TABLE V

Cpd.	2-Aminopurine, mg.	Ether extraction, hr.	Yield of 2-fluoropurine: Crude, mg.	Pure, mg.	Pure, %	Recrystd. volume EtOH, ml.	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	850	4	422	353	40	6	216[a]	43.48	43.52	2.20	2.01	40.60	40.37
VII	2000	16	960	470	23	50	260	39.13	39.23	2.74	3.03	30.45	30.01
VIII	2250	72	664	532	23	110	>280[a]	46.41	46.26	4.46	4.40	38.65	38.22
IX	923	8	405	223	26	5	194	47.37	47.48	3.32	3.90	36.01	35.75
XI	500	48	147	83	16	20	272[a]	59.27	59.23	4.16	4.26	28.80	28.80

[a] Decomposition point.

adsorbed on a column of Dowex 50 (5 g. Dowex 50, 200–400 mesh). The column was washed with water (700 ml.) and then 0.1 *N* hydrochloric acid (400 ml.) which eluted a small amount of xanthine. The eluant was changed to 0.5 *N* hydrochloric acid and the 2-fluoroadenine appeared in the eluant between 200–430 ml. Evaporation of this solution gave 2-fluoroadenine hydrochloride, which after trituration with ethyl alcohol and drying, weighed 147 mg. (12%), m.p. >350°.

Anal. Calcd. for $C_5H_4FN_5 \cdot HCl$: C, 31.74; H, 2.67; N, 37.04. Found: C, 31.64; H, 3.15; N, 37.22.

4. 2-Fluoro-9-β-D-ribofuranosyl-6-purinethiol (VI).—The neutral slurry resulting from the treatment of thioguanosine (6.7 g.) as described in A above was allowed to stand in an ice-bath for several hours before the yellow solid was collected by filtration, washed thoroughly with two portions of ice-water followed by ethanol and then ether giving 2.6 g. of crude product. Recrystallization of this material from water (330 ml.) with charcoal treatment gave the pure product which was collected by filtration, washed with water, and dried *in vacuo* at 78°; yield 505 mg. (7%), m.p. 187–188°, $[\alpha]^{22}D$ 70.4 ± 2.5° (0.1 *N* NaOH).

Anal. Calcd. for $C_{10}H_{11}FN_4O_4S \cdot {}^1/_2\ H_2O$: C, 38.58; H, 3.90; N, 18.01; S, 10.29. Found: C, 38.52; H, 4.00; N, 18.11; S, 10.47.

5. 2-Fluoro-6-purinethiol (V).—The neutral slurry obtained from the treatment of thioguanine (400 mg.) as described in A was filtered and the solid was washed and dried giving a crude yield of 665 mg. This material was partitioned on a Celite column (8.5 × 35 cm.) using water-saturated butanol as the eluant. Fractions 107–153 (690 ml.) containing the 2-fluoro-6-purinethiol were combined and evaporated to dryness *in vacuo*. The residue (217 mg., 54%) was recrystallized from ethyl alcohol (30 ml.); yield 49 mg. (12%), m.p. >360°. Qualitative tests for fluorine and sulfur were positive.

Anal. Calcd. for $C_5H_3FN_4S$: C, 35.30; H, 1.78; N, 32.96. Found: C, 35.48; H, 2.23; N, 33.46.

6. 2-Fluorohypoxanthine (IV).—The thick slurry resulting from the treatment of guanine (5 g.) as described in A was concentrated to one-third volume *in vacuo*, and the residue was triturated with absolute alcohol (100 ml.). The insoluble material was removed by filtration and washed with 75% ethyl alcohol and then with absolute alcohol. The filtrate and washes were combined and evaporated to dryness *in vacuo*. The residue was triturated with absolute ethyl alcohol (75 ml.) and the insoluble inorganic salts removed by filtration. Evaporation of the filtrate to dryness gave 945 mg. of crude 2-fluorohypoxanthine, which was partitioned on a Celite column (8.5 × 35 cm.) using butyl alcohol–water as the eluent.

Fractions 107–150 (645 ml.) were combined and evaporated to dryness, giving 2-fluorohypoxanthine (114 mg., 2.2%).

Purified material (244 mg.) from two runs was dissolved in warm absolute ethyl alcohol (20 ml.) and an insoluble residue removed by filtration. The filtrate was evaporated to dryness *in vacuo*, and the residue was triturated with ether, collected by filtration, and dried; yield 204 mg. This material decomposed without melting above 260°.

