oxy-4,3′,5′-trimethyl-5-carboxypyrromethane, 10 ml. of acetic anhydride and 0.1–0.3 g. of anhydrous sodium acetate were refluxed together for 1 hr. and the mixture then cooled on the ice-bath. The precipitate was filtered off, washed well with ether, triturated with ether, refiltered and dried at 75°; 770 mg. (80%) of orange, fibrous crystals was obtained, m.p. 262–265°. A sample was recrystallized five times from dioxane–water, m.p. 266.5–268°.

Anal. Calcd. for $C_{38}H_{40}N_4O_{10}\cdot 2H_2O$: C_2H_5O, 24.07. Found: C_2H_5O, 24.13.

(b) **Monohydrate.**—Two hundred fifty mg. of 1,6-dimethyl-2,7-dicarbethoxy-3,8-dibromomethylpyrocoll was mixed with 1.00 g. of 2,4-dimethyl-3-carbethoxypyrrole[17] in a 13 by 100 mm. test-tube. The mixture was heated on the oil-bath at 106° for 3–3.5 min. while agitating with the spatula. The mixture liquefied and then resolidified rapidly. When cool, the red-orange, gummy material was triturated with ether and filtered. It was again triturated with ether, filtered and dried at 70°; 525 mg. of bright orange solid was obtained. The solid was warmed with 25 ml. of chloroform until it dissolved, 75 ml. of isoöctane was added to the hot solution and the mixture was cooled. The orange precipitate was filtered off and dried at 70° (methane pyrocoll VIII was obtained from this filtrate); 266 mg. (79%) of the methene pyrocoll was obtained, m.p. 245–248°. A sample was recrystallized from dioxane–water four times, m.p. 266–267°.

Anal. Calcd. for $C_{38}H_{40}N_4O_{10}\cdot H_2O$: C_2H_5O, 24.66. Found: C_2H_5O, 24.76.

(c) **Anhydrous.**—The reaction was run as in (b) above, using the same quantities, except that the reactants were dried under vacuum at 50° for 2 hr., and the reaction was run in an atmosphere of dry hydrogen. After heating at 106° and allowing to cool, 3 ml. of ethanol was added. The product was triturated with ethanol, washed into a flask and refluxed with 80 ml. of ethanol for 30 min. The undissolved material was removed; 237 mg. (72%) was obtained, m.p. 256–258°. A sample was recrystallized four times from dioxane–ethanol and then dried 2.5 hours at 70°, m.p. 266.5–268°.

Anal. Calcd. for $C_{38}H_{40}N_4O_{10}$: C_2H_5O, 25.29. Found: C_2H_5O, 25.68.

1,6-Dimethyl-2,7-dicarbethoxy-3,8-bis-(3,5-dimethyl-4-carbethoxy-2-pyrrylmethyl)-5,5,10,10-tetrahydroxydipyrrolo[a,d]pyrazine (VII).—The filtrate from the preparation of methene pyrocoll VII·H_2O (b, above) was evaporated to a volume of 25 ml. in the air stream. A yellow scum had collected on the sides of the flask, and this was discarded. Needles collected on the bottom of the flask. The needles were removed and dried in the air overnight; 84 mg. (21%) was obtained, m.p. 124–125°, becoming orange. The crystals decomposed slowly over a period of months. A sample was recrystallized from chloroform–isoöctane, m.p. 126.5–128°.

Anal. Calcd. for $C_{38}H_{48}N_4O_{12}\cdot 5H_2O$: C_2H_5O: 21.38. Found: C_2H_5O, 21.33.

Ultraviolet absorption curves were taken of dioxane solutions in the Beckman DU spectrophotometer. Infrared absorption curves were taken of mineral oil mulls in the Perkin–Elmer 21 double-beam recording spectrophotometer without a compensating cell.

Acknowledgments.—Acknowledgment is made for a grant-in-aid from the Hynson, Westcott and Dunning Research Fund to B. H. Thanks are due Mr. Joseph A. Walter for some of the carbon and hydrogen analyses and Mrs. Ann L. Claggett for the bromine analyses.

Baltimore, Md.

(17) J. L. Rainey and H. Adkins, This Journal, **61**, 1107 (1939).

