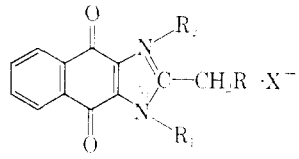
TABLE III

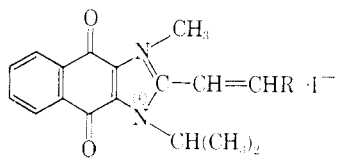
NAPHTH[2,3-*d*]IMIDAZOLIUM SALTS



No.	R	R_1	R_2	X	M.p., °C.	Yield, %	Formula	%N Calcd.	%N Found	%I Calcd.	%I Found
1	H	C_2H_5	CH_3	I	247–250	85	$C_{15}H_{15}IN_2O_2$	7.33	7.27	33.21	33.51
2	H	C_2H_5	$CH_3(CH_2)_2$	I	177–181	60	$C_{17}H_{19}IN_2O_2$	6.83	6.78	30.93	31.30
3	H	$(CH_3)_2CH$	CH_3	I	249–251	92	$C_{16}H_{17}IN_2O_2$	7.07	6.93	32.04	32.38
4	H	$(CH_3)_2CH$	$CH_3(CH_2)_2$	I	211–214	81	$C_{18}H_{21}IN_2O_2$	6.60	6.90	29.91	30.48
5	H	$CH_3(CH_2)_3$	CH_3	I	224–226	91	$C_{17}H_{19}IN_2O_2$	6.83	6.89		
6	H	$CH_3(CH_2)_3$	C_2H_5	I	127–129	35	$C_{18}H_{21}IN_2O_2$	6.60	6.51		
7	H	$CH_3(CH_2)_3$	$C_6H_5CH_2$	Cl	179–181	30	$C_{23}H_{23}ClN_2O_2$	7.09	7.19		
8	H	$CH_3(CH_2)_3$	$4\text{-}O_2NC_6H_4CH_2$	Br	235–236	83	$C_{23}H_{22}BrN_3O_4$	8.68	8.72		
9	H	$CH_3(CH_2)_3$	$4\text{-}O_2NC_6H_4COCO_2$	Br	224–225	75	$C_{24}H_{22}BrN_3O_5$	8.20	8.18		
10	H	$CH_3(CH_2)_3$	$C_6H_5CH_2CH_2$	Br	203–206	75	$C_{24}H_{25}BrN_2O_2$	6.18	6.11		
11	H	$C_6H_5CH_2$	CH_3	I	210 dec.	87	$C_{20}H_{17}IN_2O_2$	6.31	6.22	28.57	28.97
12	H	C_6H_5	CH_3	I	273–275	60	$C_{19}H_{15}IN_2O_2$	6.52	6.63	29.50	30.30
13	H	$2\text{-}CH_3OC_6H_5$	CH_3	I	277–280	50	$C_{20}H_{17}IN_2O_3$	6.10	6.23	27.63	27.93
14	H	C_6H_5	$4\text{-}O_2NC_6H_4CH_2$	Br	234–236	74	$C_{23}H_{18}BrN_3O_4$	8.34	8.30		
15	H	$(CH_3)_2CHCH_2$	CH_3	I	226–227	62	$C_{17}H_{19}IN_2O_2$	6.83	6.72	30.93	31.30
16	H	$(CH_3)_2CHCH_2$	$4\text{-}O_2NC_6H_4COCH_2$	Br	230–231	86	$C_{24}H_{22}BrN_3O_5$	8.20	8.27		
17	C_6H_5	$CH_3(CH_2)_3$	CH_3	I	135–136	71	$C_{23}H_{23}IN_2O_2$	5.76	5.69		