Anal. Calcd. for $C_5H_3FN_4O \cdot {}^1/_8C_2H_5OH$: C, 39.38; H, 2.37; F, 11.87; N, 35.00. Found: C, 39.53; H, 2.68; F, 11.88; N, 34.91.

7. 6-Chloro-2-fluoropurine (X).—The neutral solution from the treatment of 2-amino-6-chloropurine (385 mg.) as described in A was extracted with ether in a continuous liquid–liquid extractor for 10 hours. Evaporation of the ether extract gave 277 mg. of crude 6-chloro-2-fluoropurine which was recrystallized from ethyl alcohol (1.5 ml.); yield 41 mg. (13%), m.p. 174°.

Anal. Calcd. for $C_5H_2ClFN_4$: C, 34.80; H, 1.17; N, 32.47. Found: C, 34.84; H, 1.11; N, 32.88.

Preparation of 2-Fluoroadenine by the Debenzylation of 9-Benzyl-2-fluoroadenine.—To a suspension of 9-benzyl-2-fluoroadenine (100 mg.) in 10 ml. of liquid ammonia was added metallic sodium (52 mg.) in several pieces. After the solution was stirred for 10 minutes, it was neutralized with ammonium chloride and then allowed to evaporate at room temperature. The residue was slurried with ether, and the ether distilled off to remove the last traces of ammonia. The residue was dissolved in water and extracted with ether. The extraction of ether-soluble materials caused precipitations of a solid which was removed by filtration, washed, and dried *in vacuo* over phosphorus pentoxide: yield 41 mg. (66%); λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 266 (11.5); *p*H 7, 262 (12.2); *p*H 13, 269 (12.3).

9-Benzyl-6-dimethylamino-2-fluoropurine.—Benzyl chloride (64 mg., 0.5 mmole) was added to a suspension of potassium carbonate (34.5 mg., 0.25 mmole) and 6-dimethylamino-2-fluoropurine (45 mg., 0.25 mmole) in dimethyl sulfoxide (2.5 ml.), and the reaction mixture was stirred at 50° for 4 hours. After standing overnight at room temperature, the reaction mixture was diluted with water (7.5 ml.), and the solid that separated from solution was collected by filtration, washed with water, and dried *in vacuo* at 78°; yield 38 mg. (57%), m.p. 137°.

Anal. Calcd. for $C_{14}H_{14}FN_5$: C, 61.99; H, 5.22; N, 25.83. Found: C, 62.06; H, 5.52; N, 25.34.

BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Nitrogen Compounds of Petroleum Distillates. XXVIII. Isolation of 2-Methyl-6,7-dihydro-1,5-pyrindine. Preparation of Some Methyl-dihydro-pyrindines[1]

BY H. L. LOCHTE AND A. G. PITTMAN

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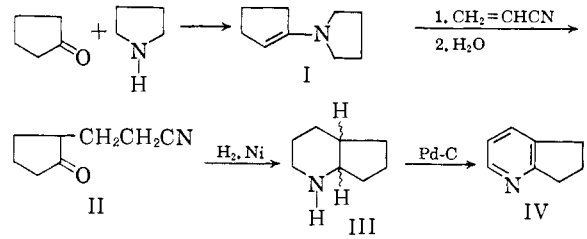
Utilizing preparative gas chromatography several $C_9H_{11}N$ bases were isolated from California petroleum. One of these proved to be 2-methyl-6,7-dihydro-1,5-pyrindine thus confirming the presence of the dihydropyrindine type in California petroleum. A new method of synthesis was developed for 6,7-dihydro-1,5-pyrindine (IV) which was extended to the preparation of 3- and 4-methyl-6,7-dihydro-1,5-pyrindine (X) and (VIII).

The presence of dihydropyrindines in California petroleum bases has been suspected for a number of years since Eguchi,[2] in 1928, identified "pyrindane" (6,7-dihydro-1,5-pyrindine) (IV) in shale oil bases, and a slight elevation in refractive index observed in California bases boiling from 208–218° seemed to indicate the presence of some new type of bicyclic bases in this region. After Arnall[3] isolated 6,7-dihydro-2,5-pyrindine and 2-methyl-6,7-dihydro-1,5-pyrindine from coal tar bases boiling at 209–212°, it was decided to study available California bases originally fractionated by J. R. Bailey and students in 1931–1938.