[Contribution from the Department of Chemistry of the University of Wisconsin]

Piperidine Derivatives. XXVIII. 1-Methyl-3-alkyl-4-phenyl-4-acyloxypiperidines

By S. M. McElvain and Martin D. Barnett[1]

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1-Methyl-3-carbethoxy-4-piperidone has been C-benzylated and C-allylated in the 3-position with benzyl- and allyldimethylanilinium halides. The resulting piperidones were converted to two series of 1-methyl-3-alkyl-4-phenyl-4-acyloxypiperidines (IX and X). These compounds with the 3-benzyl substituent are completely inactive as analgesics; however, the members of the corresponding 3-propyl series are all quite active. The 4-propionoxy derivative (Xb) of this latter series is significantly more active than the homologous 4-acetoxy (Xa) or 4-butyroxy (Xc) compounds.

Several 1-alkyl-4-phenyl-4-acyloxypiperidines have been prepared and found to possess significant analgesic action.[2] Those compounds with the 4-propionoxy substituent appear to be the most potent analgesics. Ziering and Lee[3] found that further modification of this structure by the introduction of a 3-methyl substituent into the piperidine nucleus greatly enhanced the pharmacological activity, *e.g.*, one of the stereoisomeric forms of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine showed analgesic action comparable to that of dihydrodesoxymorphine-D, which is 5–10 times as active as morphine.

The 1,3-dimethyl-4-piperidone required for the preparation of this analgesic was obtained by the Dieckmann cyclization of methyl-(β-carbomethoxyethyl)-(β-carbomethoxypropyl)-amine, which was prepared by the addition of methylamine to methyl methacrylate and the addition of the resulting secondary amino ester to methyl acrylate. While the 1,3-dimethyl-4-piperidone could be prepared satisfactorily by this procedure, it would appear to have some serious limitations as a general method for 1-methyl-3-alkyl-4-piperidones.

The C-alkylation of the enolate anion of a 3-carbalkoxy-4-piperidone and the decarbalkoxylation of the resulting keto ester seemed to offer another, and perhaps a more general, approach to the 3-alkyl-4-piperidones. This procedure has been utilized for the introduction of a 3-ethyl substituent into the 1-benzoyl-3-carbethoxy-4-piperidone[4a]; however, attempts to alkylate the 1-methyl-3-carbethoxy-4-piperidone anion (I) with an alkyl halide resulted in N- rather than C-alkylation.[4b]

In the work now reported it was found that the anion I can be C-alkylated to the 3,3-disubstituted

(1) Wisconsin Alumni Research Foundation Research Assistant, 1953–1955.

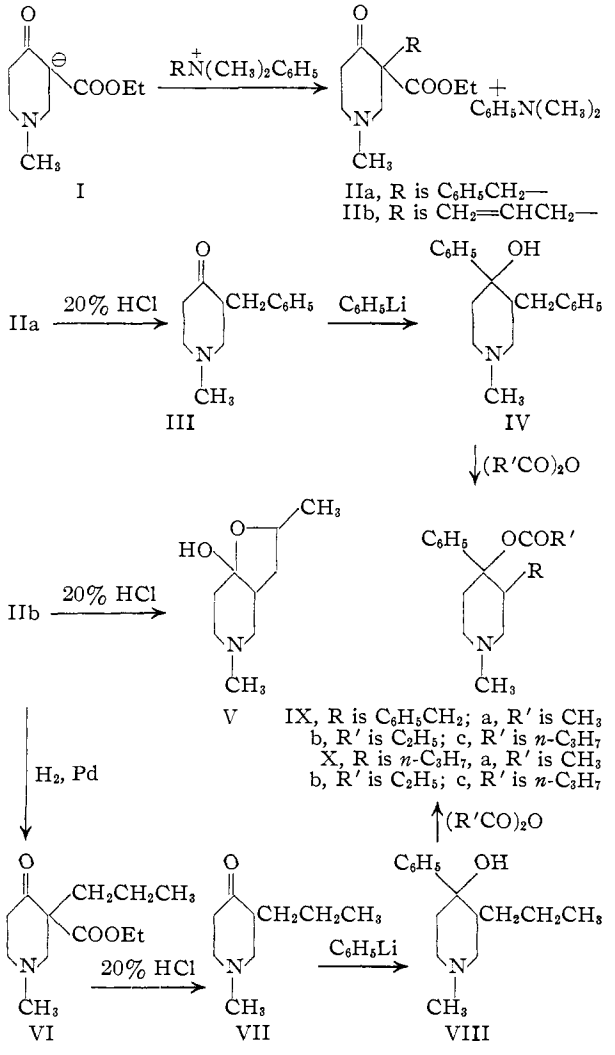
(2) (a) K. A. Jensen and F. Lundquist, *Dansk. Tids. Farm.*, **17**, 173 (1943); (b) A. Ziering, *et al.*, *J. Org. Chem.*, **12**, 894 (1947).