TABLE IV

STYRYL DERIVATIVES OF NAPHTH[2,3-*d*]IMIDAZOLIUM SALTS



No.	R	M.p., °C.	Yield, %	Formula	%N Calcd.	%N Found
1	C_6H_5	218–219.5	90	$C_{23}H_{21}IN_2O_2$	5.79	6.22
2	$2\text{-}ClC_6H_4$	214–215	13	$C_{23}H_{20}ClIN_2O_2$	5.40	5.69
3	$4\text{-}(CH_3)_2NC_6H_4$	212–214	31	$C_{25}H_{26}IN_3O_2$	7.97	8.01
4	$4\text{-}CH_3OC_6H_4$	210–211	30	$C_{24}H_{23}IN_2O_3$[a]	5.45	5.59
5	$4\text{-}HOC_6H_4$	245–247	36	$C_{23}H_{21}IN_2O_3$[b]	5.60	5.87

[a] *Anal.* Calcd.: I, 24.70. Found: I, 25.03. [b] *Anal.* Calcd.: I, 25.36. Found: I, 25.39.

2-Methyl-1-phenylnaphth[2,3-*d*]imidazole-4,9-dione. A.—A mixture of 30.6 g (0.10 mole) of 2-acetamido-3-phenyl-1,4-naphthoquinone[4] and 500 ml. of ethanol was heated to reflux and 50 ml. of 2 *N* NaOH was added. The mixture was heated 30 min., diluted with 500 ml. of hot water, 50 ml. of 2 *N* HCl added, filtered, and cooled. The yellow needles were recovered and dried yielding 25 g. (80%), m.p. 240–241°.

Other imidazoles were prepared in the same manner and when necessary they were recrystallized from dioxane. The data for these compounds are recorded in Table II.

B.—A solution of 24.95 g. (0.10 mole) of 2-acetamido-3-chloro-1,4-naphthoquinone in 200 ml. of ethanol was heated to reflux and a solution of 9.3 g. (0.10 mole) of aniline in 25 ml. of ethanol was added. The mixture was refluxed for 6 hr., diluted with 100 ml. of water, and cooled. The yellow precipitate was collected and dried, m.p. 238–240°. Recrystallization gave 21 g. (73%) of bright yellow needles of the imidazole, m.p. 239–241°.

4,9-Dihydro-1,2-dimethyl-4,9-dioxo-3-(2-propyl)naphth[2,3-*d*]imidazolium Iodide.—A solution of 25.4 g. (0.10 mole) of 2-methyl-1-(2-propyl)naphth[2,3-*d*]imidazole-4,9-dione, 200 ml. of Methyl Cellosolve, and 19 g. of methyl iodide was refluxed for 4 hr., cooled, and a reddish powder recovered. Recrystallization from methanol gave 35 g. (88.5%), m.p. 249–251° dec., of the quaternary salt (see Table III).

The other quaternary salts were prepared and purified in the same manner and all the data for these compounds are included in Table III.

4,9-Dihydro-4,9-dioxo-1-methyl-1-(2-propyl)-2-(β-styryl)naphth[2,3-*d*]imidazolium Iodide.—A mixture of 5 g. (0.0126 mole) of 4,9-dihydro-1,2-dimethyl-4,9-dioxo-3-(2-propyl)naphth[2,3-*d*]imidazolium iodide, 3 g. (0.028 mole) of benzaldehyde, 60 ml. of dioxane, and 1 ml. of piperidine was refluxed for 2 hr. The mixture was cooled, filtered, and the orange product (5.5 g., 90%) was recrystallized from methanol, m.p. 218–219.5° dec.

Other styryl derivatives were prepared in the same manner and are included in Table IV.

2-Chloro-3-(N-methylacetamido)-1,4-naphthoquinone.—A mixture of 8 g. (0.0362 mole) of 2-methylamino-1,4-naphthoquinone (m.p. 117–119°), 5 ml. of acetic anhydride, and 2 drops of H_2SO_4 was stirred and warmed on a steam bath for 2 hr. The thick paste was washed with ether and water and finally recrystallized from methanol. Nine grams (94.7%) of yellow-orange crystals was obtained, m.p. 123–125°.

