Experimental Section[15]

Anthranilohydroxamic Acid.—This procedure consistently gave good results in the synthesis of the hydroxamic acid from ethyl anthranilate. When the published conversion of methyl anthranilate into anthranilohydroxamic acid[16] was applied to ethyl anthranilate in hot ethanol, little hydroxamic acid was isolated.

Sodium ethoxide, prepared from 4.6 g (0.2 g-atom) of sodium in 50 ml of ethanol, was added to a stirred solution of dried hydroxylamine hydrochloride (14.0 g, 0.2 mol) in ethanol (130 ml). After 1 hr the solution was filtered and to the filtrate was added ethyl anthranilate (16.5 g, 0.1 mol) followed by sodium ethoxide, prepared from 2.3 g (0.1 g-atom) of sodium in 50 ml of ethanol. The reaction mixture was stirred at 25° for 2 days. The solid was collected, washed with petroleum ether (bp 30–60°), dissolved in the minimum amount of water, filtered, and acidified with acetic acid. Recrystallization from water yielded the hydroxamic acid in 60% yield, mp 144–145° (lit. mp 142–143°,[14] 149°[6]).

2-Benzimidazolone.—Benzenesulfonyl chloride (14.13 g, 0.08 mol) was added dropwise to a stirred solution of anthranilohydroxamic acid (6.1 g, 0.04 mol) in freshly prepared 5% NaOH solution (64 ml). The reaction mixture was stirred at 25°, maintaining the pH at 8 or above by the addition of 10% NaOH as required. After 2 hr, the presence of the hydroxamic acid group could not be detected by means of the ferric chloride test. The solution was cooled in an ice–water bath and acidified with dilute HCl (1:1) to pH 4. The crystalline product was collected, washed with petroleum ether (bp 30–60°), dried *in vacuo*, and recrystallized from 95% ethanol to give the product (5.09 g, 95%), mp 309–310°, (lit. mp 300°,[6,17,18] 307–308°,[19] 310°,[20,21] 313–316°[7]). Its ir spectrum, melting point, and mixture melting point were identical with that of an authentic sample:[14] ir, 3120 (NH) and 1725 cm^{-1} (C=O); nmr (DMSO), δ 7.0 (s, C_6H_4).

2-Benzoxazolone.—Salicylohydroxamic acid (6.1 g, 0.04 mol) was treated with benzenesulfonyl chloride (7.07 g, 0.04 mol) as described above. After 0.75 hr, at which time the reaction mixture did not give a purple color with ferric chloride, it was treated with 20% NaOH solution (20 ml) and filtered, and the filtrate was acidified with dilute HCl (1:1). The product (4.65 g, 86%, mp 122–125°) was recrystallized from water: mp 131–133° (lit.[9] mp 139°); ir, 3215 (NH) and 1750 cm^{-1} (C=O); nmr (DMSO), δ 7.15 (s, C_6H_4); mass spectrum (70 eV), *m/e* (relative intensity) 136 (9.6), 135 (100), 91 (24), 79 (53), 78 (7.7), 67.5 (5.8), 64 (17.4), 63 (12.5), 53 (6.7), 52 (45), 51 (21), 50 (11.5), 39.5 (7.7), 39 (8.6), 38.5 (4.8), 38 (9.6), 32 (7.7), 28 (26).

2-Oxo-1H,3H-imidazo[4,5-*b*]pyridine.—Benzenesulfonyl chloride (1.06 g, 0.006 mol) was added dropwise to a stirred solution of 2-aminonicotinohydroxamic acid (0.9 g, 0.006 mol) in 10% NaOH (10 ml). After 10 min the reaction mixture was filtered and the filtrate was acidified to pH 6 with dilute HCl (1:2). The solid (0.85 g, mp 259–262°). was recrystallized from 95% ethanol to furnish the pure product (0.58 g, 71%): mp 269–272° (lit. mp 238–239°,[22] 265–266°,[8,11] 270–272°,[7] 274°[23]); ir, 3100 (NH) and 1700 cm^{-1} (C=O); nmr (DMSO), δ 7.93 (d of d, H_6 $J_{4,6}$ = 1.6 Hz), 7.00 (d of d, H_5, $J_{4,5}$ = 7.6 Hz), 7.34 (d of d, H_4, $J_{5,6}$ = 5.0 Hz); mass spectrum (70 eV), *m/e* (relative intensity) 136 (8.34), 135 (100), 108 (4.2), 107 (23), 92 (6.2), 80 (20.8), 79 (5.2), 64 (12.5), 63 (6.2), 55 (5.2), 53 (19.8), 52 (13.5), 39 (7.3), 38 (10.4), 32 (7.3), 28 (26.1).

