pH effect was observed with tetrahydroaminopterin in the absence of formaldehyde. Thus removal or migration of formaldehyde does not account for the increased inhibition at lower pH.

Peaks A′, B′, A, and B showed no inhibition of *Escherichia coli* thymidylate synthetase when tested at 10^{-5} *M* either at pH 9.0 or 7.4. This result was unexpected because *dl*-L-tetrahydroaminopterin inhibits this enzyme 50% at the same concentration.[3b] Further investigation revealed that reaction of *dl*-L-tetrahydroaminopterin with 0.1 *M* formaldehyde abolished inhibition. Details of the interaction of formaldehyde with tetrahydroaminopterin will be reported separately.

Recovery of Diastereoisomers.—Data on the recovery of diastereoisomers based on absorption at 295 mμ is shown in Table IV. We have consistently observed with tetrahydroaminopterin derivatives that peak B is smaller than peak A. With tetrahydrofolate, the diastereoisomers were present in equal amounts as observed earlier.[4a]

TABLE IV
RECOVERY OF DIASTEREOISOMERS AFTER CHROMATOGRAPHY

	% of total eluted absorbing material (295 mμ) in each fraction	
Peak	Tetrahydrofolate	Tetrahydroaminopterin
A′	5	9
B′	5	12
A	45	43
B	45	36
	Recovery of tetrahydropteridine added to column, %	
	60	40

The ratio of formaldehyde to tetrahydropteridine of about 0.75 observed for peaks A and B shows that they cannot be pure 5,10-methylene compounds since there are four tetrahydropteridine molecules for every three molecules of CH_2O. These peaks may contain 50% tetrahydropteridines linked intermolecularly between the 5 positions (or between the 5 and 10 or 5 and 8 positions) giving a ratio of 0.5, plus 50% which are intramolecular 5,10-methylene compounds having a ratio of 1. The extent to which these complexes dissociate under various assay conditions is not known.

Experimental Section

Reduced Pteridines.—Tetrahydrofolic acid and tetrahydroaminopterin were synthesized by reduction in AcOH.[7] The analysis of tetrahydroaminopterin prepared in this manner has been reported.[3b]

5,10-Methylene Derivatives of Tetrahydropteridines.—The method described by Kaufman, *et al.*,[4a] was followed except for minor modifications. Tetrahydropteridine (10 mg, 22 μmoles) was added to 1 ml of acetate buffer, pH 5.5, containing 50 μmoles of CH_2O-^{14}C (33 μCi/μmole), and the solution was brought to pH 7.0 with 1 *N* KOH and immediately added to a DEAE column.

The 2.2 × 25 cm column was prepared by washing with 0.5 *N* KOH until the washings were colorless, with H_2O until the effluent was neutral, with 1 l. of 0.4 *M* $NaHCO_3$ buffer, pH 9.5, and finally with 1 l. of 4×10^{-3} *M* HCO_3^-, pH 9.5. The water-jacketed column was kept at 0°. The compounds were eluted with a HCO_3^- gradient. Five-milliliter portions were collected and the concentrations of folate derivatives were estimated by the absorbancy at 295 mμ using a value of 28,000 for the extinction coefficient at this wavelength.

Radioactivity Measurement.—Radioactivity was determined in a Packard Tri-Carb liquid scintillation spectrophotometer Series 314 E with dioxane–anisole–dimethoxyethane (6:1:1) containing 1.2% of 2,5-diphenyloxazole and 0.05% of 1,4-bis-2-(5-phenyloxazolyl)benzene[8] as counting fluid. Aliquots (20 μl) were added to 15 ml of scintillation fluid. The absence of quenching was determined with internal ^{14}C-toluene standards.

Assays.—The enzymatic and microbiological assays were carried out as described.[3b,9]

Determination of D-Glutamic Acid.—Tetrahydroaminopterin was hydrolyzed by autoclaving for 3 hr in 3 *N* HCl in a sealed tube. Glutamate was isolated by Dowex 50 chromatography and assayed for D-glutamate.[6]

(7) B. L. O'Dell, J. M. Vandenbelt, E. S. Bloom, and J. J. Pfiffner, *J. Am. Chem. Soc.*, **69**, 250 (1947).

(8) J. D. Davidson and P. Feigelson, *Intern. J. Appl. Radiation Isotopes*, **2**, 1 (1957).