Bases boiling in the 209–212° range were separated by distribution of the hydrochlorides between chloroform and dilute hydrochloric acid, in which the bases with high index of refraction are concentrated in the aqueous layer.[4] The bases recovered from the aqueous layer were next fractionally distilled into 1-degree cuts which were individually distributed into 10 fractions of increasing base strength by the use of a counter-current pulse column. The resulting fractions showed an increase of refractive index with increase in base strength. However, since most of these fractions gave only poor yields of solid picrate derivatives at this stage, they were next fractionated on a preparative gas chromatography unit. This operation revealed a peak at the end of the run with an index of refraction of 1.5135, whereas previous peaks showed values from 1.4905–1.4960. The material collected in this peak was readily converted to solid picrates which were not easily separable by recrystallization so the corresponding last peaks from several runs were rechromatographed. From various portions of the resulting broad peak, four different crystalline picrates were obtained their composition indicated formula $C_9H_{13}N$ for two of the bases and $C_9H_{11}N$ for the others.

The only methyl-6,7-dihydro-1,5-pyrindine ($C_9H_{11}N$) described was 2-methyl-6,7-dihydro-1,5-pyrindine synthesized by Basu,[5] who reported the picrate melting at 151–152°. The picrate of 2-methyl-6,7-dihydro-1,5-pyrindine, prepared by the method of Basu,[5] proved to be identical with the picrate of one of our $C_9H_{11}N$ bases.

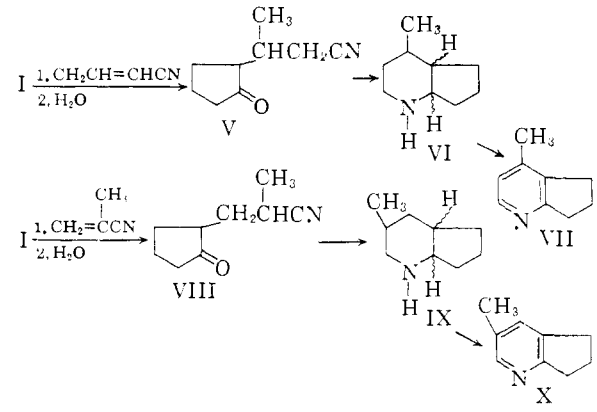
Although Robison[6] has improved the yields in the preparation of pyrindane (IV) through extensions of a method of synthesis of 2,4-dihydroxy-6,7-dihydro-1,5-pyrindine developed by Schroeder and Rigby,[7] there appeared no convenient route for preparing various alkylated dihydro-1,5-pyrindines. Consequently, an attempt was first made to synthesize pyrindane (IV) by a procedure which might also be used in preparing the methyl-dihydro-1,5-pyrindines. This attempt involved first the monocyanoethylation of the enamine of cyclopentanone (I) by the method of Stork and co-workers,[8,9] then a reductive ring closure of the ketonitrile and subsequent catalytic dehydrogenation. 2 - (2-Cyanoethyl)-cyclopentanone (II), obtained in a 56% yield,[10] was reductively cyclicized by a method similar to that described by Albertson.[11] The stereochemistry of the resulting octahydro-1,5-pyrindine (III), obtained in a 76% yield by this manner, was not established. Evidently, only one form is produced since picrate and picrolonate derivatives of the amine have sharp melting characteristics unchanged by recrystallization. The dehydrogenation of octahydro-1,5-pyrindine (III) was expected to produce the pyrindane (IV) and not 1,5-pyrindine since attempts at dehydrogenation of pyrindane (IV) by Prelog[12] resulted only in the recovery of starting material. Dehydrogenation was first attempted with chloranil but was not effective even after refluxing in xylene for 40 hours. A vapor phase chromatographic analysis indicated that several products were obtained, with pyrindane (IV) produced only in a negligible yield. Dehydrogenation in the vapor phase over palladium-on-charcoal succeeded with a yield of 77–80%.



The preparation of 3- and 4-methyl-6,7-dihydro-1,5-pyrindine (X) and (VII) was then undertaken using methacrylonitrile and crotononitrile in the addition with the pyrrolidine enamine of cyclopentanone (I).

The addition of these α,β-unsaturated nitriles occurred in a 33% yield, with the subsequent steps

(1) Paper XXVII, THIS JOURNAL, **72**, 3007 (1950).
(2) T. Eguchi, *Bull. Chem. Soc. Japan*, **3**, 235 (1928).
(3) P. Arnall, *J. Chem. Soc.*, 1702 (1958).
(4) T. S. Perrin and J. R. Bailey, THIS JOURNAL, **55**, 4136 (1933).
(5) U. Basu, *Ann.*, **530**, 131 (1937).
(6) M. M. Robison, THIS JOURNAL, **80**, 6254 (1958).
(7) H. E. Schroeder and G. W. Rigby, *ibid.*, **71**, 2205 (1949).
(8) G. Stork, R. Terrell and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).
(9) G. Stork and H. K. Landesman, *ibid.*, **78**, 5128 (1956).
(10) G. Stork and H. K. Landesman, ref. 9, report 65% yield.
(11) N. F. Albertson, THIS JOURNAL, **72**, 2594 (1950).
(12) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1945).



occurring in approximately the same yields as in the preparation of pyrindane (IV).

