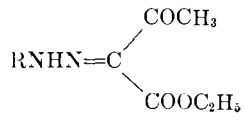
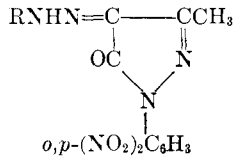
TABLE I

ETHYL 2,3-DIOXOBUTYRATE 2-ARYLHYDRAZONES AND 1-(2,4-DINITROPHENYL)-3-METHYL-4-ARYLAZO-2-PYRAZOLIN-5-ONES





No.	R	Mp, °C	Color and form	Formula[b]	Mp, °C	Color and form	Formula[b]
1	Phenyl	75–76[a]	Pale yellow crystals	$C_{12}H_{14}N_2O_3$	216–217	Violet-red needles[c]	$C_{16}H_{12}N_6O_5$
2	2-Nitrophenyl	94–95[a]	Yellow needles	$C_{12}H_{13}N_3O_5$	235–236	Red crystals	$C_{16}H_{11}N_7O_7$
3	3-Nitrophenyl	115–117[a]	Yellow needles	$C_{12}H_{13}N_3O_5$	252–253	Orange	$C_{16}H_{11}N_7O_7$
4	4-Nitrophenyl	125[a]	Yellow needles	$C_{12}H_{13}N_3O_5$	260–261	Orange-red needles	$C_{16}H_{11}N_7O_7$
5	3-Chlorophenyl	71[a]	Lt yellow needles	$C_{12}H_{13}N_3O_5$	221	Orange-red needles	$C_{16}H_{11}ClN_6O_5$
6	4-Chlorophenyl	82[a]	Canary yellow needles	$C_{12}H_{13}ClN_2O_3$	242	Orange-red needles	$C_{16}H_{11}ClN_6O_5$
7	2-Methylphenyl	45–46[a]	Pale yellow needles	$C_{13}H_{16}N_2O_3$	215	Violet-red needles	$C_{17}H_{14}N_6O_5$
8	3-Methylphenyl	72[a]	Yellow needles	$C_{13}H_{16}N_2O_3$	228–229	Orange	$C_{17}H_{14}N_6O_5$
9	4-Methylphenyl	75[a]	Orange crystals	$C_{13}H_{16}N_2O_3$	238–239	Brown-red needles	$C_{17}H_{14}N_6O_5$
10	2-Methoxyphenyl	99–100[a]	Red crystals	$C_{13}H_{16}N_2O_4$	210–211	Red needles	$C_{17}H_{14}N_6O_6$
11	3-Methoxyphenyl	69–78	Dull red crystals	$C_{13}H_{16}N_2O_4$	212–213	Orange-red crystals	$C_{17}H_{14}N_6O_6$
12	4-Methoxyphenyl	68[a]	Yellow crystals	$C_{13}H_{16}N_2O_4$	218	Brown-red needles	$C_{17}H_{14}N_6O_6$
13	2-Ethoxyphenyl	104	Pale yellow needles	$C_{14}H_{18}N_2O_4$	209–210	Orange-red needles	$C_{18}H_{16}N_6O_6$
14	4-Ethoxyphenyl	88–89	Pale yellow needles	$C_{14}H_{18}N_2O_4$	219–220	Violet-red needles	$C_{18}H_{16}N_6O_6$
15	2,5-Dichlorophenyl	101[a]	Lt yellow needles	$C_{12}H_{12}Cl_2N_2O_3$	233	Orange needles	$C_{16}H_{10}Cl_2N_6O_5$
16	2,5-Dimethylphenyl	76–77	Yellow needles	$C_{14}H_{18}N_2O_3$	214	Red needles	$C_{18}H_{16}N_6O_5$
17	2,5-Dimethoxyphenyl	118–119	Brick red crystals	$C_{14}H_{18}N_2O_5$	231	Red needles	$C_{18}H_{16}N_6O_7$
18	2,6-Dichlorophenyl	74	Yellow needles	$C_{12}H_{12}Cl_2N_2O_3$	186–187	Red-orange	$C_{16}H_{10}Cl_2N_6O_5$
19	2,4-Dimethylphenyl	120–121	Pale yellow needles	$C_{14}H_{18}N_2O_3$	218–219	Red needles	$C_{18}H_{16}N_6O_5$
20	2-Chloro-4-nitrophenyl	111[a]	Yellow needles	$C_{12}H_{12}ClN_3O_5$	226–229	Orange needles	$C_{16}H_{10}ClN_7O_7$
21	4-Sulfanilamidophenyl	133–134	Yellow-orange needles	$C_{12}H_{15}N_3O_5S$	291–292	Orange	$C_{16}H_{13}N_7O_5S$

