Dibutyl 2-methyl-5-pyrimidylphosphonate. A warm solution of 6.9 g. of sodium in 115 ml. of absolute ethanol was prepared and 72 ml. of this was added, with stirring, to 18 g. of acetamidine hydrochloride in 20 ml. of absolute ethanol, after which a solution of 20.6 g. of mucobromic acid in 35 ml. of absolute ethanol was added gradually, the mixture being kept at 50–55°, which temperature range is the optimum for this reaction. When the reaction within the mixture began to subside, the remaining sodium ethoxide solution was added over 2 min. and the dark brown solution was stirred for 24 hr. at room temperature. The solids were filtered off and the filtrate, after having been evaporated *in vacuo*, was treated with 50 ml. of 2*N* hydrochloric acid and shaken vigorously, yielding 17.4 g. (57.5%) of 2-methyl-5-bromo-4-pyrimidinecarboxylic acid, which decomposed at 170–172°.[12] This acid was decarboxylated thermally and yielded 86.5% of 2-methyl-5-bromouracil, which melted at 83–84°.[12] A reaction of 6.37 g. of this substance in refluxing toluene with dibutyl sodium phosphite, prepared from 0.85 g. of sodium and 7.15 g. of dibutyl hydrogen phosphite, gave a considerable precipitate of sodium bromide after the mixture had been refluxed for 6 hr. The mixture was filtered and the filtrate evaporated *in vacuo*. However, the distillation of residual material yielded only some dibutyl butylphosphonate and tar. However, a reaction of 9.25 g. of 2-methyl-5-bromopyrimidine with butyllithium, prepared from 1.11 g. of lithium and 8.7 g. of butyl bromide in ethyl ether at −40°, followed by the addition, after 7 min., of 13.7 g. of dibutyl phosphorochloridate over 5 min., gave a moderate precipitate in the reaction mixture. The whole was allowed to warm up to −20° over 5 min. and to 0° over 10 min. After the temperature had risen to 20°, a brownish precipitate began to form and the mixture was stirred for 16 hr., after which the reaction appeared to be complete. The filtered solution was washed with dilute hydrochloric acid and sodium carbonate, after which it was dried and distilled, yielding three fractions: (1) b.p. of 100–130° at 0.05 mm., n_D^{25} 1.4347 (1.54 g.), (2) b.p. of 130–134° at 0.05 mm., n_D^{25} 1.4552 (1.2 g.), and (3) b.p. of 134° at 0.05 mm., n_D^{25} 1.4538 (0.9 g.). Fraction (1) was almost nitrogen-free. The other fractions were combined and chilled for several hours, yielding a small amount of a solid, which melted at 134°; this solid was devoid of phosphorus. The filtrate from this solid was adsorbed on a column of aluminum oxide and was eluted with 1:1 benzene–petroleum ether mixture. The first eluate was free of nitrogen, but the following fractions yielded a very small amount of a light yellow liquid, which boiled at 134° at 0.05 mm.; n_D^{25} 1.4540. This appeared to be the desired dibutyl 2-methyl-5-pyrimidylphosphonate, which showed the expected pyrimidine absorption in the ultraviolet. The product was not pure, but the very low yield of it prevented a further purification.

Anal. Calcd.: P, 10.51; N, 9.89. Found: P, 10.51; N, 9.48.

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AUBURN, ALA.

(12) Z. Budesinsky, *Collection of Czechoslov. Chem. Commun.*, 14, 223 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

2-Amino-3(2H)isoquinolone, 2,3-Benzodiazepin-4(5H)one, and Related Compounds

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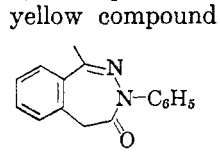
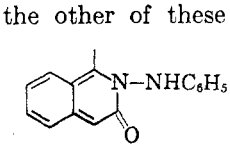
Two isomeric dehydration products of *o*-acetylphenylacetic acid phenylhydrazone are characterized by their hydrolysis products and spectra as 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)-one and 1-methyl-2-(phenylamino)-3(2H)isoquinolone. Additional benzodiazepinones and *N*-aminoisoquinolones obtained from the *o*-acetylphenylacetic acid semicarbazone and from the phenylhydrazone and semicarbazone of *o*-formylphenylacetic acid are described. The structure assignment is supported by the easy acid hydrolysis of 1-methyl-2-amino-3(2H)isoquinolone to *o*-acetylphenylacetic acid hydrazone hydrochloride. Methyl *o*-acetylphenylacetate, *o*-acetylphenylacetic acid methylphenylhydrazone, *o*-acetylphenylacetic acid azine, *o*-acetylphenyldimethylacetic acid, and *o*-acetylphenyldimethylacetic acid phenylhydrazone phenylhydrazide have been synthesized.

