seen that the protonated amino group of histamine gives no assistance in the catalysis of *p*-NPA hydrolysis and k_2' for the reaction of histamine with phenyl acetate (*p*H 8.0) is 0.044 l. mole^{-1} min.$^{-1}$ ($\rho \sim 1.7$).

The Catalysis of *p*-NPA Hydrolysis by Purines and Pyrimidines.—Just as the catalytic property of the imidazole ring is retained in the benzimidazoles, it would also be expected to be present in the pyrimidoimidazoles (purines). To be able to separate the catalysis due to the pyrimido ring from that of the imidazole ring we have studied the catalysis of hydrolysis of *p*-NPA by both purines and pyrimidines (Table VI). At *p*H 8.0 the pyrimidines uracil, cytosine and cytidine proved to be non-catalytic up to 2×10^{-4} *M*, a concentration at which the purines exhibited easily measurable rate constants.

Little can be made of the data of Table VI and there seems to be no relation of pK_a' to k_2'. It can be noted, however, that the k_2' values are in the range found for the benzimidazoles and that ribosidation of adenine markedly decreases k_2' and the 6-$SeCH_3$, 6-SCH_3 and 6-OCH_3 substituted purines have greater rates than the 6-Se, 6-S and 6-O purines.

Acknowledgments.—We wish to express our appreciation to Dr. M. L. Bender for the use of preprints, and particularly our gratitude to Dr. F. M. Richards for instruction in the use of the Radiometer autotitrator. This work was supported by grants from the Rockefeller Foundation and from the Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

3-Benzoyl-4-piperidones

BY EARLE VAN HEYNINGEN

RECEIVED AUGUST 22, 1957

The products of Mannich reactions between acetophenones and β-alkylaminopropionic esters were cyclized to 3-benzoyl-4-piperidones.

Although there are many known substituted 4-piperidones, a search of the literature has failed to reveal any 3-benzoyl derivatives. This paper reports the synthesis of several of these compounds.

It was assumed by analogy with the ring closure of bis-(β-carbalkoxyethyl)-amines[1] to 3-carbalkoxy-4-piperidones that β-(β-benzoylethylamino)-propionic esters could be cyclized to the desired 3-benzoyl-4-piperidones. With this in mind a search was made for an adequate synthesis of the precursory esters.

The first method investigated was the addition of methyl β-methylamino-α-methylpropionate (II) to phenyl vinyl ketone (I). This condensation yielded the desired aminoester III in quite satisfactory yield (63.5%). As was expected this ester could be cyclized by sodium hydride in ether to a 3-benzoyl-4-piperidone (IV). An attempt was made to extend this method to the synthesis of the *p*-anisyl analog, but the attempt was unsuccessful since the pyrolysis of β-dimethylamino-*p*-methoxypropiophenone hydrochloride yielded the requisite *p*-anisyl vinyl ketone only in trace amounts. As a consequence, this approach to analogs of III was abandoned in favor of a search for a more general method.

A general method was developed that was characterized by simplicity which to some degree compensated for the moderate yields of VII obtained by its use. A Mannich reaction between acetophenone or its derivatives V and a substituted β-alkylaminopropionic ester VI gave the desired ketoaminoester VII. Some of these intermediates could be purified by distillation in vacuum to give analytically pure material with only very slight

(1) S. M. McElvain and K. Rorig, THIS JOURNAL, **70**, 1820 (1948).

CHART I

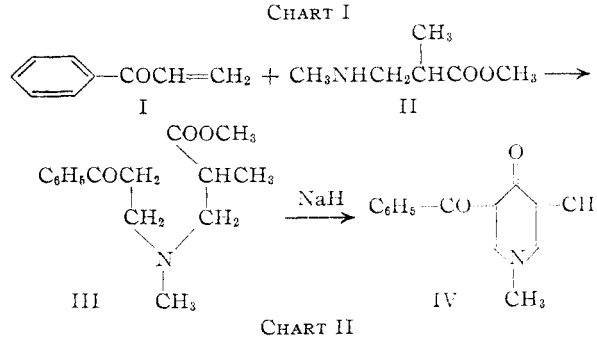
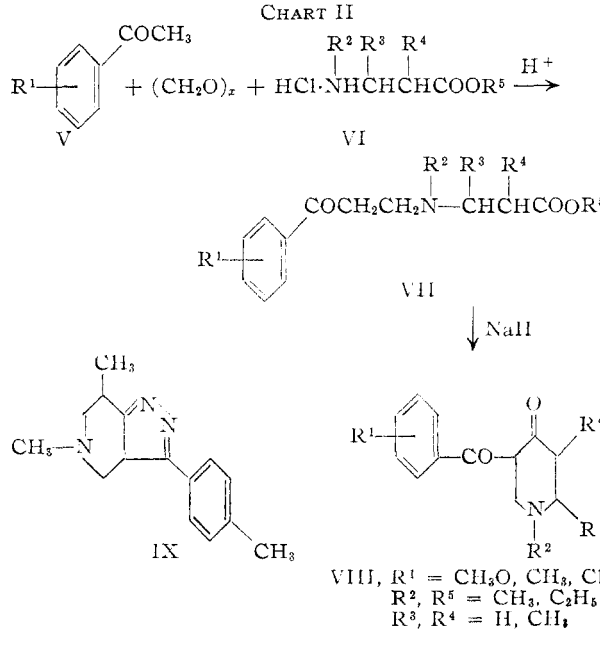


