Phosphorus Analogs of Carbromal

SHREEKRISHNA M. GADEKAR AND ERNEST ROSS

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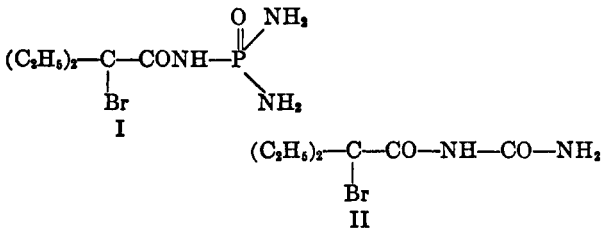
In view of the carry over of biological activity observed by Ramaswami and Kirch[1] for dialkylanilidophosphates, which may be considered as phosphoryl analogs of phenylurethane by substituting the P=O group for the C=O group, it seemed desirable to prepare a series of 2-bromo-*N*-diaminophosphinyl-2-ethylbutryamides I for evaluation as sedatives. These compounds may also be looked upon as phosphorus analogs of carbromal II, in which the ureido carbonyl group is replaced by the P=O group.



The compounds described were prepared by the reaction of (2-bromo-2-ethylbutyryl)phosphoramidic dichloride with either ammonia or substituted amines in dry ether and are listed in Table I.

Pharmacological evaluation of these compounds in experimental animals as sedatives revealed that the most potent compound in the series was the one where R was NH_2 (Table I); however, it was considerably less active than carbromal.

EXPERIMENTAL[2]

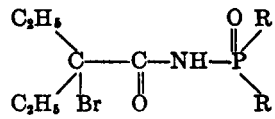
(2-Bromo-2-ethylbutyryl)phosphoramidic dichloride. A well integrated mixture of 3.9 g. (0.20 mole) of α-bromodiethylacetamide, 4.2 g. (0.20 mole) of phosphorus pentachloride, and 15 ml. of dry benzene was maintained at 50–55° for 25 min. The reaction mixture was then chilled in ice water bath and treated cautiously with 0.57 g. of concd. hydrochloric acid[3] with vigorous stirring. This was allowed to warm to room temperature and then concentrated *in vacuo* to a solid residue. One recrystallization of this from petroleum ether (b.p. 90–100°) afforded 4.5 g. (70%) of a crystalline, white solid; m.p. 103–104°.

Anal. Calcd. for $C_6H_{11}BrCl_2NO_2P$: C, 23.2; H, 3.53; Br, 25.7; Cl, 22.8; P, 9.95. Found: C, 23.5; H, 3.80; Br[4], 24.7; Cl, 22.9; P, 9.54.

2-Bromo-N-diaminophosphinyl-2-ethylbutyramide. A solution of 0.93 g. (0.0030 mole) of (2-bromo-2-ethylbutyryl)-phosphoramidic dichloride in ether was cooled in an ice water bath under anhydrous conditions and then saturated with ammonia. The mixture, after standing at room temperature for 1 hr., was filtered and the solid on the funnel was thoroughly washed with ice water to remove salts. The insoluble residue, 0.8 g. (98%) after two recrystallizations from an ethanol–petroleum ether (b.p. 90–100°) mixture, gave a satisfactory analysis. The physical data on this and other amides which were prepared similarly is given in Table I.