The elimination of one molecule of water from *o*-acetylphenylacetic acid phenylhydrazone[1] yields two isomeric products, one colorless, the other bright yellow. Pyrolytic dehydration at 190° produces principally the colorless product, while warming in a 1*M* solution of sulfuric acid in acetic acid gives the yellow isomer as the main product.

Upon treatment with sodium hydroxide in boiling ethylene glycol and subsequent acidification, the colorless isomer reverts to *o*-acetylphenylacetic acid phenylhydrazone. With hot concentrated hydrochloric acid, the yellow isomer is converted to *o*-acetylphenylacetic acid. These observations limit the acceptable structures for the colorless compound to I (1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)one) and II (1-methyl-2-(phenylamino)-3(2H)isoquinolone). It is most probable that the yellow compound is the other of these two



I



II

structures. As no procedure has been found which will remove the nitrogen atoms one at a time from these compounds, and as the absorption of the

(1) J. O. Halford and B. Weissmann, *J. Org. Chem.* 18, 30 (1953).

yellow compound in the visible and ultraviolet closely resembles that of other known *ortho* quinonoid compounds, the benzodiazepinone structure (I) can be assigned to the colorless compound and the isoquinolone structure (II) to the yellow compound. These assignments are supported by the appearance in the infrared spectrum (Nujol mulls) of the yellow compound of an NH frequency and an ethylenic CH frequency, neither of which is shown by the colorless compound. In addition, the carbonyl frequency for both compounds is low, in the amide region, and in the yellow compound is associated with a series of satellites which suggest conjugation with a polyene structure.

Further support for these assignments is obtained from the rapid acid hydrolysis of 1-methyl-2-amino-3(2H)isoquinolone, described below, to *o*-acetylphenylacetic acid hydrazone hydrochloride. This hydrazone salt is also obtained in low yield by the action of concentrated hydrochloric acid on *o*-acetylphenylacetic acid hydrazide phenylhydrazone, possibly through the intermediate formation of an aminoisoquinolone.

Upon addition of colorless 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)one to 1*M* sulfuric acid in acetic acid, the solution quickly exhibits the bright yellow color of the isomeric aminoisoquinolone derivative. The isomerization, however, is slow, giving optimum yields only after about eight hours at the steam bath temperature. In contrast, the original dehydration of the phenylhydrazone in the same medium was virtually complete in a few minutes. It is clear that the benzodiazepinone structure is not a precursor of the isoquinolone in its formation from the phenylhydrazone. The isomerization is probably a transannular reaction held to lower velocity by the geometrical restriction imposed by the seven membered ring.

Extrusion of a nitrogen atom from the ring in the conversion of I to II in an acid medium is consistent with known reactions in the phthalazine series and with the conversion by Whitmore and Cooney[2] of their homophthalyl cyclic hydrazide in acetic acid to a yellow *N*-aminohomophthalimide.

o-Acetylphenyldimethylacetic acid has been synthesized as a compound which might be converted to a benzodiazepinone derivative but could not form the corresponding aminoisoquinolone without an unlikely internal shift. The attempt to produce a phenylhydrazone from this keto acid resulted in the phenylhydrazone phenylhydrazide which was not successfully cyclized to the projected benzodiazepinone. A similar attempt to produce an aminoisoquinolone without concomitant benzodiazepinone formation, from *o*-acetylphenylacetic acid methylphenylhydrazone, was also unsuccessful.

o-Formylphenylacetic acid phenylhydrazone proved to be more heat resistant than the acetyl derivative. Pyrolysis of this compound did not lead to any pure products. Dehydration in the sulfuric-acetic acid solution, however, produced a low yield of yellow crystals which, from the analysis and spectra, were evidently 2-(phenylamino)-3-(2H)isoquinolone. The expected isomeric benzodiazepinone was not obtained.

o-Acetylphenylacetic acid reacted with hydrazine to produce the azine rather than the hydrazone. Pyrolysis of the azine gave a low yield of colorless 1-methyl-3H-2,3-benzodiazepin-4(5H)-one, evidently by eliminating *o*-acetylphenylacetic acid. This benzodiazepinone derivative was obtained, along with the isomeric 1-methyl-2-amino-3(2H)isoquinolone, by the pyrolytic elimination of carbamic acid from *o*-acetylphenylacetic acid semicarbazone. The similar pyrolysis of *o*-formylphenylacetic acid semicarbazone produced the isomers 3H-2,3-benzodiazepin-4(5H)one and 2-amino-3(2H)isoquinolone.

