TABLE II
AMINOAMIDE DERIVATIVES OF 5-ANDROSTEN-3β-OL

Compd	Formula	Yield, %	Mp, °C	$[\alpha]^{25}D$, deg	Recrystn solvents
IIIa	$C_{25}H_{42}N_2O_2$	57	194–196	−39 (*c* 1, EtOH)	EtOH–hex
IIIb	$C_{28}H_{40}N_2O_3$	63	258–260	−37 (*c* 0.95, EtOH)	EtOH–$CHCl_3$–hex
IIIc	$C_{22}H_{36}N_2O_3$	50	204–206	−117 (*c* 1, DMF)	MeOAc
IIId	$C_{21}H_{34}N_2O_2$	56	255–259	−107.5 (*c* 0.92, EtOH)	EtOH–hex
IIIe	$C_{28}H_{37}N_3O_3$	57	289–291	−78.6 (*c* 1, DMF)	EtOH–hex
IIIf	$C_{22}H_{36}N_2O_3$	30	257–260	−120 (*c* 1, AcOH)	MeOH–THF
IV	$C_{22}H_{36}N_2O_3$	49	199–202	−17.6 (*c* 1, EtOH)	THF–EtOH–Et_2O–hex

recrystallized to obtain the product as indicated in Table II.

N-Hydroxysuccinimidyl Glycolate.—Dicyclohexylcarbodiimide (1.237 g, 0.006 mole) was added to a cold (0°) solution of N-hydroxysuccinimide (0.691 g, 0.006 mole) and glycolic acid (0.456 g, 0.006 mole) in 12 ml of dioxane. After stirring 2 hr at 0° and 20 hr at 25°, the solution was filtered to remove dicyclohexylurea. The combined filtrate and washings (dioxane) were evaporated *in vacuo;* the residue was recrystallized (EtOH–hexane) to yield 0.85 g, mp 135–136°. *Anal.* ($C_6H_7NO_5$).

17β-Glycolamido-5-androsten-3β-ol.—The hydroxysuccinimidyl glycolate (173 mg, 0.001 mole) was added to a solution of the amine I (289 mg, 0.001 mole) in 3 ml of dioxane. A precipitate which formed almost immediately was redissolved by warming. After 16 hr the crystalline product was separated (yield 317 mg, mp 266–270°) and recrystallized (EtOH–$CHCl_3$–Et_2O) to give 258 mg, mp 270–273°, $[\alpha]^{26}D$ −109° (*c* 1.0, AcOH). *Anal.* ($C_{21}H_{33}NO_4$).

Acknowledgment. The authors are indebted to Dr. E. B. Goodsell for the pharmacological testing and the evaluation of antidepressant activity, to Dr. Ray Oslapas and Mr. T. Kallal for endocrine assays, to Mr. W. Washburn and associates for ir spectra, and to Mr. V. Rauschel and associates for elemental analyses.

Notes

The Mitomycin Antibiotics. Synthetic Studies. XX.[1] N-Substituted Carbamoyl and Acyl Esters of a Related 3-Hydroxymethyl-4,7-indoloquinone

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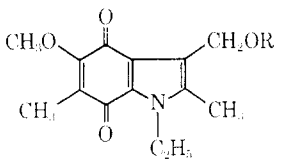
The finding that the mitomycin-related indoloquinone **1** possessed interesting *in vitro* and *in vivo* antibacterial activity[2] prompted the preparation of a variety of congeners. In the present paper we report the synthesis and antibacterial properties of compounds wherein the carbamoyl moiety present in **1** is variously

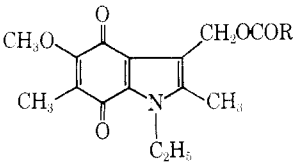


1, R = $CONH_2$
2, R = H
3, R = $COOC_6H_5$

substituted on the nitrogen atom or replaced by other acyl groups. Variations of the group attached to the 3-methylene carbon are of special interest in the delineation of the structure–activity relationships, inasmuch as this carbon is one of the sites for biological alkylation, which may be implicated in the mechanisms by which the mitomycins exert their effect.[3]

