Cyclized Substituted Thioureas I

Preparation of Some 3-Substituted 1,2,3,4-Tetrahydroquinazoline-2-thiones and Their Intermediates

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Some 3-substituted 1,2,3,4-tetrahydroquinazoline-2-thiones were prepared by first synthesizing the N-substituted-*o*-nitrobenzylamines, then the corresponding N-substituted-*o*-aminobenzylamines. The tetrahydroquinazoline-2-thiones were then obtained by refluxing the diamine with carbon disulfide. It is suggested that antithyroidal, antitubercular, and/or antifungal properties might be present in these condensed ring thiones.

THE THERAPEUTICALLY active antithyroid drugs marketed today contain the thiourea moiety. It is demonstrable that to obtain appreciable activity at least one of the nitrogen atoms of the moiety has an attached hydrogen atom. Recent work leads to the belief that toxicity is reduced when the thiourea group is incorporated into certain ring systems and one of the nitrogens is substituted. The purpose of this investigation was to prepare some active, nontoxic heterocycles which incorporate the active thiourea moiety.

No quinazoline pharmaceuticals are available at this time, however, some alkaloids which contain this nucleus are known. Peganine; the carboline alkaloids rutecarpine and evodiamine; febrifugine, which has a high antimalarial activity and toxicity; and dichroine, a febrifuge from the roots of *dichroa febrifuga* Lour, are a few. The latter has been used in China for centuries under the name of Ch'ang Shan (1). 2-Amino-5,6,7,8-tetrahydroquinazoline has given slight protection to mice against β-hemolytic streptococcus (2). The 2- and 4-chloroquinazolines and derivatives condensed with a wide variety of aromatic amino, hydroxyl, and sulfhydryl compounds containing chromophoric groups have been used in the dye industry (3). U. S. patent 2,400,649 (4) describes the preparation of N-[4-(4-quinazoline)-aminobenzoyl]-glutamic acid which is a relative of folic acid and is claimed to be useful as a vitamin and chemotherapeutic agent. The partial synthesis of the quinazoline analog of papaverine has been reported by Marr and Bogert (5). The majority of the work involving the quinazoline nucleus has been in the field of antimalarials. In 1919 Wilkendorf (6) synthesized some quinazoline analogs of 8-aminoquinoline (pamaquine) and in 1924 Bogert, *et al.* (7), made an analog of cinchophen, 2-phenyl-quinazoline-4-carboxylic acid. Rodionov, *et. al.* (8), synthesized a group of 3-(dialkylaminoalkyl)-4-quinazolones. Christensen, *et al.* (9), prepared 2,4-dimethyl-7-(1-hydroxy-3-amino-4-hydroxy- and 2,4-diamino-5,6,7,8-tetrahydroquinazolines). Price, *et al.* (10), made quinazoline analogs of 4-aminoquinoline (chloroquine). In 1946 Bunnett, *et al.* (11), made antimalarials having the general formula 2-(dialkylaminoalkylamino)-4-quinazolone. A number of N′-quinazolylsulfanilamides were synthesized by MacBeth and Rodda (12) but they were too insoluble to be active as antimalarial agents. The above references are evidence that, although the quinazolines are not common in human medication, they have been of interest for many years.

The 3-substituted 1,2,3,4-tetrahydroquinazoline-2-thiones were synthesized by first preparing α-bromo-*o*-nitrotoluene by the method of Kornblum (13). A number of N-substituted *o*-nitrobenzylamines were formed and characterized by their hydrochloride salts, as shown in Table I. The *o*-nitro groups were reduced to *o*-amino groups and the resulting compounds were characterized as dihydrochlorides, as shown in Table II. These diamines were refluxed with carbon disulfide causing ring closure and the formation of the corresponding 3-substituted tetrahydroquinazoline-2-thiones. See Table III.