Arnall[3] has shown that the ultraviolet spectrum of 2-methyl-6,7-dihydro-1,5-pyrindine has the same similarity to the spectrum of 2,3,6-trimethylpyridine as the spectrum of pyrindane (IV) has to that of 2,3-dimethylpyridine. This similarity also occurs in a comparison of the ultraviolet spectrum of 3-methyl-6,7-dihydro-1,5-pyrindine (X) and 2,3,5-trimethylpyridine, as well as between 4-methyl-6,7-dihydro-1,5-pyrindine (VII) and 2,3,4-trimethylpyridine (Fig. 1).

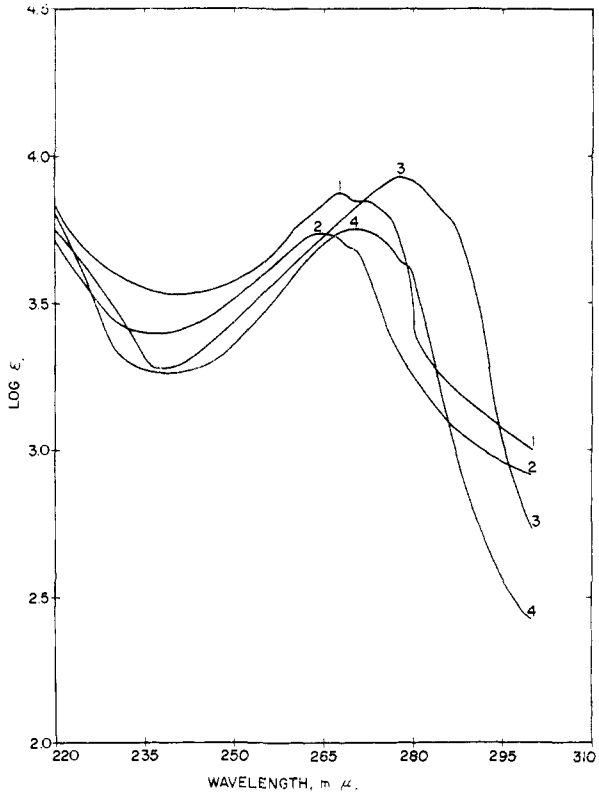


Fig. 1.—Ultraviolet absorption spectra in 95% ethanol of: 4-methyl-6,7-dihydro-1,5-pyrindine (VII), curve 1; 2,3,4-trimethylpyridine, curve 2; 3-methyl-6,7-dihydro-1,5-pyrindine (X), curve 3; 2,3,5-trimethylpyridine, curve 4.

The second $C_9H_{11}N$ base isolated from petroleum also appears to be a methyl-6,7-dihydro-1,5-pyrindine with the methyl group situated in the cyclopentane ring (homologs of the methyl-6,7-dihydro-2,5-pyrindines were excluded because of their higher b.p.'s, *ca.* 10°; it seems unlikely that compounds with such a wide difference in b.p.'s would have been obtained from the same chromatographic peak). The synthesis of the remaining methyl-6,7-dihydro-1,5-pyrindines is presently being undertaken.

Experimental[13-16]

Isolation of Bases.—Approximately 2 liters of California bases boiling 209–212° were treated by the "cumulative" extraction method of Perrin and Bailey.[4] The bases recovered from the aqueous fraction (*ca.* 800 ml.) were distilled through a Todd column packed with glass helices rated at 50 plates into 1-degree fractions. Each one-degree fraction was then distributed into 10 fractions of increasing basicity by fractional neutralization on a countercurrent pulse column. The column used for fractional neutralization of the bases was constructed from a 90-cm. glass cylinder with an inside diameter of 3.5 cm. The column was packed with 3-mm. glass beads. An outlet was provided at the bottom for the removal of the heavy phase and one at 8 cm. from the top for the removal of the light phase. An inlet was provided 10 cm. from the bottom for the introduction of the light phase and an inlet 14 cm. from the top for the introduction of the heavy phase. Intimate mixing of the phases was established by means of a pulsating action which was produced by a motor, cam gear and piston arrangement connected 5 cm. from the bottom of the column. In a typical pulse column run, 147 ml. of bases boiling 210–211° were dissolved in Skellysolve B[17] to a total volume of 1 liter. The Skellysolve B solution was introduced into the pulse column as the light phase while 1 liter of 0.08 *N* HCl was introduced as the heavy phase. The flow rate of the two phases was 250 ml./hr. On completion of the run the aqueous phase was evaporated *in vacuo* to a sirupy residue of base–hydrochlorides. The free bases were recovered from the base–hydrochloride mixture by careful treatment with NaOH. The Skellysolve B phase was re-run on the pulse column against 1 liter of 0.08 *N* HCl with the aqueous phase obtained worked up in the manner just described. This procedure was repeated until 10 fractions had been obtained (Table I).