Anal. Calcd. for $C_{13}H_{10}ClNO_3$: N, 5.31. Found: N, 5.69.[15]

2-(N-Methylacetamido)-3-(2-propylamino)-1,4-naphthoquinone. (VI).—A mixture of 2.6 g. (0.01 mole) of 2-chloro-3-(N-methylacetamido)-1,4-naphthoquinone, 2 g. of isopropylamine, and 50 ml. of ethanol was warmed on a steam bath for 2 hr. Isolation and recrystallization of the orange crystals from methanol gave 1.5 g. (50%) of product, m.p. 198–199.5° dec.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: N, 9.78. Found: N, 9.68.

Hydrolysis of 4,9-dihydro-1,2-dimethyl-4,9-dioxo-3-(2-propyl)naphth[2,3-*d*]imidazolium Iodide (V).—A mixture of 1 g. of V and 100 ml. of ethanol was stirred with 10 ml. of 2 *N* sodium hydroxide for 10 min. The orange solid was removed and recrystallized from methanol, m.p. 198–199°. The infrared spectrum of this product was identical with 2-(N-methylacetamido)-3-(2-propyl)-1,4-naphthoquinone (IV).

(15) All nitrogen determinations were made with a Coleman Model 99 nitrogen analyzer.

Pyridylurethanes of Pharmacological Interest

N. P. BUU-HOÏ, RICHARD RIPS, AND CHRISTIAN DERAPPE

Institut de Chimie du C.N.R.S., Gif-sur-Yvette (S.-et-O.), and Institut d'Anesthesiologie de la Faculté de Médecine de Paris, Paris, France

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Although urethanes of the pyridyl group have occasionally been prepared and their chemical properties investigated, their pharmacological potentialities have not, to our knowledge, yet been explored. In view of the interesting biological activity of certain urethanes,

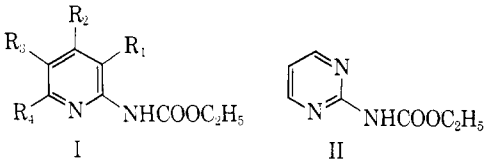
TABLE I

SYMMETRICAL N,N'-DIPYRIDYLUREAS (III)

Urea	M.p., °C.	Yield, %	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
N,N'-Di(3-methyl-2-pyridyl)-[a]	133	8	$C_{13}H_{14}N_4O$	64.4	64.7	5.8	5.9	23.1	23.3
N,N'-Di(4-methyl-2-pyridyl)-[b]	228	5–10	$C_{13}H_{14}N_4O$	64.4	64.5	5.8	5.8	23.1	22.8
N,N'-Di(5-methyl-2-pyridyl)-[c]	215	6	$C_{13}H_{14}N_4O$	64.4	64.3	5.8	5.8	23.1	22.9
N,N'-Di(6-methyl-2-pyridyl)-[d]	186	2	$C_{13}H_{14}N_4O$	...	...	...	...	...	...
N,N'-Di(4,6-dimethyl-2-pyridyl)-[e]	240	2	$C_{15}H_{18}N_4O$	66.7	66.8	6.7	6.4	20.7	20.8
N,N'-Di(5-nitro-2-pyridyl)-[f]	303	0.5	$C_{11}H_8N_6O_5$	43.4	43.8	2.7	2.7	27.6	27.2

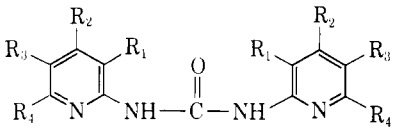
[a] *Anal.* Calcd.: O, 6.6. Found: O, 6.7; crystallized from heptane. [b] *Anal.* Calcd.: O, 6.6 Found: O, 6.9; crystallized from acetone; lit.[2] m.p. 222–224°. [c] Crystallized from acetone. [d] Crystallized from acetone: H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951), report m.p. 190°. [e] *Anal.* Calcd.: O, 5.9. Found: O, 6.1; crystallized from cyclohexane–benzene. [f] Pale yellow prisms; crystallized from pentanol.

especially for tranquillizing activity,[1] we have prepared a number of urethanes (I) derived from 2-aminopyridines, for pharmacological evaluation. The most convenient method was to react these amines with ethyl chloroformate in pyridine medium[2]; we found that in almost every instance, the reaction product was a mixture of small amounts of the symmetrical dipyridylurea with the urethane as main product, the exception being 2-amino-5-chloropyridine, where no symmetrical urea was obtained. In the case of 2-



I

II



III

amino-3-methylpyridine, whose amino group is sterically hindered, the yield of the urethane was much lower than with the other isomers, and considerable amounts of the starting material were recovered. Separation of the urea from the urethane was readily achieved by using the zone-melting procedure,[3] save in the case of 5-nitro-2-pyridylurethane, which was decomposed by prolonged heating.