(3) A. Ziering and J. Lee, *ibid.*, **12**, 911 (1947).

(4) (a) G. Stork and S. M. McElvain, This Journal, **68**, 1053 (1946); (b) W. B. Thomas, Ph.D. Thesis, University of Wisconsin, 1932.

piperidones IIa and b with benzyl- and allyldimethylanilium halides in 72 and 48% yields, respectively. The 3-benzyl keto ester IIa was converted *via* III and IV to the 3-benzyl-4-phenyl-4-acyloxypiperidines IXa, b and c. After hydrogenation, the 3-allyl ketoester IIb was similarly converted into the corresponding 3-propyl-4-acyloxypiperidines Xa, b and c. The direct decarbethoxylation of IIb with 20% hydrochloric acid led to the cyclic hemiacetal V, which was characterized by analyses, C-methyl value and conversion to the methyl acetal; attempts to prepare the acetate of V gave only a dehydration product.

Pharmacological Report.—The hydrochlorides of the tetrasubstituted piperidines IX and X were tested for analgesic activity by Mr. E. B. Robbins of The Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind., to whom the authors are indebted for the following data. The 3-benzyl derivatives IXa, b and c were found to be completely inactive in rats. In contrast to this behavior the 3-propyl derivatives proved to be quite active analgesics. Xa showed marked activity at doses of 20 mg./kg., Xb produced profound analgesia at 8 mg./kg., and Xc produced similar analgesia at 32 mg./kg. The most active 4-propionoxy compound, Xb, produced a 4-aminoantipyrine type of analgesia at a dosage of 4 mg./kg., ataxia at 10 mg./kg., prostration at 20 mg./kg. and sometimes death at 40 mg./kg.



Experimental

1-Methyl-3-benzyl-3-carbethoxy-4-piperidone (IIa).—A solution of 1-methyl-3-carbethoxy-4-piperidone obtained by the cyclization of 150.0 g. of methyl-di-(β-carbethoxyethyl)-amine[5] was added to slurry of 14.04 g. (0.585 mole) of sodium hydride in 250 ml. of anhydrous thiophene-free benzene, after which the mixture was refluxed with stirring for one hour. To the cooled slurry was added 137.5 g. (0.555 mole) of benzyldimethylanilinium chloride[6] in one portion. A mildly exothermic reaction ensued, after which the reaction mixture was refluxed with stirring for seven hours. The yellow reaction mixture was poured into 250 ml. of water, the layers separated, and the benzene layer washed with three 100-ml. portions of water. After drying over potassium carbonate, distillation yielded 54.5 g. (75%) of dimethylaniline, b.p. 88–90° (25 mm.), and 110.0 g. (72%) of 1-methyl-3-benzyl-3-carbethoxy-4-piperidone as a light yellow liquid, b.p. 139–140° (0.3 mm.), $n^{25}D$ 1.5188.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.57; H, 7.86; N, 5.14.

The picrate recrystallized from ethanol melted at 150–151.5°. *Anal.* Calcd. for $C_{22}H_{24}N_4O_9$: C, 52.40; H, 4.79. Found: C, 52.41; H, 4.98.

The methiodide, recrystallized from ethanol, melted at 147–148.5°. *Anal.* Calcd. for $C_{17}H_{24}INO_3$: C, 48.93; H, 5.80. Found: C, 48.84; H, 6.11.

1-Methyl-3-benzyl-4-piperidone (III).—A mixture of 47.2 g. (0.096 mole) of 1-methyl-3-benzyl-3-carbethoxy-4-piperidone and 160 ml. of 20% hydrochloric acid was refluxed for 24 hours, after which it was evaporated to dryness under diminished pressure. The residue was dissolved in 50 ml. of water and the water solution made strongly basic with solid potassium hydroxide. After saturation with potassium carbonate the solution was extracted with several small portions of ether. The combined ether extracts were dried over potassium carbonate and distilled; 23.7 g. (68%) of 1-methyl-3-benzyl-4-piperidone was obtained as a light yellow oil, b.p. 111–113° (0.4 mm.), $n^{25}D$ 1.5320.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.59; H, 8.37.