EXPERIMENTAL

N-Ethyl-*o*-nitrobenzylamine Hydrochloride.—Twenty milliliters of 70% aqueous ethylamine (0.3 mole) and 0.03 mole of α-bromo-*o*-nitrotoluene were dissolved in 50 ml. of 95% ethanol and shaken in a sealed flask for one hour. The mixture then was set aside at room temperature for eight days, after which it was filtered. The clear filtrate was evaporated on a steam bath until a semisolid (oil) formed. This semisolid was treated with 200 ml. of dilute hydrochloric acid which produced a clear solution. The water was removed on the steam

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TABLE I.—HYDROCHLORIDE SALTS OF N-ALKYL- AND N-ARYL-*o*-NITROBENZYLAMINE

R	C, %		H, %		N, %		Yield, %	M. P., or Decompn., Pt., °C.
	Calcd.	Found	Calcd.	Found	Calcd.	Found		
Methyl	47.6	48.1	5.45	6.00	13.9	14.1	22	185–187[b]
Ethyl	50.0	50.7	6.02	6.12	13.0	13.7	28	223–225[b]
n-Propyl	52.1	53.1	6.54	6.84	12.2	12.8	18	138[b]
Isopropyl	52.1	51.9	6.54	6.57	12.2	12.0	47	255[b]
Allyl	52.6	51.7	5.70	5.44	12.3	11.7	17	168–170[b]
Isobutyl	54.1	54.4	6.97	7.21	11.5	11.2	52	189[b]
t-Butyl	54.1	53.9	6.97	6.89	11.5	11.5	63	173–174[b]
Phenyl	59.0	59.5	4.91	4.93	10.6	10.9	73	182–184[b, c]
Benzyl[a]	69.5	69.5	5.30	5.47	11.6	11.1	87	225
Cyclohexyl	60.5	59.8	7.41	7.55	10.9	10.7	45	250–252[b]

[a] Free base. [b] Decomposed. [c] Literature 140–145°.

TABLE II.—DIHYDROCHLORIDE SALTS OF *o*-AMINO-N-ALKYL- AND N-ARYLBENZYLAMINE

R	C, %		H, %		N, %		Yield, %	M. P., or Decompn. Pt., °C.
	Calcd.	Found	Calcd.	Found	Calcd.	Found		
Hydrogen	42.9	42.7	6.15	6.31	14.4	...	97	167[b]
Methyl	45.8	44.8	6.70	6.51	13.4	...	96	217[b]
Ethyl	48.4	48.8	7.16	7.00	12.5	12.2	78	210[b]
n-Propyl	50.8	50.5	7.63	8.15	11.8	11.7	51	275[b]
Isopropyl	50.8	50.7	7.63	7.99	11.8	11.6	63	191[b]
Allyl	51.0	50.2	6.84	6.79	11.9	11.7	58	163[b]
Benzyl	59.0	59.3	6.32	6.66	9.8	...	87	210[b]
Phenyl[a]	78.7	77.9	7.06	7.42	14.2	...	90	86
Cyclohexyl	56.3	55.9	7.94	7.87	10.1	9.95	54	234[b]

[a] Free base. [b] Decomposed.

TABLE III.—3-ARYL- AND 3-ALKYL-1,2,3,4-TETRAHYDROQUINAZOLINE-2-THIONES

R	C, %		H, %		N, %		Yield, %	M. P., or Decompn., Pt., °C.
	Calcd.	Found	Calcd.	Found	Calcd.	Found		
Hydrogen	58.2	57.7	4.87	4.22	17.0	...	43	212[a]
Methyl	60.5	58.9	5.63	5.61	15.7	...	48	181[a]
Ethyl	62.5	62.1	6.25	5.95	14.6	14.7	31	185[a]
Isopropyl	64.0	63.3	6.80	6.71	13.6	13.3	24	110
Phenyl	70.0	69.2	5.00	5.11	11.7	...	87	212[a]
Cyclohexyl	68.2	68.4	7.32	7.21	11.4	11.5	39	147[a]
Benzyl	71.5	70.9	5.56	5.81	11.1	11.7	43	112

[a] Decomposed.

bath leaving an amber, crystalline mixture. Dilute sodium hydroxide, 300 ml., was added to liberate the free oily base. The oil was separated from the aqueous layer and picked up in ether. The ether solution was dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated to dryness and the residue dissolved in 200 ml. of dilute hydrochloric acid. Upon evaporation to dryness, pale yellow crystals of the hydrochloride of N-ethyl-*o*-nitrobenzylamine were obtained. Washing with small quantities of ether gave small, white crystals which melted at 223–225°.

