methyl group.[9] Presumably, on the basis of this mechanism, the effectiveness of a reagent in bringing about this elimination reaction would be a function of its basicity and in this connection it should be noted that Segaller[10] found that the reagents which he studied stood in the following order, potassium hydroxide > sodium ethoxide > sodium phenoxide > sodium nitrophenoxide in their ability to form isobutylene from tertiary butyl iodide.

The mechanism by which the replacement of the halogen by the piperidino radical takes place is not so clear. It does not seem that the incipient ionization of the halogen is the rate controlling factor for this should be increased by the inductive (I) effect of the alkyl groups in the secondary and tertiary halides and hindered by both the I and T effect of the carbethoxy group (particularly when the bromine is on the α-carbon atom). It remains, therefore, to suggest that the rate-determining factor in this replacement reaction is the ability of the reagent to approach the carbon atom carrying the halogen. The concentration of electrons about this carbon by the inductive effect of the alkyl groups in secondary and tertiary bromides would make more difficult the approach and attachment of the unshared electron pair of the piperidine molecule while the withdrawal of electrons through the I and T effects of the carbethoxy group would facilitate the attachment of piperidine to the α-carbon atom in the case of ethyl bromoacetate. On the basis of such a mechanism the effects of the associated groups appear to explain the reactivities of the various bromides whose replacement reactions with piperidine have been studied.

(9) In this connection it should be noted that in a footnote to a paper by Noller and Dinsmore, THIS JOURNAL, **54**, 1032 (1932), it is stated that a referee suggested the removal of a proton by the base (in this case, pyridine) as the first step in the elimination of halogen acid from a halide and that tertiary halides lose halogen acid more readily than other types because of the larger number of hydrogens available for the reaction.

(10) Segaller, *J. Chem. Soc.*, **103**, 1421 (1913).

Summary

The rate and course of the reaction of thirteen different bromo esters with piperidine have been determined and from the results obtained mechanisms for the elimination of halogen acid and for the reaction involving replacement of the halogen by the piperidino radical have been suggested.

MADISON, WISCONSIN RECEIVED NOVEMBER 24, 1933

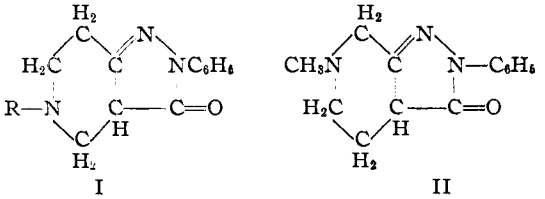
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Pyrazolones Derived from the Carbethoxypiperidones

BY S. M. ELIZABETH ENGLERT AND S. M. MCELVAIN

In previous publications[1] a variety of carbethoxypiperidones has been described. It seemed worth while to study the reaction of these substances with phenylhydrazine and to isolate, if possible, the various bicyclic pyrazolones that would be expected to result from such a condensation. The preparation of compounds of this type would not only extend the list of bicyclic pyrazolones to the heterocyclic field, but also would yield materials of possible pharmacological interest.

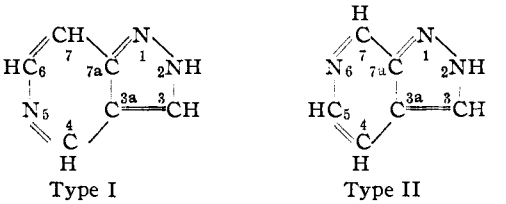
The present paper describes a series of 4,5,6,7-tetrahydro-2-phenyl-5-alkyl-2,1,5-pyrazolo-pyridin-3(3a)-ones[2] (I) derived from 1-alkyl-3-carbethoxy-4-piperidones,[1a] and also the isomeric 4,5,6,7-tetrahydro-2-phenyl-6-methyl-2,1,6-pyrazolopyridine-3(3a)-one (II) derived from 1-methyl-4-carbethoxy-3-piperidone.[1b]