The picrate, recrystallized from ethanol, melted at 169.5–171°.

Anal. Calcd. for $C_{19}H_{20}N_4O_8$: C, 52.77; H, 4.66. Found: C, 52.49; H, 4.84.

1-Methyl-3-benzyl-4-phenyl-4-piperidinol (IV).—To a stirred solution of phenyllithium prepared from 2.22 g. (0.33 mole) of lithium wire and 25.9 g. (0.16 mole) of bromobenzene, cooled in an ice bath, was added 29.5 g. (0.145 mole) of 1-methyl-3-benzyl-4-piperidone (III) in 50 ml. of anhydrous ether. After completion of the addition (1 hour) the solution was stirred and allowed to warm to room temperature for 2 hours. The reaction mixture was decomposed with 40 ml. of water, the layers separated, and the water layer saturated with potassium carbonate. After extraction with small portions of ether and drying over potassium carbonate, distillation gave 7.2 g. (24%) of recovered 1-methyl-3-benzyl-4-piperidone, b.p. 100–120° (0.20 mm.), and 26.0 g. (64% based on unrecovered piperidone) of 1-methyl-3-benzyl-4-phenyl-4-piperidinol, b.p. 150–200° (0.2–0.5 mm.). Scratching under hexane brought about crystallization. Recrystallization from this solvent yielded colorless needles, m.p. 127–128°.

Anal. Calcd. for $C_{19}H_{27}NO$: C, 81.10; H, 8.24. Found: C, 81.01; H, 7.94.

1-Methyl-3-benzyl-4-phenyl-4-piperidyl Esters (IX).—A mixture of 2.0 g. (0.007 mole) of 1-methyl-3-benzyl-4-phenyl-4-piperidinol, 20 ml. of the acid anhydride and 0.01 mole of the corresponding sodium salt were heated with protection from moisture on a water-bath for 3 hours. In the case of the acetate the reaction mixture was poured into 50 ml. of water and allowed to stand until the acetic anhydride layer disappeared (usually 1 hour). For the propionate and

(5) S. M. McElvain and K. Rorig, THIS JOURNAL, **70**, 1820 (1948).
(6) H. Emde, *Arch. Pharm.*, **249**, 108 (1911).

Table I

1-Methyl-3-alkyl-4-phenyl-4-piperidyl Esters

Ester	Formula	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Hydrochloride m.p., °C.	Chlorine, % Calcd.	Chlorine, % Found
IXa	$C_{21}H_{25}NO_2$	110–111	77.98	7.79	77.61	7.53	204–206	9.85	9.80
IXb	$C_{22}H_{27}NO_2$	78–79	78.30	8.07	77.71	7.94	211–213	9.48	9.39
IXc	$C_{23}H_{29}NO_2$	76–77	78.59	8.32	78.12	8.13	153–157	9.14	9.23
Xa	$C_{17}H_{25}NO_2$	45–46	74.14	9.15	74.15	9.24	220–222	11.37	11.49
Xb	$C_{18}H_{27}NO_2$	Oil	...	..	...	..	202–204[a]	10.88	10.55
Xb	$C_{19}H_{29}NO_2$	Oil	...	..	...	..	110–116	10.43	10.66

[a] *Anal.* Calcd. for $C_{18}H_{28}ClNO_2$: C, 66.34; H, 8.66. Found: C, 66.51; H, 8.82.

butyrate esters the reaction mixtures were poured into 50 ml. of water and the two-phase systems stirred magnetically at room temperature until solution was accomplished (usually 2 days). The water solutions were made basic and saturated with potassium carbonate and extracted with several small portions of ether. Drying of the extracts over potassium carbonate and removal of the solvent under diminished pressure left light yellow oils (90–95%) which crystallized upon scratching under hexane.

The hydrochlorides of these esters were obtained in quantitative yield by the careful addition of an ether solution saturated with dry hydrogen chloride to an ether solution of the ester. The salts were recrystallized from ethyl alcohol–ethyl acetate except the acetate IXa, which was recrystallized from ethyl acetate–ether. Each of these salts is quite hygroscopic.

The melting points and analyses of these esters and their salts are collected in Table I.

