and one-half grams (0.015 mole) of 1,4-dimethylcarbostyril was dissolved in chloroform and heated on a steam bath with 2.7 g. (0.015 mole) of bromine. After removing the excess chloroform and recrystalling from carbon tetrachloride, 4.0 g. (80%) of orange needles melting at 165–170° dec. were obtained. Warming the compound with 50 ml. of water and recrystalling from alcohol gave the known 3-bromo-1,4-dimethylcarbostyril which melted at 174–176°.

Anal. Calcd. for $C_{11}H_{11}ONBr_2$: Br, 48.0. Found: Br, 48.3.

3,4-Dibromodihydro-1-methylcarbostyril. (XXI). In a similar manner as described for the above compound, 4.0 g. (0.025 mole) of 1-methylcarbostyril was dissolved in carbon tetrachloride and heated on the steam bath with 4.5 g. of bromine for 15 min. A yellow compound melting at 142–147° was obtained. When a sample of this compound was heated with pyridine for 15 min., diluted with water, and the excess pyridine removed under vacuum, an oil was obtained. Crystallization of this oil from petroleum ether gave the known 3-bromo-1-methylcarbostyril which melted at 147–149°. Decker reported a m.p. of 149°.[23]

Anal. Calcd. for $C_{10}H_9ONBr_2$: Br, 50.2. Found: Br, 50.0.

Acknowledgment. The authors wish to gratefully acknowledge the financial help which the Research Corp. of New York has supplied in the form of aid for the purchase of equipment plus the Frederick Gardner Cottrell Fellowship grant for Ronald E. Bowen during the year, 1959–1960.

(23) H. Decker, *J. prakt. Chem.*, [2] 45, 162 (1891).

GREENCASTLE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, MEAD JOHNSON RESEARCH CENTER, MEAD JOHNSON AND CO.]

Pyrrolidines. V. 3-Pyrrolidinylmethylamines and Quinoline Derivatives[1]

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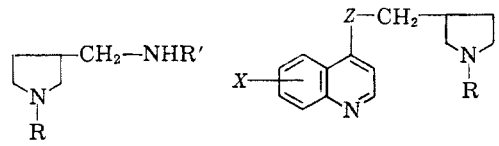
Treatment of methyl 1-substituted 5-oxo-3-pyrrolidinecarboxylates with ammonia or methylamine furnished 1-substituted 5-oxo-3-pyrrolidinecarboxamides which were reduced with lithium aluminum hydride to 1-substituted 3-pyrrolidinylmethylamines. The latter were incorporated into 4-(1-substituted 3-pyrrolidinylmethylamino)quinolines. 4-(1-Substituted 3-pyrrolidinylmethoxy)quinolines were also prepared. The reaction of itaconate esters with methanolic ammonia to furnish 5-oxo-3-pyrrolidinecarboxamide is discussed in the light of earlier literature reports.

1 - Substituted 3 - pyrrolidinylmethylamines (I) were considered key intermediates for the synthesis of potential pharmacodynamic and chemotherapeutic agents. In the present work we wish to report the synthesis of these amines and their incorporation into 4-(1-substituted 3-pyrrolidinylmethylamino)quinolines (IIa). The isosteric 4-(1-substituted 3-pyrrolidinylmethoxy)quinolines (IIb) were also prepared.

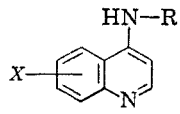


I II

IIa. Z = NH or CH_3N; IIb. Z = O; X = 6-CH_3O or 7-Cl

R = alkyl or arylalkyl

R′ = H or CH_3



IIIa. R = $CH_2CH_2N(CH_3)_2$; X = 6-CH_3O·Theophylline

IIIb. R = $CH(CH_3)(CH_2)_3N(C_2H_5)$; X = 7-Cl.

Quinolines substituted in the 4-position with a dibasic function have found divergent utilities as medicinal agents. Phthalamaquin (III-a) has found application as a bronchodilator,[2] while Chloroquin (III-b) is used as an antimalarial and anti-inflammatory agent.[3] In the present work, the terminal nitrogen of the 4-diamino function has been incorporated into a 3-pyrrolidinylmethyl ring system.[4]

Dimethyl itaconate proved to be a versatile intermediate for the synthesis of I. It has previously been shown that the reaction of dimethyl itaconate with primary amines yields methyl 1-substituted 5-oxo-3-pyrrolidinecarboxylates (IV).[5] In the present work, the latter were treated, without isolation, with ammonia or with methylamine to form 1-substituted 5-oxo-3-pyrrolidinecarboxamides (V) in good yields (Table I). Lithium aluminum hydride reduction in tetrahydrofuran then furnished the desired 1-substituted 3-pyrrolidinylmethylamines (I) (Table II).