(9) S. B. Horwitz and R. L. Kisliuk, *J. Med. Chem.*, **11**, 907 (1968).

Synthesis and Antiinflammatory Activity of 2-Aryl-2-α-piperidyl-1,3-dioxanes

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A series of 2-aryl-2-α-pyridyl- and 2-aryl-2-α-piperidyl-1,3-dioxanes have been prepared and evaluated for antiinflammatory activity. The most active members, 2-aryl-2-α-piperidyl-5,5-diphenyl derivatives, were twice as potent as phenylbutazone.

The interest in obtaining a nonsteroidal antiinflammatory agent is indicated by the amount of research that has been carried out in this area during the last few years.[2] In our laboratories we have found that certain 2-aryl-2-α-pyridyl- and 2-aryl-2-α-piperidyl-1,3-dioxanes[3] (II–IV) possess activity in the antiinflammatory[4] area. The present paper reports on the synthesis and antiinflammatory activity of some analogs of II–IV.

Chemistry.—The preparation of the 1,3-dioxanes reported in this work was accomplished by the proce-

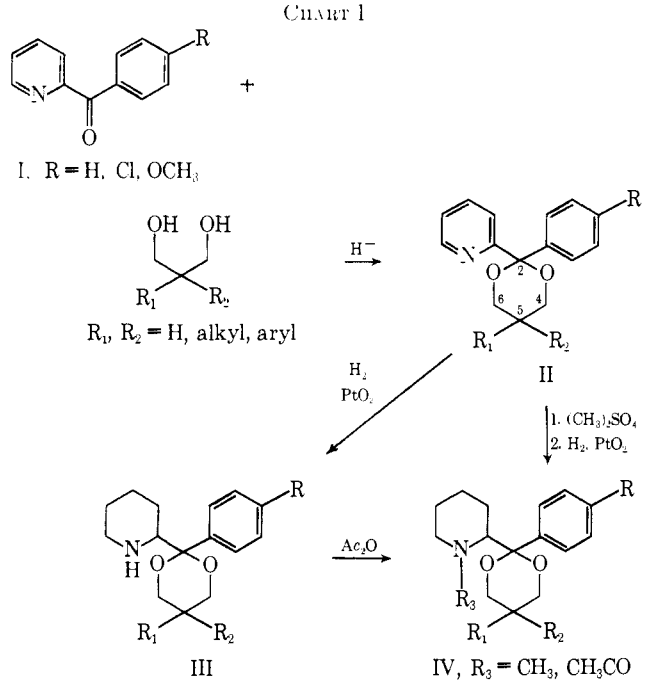
(1) To whom inquiries should be addressed.

(2) T. Y. Shen in "Annual Reports in Medicinal Chemistry, 1966," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966, pp 217–226; R. A. Scherrer in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press, New York, N. Y., 1965, pp 224–232; M. W. Whitehouse, *Progr. Drug Res.*, **8**, 321 (1965); International Symposium on Non-Steroidal Anti-Inflammatory Drugs, Milan, Sept 1964, S. Garattini and M. N. Dukes, Ed., Excerpta Medica Foundation, New York, N. Y., 1965; Abstracts of the 9th National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minn., June 1964, p 11.

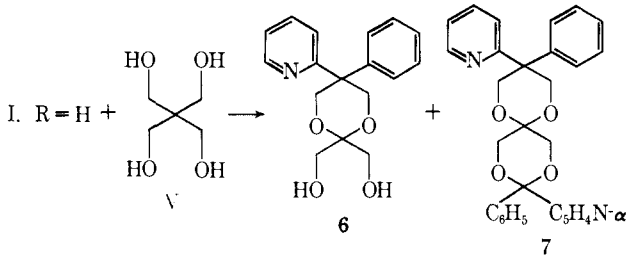
(3) Arabic numerals refer to compounds described also in the tables, while Roman numerals refer to compounds mentioned only in the text.

(4) The closely related 2-R_1-2-R_2-4- and -5-α-piperidyl-1,3-dioxanes have recently been reported to possess antiinflammatory, antispasmodic, local anesthetic, and preferential ganglionic blocking activity: W. R. Hardie, U. S. Patent 3,256,289 (1966); *Chem. Abstr.*, **65**, 7190 (1966).