CHART II



decomposition. Others, although distillable, decomposed more extensively so that analytically pure material could not be obtained. And still others were so unstable that attempted distillation had to be interrupted to preserve the compounds. Consequently, when several purified examples proved that esters VII actually were formed, no further attempts were made to purify the more unstable esters and the crude preparations were used instead. The crude and purified esters VII could be cyclized in yields ranging from 25 to 55%.

Some deductions of a general nature can be made about the esters VII from the data on yields and stability. Those esters possessing N-methyl substitution seemed to be more stable than the corresponding N-ethyl compounds. Substitution of the benzene ring gave products that had higher boiling points and so were more susceptible to decomposition during distillation. Those esters with α-methyl rather than β-methyl substitution on the propionic ester portion appeared to cyclize more readily and gave products that were much easier to purify.

A brief investigation was made employing two active methylene compounds that were not acetophenones to determine the scope of the cyclization reaction. Cyclohexanone reacted in a Mannich reaction with methyl β-methylaminopropionate (II) to give the expected Mannich base. α-Vinylpyridine with II gave a similar product, methyl β-[β-(α-pyridyl)-ethylmethylamino]-α-methylpropionate. Neither of these esters could be cyclized with sodium hydride in ether, starting material being recovered. Because a quaternary carbon atom would be formed by the ring closure of the cyclohexanone compound, the failure to ring-close can be explained as due to steric factors. No further attempt was made to force this ring closure. The conditions for the cyclization of the pyridine compound were varied, however, by using as condensation agents and medium, sodium amide in refluxing benzene, sodium amide in refluxing toluene and lithium amide in refluxing benzene. Cyclization was not effected by any of these changes and the reaction in boiling toluene caused complete decomposition of the starting material. This lack of success must be due to insufficient activation of the methylene group by the pyridine ring.

The chemical reactions of the benzoylpiperidines were not investigated, but a condensation of hydrazine with 1,5-dimethyl-3-*p*-toluoyl-4-piperidone gave the bicyclic compound IX.

Acknowledgment.—The author is indebted to Messrs. W. L. Brown, G. M. Maciak and H. L. Hunter and Miss G. Beckmann for the microanalyses.

Experimental[2]

Preparation of Methyl α-Methyl-β-[(β-benzoylethyl)-methylamino]-propionate (VII).—Phenyl vinyl ketone was prepared by the method of Young and Roberts[3] in 42% yield, b.p. 52° (0.16 mm.), n^{25}D 1.5530. Methyl α-methyl-β-methylaminopropionate[4] was made in 85% yield, b.p. 31–32° (0.23 mm.), n^{25}D 1.4221. Then a mixture of 19.2 g. (0.146 mole) of methyl α-methyl-β-methylaminopropionate and 19.3 g. (0.146 mole) of phenyl vinyl ketone in 50 ml. of ethanol was allowed to stand at room temperature for 4 days. The residue after removal of the ethanol was fractionated. The product obtained weighed 24.4 g. (0.093 mole), 63.5%, n^{25}D 1.5057, b.p. 76–78° (0.14 mm.).

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04. Found: C, 68.21; H, 8.12.

Preparation[5] of 1,5-Dimethyl-3-benzoyl-4-piperidone (VIII).—In a 200-ml., 3-necked flask equipped with stirrer, dropping funnel, reflux condenser and drying-tube, 5.0 g. (0.208 mole) of sodium hydride was suspended in 75 ml. of dry benzene under an atmosphere of nitrogen. Then a few milliliters of methyl β-[(β-benzoylethyl)-methylamino]-α-methylpropionate was added to the rapidly stirred suspension, followed by 0.2 ml. of dry methanol. After the reaction obviously had started, the remainder of a total of 24.4 g. (0.093 mole) of the ester was added over a 40-min. period and the mixture was heated to reflux for 5 hr. At the end of this time no hydrogen evolution was detected so the reaction was cooled to 5° and decomposed by the cautious addition of 12.5 ml. of glacial acetic acid, followed by 11.3 ml. of water. The sodium acetate trihydrate that precipitated was removed by filtration and washed with benzene, the benzene solution combined with the benzene extract of the filtrates and evaporated to dryness and the solid residue recrystallized from petroleum ether (60–64°), m.p. 83–86°, yield 11.0 g. (0.0476 mole), 23%.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 73.16; H, 7.39; N, 6.06.

