Synthesis of Some Phenanthridone Derivatives

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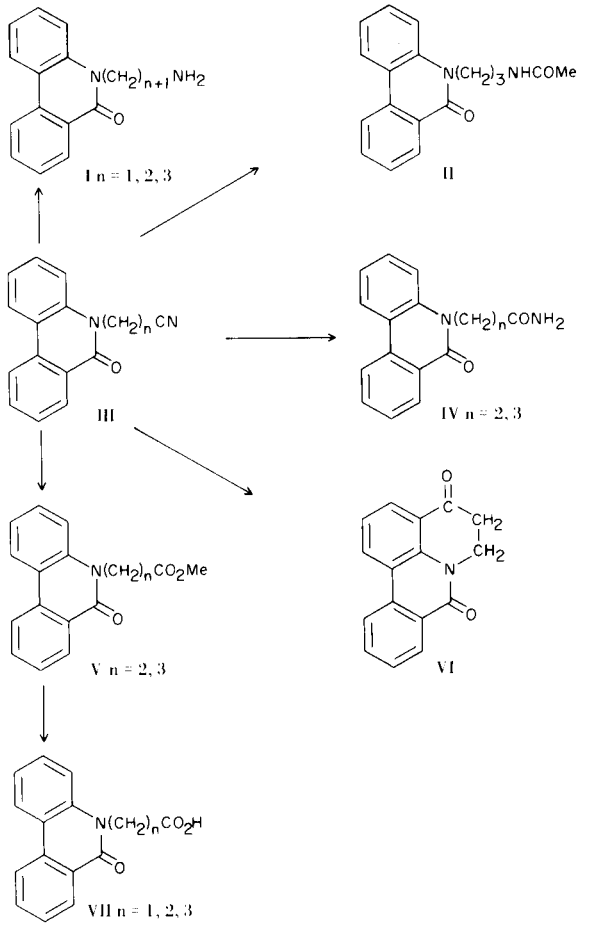
The alkylation of phenanthridone and some nuclear-substituted phenanthridones using sodium hydride in DMF/benzene is reported. Various 5-cyanoalkylphenanthridones were converted to further derivatives by either hydrolysis or reduction.

As an extension of our interest (1) in *N*-substituted phenanthridones, we have reacted phenanthridone and several 2- or 3-substituted phenanthridones with various alkylating agents. This is the first attempt at a systematic study of *N*-substituted phenanthridone derivatives, although other workers (2-8) have reported the alkylation of phenanthridones using a variety of methods.

REACTION SCHEME



We carried out the alkylations in a mixture of benzene and DMF at 90° using sodium hydride to generate the phenanthridone anion. In each reaction (see Table I), the main product was the *N*-substituted compound. Traces of *O*-substituted product were readily removed during crystallization.

Certain compounds required for the study could not be prepared by direct alkylation as the requisite alkylating agents were not readily available or would have been unstable under the basic reaction conditions. The easily synthesized cyanoalkyl substituted compounds III were, therefore, used as intermediates to prepare homologous series of esters, carboxylic acids, amides, and primary amines (see Table II and Reaction Scheme).

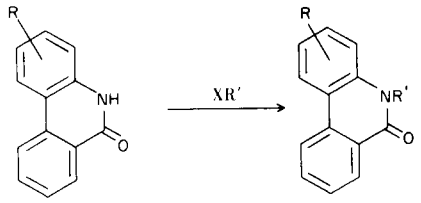
The esters V were obtained from the nitriles *via* their imino ethers. Crystallization of the crude methoxycarbonylpropyl compound from ethanol resulted in ester exchange and the formation of the corresponding ethyl ester. Alkaline hydrolysis of the esters using a 15% aqueous alcoholic solution of 4 *N* sodium hydroxide gave the corresponding acids on acidification.