Although the acylphenylacetic acid phenylhydrazones could be readily dehydrated in the acid medium to the corresponding (phenylamino)-isoquinolones, a parallel synthesis of the unsubstituted aminoisoquinolones could not be effected because of their rapid hydrolysis in aqueous acid to the simple hydrazone salts. In contrast, the (phenylamino)isoquinolones are stable in dilute acid.

Dilute aqueous hydrochloric acid rapidly attacks 1-methyl-2-amino-3(2H)isoquinolone to add one mole each of water and hydrochloric acid. The neutral equivalent of the product identifies it as the hydrazone hydrochloride.

The two 2,3-benzodiazepin-4(5H)ones obtained by semicarbazone pyrolysis are taken to be 3H structures because of the very close similarity of their infrared and ultraviolet spectra to the spectra of 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)one which must be a 3H compound. The possibility of the 1H structure in the absence of the phenyl group has not, however, been excluded.

EXPERIMENTAL

Dehydration of o-acetylphenylacetic acid phenylhydrazone. (a) A 250-ml. flask containing 8.0 g. of the phenylhydrazone was evacuated to 20 mm. The bottom of the flask, after previous warming, was immersed for 35 min. in a metal bath at 190°. An initial brisk gas evolution slackened during the reaction period. Vacuum sublimation (160–190°, 0.2 mm. 2 hr.) gave 4.8 g. of yellow sublimate which was recrystallized from ethanol to yield 3.0 g. of greenish yellow plates, m.p. 156–157°. When passed through an alumina column, 19 × 100 mm., with chloroform as solvent and developer, the color was concentrated in the later fractions. Recrystallization of material from the initial colorless fraction gave plates, m.p. 158–158.5°, of 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)one which was readily soluble in chloroform and hot ethanol, moderately soluble in benzene and hot acetic acid, and insoluble in water, dilute hydrochloric acid, or dilute sodium hydroxide.

Anal. Calcd. for $C_{16}H_{14}ON_2$: C, 76.79; H, 5.64; N, 11.20; mol. wt. 250.3. Found: C, 76.70; H, 5.53; N, 11.52; mol. wt. (Menzies, chloroform), 264.

(2) W. F. Whitmore and R. C. Cooney, *J. Am. Chem. Soc.* 66, 1237 (1944).

Subjection of the filtrates, etc., to repeated chromatography brought the yield of the purified benzodiazepinone derivative to 3.2 g. (43%). Later fractions of the chromatograms gave 0.2 g. of a bright yellow isomer, 1-methyl-2-(phenylamino)-3(2H)isoquinolone, further described below.

A third product, greenish yellow, 0.1 g., m.p. 212° dec., was isolated. This solid, recrystallized from ethanol, was insoluble in chloroform, water or sodium bicarbonate solution, but dissolved readily in dilute hydrochloric acid or dilute sodium hydroxide and gave a lavender color with aqueous ferric chloride.

(b) One gram of the phenylhydrazone, dissolved in 10 ml. of a 1*M* solution of sulfuric acid in glacial acetic acid, was warmed for 30 min. on the steam bath. The cooled solution was diluted with water and neutralized with aqueous sodium hydroxide to precipitate 0.84 g. of yellow solid, m.p. 195–197° dec. Recrystallization from benzene gave 0.68 g. of bright yellow crystals of 1-methyl-2-(phenylamino)-3(2H)isoquinolone, m.p. 213–214° dec. Further recrystallization brought the melting point to 215.5–216° dec. It was insoluble in water, dilute acid, or dilute alkali and soluble in chloroform or hot benzene; it gave a deep orange-brown color with alcoholic ferric chloric which faded upon addition of water.

