TABLE I

OXIDATION OF PRIMARY ALKANENITRONATES WITH POTASSIUM PERMANGANATE

Nitro compound	Moles × 10³ of nitronate	Equiv. × 10³ of $KMnO_4$[a]	Ratio of reactants[b]	Aldehyde 2,4-DNPH,[c] g.	Yield,[d] %	Yield[e] (cor.), %
1-Nitrobutane	5.77	5.77	1.00	1.110	76	83
1-Nitrobutane	3.11	3.11	1.00	0.599	77	84
1-Nitrobutane	3.46	3.11	0.90	0.703	90	97
1-Nitrobutane	6.88	6.22	.90	1.390	89	96
2-Methyl-1-nitropropane	6.6	6.6	1.00	1.21	73[f]	
2,2-Dimethyl-1-nitropropane	0.835	0.835	1.00	0.14	63[f]	
2,2-Dimethyl-1-nitropropane	1.6	1.2	0.75	.22	69[f]	
Cyclobutylnitromethane	0.92	0.62	.67	.155	91[f]	
Phenylnitromethane	2.22	2.22	1.00	.401	63	68
Phenylnitromethane	4.5	3.1	0.70	.800	90	97

[a] Based on equation 2. [b] Equivalents of potassium permanganate to moles of nitronate. [c] The aldehyde formed was isolated as its 2,4-dinitrophenylhydrazone, see Experimental. The melting points of the derivatives after crystallization from ethanol agreed satisfactorily with literature values. [d] Based on potassium permanganate added and weight of derivative isolated. [e] Equals yield multiplied by experimental correction factor, see Experimental. [f] Minimum yield; corrections were not made for solubility losses.

TABLE II

OXIDATION OF SECONDARY ALKANENITRONATES WITH POTASSIUM PERMANGANATE

Nitro compound	Moles × 10³ of nitronate	Equiv. × 10³ of $KMnO_4$[a]	Ratio of reactants[b]	Ketone 2,4-DNPH,[c] g.	Yield, %
2-Nitropropane					96[d]
2-Nitrobutane	2.03	2.18	1.07	0.478	94
3-Methyl-3-nitrobutane	2.22	2.30	1.04	.552	94
2,2-Dimethyl-3-nitrobutane[e]	1.795	1.87	1.03	.264	66
1-Cyclopropylnitroethane	2.22	2.85	1.28	.450	77[f]
Dicyclopropylnitromethane[f]	2.05	2.85	1.39	.485	81[f]
Nitrocyclobutane[g]					94[g]

[a] Based on equation 2. [b] Equivalents of potassium permanganate to moles of nitronate. [c] The ketone was isolated as its 2,4-dinitrophenylhydrazone, see Experimental. Melting points of recrystallized derivatives agreed satisfactorily with literature values. [d] Yield reported in reference 12a. [e] There is question about the purity of the sample of 2,2-dimethyl-3-nitrobutane used. The experimental extinction coefficient at its absorption maximum (229 mμ) is 8600. Related nitronates have extinction coefficients of ~11,000 at their absorption maxima. [f] The results were obtained before the optimum present procedure was developed. The yields should be regarded as minimal. [g] P. W. K. Flanagan, Ph.D. dissertation, The Ohio State University, 1957. The yield has been corrected for solubility losses.

procedure. The procedure used in determining the correction factor was as follows. A purified sample of aldehyde (0.002–0.006 mole) was steam distilled (*ca.* 100 ml.) into an aqueous solution of hydrochloric acid (2 *N*) saturated with 2,4-dinitrophenylhydrazine. The precipitate obtained was filtered, dried at 5 mm. over calcium chloride and weighed. The correction factor for the yield of butyraldehyde and of benzaldehyde 2,4-dinitrophenylhydrazones was 1.09.

2,3-Dihydrothiazolo[2,3-*b*]quinazolin-5-one

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Received April 16, 1962

As part of synthesis program aimed at discovering new chemotherapeutic agents it was desirable to synthesize the title compound (I). Although this substance (m.p. 240°) was reported by Narang and co-workers as the product of the reaction between ethyl N-thiocarbamoylanthranilate and ethylene bromide, structure assignment was tentative and attempts to synthesize it by an unequivocal route failed.[2,3] We repeated the synthesis and obtained a compound of identical melting point and correct elemental analysis.

