and was decomposed by acid with the evolution of sulfur dioxide.

Anal. Calcd. for $C_{15}H_{22}O_2N_2.SO_2$: N, 8.58. Found: N, 8.50.

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Preparation of N-Substituted Aminoacetals[1]

In the course of an extensive investigation involving the syntheses of compounds possessing anti-histaminic or spasmolytic properties, the need arose for some N-substituted aminoacetals of the general formula $R'\text{-}N(R'')\text{-}CH_2\text{-}CH(OR)_2$, where R may be methyl or ethyl and R′ and R″ may be hydrogen, alkyl, N-substituted aminoalkyl, -arylalkyl or heterocyclic groups. The products were all prepared by refluxing ethyl chloroacetal or methyl chloroacetal[2] with two or more equivalents of the amine[3] for a flux was decreased in the preparations of dimethyl benzylaminoacetal to two and one-half hours, of dimethyl cyclohexylaminoacetal to sixteen hours, of dimethyl piperidinoacetal to twenty hours and of dimethyl morpholinoacetal and of dimethyl methyl benzylacetal to six and one-half hours because the yields of these products were not improved, and in many cases were actually decreased, by a longer reaction time. Dimethyl diethylaminoacetal was prepared by refluxing the reaction mixture for twenty-four days because of the low boiling point of diethylamine. After cooling, ether was added until precipitation of the amine hydrochloride seemed complete. This mixture was filtered and the precipitate washed well with ether. After removal of the ether, the residue was fractionated *in vacuo*, using a short Vigreux column.

The hydrochlorides were prepared by treating an anhydrous ether solution of the free base with ethereal hydrogen chloride. The salt was separated by filtration, washed well with dry ether and recrystallized from an appropriate solvent. Oxalates were similarly prepared. Methiodides were prepared by treating the free base with

TABLE I

N-SUBSTITUTED AMINOACETALS OF FORMULA $\begin{matrix} R' \\ R'' \end{matrix}\!\!>\!N\text{—}CH_2\text{—}CH(OR)_2$

Aminoacetals							Derivatives			N Analyses, %	
R	R′	R″	B. p. °C.	B. p. Mm.	Yield, %	Formula	Solvent	M. p., °C.	Calcd.	Found
Me	Et	Et	155–163	764	24.4[a]	$C_8H_{19}NO_2\cdot CH_3I$	Acetone–ether	75–76	4.62	4.64
Me	*n*-Pr	*n*-Pr	96–97	22	53.2[b]	$C_{10}H_{23}O_2N\cdot CH_3I$	[c]	53–55	4.23	4.12
Me	Allyl	Allyl	77–83	10	44.8	$(C_{10}H_{19}NO_2)_2H_2C_2O_4$	Ethyl acetate–ether	61–62	6.08	5.73
Me	*n*-Bu	H	86–90	19	76.6[d]	$C_8H_{19}NO_2\cdot HCl$	Methanol–ether	158.5 (dec.)	7.09	7.08
Me	*n*-Bu	*n*-Bu	119–120	18	68.3	$(C_{12}H_{27}NO_2)_2H_2C_2O_4$	Acetone	98–99	5.34	5.16
Et	*n*-Bu	*n*-Bu	115.5–117.5	12	81	$C_{14}H_{31}NO_2\cdot CH_3I$	Ethyl acetate–ether[e]	72–73	3.61	3.76
Me	Methallyl	H	75	25	57.8	$(C_8H_{17}NO_2)_2H_2C_2O_4$	Ethanol	185–186.5	6.86	7.19
Me	Methallyl	Methallyl	102–104	13	35	$(C_{12}H_{23}NO_2)\cdot HCl$	Methanol–ether	116–117	5.60	5.42
Me	$(Et)_2N(CH_2)_4\text{—}\underset{\displaystyle CH_3}{\underset{\vert}{CH}}$	H	137.5–139	10	38.2	$C_{18}H_{30}N_2O_2\cdot 2HCl$	Isopropyl alc.–ether	131–132 (dec.)	8.77	8.77
Me	Cyclohexyl	H	118–119	17	77.8	$C_{10}H_{21}NO_2\cdot HCl$	Methanol–ether	139–140	6.26	6.59
Et	Cyclohexyl	H	141–145	23	80	$C_{12}H_{25}NO_2\cdot HCl$	Methanol–ether	120.5–121 (dec.)	5.56	5.65
Me	Piperidino[f]		94–96	19	91.7	$C_9H_{19}NO_2\cdot CH_3I$	Acetone[g]	134.5–134.8	4.44	4.35
Et	Piperidino[f]		110	18	80.5[h]	$C_{11}H_{23}NO_2\cdot CH_3I$	Acetone–ether	118–119	4.08	4.12
Me	Morpholino[f]		107–108	19	76.3	$C_8H_{17}NO_3\cdot HCl$	Acetone[i]	136–138 (dec.)	6.62	6.71
Et	Morpholino[f]		123	25	70.8	$C_{10}H_{21}NO_3\cdot HCl$	Acetone[j]	146–147 (dec.)	5.84	5.57
Me	Benzyl	H	147–149	18	72.7	$C_{11}H_{17}NO_2\cdot HCl$	Methanol–ether	110–111 (dec.)	6.05	5.87
Me	Benzyl	Me	130–132	13	60.1	$C_{12}H_{17}NO_2\cdot HCl$	[c]	107–108 (dec.)	5.70	5.96
Me	Benzyl	Benzyl	96	0.03	73.9	$C_{18}H_{23}NO_2\cdot HCl$	Methanol–ether	154 (dec.)	4.35	4.33
Me	Phenylethyl	H	149–153	12	43	$C_{13}H_{21}O_2N\cdot HCl$	Ethyl acetate	109–111 (dec.)	13.65[k]	13.75