Acylation of the indoloquinone-3-carbinol **2**[2] with certain acid anhydrides or acyl halides in pyridine gave the ester derivatives described in Table I. For the

TABLE I
CARBOXYLIC ESTERS OF 1-ETHYL-3-HYDROXYMETHYL-5-METHOXY-2,6-DIMETHYL-4,7-INDOLOQUINONE[a]



Compd	R	Yield, %[b]	Mp, °C[c]	Formula
5	CH_3	91	144–145[e]	$C_{16}H_{19}NO_5$
6	C_2H_5	85	127–128	$C_{17}H_{21}NO_5$
7	*i*-C_3H_7	82	113–114[f]	$C_{18}H_{23}NO_5$
8	C_6H_{11}	70	127–128	$C_{21}H_{27}NO_5$
9	C_6H_5	71	139–141	$C_{21}H_{21}NO_5$[g]
10	2-C_4H_4O	91	156–157	$C_{19}H_{19}NO_6$
11	$C_6H_5CH{=}CH$	66	123–125	$C_{23}H_{23}NO_5$
12	C_6H_5CHOAc	20	100–101	$C_{24}H_{25}NO_7$
13	CH_3O	80	137–138	$C_{16}H_{19}NO_6$
14	C_2H_5O	80	112–113	$C_{17}H_{21}NO_6$

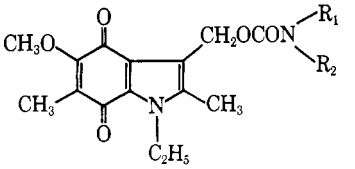
[a] Prepared by method A. [b] Material of analytical purity. [c] Unless noted otherwise, all compounds were recrystallized from CH_2Cl_2–petroleum ether (bp 30–60°). [d] Analyses for C, H, and N were within ±0.4% of the theoretical values except where noted. [e] Recrystallized from Me_2CO–hexane. [f] Recrystallized from EtOAc–hexane. [g] N: calcd, 3.81; found, 4.32.

(1) Paper XIX: J. F. Poletto, G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 95 (1967).

(2) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **10**, 1 (1967).

(3) (a) W. Szybalski and V. N. Iyer, *Fed. Proc.*, **23**, 946 (1964); (b) A. Weissbach and A. Lisio, *Biochemistry*, **4**, 196 (1965).