I II

(1) (a) McElvain, THIS JOURNAL, **46**, 1721 (1924); **48**, 2179 (1926); (b) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(2) The nomenclature for this type of bicyclic structure was suggested by Dr. Leonard T. Capell, associate editor of *Chemical Abstracts*. Compounds I and II are considered as derivatives of pyrazolopyridine and the ring system is numbered thus



Type I Type II

The points of fusion of the pyridine and pyrazoline rings are indicated by the numbers of the three nitrogen atoms in the bicyclic system. Thus, giving the number of the nitrogen which carries the hydrogen first, type I is a 2,1,5-pyrazolopyridine and type II a 2,1,6-pyrazolopyridine. The hexahydro nature of I and II (piperidine derivatives) is indicated by the 4,5,6,7-tetrahydro prefix and the " 3(3a)-one" part of the name, since in order to form the keto group in position 3 another hydrogen must be added and is shown by the 3a in parentheses.

All attempts to prepare these pyrazolones from the free piperidone bases and phenylhydrazine were unsuccessful, probably on account of the instability of the former at the temperature necessary for the condensation. However, a modification of a method described by Michael[3] in which an intimate mixture of phenylhydrazine hydrochloride and the piperidone hydrochloride was heated at 120–160° with a small amount of hydrochloric acid gave yields of the pyrazolones varying from 30–70%. Compound II and compounds of type I in which R is methyl, ethyl and *n*-propyl were isolated in the form of their monohydrochlorides, while those compounds of type I in which R is *n*-butyl and isoamyl were isolated as free bases.

Several unsuccessful attempts were made to prepare the 1-methyl derivative of I (when R is methyl), an analog of antipyrine. Direct methylation with dimethyl sulfate according to the procedure of Mannich[4] gave a quaternary compound in which the nitrogen atom of the piperidine ring was methylated. Thomas[5] encountered the same difficulty in attempting the methylation of 1-methyl-3-carbethoxy-4-piperidone. A method of preparing antipyrine by heating 1-phenyl-3-methyl-pyrazolone-5 with methyl alcohol saturated with hydrogen chloride[6] when applied to I was without effect and I was recovered unchanged from the reaction. Finally the preparation of the analog of antipyrine was attempted through the reaction of symmetrical methylphenylhydrazine[7] with 1-methyl-3-carbethoxy-4-piperidone, but it was not possible to isolate any definite product, either as a free base or as a hydrochloride, from this reaction.

Two compounds of type I in which R is methyl and *n*-propyl were tested pharmacologically by Mr. Charles L. Rose of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. The M. L. D. by intravenous injection into white mice was found to be 800 and 500 mg./kg. for the methyl and *n*-propyl derivatives, respectively. Neither of these compounds showed any analgesic effect even in doses within the lethal range.

Experimental

Tetrahydro-2-phenyl-pyrazolopyridin-3(3a)-ones (I and II).—An intimate mixture of 1 g. of the 1-alkyl-3-carbethoxypiperidone-4-hydrochloride and the corresponding amount (0.51–0.65 g.) of phenylhydrazine hydrochloride was placed in a test-tube or 25-cc. flask provided with a reflux condenser. One drop of concentrated hydrochloric acid was added and the mixture heated in an oil-bath. When the temperature of the bath reached 110–120° a reaction set in; the mass fused and water and alcohol were liberated. The temperature of the bath was maintained at 110–120° until the reaction mixture had completely fused and then raised to 130–150°. In a few minutes the reaction subsided and the contents of the flask completely solidified. This solidification of the reaction mass indicated the completion of the reaction. The product was dissolved in 5 cc. of water and poured into 8–10 cc. of 10–15% sodium hydroxide. The alkaline solution was extracted several times with small portions of ether and then poured into 5 cc. of concentrated hydrochloric acid. This acid solution was saturated with hydrogen chloride; on standing and cooling, if the volume of solution did not exceed 20–25 cc. a voluminous precipitate of fine white needles separated. The precipitate was filtered off, dried and extracted with 20 cc. of 95% alcohol. An equal volume of ether was added to the filtered alcoholic extract and the hydrochloride of the pyrazolone precipitated. In the case of those compounds of type I in which R is methyl, ethyl and *n*-propyl the yields of recrystallized hydrochlorides amounted to 65–70% of the theoretical. This same procedure when applied to 1-methyl-4-carbethoxy-3-piperidone gave only a 30% yield of the hydrochloride of II.