[a] The corresponding diethyl acetal has been described by Stoermer and Prall, *Ber.*, **30**, 1505 (1897) and Guha, Rao and Verghese, *Current Sci.*, **12**, 82–83 (1938). [b] Refluxing for nineteen and one-half hours gave only a 27.4% yield. [c] The salt was not recrystallized. [d] The corresponding diethyl acetal has been prepared by Paal and Van Gember, *Arch. Pharm.*, **246**, 307–311 (1908). [e] The oxalate, recrystallized from the same mixture, melted at 118–119°. Analysis of the free base, $C_{14}H_{31}O_2N$; Calcd.: N, 5.71. Found: N, 5.70. [f] The radical replaces R′R″N–. [g] The hydrochloride, recrystallized from the same solvent, melted at 130–131°. [h] Prepared by Stoermer and Burkert, *Ber.*, **28**, 1248 (1895). [i] The methiodide, recrystallized from methanol–ether, melted at 194–196°. [j] The methiodide, recrystallized from acetone–ether, melted at 131.5–132.5°. [k] Chloride analysis.

period of time which varied with the nature of the amine. In the case of di-*n*-butylaminoacetal best yields were obtained after a reflux period of five days. Most of the products were refluxed for three to five days. The time of reflux was decreased in the preparations of dimethyl benzylaminoacetal to two and one-half hours, of dimethyl cyclohexylaminoacetal to sixteen hours, of dimethyl piperidinoacetal to twenty hours and of dimethyl morpholinoacetal and of dimethyl methyl benzylacetal to six and one-half hours because the yields of these products were not improved, and in many cases were actually decreased, by a longer reaction time. Dimethyl diethylaminoacetal was prepared by refluxing the reaction mixture for twenty-four days because of the low boiling point of diethylamine. After cooling, ether was added until precipitation of the amine hydrochloride seemed complete. This mixture was filtered and the precipitate washed well with ether. After removal of the ether, the residue was fractionated *in vacuo*, using a short Vigreux column.

The hydrochlorides were prepared by treating an anhydrous ether solution of the free base with ethereal hydrogen chloride. The salt was separated by filtration, washed well with dry ether and recrystallized from an appropriate solvent. Oxalates were similarly prepared. Methiodides were prepared by treating the free base with excess methyl iodide at room temperature until the mass solidified. This was suspended in dry ether, filtered, washed well with ether and recrystallized.

When condensation with di-isopropyl- or dicyclohexylamines was attempted, no precipitate of amine hydrochloride of any significant amount appeared even after a week's refluxing, and the starting materials were recovered unaltered. This has been experienced similarly by others. Smith and Burn[4] were unable to esterify dicyclohexylacetic acid with ethyl alcohol while Braun and Fischer[5] experienced the same difficulty with di-isopropylacetic acid. Burnet, *et al.*,[6] reported a very low yield of product

(1) The authors gratefully acknowledge the financial assistance in this project of Endo Products, Inc.

(2) When this project was initiated, ethyl chloroacetal was available from the Niacet Chemicals Corp. and this compound was used in the preparation of several of the compounds described in this paper. When the company discontinued production of this compound, it was replaced by methyl chloroacetyl, presently available from the General Aniline and Film Corp.

(3) The amines were all commercial products and were used without further purification. Diallylamine, methallylamine and dimethallylamine were generously contributed by the Shell Chemical Co., Emeryville, Calif.

(4) Smith and Burn, THIS JOURNAL, **66**, 1494 (1944).

(5) Braun and Fischer, *Ber.*, **66B**, 101 (1933).