CHART I



dures given in Chart I. The pyridyl-1,3-dioxanes (II) were obtained by condensing a 2-aroylpyridine with a 1,3-diol in the presence of 1.33 molar equiv of *p*-toluenesulfonic acid. If the acid–ketone ratio was reduced to less than 1 molar equiv, considerably lower yields of II were obtained. When pentaerythritol (V) was treated with 2-benzoylpyridine, the spiro compound **7** was also obtained together with the desired 1,3-dioxane **6**. The piperidyl-1,3-dioxanes (III) were



prepared by hydrogenating an acetic acid solution of II in the presence of PtO_2. N-Methylpiperidyl-1,3-dioxanes (IV, R = CH_3) were obtained from the hydrogenation of the methylpyridinium analogs of II. Acylation of III to give IV (R_3 = $COCH_3$) could be effected by an acetic anhydride–pyridine mixture.

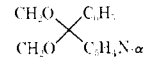
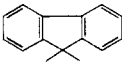
The derivatives of II–IV where $R_1 \neq R_2$ (**5**, **7**, **9**, **18**, **20**, **22**) are capable of existing as *cis* or *trans* isomers. The geometrical orientation in these compounds has not been determined.

Two nmr features of II–IV are worthy of mention. The *gem*-dimethyl[5] signals in **15**–**17** are found as two 3 H singlets separated by 0.66, 0.62, and 0.72 ppm, respectively. This unusually large[6] separation does not occur in the *gem*-dimethyl-substituted compounds **2** and **4**. The second feature relates to the coupling exhibited by the C-4 and C-6 methylene groups in the 1,3-dioxane ring. The usual singlet or AB quartet pattern of these protons was found in all compounds studied excepting **5**, **15**, **23**, and **26**. In these substances the AB quartet was further split into triplets with $J' = 1.8$–2.0 cps.

Pharmacology.—The antiinflammatory activity, as determined by the carrageenan foot edema assay[7] in rats, for compounds II–IV is given in Tables I and II. The 2-aryl-2-α-pyridyl analogs (II, Table I) were all weak or nearly inactive in this test. The 2-aryl-2-α-piperidyl derivatives (III and IV, Table II) possessed good levels of antiinflammatory activity when both R_1 and R_2 were alkyl or aryl groups and weak activity when R_2 was H, NH_2, or CH_2OH (compare **14**, **18**, **19**, **20**, **23** with **15**, **18**, **19**, **22**). Placement of a chlorine atom in the *para* position of the 2-phenyl group resulted either in decreased (**15** *vs.* **16**) or increased (**23** *vs.* **24**) activity while a *p*-OH or *p*-OCH_3 group decreased activity (**17** and **25**). An N-methyl or N-acetyl group also resulted in decreased activity (**15** *vs.* **15b** and **15c**). The (+) and (−) optical isomers (**23b** and **23c**) had the same activity as the racemic mixture **23**.

TABLE I

ANTIINFLAMMATORY DATA ON 2-ARYL-2-α-PYRIDYL-1,3-DIOXANES (II)

No.	R	R_1	R_2	Carrageenan foot edema[a] ED_{50}, mg/kg
1	H	H	H	...
2	H	CH_3	CH_3	150
3	Cl	CH_3	CH_3	>50
4	OCH_3	CH_3	CH_3	>50
5	H	CH_3	NO_2	200
6	H	CH_2OH	CH_2OH	>50
7	H			50
8	H	C_2H_5	C_2H_5	75
9	H	H	C_6H_5	>50
10	H	C_2H_5	C_6H_5	75
11	H	C_6H_5	C_6H_5	>50
11a[b]	H	C_6H_5	C_6H_5	>50
12	OH	C_6H_5	C_6H_5	>50
13	H			>50

[a] All compounds were administered orally to rats. The procedure for measuring inflammation is given in ref 7. [b] N-Methyl methosulfate salt of **11**.

One of the more potent compounds, (±)-2,5,5-triphenyl-2-α-piperidyl-1,3-dioxane (**23**), was selected for further testing in the antiinflammatory area. In hypophysectomized and adrenal demedullated male and female rats **23** had about the same ED_{50} in the carrageenan foot edema test as in intact animals. In completely adrenalectomized rats the compound was about one-half as potent. Against other phlogistic agents such as formalin, mustard, or yeast[8] **23** gave activity similar to aspirin and phenylbutazone. The compound was orally effective at 10 mg/kg in lowering the pyrexia caused by *Escherichia coli* lipopolysaccharide in rats without a hypothermic effect

(5) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 7.