1-Methyl-3-allyl-3-carbethoxy-4-piperidone (IIb).—A solution of 1-methyl-3-carbethoxy-4-piperidone obtained by the cyclization of 150.0 g. (0.650 mole) of methyl-di-(β-carbethoxyethyl)-amine[5] was added to a slurry of 14.04 g. (0.585 mole) of sodium hydride in 250 ml. of anhydrous thiophene-free benzene, after which the mixture was refluxed with stirring for one hour. To the cooled slurry was added 134.4 g. (0.555 mole) of allyldimethylanilinium bromide[7] in one portion and the reaction mixture refluxed with stirring for 46 hours. The mixture was poured into 250 ml. of water, the benzene layer separated and washed with three 100-ml. portions of water. After drying over potassium carbonate, distillation yielded 59.6 g. (89%) of dimethylaniline, b.p. 85–90° (25 mm.), and 59.7 g. (48%) of 1-methyl-3-allyl-3-carbethoxy-4-piperidone as a light yellow liquid, b.p. 85–105° (0.25 mm.), $n^{25}D$ 1.4694. This base is quite unstable and rapidly turns dark on standing.

The hydrochloride of IIb, after recrystallization from ethanol and ether, melted at 176–177°. *Anal.* Calcd. for $C_{12}H_{20}ClNO$: C, 55.27; H, 7.34. Found: C, 55.35; H, 7.57.

The methiodide, recrystallized from ethanol, melted at 145–146°. *Anal.* Calcd. for $C_{13}H_{22}INO_3$: C, 42.51; H, 6.04. Found: C, 42.81; H, 6.04.

2,5-Dimethyltetrahydrofuro[3,2-c]piperidin-7a-ol (V).—A solution of 15.0 g. (0.067 mole) of 1-methyl-3-allyl-3-carbethoxy-4-piperidone (IIb) in 75 ml. of 20% hydrochloric acid was refluxed in an oil-bath for 36 hours. The dark brown mixture was evaporated to dryness under diminished pressure, the residue dissolved in 25 ml. of water, and the solution made strongly basic with solid potassium hydroxide. The basic solution was saturated with potassium carbonate, the amine extracted with several small portions of ether, and the extracts combined and dried over potassium carbonate. After removal of the solvent under diminished pressure, the residual brown semi-sold (11.5 g.) was sublimed (80°, 0.1 mm.). There was obtained 10.2 g. (89%) of V as a light yellow solid, m.p. 85–92°. One recrystallization from heptane and two sublimations gave analytically pure material, m.p. 95–96°; C-methyl value, 0.96.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.12; H, 10.01. Found: C, 62.97; H, 9.68.

The methiodide recrystallized from ethanol–ether, melted at 176–179° dec. *Anal.* Calcd. for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44. Found: C, 38.67; H, 6.36.

2,5-Dimethyl-7a-methoxytetrahydrofuro[3,2-c]-piperidine.—A solution of 5.54 g. (0.0323 mole) of V in 100 ml. of absolute methanol was treated with 5.00 ml. of 10 *N* hydrochloric acid (0.0518 mole) and the reaction mixture refluxed for 2 hours. After cooling, the mixture was treated with a methanolic solution of sodium methoxide prepared from 1.19 g. (0.0520 mole) of sodium metal dissolved in 25 ml. of absolute methanol. The precipitated sodium chloride was filtered off and the filtrate distilled at 0.5 mm. The following fractions were obtained: (1) 1.30 g., $n^{25}D$ 1.4595, b.p. 68–70°; (2) 0.70 g., $n^{25}D$ 1.4594, b.p. 68–68.5°; (3) 0.47 g., $n^{25}D$ 1.4597, b.p. 68–69°; (4) 1.04 g., $n^{25}D$ 1.4596, b.p. 68–70°; (5) 0.96 g., $n^{25}D$ 1.4597, b.p. 69–70°; (6) 0.48 g., $n^{25}D$ 1.4598, b.p. 69–70°. The total yield was 4.95 g. (83%). Fraction 5 was selected for analysis.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34. Found: C, 64.58; H, 10.19.