A 3-ml. sample from fraction 1A (Table I) was chromatographed on the preparative gas chromatography unit and 5 cuts collected as indicated in Fig. 2. The preparative

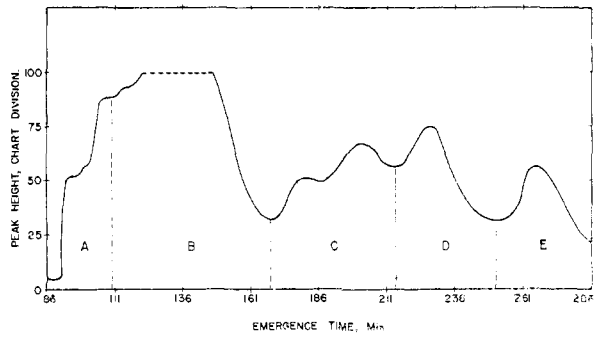


Fig. 2.—Gas chromatographic curve of a 3-ml. sample of petroleum bases; for explanation, see text.

unit consisted of a 20-foot column constructed from four 5-ft. lengths of 1-inch o.d. copper tubing joined by bends of 0.25-inch o.d. copper tubing. The column was packed with 35–60 mesh Johns–Manville C-22 firebrick treated with

(13) All m.p.'s are corrected; all b.p.'s are uncorrected.

(14) The ultraviolet spectra were obtained on a Beckman DK-1 recording spectrophotometer; the infrared spectra were obtained on a Baird recording spectrophotometer.

(15) Neutralization equivalents were determined by non-aqueous titration by the method of J. S. Fritz, *Anal. Chem.*, **22**, 1028 (1950).

(16) Microanalyses were performed at the Huffman Microanalytical Laboratories, Wheatridge, Colo.

(17) A hydrocarbon solvent, b.p. 60–69°.

TABLE I

Fraction[a]	Vol., ml.	$n^{25}D$	Fraction[a]	Vol., ml.	$n^{25}D$
1A	11	1.5048	6A	13	1.4996
2A	14	1.5016	7A	15	1.5004
3A	13	1.5000	8A	15	1.5007
4A	13	1.4997	9A	14	1.5040
5A	10	1.4996	10A	14	1.5002

[a] Decreasing base strength from 1A to 10A.

20% (by weight) of Reoplex 400.[18] A Gomac thermal conductivity sensing element served as the detector. The furnace measuring 6.5 ft. × 1 ft. × 0.5 ft., was constructed from transite material with heat supplied by three spirally wound 22-ft. lengths of 21-gauge chromel wire mounted on a transite panel. Forced circulation with a blower held the temperature differential from top to bottom of the furnace to 3–5°. Nitrogen served as a carrier gas at a flow rate of 95 cc./min. The column temperature was maintained at 175° with the flash vaporizer for the sample maintained at 235°. The five chromatographic fractions had the following indices of refraction: A, $n^{29}D$ 1.4905; B, $n^{29}D$ 1.4918; C, $n^{29}D$ 1.4940; D, $n^{28}D$ 1.4960; E, $n^{29}D$ 1.5135.

The same general chromatographic curve was obtained with a 3-ml. sample of fraction 2A (Table I) with the peak E (Fig. 2) reduced in size. Peak E was further reduced in size with fraction 3A and had disappeared by fraction 6A. When a sufficient quantity of the high index material from peak E had been collected, it was rechromatographed. From material collected before the main body of the peak E (emergence time *ca.* 238–254 min.) two $C_9H_{13}N$ bases were obtained by fractional crystallization of the picrate derivatives; m.p. 144° and 164.5–166°. Two $C_9H_{11}N$ bases were obtained as picrate derivatives from the main body of peak E (emergence time *ca.* 254–286 min.); m.p. 147–149° and 151–152°.