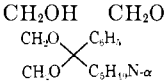
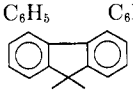
(6) Additional examples of larger *gem*-dimethyl signal separation can be found in P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **30**, 1681 (1965); D. S. Tarbell, D. A. Buckley, P. P. Brownlee, R. Thomas, and J. S. Todd, *ibid.*, **29**, 3311 (1964).

(7) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(8) C. A. Winter, E. A. Risley, and G. W. Nuss, *J. Pharmacol. Exptl. Therap.*, **141**, 369 (1963).

TABLE II

ANTIINFLAMMATORY DATA ON 2-ARYL-2-α-PIPERIDYL-1,3-DIOXANES (III and IV)

No.	R	R_1	R_2	R_3	Carrageenan foot edema[a] ED_{50}, mg/kg
14	H	H	H	H	60
15	H	CH_3	CH_3	H	20
15b	H	CH_3	CH_3	CH_3	>50
15c	H	CH_3	CH_3	$COCH_3$	45
16	Cl	CH_3	CH_3	H	50
17	OCH_3	CH_3	CH_3	H	>50
18	H	CH_3	NH_2	H	>50
19	H	CH_2OH	CH_2OH	H	>50
20	H			H	50
21	H	C_2H_5	C_2H_5	H	40
22	H	C_6H_5	H	H	>50
23[b]	H	C_6H_5	C_6H_5	H	15
23a	H	C_6H_5	C_6H_5	H	15
23b	H	C_6H_5	(+)-C_6H_5	H	15
23c	H	C_6H_5	(−)-C_6H_5	H	15
24	Cl	C_6H_5	C_6H_5	H	7.5
25	OH	C_6H_5	C_6H_5	H	50
26	H			H	75
Aspirin					90
Phenylbutazone					30

[a] See footnote *a* in Table I. [b] LD_{50} = 137 mg/kg ip, mouse; LD_{50} = 300 mg/kg *po*, rat.

per se. It was ineffective in the mouse writhing test[9] and bradykinin bronchoconstriction in guinea pigs.[10]

Further development of **23** as a potential antiinflammatory agent was terminated because the substance was found to produce microconcretions in the corticomedullary area of rat kidneys.[11]

Experimental Section[12]

The yields, melting points, and analyses for compounds **1–26** are given in Table III.

1,3-Diol Synthesis.—2,2-Diphenyl-1,3-propanediol was prepared by the procedure of Burr[13] and 9,9-bis(hydroxymethyl)-fluorene by the procedure of Ghera and Sprinzak.[14] The other diols were obtained from commercial sources.

2-Aryl-2-α-pyridyl-1,3-dioxanes (II), listed in Table I, were prepared by the following procedure. To a flask equipped with a Dean–Stark water separator was added 0.50 mol of 2-aroylpyridine, 0.33 mol of 1,3-diol, 0.66 mol of *p*-toluenesulfonic acid, and 500 ml of toluene. The mixture was stirred and refluxed until the level of the H_2O layer in the Dean–Stark tube remained constant (20–36 hr). The toluene was removed *in vacuo* on a rotary evaporator and the residue was made alkaline with 500 ml of 2 *N* NaOH. The resultant solid was filtered off and crystallized from an appropriate solvent with charcoal treatment if necessary.

2-Aryl-2-α-piperidyl-1,3-dioxanes (III), listed in Table II (except **15b** and **15c**), were prepared by the following procedure. A mixture of 2-aryl-2-α-pyridyl-1,3-dioxane (0.05 mol), PtO_2 (0.2 g), and AcOH (150 ml) were hydrogenated at 3.5 kg/cm² at room temperature until the desired 3 equiv of H_2 had been taken up. The catalyst was filtered off and the filtrate was concentrated *in vacuo* on a rotary evaporator. The residue was treated with 30% KOH until the aqueous phase had pH 9–10. It was extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was then either crystallized from an appropriate solvent or converted to the HCl salt in THF solution.