Hydrogenation of 1-Methyl-3-allyl-3-carbethoxy-4-piperidone. (a) Over Platinum Oxide.—A solution of 7.91 g. (0.035 mole) of 1-methyl-3-allyl-3-carbethoxy-4-piperidone in 42.00 ml. of 0.839 *N* hydrochloric acid was hydrogenated over platinum oxide (0.5 g.) for 3.5 hours. During this time slightly more than twice the theoretical amount of hydrogen was taken up at a regular rate. After removal of the catalyst by filtration, the solution was made basic with solid potassium hydroxide, saturated with potassium carbonate, and extracted with small portions of ether. After drying the extracts over potassium carbonate and removing the solvent there remained 7.21 g. of colorless semi-solid. Filtration of this material yielded 6.11 g. of 1-methyl-3-carbethoxy-3-propyl-4-piperidinol, m.p. 92–98°, and 1.10 g. of liquid. The solid was sublimed to constant melting point, 98–99.5°.

Anal. Calcd. for $C_{12}H_{23}NO_3$: C, 63.12; H, 9.72. Found: C, 62.51; H, 9.74.

(b) Over 10% Palladium-on-charcoal.—A solution of 21.2 g. (0.081 mole) of the hydrochloride salt of 1-methyl-3-allyl-3-carbethoxy-4-piperidone in 75 ml. of absolute methanol was hydrogenated over 0.5 g. of palladium-on-charcoal. One molar equivalent was taken up in 10 minutes. After removal of the catalyst by filtration, the solvent was removed under diminished pressure and the residual solid decarbethoxylated (24 hours) using 75 ml. of 20% hydrochloric acid. The water was removed under diminished pressure, the residue dissolved in 25 ml. of water, and the solution made strongly basic with solid potassium hydroxide. The amine was salted out with potassium carbonate and extracted with four 25-ml. portions of ether. After drying the extracts over potassium carbonate, distillation yielded 10.6 g. (86%) of 1-methyl-3-propyl-4-piperidone (VII), b.p. 83–83.5° (0.2 mm.), as a colorless liquid, $n^{25}D$ 1.4584.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H. 11.04. Found: C, 69.66; H, 10.92.

The picrate, recrystallized from ethanol, melted at 127–128°. *Anal.* Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.28. Found: C, 46.47; H, 5.58.

The methiodide, recrystallized from ethanol, melted at 193–195° dec. *Anal.* Calcd. for $C_{10}H_{20}INO$: C, 40.41; H, 6.78. Found: C, 40.62; H, 6.55.

1-Methyl-3-propyl-4-phenyl-4-piperidinol (VIII).—To a stirred solution of phenyllithium prepared from 0.96 g. (0.138 mole) of lithium wire and 10.5 g. (0.069 mole) of bromobenzene, cooled in an ice-bath, was added 10.8 g. (0.069 mole) of 1-methyl-3-propyl-4-piperidone (VII) in 25 ml. of anhydrous ether. After completion of the addition (0.5 hour) the solution was stirred and allowed to warm to room temperature for 2 hours. The reaction mixture was decomposed with 25 ml. of water, the water layer saturated with potassium carbonate, and the amine extracted with several small portions of ether. After drying over potas-

(7) D. Tarbell and J. Vaughn, This Journal, **65**, 232 (1943).

sium carbonate, distillation gave 1.6 g. (23%) of recovered 1-methyl-3-propyl-4-piperidone, b.p. 50–60° (0.2 mm.), and 11.2 g. (65% based on unrecovered piperidone) of 1-methyl-3-propyl-4-phenyl-4-piperidinol, b.p. 140–160° (0.2 mm.), as a light yellow viscous liquid, which crystallized spontaneously. An analytical sample recrystallized from hexane melted at 105–106°.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.93. Found: C, 77.60; H, 10.31.

1-Methyl-3-propyl-4-phenyl-4-piperidyl Esters (X).—A mixture of 2.0 g. (0.0086 mole) of 1-methyl-3-propyl-4-phenyl-4-piperidinol, 20 ml. of the acid anhydride and 0.01 mole of the corresponding sodium salt were heated with protection from moisture on a water-bath for 3 hours. The remainder of the procedure was exactly the same as that described for the 3-benzyl-4-piperidyl esters. The acetate was recrystallized from hexane; the other esters, Xb and Xc, could not be induced to crystallize.

The hydrochloride salts of these esters were prepared by adding a saturated solution of dry hydrogen chloride in ether to an ether solution of the esters. These salts were recrystallized from ethyl acetate–ethyl alcohol and were extremely hygroscopic.

