identical.[8] Rotation: $[\alpha]^{25}D$ −89.6° (*c*, 1.115, absolute ethanol), $[\alpha]^{26}D$ −97.0° (*c*, 1.25, acetone).

Methyl Obacunoate.—Obacunoic acid (242 mg.) dissolved in a few ml. of acetone was treated with a slight excess of an ether solution of diazomethane. After standing a few minutes, the solvents were pumped off, and the residue taken up in a small amount of *t*-butyl alcohol. Crystallization was obtained by adding a little petroleum ether, yield 222 mg., m.p. 175–177°. A second recrystallization brought the melting point to 177–178°. For analysis the substance was dried to constant weight at 100° at 0.1 mm.

Anal. Calcd. for $C_{27}H_{34}O_8$: C, 66.65; H, 7.05. Found: C, 66.54; H, 7.02.

Acetyl Obacunoic Acid.—Obacunoic acid (100 mg.) was acetylated by heating on the steam-bath for one hour with 2 ml. of acetic anhydride and 50 mg. of fused, powdered sodium acetate. After pumping off the excess acetic anhydride, the residue was washed with water and crystallized from a mixture of ethyl acetate, benzene and isoöctane, m.p. about 145°, although not very sharp. For analysis the product was dried as described above.

Anal. Calcd. for $C_{28}H_{34}O_9$: C, 65.36; H, 6.65. Found: C, 65.84; H, 6.95.

Obacunone Oxime.—Obacunone (112 mg.) with an equal weight of hydroxylamine hydrochloride was refluxed four hours with 2 ml. of absolute ethanol and 2 ml. of pyridine. The solvents were pumped off, and the residue washed with water, and crystallized from a small amount of methanol, in which it was quite soluble. The substance crystallized in fine prisms which decomposed when heated above 200°, rapidly above 230° yielding a dark red oil. For analysis the substance was dried to constant weight at 100° and 0.1 mm.

Anal. Calcd. for $C_{26}H_{31}NO_7$: C, 66.52; H, 6.65; N, 2.98. Found: C, 66.85; H, 6.97; N, 3.01.[9]

Conversion of Nomilin to Obacunone.—Nomilin (520 mg.) was refluxed for two hours with a mixture of 5 ml. of acetic anhydride and 5 ml. of pyridine. After the solvents were pumped off, the residue was crystallized from acetone, yielding 289 mg. of a slightly impure obacunone. A second recrystallization brought the melting point up to 227–229°, and the product gave no depression on admixture with natural obacunone. Dr. F. T. Jones, of the Western Regional Research Laboratory, examined the optical properties of the crystals, and found they checked perfectly with those of natural obacunone from the citrus seed oil.

Acknowledgment.—The author wishes to express his sincerest thanks to Dr. C. W. Koch and Mr. V. H. Tashinian of the Chemistry Department of the University of California, Berkeley, California, for the microcarbon–hydrogen determinations, and to the following gentlemen of the Western Regional Research Laboratory, Albany, California: Messrs. Glen F. Bailey and Stanley Friedlander for the measurements of the absorption spectra, Dr. R. M. McCready for the polarimetric measurements and Dr. F. T. Jones for the microscopic examination of many preparations.

(8) A description of the crystallographic properties of the substances described in this paper is to appear shortly.

(9) Dumas analysis by Walter Mann, Jr.

ALBANY, CALIF. RECEIVED NOVEMBER 20, 1950

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Role of Phenol in the Reaction of 4,7-Dichloroquinoline with Novol Diamine

BY ALEXANDER R. SURREY AND ROYAL A. CUTLER

A study was undertaken to investigate the role of phenol in the reaction of 4-chloroquinolines with aliphatic amines. Evidence is presented for a proposed mechanism involving the formation of 4-phenoxyquinoline hydrochloride as an intermediate. The effect of acid and base on the reaction is also reported.