While searching for a more convenient synthesis we prepared a compound isomeric with that described by Narang and have established its structure as I by independent synthesis. The preparation of I was effected by the reaction of the sodium salt of 2-mercapto-4(3H)-quinazolinone (III) with ethylene bromide. This method, of course, might have produced either I or the "angular" isomer II. To provide an unambiguous route to I we applied the thiazoline synthesis first reported by Gabriel and Stelgner.[4] Ethyleneimine was added to methyl *o*-isothiocyanatobenzoate (IV) and the resulting aziridine (V) was refluxed in concentrated hydrochloric acid. The intermediate thiazoline (VI) was not isolated, apparently the

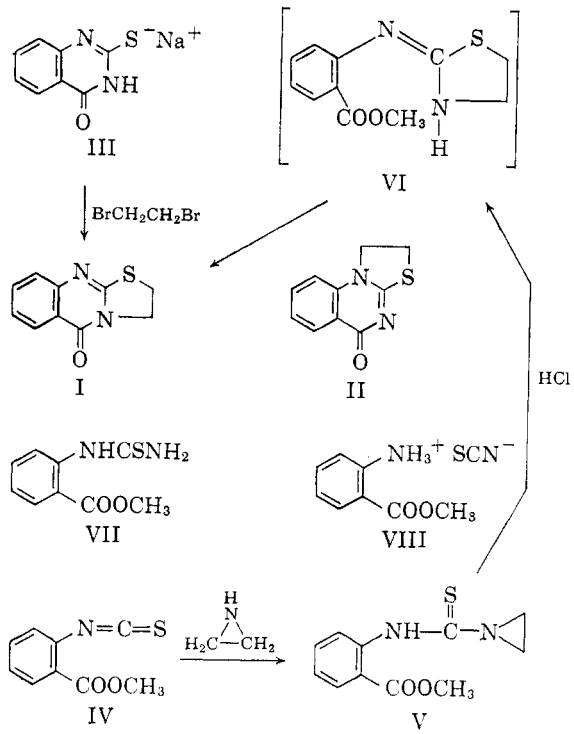
(1) To whom inquiries should be sent. Present address: Biochemistry Department, Medical College of Georgia. Augusta, Georgia.

(2) K. S. Narang, M. C. Khosla, O. P. Vig, and I. S. Gupta, *J. Sci. Ind. Res.* (India), **12B**, 466 (1953).

(3) K. S. Narang, G. M. Sharma, and I. S. Gupta, *Res. Bull. Panjab Univ.*, **87**, 49 (1956); *Chem. Abstr.*, **51**, 7379 (1957).

(4) S. Gabriel and R. Stelgner, *Ber.*, **28**, 2929 (1895).

vigorous conditions caused its cyclization to the desired product (I). This result strongly implies that the Narang synthesis yielded the "angular" isomer (II).



During the course of this work we prepared as a starting material for III, a considerable amount of "methyl N-thiocarbamoylanthranilate" (VII)[5] by treatment of methyl anthranilate hydrochloride with potassium thiocyanate. The fact that this substance was formed by merely mixing the reagents in the cold, and that its aqueous solutions smelled strongly of methyl anthranilate are both properties more consistent with the isomeric methyl anthranilate thiocyanate (VIII) than the thiourea.[6] That the substance was the amine thiocyanate was confirmed by the infrared spectrum which showed characteristic thiocyanate ion absorption at 4.7–4.9 μ, and by titration with silver nitrate. This finding explains the "retrogression" of ethyl N-thiocarbamoyl anthranilate to thiocyanate and ethyl anthranilate recently described by Narang and co-workers.[7]

Experimental[8]

Methyl Anthranilate Thiocyanate (VIII).—A solution of 151 g. (1.0 mole) of methyl anthranilate in 800 ml. of water and 100 ml. of concentrated hydrochloric acid was added rapidly with stirring to 117 g. (1.2 moles) of potassium thiocyanate in 500 ml. of water. The product crystallized rapidly and after cooling in an ice bath was collected and washed with a little cold water. After drying to constant weight at 60° the yield was 160 g. (76%), m.p. 122–123° (melt resolidified). Recrystallization from isopropyl alcohol did not raise the melting point; the reported m.p. is 124°.[5] Titration of an aqueous solution with standard silver nitrate using eosin as an indicator gave a pink end point corresponding to a thiocyanate purity of 99%.

Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; S, 15.25. Found: C, 51.20; H, 4.61; S, 15.31.

The infrared spectrum showed strong absorption at 4.7–4.9 μ (thiocyanate) both in chloroform solution and as a mineral oil mull.