TABLE II
CARBAMATE ESTERS OF 1-ETHYL-3-HYDROXYMETHYL-5-METHOXY-2,6-DIMETHYL-4,7-INDOLOQUINONE

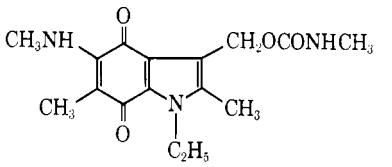


Compd	R_1	R_2	Method	Yield, %[a]	Mp, °C	Formula[b]
15	CH_3	H	B	40	170–171[c]	$C_{16}H_{20}N_2O_5$
16	C_2H_5	H	B	64	159–160[d]	$C_{17}H_{22}N_2O_5$
17	C_3H_7	H	B	64	129–130[d]	$C_{18}H_{24}N_2O_5$
18	i-C_3H_7	H	B	65	151–153[d]	$C_{18}H_{24}N_2O_5$
19	C_4H_9	H	B	57	116–117[d]	$C_{19}H_{26}N_2O_5$
20	C_5H_{11}	H	B	69	124–125[d]	$C_{20}H_{28}N_2O_5$
21	$CH_2CH_2{=}CH_2$	H	B	70	124–125[e]	$C_{18}H_{22}N_2O_5$
22	C_6H_{11}	H	B	67	159–160[d]	$C_{21}H_{28}N_2O_5$
23	C_6H_5	H	B	73	156–158[d]	$C_{21}H_{22}N_2O_5$
24	o-$CH_3OC_6H_4$	H	B	54	170–171[e]	$C_{22}H_{22}N_2O_6$
25	m-ClC_6H_4	H	B	48	148–149[e]	$C_{21}H_{21}ClN_2O_5$
26	CH_3	CH_3	C	53	119–120[e]	$C_{17}H_{22}N_2O_5$
27	C_2H_5	C_2H_5	C	35	103–106[e]	$C_{19}H_{26}N_2O_5$[f]
28	CH_2CH_2OH	H	C	22	110–113[e]	$C_{17}H_{22}N_2O_6$
29	$(CH_2)_3OH$	H	C	42	125–126[e]	$C_{18}H_{24}N_2O_6$
30	$CH_2CH_2OC_2H_5$	H	C	43	109–110[d]	$C_{19}H_{26}N_2O_6$
31	CH_2CH_2CN	H	C	53	147–149[d]	$C_{18}H_{21}N_3O_5$
32	$(CH_2)_3SCH_3$	H	C	48	116–118[d]	$C_{19}H_{26}N_2O_5S$
33	$(CH_2)_3N(CH_3)_2$	CH_3	C	62	60–61[g]	$C_{21}H_{31}N_3O_5$
34	$CH_2C_6H_5$	H	C	55	117–118[d]	$C_{22}H_{24}N_2O_5$
35	$-(CH_2)_5-$		C	69	163–164[d]	$C_{20}H_{26}N_2O_5$
36	$-CH_2CH_2N(CH_3)CH_2CH_2-$		C	51	134–136[d]	$C_{20}H_{27}N_3O_5$
37	$-CH_2CH_2NCH_2CH_2-$ $\vert$ $(CH_2)_3N(CH_3)_2$		C	23	126–128[g]	$C_{24}H_{36}N_4O_5$

[a] Material of analytical purity. [b] Except where noted otherwise, analyses for C, H, Cl, N, and S were within ±0.4% of the theoretical values. [c] Recrystallized from ether. [d] Recrystallized from CH_2Cl_2–petroleum ether. [e] Recrystallized from ether–petroleum ether. [f] C: calcd, 62.96; found, 62.47. [g] Recrystallized from petroleum ether.

preparation of the more pertinent substituted carbamoyl esters (Table II) either of two procedures was used. Treatment of carbinol **2** with the appropriate isocyanate gave the alkyl- (**15–20**), alkenyl- (**21**), cycloalkyl- (**22**), and aryl-substituted (**23–25**) carbamate esters. Unexpectedly, carbinol **2** proved inert to several representative alkyl and aryl isothiocyanates. The second procedure, involving treatment of the phenyl carbonate **3**[2] with the appropriate amine, furnished the dialkyl- (**26, 27**) and monofunctional alkyl- and dialkyl-substituted (**28–34**) carbamate esters, as well as the piperidine (**35**) and 4-substituted (**36, 37**) derived carbamates. A potentially useful procedure for the preparation of the substituted carbamate esters, namely acylation of alcohol **2** with the appropriately substituted carbamoyl halide, proved to be of limited value. Thus, despite the successful preparation of the diphenylcarbamate ester **38,** attempts to prepare the dimethyl- and diethylcarbamate esters with the corresponding dialkylcarbamoyl halides were unsuccessful.

With respect to the second procedure, *i.e.*, treatment of phenyl carbonate **3** with the appropriate amine, we would note that concomitant displacement of the quinoid methoxyl group was sometimes observed, and in these cases could not be avoided. Thus, methylamine reacted cleanly with **3** to give only the 5-methylaminoquinone carbamate **4**;[4] but the more basic dialkylamines gave only the 5-methoxy carbamates. Of the cyclic amines, pyrrolidine reacted at both sites, whereas piperidine and 1-methylpiperazine reacted preferentially with the carbonate function. Ammonia[1] and those amines having a pK_b of the same magnitude, *e.g.*, benzylamine and ethanolamine, gave only the 5-methoxycarbamates. Finally, no reaction with **3** was noted with the weakly basic aniline and N-methylaniline.