Anal. Calcd. for $C_{16}H_{14}ON_2$: C, 76.79; H, 5.64; N, 11.20; mol. wt. 250.3. Found: C, 77.25; H, 5.64; N, 11.20; mol. wt. 226.

Chromatography of the filtrates from the above reaction, followed by recrystallization, gave 0.15 g. of 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)one, m.p. 158–158.5°.

When the original phenylhydrazone was heated in the acid medium for only 5 min., the yield of the aminoisoquinolone was only slightly less. At lower sulfuric acid concentrations, the reaction took the same course at a slower rate.

Dehydration of o-formylphenylacetic acid phenylhydrazone. (a) Gas evolution from this phenylhydrazone was slower and could be completed only at 220°. No pure compounds were isolated from the resulting mixture.

(b) A solution of 0.39 g. of the phenylhydrazone in 4 ml. of 1*M* sulfuric acid in acetic acid was warmed for 5 min. on the steam bath, then cooled, diluted with water, and neutralized with sodium carbonate. The resulting yellow oily solid, when extracted with 50 ml. of warm chloroform in portions, left a residue of 0.09 g. of amorphous material. Chromatography gave small amounts of colorless oil followed by a larger quantity of yellow solid. Recrystallization from chloroform gave 0.07 g. of bright yellow flakes, which, after further recrystallization from acetone, melted at 197–198° dec. Spectrographic data indicated that the compound was 2-(phenylamino)-3(2H)isoquinolone.

Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.63; H, 5.27; N, 11.84.

Isomerization of 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)-one to 1-methyl-2-(phenylamino)-3(2H)isoquinolone. A solution of the benzodiazepinone derivative in 1*M* sulfuric acid in glacial acetic acid was warmed on the steam bath for 8 hr. Dilution with water and neutralization precipitated yellow solid, m.p. 208–211° dec. after two recrystallizations from benzene. Mixture melting point with a directly prepared sample of the isomeric isoquinolone derivative, 210–212°.

Hydrolysis of 1-methyl-3-phenyl-2,3-benzodiazepin-4(5H)-one. This compound, 0.0036 mole, with 0.0125 mole of sodium hydroxide, was heated to boiling in 18 ml. of ethylene glycol. White solid, precipitated by adding water and acidifying with acetic acid, was washed with glacial acetic acid, then dilute acetic acid (0.18 g.) m.p., 174–176°. Mixture m.p. with *o*-acetylphenylacetic acid phenylhydrazone, 174–176°.

Pyrolysis of o-acetylphenylacetic acid semicarbazone. The semicarbazone, 1.50 g., in a flask attached to an air reflux condenser, was heated under nitrogen for 8 min. in an oil bath at 195°. An initially rapid gas evolution diminished and ammonium carbamate sublimed into the condenser. After cooling under nitrogen and extracting with 25 ml. of warm chloroform in portions, 15 mg. of yellow-green solid remained.

The chloroform solution was passed through the alumina column, with first chloroform and later chloroform containing a little ethanol as developer. From the later fractions a bright yellow solid, 1-methyl-2-amino-3(2H)isoquinolone, was obtained; initial yield, 0.40 g. (m.p. 182–183° dec.), later recoveries, 0.10 g., m.p. from chloroform 183–184° dec.

Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.94; H, 5.79; N, 16.08; mol. wt. 174.2. Found: C, 68.85; H, 5.82; N, 15.78; mol. wt. (Menzies, chloroform) 158.

1-Methyl-2-amino-3(2H)isoquinolone was readily soluble in chloroform, insoluble in water or aqueous alkali, reacted rapidly with dilute aqueous acid and gave a stable purple color with aqueous ferric chloride. Exposure to bright sunlight changed the compound in a few hours to a nearly colorless infusible solid. Decomposition at the melting point was slow. A sample stirred with half its weight of Adams' platinum catalyst in ethanol absorbed 1.1 molar quantity of hydrogen at 1 atm. in 30 min.; further absorption was negligible. The hydrogenation product was a nearly colorless oil.

Aqueous hydrochloric acid, 3*M*, changed 1-methyl-2-amino-3(2H)isoquinolone to a hydrate hydrochloride in a few seconds, evidently a ring opening reaction producing either the hydrazone hydrochloride or the hydrazide hydrochloride of *o*-acetylphenylacetic acid. Purification was effected by precipitation of the salt from methanol solution by adding ether; or from aqueous solution by excess hydrochloric acid m.p. 202–205° dec. The salt was hygroscopic, gave a chloride ion test, and a stable purple color with ferric chloride. From the equivalent weight it is evident that this product is *o*-acetylphenylacetic acid hydrazone hydrochloride.

