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Pyrrolidines. VI. Synthesis of 4-(1-Substituted 3-Pyrrolidinylmethylamino)- and 4-(1-Substituted 3-Pyrrolidinylmethoxy)quinazolines[1]

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4-(1-Substituted 3-pyrrolidinylmethylamino)- and 4-(1-substituted 3-pyrrolidinylmethoxy)quinazolines have been prepared. Improved procedures have been developed for the synthesis of some intermediate 4-chloroquinazolines. Formation of 4-chloro-2-diethylaminoquinazoline during triethylamine-phosphorus oxychloride chlorination of 2,4-quinazolinedione is discussed.

A number of 4-(1-substituted 3-pyrrolidinylmethylamino)- and 4-(1-substituted 3-pyrrolidinylmethoxy)quinolines exhibited the ability to reduce formalin induced edema in the rat paw.[1] In the present report, the quinoline heterocyclic moiety has been replaced by quinazoline. During the course of this work the chemistry of some 4-substituted quinazolines has been further investigated.

Several groups of workers have reported the preparation of 4-(dialkylaminoalkylamino)quinazolines, presumably for antimalarial screening.[2] Apparenly the results were disappointing, since no such compounds have been reported since 1947. A recent report describes the preparation of 4-(dialkylaminoethyl)(arylalkyl)aminoquinazolines for antihistamine evaluation.[3]

The first synthetic route investigated was the condensation of 4-chloroquinazoline with an appropriate 1-substituted 3-pyrrolidinylmethylamine. 4-Chloroquinazoline could be prepared as reported[4] but the yields were poor and the product prone to explosive decomposition. The method of heating 4-quinazolone with phosphorus oxychloride and phosphorus pentachloride followed by concentration and extraction of the product in ether was modified with consideration of the reported instability of 4-chloroquinazoline to acid and stability to base.[5] As in triazine syntheses,[6] triethylamine was added a reaction mixture of phosphorus oxychloride and 4-quinazolone which was then heated and concentrated. 4-Chloroquinazoline was conveniently obtained as a stable product by extraction of the residue with heptane containing triethylamine. 4-Chloroquinazolines substituted with 5-chloro, 6-bromo, 6-methyl,[7] and 7-chloro[2a] groups were prepared by this method. In the preparation of 4-chloro-2-methylquinazoline by this method a tendency to the formation of tarry products was observed. However, if the amount of phosphorus oxychloride were reduced to two-thirds mole per mole of 2-methyl-4-quinazolone, tar formation was minimized and 4-chloro-2-methylquinazoline was readily obtained. The reaction of 2-methyl-4-quinazolone with phosphorus oxychloride and phosphorus pentachloride furnishes products chlorinated on the benzo ring.[8a]

The reaction of a 4-chloroquinazoline with a 1-substituted 3-pyrrolidinylmethylamine[1] furnished a 4-(1-substituted 3-pyrrolidinylmethylamino)quinazoline, I. Other compounds prepared by this method are listed in Table I (method A).

The reaction of 2,4-dichloroquinazoline with 1-methyl-3-pyrrolidinylmethylamine yielded 2-chloro-4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline, III, whose structure was proved by reduction to 4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline. Others have reported that the 4-chloro is the first to be replaced in the reaction of 2,4-dichloroquinazoline with amines.[2e]

When triethylamine was used as the acid binder in the phosphorus oxychloride chlorination of 2,4-quinazolinedione, no 2,4-dichloroquinazoline was obtained. Instead, a distillable oil was isolated which had an analysis agreeing with $C_{12}H_{14}ClN_3$, IV. Since chlorination of uric acid with phosphorus

(1) H. C. Scarborough *et al.*, Pyrrolidines. V. 3-Pyrrolidinylmethylamines and Quinoline Derivatives, *J. Org. Chem.*, in press.