2-Oxo-1H,3H-imidazo[4,5-*b*]pyrazine.—Benzenesulfonyl chloride (15.90 g, 0.09 mol) was added dropwise to a stirred solution of 2-amino-3-pyrazinecarbohydroxamic acid (14.05 g, 0.09 mol) in 4% NaOH solution (200 ml). The reaction mixture was stirred at 25° for 1 hr, then acidified at 0° to pH 4 with dilute HCl (1:3). The red-brown product (7.95 g, 65%) was recrystallized from water: mp 334–336° (lit.[13] mp 336°); ir, 3480, 3330 (NH) and 1720 cm^{-1} (C=O); nmr (DMSO), δ 7.93 (s); mass spectrum (70 eV), *m/e* (relative intensity) 137 (5.1), 136 (66.8), 109 (7.9), 108 (6.5), 94 (13.5), 81 (9.8), 71 (6.1), 69 (6.5), 66 (10.7), 57 (13.5), 56 (5.6), 55 (10.28), 54 (13.08), 53 (10.7), 44 (7.0), 43 (12.1), 41 (11.7), 40 (5.6), 39 (8.4), 32 (42.5), 28 (100), 27 (7.5).

Anal. Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.03; H, 3.10; N, 41.18.

Registry No.—**4** (X = NH) 615-16-7; **4** (X = O) 59-49-4; **6**, 16328-62-4; **8**, 16328-63-5.

(15) Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined as Nujol mulls (NaCl plates) with a Perkin-Elmer spectrophotometer, Model 337. Nmr spectra were determined with a Varian A-60 spectrometer, calibrated with tetramethylsilane (TMS)(0) and $CHCl_3$(7.28); chemical shifts are reported in parts per million (δ) downfield from internal TMS. Mass spectra were obtained from a Hitachi Perkin-Elmer model RMU-6D spectrometer. The analysis (C, H) was performed by Dr. Kurt Eder, Geneva, Switzerland and that for N by Leo Horner using a Coleman Nitrogen Analyzer.

(16) M. A. Stolberg, W. A. Mosher, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, **79**, 2615 (1957).

(17) L. C. Raiford, E. Conrad, and W. H. Coppock, *J. Org. Chem.*, **7**, 346 (1942).

(18) F. Montanari and A. Risaliti, *Gazz. Chim. Ital.*, **83**, 278 (1953).

(19) A. Hartman, *Ber.*, **23**, 1046 (1890).

(20) S. von Niementowski, *Ber.*, **43**, 3012 (1910).

(21) D. G. Crosby and C. Niemann, *J. Amer. Chem. Soc.*, **76**, 4458 (1954).

(22) J. R. Vaughan, Jr., J. Krapcho, and J. P. English, **71**, 1885 (1949).

(23) V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

Nitration of 2-Methylthiazole

GORO ASATO

Chemical Research and Development Laboratories, Agricultural Division, American Cyanamid Company, Princeton, New Jersey 08540

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Although it is known that 4-methyl- and 5-methylthiazoles undergo nitration[1] with relative ease, 2-methylthiazole has been nitrated only in very low yield (3–4%) through the use of fuming sulfuric acid and potassium nitrate at 330°.[2] The product, mp 131–133°, was reported to be 2-methyl-5-nitrothiazole, but no proof of structure was given. Under milder conditions, Ganapathi and Kulkarni[3] obtained similar yields of what was presumably the same compound. Since we intended to utilize 2-methyl-5-nitrothiazole as an intermediate, the nitration of 2-methylthiazole was investigated using nitronium tetrafluoroborate[4] and the nitrogen tetroxide–boron trifluoride complex.[5,6] These reagents, however, were unstable in the presence of 2 methylthiazole. Nitrogen dioxide was evolved and only low yields[7] (8–19%) of a 2-methyl nitrothiazole, mp 70.5–72.5°, were obtained.[8] This material was homogeneous by glpc and did not appear to be the same compound as that which had been alleged to be 2-methyl-5-nitrothiazole by Babo and Prijs. It was suspected that decomposition of the reagent could be cir-

(1) J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 634.