Anal. Calcd. for $C_{10}H_{13}O_2N_2Cl$: C, 52.51; H, 5.73; N, 12.25; equiv. wt. 114.3. Found: C, 52.64; H, 5.88; N, 12.17; equiv. wt., 115.

Earlier fractions of the chromatogram from the pyrolysis gave nearly colorless solid which was combined with material obtained by chromatography of the filtrates from the 1-methyl-2-amino-3(2H)isoquinolone isolation. Recrystallization from benzene gave after several hours, 0.06 g. of a neutral yellow-green product, m.p. 184.5–185.5°, which was shown by mixture melting point to be different from the major product of the same melting point. The filtrate on further standing gave 0.18 g. of compact needles, 1-methyl-3H-2,3-benzodiazepin-4(5H)one, m.p. 184.5–185.5°, after further recrystallization from ethanol. This product was insoluble in water, dilute hydrochloric acid or dilute aqueous sodium hydroxide and gave no color with ferric chloride.

Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.94; H, 5.79; N, 16.08; mol. wt., 174.2. Found: C, 68.75; H, 5.80; N, 15.82; mol. wt. 194.

Pyrolysis of o-formylphenylacetic acid semicarbazone. Because of the high melting point of the semicarbazone, a solution, 0.5 g. in 2.0 g. of diphenyl ether, was heated for 3 min. at 220° and subsequently subjected to chloroform extraction and chromatography. A yellow solid, 2-amino-3(2H)isoquinolone, 0.07 g., m.p. 172–173° dec., was obtained.

Anal. Calcd. for $C_9H_8ON_2$: C, 67.48; H, 5.03. Found: C, 67.51; H, 5.27.

The compound was less sensitive to light than its 1-methyl derivative. It was insoluble in water and aqueous alkali and reacted rapidly with aqueous hydrochloric acid to give a product which, although not analyzed, was undoubtedly the *o*-formylphenylacetic acid hydrazone hydrochloride.

From the earlier chromatographic fractions, colorless 3H-2,3-benzodiazepin-4(5H)one was isolated.

Anal. Calcd. for $C_9H_8ON_2$; C, 67.48; H, 5.03; N, 17.49. Found: C, 67.66; H, 5.11; N, 17.32.

Hydrolysis of 1-methyl-2-(phenylamino)-3(2H)isoquinolone. Refluxing for 7 hr. with concd. hydrochloric acid effected a

partial hydrolysis of this isoquinolone derivative to *o*-acetylphenylacetic acid.

o-Acetylphenylacetic acid azine. The keto acid, 0.6 g., reacted with hydrazine hydrochloride, 0.4 g., with 0.8 g. of sodium acetate present, to give, after recrystallization from ethanol, 0.38 g. of *o*-acetylphenylacetic acid azine, m.p. 209–210°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.15; H, 5.68. Found: C, 67.98; H, 5.64.

When the azine was heated at 220°, gas evolution occurred, and a low yield of colorless crystals was obtained by chromatography from the viscous residue. The product was identified by mixture melting point as 1-methyl-3H-2,3-benzodiazepin-4(5H)one.

o-Acetylphenylacetic acid 1-methyl-1-phenylhydrazone. 1-Methyl-1-phenylhydrazine was prepared by nitrosating *N*-methylaniline and subsequently reducing with zinc and acetic acid.[3] *o*-Acetylphenylacetic acid and 1-methyl-1-phenylhydrazine were mixed and allowed to stand for 8 hr. The resulting viscous mixture was extracted with ether and the ether solution was extracted with 2% sodium hydroxide solution. Acidification gave a yellow solid, *o*-acetylphenylacetic acid 1-methyl-1-phenylhydrazone, which was recrystallized from aqueous ethanol, m.p. 117–118°. Attempts to produce this compound by reaction in buffered aqueous solution were not successful.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.35; H, 6.39; neut. equiv., 282. Found: C, 72.01; H, 6.37; neut. equiv., 272.

