3.55 g. (0.0116 mole) of the 4-methyl derivative in 15 ml. of N,N-dimethylformamide was treated with a methanolic solution of sodium methoxide (0.014 mole of $NaOCH_3$)[10] and then with 1.05 ml. (0.0168 mole) of methyl iodide as described under C. The mixture was worked up as described under C and yielded 2.7 g. (73%), of a compound identical in every respect with that obtained under F.

Acknowledgments.—We are indebted to Dr. Al Steyermark and his staff for microanalytical data, to Dr. A. Motchane and Mr. S. Traiman for infrared determinations, and to Miss Barbara Petlack for the compilation of data in the tables.

Derivatives of 2-(2-Pyrimidinyl)acetophenone[1]

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Cyclic amidines and guanidines are well known classes of diuretic agents.[3] This paper reports the synthesis of some derivatives of 2-(2-pyrimidinyl)acetophenone (I),[4-6] a cyclic amidine, as potential diuretic agents. When the ketone I was reacted with an equimolar amount of phenylmagnesium bromide the phenylcarbinol was obtained in 31% yield, with recovery of 67% of I; phenyllithium gave similar results. If one assumes that part of the Grignard reagent complexes with the pyrimidine ring nitrogens, then excess reagent should increase the yield of carbinol. This was found to be true, as the yield increased to 61% and 81% for 2:1 and 3:1 *M* ratios, respectively, of Grignard reagent to ketone.

Catalytic hydrogenation of the methochloride of I produced a tetrahydro carbinol. The structure assignment was based on the formation of benzaldehyde (retroaldol) on treatment with dilute sodium hydroxide solution. Stopping the hydrogenation after 2 moles of hydrogen were added yielded a compound which did not yield benzaldehyde when reacted with base; therefore, the tetrahydro ketone structure was assigned to the product.

Experimental[7]

α,α-Diphenyl-2-pyrimidineethanol. A.—To 14.9 g. (0.082 mole) of phenylmagnesium bromide in 85 ml. of ether was added over 3 min., 5.4 g. (0.0273 mole) of the ketone I[5] in 225 ml. of benzene and 60 ml. of ether. The solution was heated at reflux for 30 min., cooled, acidified with 50 ml. of 10% sulfuric acid, and the solid filtered to give 7.9 g. (81%), m.p. 221–224° dec., of the **hydrobromide** salt, after two recrystallizations from nitromethane, m.p. 231° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O \cdot HBr$: C, 60.51; H, 4.80; N, 7.84. Found: C, 60.11; H, 4.86; N, 7.80.

The free **base** melted at 141–143°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: N, 10.14. Found: N, 10.07.

B.—To 1.71 g. (0.0204 mole) of phenyllithium in 50 ml. of ether was added over 10 min. 3.6 g. (0.0182 mole) of I in 150 ml. of benzene and 50 ml. of ether. The solution was diluted with 50 ml. of ether, stirred for 30 min., adjusted to pH 5 with 5% sulfuric acid, and the solid filtered. The yield of hydrobromide salt was 1.6 g. (25%), m.p 231–233° dec. From the aqueous and organic layers 56% of I was recovered.

2-(2-Hydroxy-2,2-diphenylethyl)-1-methylpyrimidinium Iodide.—A mixture of 2.0 g. (0.0073 mole) of α,α-diphenyl-2-pyrimidineethanol and 10 ml. of methyl iodide was allowed to stand in a closed flask for 1 week. Removal of excess methyl iodide by evaporation yielded 3.0 g. (99%), m.p. 235–240° dec., of yellow methiodide. One recrystallization from 30 ml. of water yielded 2.22 g. (73.3%), m.p. 239–240° dec.

Anal. Calcd. for $C_{19}H_{19}IN_2O$: I, 30.34. Found: I, 29.92.