(2) H. v. Babo and B. Prijs, *Helv. Chim. Acta*, **33**, 306 (1950).

(3) K. Ganapathi and K. D. Kulkarni, *Curr. Sci.*, **21**, 314 (1952); *Proc. Indian Acad. Sci., Sect. A*, **37**, 758 (1953).

(4) G. A. Olah, S. Kuhn, and A. Mlinko, *J. Chem. Soc.*, 4257 (1956).

(5) G. B. Bachman, H. Feuer, B. R. Bluestein, and C. M. Vogt, *J. Amer. Chem. Soc.*, **77**, 6188 (1955).

(6) The stoichiometry involved in the formation of the complex is believed to be

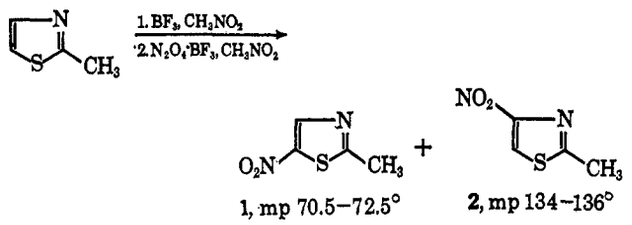
$$3N_2O_4 + 8BF_3 \longrightarrow 3NOBF_4 + 3NO_2BF_4 + B_2O_3$$

Cf. G. A. Olah and M. W. Meyer in "Friedel-Crafts and Related Reactions," Vol. 1, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1963, pp 124, 125, and 684.

(7) The higher yield was obtained by using the method of R. A. Parent [*J. Org. Chem.*, **27**, 2282 (1962)].

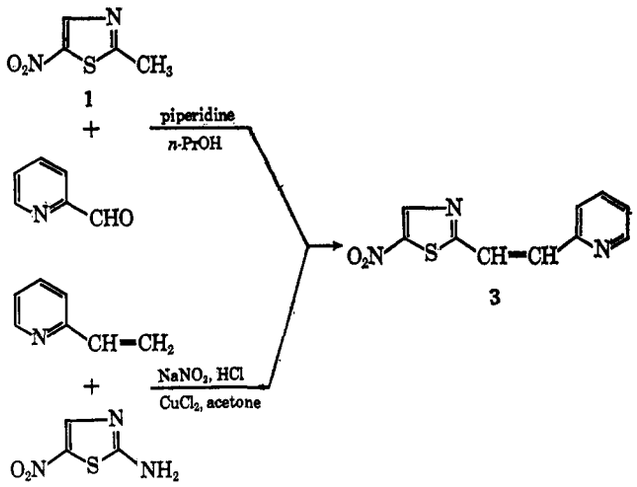
(8) For nucleophilic attack by pyridine on nitronium tetrafluoroborate, *cf.* G. A. Olah, J. A. Olah, and N. A. Overchuk, *J. Org. Chem.*, **30**, 3373 (1965); J. Jones and J. Jones, *Tetrahedron Lett.*, 2117 (1964).

cumvented by prior complexing of 2-methylthiazole with boron trifluoride. Indeed, when boron trifluoride-complexed 2-methylthiazole was treated with excess nitrogen tetroxide–boron trifluoride complex in nitromethane at room temperature, a crude yield of *ca.* 86% of a mixture which contained predominantly mononitro products **1** and **2**, in a ratio of *ca.* 3.6:1, was isolated after 19.5 hr. Purification subsequently led to combined yields of 50–60% of **1** and **2**. The reaction proceeded equally well with nitronium tetrafluoroborate as the nitrating agent. Because it is well documented[9] that electrophilic substitution



