The product was given a quick distillation (1–2 mm.) to yield 6.5 g. of a yellow oil. The oil was extracted with 1.1 *N* sodium hydroxide solution to separate the naphthol as the sodium salt. Acidification of the aqueous phase yielded 4 g. of crude V. Recrystallizations from isoöctane gave pure 2-isopropyl-1-naphthol (V), m.p. 47–48°.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.5; H, 7.58.

The benzoate of V was prepared by reaction with benzoyl chloride in the presence of pyridine (as described by Meyer and Bernhauer[1]) and after recrystallization from ethanol and isoöctane was found to melt at 67–68°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.4; H, 6.16.

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Polybenzyls from Benzyl Alcohol and Sulfuryl Chloride

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RECEIVED JULY 8, 1955

Gladstone and Tribe[2] noted the production of hydrocarbons of the formula $(C_7H_6)_n$ on pouring benzyl bromide over a copper–zinc couple. Friedel and Crafts[3] obtained similar material of the same empirical formula by the action of aluminum chloride upon benzyl chloride, a reaction which was studied further by Jacobson,[4] who noted that the substance formed with stannic chloride contained 1.4% chlorine. The products were considered to be essentially polybenzyls formed from the polymerizing unit —  —CH_2—.

What is probably a closely similar material was formed in an attempt to prepare benzyl chlorosulfonate by the action of sulfuryl chloride upon benzyl alcohol. The product was a green solid which slowly turned pink on exposure to air. Its analysis was in accord with the formula $H(C_7H_6)_{10}Cl$. The chlorine may be a chain terminal unit. Hydrogen chloride and sulfur dioxide were evolved in the reaction, the stoichiometry of which is not established.

Experimental

In an attempt to prepare benzyl chlorosulfonate, 21.6 g. (0.2 mole) of benzyl alcohol was added slowly to 27 g. (0.2 mole) of sulfuryl chloride at 0°, according to the general procedure described by Binkley and Degering.[5] During the addition of benzyl alcohol (about 90 min.), hydrogen chloride was evolved continuously. The resultant pale yellow viscous liquid (which sometimes contained a small amount of solid material) was stable provided that the temperature was maintained below 5°. On warming to room temperature, the mixture underwent a vigorous exothermic reaction. Hydrogen chloride and sulfur dioxide were evolved and a greenish mud was produced which solidified on cooling and slowly turned pink on exposure to air. The resin as obtained was contaminated by trapped gases and by a sulfur-containing material. Purification was complicated by the tendency of the material to form emulsions. The original resin was dissolved in benzene, washed with water, and precipitated from the benzene with methanol, a white "milk" being decanted from the pink resinous material. The resin was washed free of organic solvents in boiling water and on cooling a slightly brittle, pinkish-brown resin was obtained; yield 3–5 g., m.p. *ca.* 60° with preliminary softening. The resin was readily soluble in benzene, dioxane, N,N-dimethylformamide, pyridine, chloroform, carbon tetrachloride and benzaldehyde. It was insoluble in water, ethanol, formamide, hexane, 1-butanol and *t*-butyl alcohol. It swelled or was slightly soluble in ether, acetone, ethyl acetate, butanone, diethylamine and benzyl alcohol.

Anal. Calcd. for $H(C_7H_6)_{10}Cl$: C, 89.76; H, 6.46; Cl, 3.79. Found: C, 89.24; H, 6.25; Cl, 3.87.

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(1) Fellow of the Foreign Research Scientists Program of the Foreign Operations Administration.

(2) J. H. Gladstone and A. Tribe, *J. Chem. Soc.*, **47**, 448 (1885).

(3) C. Friedel and J. M. Crafts, *Bull. soc. chim.*, [2] **43**, 53 (1885).

(4) R. A. Jacobson, THIS JOURNAL, **54**, 1513 (1932); see also M. Kikkawa and S. Tsuruta, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **53**, 405 (1950); *C. A.*, **47**, 345 (1953).

(5) W. W. Binkley with E. F. Degering, THIS JOURNAL, **60**, 2810 (1938).