This urethane synthesis was successfully extended to 2-aminopyrimidine, which gave a 33% yield of 2-pyrimidylurethane (II); no N,N'-di(2-pyrimidyl)-urea could be isolated.

Experimental

Reaction of Ethyl Chloroformate with Aminopyridines.—After a study of the influence of various factors (temperature, solvents, treatment of reaction product), the following technique was adopted. To a well-stirred solution of 10 g. of a 2-aminomethylpyridine (or the equivalent of the appropriate amine) in 15 ml. of anhydrous pyridine, 17 ml. of ethyl chloroformate was added dropwise during 40 min., the temperature being maintained between 2° and 10° by external refrigeration; the mixture was then stirred for 45 min., and treated with 500 ml. of water. After 1 hr., the precipitate which formed was collected, washed thoroughly with water, and dried *in vacuo*. Separation of the urethane from the symmetrical urea was achieved either by fractional crystallization from hexane or heptane, which left an insoluble residue of the urea, or by means of a zone-melting apparatus (10 to 30 runs at 3 cm./hr.). All the urethanes were shiny colorless needles. In the case of 2-amino-3-methylpyridine, the urethane tended to remain oily and was therefore taken up in methylene chloride, the organic layer washed several times with water, and dried over sodium sulfate, and the solvent distilled; the residue was vacuum fractionated, and the portion, b.p. 170–175° (21 mm.) was recrystallized from hexane.

The 4-methyl-,[2] 5-methyl-,[4] 6-methyl-,[5] 4,6-dimethyl-,[4] and 5-nitro-2-pyridylurethanes[6] are known compounds. The following new urethanes were prepared: **3-methyl-2-pyridylurethane,** 20% yield, m.p. 78°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.7; N, 15.5. Found: C, 59.8; H, 6.8; N, 15.7;

5-Chloro-2-pyridylurethane, 55% yield, m.p. 180°.

Anal. Calcd. for $C_8H_9N_2O_4$: C, 47.9; H, 4.5; N, 14.0. Found: C, 48.0; H, 4.5; N, 13.8;

2-Pyrimidylurethane, prepared in 25% yield from 2-aminopyrimidine; crystallized from heptane as shiny colorless needles, m.p. 114°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.3; H, 5.4; N, 25.1. Found: C, 50.4; H, 5.4; N, 25.3.

Pharmacological Investigations.—4-, 5-, and 6-methyl-2-pyridylurethane were selected for an extensive evaluation of their potential activity on the central nervous system, by means of various tests. As 5-chloro- and 5-nitropyridylurethanes proved toxic, they were not submitted to pharmacological testing. The ureas were tested for other types of activity (antimitotic and bacteriostatic) and results will be reported later.

(1) **Acute Toxicities.**—These were determined in mice, by oral administration. The LD_{50} was 6–7 g./kg. for 4-methyl-2-pyridylurethane, and 3–4 g./kg. for 6-methyl-2-pyridylurethane; 5-methyl-2-pyridylurethane showed a very low degree of toxicity, a dose of 4 g./kg. producing only a 20% mortality rate. The acute symptoms observed were prostration, lethargy, and, with 6-methyl-2-pyridylurethane, paresia of the hind quarters, loss of balance, and deep sleep.

(2) **Determination of Analgesic Activity.**—This was effected by the Haffner method,[7] using a technique of Buchel and Tanguy[8] based on induction of pain in the mouse tail by a mechanical stimulus. Aminopyrine (administered orally to the controls in a dose of 250 mg./kg., which produced analgesia during 2 hr. following administration) was used as the reference. 4-Methyl-2-pyridylurethane showed a weak analgesic activity, lasting 30 min. after oral administration of a dose of 1 g./kg.; the other two compounds showed no activity at the same dosage.