occurs preferentially at the 5 position when an *ortho,-para* directing group is in the 2 position, it appeared on the basis of the isomer ratio that **1** was the 5-nitro isomer and **2** was the 4-nitro isomer. To support the contention the nmr spectra of **1** and **2** were compared with those of thiazole, 2-methylthiazole, and 2-bromo-5-nitrothiazole. The spectrum of thiazole in cyclohexane (TMS as the internal reference) is reported[10] to contain bands at τ 2.17 (H_4) and 2.91 (H_5) and of 2-methylthiazole[11] as a pure liquid (water as the external reference) at τ 2.8 (H_4) and 3.25 (H_5). In this work[12] 2-methylthiazole showed two doublets (J = 3.8 Hz) at τ 2.37 (H_4) and 2.87 (H_5), whereas 2-bromo-5-nitrothiazole exhibited a singlet at 1.67 (H_4). The spectrum of **1** revealed a singlet at τ 1.53 whereas that of **2** showed a singlet at 1.80. Thus it is clear that **1** is the 5-nitro isomer and **2** is the 4-nitro isomer and this is in accord with theory since the H_4 proton is deshielded more than the H_5 proton owing to the proximity of both the electronegative ring nitrogen[10,11] and the C_5-nitro group.

On the basis of this assignment, it is reasonable to predict that **1** should contain a more acidic methyl group than **2** because the methyl anion of **1** will be stabilized by conjugation with the nitro group. In good agreement with this prediction, **1** condensed readily with aromatic aldehydes,[13] whereas **2** did not; *e.g.*, **1** condensed with 2-picolinaldehyde to give the olefin **3** in 65% yield, whereas no reaction occurred with **2** under the same conditions. The structure **3** was confirmed by an alternate synthesis *via* the Meerwein arylation[14] of the diazonium chloride derived from 2-amino-5-nitrothiazole[15] with 2-vinylpyridine.



For comparative purposes, 2-methylthiazole was also nitrated with a mixture of nitric and fuming sulfuric acids at 180–197°, and the course of the reaction was followed by glpc. The analyses revealed the isomer ratio of 5-nitro/4-nitro changed from 5:4 in 0.5 hr to 1:2 in 1 hr. After 18 hr there was no 5-nitro isomer remaining, clearly showing that it was unstable under the reaction conditions. Thus there is undoubtedly a preference for electrophilic substitution at the 5 position even under these conditions at the outset of the reaction.

Since the nitration with the 2-methylthiazole–boron trifluoride complex was facile as compared with the mixed acid nitration, it was thought that this reaction might be another example of the "swamping catalyst effect" which has been studied by Pearson.[16] Under the same conditions, however, 2-methylthiazole hydrochloride was also readily nitrated to give a 54% yield of isomers, which indicated that ease of nitration is not dependent upon the presence of a Lewis acid and absence of a proton acid.

The scope of the prior-complexing nitration technique appears to be limited; BF_3-complexed pyridine and 2-picoline gave only traces (1–2%) of nitrated products with N_2O_4–BF_3.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Glpc analyses were performed on an F & M Model 720 dual column unit. Infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Nitration of 2-Methylthiazole. A. N_2O_4–BF_3.—To 150 ml of nitromethane at 10°, 45 ml (*ca.* 0.705 mol) of nitrogen tetroxide was added and boron trifluoride was bubbled into this solution while the temperature was maintained below 10°. After excess boron trifluoride was observed at the top of the condenser, the flow was terminated. In a separate flask, 30 g (0.30 mol) of 2-methylthiazole in 50 ml of nitromethane at −20 to −10° was also saturated with boron trifluoride, and this solution was added over a 0.5-hr period to the slurry of nitrogen tetroxide–boron trifluoride complex at 5–25°. The heterogeneous mixture was stirred at ambient temperature for 19.5 hr and then heated[17] to 65–70° for 2 hr. The mixture was cooled, poured on ice, made alkaline with 10% sodium hydroxide, extracted with six 100-ml

(9) See ref 1, pp 495 and 552.

(10) B. Bak, J. T. Nielsen, J. Rastrup-Anderson, and M. Schottländer, *Spectrochim. Acta*, **18**, 741 (1962).

(11) A. Taurins and W. Schneider, *Can. J. Chem.*, **38**, 1237 (1960).

(12) Nmr spectra were taken in deuterated chloroform on a Varian A-60 instrument with tetramethylsilane (TMS) as the reference.

(13) Biological test results on these and related compounds will be published elsewhere.

(14) C. S. Rondestvedt, Jr., *Org. Reactions*, **11**, 189 (1960).

(15) Although the nitration of 2-aminothiazole has long been assumed to give 2-amino-5-nitrothiazole (ref 1, p 609), its structure has been confirmed only recently by Parent[7] by reductive acetylation to give 2,5-diacetamidothiazole, which differed from 2,4-diacetamidothiazole which had been synthesized unequivocally.