(2) (a) C. C. Price, N. J. Leonard, and D. Y. Curtin, *J. Am. Chem. Soc.*, **68**, 1305 (1946). (b) O. Yu. Magidson and E. S. Golovchinskaya, *J. Gen. Chem. (U.S.S.R.)*, **8**, 1797 (1938); *Chem. Abstr.*, **33**, 4993 (1939). (c) M. E. Smith, E. Elisberg, and M. L. Sherrill, *J. Am. Chem. Soc.*, **68**, 1301 (1946). (d) N. B. Chapman, G. M. Gibson, and F. G. Mann, *J. Chem. Soc.*, 890 (1947). (e) F. H. S. Curd, J. K. Landquist, and F. L. Rose, *J. Chem. Soc.*, 775 (1947).

(3) N. B. Chapman and H. Taylor, *J. Chem. Soc.*, 1908 (1961).

(4) M. M. Endicott *et al.*, *J. Am. Chem. Soc.*, **68**, 1299 (1946).

(5) (a) A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.*, **67**, 2112 (1945). (b) W. L. F. Armarego in *J. Appl. Chem.*, **11**, 70 (1960), has reported an improved synthesis of quinazoline from 4-chloroquinazoline. The latter was prepared from 4-quinazolone by a conventional phosphorus oxychloride–phosphorus pentachloride chlorination, using ammonium hydroxide in the isolation.

(6) H. S. Schroeder and C. Grundmann, *J. Am. Chem. Soc.*, **78**, 2447 (1956).

(7) S. Gabriel and J. Colman, *Ber.*, **38**, 3559 (1905).

(8) (a) A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.*, **70**, 2423 (1948). (b) P. B. Russell *et al.*, *J. Am. Chem. Soc.*, **71**, 2279 (1949).

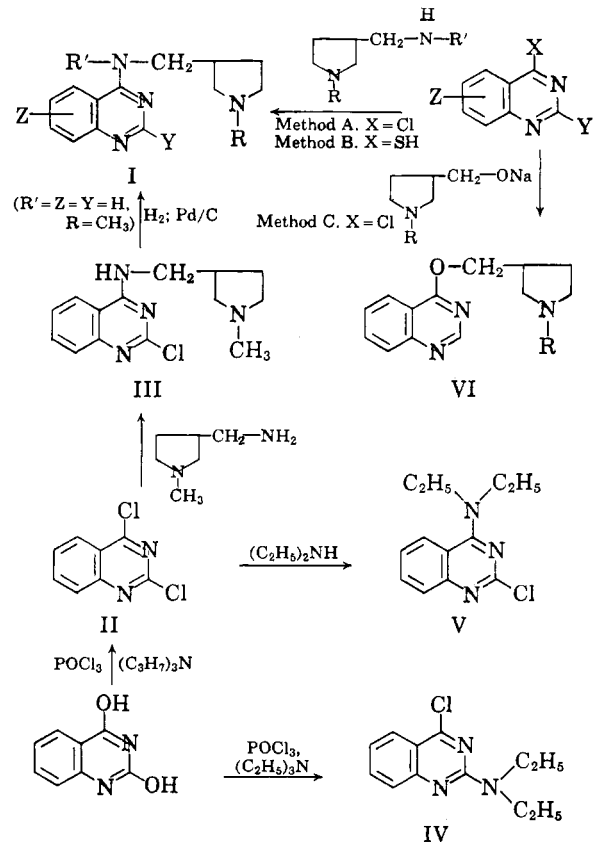
oxychloride and tertiary amines has been reported to yield dialkylaminopurines, presumably through chloropurines,[9] it was at first assumed that this oil was 2-chloro-4-diethylaminoquinazoline. However, the reaction of 2,4-dichloroquinazoline with diethylamine yielded a solid (m.p. 67.5°) isomeric with the oil. Assignment of the solid as 2-chloro-4-diethylaminoquinazoline, V, is based on consideration of the previously noted greater reactivity of the 4-chloro of 2,4-dichloroquinazoline. Further, the ultraviolet absorption of the solid between 290–350 mμ was quite similar to the quinoid bands exhibited by 2-chloro-4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline dihydrate in the same region. The oil, exhibiting strong absorption around 250 mμ and no appreciable absorption between 290–350 mμ, is therefore formulated as 4-chloro-2-diethylaminoquinazoline.