The Anticholinesterase Activity of Arylarsonic and Diarylarsinic Acids

BY LEON D. FREEDMAN AND G. O. DOAK

RECEIVED JULY 21, 1955

Certain aromatic phosphonic and phosphinic acids are active as inhibitors of plasma cholinesterase.[1] In the present note we are reporting on the anticholinesterase activity of a series of aromatic arsonic and arsinic acids.[2]

Experimental

p-Hydroxybenzenearsonic acid was Eastman Kodak White Label; *p*-arsanilic acid was obtained from the B. L.

TABLE I

ANTICHOLINESTERASE ACTIVITY OF ARYLARSONIC AND DIARYLARSINIC ACIDS

Compound	I_{50}[a] (moles/l.)
Arylarsonic acids	
$C_6H_5AsO_3H_2$	1.1×10^{-5}
m-$ClC_6H_4AsO_3H_2$	2×10^{-5}
p-$ClC_6H_4AsO_3H_2$	4×10^{-5}
p-$CH_3C_6H_4AsO_3H_2$	4×10^{-5}
p-$BrC_6H_4AsO_3H_2$	4×10^{-5}
o-$ClC_6H_4AsO_3H_2$	7×10^{-5}
p-$HOC_6H_4AsO_3H_2$	1.2×10^{-4}
p-$NH_2C_6H_4AsO_3H_2$	1.2×10^{-4}
o-$BrC_6H_4AsO_3H_2$	1.4×10^{-4}
m-$O_2NC_6H_4AsO_3H_2$	4×10^{-4}
p-$O_2NC_6H_4AsO_3H_2$	8×10^{-4}
p-$NH_2O_2SC_6H_4AsO_3H_2$	4×10^{-3}
Diarylarsinic acids	
$(o\text{-}BrC_6H_4)_2AsO_2H$	5×10^{-5} (2×10^{-4})[b]
$(o\text{-}ClC_6H_4)_2AsO_2H$	5×10^{-5} (2×10^{-4})[b]
$(o\text{-}BrC_6H_4)C_6H_5AsO_2H$	5×10^{-4}
$(m\text{-}ClC_6H_4)_2AsO_2H$	1×10^{-3} (1×10^{-3})[b]
$(p\text{-}ClC_6H_4)_2AsO_2H$	2×10^{-3}
$(m\text{-}O_2NC_6H_4)_2AsO_2H$	[c]
$(p\text{-}O_2NC_6H_4)_2AsO_2H$	[c]

[a] Concentration necessary for 50% inhibition when the enzyme and inhibitor were incubated for 20 minutes prior to the addition of the substrate solution. The value given is the final concentration after the addition of the substrate solution. [b] The value in parentheses was obtained with a second batch of the arsinic acid. [c] No significant inhibition at a concentration of 0.003 *M*.

(1) L. D. Freedman, H. Tauber, G. O. Doak and H. J. Magnuson, THIS JOURNAL, **75**, 1379 (1953).

(2) D. Vincent and P. Brygoo, *Bul. soc. chim. biol.*, **28**, 174 (1946), investigated the effect of a number of arsenical drugs on serum cholinesterase and noted that the few aromatic arsonic acids tested were inhibitors.

TABLE II

BROMO-SUBSTITUTED ARYLARSONIC AND DIARYLARSINIC ACIDS

Compound	Yield,[a] %	M.p.,[b] °C.	As analyses, % Calcd.	As analyses, % Found	Neut. equiv.[c] Calcd.[d]	Neut. equiv.[c] Found
o-$BrC_6H_4AsO_3H_2 \cdot H_2O$[e]	29,[f] 46[g]	173–175	25.06	24.61	299.0	297.9
p-$BrC_6H_4AsO_3H_2 \cdot {}^1/_2H_2O$[h]	35[g]	>300	25.84	25.81	289.9	288.8
$(o\text{-}BrC_6H_4)_2AsO_2H$	12,[f] 5[g]	275–278	17.84	17.71	419.9	422.3
$(p\text{-}BrC_6H_4)_2AsO_2H$[i]	3[g]	189–190	17.84	17.67	419.9	419.6
$(o\text{-}BrC_6H_4)C_6H_5AsO_2H$	13[g]	191–198	21.97	21.75	341.0	341.6

[a] The yield data are the results obtained in a single experiment. [b] Melting points were taken as previously described; *cf.*, G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951). [c] The indicator used for the arsonic acids was methyl-purple (from the Fleisher Scientific Company); the indicator used for the arsinic acids was phenolphthalein. [d] Calculated for one ionizable hydrogen per molecule. [e] Previously prepared by L. Kalb, *Ann. Chem., Justus Liebigs*, **423**, 39 (1921). [f] This yield was obtained by the use of 80% ethanol as the solvent and cuprous bromide as the catalyst. [g] This yield was obtained by the use of absolute ethanol as the solvent and cuprous bromide as the catalyst. [h] Previously prepared by H. Bart, German Patent 250,264 (1910). [i] Not sufficiently soluble at *p*H 1 to be tested as an inhibitor by Hestrin's method.