(16) D. E. Pearson, W. W. Hargrove, J. K. Chow, and B. R. Suthers, *J. Org. Chem.*, **26**, 789 (1961).

(17) Heating was found to be unnecessary in subsequent runs.

volumes of methylene chloride, dried, and evaporated to dryness *in vacuo* to afford 37.55 g (86%) of a red-brown semisolid. Analysis by glpc on a 2% SE 30, 6-ft column starting at 100° and temperature programmed at 30°/min, showed that only *ca.* 2.6% of the starting material was present after stirring overnight at room temperature and that the ratio of 5-nitro(1)/4-nitro(2) was approximately 3.6:1. Only *ca.* 5% of volatile side products were detectable. The crude mixture was triturated with 150 ml of carbon tetrachloride and then filtered to leave, predominantly, 5.89 g of **2**, mp 80–125°. Recrystallization from methanol gave two fractions, 3.71 g (mp 133–136°) and 1.35 g (mp 125–132°).

Anal.[18] Calcd for $C_4H_4N_2O_2S$ (**2**): C, 33.32; H, 2.80; N, 19.43; S, 22.24. Found: C, 33.24; H, 2.97; N, 19.30; S, 22.10.

The carbon tetrachloride filtrate was evaporated to dryness *in vacuo*, the residue was redissolved in methylene chloride, the solution was decolorized with activated carbon and evaporated to dryness, and the solid was recrystallized from methanol to give 9 g of **1**, mp 70–72°. Subsequently, 11.98 g of lower melting fractions (mp 58–71°) were obtained by work-up of mother liquors. The combined isolated yield was 59.5%.

Anal.[18] Found for **1**: C, 33.37; H, 2.98; N, 19.54; S, 22.11.

Similarly, 2-methylthiazole hydrochloride afforded a 54% yield of mixed product but the 1:2 ratio was 2.8:1.

B. Mixed Acids.—To 7 ml of 20% fuming sulfuric acid at 20°, 1.7 g (93% pure by glpc, 1.6 mmol) of 2-methylthiazole was added and the mixture was heated to 100° before 2 g of potassium nitrate was gradually added. At the end of the addition the temperature was 170°, and, at this point, 1 ml of fuming nitric acid was added. The temperature was then kept at 180–197° for 18 hr. Glpc analysis (on a 6-ft, 10% SF 96 column[19]) of a 1-hr sample which had been basified, extracted, and dried over magnesium sulfate indicated a 1:2 ratio of 1:2; after 18 hr. Compound **2** was detected but **1** was no longer detectable. In a similar run using concentrated nitric acid instead of fuming nitric acid a 0.5-hr sample showed a 1:2 ratio of 5:4.

2-[2-(5-Nitro-2-thiazolyl)vinyl]pyridine (3). A. Condensation Method.—In 15 ml of 1-propanol containing 0.5 ml of piperidine, 2 g (14 mmol) of 2-methyl-5-nitrothiazole was refluxed with 3 g (28 mmol) of 2-pyridinecarboxaldehyde for 1 hr. The mixture was cooled and the solid was collected and washed with cold methanol to give 2.12 g (65%) of product, mp 179–181°. Recrystallization from methanol afforded yellow crystals: mp 181.5–183°; ir spectrum (Nujol), 3050, 1500, 1350, and 980 (*trans* H?) cm^{-1}. The AB quartet for the olefinic protons could not be resolved in deuterated chloroform on the Varian Model A-60 nmr instrument.

Anal. Calcd for $C_{10}H_7N_3SO_2$: C, 51.49; H, 3.03; N, 18.02; S, 13.75. Found: C, 51.22; H, 3.16; N, 17.97; S, 13.59.