N-*n*-Propyl-*o*-nitrobenzylamine Hydrochloride.—Two-tenths mole of *n*-propylamine and 0.03 mole of α-bromo-*o*-nitrotoluene were dissolved in 70 ml. of 95% ethanol. The procedure used for preparing N-ethyl-*o*-nitrobenzylamine hydrochloride was followed here. White crystals, melting at 138° were obtained.

N-Isopropyl-*o*-nitrobenzylamine Hydrochloride.—The same procedure as used in preparing the ethyl analog was followed starting with 0.25 mole of isopropylamine and 0.03 mole of the α-bromo-*o*-nitrotoluene dissolved in 110 ml. of 95% ethanol. However, the impurities were best eliminated by washing first with absolute ether, then with absolute acetone, and finally with absolute alcohol. Recrystallization was not used because of the small quantities dealt with here. The substance had a white, cubical, crystalline appearance. It sublimed at 200° and melted at 255°.

N-Allyl-*o*-nitrobenzylamine Hydrochloride.—One-fourth mole of allylamine and 0.03 mole of α-bromo-*o*-nitrotoluene in 70 ml. of 95% ethanol were shaken for six hours. The procedure then followed that used for the ethyl derivative. A small yield of white crystals, which decomposed at 168–170° was obtained.

N-Isobutyl-*o*-nitrobenzylamine Hydrochloride.—One-fourth mole of isobutylamine, which boils at 68–69°, was refluxed with 0.03 mole of α-bromo-*o*-nitrotoluene for twelve hours in ethanol to complete the reaction. Cooling the reaction mixture resulted in a dark solution. The ethanol was distilled off leaving a very thick, viscous oily amine. The amine was picked up in absolute ether, dried over anhydrous sodium sulfate and filtered. The ethereal filtrate was evaporated to obtain the amine. The amine was then treated with 10% hydrochloric acid and the resulting solution was evaporated to dryness. The crystals melted at 189°.

N-*t*-Butyl-*o*-nitrobenzylamine Hydrochloride.—A solution consisting of 0.25 mole of tertiary-butylamine, 0.03 mole α-bromo-*o*-nitrotoluene, and 80 ml. of ethanol was refluxed for two hours. The procedure followed for the isolation of the isobutyl derivative was used. The large, white, rectangular crystals decomposed at 173–174°.

N-Benzyl-*o*-nitrobenzylamine.—One-fourth mole of benzylamine and 0.03 mole of α-bromo-*o*-nitrotoluene were dissolved in 50 ml. of 95% ethanol and refluxed twelve hours. Using the same procedure as that for preparing the isobutyl derivative, white platelets melting at 225° were obtained.

N-Cyclohexyl-*o*-nitrobenzylamine Hydrochloride.—One-fourth mole of α-bromo-*o*-nitrotoluene was shaken with 0.2 mole of cyclohexylamine until the exothermic reaction seemed to be complete. It was then placed on a steam bath for one-half hour to insure complete reaction. The mixture was then extracted with five 100-ml. portions of ether. The ether extracts were dried over sodium sulfate and filtered. The filtrate was distilled under vacuum to remove the ether and any remaining unreacted primary amine. The oil remaining was treated with 10% hydrochloric acid to form a salt. The salt was taken up in hot 95% ethanol and precipitated as light yellow crystals upon cooling. The crystals were reprecipitated from ethanol and washed with absolute ether. The crystals decomposed at 250–252°.