Lemke Company and was free from the *ortho* isomer. A previous paper[3] has described the preparation of most of the remaining compounds listed in Table I. Benzene- and *p*-toluenearsonic acids were obtained by the Bart reaction; the Scheller modification was used for *p*-sulfamylbenzenearsonic acid.[4] *o*-Bromobenzenearsonic and bis-(*o*-bromophenyl)-arsinic acids were prepared from the corresponding diazonium fluoborate by the method previously reported.[3] (*o*-Bromophenyl)-phenylarsinic acid was prepared under similar conditions by the reaction between *o*-bromobenzenediazonium fluoborate and phenyldichloroarsine. *p*-Bromobenzenearsonic and bis-(*p*-bromophenyl)-arsinic acids were obtained from the diazonium chlorozincate.[5] Analytical data, yields and m.p.'s for the bromo-substituted acids are listed in Table II.

The procedure used in the inhibition studies was similar to that previously reported.[1] Any changes made are mentioned in the tables or text. The enzyme solution was prepared by suspending 44.8 mg. of plasma cholinesterase[6] in 40.0 ml. of 0.6% sodium chloride solution and removing the insoluble material by filtration; 0.5 ml. of this solution caused approximately 50% hydrolysis of the acetylcholine under the conditions of our experiments.

Results

Table I lists the arsonic acids tested and the concentrations necessary for 50% inhibition when the enzyme and arsenical were incubated at 23° for 20 minutes before the addition of the substrate solution. All arsonic acids tested showed some activity; there was no correlation between the activities of the corresponding arsonic and phosphonic acids. Also shown in Table I are the activities of several diarylarsinic acids. In two cases, different batches of the same arsinic acid did not have the same anticholinesterase activity.[7] We are unable to explain this variation. However, it appears that the generalizations previously noted for the phosphorus compounds[1] hold for the arsinic acids. Thus, the order of activity for the halo-substituted arsinic acids is *ortho* > *meta* > *para*, while the nitro-substituted arsinic acids show no activity.

The anticholinesterase activity of the arsonic acids differs in several respects from that of the three other types of acids we have studied. The inhibition of plasma cholinesterase by phosphonic, phosphinic and arsinic acids can be readily reversed by dialysis, whereas the inactivation by arsonic acids is not changed. Some typical experiments are given in Table III.

TABLE III

EFFECT OF DIALYSIS ON THE DEGREE OF INHIBITION

Compound	Concn.[a] (moles/l.)	Inhibition[b] (%)	Inhibition after dialysis (%)
o-$BrC_6H_4PO_3H_2$	2.0×10^{-2}	94	7
$(o\text{-}BrC_6H_4)_2PO_2H$	7.0×10^{-4}	95	34[d]
o-$BrC_6H_4AsO_3H_2$	7.5×10^{-4}	87	87
$(o\text{-}BrC_6H_4)_2AsO_2H$	1.5×10^{-4}	79	14

[a] Final concentration after the addition of the substrate solution. [b] Under our usual test conditions; *i.e.*, enzyme and inhibitor were incubated at 23° for 20 minutes before the substrate solution was added. [c] Inhibitor and enzyme were incubated at 23° for 20 minutes and then dialyzed for 24 hours against 0.033 *M* phosphate, *p*H 7.0, containing 0.1% sodium chloride. Dialysis was performed at 5° against 2 successive 6-liter volumes of buffer. After the 24 hour dialysis, 3-ml. aliquots of the dialyzed solutions were run with 1 ml. substrate solution in the usual manner. [d] After 48 hours dialysis against 4 successive 6-liter volumes of buffer, % inhibition was nil.