The properties and analyses of these esters and their salts are listed in Table I.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XV. Some Pyrazolo[3,4-d]pyrimidines

BY ELVIRA A. FALCO AND GEORGE H. HITCHINGS

RECEIVED OCTOBER 8, 1955

A series of pyrazolo[3,4-d]pyrimidines has been synthesized. Treatment of pyrazole-3,4-dicarboxamide with sodium hypochlorite yielded 4,6-dihydroxypyrazolo[3,4-d]pyrimidine (III) from which 6-hydroxy-4-mercapto- (IV) and 4,6-dimercaptopyrazolo[3,4-d]pyrimidine (V) could be prepared. The mercapto derivatives reacted with ammonia and amines to furnish mercaptoamino, hydroxyamino and amino derivatives.

Antagonists of the natural purines have been prepared both by alterations in the functional groups and by changes in the nature or position of one or more ring atoms.[1] The present paper deals with derivatives of the pyrazolo[3,4-d]pyrimidine system. This ring structure may be regarded as being formed by an interchange of the 7-N and 8-C atoms of the purine skeleton. During the preparation of this paper there appeared a preliminary report dealing with the synthesis of some of the present compounds by another method.[2]

The approach adopted in the present, as in several previous problems,[3–5] was the preparation of a dihydroxy intermediate which could be converted by means of transformation reactions into derivatives with a variety of functional groups.

The 4,6-dihydroxypyrazolo(3,4-d)pyrimidine (III) was obtained by means of the Hofmann reaction[6] on pyrazole-3,4-dicarboxamide (II). The method of preparation, however, failed to provide a definitive proof of structure since either III or X might be formed in this reaction. The exclusion of 5,7-dihydroxypyrazolo(4,3-d)pyrimidine (X) as a possible product was based on the preparation of two derivatives of both ring systems, the bismethylmercapto derivatives XI and XII, and the two hydroxydimethylamino derivatives VII and XIII. Both XII and XIII had been synthesized by Rose[7] by unequivocal methods. The corresponding derivatives of the pyrazolo(3,4-d)pyrimidine system were readily prepared, XI by methylation of V and VII from IV as shown in the Reaction Scheme. Comparison of XI with XII and of XIII with VII established the non-identity of these representative derivatives of the two ring systems. Moreover, examination of the ultraviolet absorption spectra and paper chromatography of III failed to suggest the presence of a second isomer in detectable amounts.

A number of transformation reactions in the pyrazolo(3,4-d)pyrimidine series was studied as shown in the Reaction Scheme. The Hofmann reaction (II → III) ran smoothly with sodium hypochlorite in sodium hydroxide but did not go well with hypobromite under standard conditions. Treatment of the dihydroxy compound with phosphorus pentasulfide in pyridine gave chiefly the 6-hydroxy-4-mercapto derivative IV together with a small amount of the dimercapto derivative V. The preparation of the latter in two steps, as indicated, was generally more fruitful than when it was attempted, through alteration of the reaction conditions, to prepare the dimercapto compound directly from the dihydroxy derivative. In general the reactions of the pyrazolo(3,4-d)pyrimidine are typical of condensed pyrimidine systems and require no particucular comment. Similarly the physical properties, including the ultraviolet absorption spectra (Table I), closely resemble those of the corresponding purines.

Acknowledgments.—The authors are indebted to Samuel W. Blackman, P. R. W. Baker and Mrs. Veronica Purdy for microanalyses.

Experimental

Pyrazole-3,4-dicarboxamide.—To 7.5 g. of pyrazole-3,4-dicarboxylic acid[8] was added 150 ml. of thionyl chloride, and the mixture was heated under reflux conditions for 10 hours. The thionyl chloride was removed *in vacuo* and the powdery residue was added in portions to a vigorously stirred, self-cooled flask of liquid ammonia (250 ml.) over the course of one hour. The reaction mixture was stirred until the ammonia had all evaporated. The residue was taken up in boiling water and, on cooling, colorless plates, melting at 327° dec., precipitated.

(1) G. H. Hitchings and G. B. Elion, *3ème Congrès International de Biochemie Rapports*, 185 (1955).

(2) R. K. Robins, 128th Meeting of the American Chemical Society, Abstracts, p. 11N (1955).

(3) E. A. Falco and G. H. Hitchings, THIS JOURNAL, **72**, 3203 (1950).

(4) A. Maggiolo and G. H. Hitchings, *ibid.*, **73**, 4226 (1951).

(5) R. K. Robins and G. H. Hitchings, *ibid.*, **77**, 2256 (1955).

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