Preparation of the primary amides from the cyanoalkyl compounds was more difficult. The amide IV, n = 3 was obtained from the cyanopropyl compound using polyphosphoric acid at 110°. The cyanoethyl compound gave the amide IV, n = 2 with concentrated sulphuric acid at room temperature. An attempt to use polyphosphoric acid to prepare this amide resulted in much decomposition and the isolation of a small amount of the cyclized compound VI, which has previously been prepared (9) by cyclization of the known phenanthridone propionic acid derivative.

The primary amines I were obtained by reduction of the nitriles using Raney nickel and hydrogen under pressure. Significant amounts of secondary amine formation were avoided by performing the reduction in dioxan saturated with ammonia. Reduction of the cyanoethyl compound at atmospheric pressure using platinum in

TABLE I

Alkylation of Phenanthridones



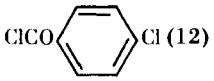
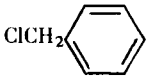
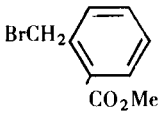
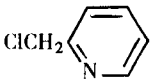
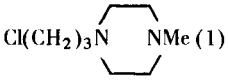
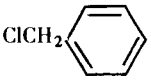
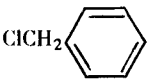
Compound	R	XR'	Yield %	Solvent	M.p., °C (11)	Formula
1	H	$Cl(CH_2)_3CN$	60	A/B	103-105	$C_{17}H_{14}N_2O$
2	H	CH_2=CHCN (7)	88	A	175-176 (a)	$C_{16}H_{12}N_2O$
3	H	$ClCH_2CN$	74	C	229-230	$C_{15}H_{10}N_2O$
4	H	$ClCH_2CO_2Me$ (5)	80	D	174-175 (b)	$C_{16}H_{13}NO_3$
5	H	$ClCH_2CO_2Et$	50	D	147-148	$C_{17}H_{15}NO_3$
6	H	$ClCH_2COMe$	32	D	169-172	$C_{16}H_{13}NO_2$
7	H	Br^nBu	40		58-60 (c)	$C_{17}H_{17}NO$
8	H	$Br\,CH_2C{\equiv}CH$	34	E	168-170	$C_{16}H_{11}NO$
9	H	 (12)	21	A	200-202 (d)	$C_{20}H_{12}ClNO_2$
10	H		52	F	153-154	$C_{20}H_{14}ClNO$
11	H		50	D	149-151	$C_{22}H_{17}NO_3$
12	H		45	D	146-148	$C_{19}H_{14}N_2O$
13	H	$Cl(CH_2)_3NMe_2$ (1)	60	F/G	225-226 (e)	$C_{18}H_{20}N_2O{\cdot}HCl{\cdot}H_2O$
14	H	$Cl(CH_2)_2NEt_2$ (13)	45	A/G	199-200 (f)	$C_{19}H_{22}N_2O{\cdot}HCl$
15	H	 (1)	20	H	185-188 dec.	$C_{21}H_{25}N_3 0.2C_4H_4O_4$
16	H	$Cl(CH_2)_3N(CH_2Ph)_2$	28	D	136-137	$C_{30}H_{28}N_2O$
17	H	$Cl(CH_2)_2N(CH_2Ph)_2$	52	I	150-151 (g)	$C_{29}H_{26}N_2O$
18	H	$Cl(CH_2)_3NMeCH_2Ph$ (1)	40	F/G	211-213	$C_{24}H_{24}N_2O{\cdot}HCl$
19	2-Br	IMe	81	D	190	$C_{14}H_{10}BrNO$
20	2-Br	$ClCH_2Ph$	62	D	165-167	$C_{20}H_{14}BrNO$
21	2-Br	$Cl(CH_2)_3NMe_2$	76	A	225-228	$C_{18}H_{19}BrN_2O{\cdot}HCl{\cdot}H_2O$
22	2-Br	$Cl(CH_2)_3CN$	67	D	127-130	$C_{17}H_{13}BrN_2O$
23	2-NO_2		62	J	235-237	$C_{20}H_{13}ClN_2O_3$
24	2-NO_2	$Cl(CH_2)_3NMe_2$ (1)	40	D	284-286 (h)	$C_{18}H_{19}N_3O_3{\cdot}HCl{\cdot}H_2O$
25	2-NO_2	$ClCH_2CO_2Me$	67	D	235-237	$C_{16}H_{12}N_2O_5$
26	2-CO_2Me		83	D	202-204	$C_{22}H_{16}ClNO_3$
27	2-CO_2Me	$Cl(CH_2)_3NMe_2$	72	A	225-227	$C_{20}H_{22}N_2O_3{\cdot}HCl$