In the case of those compounds of type I in which R is *n*-butyl and isoamyl the hydrochlorides could not be isolated satisfactorily. Consequently they were isolated as the free bases by the following procedure: after the reaction mixture from the condensation of the piperidone hydrochloride and phenylhydrazine hydrochloride had been poured into the 10–15% sodium hydroxide solution and extracted with several small portions of ether it was exactly neutralized with dilute hydrochloric acid. The precipitated pyrazolone was filtered off, washed with water until the water showed no coloration and finally washed with ether until the ether washings became practically colorless. The white crystalline product was then recrystallized from an alcohol–ether mixture.

The mother liquor from the recrystallization of the isoamyl derivative left on evaporation a brownish-red oily residue which contained some large needle-shaped crystals. These crystals were freed from the oily residue by washing with cold methyl alcohol in which the oil was quite soluble and the crystals practically insoluble. The crystals, however, were very soluble in hot methyl alcohol and were recrystallized from this solvent. From 1 g. of the 1-isoamyl-3-carbethoxy-4-piperidone hydrochloride 0.15 g. of this material was obtained. It melted at 117–118° (the isoamyl derivative obtained above melted at 125–126°) and contained 14.23% N, which indicated that it was possibly isomeric with the isoamyl derivative obtained above. This 117–118° melting material was not investigated further, but it should be noted that Freer[8] obtained two isomeric compounds from the condensation of acetoacetic ester with phenylhydrazine hydrochloride in absolute alcohol.

(3) Michael, *Am. Chem. J.*, **14**, 516 (1892).
(4) Mannich, *Arch. Pharm.*, **267**, 699 (1929).
(5) W. B. Thomas, Ph.D. Thesis, University of Wisconsin, 1932.
(6) *Cf. Chem. Abs.*, **24**, 5751 (1930).
(7) Knorr, *Ann.*, **238**, 137 (1887).
(8) Freer, *Am. Chem. J.*, **14**, 409 (1892).

The following table gives the properties, yields and analyses of the pyrazolones which were prepared.

TETRAHYDRO-2-PHENYL-PYRAZOLOPYRIDINE-3(3a)-ONES (I AND II)

Compound Type	R is	Form isolated	Formula	M. p., °C.	Yield, %	Analyses, N[a], % Calcd.	Found
I	Methyl	HCl	$C_{13}H_{16}N_3OCl$	224–225	70	15.82	15.76
II		HCl	$C_{13}H_{16}N_3OCl$	191–193	30	15.82	15.71
I	Ethyl	HCl	$C_{14}H_{18}N_3OCl$	187–188	68	15.03	14.91
I	*n*-Propyl	HCl	$C_{15}H_{20}N_3OCl$	191–192	65	14.31	14.51
I	*n*-Butyl	Base	$C_{16}H_{21}N_3O$	117–118	40	15.50	14.60[b]
I	Isoamyl	Base	$C_{17}H_{23}N_3O$	125–126	60	14.74	14.61

[a] Semi-micro Dumas. [b] No explanation can be advanced as to why the analyses for this particular compound persisted in being so far below the calculated value.