2-Mercapto-4(3H)-quinazolinone.—(The method of Rupe[9] was modified.) A suspension of 202 g. (0.96 mole) of methyl anthranilate thiocyanate in 1 l. of xylene was heated to about 100°. A vigorous reaction began and heating was suspended. After the reaction subsided, heating was continued until the temperature reached 125°. The mixture was then cooled and the pale yellow solid was collected; the yield was 128 g. (75%), m.p. 298–300° (cap.). Although this material was pure enough for synthetic purposes, the m.p. was raised to 304–305° by recrystallization of 1 g. from 400 ml. of ethanol.

Anal. Calcd. for $C_8H_6N_2OS$: C, 53.91; H, 3.39; S, 17.99. Found: C, 54.0; H, 3.19; S, 17.63.

2,3-Dihydrothiazolo[2,3-b]quinazolin-5-one (I).—Two methods were developed.

Method A.—In a flask equipped with stirrer, thermometer, and addition funnel were placed 18 g. (0.1 mole) of 2-mercapto-4(3H)-quinazolinone and 150 ml. of dimethylformamide. Sodium hydride (8.8 g., 0.2 mole) as a 55% dispersion in mineral oil[10] was added during 15 min. at 8–15°. Ethylene bromide (17 ml., 0.2 mole) was added during 22 min. at 9–17°. After stirring 1 hr. the reaction mixture was poured into 500 ml. of ice water and the pH adjusted to 7. The precipitate was collected, washed with water and ether, and dried at 100°. The crude product (12.6 g., m.p. 150–155°) was recrystallized from 1.5 l. of water with the addition of 8 g. of Darco. The yield was 7.5 g. (37%) of colorless needles, m.p. 155–156°.

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; S, 15.70. Found: C, 58.8; H, 3.66; S, 15.64.

Method B.—A solution of 72 g. (0.4 mole) of 2-mercapto-4(3H)-quinazolinone and 16 g. of sodium hydroxide in 2.5 l. of 60% aqueous isopropyl alcohol was added during a 2-hr. period to a refluxing suspension of 136 g. of sodium bicarbonate, 200 ml. of ethylene bromide, and 1 l. of isopropyl alcohol. The mixture was refluxed an additional hour, filtered, and the filtrate was evaporated to dryness in the rotary evaporator at 90–100°. The residue was stirred into 5% sodium hydroxide solution and the insoluble solid was collected. The yield was 25.5 g. (31%), m.p. 155–157°.

Methyl *o*-Isothiocyanatobenzoate (IV).—A mixture containing 75 g. (0.50 mole) of methyl anthranilate and 42 ml. (0.50 mole) of concentrated hydrochloric acid in 200 ml. of water was added to a stirred suspension of 100 g. of calcium carbonate, 250 ml. of ethylene chloride, and 250 ml. of water. To this well stirred mixture was added, with efficient ice-bath cooling, 61 g. (0.53 mole) of thiophosgene at a rate sufficient to keep the organic phase orange. The temperature was kept at 30–35°. After addition was complete, the mixture was stirred for an hour and the inorganic salts removed by filtration. The organic phase was separated and washed successively with 100 ml. of 0.1 *N* hydrochloric acid, 100 ml. of 5% aqueous sodium bicarbonate, and 200 ml. of water. After drying over magnesium sulfate, the ethylene chloride was evaporated at 50–60° (20 mm.). The residue was distilled under reduced pressure; a yield of

(5) M. Shimotani, *J. Pharm. Soc. Japan*, **72**, 328 (1952).

(6) We are indebted to Mr. Frank Ebetino of this laboratory for this suggestion.

(7) G. M. Sharma, H. S. Sachdev, N. K. Ralhan, H. Singh, G. S. Sandhu, K. Gandhi, and K. S. Narang, *Tetrahedron*, **15**, 53 (1961).

(8) Elemental analyses were performed by Mr. G. Ginther and coworkers of this laboratory. Melting points were determined on a calibrated Fisher-Johns block except where noted. Capillary melting points are uncorrected.

(9) H. Rupe, *Ber.*, **30**, 1097 (1897).

(10) Metal Hydrides, Inc., Beverly, Mass.

61 g. (63%) of light yellow liquid, b.p. 100–102° (0.35 mm.), was obtained.

Anal. Calcd. for $C_9H_7NO_2S$: C, 55.94; H, 3.65; S, 16.59. Found: C, 56.02; H, 3.81; S, 16.25.