It is generally known that in the 9-chloroacridine series the use of phenol[1] greatly facilitates the reaction with aliphatic amines. It is not surprising, therefore, to find a carry-over of the use of phenol into the quinoline series. However, although there are numerous examples in which phenol has been used in the condensation of aliphatic amines with 4-chloroquinolines, only isolated statements have been reported regarding its efficacy in this series. For example, Walker[2] stated that "occasionally phenol has been added as a catalyst but it does not appear to have the same marked influence in the quinoline series as it has with 9-chloroacridines." Kenyon, Wiesner and Kwartler[3] stated that 4,7-dichloroquinoline reacts with molten phenol (by analogy with the 9-chloroacridine series) to form the phenoxy compound which then reacts with novol diamine at 135° to give chloroquine. Actually, there has been no conclusive evidence that the phenoxy quinoline (hydrochloride) is the intermediate in these reactions. One objection to the formation of the latter as an intermediate is that it involves the reaction of phenol in preference to the more strongly nucleophilic amine. On the other hand, one might picture the phenol as exerting primarily a solvolytic effect on the 4-chlorine thus making the 4-carbon more susceptible to attack by the amine.[4]

In connection with some of our work on the reaction of 2- and 4-chloroquinolines with secondary amines[5] and particularly in the preparation of chloroquine from the condensation of 4,7-dichloroquinoline with novol diamine,[6] N^1,N^1-diethyl-1,4-pentanediamine, it seemed desirable to investigate more carefully the role of phenol in these reactions.

The beneficial effect of phenol can be demonstrated very clearly in the reaction of some 2- and 4-chloroquinolines with secondary amines.[5] In the presence of phenol the reactions occurred readily and the products were obtained in good

(1) (a) The use of phenol as a reaction medium was introduced by O. J. Magidson and A. M. Grigorowski, *Ber.*, **66**, 866 (1933). (b) In a later paper, *ibid.*, **69**, 346 (1936), these authors showed that the 9-chloroacridines can react with phenol to form the 9-phenoxyacridines, and that the latter can react with an amine to form the 9-amino derivative. On this basis, it was postulated that the 9-phenoxyacridine was an intermediate in the reaction of a 9-chloroacridine with an amine in the presence of phenol.

(2) J. Walker, *J. Chem. Soc.*, 1552 (1947).

(3) R. L. Kenyon, J. A. Wiesner and C. B. Kwartler, *Ind. Eng. Chem.*, **41**, 654 (1949).

(4) The strong solvolytic action of phenol toward halogen has been demonstrated; (a) P. D. Bartlett and H. J. Dauben, THIS JOURNAL, **62**, 1339 (1940). Its marked effect in promoting ether formation in the case of triphenylmethyl halides is particularly demonstrative of this point; (b) C. G. Swain, *ibid.*, **70**, 1119 (1948).

(5) Work to be published.

(6) A. R. Surrey and H. F. Hammer, THIS JOURNAL, **68**, 113 (1946).

yields. In the absence of phenol, the reaction appeared to be negligible.

In the present work, the effect of phenol in facilitating the reaction between 4,7-dichloroquinoline (I) and novol diamine (III) is shown in Table I (Runs 1 and 2). In twenty-four hours at 125°, I reacted with the diamine III to give a 45% yield of chloroquine (IV), isolated as the diphosphate. Twenty-six per cent. of unchanged I was recovered. Under otherwise identical conditions (Run 2) the addition of one mole of phenol increased the yield of IV to 81%.

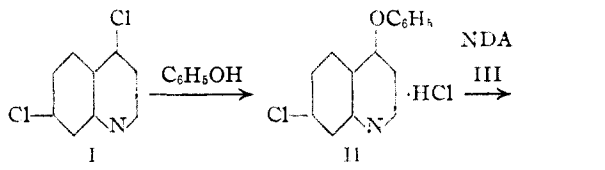
TABLE I

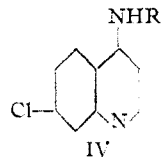
RESULTS OF EXPERIMENTS CARRIED OUT AT 125 ± 2° WITH 4-X-7-CHLOROQUINOLINE