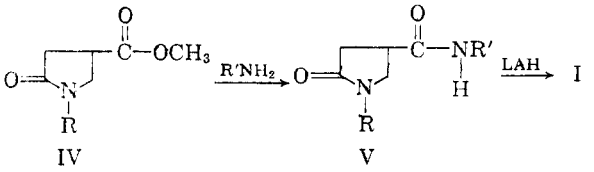
(1) Paper IV, Y. H. Wu, J. R. Corrigan, and R. F. Feldkamp, *J. Org. Chem.*, 26, 1531 (1961).

(2) (a) C. F. Geschickter, *Southern Med. J.*, 48, 497 (1955). (b) C. F. Geschickter and L. M. Rice, Brit. Patent 773,753.

(3) J. P. Young, *Ann. Int. Med.*, 51, 1159 (1959).

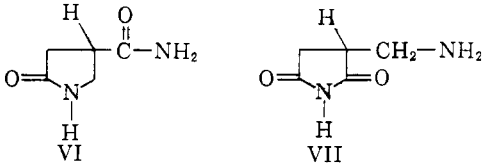
(4) (a) Fr. 1,001,411 (Rhone-Poulenc) describes 4-(1-substituted 3-piperidylmethylamino)quinolines. (b) T. R. Norton *et al.*, *J. Am. Chem. Soc.*, 68, 1330 (1946), report 4-(2-piperidylmethylamino)-7-chloroquinoline by reaction of 4,7-dichloroquinoline with 2-piperidinylmethylamine.

(5) Y. H. Wu and R. F. Feldkamp, *J. Org. Chem.*, 26, 1519 (1961).

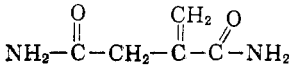


IV V

The reaction of dimethyl itaconate with an excess of methanolic ammonia gave a good yield of product melting at 193–195°. The reported[6] literature value for the melting point of 5-oxo-3-pyrrolidinecarboxamide (VI) is 217°. It was allegedly prepared by the reaction of dimethyl itaconate and liquid ammonia at "the usual temperature." We were able to recover only starting material when these reagents were placed together in a bomb and kept at room temperature for twenty-four hours.



VI VII



VIII

The same authors report that homoaspartimide, VII, m.p. 185°, is formed from the reaction of diethyl itaconate and hot ethanolic ammonia. Under these conditions we obtained only a small yield of a solid product, m.p. 193–195°. Earlier, Strecker[7] reported the formation of itaconamide VIII, m.p. 192°, from the reaction of dimethyl itaconate and ammonium hydroxide. The itaconamide is reported as forming less readily from the ethyl ester. Strecker did not offer a structure proof for his product nor did he propose an alternative formulation.

That the product, m.p. 193–195°, was not VII or VIII was shown as follows: The homoasportimide VII possibility was eliminated on the basis that the product failed to titrate. As diethyl itaconate reacted instantly with neutral permanganate and the product melting at 193–195° showed only a trace of reaction after twenty-four hours, structure VIII was eliminated. On the basis of the above, analytical data and the analogous formation of 1-substituted 5-oxo-3-pyrrolidinecarboxamides, we feel that structure VI is correct for the product melting at 193–195°.

The 4-aminosubstituted quinolines (IIa) were best prepared by heating a 4-phenoxyquinoline hydrochloride with an excess of 1-substituted 3-pyrrolidinylmethylamine (I) at 125° for twenty-four hours. The method of treating aliphatic diamines with 4-chloroquinolines in phenol[8] failed to give compounds IIa unless one mole of hydrogen chloride was added. Hydrogen chloride has been reported to shorten reaction times in the reaction of 4,7-dichloroquinoline with aliphatic diamines.[8] Compounds IIb were prepared by heating sodium 1-substituted 3-pyrrolidinylmethoxides[5] and 4-chloroquinolines under reflux in toluene. The compounds IIa and IIb are listed in Table III.