When tri-*n*-propylamine was employed as an acid binding agent in place of triethylamine, 2,4-quinazolinedione was smoothly converted to 2,4-dichloroquinazoline. Dimethylaniline may be employed for the preparation of 2,4-dichloroquinazoline.[2e]

A second method preparing 4-(1-substituted 3-pyrrolidinylmethylamino)quinazolines was by the reaction of a 4-mercaptoquinazoline with a 1-substituted 3-pyrrolidinylmethylamine. The use of butyl alcohol as solvent proved expedient compared to the usual fusion method.[8] The compounds obtained from 4-mercaptoquinazolines are shown in Table I (method B).

The reaction of 4-chloroquinazoline with sodium 1-substituted 3-pyrrolidinylmethoxides in refluxing toluene furnished the ethers, VI, of Table I (method C).[10]

These compounds were tested for their ability to reduce formalin induced edema in the rat paw.[11] 4 - (1 - Methyl - 3 - pyrrolidinylmethylamino)-quinazoline, which may be considered the parent compound, gave a 35% reduction at a subcutaneous dose of 75 mg./kg. after 1 hour. The mouse subcutaneous ALD_{50} was 335 mg./kg.[12]



A. Y = H or Cl; Z = H, Cl, Br, or CH_3; R = alkyl or arylalkyl; R' = H or CH_3
B. Y = H, SH or CH_3; Z = H; R = alkyl or arylalkyl; R' = H
C. Y = Z = H; R = alkyl or arylalkyl

EXPERIMENTAL[13]

4-Chloroquinazoline. A mixture of 15 g. (0.103 mole) of 4- quinazolone,[2a,4] 180 ml. of phosphorus oxychloride, and 37 ml. of triethylamine was refluxed for 2.5 hr. and then concentrated to a dark oily residue at reduced pressure. The residue was extracted three times with a total of 800 ml. of hot *n*-heptane containing 5% of triethylamine. The combined extracts which contained a brown flocculent material were washed once with 14% ammonium hydroxide and twice with water. The wet heptane was concentrated on the hot plate to approximately 300 ml. A yellow amorphous solid was removed with charcoal and the solution chilled at −20° to furnish 9.1 g. of product, m.p. 96–97°. Concentration of the liquor gave 0.8 g. of a second crop, m.p. 94.5–96°. Yield, 59%. Lit.[4]: m.p. 96.5–97.5°.

2,4-Dichloroquinazoline. A mixture of 20 g. (0.123 mole) of 2,4-quinazolinedione,[14] 200 ml. of phosphorus oxychloride and 38 g. (0.226 mole) of tri-*n*-propylamine was refluxed for 30 min. to yield a clear solution and then concentrated under partial vacuum (water aspirator) on the steam bath. All the volatile liquid was removed using a receiver immersed in Dry Ice and isopropyl alcohol. The crude product was extracted from the residue (mostly solidified) with four 200-ml. portions of hot *n*-heptane containing 2% tri-*n*-propylamine. The combined extracts, at room temperature, were diluted with enough benzene to dissolve crystallized solid. The organic solution was washed with 400 ml. of 5% sodium hydroxide and three times with water. The solvent was removed *in vacuo*, and the residual solid was recrystallized from 2:1 ethyl acetate-*n*-heptane to give 12.5 g. of 2,4-dichloroquinazoline as white needles, m.p. 117–118.2°.[2e] A second crop of product, weight 7.1 g., m.p. 116–117.5°, was obtained by reducing the mother liquor to one-fourth

(9) R. K. Robins and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 3624 (1952).

(10) M. M. Endicott, B. W. Alden, and M. L. Sherrill in *J. Am. Chem. Soc.*, **68**, 1303 (1946), report 4-(3-diethylaminopropionoxy)-6-chloroquinazoline using excess amino alcohol as solvent.