Identification of a $C_9H_{11}N$ Base as 2-Methyl-6,7-dihydro-1,5-pyrindine.—2-Methyl-6,7-dihydro-1,5-pyrindine was synthesized by the method of Basu[5]; b.p. 208–209° (755 mm.) (lit.[5] b.p. 195–196° (750 mm.); (lit.[3] b.p. 211.9° (761 mm.), $n^{24.5}D$ 1.5316 (lit.[3] $n^{32.5}D$ 1.5297).

The picrate of the synthetic base was prepared which had a m.p. 151–152° (lit.[5] m.p. 151–152°, lit.[3] m.p. 155°); a mixed m.p. with the petroleum base picrate with m.p. 151–152° gave no depression.

Anal. Calcd. for $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.86. Found: C, 49.43; H, 3.82.

The styphnate of the synthetic base melted at 137.5–139° (lit.[3] m.p. 138–139°); **picrolonate**, m.p. 170° dec. (lit.[3] 170° dec.).

The infrared spectrum of the picrate of the synthetic base and the petroleum base picrate (m.p. 151–152°) was superimposable.

Cyclopentanonepyrrolidine Enamine (I).—The procedure used was similar to that used by Heyl and Herr[19] in their preparation of certain steroid enamines. A solution of 68 g. of cyclopentanone (0.81 mole), 1 liter of dry benzene and 200 g. (2.8 moles) of pyrrolidine was refluxed in an apparatus fitted with a water trap. Refluxing was continued until no more water collected in the trap (*ca.* 3 hr.). At the end of this time, the benzene and excess pyrrolidine were removed *in vacuo* leaving a partially solidified reddish-brown liquid which was used without further purification in the subsequent reaction.

2-(2-Cyanoethyl)-cyclopentanone (II).—The cyanoethylation was carried out in a manner similar to that described by Stork and Landesman.[9] One liter of 1,4-dioxane was added to the enamine I prepared in the preceding step and to this solution 52 g. of acrylonitrile (0.99 mole) was then added. This solution was refluxed, protected from moisture, for a period of 7 hours. The 1,4-dioxane was then removed by distillation *in vacuo* and to the residue was added 400 ml. of H_2O and 20 ml. of glacial acetic acid. This solution was refluxed for two hours. The cooled solution was extracted 3 times with ether. The combined ether extracts were washed 3 times with 10% HCl, twice with 10% K_2CO_3 solution, and once with H_2O and dried over Na_2SO_4. After removal of the ether, the residue was distilled *in vacuo* giving 60 g. (56%) of liquid, b.p. 149–151° (17 mm.) (lit.[9] b.p. 144–147° (13 mm.)).

Octahydro-1,5-pyrindine (III).—Three grams of Raney nickel was added to 30 g. of 2-(2-cyanoethyl)-cyclopentanone (II) dissolved in 100 ml. of absolute ethanol. This mixture was hydrogenated at 34 atm. initial H_2 pressure and 120° for 7 hours. The Raney nickel was filtered off and the solvent removed by distillation *in vacuo*. The residual liquid was distilled through a 50-plate Todd column yielding 21 g. (76%) colorless liquid, b.p. 83° (19 mm.), $n^{19}D$ 1.4890.

Anal. Calcd. for $C_8H_{15}N$: C, 76.80; H, 12.00; N, 11.20; neut. equiv., 125.2. Found: C, 76.45; H, 12.14; N, 11.29; neut. equiv., 125.5.

The picrate melted at 120–121°; picrolonate, m.p. 202–204°.[20]

6,7-Dihydro-1,5-pyrindine (IV).—The dehydrogenation of octahydro-1,5-pyrindine (III) was carried out in the vapor phase at 310° over 30% Pd–C. Hydrogen was used as a carrier gas for the vapors. Two grams of the amine yielded in 4 hours 1.45 g. (77%) of product, $n^{28}D$ 1.5384 (lit.[12] $n^{20}D$ 1.5446).

Anal. Calcd. for C_8H_9N: neut. equiv., 119.2. Found: neut. equiv., 118.3.