Preparation of Methyl β-[(β-*p*-Anisoylethyl)-methylamino]-α-methylpropionate (VII).—Methyl α-methyl-β-methylaminopropionate was converted into its hydrochloride by saturation of its ether solution with gaseous hydrogen chloride. The crude, solid product was isolated by filtration, washed with ether and dried over calcium chloride and sodium hydroxide and used without purification. The Mannich reaction was run in a 300-ml. flask: 33.5 g. (0.2 mole) of the above ester amine hydrochloride was mixed with 0.5 ml. of concentrated hydrochloric acid, 9.0 g. (0.3 mole) of paraformaldehyde, 30.2 g. (0.20 mole) of *p*-methoxyacetophenone in 60 ml. of methanol and refluxed for 1 hr. Then 6 g. more of paraformaldehyde was added and the mixture was refluxed two more hours and allowed to stand overnight. The methanol was evaporated in vacuum and then 100 ml. of water was added and the unreacted ketone extracted with ether. Evaporation gave 14 g. of recovered ketone. The water solution was basified with sodium bicarbonate and extracted with 800 ml. of ether in portions. The ether solution was dried and evaporated. Distillation was attempted and 2.7 g. of methyl α-methyl-β-methylaminopropionate was obtained boiling at 29° (0.3 mm.), n^{25}D 1.4215. When the temperature was raised, however, the residue started to decompose so distillation was stopped. The crude residue weighed 25.5 g. (0.087 mole), 43.5%. A small sample was dissolved in ethanol and a saturated alcoholic solution of picric acid was added. The mixture was heated to form the picrate, m.p. 113–114.5°.

Anal. Calcd. for $C_{22}H_{25}N_4O_{11}$: C, 50.67; H, 4.83. Found: C, 50.62; H, 5.05.

Preparation of Alkyl β-[(β-Aroylethyl)-alkylamino]-α-(or β)methylpropionates (VII).—The preceding method was used without significant variation to prepare the other keto-aminoesters listed in Table I. The ethyl β-methylaminobutyrate used in the preparation of some of these esters was made by the same method as given above for methyl α-methyl-β-methylaminopropionate. Use of ethylamine gave N-ethyl analogs. Some of the esters resulting from this synthesis could be distilled and obtained pure enough for analysis. The distillations were done over the shortest path possible through a Claisen-type still-head; consequently, the boiling points are not very sharp. Others though distillable were obviously decomposing during distillation, but it was considered worthwhile to continue the distillation as the distillate appeared to be purer than the crude products. These esters gave poor analyses which are included to indicate, possibly, the degree of impurity. When, as in the preceding experiment, materials were obtained that obviously were not stable to heat, the distilla-

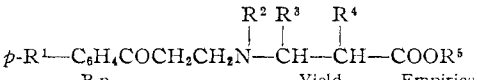
(2) All melting points and boiling points are uncorrected.

(3) W. G. Young and J. D. Roberts, THIS JOURNAL, **68**, 649 (1946).

(4) D. R. Howton, *J. Org. Chem.*, **10**, 278 (1945).

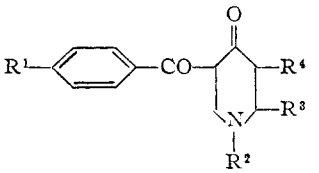
(5) This method was developed by S. M. McElvain and K. Rorig (see ref. 1) for the synthesis of 3-carbalkoxy-4-piperidones.

TABLE I



R	R^2	R^3	R^4	R^5	B.p. °C.	Mm.	$n^{25}D$	Yield, %	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	C_2H_5	H	CH_3	CH_3	97–114	0.3	1.5065	26.3	$C_{16}H_{23}NO_3$	69.28	69.90	8.36	8.17
CH_3O	C_2H_5	H	CH_3	CH_3	117–128	.4	1.5250	35.5	$C_{17}H_{25}NO_4$	66.42	67.21	8.20	8.11
H	CH_3	H	CH_3	CH_3	128–130	.16	1.5070	11.6	$C_{15}H_{21}NO_3$	68.41	68.14	8.04	8.04
H	CH_3	CH_3	H	C_2H_5	68–75	.25	1.5065	25.7	$C_{18}H_{23}NO_3$	69.28	69.14	8.36	8.23
CH_3O	CH_3	CH_3	H	C_2H_5				85.5					
Cl	CH_3	CH_3	H	C_2H_5	92–96.5	.27	1.5205	29.5	$C_{16}H_{22}ClNO_3$	61.75	61.65	7.13	7.36
CH_3	CH_3	H	CH_3	CH_3				71.0					

