When the reaction time was decreased to 5 hr., IV was also obtained. The ratio of IV to V was roughly 1:2 in contrast to the 1:1 ratio of the two obtained in refluxing acetone–ethanol (see above).

The infrared spectra of IV and V were distinctly different throughout the entire spectral range (Figure 1). That IV was obtained pure, uncontaminated with its rearranged isomer V, is indicated by the sharp medium-intensity band at 10.2 μ present in the mull spectrum of V and completely absent from that of IV.

Treatment of 4,6-Diamino-1-benzyl-1,2-dihydro-2,2-dimethyl-*s*-triazine with HCl. A. In Refluxing Acetone–Ethanol.—A solution of 100 mg. (0.37 mmole) of IV in a mixture of 1.3 ml. of commercial absolute ethanol and 0.5 ml. of reagent grade acetone containing 0.05 ml. (0.5 mmole) of concentrated HCl was heated under gentle reflux for 27 hr. The residue obtained after evaporating the solvents was dissolved in 1 ml. of water and the solution was neutralized with 2 *N* NaOH. IV (50 mg.) was recovered (the compound began separating as the pH of the solution approached neutrality), m.p. 197–198.5°. Its infrared spectrum was identical with that of authentic IV. Evaporation of the aqueous filtrate left a 19-mg. residue. Its very simple infrared spectrum was considerably different from either IV or V. Thus 72.5% of the material isolated was unrearranged IV.

B. In Acetone–Ethanol at 110°.—The reaction mixture described in A was heated at 110° (sealed tube) for 17.5 hr. The resulting yellow solution was evaporated, the residual oil was taken up in 0.7 ml. of water, and the pH of the solution was adjusted to 6–7 (alkacid test paper) with 2 *N* NaOH. The solution remained homogeneous (compare with A). After 15 min. at room temperature, the solution was refrigerated (0 to −10°) for 2 days. The highly crystalline solid which separated melted 190–193°, yield 47 mg. (47%). Its infrared spectrum was identical with that of authentic V.

Base-Catalyzed Rearrangement of IV to V.—A suspension of 155 mg. of IV in 1 ml. of 2 *N* NaOH was heated on a steam bath for 15 min. An additional 1 ml. of water was added, and heating continued for 1 hr. The reaction mixture was cooled and the pH of the solution was adjusted to 6–7 (alkacid test paper) with dilute HCl. Crystalline material began separating from the resulting turbid solution within 1 hr. After refrigerating at 0 to −10° overnight, 115 mg. (74%) of V was collected, m.p. 194–196°, m.m.p. 181–193° with IV. Its infrared spectrum was identical with that of an authentic sample of V prepared from VI and benzylamine hydrochloride.

When IV was treated with 2 *N* NaOH at room temperature (aqueous phase strongly alkaline), it dissolved, and almost immediately thereafter a new solid separated which was collected after 10 min. Acidification of this material with a small amount of concentrated HCl caused it to dissolve. Dilution with a small amount of water resulted in the separation of a crystalline solid which was collected after adjusting the pH of the aqueous phase to 3–4 with 2 *N* NaOH. This compound was identified as unchanged IV by its melting point (198–201°), mixture melting point (197–200°), and infrared spectrum (identical with that of an authentic sample).

4-Amino-6-benzylamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride V from Benzylamine Hydrochloride and 4-Amino-1,2-dihydro-2,2-dimethyl-6-methylthio-*s*-triazine (VI).—The procedure described by Birtwell, *et al.*,[16] for the preparation of the 6-anilinodihydrotriazine from aniline hydrochloride and VI was extended to the preparation of the 6-benzylamino analog. Thus, a solution of 2 g. (0.012 mole) of VI and 1.6 g. (0.011 mole) of benzylamine hydrochloride in 5 ml. of water was heated under reflux for 26 hr., and the gummy residue obtained by evaporating the aqueous solution to dryness *in vacuo* was treated with dilute Na_2CO_3 solution. After rubbing with a metal spatula, the reaction mixture solidified on standing for a short while. The solid was collected and heated in boiling acetone; 18 g. of the bicarbonate was thus obtained, which was converted to the hydrochloride salt V as described above; m.p. 194–195.5°, m.m.p. 194–195.5° with V prepared *via* the sealed tube reaction. The infrared spectra of the compounds prepared by the two routes were identical.