[a] Reference 4 and other references cited therein. [b] All the new compounds were analysed for N, and the analytical values were within ±0.4% of the calculated values. [c] C. Bülow and A. Hecking, *Ber.*, **44**, 467 (1911).

Lysergic Acid Diethylamide (LSD) and Tryptamine Analogs as Potential Psychotomimetics

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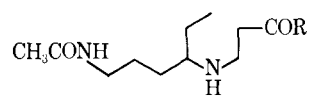
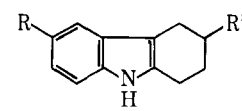
We have been preparing analogs of hallucinogens and now report the synthesis of two series of analogs, one patterned after lysergic acid diethylamide (LSD) (I), and the other (II) after the tryptamine moiety found in many naturally occurring and synthetic hallucinogens.



I, LSD analogs
R = OEt, NEt_2



II, tryptamine analogs
R = H, OMe; R' = Cl, OH

Structures of compounds were confirmed by uv, ir, or nmr spectra.

Compounds in Table I, series I, were prepared by adding the appropriate amine to either ethyl acrylate or N,N-diethylacrylamide.[1,2] The typtamine analogs (II) were prepared by the Borsche reaction,[3] except for 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrocarbazole which was prepared from the corresponding 3-chloro compound, by prolonged pH 8–9 hydrolysis.

4-Amino-N-acetylhexylamine.—W-2 Raney nickel reduction of 4-nitro-N-acetylhexylamine gave the desired compound in 79% yield as a colorless oil, bp 131–133° (0.5 mm), $n^{24}D$ 1.4742. *Anal.* ($C_8H_{18}N_2O$) C, H, N.

TABLE I

Series I	Bp, °C (mm)	n_D (*t*, °C)	Reaction time, days	Yield, %	Formula	Analyses
R = NEt_2[a]	153 (0.5)	1.4765 (26)	4[b]	55	$C_{15}H_{31}N_3O_2$	C, H, N
R = OEt[c]	190–192 (1.2)	1.4708 (23)	3[d]	53	$C_{13}H_{26}N_2O_3$	C, H, N

Series II	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
R = OMe, R' = Cl[e]	157–160	Acetic acid	59	$C_{13}H_{14}ClNO$	C, H, Cl, N
R = OMe, R' = OH	101–102	Water	30	$C_{13}H_{15}NO_2$	C, H, N
R = H, R' = Cl[f]	116–118	Acetic acid	56[g]	$C_{12}H_{12}ClN$	C, H, N

[a] From 4-amino-N-acetylhexylamine and N,N-diethylacrylamide. [b] At room temperature. [c] From 4-amino-N-acetylhexylamine and ethyl acrylate. [d] At room temperature under N_2. [e] From 4-chlorocyclohexanone and 4-methoxyphenylhydrazine. [f] From phenylhydrazine and 4-chlorocyclohexanone, prepared according to R. Grewe, W. Lorenzen, L. Viving, *Chem. Ber.*, **87**, 797 (1954). The boiling point of the compound, the melting point of its semicarbazone, and the ir spectrum were confirmatory. [g] Semi-crude yield.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.25% of the theoretical values. Melting points were determined in capillary tubes in a melting point bath and, as with boiling points, are uncorrected. Microanalyses were performed by Galbraith Laboratories.

4-Nitro-N-acetylhexylamine.—Catalytic reduction of 4-nitro-

(1) P. E. Norris and F. F. Blicke, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 637 (1952).

(2) G. H. Stempel, Jr., R. P. Gross, and R. P. Mariella, *J. Am. Chem. Soc.*, **72**, 2299 (1950).