(3) **Synergism Tests with Thiopental.**—These were performed in mice weighing 18 to 22 g., which were given, by intraperitoneal injection, a dose of 40 mg./kg. of thiopental (sodium derivative). The animals were divided into two groups, one group serving as controls and the other receiving, orally, the urethane to be tested. Results are expressed in the percentage of animals which fell asleep and the average duration of the sleep. They show that all three urethanes potentiate the action of thiopental: with 4-methyl-2-pyridylurethane, a dose of 100 mg./kg. produced a 50% increase in the number of mice falling asleep and doubled the duration of the sleep; with 5-methyl-2-pyridylurethane, a

(1) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **112**, 413 (1954).
(2) A. R. Katritzky, *J. Chem. Soc.*, 2063 (1956).
(3) E. F. G. Herington, "Zone Melting of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1963.
(4) A. R. Katritzky, *J. Chem. Soc.*, 4385 (1957).
(5) G. R. Clemo, B. W. Fox, and R. Raper, *ibid.*, 2693 (1954).
(6) H. M. Curry and J. P. Mason, *J. Am. Chem. Soc.*, **73**, 5043 (1951).
(7) F. Haffner, *Deut. Med. Wochschr.*, **55**, 731 (1929).
(8) L. Buchel and O. Tanguy, *Anesthésie Analgésie*, **13**, 879 (1956).

dose of 1 g./kg. produced a 33% increase in the number of animals falling asleep and likewise doubled the duration of the sleep, and the same results were achieved when 6-methyl-2-pyridylurethane was given in a dose of 500 mg./kg. The three urethanes did not interfere with the potentiating activity of serotonin on the hypnotic properties of thiopental.

(4) Tests for Antagonistic Activity Toward Agitation Induced by 1,4-Dipyrrolidino-2-butyne (Tremorine) and Amphetamine.—With oral doses of 100 mg./kg., none of the three urethanes displayed an antagonistic effect toward agitation induced in mice by an intraperitoneal injection of 25 mg./kg. of 1,4-dipyrrolidino-2-butyne. In the amphetamine test,[9] 4-methyl- and 5-methyl-2-pyridylurethane showed a slight, and 6-methyl-2-pyridylurethane a more pronounced, protective effect against agitation induced in mice by an oral dose of 25 mg./kg. given 30 min. after ingestion of 100 mg./kg. of the urethane.

(5) Tests for Neuroleptic Activity.—Mice were used. In the jiggle cage test,[9] 4-methyl-2-pyridylurethane produced a reduction of spontaneous motility of the mice lasting several hours after the oral administration of 100 mg./kg. and higher. The other two urethanes were inactive in this respect.

In the Julou and Courvoisier hoist test in mice,[9] only a slight sedative effect was observed with a dose of 1 g./kg. given orally. In this test, a horizontal wire is presented to the forepaws of the mouse; in normal conditions, the mouse will grasp the wire and, in under 5 sec., hoist itself up so that at least one of its hindpaws gets on the wire. This hoist effect is suppressed by neuroleptics, including drugs of the meprobamate type.

(6) Test for Antipyretic Activity.—This test, based on observation of the thermoregulation in rabbits submitted to the hyperthermia-inducing action (increase in rectal temperature) of a standardized antigonococcal vaccine given intraveneously, was performed only with 4-methyl-2-pyridylurethane. An oral dose of 100 mg./kg. reduced by about 0.5–0.9° the central hyperthermia induced by a dose of 100 × 10^6 germs/kg. of vaccine.

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(9) *Cf.* J. R. Boissier, *Acta Neurophysiologia*, **2**, 253 (1960).