TABLE I (continued)

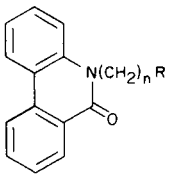
Compound	R	XR′	Yield %	Solvent	M.p., °C (11)	Formula
28	2-CO_2Me	$Cl(CH_2)_3CN$	47	E	166-168	$C_{19}H_{16}N_2O_3$
29	2-CO_2Me	$ClCH_2CO_2Me$	77	E	200-202	$C_{18}H_{15}NO_5$
30	3-Cl	$Cl(CH_2)_3NMe_2$ (1)	30	A	223-226	$C_{18}H_{19}ClN_2O\cdot HCl\cdot 1\frac{1}{2}H_2O$

(a) Lit. m.p. 169-170.5°. (b) Lit. m.p. 161°. (c) B.p. 160-165°/0.2 mm. (d) Lit. m.p. 198-200°. (e) Base m.p. 83-84.5° ex B. (f) Lit. m.p. 193-195°. (g) Hydrochloride, m.p. 232-233° ex D. (h) Base m.p. 113-114° ex I/B.

Solvents: A, 2-propanol. B, petrol (b.p. 40-60°). C, 2-ethoxyethanol. D, industrial methylated spirits. E, methanol. F, absolute alcohol. G, diethyl ether. H, nitromethane. I, acetone. J, benzene.

TABLE II

Compounds from Cyanoalkylphenanthridones



Compound	n	R	Yield, %	Solvent	M.p., °C	Formula
31	3	CO_2H	81	A/B	136-137	$C_{17}H_{15}NO_3$
32	2	CO_2H (9)	80	C	171-172	$C_{16}H_{13}NO_3$
33	1	CO_2H	41	A	260-261	$C_{15}H_{11}NO_3$
34	3	CO_2Me	99	D	114-115	$C_{18}H_{17}NO_3$
35	2	CO_2Me	99	D	132-133	$C_{17}H_{15}NO_3$
36	3	CO_2Et	95	E	98-100	$C_{19}H_{19}NO_3$
37	4	NH_2	35	A/F	212-214	$C_{17}H_{18}N_2O\cdot HCl$
38	3	NH_2	47	A	265-267	$C_{16}H_{16}N_2O\cdot HCl\cdot H_2O$
39	2	NH_2	21	D/F	*ca.* 260 dec.	$C_{15}H_{14}N_2O\cdot HCl$
40	3	$CONH_2$	74	D	216-217	$C_{17}H_{16}N_2O_2$
41	2	$CONH_2$	31	D	232-234	$C_{16}H_{14}N_2O_2$
42	3	NHCOMe	60	G	142-143	$C_{18}H_{18}N_2O_2$

Solvents: A, industrial methylated spirits. B, water. C, 2-propanol. D, methanol. E, absolute alcohol. F, diethyl ether. G, acetone.

acetic anhydride gave the acetamido compound II. This was also obtained by acetylation of the corresponding primary amine.

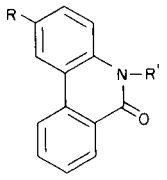
Reductive debenzylation of the dibenzylaminoethyl- and the benzylmethylaminopropyl compounds (see Table I) was achieved using palladium on charcoal in methanol at room temperature (see Table III). The second benzyl group in the dibenzylamino compound could not be removed by this method.

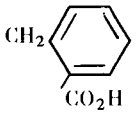
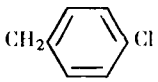
2-Methoxycarbonyl phenanthridone was prepared by esterification of the known 2-carboxy compound (10). Subsequent alkylation and alkaline hydrolysis afforded the 2,5-disubstituted compounds.