(3) C. U. Robers and B. B. Corson, *ibid.*, **69**, 2910 (1947).

hexanenitrile[4] with Adam's catalyst in the presence of acetic anhydride gave the desired compound in 58% yield as a red, viscous liquid, bp 173° (0.5 mm), n^{24}D 1.4679. *Anal.* ($C_8H_{16}N_2O_3$) C, H, N. Nef hydrolysis of this 4-nitro compound gave the previously unreported 4-ketohexanenitrile, bp 75–80° (0.5 mm), n^{20}D 1.4338. *Anal.* (C_6H_9NO) C, H, N.

(4) G. D. Buckley, T. J. Elliott, F. G. Hone, and A. Lowe, *J. Org. Chem.*, **8**, 10 (1943).

Cysteine Derivatives of Keto Steroids

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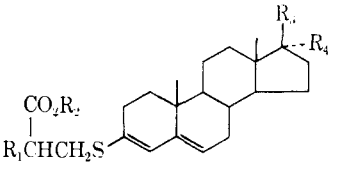
The condensation of L-cysteine derivatives with Δ^4-3-keto steroids in the presence of pyridinium chloride[1] has been found to give the corresponding diene thioethers.[2] When compared with testosterone in mice, **3** was devoid of androgenic, myotropic, and antiestrogenic activity.[3]



1, R_1 = $C_6H_5CH_2CONH$; R_2 = CH_3; R_3 = C_8H_{17}; R_4 = H
2, R_1 = $Cl^-H_3N^+$; R_2 = C_2H_5; R_3 = OH; R_4 = H
3, R_1 = $Cl^-H_3N^+$; R_2 = C_2H_5; R_3 = OH; R_4 = CH_3

Experimental Section[4]

Methyl S-(3,5-Cholestadien-3-yl)-N-phenylacetyl-L-cysteinate (1).—A solution of 500 mg (1.3 mmoles) of cholestenone in 25 ml of C_6H_6 was distilled until 5 ml had collected. A solution composed of 880 mg (5.2 mmoles) of methyl N-phenylacetyl-L-cysteinate,[5] 48 mg of pyridinium chloride, 6 ml of EtOH, and 4 ml of C_6H_6 was added. The solution was refluxed 3 hr, cooled, diluted with 30 ml of ether, and washed with two 25-ml portions of 1 *N* NaOH. After one H_2O wash the ethereal solution was dried (Na_2SO_4) and evaporated leaving 740 mg of semisolid. Precipitation from acetone–petroleum ether (bp 30–60°) gave 264 mg of **1**, mp 119–125°. Further work-up of the mother liquor gave another 100 mg of **1**, mp 100–119°, and 167 mg of recovered cholestenone. The analytical sample (*i*-Pr_2O) had mp 158–159°. *Anal.* ($C_{39}H_{57}NO_3S$) H, N, S.

Ethyl S-(17β-Hydroxy-3,5-androstadien-3-yl)-L-cysteinate Hydrochloride (2).—A similar condensation between testosterone and ethyl L-cysteinate hydrochloride gave **2** as an amorphous solid (acetone), mp 176–179°. *Anal.* ($C_{21}H_{35}ClNO_3S$) C, H, Cl, N, S.

Ethyl S-(17β-Hydroxy-17α-methyl-3,5-androstadien-3-yl)-L-cysteinate Hydrochloride (3).—Similarly, 17α-methyltestosterone and ethyl L-cysteinate hydrochloride gave **3**, needles (Me_2CO–C_6H_6), mp 171–172°. *Anal.* ($C_{25}H_{40}ClNO_3S$) C, H, Cl, N, S.

Acknowledgment.—This work was supported in part by U. S. Public Health Service Research Grant AM-04531.

(1) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951).

(2) Δ^4-3-Keto steroids are reported *not* to react with cysteine or ethyl cysteinate: S. Lieberman, *Experientia*, **2**, 411 (1945).

(3) We are indebted to Dr. R. Kraay, Eli Lilly and Co., for these assays.

(4) Ir spectra were obtained on an Infracord, uv spectra on a Beckman DU. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(5) Z. Foldi, *Acta Chim. Acad. Sci. Hung.*, **5**, 187 (1954); *Chem. Abstr.*, **50**, 9811 (1956).