TABLE I

2-BROMO-*N*-DIAMINOPHOSPHINYL-2-ETHYLBUTYRAMIDES



R	M.p.	Yield, %	Formula	Calcd. C	H	Br	N	P	Found C	H	Br	N	P
NH_2	133–135	98	$C_6H_{15}BrN_3O_2P$	26.4	5.51	29.4	15.4	11.4	26.8	5.72	29.5	15.2	11.1
$NHCH_3$	146–148	85	$C_7H_{17}BrN_3O_2P$	32.0	6.33	26.6	14.0	10.3	32.3	6.59	26.9	13.9	10.1
$NHCH(CH_3)_2$	154–155	64	$C_{12}H_{27}BrN_3O_2P$	40.4	7.57	22.4	11.7	8.58	40.7	7.85	22.5	11.9	8.53
	103–104	56	$C_{14}H_{27}BrN_3O_2P$	44.2	7.10	21.0	11.1	8.15	44.3	7.03	20.8	11.2	...
	119–120	36	$C_{14}H_{27}BrN_3O_4P$	40.7	6.55	19.4	10.1	7.52	40.8	6.74	19.7	10.2	7.49
NHC_6H_5	185–186	33	$C_{18}H_{23}BrN_3O_2P$	50.8	5.41	18.8	9.87	7.29	50.8	5.76	19.2	10.1	6.94
$N(CH_3)C_6H_5$	110–111	45	$C_{20}H_{27}BrN_3O_2P$	53.1	5.96	17.7	9.30	6.86	52.8	6.15	18.0	8.93	6.84
p-NHC_6H_4Cl	206–207	51	$C_{18}H_{21}BrCl_2N_3O_2P$	43.8	4.27	16.2	8.53	6.29	44.0	4.50	15.8	8.25	6.02
$NHCH_2C_6H_5$	122–123	82	$C_{20}H_{27}BrN_3O_2P$	53.1	5.96	17.7	9.30	6.86	53.4	6.51	17.9	9.44	6.75

The phosphoramidic dichloride was prepared from α-bromodiethylacetamide and phosphorus pentachloride as described in the experimental section.

Acknowledgment: The authors are indebted to Dr. S. Kushner for encouragement and interest

(1) D. Ramaswami and E. R. Kirch, *J. Am. Pharm. Assoc.*, 42, 495 (1953). These workers observed that dialkylanilidophosphates exhibited anticonvulsant action in mice, and a selective inhibitory effect on the germination of oat and yellow charlock seeds.

(2) All melting points are uncorrected.

(3) A. W. Titherley and E. Woerall, *J. Chem. Soc.*, 1143 (1909). These workers prepared benzoylphosphoramidic dichloride by exposing the benzene solution of benzamide and phosphorus pentachloride to air for twelve hours. We obtained better yields of our phosphoramidic dichloride by adding the required amount of water in the form of concd. hydrochloric acid.

in the work, Dr. A. C. Osterberg, Pharmacology Department, Experimental Therapeutic Section, for the activity data, Mr. L. Brancone and his associates for the analyses, and Mr. W. L. McEwen and his staff for certain large scale preparations of intermediates.

ORGANIC CHEMICAL RESEARCH SECTION
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID CO.
PEARL RIVER, N. Y.

(4) A satisfactory bromine analysis was not obtained.

Heterocyclic Compounds. VIII. 2-(2-Thenoyl)-1-naphthoic Acid and 1-(2-Thenoyl)-2-naphthoic Acid[1]

MILTON C. KLOETZEL, WILLIAM KING, WILLIAM J. WASSERMAN, CHARLES K. WARREN, AND PER A. LARSSEN

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Projected syntheses of certain benzothiophanthrene derivatives required that we prepare 2-(2-thenoyl)-1-naphthoic acid (IX) and 1-(2-thenoyl)-2-naphthoic acid (X) as intermediates. New methods for obtaining these known[2a,2b] acids are reported at this time.

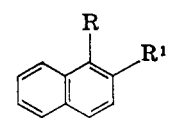
As the first step toward the synthesis of IX, commercially available 2-aminonaphthalene-1-sulfonic acid (I) was acetylated and the product was isolated either as the free acid (II) or its pyridinium salt. The latter was readily handled but the free acid was not recrystallized successfully without decomposition.