(6) Burnett, Jenkins, Peet, Drager and Adams. THIS JOURNAL, **59**, 2349 (1937).

in the condensation of dicyclohexylamine with ethylene oxide. When Gilman and Clark[7] could not condense isopropyllithium with tri-isopropylsilane, they attributed this to the sterically hindered nature of the isopropyl group.

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(7) Gilman and Clark, *ibid.*, **69**, 1499 (1947).

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4-*n*-Butyl-2,6-di-*t*-butylphenol

Following the method of Stevens,[1] isobutylene was bubbled into 9.2 g. of 4-*n*-butylphenol[2] containing 0.25 ml. of concentrated sulfuric acid until the gain in weight of the reaction mixture showed that slightly more than the theoretical amount (6.9 g.) had been added, then the excess isobutylene was swept out with natural gas. The reaction mixture was washed free from acid with successive 5% sodium carbonate washes, dried by adding benzene and distilling, and the product vacuum distilled. The main fraction of 11 g. (68%) boiled at 154–157° (10.5 mm.), and on refractionation gave a clear, colorless, rather viscous product, b. p. 144–144.5° (6 mm.), $n^{20}D$ 1.5019, d^{20}_4 0.920.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.30; H, 11.52.

(1) D. R. Stevens, *Ind. Eng. Chem.*, **35**, 655–660 (1943).

(2) R. V. Rice and W. C. Harden, *J. Am. Pharm. Assoc.*, **25**, 7–9 (1936).

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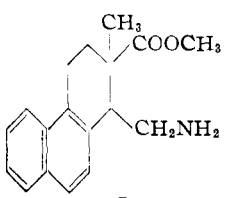
COMMUNICATIONS TO THE EDITOR

THE LACTAMS OF *cis*- AND *trans*-1-AMINOMETHYL-2-CARBOMETHOXY-2-METHYL-1,2,3,4-TETRAHYDROPHENANTHRENE

Sir:

In order to secure more information concerning the configuration of the steroids at the C/D ring juncture, we have prepared the diastereoisomeric (*cis* and *trans*) amino esters (I) which correspond in configuration to desoxyequilenin and desoxyisoequilenin and have studied their tendency to form γ-lactams (II). It was hoped that their



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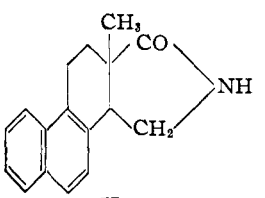

II

behavior in this respect would indicate which amino ester had the *cis* and which the *trans* configuration. It was found that both amino esters yielded lactams, one of which must be the *cis* lactam and the other the *trans* lactam. However, the lactam from the amino ester related to desoxyisoequilenin formed more rapidly than the lactam from the amino ester related to desoxyequilenin. Thus, when an aqueous solution of the amine ester hydrochloride corresponding to desoxyequilenin was treated with one equivalent of alkali and the liberated product was extracted immediately into ether (total time, ten minutes), only the free amino ester was formed. Under identical conditions the amino ester corresponding to desoxyisoequilenin gave a 60% yield of the γ-lactam (II) (m. p. 205–206°. *Anal.* Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.77; N, 5.58. Found: C, 81.11; H, 6.86; N, 5.46). The lactam (m. p. 234–236°. *Anal.* Found: C, 81.20; H, 6.83; N, 5.33) of the desoxyequilenin series was obtained when an excess of alkali was employed and the ether solution of the amino ester was allowed to stand for a longer period of time.

The more rapid formation of the lactam from the amino ester corresponding to desoxyisoequilenin may be indicative of the *cis* configuration which is currently assigned to desoxyisoequilenin. Further evidence is being sought in experiments in progress on the preparation of the corresponding 2-methyl-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acids and a study of their ability to form anhydrides.

The amino esters were prepared by Curtius degradation of the acetic acid side chain of the two diastereoisomeric (*cis* and *trans*) 2-carbomethoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene-1-acetic acids.[1] The degradation was accomplished by treatment of the acid chloride with sodium azide,[2] followed by rearrangement of the resulting azide to the isocyanate, which was hydrolyzed by concentrated hydrochloric acid to the amine ester hydrochloride in good yield; m. p.: normal (desoxyequilenin) form, 241–242°; iso form, 212–213°. *Anal.* Calcd. for $C_{18}H_{22}ClNO_2$:

(1) Bachmann and Wilds, THIS JOURNAL, **62**, 2084 (1940). The α acid has been shown to have the configuration of desoxyisoequilenin; the β acid corresponds to desoxyequilenin. The results of these experiments will be published soon.

(2) After our work had been completed, Billeter and Miescher, *Helv. Chim. Acta*, **31**, 1302 (1948), reported that the acid chloride of the 7-methoxy derivative of the acid did not react with sodium azide.