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

(12) Biological testing was under the supervision of Dr. G. R. McKinney and Dr. P. M. Lish of the Department of Pharmacology, Mead Johnson Research Center. Further details will be reported elsewhere.

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

(14) N. A. Lange and F. E. Sheibley, *Org. Synthesis*, Coll. Vol. II, 79 (1943).

the volume. The combined yield of the two crops was 19.6 g. (80%). In another run, the yield was 91%.

In a run using only 1 equivalent of tri-*n*-propylamine, 3 hr. was required to dissolve completely the 2,4-quinazolinedione. The yield was 84%.

When the crude product, in benzene-*n*-heptane, was washed first with water or insufficient alkali, extensive decomposition of the product resulted.

Material prepared in this manner was satisfactory for further use. The literature procedure,[2e] which employed dimethylaniline as an acid binder but no alkali wash, required vacuum distillation for further purification.

There were no significant differences when stock, freshly distilled and "aged"[15] phosphorus oxychloride were employed in these syntheses.

4,5-Dichloroquinazoline. This material was prepared in 29% yield as above from 5-chloro-4-quinazolone.[16] It was recrystallized from heptane, m.p. 131.5–133°.

Anal. Calcd. for $C_8H_4Cl_2N_2$: C, 48.27; H, 2.02; Cl, 35.63; N, 14.08. Found: C, 48.31; H, 2.06; Cl, 35.50; N, 13.95.

6-Bromo-4-chloroquinazoline. This material was prepared in 33% yield from 6-bromo-4-quinazolone.[16] After recrystallizations from isopropyl ether and cyclohexane, it melted at 164–166°.

Anal. Calcd. for $C_8H_4BrClN_2$: C, 39.46; H, 1.66; N, 11.51. Found: C, 39.48; H, 1.63; N, 11.41.

In the same manner, 6-methyl-4-quinazolone[16] furnished 80% of 4-chloro-6-methylquinazoline, m.p. 105–106°. Lit.:[7] m.p. 107–108°. 7-Chloro-4-quinazolone gave 76% of 4,7-dichloroquinazoline, m.p. 131–134°. Lit.[2a]: m.p. 135–136°.

4-Chloro-2-methylquinazoline. A mixture of 4.8 g. (0.03 mole) of 2-methyl-4-quinazolone, 9.0 g. (0.06 mole) of dimethylaniline and 3.1 g. (0.02 mole) of phosphorus oxychloride in 100 ml. of dry benzene was stirred under reflux for 2 hr. The reaction mixture was then cooled and a small amount of gummy material was removed by filtration. The benzene liquor was then diluted with 100 ml. of benzene and the solution washed with 100 ml. of water and then with two 125-ml. portions of 20% aqueous sodium hydroxide. The solution was then washed with water, dried and finally concentrated to a yellow oil which solidified upon cooling. One recrystallization from heptane furnished 3.1 g. (57%) of product melting at 77–80°. Analytically pure material, m.p. 81.5–83°, was obtained by a second recrystallization from heptane.

Anal. Calcd. for $C_9H_7ClN_2$: C, 60.50; H, 3.95; Cl, 19.85; N, 15.69. Found: C, 60.57; H, 4.24; Cl, 19.55; N, 15.43.

Representative examples for Methods A, B and C are given for the compounds in Table I. Preparation of the intermediate 1-substituted 3-pyrrolidinemethanols[17] and 1-substituted 3-pyrrolidinemethylamines[1] have been reported, except for the following amines.

1-(2-Hydroxyethyl)-3-pyrrolidinylmethylamine. Reduction of 60 g. (0.35 mole) of 1-(2-hydroxyethyl)-5-oxo-3-pyrrolidinecarboxamide with 30 g. (0.788 mole) of lithium aluminum hydride in 500 ml. of tetrahydrofuran as reported[1] furnished 8.3 g. or 16.5% of a heavy oil, b.p. 86° at 0.06 mm., $n^{20}D$ 1.5050.