The compounds of Table III were tested as agents to reduce formalin-induced edema[9] in the rat paw. The most active compound of the series was 7-chloro-4-(1-methyl-3-pyrrolidinylmethylamino)-quinoline which caused a 35% reduction at a subcutaneous dose of 80 mg./kg. after 1 hour. The LD_{50} of this compound by subcutaneous injection in the mouse is 260 mg./kg.[10]

EXFERIMENTAL[11]

Preparation of 1-substituted 5-oxo-3-pyrrolidinecarboxamides (Table I). Equimolar amounts of dimethyl itaconate and the appropriate primary amine were dissolved in 600 ml./mole of absolute methanol and the solution allowed to stand at room temperature for 3 days. Anhydrous ammonia was then added until a large excess was present. After standing at room temperature for 3 days the solution was heated to boiling to drive off most of the excess ammonia while concentrating to one-half volume. Cooling gave crystalline products. In the case of the ethyl compound it was necessary to remove all the solvent and crystallize the syrupy residue from butanone. In the case of 1-*N*-dimethyl-5-oxo-3-pyrrolidinecarboxamide, excess methylamine was treated with dimethyl itaconate as above. The products were recrystallized from tetrahydrofuran or from butanone. The yields in Table I are of purified product used in the next step.

5-Oxo-3-pyrrolidinecarboxamide. To 1.5 l. of absolute methanol contained in a 3-l. Erlenmeyer flask was added 316 g. (2.0 moles) of dimethyl itaconate. The flask was cooled in an ice bath and anhydrous ammonia added until a large excess was present. The flask was allowed to stand at room temperature for 4 days, a white crystalline solid separating after 2 days. The solid was collected and 155 g. (59% yield), m.p. 193–195°, was obtained. The product was reduced without further purification. A sample was recrystallized from water, m.p. 195–197°.

Anal. Calcd. for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.87. Found: C, 46.93; H, 6.37; N, 21.92.

Preparation of 1-substituted 3-pyrrolidinylmethylamines (Table II). The following mole ratios were employed: 1-substituted 5-oxo-3-pyrrolidinecarboxamide, 1; lithium aluminum hydride, 2; tetrahydrofuran, 650 ml./mole of lithium aluminum hydride; (water, 3 mole/mole of lithium aluminum hydride). The lithium aluminum hydride was pulverized by hammering in aluminum foil and was placed

(6) K. Stosius and E. Philippi, *Monatsh. Chem.*, **45**, 457 (1925).

(7) O. Strecker, *Ber.*, **15**, 1639 (1882).

(8) A. R. Surrey and R. A. Cutler, *J. Am. Chem. Soc.*, **73**, 2623 (1951).

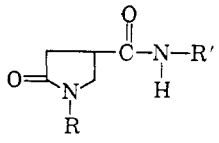
(9) (a) P. M. Lish *et al.*, *Arch. int. pharmacody* ., **129**, 77 (1960). (b) R. Domenjoz, *Int. Rec. Med.*, **165**, 467 (1952).

(10) Biological testing was under the supervision of Dr. P. M. Lish and Dr. G. R. McKinney of the Mead Johnson Department of Pharmacology.

(11) All melting points and boiling points are uncorrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

TABLE I

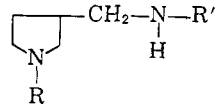
1-SUBSTITUTED 5-OXO-3-PYRROLIDINECARBOXAMIDES



R	R′	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
CH_3	H	140–141	92	$C_6H_{10}N_2O_2$	50.68	7.09	19.71	50.95	7.22	19.85
CH_3	CH_3	53–55	95	$C_7H_{12}N_2O_2$	53.83	7.75	17.94	54.12	7.18	17.72
C_2H_5	H	102–103	79	$C_7H_{12}N_2O_2$	53.83	7.75	17.94	53.76	7.71	18.16
CH_2=CH—CH_2	H	78–80	73	$C_8H_{12}N_2O_2$	57.13	7.19	16.66	57.24	7.33	16.83
$CH_3(CH_2)_3$	H	121–123	71	$C_9H_{16}N_2O_2$			15.21			15.31
$C_6H_5CH_2$	H	166–168	86	$C_{12}H_{14}N_2O_2$			12.84			12.66
$C_6H_5CH_2CH_2$	H	159–161	77	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.29	7.07	12.16