The picrate melted at 181–182° after one recrystallization from ethanol. This picrate, on admixture with a sample prepared by the method of Prelog and Szpilfogel,[12,21] gave no melting point depression. **Styphnate and picrolonate** derivatives were prepared having the same melting points as previously reported for pyrindane.[12]

2-(1-Methyl-2-cyanoethyl)-cyclopentanone (V).—Two hundred and twenty-five ml. of N,N-dimethylformamide was added to the pyrrolidine enamine of cyclopentanone (I) prepared in the manner previously described from 30 g. of cyclopentanone (0.36 mole) and 88 g. (1.2 moles) of pyrrolidine. Twenty-eight and one-half grams (0.42 mole) of *cis-trans*-crotononitrile, prepared by rearrangement of allyl cyanide,[22] and a trace of hydroquinone was then added to this solution. The mixture was refluxed gently, protected from moisture, for 32 hr. At the end of this time the solvent was removed *in vacuo* and 200 ml. of H_2O plus 10 ml. of glacial acetic acid was added to the residue which was then refluxed for two hours. The product, obtained in the manner previously described in the workup of II, was distilled through a 50-plate Todd column and 17.8 g. of product (33%), b.p. 96–97° (0.5 mm.), $n^{20}D$ 1.4675, was obtained.

A semicarbazone was prepared for analytical purposes which melted at 195–196° dec.

Anal. Calcd. for $C_{10}H_{16}N_4O$: C, 57.69; H, 7.69; N, 26.92. Found: C, 57.54; H, 7.68; N, 26.68.

4-Methyl-octahydro-1,5-pyrindine (VI).—Thirty grams of 2-(1-methyl-2-cyanoethyl)-cyclopentanone (V) in 100 ml. of absolute ethanol was hydrogenated in the presence of 3 g. of Raney nickel in the same manner as previously described for the preparation of III. The product obtained from two such runs was distilled *in vacuo* to yield 41 g. (75%) of a colorless liquid, b.p. 86.5–87° (20 mm.), $n^{22.5}D$ 1.4840.

Anal. Calcd. for $C_9H_{17}N$: C, 77.70; H, 12.23; N, 10.07; neut. equiv., 139.2. Found: C, 77.88; H, 12.38; N, 10.24; neut. equiv., 139.6.

4-Methyl-6,7-dihydro-1,5-pyrindine (VII).—Dehydrogenation of 4-methyl-octahydro-1,5-pyrindine (VI) over Pd–C as previously described for the preparation of IV yielded a colorless liquid which darkened on standing, b.p. 226° (752 mm.), $n^{24.5}D$ 1.5360, d^{20}_{20} 1.0270.

Anal. Calcd. for $C_9H_{11}N$: neut. equiv., 133.2. Found: neut. equiv., 132.5.

Since difficulty has been encountered in analysis of dihydropyrindines a **picrate** was prepared for analytical purposes from equimolar quantities of picric acid and the amine in 95% ethanol. Recrystallization from ethanol yielded yellow needles, m.p. 169–170°.

(18) Material kindly furnished by Geigy Pharmaceuticals, Ardsley, N. Y.

(19) F. E. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953).

(20) Prelog (ref. 12) reported a picrolonate, m.p. 241°, from the product obtained by reduction of pyrindane with sodium–ethanol. This product was presumably the *trans* form.

(21) Prepared by T. H. Cheavans, Ph.D. Thesis, University of Texas, 1955.

(22) H. A. Bruson and T. W. Riener, THIS JOURNAL, **65**, 18 (1943).

Anal. Calcd. for $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.86; N, 15.46. Found: C, 49.86; H, 3.75; N, 15.36.

A styphnate melted at 212–214° dec.; picrolonate, m.p. 230–232° dec.

2-(2-Methyl-2-cyanoethyl)-cyclopentanone (VIII).—The pyrrolidine enamine of cyclopentanone (I) was prepared as before from 20 g. of cyclopentanone (0.24 mole) and 58 g. of pyrrolidine (0.82 mole). Nineteen grams (0.28 mole) of methacrylonitrile, prepared by dehydration of methacrylamide with P_2O_5, was then added to a solution of the enamine dissolved in 200 ml. of N,N-dimethylformamide. This solution was refluxed for 32 hours protected from moisture. After removal of solvent and hydrolysis, the product, recovered in the usual manner, was distilled *in vacuo* to give 12 g. (34%) of liquid boiling 126–128° (5 mm.), $n^{25.5}D$ 1.4624.

The semicarbazone prepared for analytical purposes melted at 195° dec.

Anal. Calcd. for $C_{10}H_{16}N_4O$: C, 57.69; H, 7.69; N, 26.92. Found: C, 57.23; H, 7.64; N, 26.76.

3-Methyl-octahydro-1,5-pyrindine (IX).—2-(2-Methyl-2-cyanoethyl)-cyclopentanone (VIII) was reduced in the presence of Raney nickel as previously described. Several runs were combined and distilled through a 50-plate Todd column to give a colorless liquid, b.p. 84° (18 mm.), $n^{25.5}D$ 1.4820.

Anal. Calcd. for $C_9H_{17}N$: N, 10.07; neut. equiv., 139.2. Found: N, 9.83; neut. equiv., 139.2.