Anal. Calcd. for $C_7H_{16}N_2$: C, 58.30; H, 11.18; N, 19.43. Found: C, 58.05; H, 11.13; N, 19.51.

The intermediate *1-(2-hydroxyethyl)-5-oxo-3-pyrrolidinecarboxamide* was prepared by the reaction of 158.2 g. (1 mole) of dimethyl itaconate with 61.1 g. (1 mole) of ethanolamine in 1 l. of methanol.[1] After standing for 3 days the solution was saturated with ammonia and allowed to stand for 3 days. Removal of methanol gave an oil which crystallized on standing at 4° for one week. Recrystallizations from absolute ethanol gave 123.1 g. (71%) of a white solid, m.p. 118–119°.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.72; H, 6.83; N, 16.13.

1-Isopropyl-3-pyrrolidinylmethylamine. Lithium aluminum hydride reduction of 1-isopropyl-5-oxo-3-pyrrolidinecarboxamide furnished a colorless liquid in 38% yield, b.p. 106–108°, $n^{25}D$ 1.4663.

Anal. Calcd. for $C_8H_{12}N_2$: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.73; H, 12.65; N, 19.90.

The intermediate *1-isopropyl-5-oxo-3-pyrrolidinecarboxamide* was prepared by the reaction of isopropylamine with dimethyl itaconate followed by a subsequent treatment with ammonia. After recrystallization from tetrahydrofuran there was obtained a 69% yield of white solid, m.p. 151–152°.

Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.15; H, 8.04; N, 16.36.

4-(1-Methyl-3-pyrrolidinylmethylamine)quinazoline (method A). To a solution of 8 g. (0.49 mole) of 4-chloroquinazoline in 200 ml. of anhydrous ether was added in one portion 11.1 g. (0.097 mole) of 1-methyl-3-pyrrolidinylmethylamine.[1] The solution became cloudy immediately with precipitated hydrochloride. After standing at room temperature for 24 hr. the ether was removed on a steam bath and the residue dissolved in approximately 150 ml. of water. The solution was made basic with 20% aqueous sodium hydroxide and extracted three times with chloroform. The combined chloroform extracts were washed once with water, once with saturated sodium chloride solution and then dried over magnesium sulfate. After removal of chloroform the residue was purified as in Table I.

2-Mercapto-4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline (method B). A mixture of 6.5 g. (0.0335 mole) of 2,4-dimercaptoquinazoline[18] and 3.82 g. (0.0335 mole) of 1-methyl-3-pyrrolidinylmethylamine in 50 ml. of *n*-butyl alcohol was stirred under reflux (nitrogen) for 6 hr. and then allowed to stand overnight. The mixture was concentrated to a resin which was purified as in Table I. It has been shown that only the 4-mercapto group is replaced when 2,4-dimercaptoquinazoline is fused with an excess of amine.[8b]

The intermediate 4-mercaptoquinazoline, and its 6-chloro, 2-methyl, and 6-chloro-2-methyl derivatives were prepared as reported.[3,8a]

4-(1-Methyl-3-pyrrolidinylmethoxy)quinazoline hydrochloride (method C). To a suspension of sodium hydride emulsion (0.082 mole of sodium hydride) in 90 ml. of dry toluene contained in a 250 ml. three-necked flask equipped with reflux condenser, drying tube, stirrer and dropping funnel was added dropwise a solution of 9.45 g. (0.082 mole) of 1-methyl-3-pyrrolidinemethanol[17] in 60 ml. of dry toluene. After addition was complete the solution was refluxed for 0.5 hr. and then cooled to room temperature. After the addition of 11.8 g. (0.072 mole) of 4-chloroquinazoline the solution was refluxed for 4 hr. After cooling, the mixture was washed with water and the toluene removed to furnish an oil which was dissolved in absolute ethanol. The addition of one equivalent of alcoholic hydrogen chloride gave a solid which was purified as in Table I.