Attempted Preparation of 4,5,6,7-Tetrahydro-2-phenyl-1,5-dimethyl-2,1,5-pyrazolopyridin-3(3a)-one.—(a) Five grams of the pyrazolone (I, R is methyl) hydrochloride was dissolved in 10 g. of 20% sodium hydroxide. This alkaline solution was cooled in ice and 3 g. of dimethyl sulfate added slowly with stirring.[4] The solution was heated on the steam-bath for ten minutes to destroy the unreacted dimethyl sulfate. On cooling no precipitate of the alkali-insoluble 1-methyl derivative was apparent. The solution was then saturated with sodium hydroxide whereupon an oil precipitated which on account of its insolubility in ether and benzene and its solubility in water and chloroform was judged to be a quaternary compound.

(b) Five grams of the pyrazolone (I, R is methyl) hydrochloride and 20 cc. of methyl alcohol containing 35% hydrogen chloride[6] were heated in a sealed tube for two hours at 140°. The crystalline product obtained from the reaction mixture was the unchanged pyrazolone hydrochloride.

(c) An intimate mixture of 1 g. of 1-methyl-3-carbethoxy-4-piperidone hydrochloride and 0.72 g. of *sym*-methylphenylhydrazine hydrochloride was heated under a reflux condenser as in the reaction described above with phenylhydrazine hydrochloride. The reaction mixture was dissolved in water and the solution made alkaline with 10 cc. of 25% sodium hydroxide. An oil separated which was completely soluble in ether. No crystalline product could be isolated from this ethereal solution. Dry hydrogen chloride gave a gummy precipitate from this ethereal solution and this precipitate, likewise, could not be caused to crystallize.

Summary

A number of pyrazolones have been prepared from the isomeric and homologous 1-alkylcarbethoxypiperidones by the condensation of the piperidone hydrochloride with phenylhydrazine hydrochloride. It has not been possible to methylate these pyrazolones to analogs of antipyrine.

MADISON, WIS. RECEIVED NOVEMBER 27, 1933

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Analysis of Gamma-Methylfructoside Mixtures by Means of Invertase. I[1]

BY C. B. PURVES AND C. S. HUDSON

Although the sirupy mixture of non-reducing fructose derivatives, formed from fructose by methyl alcoholic hydrogen chloride, was discovered by Fischer[2] as early as 1895, the literature records no successful attempt to separate its constituents in crystalline form. This handicap did not prevent Menzies[3] and the earlier authors, whose work he reviewed, from showing that the elementary analysis of the mixture approximated to that of a methylfructoside; that the greater portion consisted of readily hydrolyzable fructose derivatives of a gamma type and that the latter, on methylation and subsequent hydrolysis, yielded a liquid tetramethylfructose similar to the specimens derived from sucrose and from inulin. More recently Schlubach and Rauchalles[4] followed up an old observation of Fischer[2] and hydrolyzed a portion of the liquid fructoside sirup back to fructose by means of invertase. After noting the consequent change in the copper reduction and optical rotation of the solution, the authors were led through a mathematical error to assign to the hydrolyzable constituent a specific rotation of $[\alpha]_D$ −17° instead of the value correct for their data, −51.5° in water.[5] In company with the above authors, the present paper occasionally implies that the enzyme exerts its specific effect upon a true methylfructoside of molecular weight 194. Although this assumption was justified in part by the analyses of the liquid methylfructoside mixture, fructose mono- and

(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Fischer, *Ber.*, **28**, 1160 (1895).

(3) Menzies, *J. Chem. Soc.*, **121**, 2238 (1922).

(4) Schlubach and Rauchalles, *Ber.*, **58**, 1842 (1925).

(5) In Schlubach and Rauchalles' calculation the 33% of the gamma-methylfructoside mixture which was hydrolyzed by invertase and denoted by β contributed an optical rotation of $[\alpha]_D$ −17° *to the whole*. The specific rotation of the portion β *by itself* was therefore −17 × 100/33 or −51.5°. For the same reason the specific rotation of the remaining non-hydrolyzed 67% of the original was not +36.36° but 36.36 × 100/67 or $[\alpha]_D^{25}$ +54.3°.