4

Biology.—The compounds prepared in this investigation were tested for their *in vitro* antibacterial activity ultilizing the standard agar-dilution technique.[5] Included in the spectrum of microorganisms are a tetracycline-resistant species (*Staphylococcus aureus* strain Rose) and tetracycline- as well as penicillin-resistant species (*Streptococcus* sp., β-hemolytic 80, and *Streptococcus* sp., nonhemolytic, γ11). Among the most interesting carboxylate esters were **5–10** and **14** (Table III); however, none of these compounds were equivalent to the unsubstituted carbamate ester **1** in activity. Of the various substituted carbamate esters prepared in this study, few possessed an *in vitro* potency approaching that of the unsubstituted carbamate ester **1**. Those most nearly approximating the activity of **1** were the N-methyl (**15**) and the monofunctional-substituted alkyl (**28–32**) carbamates (Table IV). Although apparently less active *in vitro*, one of this latter class, the hydroxyethylcarbamate **28,** proved superior

(4) W. A. Remers and M. J. Weiss, *J. Med. Chem.*, **11**, 737 (1968).

(5) For a description of this assay as conducted in these laboratories by Mr. A. C. Dornbush see G. R. Allen, Jr., B. R. Baker, A. C. Dornbush, J. P. Joseph, H. M. Kissman, and M. J. Weiss, *ibid.*, **2**, 391 (1960).

TABLE III

In Vitro ANTIBACTERIAL ACTIVITY OF THE 1-ETHYL-3-HYDROXYMETHYL-5-METHOXY-2,6-DIMETHYL-4,7-INDOLOQUINONE CARBONYLATES

	Min inhib concn (μg/ml)[a] against											
Compd	*Myco.* 607	*Staph.* 6538P	*Staph.* Rose	*S. lutea*	*S. faec.*	*Strep.* C203	*Strep.* β80	*Strep.* γ11	*B. subt.*	*C. xerose*	*B. cereus*	*Past.* 310
5[b]	3.12	6.25	6.25	6.25		1.56	12.5	6.25	1.56	12.5	≤0.2	c
6	3.12	6.25	6.25	25		6.25	25	12.5	3.12	50	≤0.78	c
7	3.12	12.5	12.5	12.5		6.25	25	25	6.25		0.78	
8	1.56					25					3.12	
9	3.12	25	25	25		1.56	25	25	25		0.78	
10[d]						50			100		6.25	
14	25					50			25		12.5	50

[a] Highest test level 50 μg/ml unless noted otherwise. All data are from concurrent assays. Abbreviations for microorganisms: *Myco.* 607 = *Mycobacterium smegmatis*, ATCC 607; *Staph.* 6538P = *Staphylococcus aureus* ATCC 6538P; *Staph.* Rose = *Staphylococcus aureus* strain Rose; *S. lutea* = *Sarcina lutea*, ATCC 9341; *Strep. faec.* = *Streptococcus faecalis*, ATCC 8043; *Strep.* C203 = *Streptococcus pyogenes*, C203; *Strep.* β80 = *Streptococcus* sp., β-hemolytic, 80; *Strep.* γ11 = *Streptococcus* sp., nonhemolytic, 11; *B. subt.* = *Bacillus subtilis*, ATCC 6633; *C. xerose* = *Corynebacterium xerosis*, NRRL B1397; *B. cereus* = *Bacillus cereus*, ATCC 10702; *Past.* 310 = *Pasteurella multocida*, γ310. [b] Highest test level = 12.5 μg/ml. [c] Not determined. [d] Highest test level = 100 μg/ml.