Catalytic dehalogenation of 2-chloro-4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline. A solution of 1.56 g. (0.005 mole) of 2-chloro-4-(1-methyl-3-pyrrolidinylmethylamino)quinazoline dihydrate in 25 ml. of water and 3 ml. of glacial acetic acid was hydrogenated with 0.3 g. of 10% palladium on carbon and hydrogen at 60 p.s.i. After the absorption of 0.005 mole of hydrogen in 2 hr., the reaction mixture was diluted with 25 ml. of water and filtered to remove catalyst. Neutralization of the filtrate with 3 *N* sodium hydroxide gave an oil which was taken up in chloroform. After washing with water and drying and magnesium sulfate, the solvent was removed to furnish an oil which was crystallized from acetonitrile to furnish 0.82 g. (68%) of 4-(1-

(15) C. Grundmann, H. Schroeder, and R. Rätz, *J. Org. Chem.*, **23**, 1522 (1958).

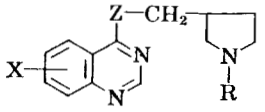
(16) B. R. Baker, *et al.*, *J. Org. Chem.*, **17**, 141 (1952).

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

(18) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **69**, 2138 (1947).

TABLE I

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



R	Z	X	Method	M.P.	Yield, % (1)	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
CH_3	NH	H	A	110.5–111.5	61[a,b]	$C_{14}H_{18}N_4$	69.39	7.49	23.12		69.69	7.80	23.30	
CH_3	NH	H	B	110.5–111.5	66[a,b]	$C_{14}H_{18}N_4$								
C_2H_5	NH	H	B	79–81	27[b]	$C_{15}H_{20}N_4$	70.28	7.86	21.86		70.14	7.52	22.25	
CH_3	CH_3N	H	A	170–180 (0.025)*	73	$C_{15}H_{20}N_4$	70.28	7.86	21.86		70.02	8.05	21.70	
$C_6H_5CH_2$	NH	H	B	105–107	34[a,b]	$C_{20}H_{22}N_4$	75.44	6.96	17.60		75.89	6.89	17.67	
$C_6H_5CH_2CH_2$	NH	H	A	107–108.5	59[b]	$C_{21}H_{24}N_4$	75.87	7.28	16.86		75.98	7.40	16.62	
CH_2CH_2OH	NH	H	B	139–141	38[a,b,c]	$C_{15}H_{20}N_4O$	66.15	7.40	20.57		66.34	7.60	20.39	
CH_3	NH	6-Cl	B	145–147	59[a,b,c]	$C_{14}H_{17}ClN_4$	60.75	6.19	20.24	12.81	61.06	6.01	20.02	12.63
CH_3	NH	2-CH_3	B	123.5–125	66[a,b,d]	$C_{15}H_{20}N_4$	70.28	7.86	21.86		70.25	8.09	21.98	
CH_3	NH	6-Cl,2-CH_3	B	125–127	45[b]	$C_{15}H_{19}ClN_4$	61.95	6.59	19.27		62.15	6.52	19.45	
CH_3	NH	5-Cl	A	63–64	45[b]	$C_{14}H_{17}ClN_4$	60.75	6.19	20.24	12.81	60.87	6.28	19.96	12.96
CH_3	NH	6-CH_3	A	116–117.5	50[b]	$C_{15}H_{20}N_4$	70.28	7.86	21.86		70.13	7.62	21.65	
CH_3	NH	6-Br	A	122–126	40[b]	$C_{14}H_{17}BrN_4$	52.32	5.33	17.44	24.88**	52.23	5.36	17.25	24.99**
CH_3	NH	7-Cl	A	112–115	32[a,b]	$C_{14}H_{17}ClN_4$	60.75	6.19	20.24	12.81	60.84	6.17	20.30	12.71
CH_3***	NH	2-Cl·$2H_2O$	A	91–96 dec.	64[f,e]	$C_{14}H_{17}ClN_4·2H_2O$	53.75	6.77	17.91	11.34	53.94	6.78	18.09	11.30
C_2H_5****	NH	2-Cl·$2H_2O$	A	93–97 dec.	78[f,e]	$C_{15}H_{19}ClN_4·2H_2O$	55.12	7.09	17.14	10.85	55.33	6.78	17.30	10.76
i-C_3H_7	NH	2-Cl	A	122–123 dec.	67[b,g]	$C_{16}H_{21}ClN_4$			18.38	11.63			18.27	11.42
$C_6H_5CH_2CH_2$	NH	2-Cl	A	129–131	44[b,g]	$C_{21}H_{23}ClN_3$	68.74	6.32	15.27	9.66	69.04	6.24	15.16	9.47
CH_3	NH	2-SH	B	223–225 dec.	71[k,h,d]	$C_{14}H_{18}N_4S$	61.29	6.61	20.43	11.67†	61.51	6.78	20.19	11.40†
CH_3	CH_3N	6-Br·2HCl	A	251–252.5 dec.	57[h,g]	$C_{15}H_{19}BrN_4·2HCl$	44.13	5.19	13.73		43.77	5.10	13.67	
CH_3	O	H·HCl	C	192–194 dec.	35[a,h,i]	$C_{14}H_{17}N_3O·HCl$	60.10	6.48		12.67	60.08	6.46		12.52
i-C_3H_7	O	H·HCl	C	183–183.5 dec.	60[j,e]	$C_{16}H_{21}N_3O·HCl$	62.43	7.21	13.64	11.52	62.43	7.48	13.65	11.42
$C_6H_5CH_2CH_2$	O	H·HCl	C	171–172 dec.	44[k,e]	$C_{21}H_{23}N_3O·HCl$			11.36	9.59			11.24	9.45