1-Methyl-2-phenacylpyrimidinium Iodide.—A mixture of 5.1 g. (0.0257 mole) of the ketone I and 25 ml. of methyl iodide was heated in a sealed tube in a water bath at 60–80° for 5 hr. The yield of yellow solid after filtration was 8.0 g. (91.5%), m.p. 189–191°. After 2 recrystallizations from a mixture of ethyl acetate and ethanol the methiodide melted at 190.5–191°.

Anal. Calcd. for $C_{13}H_{13}IN_2O$: N, 8.24. Found: N, 8.24.

The methochloride was prepared by treating a suspension of silver chloride in water with an aqueous solution of the methiodide.

2-(1,4,5,6-Tetrahydro-1-methyl-2-pyrimidinyl)acetophenone Hydrochloride.—A solution of 1.5 g. (0.0064 mole) of the methochloride of I in 25 ml. of absolute ethanol was reduced over 70 mg. of platinum oxide catalyst in a low pressure hydrogenation apparatus. The hydrogenation was stopped after 2 *M* equiv. of hydrogen was added (10 min.). The catalyst was filtered and the filtrate evaporated *in vacuo* to give 1.44 g. (95%) of solid, m.p. 250–253°. This was recrystallized from 2-propanol and then butanol to give white crystals, m.p. 252–253°.

Anal. Calcd. for $C_{13}H_{16}N_2O \cdot HCl$: C, 61.77; H, 6.78; Cl, 14.03. Found: C, 60.90; H, 6.77; Cl, 13.83.

1,4,5,6-Tetrahydro-1-methyl-α-phenyl-2-pyrimidineethanol Hydrochloride.—A solution of 1.5 g. (0.00604 mole) of I-methochloride in 25 ml. of absolute ethanol was reduced over 70 mg. of platinum oxide catalyst in a low pressure hydrogenation apparatus. The reduction was stopped after 3.5 *M* equiv. of hydrogen was added (160 min.) and the catalyst filtered. The filtrate was evaporated in vacuo, and the residual gum (1.4 g.) when added to 2-propanol crystallized to give 0.5 g. (32.5%), m.p. 223–224°, of white solid. This was recrystallized to constant melting point (223–224°) from 2-propanol.

Anal. Calcd. for $C_{13}H_{18}N_2O \cdot HCl$: C, 61.29; H, 7.52; Cl, 13.92. Found: C, 61.44; H, 7.36; Cl, 13.84.

When the hydrochloride salt was treated with 10% sodium hydroxide solution an odor of benzaldehyde was produced, and when this solution was acidified and reacted with 2,4-dinitrophenylhydrazine, a hydrazone was obtained, m.p. 238–239° (no depression with benzaldehyde 2,4-dinitrophenylhydrazone, lit.[8] m.p. 237°).

(1) Taken in part from the thesis of F. F. Ebetino submitted in partial fulfillment of the requirements for the Master of Science degree at Lehigh University, 1953.

(2) William S. Merrell Co. Fellow, 1951–1953. Author to whom inquiries should be addressed, Norwich Pharmacal Co., Norwich, N. Y.

(3) (a) W. L. Lipschitz and Z. Hadidian, *J. Pharmacol. Exptl. Therap.*, **81**, 84 (1944); (b) W. L. Lipschitz and E. Stokey, *ibid.*, **83**, 235 (1944); (c) W. L. Lipschitz and E. Stokey, *ibid.*, **92**, 131 (1948).

(4) J. M. Smith, Jr., and B. Roth, U. S. Patent 2,487,391 (1949).

(5) B. Roth and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **71**, 616 (1949).

(6) A. Dornow and E. Nense, *Ber.*, **84**, 296 (1951).

(7) Melting points are corrected.

(8) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 229.

Synthesis of Some Derivatives of 5-Aminoindole-3-acrylic Acid[1a]

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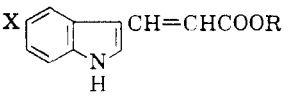
Recently we have reported on the preparation of the 5-nitrogen mustards of tryptophan[1b] and other indole-3-alkanoic acids.[1c] As a continuation of this series we have undertaken the preparation of the corresponding mustard (I) of indole-3-acrylic acid. A

(1)(a) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, under Contract No. SA-43-ph-1892. The opinions expressed in this article are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. The authors are indebted to Mr. O. P. Crews and his staff for the large scale preparation of intermediates. They are also indebted to Dr. Peter Lim and his staff for spectral measurements and interpretations. (b) J. DeGraw and L. Goodman, *J. Org. Chem.*, **27**, 1395 (1962). (c) J. DeGraw and L. Goodman, *ibid.*, **27**, 1728 (1962).