TABLE IV

In Vitro ANTIBACTERIAL ACTIVITY OF THE 1-ETHYL-3-HYDROXYMETHYL-5-METHOXY-2,6-DIMETHYL-4,7-INDOLOQUINONE CARBAMATES

	Min inhib concn (μg/ml)[a] against											
Compd	*Myco.* 607	*Staph.* 6538P	*Staph.* Rose	*S. lutea*	*Strep. faec.*	*Strep.* C203	*Strep.* β80	*Strep.* γ11	*B. subt.*	*C. xerose*	*B. cereus*	*Past.* 310
1	6.25	1.56	1.56	6.25	12.5	0.78	3.12	3.12	1.56	6.25	0.39	6.25
15	3.12	1.56	3.12	6.25		1.56	6.25	6.25	1.56	12.5	1.56	6.25
16	6.25	6.25	6.25	25		1.56	12.5	12.5	3.12	25	0.39	6.25
17	6.25	6.25	12.5	12.5		3.12	12.5	12.5	3.12	12.5	0.78	12.5
18	6.25	6.25	6.25	50		0.78	25	12.5	3.12	50	0.39	6.25
19	6.25	12.5	12.5	12.5		3.12	12.5	12.5	1.56	12.5	0.39	25
20	6.25	25	50	50		3.12	25	25	6.25		1.56	
21	6.25	12.5	6.25	12.5		3.12	12.5	12.5	3.12	12.5	0.39	6.25
22	12.5					3.12	50		6.25		0.78	
23	6.25	12.5	12.5	25		12.5	12.5	12.5	6.25	25	3.12	
25	12.5	25	25	12.5		3.12	25	25	25	12.5	1.56	
26	6.25	6.25	6.25	25		3.12	25	25	6.25	25	0.78	
27	6.25	6.25	6.25	12.5		1.56	12.5	6.25	3.12	12.5	0.39	25
28	25	3.12	3.12	12.5	25	0.39	6.25	6.25	0.78	12.5	0.39	3.12
29	25	1.56	3.12	12.5	25	0.78	6.25	6.25	0.78	12.5	0.39	25
30	6.25	6.25	6.25	25	50	0.78	12.5	12.5	1.56	25	0.39	6.25
31	12.5	3.12	3.12	12.5	25	0.78	6.25	6.25	0.78	12.5	≤0.2	6.25
32	6.25	6.25	3.12	12.5		0.78	12.5	12.5	1.56	12.5	0.78	6.25
33	25	6.25	6.25	12.5	50	1.56	12.5	12.5	3.12	6.25	0.78	6.25
34	6.25	6.25	12.5	25		1.56	6.25	12.5	3.12	25	0.78	50
35	25					1.56					1.56	
36	12.5	6.25	6.25	25		0.39	12.5	12.5	1.56	12.5	0.78	6.25
37	50	6.25	6.25	50	50	0.78	12.5	12.5	1.56	12.5	0.78	12.5

[a] Highest test level = 50 μg/ml. For definition of abbreviations see footnote *a*, Table III.

to **1** in its ability to protect mice infected with *Staphylococcus aureus* strain Smith.[6] However, **28** failed to protect mice against *Streptococcus pyogenes* C203 infections. With the exception of *Pasteurella multocida*, γ310, only marginal activity against gram-negative species was noted with the compounds of Table I and II.

Experimental Section

General.—Melting points were determined in an open capillary tube and are corrected. The petroleum ether used was that fraction boiling at 30–60° unless specified otherwise. All evaporations were carried out at reduced pressure. The uv spectra of **5–38** were characterized by the anticipated maxima at 230, 285, 345, and 455 mμ in MeOH using a Cary recording spectrophotometer. The ir spectra of **5–14** showed a carbonyl stretching frequency at 5.70–5.78 μ, whereas the carbonyl stretching frequency for **15–38** appears at 5.80–5.95 μ (in KBr disks with a Perkin-Elmer spectrophotometer, Model 21).

(6) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, submitted for publication.

Method A.—A stirred solution of 200 mg of 1-ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethyl-4,7-indoloquinone (**2**)[2] in 4–5 ml of pyridine was treated with 0.2–0.5 ml of the appropriate acid halide or anhydride for 16–20 hr. The esters were precipitated by addition of H_2O and purified as indicated in Table I.