TABLE II

3-PYRROLIDINYLMETHYLAMINES



R	R′	B.P. (Mm.)	n_D	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
H	H	78 (13)	1.4864 (24)	50	$C_5H_{12}N_2$	59.95	12.08	27.97	60.16	11.88	28.02
CH_3[a]	H	166–167 (760)	1.4648 (24)	60	$C_6H_{14}N_2$	63.10	12.36	24.54	62.71	12.52	24.72
CH_3	CH_3	54 (13)	1.4516 (24)	67	$C_7H_{16}N_2$	65.57	12.58	21.85	65.69	11.98	22.73
C_2H_5[b]	H	82–90 (20)	1.4613 (20)	68	$C_7H_{16}N_2$			21.85			21.09
CH_2=CH—CH_2	H	100 (20)	1.4853 (20)	50	$C_8H_{16}N_2$	68.52	11.50	19.98	68.36	11.52	19.58
$CH_3(CH_2)_3$	H	110–114 (20)	1.4653 (20)	51	$C_9H_{20}N_2$	69.17	12.90	17.93	69.41	12.79	17.54
$C_6H_5CH_2$	H	126 (0.3)	1.5400 (20)	71	$C_{12}H_{18}N_2$	75.74	9.54	14.72	75.67	9.56	15.14
$C_6H_5CH_2CH_2$	H	90–92 (0.06)	1.5349 (24)	66	$C_{13}H_{20}N_2$	76.42	9.87	13.71	76.56	9.86	13.62

[a] Dipicrate, m.p. 208–211. *Anal.* Calcd. for $C_6H_{14}N_2 \cdot C_6H_3N_3O_7$: C, 37.77; H, 3.52; N, 19.58. Found: C, 38.27; H, 3.60; N, 19.80. [b] Dipicrate, m.p. 197–198. *Anal.* Calcd. for $C_7H_{16}N_2 \cdot C_6H_3N_3O_7$: N, 19.11. Found: N, 19.65.

in a three-neck round-bottom flask equipped with reflux condenser, drying tube, stirrer and dropping funnel. Half of the tetrahydrofuran was added slowly through the dropping funnel to the lithium aluminum hydride, with stirring. The finely ground amide was suspended in the remainder of the trtrahydrofuran. This suspension was added through the dropping funnel to the stirred lithium aluminum hydride suspension until reflux was obtained. An ice bath was then placed around the flask and the addition continued at a rate which maintained reflux. Additional tetrahydrofuran was added through the condenser as required in order to keep the mixture fluid. After addition was complete the ice bath was replaced by a heating mantle and the mixture stirred under reflux for 2 hr. The mixture was cooled to room temperature and water (3 mole/mole of lithium aluminum hydride) was added dropwise with continuous stirring. The mixture foamed badly at this stage and it was necessary to interrupt the hydrolysis periodically to allow the foam to settle. The mixture was filtered with suction and the granular filter cake returned to the flask and refluxed with two 500-ml. portions of absolute ethanol. The ethanol and tetrahydrofuran extracts were combined and the solution concentrated under reduced pressure. The product was obtained by distillation of the residue.

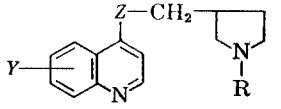
This material can be used in the next step. The yields in Table II are of analytical material obtained by redistillation.

7-Chloro-4-(1-methyl-3-pyrrolidinylmethylamino)-3-methylquinoline. To a solution of 4.9 g. (0.043 mole) of 1-methyl-3-pyrrolidinylmethylamine in 50 ml. of absolute methanol contained in a 100 ml. three-neck, round-bottom flask was added one equivalent of ethanolic hydrogen chloride. After removal of solvent at reduced pressure, the flask was fitted with a mechanical stirrer, reflux condenser, thermometer and gas inlet tube. To the flask were added 27.8 g. of molten phenol, 2.4 g. (0.021 mole) of 1-methyl-3-pyrrolidinylmethylamine, and 9.1 g. (0.043 mole) of 4,7-dichloro-3-methylquinoline.[12] The solution was heated at 125° (internal temperature) under nitrogen for 24 hr. The flask was cooled slightly and the dark red oil diluted with sufficient methanol to furnish a fluid mixture. The solution was diluted with 150 ml. of water and then basified to *p*H 12 with 20% aqueous sodium hydroxide. The mixture was extracted with three 100-ml. portions of chloroform. The chloroform extracts were combined, washed with saturated sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of the chloroform furnished a dark red oil which was diluted with a little butanone and chilled at −20° to furnish a

(12) E. A. Steck, L. L. Hallock, and A. J. Holland, *J. Am. Chem. Soc.*, **68**, 129, 380 (1946). A trace of *p*-toluenesulfonic acid was found to increase the rate of reaction between *m*-chlorotoluene and ethyl ethoxalylpropionate by five times.