TABLE II



R	R^2	R^3	R^4	M.p., °C.	Yield, %	Empirical formula	Analyses, % Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
H	C_2H_5	H	CH_3	122–123[a]	33.5	$C_{17}H_{26}ClNO_3$[e]	62.27	7.99	4.27	62.63	7.92	4.23
CH_3O	CH_3	H	CH_3	110–111[b]	54	$C_{15}H_{19}NO_3$	68.94	7.33		69.04	7.53	
CH_3O	C_2H_5	H	CH_3	193–195[c]	29	$C_{16}H_{22}ClNO_3$[f]	61.63	7.11	4.49	61.82	7.49	4.38
CH_3O	CH_3	CH_3	H	99.5–101.5[d]	34	$C_{15}H_{19}NO_3$	68.94	7.33	5.36	68.66	7.36	5.37
Cl	CH_3	CH_3	H	189–190.5[c]	14	$C_{14}H_{17}Cl_2NO_2$[f]	55.63	5.67		56.00	5.84	
CH_3	CH_3	H	CH_3	92.5–93.5	44.5	$C_{15}H_{19}NO_2$	73.44	7.81		73.32	7.72	

[a] Ethanol–ether. [b] Petroleum ether (60–64°). [c] Chloroform–ether. [d] Benzene–petroleum ether. [e] This is the hydrochloride–ethanol solvate. [f] This is the hydrochloride.

tions were interrupted and the residue, after the removal of the starting aminoesters, was used in the condensation. The crude yields of these latter esters are relatively higher than those of the purified materials but only because of large amounts of contaminating by-products.

Preparation of 1,5-Dialkyl-3-aroyl-4-piperidones (VIII).—The method employed for the preparation of 1,5-dimethyl-3-benzoyl-4-piperidone was used for the preparation of the other piperidones. The physical properties and the yields of these compounds are listed in Table II. Several of the piperidones were purified as their hydrochloride salts, which were made in an ether solution of the piperidone by passing in dry hydrogen chloride.

Preparation of Methyl β-(2-Ketocyclohexylmethylmethylamino)-α-methylpropionate and Attempted Cyclization.—The ketoaminoester was prepared by the usual Mannich reaction and in this fashion 29.4 g. (0.2 mole) of cyclohexanone yielded 41.4 g. (0.172 mole), 86%, of crude product. It was distilled, b.p. 116–118° (0.25 mm.), $n^{25}D$ 1.4872.

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60; N, 5.81. Found: C, 64.40; H, 9.22; N, 5.85.

An attempt to cyclize this compound with sodium hydride gave a 25% recovery of starting material, $n^{25}D$ 1.4867. The remainder was an undistillable glass.

Preparation of Methyl β-[β-(α-Pyridyl)-ethylmethylamino]-α-methylpropionate and Attempted Cyclizations.—In a 300-ml. flask 52.5 g. (0.5 mole) of α-vinylpyridine and 65.5 g. (0.5 mole) of methyl α-methyl-β-methylaminopropionate were heated on the steam-bath for 4 days. The dark-red oily product distilled at 108–109° (0.14 mm.), $n^{25}D$ 1.4934, 98.1 g. (0.415 mole), 83%.

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: N, 11.86. Found: N, 11.63.

An attempt to ring close this compound under the usual conditions of sodium hydride in ether was unsuccessful, starting material being recovered. When lithium amide in refluxing benzene overnight was used, a 76% recovery of starting material resulted. An attempt was then made using sodium amide and toluene in which the reactants were mixed and then heated to reflux. A vigorous frothing occurred as the temperature rose, but neither starting material nor the expected product could be isolated from this attempt. When benzene was substituted for toluene, a 63% recovery of starting material resulted.

Preparation of 5,7-Dimethyl-3-*p*-tolyl-4,5,6,7-tetrahydro-1-pyrazolo[4,3-c]pyridine (IX).—A mixture of 6.0 g. (0.0245 mole) of 1,5-dimethyl-3-*p*-toluoyl-4-piperidone and 1.25 g. (0.049 mole) of hydrazine in 50 ml. of absolute ethanol was heated for 15 minutes on a steam-bath. Then water was added and the mixture extracted with ether. Evaporation of the ether yielded an oil that solidified. It was recrystallized from benzene by admixture of a small amount of petroleum ether (60–64°) and then from dilute ethanol, m.p. 117° with prior softening at 108°. The yield was 0.6 g.

Anal. Calcd. for $C_{15}H_{19}N_3$: C, 74,65; H, 7.94. Found: C, 74.40; H, 7.97.

INDIANAPOLIS, INDIANA