Method B.—In a typical preparation a solution of 200 mg of 1-ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethyl-4,7-indoloquinone (**2**)[2] in 0.6 ml of butyl isocyanate was heated on the steam bath for 3 hr. The cooled solution was diluted with petroleum ether and chilled to give the butyl carbamate **19** as orange crystals. The characterization of this substance and other compounds prepared in a similar manner is given in Table II.

Method C.—This general procedure is illustrated by the following preparation. Me_2NH was introduced into a cold (acetone–Dry Ice bath) solution of 200 mg of 1-ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethyl-4,7-indoloquinone phenyl carbonate (**3**)[2] in 15 ml of CH_2Cl_2 until the volume of the solution was about 30 ml. The orange solution was stirred at room temperature for 75 min. The excess amine was swept from the solution in a stream of N_2, and the resulting solution was washed with saline, dried ($MgSO_4$), and evaporated. The residue was purified as indicated in Table II.

1-Ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethyl-4,7-indoloquinone Diphenylcarbamate (38).—A solution of 200 mg (0.76 mmole) of 1-ethyl-3-hydroxymethyl-5-methoxy-2,6-dimethyl-4,7-

indoloquinone (**2**) and 180 mg (0.78 mmole) of diphenylcarbamoyl chloride in 4 ml of pyridine was heated on the steam bath for about 16 hr. H_2O was added, and the mixture was extracted with CH_2Cl_2; the combined extracts were washed with saline, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a magnesia–silica gel absorbent. The material eluted by ether was recrystallized from ether–petroleum ether to give 57 mg of crystals, mp 159–161°. *Anal.* ($C_{27}H_{26}N_2O_5$) N. Elution of the column with $CHCl_3$ gave 65 mg of **2**.

Acknowledgment.—Spectra data were furnished by Mr. W. Fulmor and his associates. Microanalyses were determined by Mr. L. Brancone and his group. The *in vitro* antibacterial assays were furnished by Mr. A. C. Dornbush and his associates.

Adamantane Derivatives of *p*-Aminobenzamide and Sulfanilamide[1]

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A new antagonist of *p*-aminobenzoic acid was found to differ from sulfonamides in its mode of action. Inhibition of the growth of sensitive microorganisms by N^1-adamantyl-*p*-aminobenzamide was prevented competitively by *p*-aminobenzoic acid. When combined with sulfanilamide, synergistic inhibition occurred and this compound inhibited the growth of a strain of *Escherichia coli* resistant to sulfanilamide. Adamantyl derivatives of various drugs and antimetabolites have been synthesized in other laboratories.[2-5] Some of these compounds had remarkable pharmacological activity. In the course of the synthesis of folate antagonists, N^1-adamantyl-*p*-aminobenzamide (**3a**) and N^1-adamantylsulfanilamide (**6**) were synthesized. For comparison, the N^1-cyclohexyl-*p*-aminobenzamide (**3b**)[6] and N^1-phenyl-*p*-aminobenzamide (**3c**)[7] were also prepared. The synthesis of these compounds and preliminary evaluation of their biological activity are reported in this paper.

The general route of the synthesis of *p*-aminobenzamide derivatives is presented in Chart I. The synthetic sequence for the preparation of N^1-adamantylsulfanilamide is shown in Chart II.

The biological activity of **3a** was tested in three organisms: *Streptococcus faecalis*, *Escherichia coli* K12, and *Saccharomyces carlsbergensis*. The details concerning these tests will be published elsewhere. The concentration of **3a** required for 50% inhibition of growth of *E. coli* was 2×10^{-4} *M* and of *S. carlsbergensis*, 3×10^{-5} *M*. The concentration of sulfanilamide required for 50% inhibition of growth was