It was also found that phosphonic, phosphinic and arsinic acids react rapidly with plasma cholinesterase; the amount of inhibition caused by these compounds is not significantly different after 24 hours than after the 20 minute incubation time normally used in our tests. By contrast, the inhibition by arsonic acids is slow, and even concentrations below the I_{50} values given in Table I cause virtually complete inhibition if the incubation period is sufficiently long (for example, *o*-bromobenzenearsonic acid at a concentration of 7.5×10^{-5} mole/l. causes 98% inhibition in 24 hours). However, even when the substrate and arsonic acid are added to the enzyme simultaneously (zero incubation time) there is still appreciable inhibition. Thus, when the concentration of arsonic acid is equal to the I_{50} value given in Table I, the inhibition at zero time is about 20%. When the concentration of arsonic acid is five times the I_{50} value of Table I, the inhibition at zero time is about 50%. A similar type of inactivation of cholinesterase has been noted with mercuric chloride.[8]

The inhibition by arsonic acids resembles that by mercuric chloride in one other respect, *viz.*, that 2,3-dimercaptopropanol (BAL) does not reactivate the enzyme after inhibition by arsonic acids or mercuric chloride. The results with one arsonic acid are given in Table IV. Goldstein and Doherty[8] have suggested that plasma cholinesterase, after a

(3) G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5656 (1951).

(4) G. O. Doak, *ibid.*, **62**, 167 (1940).

(5) L. D. Freedman and G. O. Doak, *ibid.*, **75**, 4905 (1953).

(6) Prepared from Cohn's Fraction IV-6 by Cutter Laboratories.

(7) No such variation was observed with different batches of phosphonic, phosphinic or arsonic acids.

(8) A. Goldstein and M. E. Doherty, *Arch. Biochem. Biophys.*, **33**, 35 (1951).

preliminary reaction with mercuric chloride, undergoes a subsequent irreversible denaturation. Possibly a similar series of reactions is involved in the inactivation of the enzyme by arsonic acids.

TABLE IV

FAILURE OF BAL TO REVERSE THE INACTIVATION OF CHOLINESTERASE BY *o*-BROMOBENZENEARSONIC ACID[a]

o-$BrC_6H_4AsO_3H_2$[b] (moles/l.)	BAL[c] (moles/l.)	Inhibition (%)
7.5×10^{-4}	1.5×10^{-3}	90
7.5×10^{-4}	0	87
0	1.5×10^{-3}	0[d]

[a] Inhibitor and enzyme were incubated at 23° for 20 minutes and then dialyzed for 24 hours as described in Table III. After the dialysis, 6-ml. aliquots of the dialyzed solutions were mixed with 1 ml. of water or BAL solution and allowed to stand at 23° for 20 minutes. Then substrate solution (1 ml. of 0.032 *M* acetylcholine bromide in 0.2 *M* phosphate of *p*H 7.0) was added to determine the residual activity of the enzyme. [b] Concentration that would have been present in the final reaction mixture if the dialysis had not been performed. [c] Concentration present in the final reaction mixture; *i.e.*, after the addition of substrate. [d] E. C. Webb and R. van Heyningen, *Biochem. J.*, 41, 74 (1947), reported that 0.005 *M* BAL has no effect on the activity of horse serum cholinesterase.

The results obtained in this investigation suggest that phosphonic, phosphinic and arsinic acids inhibit plasma cholinesterase by the same mechanism and that arsonic acids inhibit by another mechanism.

Acknowledgments.—The authors wish to thank Mrs. Barbara Stanley for performing the analyses necessary for this research and Mr. Edward L. Petit for invaluable technical assistance. Appreciation is due also to Dr. Harold J. Magnuson for advice in planning the experiments.

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Sodium Amide Cleavage of 1-Alkylcyclobutyl Phenyl Ketones

BY K. E. HAMLIN AND URSULA BIERMACHER

RECEIVED AUGUST 3, 1955

1-Alkylcyclohexyl and 1-alkylcyclopentyl phenyl ketones are cleaved by sodium amide under conditions of the Haller–Bauer reaction to yield the corresponding 1-alkylcyclohexane- and 1-alkylcyclopentanecarboxamides.[1,2] On the other hand, 1-alkylcyclopropyl phenyl ketones have given variable results. Haller and Benoist[3] reported that 1-methylcyclopropyl phenyl ketone gave benzamide on sodium amide cleavage whereas 1-benzylcyclopropyl phenyl ketone afforded the expected 1-benzylcyclopropanecarboxamide.[4]

The cleavage of 1-alkylcyclobutyl phenyl ketones with sodium amide has not been reported in the literature. To determine their behavior under conditions of the Haller–Bauer reaction, 1-methyl- and 1-ethylcyclobutyl phenyl ketones were prepared by the alkylation of cyclobutyl phenyl ketone. In both cases, the alkylated ketones were cleaved normally to yield the corresponding cyclobutanecarboxamides.

