haved exactly like the cholestatriene analog[7] upon reduction with sodium borohydride. Thus at low temperature, the yield of pure $\Delta^{5,7}$-22-isospirostadien-3β-ol was *ca.* 70%, while at 80° the product was contaminated with an impurity absorbing at 242 mμ, most likely the $\Delta^{4,6}$-dien-3-ol. As shown by both Gallagher[4] and Dauben[5] the initial reaction appears to be hydrolysis of the enol acetate to the unconjugated ketone, which undergoes rapid reduction by the reagent to yield the unconjugated alcohol. Apparently, at higher temperature some isomerization of the unconjugated ketone to the $\Delta^{4,6}$-3-one occurs prior to reduction thus accounting for the formation of some of the $\Delta^{4,6}$-dien-3-ol. In this connection, it is of interest to note that the sodium borohydride reduction of 3-acetoxy-$\Delta^{3,5,7,9(11)}$-22-isospirostatetraene[10] (II) afforded $\Delta^{5,7,9(11)}$-22-isospirostatrien-3β-ol in essentially the same yield whether the reaction was carried out at 10° or at 80°. Evidently because of the longer conjugated triene system, the isomerization of the initially formed *un*conjugated ketone to the conjugated form is sufficiently slower so that reduction of the ketone predominates.

Experimental[11]

Sodium Borohydride Reduction of 3-Acetoxy-$\Delta^{3,5,7}$-22-isospirostatriene (I).—An ice-cold mixture of 1.0 g. of 3-acetoxy-$\Delta^{3,5,7}$-22-isospirostatriene (I)[10] in 40 cc. of dioxane and 60 cc. of methanol was added in one portion to a solution of 1.6 g. of sodium borohydride in 40 cc. of methanol and 3 cc. of water. After standing at 10° for 16 hours, the mixture was warmed for 30 minutes on the steam-bath, diluted with water and the solid was collected; yield 0.94 g., λ_{max}^{EtOH} 270, 282 and 292 mμ, log ϵ 4.07, 4.09, 3.86. Two recrystallizations from ethyl acetate furnished 0.55 g. (60%) of **$\Delta^{5,7}$-22-isospirostadien-3β-ol** with m.p. 187–190°, $[\alpha]^{20}D$ −177°, λ_{max}^{EtOH} 270, 280 and 292 mμ, log ϵ 4.17, 4.19, 3.99, infrared spectrum identical with that of an authentic specimen[12] (reported: m.p. 188.5–190°, $[\alpha]^{20}D$ −174°). Acetylation of the crystalline mother liquors afforded an additional 10–13% of **$\Delta^{5,7}$-22-isospirostadien-3β-ol acetate** with m.p. 201–203°, $[\alpha]^{20}D$ −122°, the identity of which was confirmed by comparison of its infrared spectrum with that of an authentic sample[12] (reported: m.p. 202–205°, $[\alpha]^{20}D$ −127°).

On carrying out the reaction as above but refluxing for 2 hours, the crude product (85% yield) exhibited m.p. 160–170°, $[\alpha]^{20}D$ −99°, λ_{max}^{EtOH} 242, 270, 280 and 292 mμ, log ϵ 3.52, 3.87, 3.89, 3.67.

Sodium Borohydride Reduction of 3-Acetoxy-$\Delta^{3,5,7,9(11)}$-22-isospirostatetraene (II).—One gram of the tetraene II[10] upon treatment with sodium borohydride as described above (10°) produced 0.635 g. (69%) of **$\Delta^{5,7,9(11)}$-22-isospirostatrien-3β-ol** with m.p. 187–190°, $[\alpha]^{20}D$ + 121°, λ_{max}^{EtOH} 324 mμ, log ϵ 4.14 and inflections at 312 mμ (log ϵ 4.10) and 338 mμ (log ϵ 4.00); lit.,[13] m.p. 187–190°, $[\alpha]^{20}D$ +119°, same ultraviolet absorption spectrum. **The acetate** showed m.p. 178–179°, $[\alpha]^{20}D$ +173° (reported[13]: m.p. 178–179°, $[\alpha]^{20}D$ +170°). The infrared spectra of both compounds were identical with those of authentic[13] derivatives.

In this instance, the reduction could be carried out at 80° without any diminution in yield, which in addition to a shorter reaction time had the advantage that it was possible to work in more concentrated solution. Thus, when 0.8 g. of the tetraene II was refluxed for two hours with 1.6 g. of sodium borohydride in 30 cc. each of dioxane and ethanol containing 3 cc. of water, precipitation with water afforded 0.71 g. (97%) of crude $\Delta^{5,7,9(11)}$-trien-3β-ol with m.p. 173–178°, $[\alpha]^{20}D$ +113°, λ_{max}^{EtOH} 324 mμ, log ϵ 4.11. One recrystallization from methanol led to 0.5 g. (68%) of the pure trienol.