TABLE III

YIELDS, MELTING POINTS, AND ANALYSES OF 1,3-DIOXANES

No.	Yield, %	Mp, °C	Crystn solvent	Formula	Analyses[i]
1	73	120–121	*a*	$C_{25}H_{26}NO_2$	C, H, N, O
2	83	90–91	*a*	$C_{17}H_{19}NO_2$	C, H, N, O
3	43	201–203	*b*	$C_{24}H_{26}ClNO_5S$	C, H, Cl, N, O, S
4	57	78–80	*c*	$C_{18}H_{21}NO_3$	C, H, N, O
5	21	159–160	*b*	$C_{16}H_{16}N_2O_4$	C, H, N
6	15	131–132	*d*	$C_{17}H_{19}NO_4$	C, H, N, O
7	12	91–93	*a*	$C_{29}H_{26}N_2O_4$	C, H, N, O
8	41	99–101	*a*	$C_{19}H_{23}NO_2$	C, H, N
9	28	119–120	*a*	$C_{21}H_{19}NO_2$	C, H, N, O
10	15	128–130	*c*	$C_{23}H_{23}NO_2$	C, H, N, O
11	57	250–252	*e*	$C_{27}H_{23}NO_2$	C, H, N, O
11a	92	221–222	*a*	$C_{29}H_{29}NO_6S$	C, H, N, O, S
12	...	291–292	*h*	$C_{27}H_{23}NO_3$	C, H, O
13	36	205–206	*b*	$C_{27}H_{21}NO_2$	C, H, N, O
14	72	94–96	*b*	$C_{15}H_{21}NO_2$	C, H, N, O
15	69	115–116	*f*	$C_{17}H_{23}NO_2$	C, H, O
15a	89	228–231	*a*	$C_{17}H_{26}ClNO_2$	C, H, Cl, O
15b	56	61–63	*c*	$C_{18}H_{27}NO_2$	C, H, N, O
15c	69	89–90	*g*	$C_{19}H_{27}NO_3$	C, H, N, O
16	64	282–283	*a*	$C_{17}H_{25}ClNO_2$	C, H, Cl, N, O
17	75	223–224	*a*	$C_{18}H_{28}ClNO_3$	C, H, N
18	45	125–127	*g*	$C_{16}H_{24}N_2O_2$	C, H, N, O
19	68	174–175	*h*	$C_{17}H_{25}NO_4$	C, H, N
20	82	215–217	*h*	$C_{29}H_{38}N_2O_4$	C, H, N, O
21	48	230–231	*a*	$C_{19}H_{30}ClNO_2$	C, H, N
22	68	251–252	*f*	$C_{21}H_{26}ClNO_2$	C, H, Cl, N, O
23	80	201–203	*e*	$C_{27}H_{29}NO_2$	C, H, N, O
23a	92	254–255	*a*	$C_{27}H_{30}ClNO_2$	C, H, N, Cl
23b	...	198–200	*e*	$C_{27}H_{29}NO_2$	C, H, N
23c	...	198–200	*e*	$C_{27}H_{29}NO_2$	C, H, N
24	...	155–159	*c*	$C_{21}H_{28}ClNO_2$	C, H, Cl, N, O
25	...	280–285 dec	*h*	$C_{27}H_{29}NO_3$	C, H
26	87	218–220	*h*	$C_{27}H_{27}NO_2$	C, H, N, O

[a] MeOH. [b] CCl_4–MeOH. [c] CCl_4–pentane. [d] C_6H_6. [e] Toluene. [f] Pentane–toluene. [g] Pentane. [h] MeOH–H_2O. [i] Where analyses are indicated by the symbols of the elements only, analytical results obtained for these elements were within ±0.4% of the calculated values.

2,5,5-Triphenyl-2-(α-N-methylpyridinium)-1,3-dioxane Methosulfate (11a).—A solution of **11** (6.0 g, 0.015 mol), Me_2SO_4 (2.5 g, 0.02 mol), and CH_2Cl_2 (150 ml) was stirred and refluxed for 36 hr. After cooling to room temperature, Et_2O (100 ml) was added. The resultant solid was filtered off and crystallized from *i*-PrOH to give 7.7 g (97%) of **11a**.