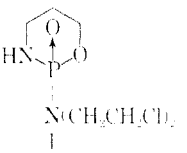
1,3,2-Diazaphosphorinane 2-Oxides. 1. Synthesis of Some 2-(N-Arylamino)-1,3,2-diazaphosphorinane 2-Oxides[1]

JOHN H. BILLMAN, JOHN L. MEISENHEIMER, AND RICHARD A. AWL

Department of Chemistry, Indiana University, Bloomington, Indiana

Received September 12, 1963

Cyclophosphamide (I),[2] prepared by Arnold, *et al.*,[3] is an inhibitor of many animal and human tumors. Its action is assumed to be through the enzymatic liberation of the bis(2-chloroethyl)amine moiety. The similar triamido compound (II) has been prepared, but unlike I, it has not displayed antitumor activity.[4,5]



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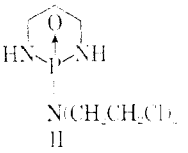
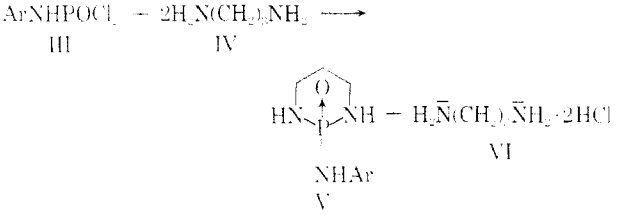


II

This paper reports on the preparation of a series of compounds of the general structure V. Early antitumor testing of the first member of this series to be prepared (IX, Table I) was suggestive of inhibitory activity. Therefore, additional members of the series were prepared to explore this structural area for possible active antitumor compounds. Since these compounds possess an arylamino group on the phosphorus atom instead of a bis(2-chloroethyl)amino substituent, any biological activity exhibited would result from some factor other than the potential alkylating action of the latter grouping.

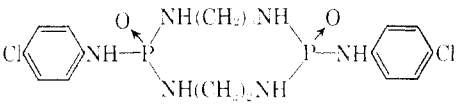
The syntheses were accomplished by reacting a phosphoramidic dichloride (III) with 2 moles of 1,3-diaminopropane (IV) in benzene to give the 2-substituted 1,3,2-diazaphosphorinane 2-oxide (V) and 1 mole of the diamine dihydrochloride (VI). The compounds V were



III IV V VI

quite polar in nature and separated from benzene along with the diamine dihydrochloride (VI). Fortunately the phosphorus–nitrogen bonds in these compounds were found to be quite stable with respect to alkaline hydrolysis so that they could be separated from VI in a basic solution by converting VI to the free diamine.

The calculated formula weight for X (Table I) is 246. A molecular weight determination for this compound by the Rast camphor method indicated a value of 510.[6] Therefore, there was the possibility that the compound might have the structure VII. A molecular weight determination was then made by a vapor pressure lowering method using methanol as a solvent.[7] This method indicated a molecular weight of 259, thus ruling out a structure such as VII. A determination



VII

of the molecular weight of compound IX by this latter method gave a value of 255. Its calculated formula weight is 241. It may be that these 2-substituted 1,3,2-diazaphosphorinane 2-oxides are dimeric in the solid state due to hydrogen bonding and are dissociated in the polar solvent, methanol.

Biological Results.—The compounds in Table I have been screened against Sarcoma 180, Carcinoma 755, Leukemia 1210, and a cell culture system.[8] It is

(1) This investigation was supported in part by a Public Health Service Fellowship (GF-13,650), National Institutes of Health, Public Health Service.

(2) Cytoxan®.

(3) H. Arnold, F. Bourseaux, and N. Brock, *Nature*, **181**, 131 (1958).

(4) H. Arnold, F. Bourseaux, and N. Brock, *Arzneimittel-Forsch.*, **2a**, 143 (1961).

(5) O. M. Friedman, E. Boger, V. Grubliauskas, and H. Sommer, *J. Med. Chem.*, **6**, 50 (1963).

(6) Bernhardt Laboratories, Mülheim, Germany.

(7) A Mechrolab Osmometer was employed.

(8) Antitumor screening was accomplished by the Cancer Chemotherapy National Service Center, Bethesda, Md.