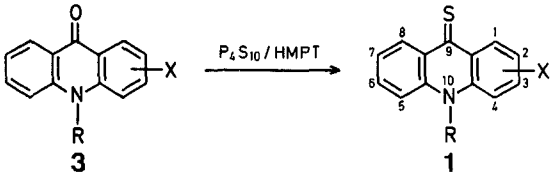
M.S.: $m/e = 338$ (M + 1) (28), 337 (100), 336 (68), 322 (18), 305 (25), 304 (82), 292 (21), 273 (18).

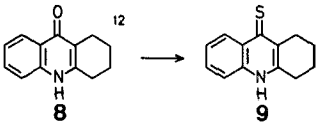
I.R. (KBr): $\nu = 1590$, 1570, 1460, 1385, 1350, 1140, 1040, 745, 735 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 1.55$ [s, 6H, $C(CH_3)_2$)]; 3.83 (s, 3H, N—CH_3); 3.94 (s, 3H, OCH_3); 5.50 (d, 1 H_{vinyl}, $J = 10$ Hz); 6.38 (s, 1H, 5-H); 6.55 (d, 1 H_{vinyl}, $J = 10$ Hz); 7–7.6 (m, 3H, 9-H, 10-H, 11-H); 8.63 ppm (m, 1H, 8-H).

0039-7881/82/0632-0493 $ 03.00

Table. 9-Acridanethiones (**1**) from 9-Acridanones (**3**)



Educt	Product	R	X	Reaction conditions [°C, h]	Yield [%]	m.p. [°C]	Molecular formula[a] or m.p. [°C] reported	
3a[11]	**1a**	H	H	115°, 2.5	97	259-261°	266°[7]	
3b[13]	**1b**	CH_3	H	115°, 3.5	98	258-260°	263°[14]	
3c[15]	**1c**	H	3-CF_3	115°, 2.5	87	259.5-260.5°	$C_{14}H_8F_3NS$	(279.2)
3d[16]	**1d**	H	6-Cl, 2-F	115°, 2.5	84	246-248°	$C_{13}H_7ClFNS$	(263.7)
3e[17]	**1e**	H	6-Cl, 3-CF_3	115°, 2.5	84	269-270°	$C_{14}H_7ClF_3NS$	(313.7)
3f[18]	**1f**	H	6-Cl, 2-OCH_3	115°, 2.5	99	259-260°	263°[19]	
3g[20]	**1g**	H	1,3-di-OCH_3	115°, 2.5	76	197-199°	$C_{15}H_{13}NO_2S$	(271.3)
3h[20]	**1h**	CH_3	1,3-di-OCH_3	115°, 18	70	149-150°	$C_{16}H_{15}NO_2S$	(285.3)
				100°, 17	62	213-215°	$C_{13}H_{15}NS$	(217.3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.25; H, ±0.14; S, ±0.13.

Received: October 29, 1981
(Revised form: December 4, 1981)

* Address for correspondence.

1 A. Edinger, W. Arnold, *J. prakt. Chem.* [2] **64,** 182 (1901).
2 E. F. Elsager, *J. Org. Chem.* **27,** 4346 (1962).
3 E. F. Elsager et al., *J. Med. Chem.* **14,** 782 (1971).
4 V. Farcasan, I. Balazs, *Stud. Univ. Babes-Bolyai* **14,** 43 (1969); *C. A.* **72,** 43555 (1970).
5 J. Jaeken, M. A. de Ramaix, *German Patent (DBP)* 1146751 (1963), Gevaert Photo-Produkten; *C. A.* **59,** 15421 (1963).
6 A. Schönberg, O. Schütz, S. Nickel, *Ber. Dtsch. Chem. Ges.* **61B,** 1375 (1928).
7 F. M. Dean, J. Goodchild, A. W. Hill, *J. Chem. Soc.* [C] **1969,** 2192.
8 J. M. F. Gagan, in: *Acridines,* R. M. Acheson, Ed., John Wiley & Sons, New York, 1973, p. 141; see references cited therein.
9 J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard, *Synthesis* **1973,** 149.
10 J. R. Dimmock, A. J. Repta, J. J. Kaminsky, *J. Pharm. Sci.* **68,** 37 (1979).
11 E. C. Horning, *Org. Synth., Coll. Vol.* II, 15 (1942).
12 R. A. Reed, *J. Chem. Soc.* **1944,** 425.
13 C. Blanchard et al., *J. Heterocycl. Chem.* **15,** 149 (1978).
14 K. Gleu, S. Nitzsche, *J. prakt. Chem.* [2] **153,** 225 (1939).
15 J. H. Wilkinson, I. L. Finar, *J. Chem. Soc.* **1948,** 32.
16 H. L. Bradlow, C. A. VanderWerf, *J. Am. Chem. Soc.* **70,** 654 (1948).
17 N. B. Ackerman, D. K. Hardorsen, F. H. Tendick, E. F. Elsager, *J. Med. Chem.* **11,** 315 (1968).
18 G. Singh, S. Singh, A. Singh, M. Singh, *J. Indian Chem. Soc.* **28,** 459 (1951); *C. A.* **46,** 11205 (1952).
19 F. Wild, J. M. Young, *J. Chem. Soc.* **1965,** 7261.
20 C. Soo Oh, V. C. Greco, *J. Heterocycl. Chem.* **7,** 261 (1970).
21 J. Hlubucek, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **23,** 1081 (1970).
22 J. Perregaard, I. Thomsen, S. O. Lawesson, *Acta Chem. Scand.* **29,** 538 (1975).
23 S. Scheibye, B. S. Pedersen, S. O. Lawesson, *Bull. Soc. Chim. Belg.* **87,** 229 (1978).

0039-7881/82/0632-0494 $ 03.00