5,5-Diphenyl-2-phenyl-2-(α-N-methylpiperidyl)-1,3-dioxane (15b).—A solution of 5,5-dimethyl-2-phenyl-2-α-pyridyl-1,3-dioxane (53.8 g, 0.20 mol), Me_2SO_4 (37.8 g, 0.30 mol), and 750 ml of Et_2O was stirred and refluxed for 28 hr. On cooling to room temperature an oil separated out. This 5,5-dimethyl-2-phenyl-2-(α-N-methylpyridinium)-1,3-dioxane methosulfate was converted to **15b** by hydrogenation (PtO_2) as given above.

5,5-Dimethyl-2-phenyl-2-(α-N-acetylpyridyl)-1,3-dioxane (15c).—A solution of **15** (4.2 g, 0.015 mol), AcCl (1.6 g, 0.02 mol), and anhydrous pyridine (10 ml) was stirred at room temperature for 15 hr. The solvent was removed *in vacuo* and the residue was treated with H_2O. The resultant solid was crystallized from pentane to give **15c**.

Resolution of 2-α-Piperidyl-2,5,5-triphenyl-1,3-dioxane (23).—A mixture of **23** (43.0 g, 0.11 mole), D-tartaric acid (16.3 g, 0.11 mol), and anhydrous MeOH (2000 ml) was stirred and refluxed for 6 hr. The clear solution was cooled to room temperature, concentrated *in vacuo* to about 250 ml, and then treated with 1000 ml of H_2O. After 2 hr at room temperature the resultant solid was filtered off to give 33.4 g of **23**·bitartrate, mp 218–220°; liberated base in 95% EtOH gave $[\alpha]^{24}_{5\text{7}6}$ +4.7° (1 dm, *c* 3.22) and filtrate A that was used below. The solid (33.4 g) was dissolved in refluxing MeOH (1000 ml) and then concentrated to about 500 ml. On standing at room temperature there was

(9) E. Sieginund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).

(10) H. Konzett and R. Rossler, *Arch. Exptl. Pathol. Pharmacol.*, **195**, 71 (1940).

(11) A detailed study will be forthcoming by H. Hardtmann, H. Schwarz, E. I. Takesue, and R. Van Ryzin.

(12) Melting points were determined in a Thomas–Hoover capillary melting point apparatus and have not been corrected. Pmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million (δ) from an internal Me_4Si standard. Ir spectra (KBr) were determined using a Perkin-Elmer Infracord. The optical rotations were measured in a Zeiss photoelectric polarimeter.

(13) J. G. Burr, *J. Am. Chem. Soc.*, **73**, 5170 (1951).

(14) E. Ghera and Y. Sprinzak, *ibid.*, **82**, 4945 (1960).

obtained 24.2 g of **23**·bitartrate, mp 209–210°; liberated base, $[\alpha]^{24}_{576}$ 0° (1 dm, *c* 2.96). This material was dissolved in refluxing MeOH–H_2O (1:1, 400 ml) and then allowed to stand for 1 hr at room temperature. The resultant solid was filtered off and the filtrate was concentrated *in vacuo* to about 100 ml. The solid was filtered off to give 9.5 g of (−)-**23**·bitartrate, mp 211–213°; liberated base, $[\alpha]^{24}_{546}$ −11.6° (1 dm, *c* 3.01), mp 198–200°. *Anal.* ($C_{31}H_{33}NO_8$): C, H, N, O.

Filtrate A from above was concentrated *in vacuo* to about one-fourth the original volume and the resultant solid was filtered off to give 19.8 g of **23**·bitartrate, mp 216–218°; liberated base, $[\alpha]^{24}_{546}$ +2.0 (1 dm, *c* 2.95). The solid was dissolved in refluxing Me_2CO–MeOH (1:1, 250 ml) and then allowed to stand about 18 hr at room temperature. Filtration gave 14.6 g of **23**·bitartrate, mp 213–215°; liberated base, $[\alpha]^{24}_{546}$ +4.7° (1 dm, *c* 2.85). This material was then recrystallized twice from MeOH–H_2O (1:1, 250 ml) to give 8.7 g of (+)-**23**·bitartrate, mp 209–212°; liberated base, $[\alpha]^{24}_{546}$ +12.3 (1 dm, *c* 2.90), mp 198–200°. *Anal.* ($C_{31}H_{33}NO_8$) C, H, N, O.

Acknowledgments.—The authors thank Messrs. Roger Riedlin and Urs Stoeckli for assistance in synthetic and analytical details. They are also grateful to Dr. Harry Dugger for allowing them to use some of his data.