Attempts to cyclize this phenylmethylhydrazone to an aminoisoquinolone were not successful.

o-Acetylphenyldimethylacetic acid. 3,3-Dimethyl-1-indanone was prepared by the method of Koelsch and LeClaire.[4] Upon several repetitions, the required intermediate oxidation of methyl β-phenylisobutyl ketone to β-phenylisovaleric acid was not uniformly satisfactory.

3,3-Dimethyl-1-indanone was converted to 1,3,3-trimethyl-1-indanol (b.p. 104–108°/25 mm.), by reaction with methylmagnesium iodide and acidification of the resulting alkoxide. The indanol (0.089 mole) was dehydrated to 1,1,3-trimethylindene, b.p. 196–197°, 12.4 g., by refluxing for 15 hr. with 25% sulfuric acid. Recovery of the product employed steam distillation and extraction with benzene.

1,1,3-Trimethylindene (0.079 mole) was added dropwise during 1 hr. to a stirred solution, at 55°, of 24.6 g. of sodium dichromate and 68 ml. of concd. sulfuric acid in 375 ml. of water. Stirring was continued until all the dichromate had reacted (8 hr.). The product separated as an oil which was filtered, washed with water, and allowed to stand in air until solidification appeared to be complete. *o*-Acetylphenyldimethylacetic acid was obtained by precipitation with excess hydrochloric acid from a solution of the crude product in 5% aqueous sodium hydroxide; yield, 0.026 mole, m.p. 105–107°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.80, H, 6.80. Found: C, 69.56; H, 6.68.

The attempt to synthesize the phenylhydrazone of this acid by the standard procedure gave light yellow plates, m.p. 179–181°, which were apparently *o*-acetylphenyldimethylacetic acid phenylhydrazone phenylhydrazide, most probably the β-phenylhydrazide.

Anal. Calcd. for $C_{24}H_{26}N_4O$: C, 74.60; H, 6.74; N, 14.51. Found: C, 74.36; H, 6.79; N, 14.13.

Attempts to convert the phenylhydrazone phenylhydrazide to a benzodiazepinone were not successful.

Methyl o-acetylphenylacetate. *o*-Acetylphenylacetic acid was esterified by refluxing for 4 hr. a solution of 5.0 g. in 55 ml. methanol with 5 drops of concd. sulfuric acid. Removal of methanol by distillation left an oil residue which solidified under water and was recrystallized from aqueous ethanol; yield, 1.4 g., m.p. 57–59°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.70; H, 6.25. Found: C, 68.58; H, 6.33.

o-Acetylphenylacetic acid hydrazone hydrochloride. *o*-Acetylphenylacetic acid phenylhydrazone was refluxed in methanol, with a trace of sulfuric acid, for 4.5 hr. Solvent was removed by distillation and hydrazine hydrate in equivalent amount was added, dissolved in methanol. The resulting solution was refluxed for 4 hr. Excess hydrochloric acid caused separation of a white solid, m.p. 200° dec., which was not identified. From the filtrates a product was separated, m.p. 194° dec., which was identical with previously synthesized *o*-acetylphenylacetic acid hydrazone hydrochloride (m.p. 202–205° dec.), mixture m.p. 202° dec.

ANN ARBOR, MICH.

(3) W. W. Hartman and L. J. Roll, *Org. Syntheses*, XIII, 66, 82 (1933).

(4) C. F. Koelsch and C. D. LeClaire, *J. Org. Chem.* 6, 516 (1941).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE & FRENCH LABORATORIES]

Analogs of Phenothiazines. II.[1] Phenoxazine and Phenoselenazine Analogs of Phenothiazine Drugs

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A general synthesis of 2-substituted phenoxazines was developed. The preparation of phenoselenazine and phenoxazine analogs of pharmacologically active 10-aminoalkylphenothiazines is reported. Spectral data on the intermediate 2-substituted phenoxazines and phenoselenazines are reported.

During the past decade a number of phenothiazine derivatives have been found to be useful therapeutic agents (see Table I). A study of compounds related to the potent antihistaminic drug, promethazine, led to the discovery of the tranquilizing and antiemetic properties of promazine and chlorpromazine.[2]

More potent therapeutic agents have been derived from the latter drug by replacement of the

(1) Presented in part at 138th National Meeting, American Chemical Society, New York, N. Y., Sept. 12, 1960. Paper I of this series: P. N. Craig, B. M. Lester, A. J. Saggiomo, C. Kaiser, and C. L. Zirkle, *J. Org. Chem.*, **26**, 135 (1961).

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