The infrared spectra of all the 5-mono substituted phenanthridones showed characteristic absorptions both in Nujol mulls and potassium bromide discs in the ranges 1660-1640 cm^{-1} (strong), 1620-1600 cm^{-1} (medium), 1600-1580 cm^{-1} (weak), 758-747 cm^{-1} (strong, occasionally split), and 732-723 cm^{-1} (strong). The pmr spectra of several *N*-substituted phenanthridones in deuteriodimethylsulphoxide showed the eight aromatic protons as a complex multiplet which was clearly divided into two

TABLE III

Other *N*-Alkyl Compounds



Compound	R	R′	Yield, %	Solvent	M.p., °C	Formula
43	H	$(CH_2)_3NHMe$ (I)	50	A	238-240	$C_{17}H_{18}N_2O$·HCl
44	H	$(CH_2)_2NHCH_2Ph$	20	B	270-272	$C_{23}H_{22}N_2O$·HCl
45	H		50	C	258-261	$C_{21}H_{15}NO_3$
46	CO_2H		71	D	308-310	$C_{21}H_{15}ClNO_3$
47	CO_2H	CH_2CO_2H	83	B	>360	$C_{16}H_{11}NO_5$
48	CO_2Me	H	92	E	283-285	$C_{15}H_{11}NO_3$

Solvents: A, absolute alcohol. B, industrial methylated spirits. C, DMF. D, acidification of solution of sodium salt. E, chloroform (ex Soxhlet).

APPENDIX

Analytical Data

Compound	Found C	Found H	Found N	Found Hal	Required C	Required H	Required N	Required Hal
1	78.1	5.4	10.7		77.8	5.4	10.7	
2	77.2	4.9	11.5		77.5	4.8	11.3	
3	76.7	4.5	11.8		77.0	4.3	11.7	
4	71.7	5.0	5.1		72.0	4.9	5.2	
5	72.6	5.3	5.2		72.6	5.3	5.0	
6	76.7	5.4	5.8		76.5	5.2	5.6	
7	81.3	6.8	5.6		81.2	6.8	5.6	
8	82.6	4.8	6.1		82.5	4.8	6.0	
9	71.8	3.8	4.2	11.2	72.0	3.6	4.2	10.7
10	75.0	4.5	4.5	11.2	75.1	4.4	4.4	11.1
11	77.1	5.1	4.1		77.0	5.0	4.1	
12	79.4	5.0	9.8		79.7	4.9	9.8	
13	64.6	6.8	8.5	10.5	64.6	6.9	8.4	10.6
14	68.8	6.9	8.3	10.7	69.0	7.0	8.5	10.7
15	61.2	5.9	7.2		61.4	5.9	7.4	
16	83.2	6.5	6.6		83.3	6.5	6.5	
17	83.4	6.3	6.9		83.3	6.3	6.7	
18	73.0	6.6	6.5	9.2	73.4	6.4	7.1	9.0
19	58.2	3.4	4.7	27.9	58.4	3.5	4.9	27.8
20	66.0	3.9	4.0	22.0	65.9	3.8	3.8	22.0
21	52.1	5.4	6.7	28.2	52.2	5.3	6.7	27.9
22	59.7	3.7	8.1	23.6	59.8	3.8	8.2	23.5