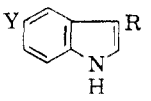
TABLE I



Compound	X	R	M.p., °C.	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
I	$N(CH_2CH_2Cl)_2$	H								
II[a]	NH_2	Et	98–99	$C_{12}H_{14}N_2O_2$	67.8	6.13	12.2	67.3	6.18	12.1
III[b]	NO_2	H	202–204	$C_{11}H_8N_2O_4$	55.8	3.62	11.8	55.4	3.60	11.9
IV	NO_2	Me	192–195	$C_{12}H_{10}N_2O_4$	58.5	4.09	11.4	58.2	4.18	11.3
V[c]	$C_6H_5CH_2OCONH$	H	240.5–241.5	$C_{19}H_{16}N_2O_4$	67.9	4.80	8.33	68.2	5.24	8.20
VI[d]	$C_6H_5CH_2OCONH$	Et	189.5–191.5	$C_{21}H_{20}N_2O_4$	69.2	5.53	7.69	69.0	5.66	7.77

[a] Prepared by hydrogenation of 500 mg. of VI with 50 mg. of 5% palladium-on-carbon in absolute ethanol at 1 atm. for 4.25 hr. and recrystallization of the product from benzene; λ_{max}^{EtOH} 232 mμ (ε 21,900), 282 (10,700), 339 (13,000), in sharp contrast to methyl 5-aminoindole-3-propionate (see ref. 1a), which had λ_{max}^{EtOH} 280 mμ (ε 5400), 310 (3400). [b] Prepared by Doebner (see K. N. Shaw, A. McMillan, A. G. Gundmunson, and M. D. Armstrong, *J. Org. Chem.*, **23,** 1171 (1958); "Organic Reactions," Vol. I, Roger Adams, Ed., John Wiley and Son, New York, N. Y., 1942, p. 210) condensation of 5 g. of VII with 5 g. of malonic acid in 60 ml. of pyridine containing 0.5 ml. of piperidine at 90–100° for 15 hr. and recrystallization of the product from ethyl acetate; λ_{max}^{EtOH} 276 mμ (ε 19,200); analysis calculated for 0.25 H_2O of solvation. [c] Condensation at 45–55° for 27 hr. using the quantities of reagents described for preparation of III. The product was recrystallized from 90% aqueous acetone. [d] Prepared by mixed anhydride procedure using isobutyl chloroformate. The product was recrystallized from ethyl acetate (see B. R. Erlanger, W. V. Curran, and N. Kobowsky, *J. Am. Chem. Soc.*, **81,** 3051 (1959)).

TABLE II



Compound	Y	R	M.p., °C.	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
VII[a]	NO_2	CHO	280–300 dec.	$C_9H_6N_2O_3$	56.8	3.18	14.7	56.7	3.41	15.1
VIII	$C_6H_5CH_2OCONH$	H	114–115	$C_{16}H_{14}N_2O_2$	72.2	5.30	10.5	72.4	5.29	10.3
IX[b]	$C_6H_5CH_2OCONH$	CHO	237.5–239.0	$C_{17}H_{14}N_2O_3$	69.4	4.80	9.52	69.2	5.10	9.67
X[c]	CH_3CONH	H	117–118	$C_{10}H_{10}N_2O$	69.0	5.79	16.1	69.3	5.96	16.2
XI[d]	CH_3CONH	CHO	231–234	$C_{11}H_{10}N_2O_2$	65.3	4.98	13.9	65.3	4.99	13.8