(1) Yields are of analytically pure material, recrystallized from: [a] butanone; [b] acetonitrile; [c] cyclohexane; [d] isopropyl acetate; [e] ethyl acetate; [f] aqueous acetonitrile; [g] isopropyl ether; [h] methanol; [i] isopropyl alcohol–butanone; [j] ethanol; [k] isopropyl alcohol. * Boiling point. ** Bromine. *** Calcd. $2H_2O$: 11.52. Found: Karl Fischer H_2O, 12.58. **** Calcd. $2H_2O$: 11.03. Found: Karl Fischer H_2O, 11.17. † Sulfur.

methyl-3-pyrrolidinylmethylamino)quinazoline, m.p. 109–110.5°, undepressed on admixture with authentic material, m.p. 110.5–111.5°. The infrared spectra of the reduction product and authentic material were identical. In 0.1 N sodium hydroxide the ultraviolet spectrum exhibited maxima at 324, 314, 302, 289, 238, and 224 mμ (ε = 9,080, 12,100, 9,680, 10,820, 13,000, and 12,000) and in 0.1 *N* hydrochloric acid at 328, 314, 305 (shoulder), 243 and 220 mμ (ε = 17,150, 18,650, 12,100, 13,760, and 17,400). In ethanol, the 2-chloroprecursor exhibited maxima at 332, 318, 306, 289 and 238 mμ (ε = 8,260, 10,630, 8,260, 10,250 and 14,660) and in 0.1 *N* ethanolic hydrogen chloride at 332, 318, 306 (shoulder), 288 and 226 mμ (ε = 13,250, 15,020, 10,320, 6,900 and 23,850).

Chlorination of 2,4-quinazolinedione with phosphorus oxychloride and triethylamine. 4-Chloro-2-diethylaminoquinazoline. A mixture of 10.0 g. (0.062 mole) of 2,4-quinazolinedione, 140 ml. of phosphorus oxychloride, and 30 ml. of anhydrous triethylamine was refluxed for 75 min. The residue left after removal of phosphorus oxychloride by vacuum distillation was extracted three times with 120-ml. portions of hot *n*-heptane containing 5% triethylamine. The extracts were washed with water, 10% sodium hydroxide, and twice with water. The heptane was then removed *in vacuo* to leave 9.5 g. of an orange oil which was distilled to give 7.0 g. of yellow distillate, (48.5%) b.p. 118–120°/5 microns, $n^{24}D$ 1.6186. The ultraviolet spectrum in ethanol showed strong absorption between 230–290 mμ, the strongest peak being at 249 mμ (ε = 30,100). Beyond 350 mμ was a broad peak at 387 mμ (ε = 3,210). The oil was unstable, darkening slowly in a sealed ampoule and forming a white solid in the atmosphere.

Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.14; H, 5.99; Cl, 15.04; N, 17.83. Found: C, 61.13; H, 6.00; Cl, 15.24; N, 17.82.

2-Chloro-4-diethylaminoquinazoline. A slurry of 0.6 g. of 2,4-dichloroquinazoline in 15 ml. of ethanol was quickly brought into solution by the addition of 3 ml. of freshly distilled diethylamine. The solution was warmed on a steam bath briefly, poured into 50 ml. of water, and the resultant crystals were collected, m.p. 76.5–77°. After two recrystallizations of petroleum ether the white needles melted at 76.5–77.5°. In ethanol the ultraviolet spectrum exhibited maxima at 343, 328, 316, 296 and 232 mμ (ε = 8,930, 11,050 8,500, and 19,050) and in 0.1 *N* hydrochloric acid at 337, 323, 312–319 (shoulder), and 232 mμ (ε = 12,290, 14,590, 10,380, and 15,750).

Anal. Calcd. for $C_{12}H_{14}ClN_3$: Cl, 15.04; N, 17.83. Found Cl, 15.40; N, 17.93.

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[CONTRIBUTION FROM MERCK SHARP & DOHME RESEARCH LABORATORIES]

Some 21-Carbamates of Hydrocortisone and Related Compounds

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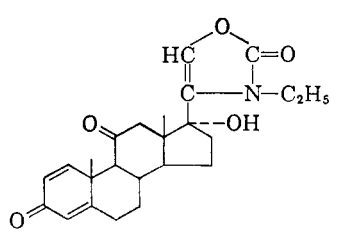
A series of 21-carbamate esters of hydrocortisone and some of its relatives was prepared and tested for biological activity. Most of these esters were quite active in the local granuloma inhibition assay but were less active in systemic tests.

Because of the stability of carbamate esters to hydrolysis, some 21-carbamates of corticosteroids were prepared and examined for biological activity. Preparation of the *N*-alkyl carbamates was accomplished in straightforward fashion using either an isocyanate in dry refluxing hydrocarbon solvents or a carbamyl chloride in pyridine. Similarly no difficulties were experienced in obtaining good yields of the corresponding *N*-arylurethans. However separation from the arylureas obtained as by-products was difficult and could best be done by chromatography. Fractional crystallization failed to separate the by-product ureas apparently because of co-precipitation or complex formation.

Reaction of ethyl isocyanate (in dimethoxyethane) with prednisone gave what is apparently the oxazolidone (I). The structure is assigned on the basis of physical data (I is very high melting and quite insoluble even by comparison with the sparingly soluble carbamates), elemental analysis, infrared spectra (the N—H bending at 6.5 μ is missing in I), and a negative blue tetrazolium test.



I

In accord with the known decreased reactivity of isothiocyanates the steroid alcohols were recovered unchanged after treatment with phenyl isothiocyanate in boiling toluene. Allyl isothiocyanate under similar conditions likewise gave no thiocarbamate ester of hydrocortisone.

For comparison in the biological tests, the 21-ethyl carbonate ester of hydrocortisone was synthesized using ethyl chlorocarbonte in pyridine. Similarly the 21-hippurate was obtained from 2-phenyloxazolone and hydrocortisone.

Biological activity. The carbamate esters were highly active in the local granuloma inhibition assay.[1] They were poorly absorbed after subcutaneous injection and little systemic activity was noted with this route of administration. However even with a water soluble carbamate (VII) local

(1) C. A. Winter, C. G. Porter, *J. Am. Pharm. Assoc.*, **46**, 515–519 (1957).