TABLE III

4-(1-SUBSTITUTED 3-PYRROLIDINYLMETHYLAMINO)QUINOLINES AND 4-(1-SUBSTITUTED 3-PYRROLIDINYLMETHOXY)QUINOLINES



R	Z	Y	M.P.	Yield, %[c]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
CH_3	NH	7-Cl	106–108	58[f,h]	$C_{15}H_{18}ClN_3$	65.33	6.58	15.24	65.44	6.69	15.47
C_2H_5	NH	7-Cl	99–100	29[d,e]	$C_{16}H_{20}ClN_3$	66.31	6.96	14.50	66.14	7.19	14.23
CH_2=CH—CH_2	NH	7-Cl	126–128	50[d]	$C_{17}H_{20}ClN_3$	67.35	6.68	13.93	67.65	6.59	14.09
$CH_3(CH_2)_3$	NH	7-Cl	104–106	22[d]	$C_{18}H_{24}ClN_3$	68.02	7.61	13.22	67.83	7.21	12.99
$C_6H_5CH_2$	NH	7-Cl	127–128	51[f,g]	$C_{21}H_{22}ClN_3$			11.94			11.87
$C_6H_5CH_2CH_2$	NH	7-Cl[a]	127–129	52[e,f]	$C_{22}H_{24}ClN_3$	72.21	6.61	11.48	72.36	6.69	11.29
CH_3	CH_3N	7-Cl	190 (0.02)[b]	85	$C_{16}H_{20}ClN_3$	66.31	6.96	12.23[j]	66.09	7.02	12.33[j]
CH_3	NH	6-CH_3O	120–121	34[e,f]	$C_{16}H_{21}N_3O$	70.82	7.80	15.49	71.09	8.07	15.58
C_2H_5	NH	6-CH_3O	102–103	27[e]	$C_{17}H_{23}N_3O$	71.54	8.12	14.73	71.48	7.89	14.40
CH_3	NH	7-Cl,3-CH_3	103–104	59[e,g]	$C_{16}H_{20}ClN_3$	66.31	6.96	14.50	66.09	7.27	14.38
CH_3	O	7-Cl	73–76	80[h]	$C_{15}H_{17}ClN_2O$	65.09	6.19	10.12	65.27	6.48	10.17
$(CH_3)_2CH$	O	7-Cl	186–187	75[i]	$C_{17}H_{21}ClN_2O.2HCl$	54.06	6.14		54.32	6.24	
$C_6H_5CH_2CH_2$	O	7-Cl	72.5–74	82[h]	$C_{22}H_{23}ClN_2O$	72.02	6.32	7.64	71.74	6.89	7.65
CH_3	O	6-CH_3O	231–232	39[i]	$C_{16}H_{20}N_2O_2.2HCl$	55.65	6.42		55.68	6.67	

[a] This material was prepared by Mr. Jerry L. Compton. [b] Boiling point. [c] Yields are of pure product recrystallized from: [d] acetone; [e] acetonitrile; [f] butanone; [g] isopropyl acetate; [h] isopropyl ether; [i] ethanol–ethyl acetate. [j] Chlorine.

crystalline mass which was recrystallized from acetonitrile and from isopropyl acetate. The physical data are given in Table III.

6-Methoxy-4-(1-methyl-3-pyrrolidinylmethylamino)quinoline. Into a 100-ml., three-neck flask equipped with gas inlet tube, thermometer, stirrer, and condenser were placed 13.7 g. (0.048 mole) of 4-phenoxy-6-methoxyquinoline hydrochloride[13] and 8.8 g. (0.072 mole) of 1-methyl-3-pyrrolidinylmethylamine. The mixture was stirred with heating at 125° (internal temperature) under a nitrogen atmosphere for 24 hr. The product was isolated according to the procedure for 7-chloro-4-(1-methyl-3-pyrrolidinylmethylamino)-3-methylquinoline.

The remaining 4-aminoquinolines of Table III were obtained from 4-phenoxyquinolines as above. 7-Chloro-4-phenoxyquinoline hydrochloride was prepared according to the method reported.[8]

7-Chloro-4-(1-methyl-3-pyrrolidinylmethoxy)quinoline. To a suspension of 2.8 g. of 51.5% sodium hydride emulsion (0.06 mole of sodium hydride) in 60 ml. of dry toluene was added dropwise with stirring a solution of 6.9 g. (0.06 mole) of 1-methyl-3-pyrrolidinemethanol[5] in 40 ml. of dry toluene. After addition was complete the mixture was warmed with stirring for 0.5 hr. and then 9.9 g. (0.05 mole) of 4,7-dichloroquinoline[14] was added. The stirred mixture was refluxed for 6 hr. and then allowed to stand overnight. The cooled mixture was extracted with three 60-ml. portions of dilute hydrochloric acid. The combined acid extracts were washed with ether and then made alkaline with 20% aqueous sodium hydroxide to furnish an oily mixture which was extracted with ether. The ether solution was dried over magnesium sulfate and concentrated to an oil which solidified on cooling. The material was purified as described in Table III.