Methyl 1-Aziridinylthiocarbamoylanthranilate (V).—To 18.1 g. (0.10 mole) of IV in 50 ml. of ether was added dropwise, with efficient stirring and ice-bath cooling, 4.5 g. (0.105 mole) of freshly distilled ethyleneimine (b.p. 55–56°). The temperature was kept at 25–30°. A crystalline solid separated during the addition; this was collected and air-dried. The yield was 21 g. (94%) m.p. 88.5–89.5°. An analytical sample was prepared by reprecipitation from methylene chloride with *n*-hexane. The melting point was unchanged.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; S, 13.57. Found: C, 55.69; H, 5.39; S, 13.59.

Rearrangement of V to 2,3-Dihydrothiazolo[2,3-*b*]quinazolin-5-one (I).—Two grams of V was refluxed for 0.5 hr. in 10 ml. of concentrated hydrochloric acid. The yellow solution was cooled and added with cooling to 30 ml. of 10% aqueous sodium hydroxide. The pale yellow product was collected and recrystallized from 100 ml. of water. The yield of colorless needles, m.p. 156–157°, was 0.3 g. (16%). The infrared spectrum and mixed melting point of the product were identical to I prepared from III and ethylene bromide.

A New One-Step Synthesis of Substituted Coumarins

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Received April 20, 1962

In a recent publication[2] we have shown that esters and carboxylic acids would react with pyrone phenols in the presence of trifluoroacetic acid. In adapting the method to benzenoid phenols we were of the opinion that flavones would have been formed; however, in every case cited in this report only coumarins were obtained.

Experiments on a large number of phenols with β-keto esters in the presence of trifluoroacetic acid has made very evident certain limitations of the reaction. Phenol, catechol, 4,6-dichlororesorcinol, cresols and hydroquinone all failed to give the reaction. It is quite apparent from the experimental results that a compound must have nucleophilic substituent groups distributed around the periphery of the ring in such a manner that the β-keto ester may displace a ring proton activated by the COMBINED *ortho* effect of one of the nucleophilic groups and the *para* effect of the other nucleophilic group. One of these groups must be phenolic. An alkyl group is not strong enough, when there are only two substituents on the ring, to furnish the needed activation; however, when an alkyl group is one of three activating groups, as in the case of orcinol, distributed alternately around the ring it does appear to have some activating effect.

Situation of the hydroxyls or other nucleophilic groups 1,3 from each other in order to obtain the combined *ortho* and *para* activating effects, never results in an attack by the ester in the position between the groups. Blocking of the position between the groups with a methyl, as in the case of 2-methylresorcinol, or with a hydroxyl, as in the case of pyrogallol, enhances the reactivity of the phenol, rather than inhibits the reaction. Blocking one of the positions *para* to the groups, as in the case of 4-chlororesorcinol, results in lowered yields and blocking both positions *para* to the nucleophilic groups, as in the case of 2,6-dichlororesorcinol, completely inhibits an attack by the β-keto ester.

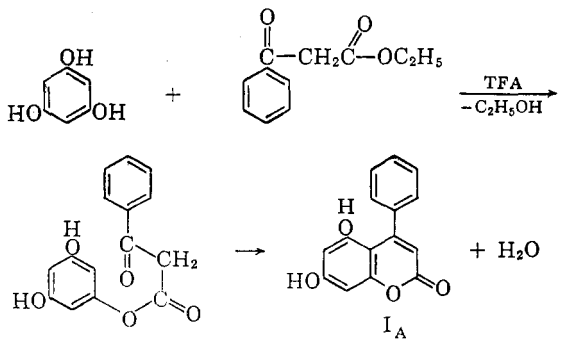
The physical properties of the coumarins produced by the series are described in Table I and the probable course of the reaction for their formation is depicted in Chart I using compound I_A as the example.

Coumarins, as a rule, give three major absorption maxima in the region of 200–350 mμ. All of the coumarins listed in Table II show this characteristic behavior except I_K which gives its third maximum beyond 350. The infrared absorption bands on all the coumarins (Table III) are either characteristic or give expected values as dictated by the nature and number of their substituents.

Compound I_I is the only substance of the series which was not converted into the anhydrous condition due to the fact that it was completely soluble in benzene and prolonged refluxing of the substance caused the formation of dark impurities. The observed fluorescence pattern of the coumarins agrees with the observations made by Elderfield.[3]

The acetates of all the hydroxycoumarins are given in Table IV as members of the II_{A-J} series.

Not included among the list of the coumarins synthesized are 4-methyl-5,7-dihydroxycoumarin



I_A

CHART I

(1) The person to whom all communications concerning this contribution should be directed.

(2) L. L. Woods, *J. Org. Chem.*, **27**, 696 (1962).

(3) R. C. Elderfield, "Heterocyclic Compounds," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 193.