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(11) Melting points are uncorrected and were determined in a sulfuric acid bath. Rotations and infrared spectra were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque and staff for these measurements. Thanks are due to Srta. Margarita Espinosa for technical assistance.

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Fatty Acid Amides. V.[1] Preparation of N-(2-Acetoxyethyl)-amides of Aliphatic Acids

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RECEIVED FEBRUARY 22, 1952

In a continuation of our studies on amides of fatty acids, we became interested in N-(2-acetoxyethyl)-amides. The only compound in this class previously described is N-(2-acetoxyethyl)-acetamide, prepared by treating ethanolamine with acetic anhydride[2] or with ketene.[3] When we attempted to prepare it by a slight modification of the former method we obtained diacetamide.

N-(2-Hydroxyethyl)-amides were acetylated (97–99%) by heating with a 100% excess of acetic anhydride for six hours. During the initial stages the temperature rose exothermically to 85–95° after which it was readily controlled at 75°. Careful control to prevent temperatures above 75° resulted in incomplete acetylation. Reactions carried out at 100° for three hours gave lower yields and undesirable side products.

Experimental

Starting Materials.—The N-(2-hydroxyethyl)-amides were prepared from pure fatty acids by refluxing 1 mole of the acid with 1.5 moles of ethanolamine for two to six hours.[4] N-(2-Hydroxyethyl)-acetamide, b.p. 145–146.7 (2.5 mm.) and $n^{25}D$ 1.4709, was distilled through a 3-foot Vigreux column. N-(2-Hydroxyethyl)-caproamide was freed of excess ethanolamine by vacuum distillation and then crystallized from ethyl ether, 4 ml./g., at 0° until pure. N-(2-Hydroxyethyl)-lauramide, m.p. 88.0–88.5°, -palmitamide, m.p. 98°, and -stearamide, m.p. 102°, were crystallized directly from the crude reaction mixtures using 95% ethanol, 4 ml./g., at 0°, 10 ml./g. at 0°, and 8 ml./g. at 25°, respectively. N-(2-Hydroxyethyl)-oleamide has already been described.[4]

Preparation of N-(2-Acetoxyethyl)-amides.—These amides were prepared by heating one mole of the N-(2-hydroxyethyl)-amide with two moles of acetic anhydride for six hours in a nitrogen atmosphere. During the initial stages the temperature rose exothermically to 85–95° after which it was readily controlled at 75°.

After the acetylation of N-(2-hydroxyethyl)-acetamide, the reaction mixture was distilled at 100 mm. to remove excess acetic anhydride and acetic acid formed. The pressure was then lowered to 5 mm. and the N-(2-acetoxyethyl)-acetamide was distilled. The acetic anhydride and acetic acid were removed similarly from the N-(2-acetoxyethyl)-caproamide reaction mixture, but in this case the crude amide remaining was crystallized five times from a mixture of equal portions of ether and petroleum naphtha, 3 ml./g. at −20°.

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TABLE I

N-(2-ACETOXYETHYL)-AMIDES OF ALIPHATIC ACIDS

N-(2-Acetoxyethyl)-	Reaction product Yield, %	Reaction product M.p., °C.	Crystallized product Yield, %	Crystallized product M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Saponification No.[a] Calcd.	Saponification No.[a] Found
Acetamide[b]	..	.....	71[c]	.....	49.6	49.8	7.64	7.35	9.65	9.33	386.5	393.8
Caproamide	99	<24	62	26.5–27.4	59.7	59.5	9.52	9.75	6.96	6.87	278.8	277.1
Lauramide	97	65.1–66.0	30	70.0–70.5	67.3	67.2	11.0	10.7	4.91	5.01	196.6	193.8
Palmitamide	99	78.4–79.0	95	79.5–80.0	70.3	70.8	11.5	11.7	4.10	4.08	164.3	164.5
Stearamide	99	83.1–84.0	92	84.1–84.4	71.5	72.0	11.7	11.7	3.79	3.82	151.8	151.8
Oleamide	99	34.5–35.2	77[d]	39.0–39.3	71.9	71.9	11.2	11.0	3.81	3.83	152.6	153.3

[a] Refluxed 1/2 hour with 0.2 *N* KOH. [b] Reference 3 gives b.p. 147–154° (8 mm.); $n^{24}D$ 1.4511; d^{24}_4 1.1015. [c] Distilled once through a 3′ Vigreux column; b.p. 142.0–142.5° (5.1 mm.); $n^{25}D$ 1.4500. [d] Iodine number; calcd. 69.1; found 70.0.