The Alkylation and Acylation of $B_{10}H_9NH_3^-$ [1,2]

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The reaction of 2-$B_{10}H_9NH_3^-$ with ethylene oxide produced $H_3NB_{10}H_7(CH_2CH_2OH)_2^-$, several salts and derivatives of which were prepared. Treatment of 2-$B_{10}H_9NH_3^-$ with NaH followed by the addition of ethyl α-chloroacetate produced $B_{10}H_9NH(CH_2COOC_2H_5)_2^-$, which was subsequently reduced to $B_{10}H_9NH(CH_2CH_2OH)_2^-$. Benzoylation of 2-$B_{10}H_9NH_3^-$ was found to give the N-substituted in preference to the B-substituted derivative. Preliminary biological results reveal that whereas the N-β-hydroxyethyl derivative is not incorporated into brain, muscle, or tumor tissues the B-β-hydroxyethyl derivative and its phosphate ester appear to be strongly bound to tumor tissues and give very favorable tumor-blood boron ratios.

The low toxicity of polyhedral boranes and their derivatives[4] has stimulated a renewed interest in the B^{10} neutron capture therapy of brain tumors.[5] The discovery that these boranes can be readily substituted with a number of organic groups[6] opened up a search for convenient "handles" for the incorporation of these boron-rich ions into tumors. The search is still on, since with few exceptions[7] the derivatives prepared so far are either too toxic or are not selectively incorporated into tumor in adequate concentrations for therapy.[8]

We decided to begin an investigation of reactions which would enable us to build up "handles" on the boron cage containing a biochemical rationale for their incorporation into neoplasm. A stepwise synthetic scheme was chosen with functional groups as close to the cage as possible thereby eliminating intervening atoms which do not contribute to the biological activity of the organic side chain. Additionally the boron percentages of these compounds would be high. The choice of $B_{10}H_9NH_3^-$ [9] as a starting point was motivated not only by the fact that it offers a choice of two reactive sites, the nitrogen and the cage, but that its chemistry has not been even superficially explored. Alkylation and acylation reactions were the first to be examined since they can provide the starting points in the syntheses of derivatives having the borane attached to the hydrocarbon backbone of the organic molecule. Of course, only alkylations where the other end of the carbon chain had a functional group capable of undergoing additional reactions were explored.

Results and Discussion

Reactions.—The principal reactions discussed in this paper are represented in Scheme I.

The alkylation with ethylene oxide provides another example of the aromatic character of the polyhedral ions,[6] since it apparently resembles an analogous reaction with benzene.[10] What is somewhat surprising is the fact that no detectable amount of N-substituted product was isolated, despite the weakly acidic nature of the NH_3^+ protons which can be exchanged for deuterium in D_2O. Also the nitrogen can be easily methylated with Me_2SO_4.[9] The acidic medium should not have been a hindrance either, since analogous alkylation of primary amines occurs readily in acidic media.[11] However, as we have shown in this work under basic conditions acylation occurs almost exclusively at the nitrogen. In the absence of the NH_3^+ group the cage is readily benzoylated even without a Friedel–Crafts

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(4) A. H. Soloway, R. L. Wright, and J. R. Messer, *J. Pharmacol. Exptl. Therap.*, **137**, 263 (1961).

(5) A. H. Soloway in "Progress in Boron Chemistry," A. L. McCloskey and H. Steinberg, Ed., Pergamon Press Inc., New York, N. Y., 1964, pp 203–234.

(6) W. H. Knoth, H. C. Miller, D. C. England, G. W. Parshall, and E. L. Muetterties, *J. Am. Chem. Soc.*, **84**, 1056 (1962).

(7) A. H. Soloway, H. Hatanaka, and M. A. Davis, *J. Med. Chem.*, **10**, 711 (1967).

(8) F. Haslinger, A. H. Soloway, and D. N. Butler, *ibid.*, **9**, 58 (1966).

(9) W. R. Herller and M. S. Raasch, *J. Am. Chem. Soc.*, **86**, 3661 (1964).

(10) H. Hopff and K. Koulen, *Chem. Ber.*, **85**, 897 (1952).

(11) T. L. Fletcher and W. H. Wetzel, *J. Org. Chem.*, **25**, 1348 (1960) F. Bergel and T. A. Stock, *J. Chem. Soc.*, 2409 (1954).