Run	4-X	Moles[a] of reactants: Novol diamine	Phenol	Additional reactants	Time, hours	Products yield, %: I	II	IV[b]
1	Cl-	1.75			24	26[c]		45[d]
2	Cl-	1.75	1		24			81[d]
3	Cl-	1.00	2		24	0	3	84[e]
4	Cl-	1.25	2		24	0	0	86[e]
5	C_6H_5O-	1.50			24		87[f]	0.2[e]
6	C_6H_5O-	1.50		AcOH (1.5)	24			77[d]
7	C_6H_5O-	1.50		HCl (1)	24			77[d]
8	C_6H_5O-	1.75		HCl (1)	24			85[d]
9	Cl-	1.75	1		4	63	[g]	15[e]
10	Cl-	1.75	2		4	[g]	31.1	34[e]
11	C_6H_5O-	1.75		HCl (1)	4		50[f]	38[e]
12	Cl-	1.75	2	HCl (1)	4	[g]	12	60[e]
13	Cl-	1.75	2	AcOH (6)[h]	4	[i]	8	36[e]
14	Cl-	1.75	2	AcOH (3.5)[j]	4		12	65[e]

[a] Based on 0.05 mole of 4-x-7-chloroquinoline taken as one. [b] Obtained as the diphosphate salt. [c] Isolated by Method B after removing IV phosphate. [d] Worked up according to Method A. [e] Worked up according to Method B. [f] Isolated as base. [g] This material may have been present but was not isolated. [h] Glacial acetic acid was introduced at the start of the reaction. [i] In addition to the products listed a 40% yield of 4-hydroxy-7-chloroquinoline was isolated. [j] The dichloroquinoline and phenol were first heated at 125° for one-half hour and the novol diamine and glacial acetic acid added.

It has been found that the dichloro compound I reacts readily with phenol to give 7-chloro-4-phenoxyquinoline hydrochloride, II. In eight hours at 125°, I reacted with one mole of phenol





R = $CH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$

to give an 89% yield of II. With two moles of phenol the yield of II was practically quantitative in less than one hour. This reaction is considerably faster than the reaction of I with novol diamine (compare with Run 1).

It has also been found that the 4-phenoxyquinoline hydrochloride II reacts with the diamine III (Run 8) to give an 85% yield of IV. The base, 7-chloro-4-phenoxyquinoline, does not react with III to any appreciable extent (Run 5).[7]

The above findings, namely, that the reaction of the dichloro compound I with phenol is much faster than with the diamine III and that the product (II) from the faster reaction is capable of reacting with III to give chloroquinine leaves little doubt that II is an intermediate in the reaction of I with III in the presence of phenol.

Further evidence for the presence of this intermediate was obtained by its actual isolation from reactions which had been allowed to go only to partial completion. By interrupting the reaction after four hours (Run 10) the yield of IV was 34%, and approximately 44% of an oil was isolated which consisted largely of 7-chloro-4-phenoxyquinoline and a small amount of unreacted I. Had the reaction time been extended, the yield of chloroquine (IV) would have been increased to over 80% (compare Runs 3 and 4). This increase could only have occurred if novol diamine reacted with the intermediate II, since only a small amount of I was unreacted. The reaction of the intermediate II with novol diamine is shown in Run 11 in which the yield of IV is essentially the same as that obtained in Run 10.

In order to determine the reason for the reaction of phenol in preference to the amine III, an investigation of the effect of acid and base on the reaction of 4,7-dichloroquinoline with phenol was next undertaken (Table II). The results can best be explained if the phenolate ion and not phenol is involved in this reaction. If phenol itself were the reactant, then addition of acid should increase the rate of the reaction due to increased activity of the 4-carbon atom by ring nitrogen protonization.[8] However, this is not the case. When one mole of hydrogen chloride was present (Run 21), only 5% of product was obtained as compared

TABLE II

THE EFFECT OF ACID AND BASE ON THE REACTION OF 4,7-DICHLOROQUINOLINE WITH PHENOL AT 100 ± 1° FOR ONE HOUR

No.	Phenol, moles[a]	Added reagents (moles)[a]	Materials isolated: 7-Chloro-4-phenoxyquinoline	4,7-Dichloroquinoline[b]
15	1.0		24	69
16	2.1		50	42
17	3.2		65	32
18	2.1	Base[c] (1.77)	3	94
19	2.1	Base[c] (0.5)	22	74
20	3.2	Base[c] (0.5)	42	53
21	2.1	HCl[d] (1)	5	86

[a] Based on amount of 4,7-dichloroquinoline present. [b] The amount of 4,7-dichloroquinoline remaining was determined by its conversion to 7-chloro-4-hydroxyquinoline in the presence of acetic acid (see Experimental). [c] The base used was N^1,N^1-diethyl-N^4,N^4-dimethyl-1,4-pentanediamine. [d] Added as 4,7-dichloroquinoline hydrochloride.