N-(2-Acetoxyethyl)-lauramide, -palmitamide and -stearamide reaction mixtures were repeatedly washed by vigorous mechanical stirring with hot water until acid-free. The acetoxyethyl amides were allowed to solidify and the cakes were dried and crystallized: N-(2-acetoxyethyl)-lauramide, once from acetone, 5 ml./g., at 0°, once from ethanol, 10 ml./g., at 0° and once from ether, 12 ml./g., at 24°; N-(2-acetoxyethyl)-palmitamide, once from ethanol, 8 ml./g., at −20°; N-(2-acetoxyethyl)-stearamide, twice from ethanol, 8 ml./g., at −20°.

The crude reaction mixture of N-(2-acetoxyethyl)-oleamide was dissolved in approximately ten times its volume of petroleum naphtha and washed repeatedly with warm water until free of acid. The petroleum naphtha was then distilled off under vacuum and the residue of crude amide was crystallized twice from ethanol, 10 ml./g., at −20°.

Results are summarized in Table I.

Acknowledgment.—The authors are indebted to Ruth B. Kelly and Mary Jane Welsh of this Laboratory for the carbon, hydrogen and nitrogen analyses.

CONTRIBUTION FROM THE
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Some 2,4,6-Triamino-5-alkyl- and 5-Benzylpyrimidines

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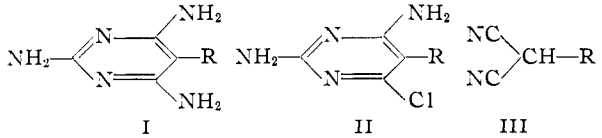
RECEIVED FEBRUARY 6, 1952

In connection with studies on 2,4-diaminopyrimidine antimalarials at present being conducted in these laboratories[1-4] it seemed desirable to prepare and test some 2,4,6-triaminopyrimidines with alkyl, benzyl and aryl substituents at the 5-position (I, R = alkyl, benzyl or aryl).



I II III

v. Merkatz[5] found that 2,4,6-trichloro-5-ethylpyrimidine reacted readily with ammonia to give 2,4-diamino-6-chloro-5-ethylpyrimidine (II, R = Et) but that further amination of this compound required vigorous treatment. This resistance to amination is general for 2,4-diamino-6-chloropyrimidines. Thus the amination of 2-amino-4,6-dichloro-5-benzylpyrimidine gives II (R = CH_2Ph)[6] while treatment of 2,4,6-trichloro-5-phenyl- and 4,6-dichloro-2-methylanilino-5-phenylpyrimidine with ammonia at elevated temperatures gives II (R = Ph) and 4-amino-6-chloro-2-methylanilino-5-phenylpyrimidine, respectively.[7] In view of these findings it seemed more profitable to prepare the triaminopyrimidines (I) by the condensation of guanidine with the substituted malonitrile (III).[8,9] The malonitriles (III) were prepared by distillation of the corresponding readily available malondiamides[10] with phosphorus pentoxide. Heretofore it has been more usual to employ the corresponding cyanacetamides.[11] The yields of III by the new method are quite satisfactory (45–90%). The nitriles (III, R = alkyl or benzyl) on refluxing with guanidine gave good yields of the triaminopyrimidines (I). Phenylmalononitrile, however, with guanidine in alcohol gave a compound which is believed to arise from the condensation of two molecules of guanidine with one of nitrile. The failure of III (R = Ph) to yield a pyrimidine with guanidine is reminiscent of the failures of phenylmalondialdehyde[12] and α-formylphenylacetonitrile[4] to condense with the same base.

The triaminopyrimidines (I, R = *n*-C_4H_9, $CH_2C_6H_5$ and $CH_2C_6H_4Cl$-*p*) were tested for antimalarial activity against *Plasmodium gallinaceum* in chicks and *P. berghei* in mice.[1] All these compounds showed antimalarial activity at doses between 10 and 100 mg./kg. (*i.e.*, between 0.1 and 0.05 the activity of N^1-*p*-chlorophenyl-N^5-isopropylbiguanide (chlorguanide)).

When tested against Sarcoma 180 by Stock and associates[13] at the Sloan-Kettering Institute four of the triaminopyrimidines (I, R = C_2H_5, $CH_2C_6H_5$, $CH_2C_6H_4Cl$-*p* and $CH_2C_6H_3Cl_2$-3,4) showed some signs of activity. Only the 2,4,6-

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