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Spiranes. IX. Amides of 3,9-Dicarboxy-2,4,8,10-tetraoxaspiro[5.5]undecane[1]

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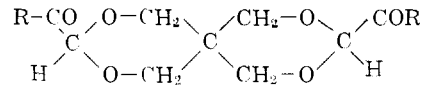
The bisalkyl- and bisdialkylaminoalkylamides of 3,9-dicarboxy-2,4,8,10-tetraoxaspiro[5.5]undecane have been prepared, and the latter possess interesting pharmacological activity. We have previously reported improved methods for the synthesis of 3,9-dicarbomethoxy-2,4,8,10-tetraoxaspiro[5.5]undecane (Ib) and several of its homologs.[2] The present report deals with the preparation of some derivatives of the parent acid Ia and their pharmacological properties.



Ia, R = OH
b, R = OCH_3
c, R = alkyl
d, R = dialkylaminoalkyl or heterocyclicalkyl

The ester Ib is saponified with remarkable ease. Indeed, simply dissolving the ester in water effects saponification. Series of bisalkyl and bisdialkylaminoalkylamides (Ic and Id), were prepared from the ester Ib by reaction with the appropriate primary amines in methanol. The reaction proceeded readily in all cases and gave high yields of pure product.

The bisalkylamides are listed in Table I and the bisdialkylaminoalkyl- and heterocyclicalkylamides in Table II. Of the bisalkylamides the lower members were soluble in water as well as common organic solvents. All of the bisdialkylaminoalkyl- and heterocyclicalkylamides prepared in this study were quite soluble in water.

Gross pharmacological screening of these amides, according to previously described techniques,[1,3] showed that the bisalkylamides possessed no remarkable pharmacological activity. However, the bisdialkylaminoalkylamides produced sedation, muscle relaxation and tranquilization in varying degree in the rat and the rabbit.

When compared with meprobamate, the bisdialkylaminoalkylamides possessed from 0.6 to 1.0 times the activity of meprobamate. Maximum activity of the compounds studied resided in the bisdimethylaminoethyl- and dimethylaminopropylamides.

Experimental

All melting points were obtained with a Thomas-Hoover capillary type apparatus and are corrected.

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TABLE I
N,N′-DIALKYLAMIDES (1c)

N-Substituent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	221–222.5	$C_{11}H_{18}N_2O_6$	48.17	48.29	6.62	6.82	10.21	9.91
Ethyl[a]	166–167	$C_{13}H_{22}N_2O_6$	51.64	51.70	7.34	7.05	9.27	9.39
Propyl[a]	161–162	$C_{15}H_{26}N_2O_6$	54.53	54.30	7.93	8.08	8.48	8.60
Butyl	146–147	$C_{17}H_{30}N_2O_6$	56.96	57.07	8.43	8.36	7.82	7.57
Amyl	151–152	$C_{19}H_{34}N_2O_6$	59.04	59.30	8.87	9.13	7.25	7.26
Hexyl	154–155	$C_{21}H_{38}N_2O_6$	60.82	60.66	9.24	9.16	6.76	7.01
Heptyl	160–160.5	$C_{23}H_{42}N_2O_6$	62.41	62.39	9.57	9.66	6.33	6.36
Octyl	154–155	$C_{25}H_{46}N_2O_6$	63.81	63.79	9.85	9.87	5.95	5.87
Nonyl	157–158	$C_{27}H_{50}N_2O_6$	65.02	65.02	10.11	10.16	5.62	5.68
Decyl	152–153	$C_{29}H_{54}N_2O_6$	66.12	66.26	10.33	10.41	5.31	5.05

[a] Recrystallized from ethyl acetate; all others from ethyl acetate–ether.