The remaining ethers of Table III were prepared as above from 4,7-dichloroquinoline[14] or 4-chloro-6-methoxyquinoline[15] and 1-substituted 3-pyrrolidinemethanols.[8]

Acknowledgment. We are indebted to Dr. R. F. Feldkamp for his helpful suggestions in the initiation of this work.

EVANSVILLE 21, IND.

(13) M. V. Rubstov, M. V. Lizgunova and E. D. Sazonova, *J. Gen. Chem. (USSR)*, 16, 1873 (1946); *Chem. Abstr.*, 41, 6254c (1947).

(14) The 4,7-dichloroquinoline was purchased from the Sterling-Winthrop Chemical Co.

(15) C. C. Price and R. N. Roberts, *J. Am. Chem. Soc.*, 68, 1204 (1946).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES, BURROUGHS WELLCOME AND CO. (U.S.A.) INC.]

4-Hydroxypyrrolo[2,3-d]pyrimidine: Mannich Reaction

ROBERT A. WEST

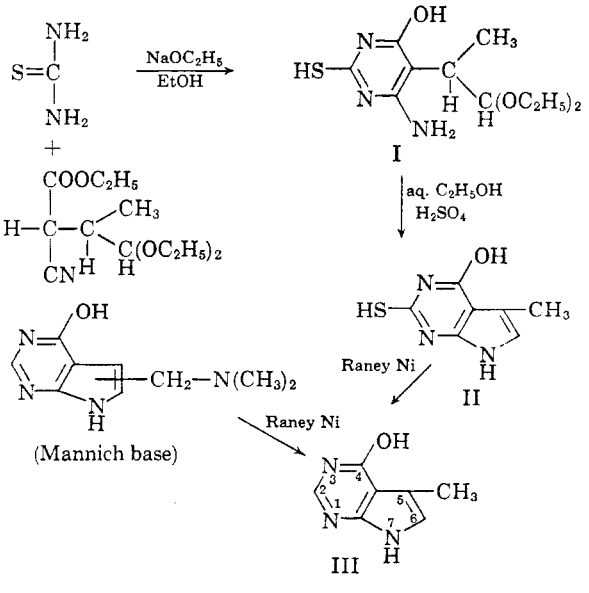
Received June 12, 1961

The pyrrolo[2,3-d]pyrimidine system undergoes the Mannich reaction with the same facility as the analogous indoles. A reaction sequence proved that the point of attack is at the β-pyrrole carbon as is true with indoles. The pyrrolopyrimidine Mannich base undergoes typical conversion to the acetamide and acetic acid derivatives.

The pyrrolo[2,3-d]pyrimidine bicycle bears structural analogy to indole and as such might be expected to undergo typical indole reactions such as the Mannich reaction. This investigation includes preparations of a simple Mannich base of 4-hydroxypyrrolo[2,3-d]pyrimidine, derivatives from this base, and proof of position of Mannich attack on this pyrrolopyrimidine system.

It has been well established that the Mannich attack in the indole series is at carbon 3 (the β-pyrrole carbon) if that position is unsubstituted. The reaction scheme shown below demonstrates that the comparable position in the pyrrolo[2,3-d]-pyrimidine system is also substituted under Mannich conditions.

The ethyl-α-cyano-β-methyl-γ,γ-diethoxy butyrate was prepared from ethyl cyanoacetate and α-bromopropionacetal by the method of West and Hitchings.[1] Reaction of this compound with thiourea conventionally gave the pyrimidine (I). Under acid catalysis, I cyclized to the pyrrolo-[2,3-d]pyrimidine (II) assumedly through hydrolysis of the acetal grouping to an aldehyde which then underwent an internal Schiff-base reaction forming the pyrrole ring. This 2-mercaptopyrrolopyrimidine was reductively desulfurized, giving



(1) R. A. West and G. H. Hitchings, Wellcome Foundation Ltd., Brit. Patent 812,366, April 22, 1959; *Chem. Abstr.*, 54, 592 (1960).