3-Methyl-6,7-dihydro-1,5-pyrindine (X).—3-Methyl-octahydro-1,5-pyrindine (IX) was dehydrogenated over Pd-C in the manner described before. A white solid collected in the dehydrogenation trap which was low melting and darkened on exposure to air. The solid melted at 39–41°, b.p. 222° (752 mm.).

Anal. Calcd. for $C_9H_{11}N$: neut. equiv., 133.2. Found: neut. equiv., 133.1.

A picrate prepared from equimolar quantities of picric acid and the amine in 95% ethanol after recrystallization from ethanol formed yellow needles, m.p. 204–206°.

Anal. Calcd. for: $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.86; N, 15.46. Found: C, 49.59; H, 4.20; N, 15.41.

The styphnate melted at 199–200.5° dec.; picrolonate, m.p. 210–212° dec.

AUSTIN 12, TEX.

[CONTRIBUTION NO. 1048 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Synthesis of Nitrogen-containing Ketones. VIII. The Acylation of 3-Picoline, 4-Picoline and Certain of their Derivatives[1-4]

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3-Picoline, 4-picoline and certain of their derivatives have been acylated at their side chains to give high yields of the corresponding ketones containing pyridine rings. For the first time it has been possible to effect the direct acylation of 3-picoline with aliphatic esters to give alkyl 3-picolyl ketones using sodium diisopropylamide as the condensing agent.

In previous papers we reported that organolithium reagents can be used to effect the lateral acylation of 2-picoline,[6] 2-picoline homologs,[7] 4-picoline,[1] quinaldine,[8] lepidine[9] and 2,4-lutidine[9] and 2,6-lutidine[8] with aliphatic, aromatic and heterocyclic esters and thus good to high yields of the corresponding heterocyclic nitrogen-containing ketones have been prepared.

It has also been observed that although the acylation of 2-picoline with ethyl benzoate, using phenyllithium as the condensing agent, gave an 80% yield[6] of the expected 2-phenacylpyridine, the comparable reaction with 4-picoline gave, under optimum conditions,[1] a mixture of 4-phenacylpyridine (33%), and the azomethine addition products, 2-phenyl-4-methylpyridine (13%) and 2,6-diphenyl-4-methylpyridine (22%).

In contrast with the results which were obtained in the benzoylation of 2- and 4-picoline, 3-picoline is not acylated at its side chain by ethyl benzoate in the presence of phenyllithium. Instead, phenyllithium reacts with this base exclusively by azomethine addition.[10] However, 3-picoline is acylated by ethyl benzoate[10] to give 3-phenacylpyridine in 37 and 38% yield, respectively, using lithium diisopropylamide in ether and potassium amide in liquid ammonia as the condensing agents. Although it has been possible to acylate 3-picolylpotassium in low yields[10] with aromatic and heterocyclic esters, previous attempts to effect similar reactions with aliphatic esters failed.[10]

The present paper is concerned with the synthesis of a number of ketones by acylating 3-picoline, 4-picoline and certain of their derivatives with aliphatic and aromatic esters using phenylsodium and sodium diisopropylamide as condensing agents.

Although the interaction of 3-picoline (two equivalents), phenylsodium in benzene (two equivalents) and ethyl benzoate (one equivalent) gave only a slightly higher yield (45%) of 3-phenacylpyridine (IV) than was obtained (38%) earlier[10] when potassium amide was used as the condensing agent, the use of sodium diisopropylamide in benzene in place of phenylsodium gave a 78% yield of the desired ketone.

The over-all reactions which are involved are shown in the equations

$$C_6H_5Na + HN(i\text{-}C_3H_7)_2\,(I) \xrightarrow{C_6H_6} C_6H_6 + NaN(i\text{-}C_3H_7)_2\,(II) \quad (1)$$

(1) For paper VII in this series, see C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 939 (1957).

(2) Part of this work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(3) Presented, in part, before the Organic Division of the 135th National A.C.S. Meeting, Boston, Mass., April 5–10, 1959.

(4) This paper is based on part of the thesis presented by Stuart Raynolds to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(5) Monsanto Chemical Co. Research Fellow for the academic year 1958–1959.

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(7) C. Osuch and R. Levine, *J. Org. Chem.*, **21**, 1009 (1956).

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(9) N. N. Goldberg and R. Levine, *ibid.*, **77**, 3647 (1955).

(10) A. D. Miller, C. Osuch, N. N. Goldberg and R. Levine, *ibid.*, **78**, 674 (1956).