17β-(4′-{*p*-[Bis(β-chloroethyl)amino]phenyl}-butanoyloxy)-4-androsten-3-one

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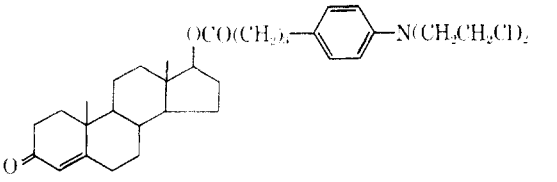
Received March 25, 1968

The synthesis and antitumor evaluation of steroidal nitrogen mustards[1] prompted us to synthesize the chlorambucil ester of testosterone by treating chlorambucil chloride with the potassium salt of testosterone in refluxing benzene.



Experimental Section[2]

17β-(4′-{*p*-[Bis(β-chloroethyl)amino]phenyl}butanoyloxy)-4-androsten-3-one.[3]—Testosterone, 0.34 g (1.1 mmoles), was dissolved in dry C_6H_6, excess K was added, and the mixture was then refluxed overnight. After filtration of the unreacted K, the C_6H_6 solution of the potassium salt was added to residual chlorambucil chloride, which was prepared from 0.35 g (1.1 mmoles) of chlorambucil and 2 ml of $POCl_3$ in refluxing C_6H_6 with subsequent solvent removal. The esterification reaction mixture was refluxed 5 hr, then left at room temperature overnight. The solvent was evaporated to give 512 mg of crude product, which was chromatographed on 10 g of Al_2O_3. C_6H_6 eluted 60 mg of acid chloride, 43 mg of the ester (analytical sample), and 34 mg of impure ester, while C_6H_6–Et_2O (4:1) eluted 154 mg of additional ester. Rechromatography of the last two fractions (188 mg) plus 82 mg of similar product from another preparation on 8 g of Al_2O_3 gave 211 mg of ester eluted by C_6H_6–Et_2O (4:1). *Anal.* ($C_{33}H_{44}Cl_2NO_3$) C, H, N.

(1) (a) G. V. Rao and C. C. Price, *J. Org. Chem.*, **27**, 205 (1962); (b) S. H. Burstein and H. J. Ringold, *ibid.*, **26**, 3084 (1961); (c) W. J. Gensler and G. M. Sherman, *ibid.*, **23**, 1227 (1958); (d) A. M. Khaletskii, M. V. Vasil'eva, and E. M. Balonova, *Sintetich. Produkty iz Kumfoli i Skipidara, Akad. Nauk Belorussk. SSR, Tsentr. Nauchn.-Issled. i Proektn. Inst. Lesokhim. Prom., Tr. Vses. Nauchn.-Tekhn. Soveshch., Gorki, 1963*, 227 (1964); *Chem. Abstr.*, **62**, 9194 (1965); (e) G. R. Yavasour, H. L. Bulker, and A. F. McKay, *Can. J. Chem.*, **30**, 933 (1952); (f) R. E. Havranek and N. J. Doorenbos, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 328 (1960); (g) T. Nogrady, K. M. Vagi, and V. W. Adamkiewicz, *Can. J. Chem.*, **40**, 2126 (1962); (h) L. N. Voloveliskii and A. B. Simkina, *Zh. Obshch. Khim.*, **37**, 1571 (1967); (i) Niedescu-Duvaz, A. Combanis, and E. Turumbeanu, *J. Med. Chem.*, **10**, 172 (1967); (j) C. R. Waik, T. C. Chou, and H. H. Lin, *ibid.*, **10**, 255 (1967).

(2) Ir spectra were obtained on an Infracord, uv spectra on a Beckman DU. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

(3) This compound was submitted to the Cancer Chemotherapy National Service Center, Public Health Service, for an evaluation of its antitumor activity against acute lymphocytic leukemia.

2,2′-Hydrazobis(5-nitropyrimidines)

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2-Amino-5-nitropyrimidine and its derivatives possess pronounced trichomonacidal activity.[1] We have shown that symmetrical 2,2′-hydrazobis(5-nitrothiazoles) also show a very strong antiprotozoal activity.[2] The combination of these two features

(1) R. M. Michaels and R. E. Strobe, *J. Pharm. Pharmacol.*, **13**, 601 (1961); R. M. Michaels, *J. Protozool.*, **9**, 478 (1962).

(2) M. Avramoff, S. Adler, and A. Founer, *J. Med. Chem.*, **10**, 1138 (1967).