(7) However, when acetic acid was added a 77% yield of chloroquine (IV) resulted (Run 6). This is comparable to the yield from the phenoxy hydrochloride (II) under the same conditions (Run 7). Similar results have been reported in the acridine series. See for example, (b) H. J. Barber, J. H. Wilkinson and W. G. H. Edwards, *J. Soc. Chem. Ind.*, **66**, 411 (1947). These workers have studied the mechanism of the reaction between amines and 9-aryloxy and alkoxy acridines and also on similar derivatives in the 4-quinoline series.

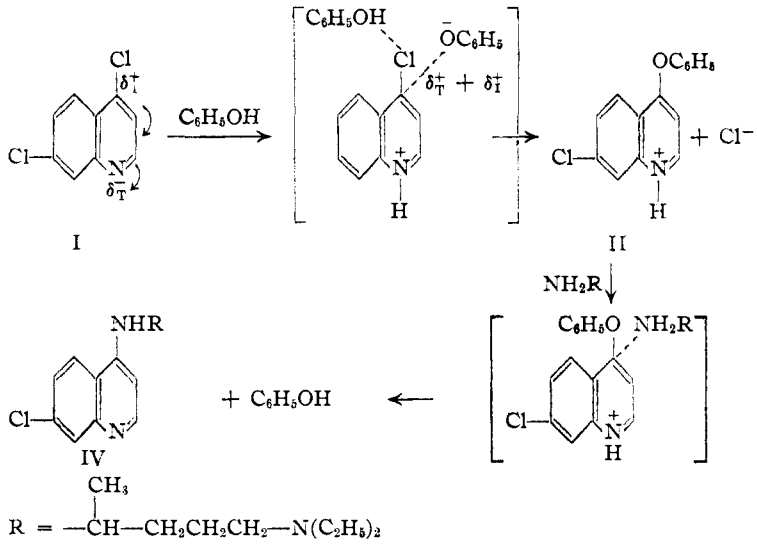
(8) C. K. Banks, THIS JOURNAL, **66**, 1127 (1944).

with 50% (Run 16) obtained in the absence of the acid. The acid, while increasing the available protons for protonization of the ring nitrogen, decreases the phenolate ion concentration. When base was added to the reaction mixture (Runs 18–20) the yields of product were also diminished. In these cases, the concentration of phenolate ions is increased. However, protonization of the ring nitrogen is minimized. The greater the concentration of base, the poorer was the yield.[9]

Obviously at least two factors, phenolate ion concentration and protonization of the ring nitrogen, are involved. The optimum conditions are apparently obtained when only the two reactants, 4,7-dichloroquinoline and phenol, are present. The phenol serves as a proton donor and the phenolate ion then can enter into the reaction.[10]

A third factor which undoubtedly influences the rate of the reaction is the solvolytic effect of phenol on the 4-chloro atom.[4] This effect must be involved in explaining the differences in the rate of reaction with varying phenol concentrations (Runs 15–17; also compare Runs 19 and 20).

On the basis of the evidence presented, the over-all reaction of 4,7-dichloroquinoline (I) with novol diamine (III) in the presence of phenol to give chloroquine (IV) can be formulated in the following manner.



It will be noted that, in the above mechanism, protonization of the ring nitrogen is involved in both the formation of the phenoxy compound and chloroquine. It would appear therefore that if additional protons were made available, without materially decreasing the phenolate ion concentration, the rate of the over-all reaction would be increased. This was found to be true. Although the optimum concentration of acid has not been determined, the effect of acid on the speed of the reaction is clearly shown by comparing Runs 10 and 12. In the latter case, the addition of one mole of hydrogen chloride almost doubled the yield.[11] The addition of acetic acid to the reaction mixture also increases the rate of the reaction (Run 14). In this case the acid was added after the formation of the phenoxy compound since acetic acid reacts with 4,7-dichloroquinoline to give 7-chloro-4-hydroxyquinoline (Run 13).

(9) In this connection, it is interesting to note that a great many preparations of phenoxyquinolines (and acridines) reported in the literature involve the reaction of a 2- or 4-chloroquinoline with an alkali phenolate. Under these conditions activation due to ring nitrogen protonization is absent. Accordingly, the reaction occurs less readily than in the reactions discussed above.