Piehl and Brown[4] reported extensive sodium amide cleavage of cyclopropyl phenyl ketone to cyclopropanecarboxamide and benzamide. Only unreacted ketone was obtained when cyclobutyl phenyl ketone was treated with sodium amide under similar conditions.

Experimental

Cyclobutyl phenyl ketone[5] was prepared by condensation of cyclobutanecarbonyl chloride with benzene in the presence of anhydrous aluminum chloride.

1-Methylcyclobutyl Phenyl Ketone.—The sodio derivative was prepared in toluene from 48 g. (0.3 mole) of cyclobutyl phenyl ketone and 11.7 g. (0.3 mole) of sodium amide. This mixture was stirred and cooled in an ice-bath while 85 g. (0.6 mole) of methyl iodide was added in one portion. Reaction was immediate causing rapid refluxing of the mixture. Stirring at room temperature was continued for 22 hours after which the toluene solution was washed with water and distilled. The 1-methylcyclobutyl phenyl ketone boiled at 103° at 3 mm., $n^{25}D$ 1.5368, yield 41 g. (79%).

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10; O, 9.18. Found: C, 83.14; H, 8.08; O, 9.31.

1-Ethylcyclobutyl Phenyl Ketone.—A suspension of the sodio derivative of 48 g. (0.3 mole) of cyclobutyl phenyl ketone in toluene, prepared as in the example above, was stirred at 75° while 46.8 g. (0.3 mole) of ethyl iodide was added dropwise. The mixture was heated at 75–80° for an additional 7 hours, was washed with water and was distilled. The desired 1-ethylcyclobutyl phenyl ketone distilled at 115–116° at 3 mm., $n^{25}D$ 1.5304, yield 19 g. (34%).

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.82; H, 8.81.

1-Methylcyclobutanecarboxamide.—A suspension of 15.5 g. (0.4 mole) of sodium amide in 200 ml. of anhydrous toluene was treated with 34.8 g. (0.2 mole) of 1-methylcyclobutyl phenyl ketone. The mixture was refluxed while stirring for 5 hours, was cooled to room temperature and was washed with water. Following distillation of the toluene *in vacuo*, 18 g. of crystalline product was obtained. After two recrystallizations from benzene, the 1-methylcyclobutanecarboxamide melted at 165° and weighed 12 g. (50% yield).

Anal. Calcd. for $C_6H_{11}NO$: C, 63.68; H, 9.80. Found: C, 63.42; H, 10.05.

1-Ethylcyclobutanecarboxamide.—In the manner described above, 1-ethylcyclobutyl phenyl ketone was cleaved with sodium amide to afford a 60% yield of product twice recrystallized from toluene, m.p. 136.5–137.5°.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.09; H, 10.32. Found: C, 66.40; H, 10.74.

Acknowledgment.—We are indebted to E. F. Sehlberg, Chief Microanalyst, and his staff for the analytical data.

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ar-2-Tetralol Derivatives

BY ROBERT L. HULL

RECEIVED JUNE 10, 1955

In light of a recent publication[1] claiming the ar-2-tetralyl ether of glycerol to be more potent and

(1) K. E. Hamlin and M. Freifelder, THIS JOURNAL, **75**, 369 (1953).
(2) G. Wash, B. Shive and H. L. Lochte, *ibid.*, **63**, 2975 (1941).
(3) A. Haller and E. Benoist, *Ann. chim.*, [9] **17**, 25 (1921).
(4) The latter reaction was recently confirmed by F. J. Piehl and W. G. Brown, THIS JOURNAL, **75**, 5023 (1953).
(5) H. R. Henze and C. W. Gayler, *ibid.*, **74**, 3615 (1952).
(1) T. Kariyone, H. Yamada, M. Takahashi, T. Omiya, K. Okamoto and Y. Kashihara, *J. Pharm. Soc. Jap.*, **72**, 1545 (1952); *C. A.*, **47**, 9314 (1953).