TABLE II
N,N′-DIALKYLAMINOALKYLAMIDES (Id)

N-Substituent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylaminoethyl	106–107	$C_{17}H_{32}N_4O_6$	52.55	52.56	8.30	8.37	14.42	14.22
Dimethylaminopropyl	117–118	$C_{19}H_{36}N_4O_6$	54.79	54.77	8.71	8.77	13.45	13.14
Pyrrolidinopropyl	105–106	$C_{23}H_{40}N_4O_6$	58.95	58.65	8.60	8.56	11.96	11.62
Piperidinoethyl	135–136.5	$C_{23}H_{40}N_4O_6$	58.95	59.28	8.60	8.97	11.96	11.67
Diethylaminopropyl	Oil	$C_{23}H_{44}N_4O_6$	58.44	57.66	9.38	9.68	11.85	11.51
Dibutylaminopropyl	Oil	$C_{31}H_{60}N_4O_6$	63.66	63.18	10.34	10.43	9.58	9.39

N,N′-Bismethyl-3,9-dicarboxamido-2,4,8,10-tetraoxaspiro[5.5]-undecane.—To 5.52 g. (0.02 mole) of 3,9-dicarbomethoxy-2,4,8,-10-tetraoxaspiro[5.5]undecane in 75 ml. of methanol was added 0.06 mole of a 25% aqueous methylamine solution. The mixture was refluxed for 1 hr. and stripped of all solvents. The bisamide was obtained quantitatively as a white powder that melted at 220–222° and at 221–222.5° on recrystallization from methanol–ether. The product was soluble in water.

N,N′-Bis(3-dimethylaminopropyl)-3,9-dicarboxamido-2,4,8,-10-tetraoxaspiro[5.5]undecane.—To a solution of 5.52 g. (0.02 mole) of the diester Ib dissolved in 100 ml. of absolute methanol, was added 4.08 g. (0.04 mole) of 3-dimethylaminopropylamine in 50 ml. of methanol. The solution was refluxed 1 hr. and all solvents were stripped at the aspirator. A clear oil resulted which solidified on slurrying with anhydrous ether. There was obtained 7.6 g. (91%) of material melting at 117–118°, unchanged on recrystallization from ethyl acetate–ether. This product was water soluble.

The Structure–Activity Relationship in Penicillins

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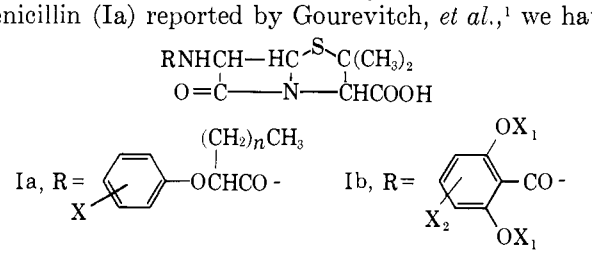
In a recent study of the activity of 22 derivatives of penicillin (Ia) reported by Gourevitch, *et al.*,[1] we have



shown, using substituent constants and regression analysis,[2] that variation in activity against resistant *Staphylococcus aureus* in the presence of serum is well correlated by eq. 1 and 2. In these equations, C is the molar concentration for CD_{50} with Smith strain *S. aureus* in the *in vivo* mice experiments and the minimum inhibitory molar concentration for the *in vitro* tests on bacteria. Human serum was used in the *in vitro* experiments. The number of points used in obtaining the constants *via* the least-squares method is represented by n; r is the correlation coefficient, and s is the standard deviation. It was shown by regression analysis that electron density on the ring as measured by $\Sigma\sigma$ for the substituents had no detectable effect on the biological activity.

	n	r	s		
$\log \frac{1}{C} = -0.445\pi + 5.673$	20	0.909	0.191	*in vivo*	(1)
$\log \frac{1}{C} = -0.468\pi + 6.437$	20	0.857	0.267	*in vitro*	(2)

Comparison of eq. 1 and 2 reveals that the slopes of the curves have the same dependence on the lipophilic character of the substituent (π). By definition,[3] a negative value of π for a substituent X indicates a preference with respect to H for the aqueous phase, and a positive value indicates a preference for the lipophilic phase. The negative sign associated with the π terms in eq. 1 and 2 means that increasing the hydrophilic character of the substituent increases its activity. Thus, as we pointed out,[2] using substituents such as $-SO_2CH_3$, $-CN$, or $-CH_2OH$ which are quite hydrophilic and possess negative values[4,5] for π would result in higher activity for compounds in the series Ia.

Recently, Sheehan[6] has published a summary of the activity of penicillins related to methicillin (Ib). These derivatives were also tested on resistant and nonresistant *S. aureus* in the presence and absence of

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