CHART I

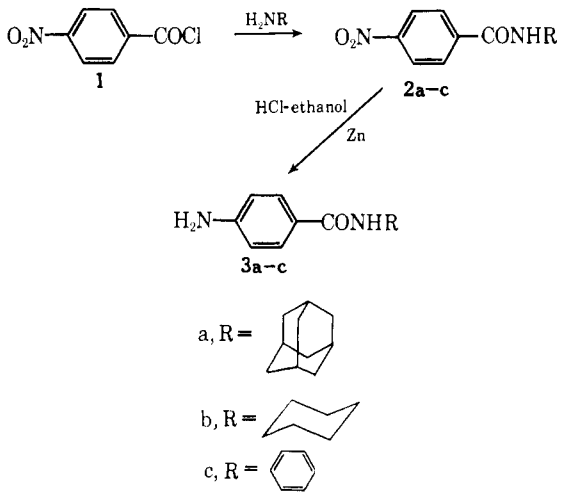
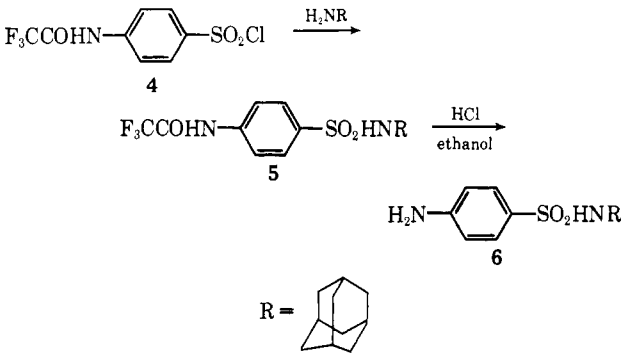


CHART II



4×10^{-4} and 5×10^{-4} *M*, respectively. *S. faecalis* was insensitive to **3a**. *E. coli* was not inhibited by **3b**, **3c**, and **6**. The growth inhibition caused by **3a** was reversed competitively by *p*-aminobenzoic acid and noncompetitively by dihydrofolic acid and folinic acid. The growth inhibition caused by sulfanilamide was reversed only by *p*-aminobenzoic acid. There was a strongly synergistic inhibition of the growth of *E. coli* when sulfanilamide and **3a** were used in combination. A strain of *E. coli* made resistant to sulfanilamide was as sensitive to **3a** as was the parent strain. It is evident from these results that **3a**, like sulfanilamide, is an antagonist of *p*-aminobenzoic acid. The metabolic pathway for the utilization of *p*-aminobenzoic acid in *E. coli*[8] may be represented by the following steps: 2-amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine + *p*-aminobenzoic acid → dihydropteroic acid → dihydrofolic acid → tetrahydrofolic acid → N^5-formyltetrahydrofolic acid.

Sulfonamides inhibit the first step in the metabolic sequence by competing with *p*-aminobenzoic acid. Further, there is strong evidence that sulfanilic acid is coupled with the pteridine to form an analog of dihydropteroate.[9] This compound seems to inhibit the synthesis of dihydropteroate irreversibly. The growth inhibition caused by **3a** and by sulfanilamide is competitively reversed by *p*-aminobenzoate. This indicates that both compounds interfere with the utilization

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(2) K. Gerzon, E. V. Krumkalus, R. L. Brindle, F. J. Marshall, and M. A. Root, *J. Med. Chem.*, **6**, 760 (1963).

(3) R. T. Rapala, R. J. Kraay, and K. Gerzon, *ibid.*, **8**, 580 (1965).

(4) K. Gerzon and D. Kau, *ibid.*, **10**, 189 (1967).

(5) J. R. Geigy, Belgian Patent 629,371 (1963); *Chem. Abstr.*, **60**, 9284*b* (1964).

(6) Kuhlman, French Patent 820,736 (Nov. 17, 1937); *Chem. Abstr.*, **32**, 3628 (1938).

(7) G. Lockemann, *Ber.*, **75**, 1911 (1942).

(8) G. M. Brown, R. A. Weisman, and D. A. Molnar, *J. Biol. Chem.*, **236**, 2534 (1961).

(9) G. M. Brown, *ibid.*, **237**, 536 (1962).