B. Meerwein Reaction.—To 450 ml of concentrated hydrochloric acid and 100 ml of water, 145 g (1 mol) of 2-amino-5-nitrothiazole was added and the slurry was cooled to about −70°. To this mixture, 69 g (1 mol) of sodium nitrite in 100 ml of water was introduced over a 0.5-hr period to give a pale green mixture. After an additional 10 min of stirring, 160 g (1.52 mol) of 2-vinylpyridine in 600 ml of acetone was added rapidly while the temperature was kept below −30°. Cupric chloride dihydrate (28 g) was then added and the mixture was stirred for 10 min before it was allowed to rise to room temperature. At −10° the green mixture became reddish and evolution of nitrogen was vigorous. After cessation of nitrogen evolution, the mixture was added to 500 ml of water. The mixture was neutralized with sodium bicarbonate, methylene chloride was added, the mixture was filtered, and the organic phase was separated. The aqueous layer was further extracted with methylene chloride, the combined organic phases were dried over magnesium sulfate and then evaporated to dryness *in vacuo* to give a viscous mixture. This was triturated with methanol and filtered to give 25.3 g of product, mp 179–182°. An additional 6 g of crude product was obtained from the methanol filtrate. Purification of products from chloroform and decolorization with activated carbon gave 25.43 g (10.5%) of yellow product, mp 180–183°, which was identical (infrared spectrum and melting point) with that obtained by the condensation reaction (*vide supra*).

(18) The analytical samples from earlier runs melted at 134–136° (hexane) for **2** and 70.5–72.5° (hexane) for **1**.

(19) The column temperature was set at 120° and then abruptly reset at 250° after 2-methylthiazole passed through the column in order to get well-defined, reproducible peaks.

Registry No.—2-Methylthiazole, 3581-87-1; **1**, 16243-71-3; **2**, 16243-72-4; **3**, 16243-73-5.

Acknowledgment.—The author is indebted to Dr. G. Berkelhammer for his continued interest and Dr. J. E. Lancaster and Mr. R. S. Wayne for the nmr data and interpretations.

The Revised Structure of the Condensation Product of N-(*p*-Methoxyphenyl)anthranilic Acid with Formamide

A. CHATTERJEE AND R. RAYCHAUDHURI

Department of Chemistry, University College of Science, Calcutta-9, India

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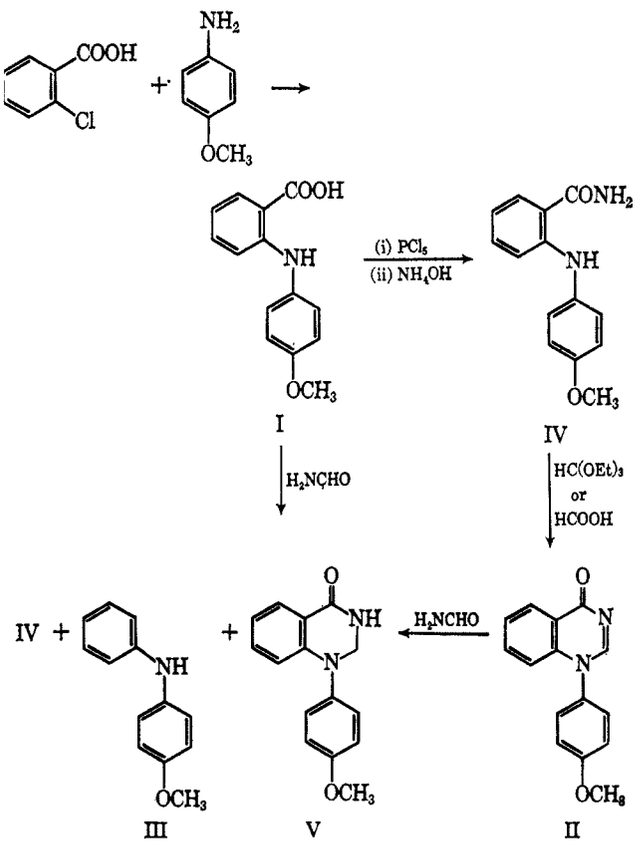
In an attempt to synthesize 1-aryl-1H-quinazolin-4-ones following the general route[1] to the synthesis of their 1-alkyl analogs, Mukherjee, *et al.*,[2] condensed N-(*p*-methoxyphenyl)anthranilic acid (I) with formamide and reported a product to which they assigned the structure II. The same experiment in our hands gave a mixture of three products (Chart I), *viz.*, 4-methoxydiphen-

CHART I



ylamine (III) and 2-(*p*-methoxyanilino)benzamide (IV) and a third one which was proven identical in all respects (melting point, mixture melting point, and uv, ir, and nmr spectra) with the compound believed to have

(1) N. J. Leonard and W. V. Ruyle, *J. Org. Chem.*, **13**, 903 (1948).

(2) S. Somasekhara, G. M. Shah, and S. L. Mukherjee, *Curr. Sci.*, **33**, 521 (1964).