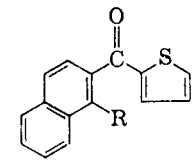
Excellent yields of 2-acetylamino-1-chloronaphthalene (III), 2-acetylamino-1-bromonaphthalene (IV), and 2-acetylamino-1-iodonaphthalene (V) were obtained rapidly from either II or its pyridinium salt merely by treatment in aqueous solution at room temperature with chlorine, bromine, and iodine monochloride, respectively. This halogenation reaction was suggested by the observation that the sulfonic acid group can be removed quantitatively from 2-amino-1-naphthalenesulfonic acid by means of bromine in aqueous solution at room temperature.[3] The sulfonic acid group was recovered quantitatively as sulfate ion but the fate of the organic nucleus was not reported at that time.

Halides III, IV, and V were identical with those obtained previously by halogenation of 2-acetylaminonaphthalene.[4-8] The method we report is advantageous, however, because halogenation is accomplished in water rather than in acetic acid, is not accompanied by dihalogenation, and affords superior yields of products.

Known methods[9,10] were employed to convert IV to 1-bromo-2-naphthoic acid, the chloride of which condensed with thiophene in the presence of anhydrous stannic chloride to give an excellent yield of 1-bromo-2-(2-thenoyl)-naphthalene (VII). Treatment of VII with cuprous cyanide in pyridine gave ketonitrile VIII, which was subsequently hydrolyzed with boiling aqueous sulfuric acid to produce 2-(2-thenoyl)-1-naphthoic acid (IX).

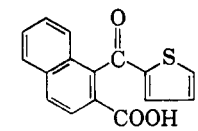
The isomeric 1-(2-thenoyl)-2-naphthoic acid (X) was isolated in 27% yield when thiophene was allowed to react with 1,2-naphthalic anhydride[11] in carbon disulfide, under the catalytic influence of aluminum chloride. This yield is nearly double that reported for this isomer from other methods of preparation.[1,2]





I. R = SO_3H; R^1 = NH_2
II. R = SO_3H; R^1 = $NHCOCH_3$
III. R = Cl; R^1 = $NHCOCH_3$
IV. R = Br; R^1 = $NHCOCH_3$
V. R = I; R^1 = $NHCOCH_3$
VI. R = Br; R^1 = COCl

VII. R = Br
VIII. R = CN
IX. R = COOH



X

EXPERIMENTAL[12]

Acetylation of 2-amino-1-naphthalenesulfonic acid. (a) Pyridinium 2-acetylamino-1-naphthalenesulfonate. To a suspension of technical 2-amino-1-naphthalenesulfonic acid (250 g.) in acetic anhydride (125 ml.) was added a mixture of pyridine (125 ml.) and acetic anhydride (125 ml.). Heat was evolved and all solid material dissolved. Upon standing at room temperature the solution deposited large colorless crystals of pyridinium 2-acetylamino-1-naphthalenesulfo-

(1) This reports part of a study supported by Research Grant No. CY-2362 (C3) from the National Cancer Institute, National Institutes of Health, Public Health Service, which we gratefully acknowledge.

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(2b) M. S. Newman and K. G. Ihrman, *J. Am. Chem. Soc.*, **80**, 3652 (1958).

(3) W. Vaubel, *Z. Angew. Chem.*, **14**, 686 (1900).

(4) H. Franzen and G. Stäuble, *J. prakt. Chem.*, (2), **103**, 352 (1921–1922).

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(6) E. Lellman and O. Schmidt, *Ber.*, **20**, 3154 (1887).

(7) P. T. Cleve, *Ber.*, **20**, 1989 (1887).

(8) H. Willstaedt and G. Scheiber, *Ber.*, **67**, 466 (1934).

(9) H. Franzen and A. Eidis, *J. prakt. Chem.* (2), **88**, 755 (1913).

(10) W. H. D. Boyes, J. L. Grieve, and H. G. Rule, *J. Chem. Soc.*, 1833 (1938).

(11) E. B. Hershberg and L. F. Fieser, *Org. Syntheses*, Coll. Vol. II, 423 (1943).

(12) Melting points are uncorrected. Microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, and by Micro-Tech Laboratories, Skokie, Ill.