23	65.8	3.8	7.8	9.7	65.8	3.6	7.7	9.7
24	56.5	5.8	11.2	9.4	56.9	5.8	11.1	9.3
25	61.5	3.9	8.8		61.5	3.9	9.0	
26	69.4	4.3	3.8	9.6	69.9	4.2	3.7	9.4
27	64.0	5.8	7.4	9.7	64.1	6.1	7.5	9.5
28	71.0	5.6	8.8		71.3	5.6	8.8	
29	66.2	5.0	4.6		66.5	4.6	4.3	
30	56.9	6.2	7.7	19.1	57.1	6.1	7.4	18.7
31	72.6	5.3	4.7		72.6	5.3	5.0	
32	71.8	4.9	5.3		71.9	4.9	5.2	
33	71.0	4.4	5.6		71.2	4.4	5.5	
34	72.8	5.8	4.7		73.2	5.8	4.7	
35	72.4	5.4	5.0		72.6	5.4	5.0	
36	73.6	6.2	4.4		73.8	6.2	4.5	
37	67.2	6.5	9.1	11.4	67.4	6.3	9.3	11.7
38	63.0	6.1	9.0	11.5	62.7	6.2	9.1	11.6
39	65.2	5.7	13.0	10.1	65.5	5.5	12.9	10.2
40	72.6	5.7	9.9		72.5	5.7	10.0	
41	72.3	5.4	10.6		72.3	5.3	10.5	
42	73.4	6.0	9.7		73.5	6.1	9.5	
43	67.3	6.4	8.6	11.9	67.4	6.3	9.2	11.7
44	72.7	5.9	8.0	9.8	72.4	5.8	7.7	9.7
45	76.2	4.5	4.2		76.5	4.6	4.3	
46	68.9	4.1	3.9	9.7	69.3	3.9	3.9	9.8
47	64.8	4.0	4.7		64.6	3.7	4.7	
48	70.6	4.6	5.6		71.1	4.4	5.5	

regions. The low field region (3 protons) at δ 8.40-8.65 is presumably due to Van der Waals deshielding of the 1- and 10-protons and deshielding of the 7-proton by the carbonyl group. The remaining five protons appear at δ 7.35-8.15.

EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer 157 instrument and nmr spectra were measured on a Perkin-Elmer R10 machine operating at 60 MHz. The 2-substituted phenanthridones were prepared from phenanthridone by established methods (10). 3-Chlorophenanthridone was prepared as described by Hollingsworth and Petrow (14).

2-Methoxycarbonylphenanthridone.

A suspension of phenanthridone-2-carboxylic acid (10) (24.1 g.) in thionyl chloride (100 ml.) was refluxed for 2½ hours. The reaction mixture was concentrated under reduced pressure and then concentrated from dry benzene (twice). The residue was taken up in dry methanol (30 ml.) and dry pyridine (20 ml.) and kept for 2 hours. After dilution with water the precipitate was collected, dried and extracted in a Soxhlet apparatus with chloroform (600 ml.) for 48 hours to give the product as white plates.

General Alkylation Procedure.

One tenth mole of the phenanthridone was added portionwise to a mechanically stirred suspension of sodium hydride (4.8 g., 0.1 mole of a 50% suspension in mineral oil) in a mixture of dry DMF (100 ml.) and dry benzene (10 ml.) and the mixture was warmed at 90-100° for ½ hour. To the cooled solution was slowly added 0.11 mole of a solution of the alkyl halide in dry DMF (50 ml.) and the mixture was stirred at 100° for 4 hours. The reaction mixture was concentrated under reduced pressure and treated with water (*ca.* 1 liter). Filtration or chloroform extraction gave a solid product which was purified by crystallization.

Typical Reduction. 5-(4-Aminobutyl)phenanthridone.

5-(3-Cyanopropyl)phenanthridone (15 g.) and Raney nickel (*ca.* 1 g.) were heated in a saturated solution of ammonia in dioxan (500 ml.) in an autoclave under hydrogen (70 atm) at 140° for 12 hours. The reaction mixture was filtered and evaporated to small volume and then dried by azeotropic distillation with chloroform. The residual oil was taken up in chloroform and treated with ethereal hydrogen chloride solution and an excess of dry ether. The solid hydrochloride mixture obtained by acetone treatment of the residual gum was treated with water

to remove the sparingly soluble secondary amine hydrochloride. Basification of the filtered solution gave an oil which was extracted into chloroform. The washed and dried extract was treated with ethereal hydrogen chloride and evaporated to dryness. Subsequent acetone treatment and crystallization from a mixture of IMS and ether gave white crystals of the product.

Acknowledgment.

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