N-Phenyl-*o*-nitrobenzylamine Hydrochloride.—Three-hundredths of a mole of α-bromo-*o*-nitrotoluene and 0.2 mole of aniline were heated together on a steam bath with constant agitation for one-half hour. The reaction mixture solidified upon cooling. The solid was treated with 36% acetic acid which dissolved all but the heavy, dark brown oily secondary amine. The two liquids were separated and the oily amine was treated with 10% hydrochloric acid, after which, the solution was evaporated to dryness on a steam bath. The impure crystalline mass was recrystallized from boiling gracial acetic acid. The resulting crystals were then washed with absolute ether giving long, fine, white, needle-like crystals which decomposed at 182–184°. The salt was previously reported to decompose at 140–145° (14). Lellman (15) prepared the free amine by another method and found the melting point to be 44°.

N-Phenyl-*o*-aminobenzylamine.—This amine was prepared by dissolving 0.025 mole of N-phenyl-*o*-nitrobenzylamine hydrochloride in glacial acetic acid on a magnetic stirrer. Small portions of zinc dust were added keeping the temperature always below 30° (preferably below 25°), until 13.2 Gm. of zinc was completely dissolved. The solution turned from yellow to transparent when all of the zinc was dissolved. Water was added in small portions from time to time in order to keep zinc acetate from precipitating. After the reduction had been carried out, concentrated sodium hydroxide solution was added until the solution was nearly neutral. At this point, colorless crystals of the base precipitated out. They were recrystallized from hot ethanol. The resulting crystals melted at 81°.

***o*-Aminoalkyl- and Arylbenzylamine Dihydrochlorides.**—Five grams of the N-alkyl- or N-aryl-*o*-nitrobenzylamine hydrochloride was added in small portions to mixture of 10 Gm. of tin and 25 Gm. concentrated hydrochloric acid. The mixture was heated for one hour on a water bath to insure complete reduction. It was then diluted with 1 L. of water and filtered. The filtrate was made alkaline with 40% sodium hydroxide solution which produced a precipitate of tin hydroxide. The precipitate was filtered out and the filtrate extracted with several small portions of ether. The ether extract was dried over anhydrous sodium sulfate and filtered. The ether was evaporated, leaving the impure amine. The amine was treated with 10% hydrochloric acid solution and evaporated to dryness. The hydrochloride salt was then recrystallized from alcohol-ether and washed with absolute acetone.

3-Aryl- and 3-Alkyl-1,2,3,4-tetrahydroquinazoline-2-thiones.—Two grams of the free base *o*-amino-N-alkyl- or *o*-amino-N-arylbenzylamine, liberated from the hydrochloride by neutralization with 20% sodium hydroxide solution, was dissolved along with 20 Gm. of carbon disulfide in 50 ml. of absolute ethanol and refluxed for several hours on a water bath. The excess carbon disulfide and ethanol were then removed by distillation and the impure quinazolinethione was picked up in boiling absolute ethanol. Upon cooling, pure 3-aryl- and 3-alkyl-1,2,3,4-tetrahydroquinazoline-2-thiones precipitated.

SUMMARY

1. The following hydrochloride salts of N-aryl- and N-alkyl-*o*-nitrobenzylamine were prepared: methyl,[1] ethyl, *n*-propyl, isopropyl, allyl, isobutyl, *t*-butyl, phenyl,[1] and cyclohexyl. The free base was prepared for benzyl derivative.

2. The following dihydrochloride salts of *o*-amino-N-alkyl and *o*-amino-N-arylbenzylamine were prepared: methyl,[1] hydrogen,[1] ethyl, *n*-propyl, isopropyl, allyl, benzyl,[1] and cyclohexyl. The free base *o*-amino-N-phenylbenzylamine was prepared.

3. The following 3-aryl- and 3-alkyl-1,2,3,4-tetrahydroquinazoline-2-thiones were prepared: hydrogen,[1] methyl,[1] ethyl, isopropyl, phenyl,[1] cyclohexyl, and benzyl.

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[1] Previously reported.