[a] Prepared by reaction of 5-nitroindole and N,N-dimethylformamide (DMF) in the presence of phosphoryl chloride (see G. F. Smith, *J. Chem. Soc.*, 3842 (1954)); previously prepared in low yield by the nitration of 3-formylindole (see G. Berti and A. DaSettimo, *Gazz. chim. ital.*, **91,** 728 (1961); W. E. Noland and R. D. Rieke, *J. Org. Chem.*, **27,** 2250 (1962)). [b] Prepared by reaction of VIII and DMF with phosphoryl chloride; an intermediate indolenine–enamine hydrochloride was the direct product on work-up and this had to be heated with 5% aqueous potassium carbonate to hydrolyze it to the aldehyde (IX) which was recrystallized from acetonitrile. [c] Prepared by reaction of 5-aminoindole and acetic anhydride in pyridine. [d] Prepared by reaction of X and DMF with phosphoryl chloride; the product was crystallized from ethanol; λ_{max}^{EtOH} 246 mμ (ε 23,600), 304 (11,500).

necessary intermediate, ethyl 5-aminoindole-3-acrylate (II) was prepared; however, the low yields encountered rendered impractical the preparation of I in quantities sufficient for biological evaluation.

Two approaches for the synthesis of II were investigated. The first, *via* 5-nitroindole-3-acrylic acid (III) failed when it was not found possible to reduce the nitro group of III or its methyl ester (IV) by various chemical or catalytic methods. The second, a successful approach, used 5-aminoindole as the starting material and utilized the selective hydrogenolysis of the carbobenzyloxy protecting group in the presence of the acrylate double bond. The properties of the new compounds isolated in the research are outlined in Tables I and II.

Synthesis of Nortriptyline and Related Compounds

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The recent publication[1] of methods for the synthesis of N-substituted 5-(3-aminopropylidene)-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptenes, of which a number are useful psychotherapeutic drugs, prompts us to report a new synthesis of one of these, nortriptyline (IX), using propargylic intermediates. The methods described have been used for the preparation of large quantities of nortriptyline hydrochloride as well as smaller amounts of various analogs and homologs.

(1) (a) S. O. Winthrop, M. A. Davis, G. S. Meyers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27,** 230 (1962); (b) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *ibid.*, **27,** 4134 (1962); (c) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *ibid.*, **28,** 1751 (1963).

Experimental

5-Hydroxy-5-(3-hydroxypropynyl)-10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene (I).—To a stirred suspension of 156 g. (4 moles) of sodamide in 3 l. of liquid ammonia there was added over a period of 90 min. a solution of 166 g. (0.8 mole) of 10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene-5-one,[1a] 112 g. (2 moles) of propargyl alcohol, and 800 ml. of dry toluene. A low temperature condenser (solid CO_2) was employed during the addition and for 30 min. thereafter. The ammonia was then allowed to evaporate. When room temperature was reached, 1 l. of toluene and 1 kg. of ice were added. The resulting suspension was filtered and the cake was washed with water and with ether until the aqueous filtrates were neutral. The crude product was then dried and dissolved in alcohol (*ca.* 25 ml./g.) containing about 0.25% acetic acid. The hot solution was decolorized, filtered, cooled, and then concentrated *in vacuo*. Crystallization gave 175 g. (83% yield), m.p. 187–195°. A sample was recrystallized from alcohol and acetone; m.p. 191–195°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.45; H, 6.14.

The dibenzoate prepared from benzoyl chloride in pyridine[2] and crystallized from carbon tetrachloride and benzene–hexane melted at 128–129°.

Anal. Calcd. for $C_{32}H_{24}O_4$: C, 81.34; H, 5.12. Found: C, 81.19; H, 5.32.

5-Hydroxy-5-(3-hydroxypropyl)-10,11-dihydro-5H-dibenzo[*a,d*]-cycloheptene (II).—A 7.04 g. sample of I (described above) dissolved in 70 ml. of absolute ethanol containing 0.22 g. of 5% palladium-on-alumina was shaken with hydrogen at 3.5 kg./cm.[2]

(2) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1948, p. 164.