(10) The results are similar to those encountered in previous work dealing with the reaction of 4,7-dichloroquinoline with glacial acetic acid in which it was shown that both protonization of the ring nitrogen and acetate ion were involved, R. A. Cutler and A. R. Surrey, THIS JOURNAL, **72**, 3394 (1950).

Experimental

The Preparation of Chloroquine (Table I).—The general procedure involved heating a stirred mixture of 0.05 mole of 4-x,7-chloroquinoline, novol diamine and additional reactants (as indicated in Table I) at 125°. After the specified time the reaction mixture was worked up according to either of the following methods.

Method A.—The mixture was dissolved in 100 ml. of methanol and the calculated amount of phosphoric acid in methanol was added. After seeding, the mixture was allowed to stand at room temperature for twenty-four hours. The product was filtered off and washed with methanol. By adding ether to the filtrate to incipient turbidity and allowing to stand, a second crop of product was obtained. In most instances, both crops were practically pure chloroquine diphosphate. The yield of diphosphate is dependent not only upon the reaction conditions but also upon the composition of the precipitating medium. The amount of novol diamine employed in the reaction has a marked effect in this respect. When the mother liquors are concentrated and worked up according to Method B, in some cases the yields are substantially improved. For example, in Runs 3 and 4 the yields of diphosphate by Method A were 53% and 68%, respectively. By working up the filtrates the yields were 84% and 86%.

Method B.—The reaction mixture was poured into water containing 10 ml. of acetic acid, and made just alkaline to litmus with ammonium hydroxide solution. The mixture was extracted with ether and the two layers were worked up separately.

The ether layer was extracted with 10% sodium hydroxide and then washed with water. After drying, the ether was removed by distillation and the residual oil was then treated for the isolation of I or/and II. The aqueous layer was treated with an excess of ammonium hydroxide and extracted with ether; the ether layer was washed with water, dried, the ether removed by distillation to give crude chloroquine base. The latter was dissolved in ten volumes of methanol and treated with phosphoric acid as in Method A. In this case the first crop represented the entire yield.

7-Chloro-4-phenoxyquinoline.—A mixture of 9.9 g. (0.05 mole) of 4,7-dichloroquinoline and 10 g. (0.106 mole) of phenol was heated at 125° for one hour.[12] After cooling, the contents of the flask solidified. The material was dissolved in warm isopropyl alcohol (10 ml.) and the solution diluted with 120 ml. of ether. The 7-chloro-4-phenoxyquinoline hydrochloride which separated was filtered off and washed with ether; yield, 99%, m.p. 135–190°.[13] The base obtained from this hydrochloride was distilled at 154.5–157° (0.2–0.3 mm.); $n^{25}D$ 1.6484. It solidified on standing and was recrystallized from Skellysolve A, m.p. 49.5–51° (cor.).

(11) In the acridine series it was shown, W. A. Cowdrey and A. G. Murray, Brit. Pat. 583,220, Dec. 12, 1946, that the yield of atebrine is increased by the use of 1–2 equivalents of anhydrous hydrogen chloride per mole of 9-chloroacridine.

(12) The reaction is exothermic. Heating the mixture to 160° causes the temperature to rise rapidly to 195°.

(13) With one mole of phenol at 125° for eight hours, the crude hydrochloride melted at 195–205°.

Anal. Calcd. for $C_{15}H_{10}ClNO$: Cl, 13.86. Found: Cl, 13.75.

The hydrochloride prepared from the purified base was recrystallized from isopropyl alcohol, m.p. 207.5–210° (cor.).

Anal. Calcd. for $C_{15}H_{10}ClNO \cdot HCl$: Cl, 24.27; N, 4.80. Found: Cl, 23.60[14]; N, 4.74.

The Effect of Acid and Base on the Reaction of 4,7-Dichloroquinoline with Phenol (Table II).—In each of seven test-tubes was placed 0.01 mole of 4,7-dichloroquinoline (or the hydrochloride, Run 21) and the phenol and other reagents were added as indicated in Table II. The stoppered tubes were heated simultaneously at 100° for one hour with initial shaking to insure thorough mixing. At the end of this time the test-tubes were cooled in an ice-bath and worked up separately.

The contents of each tube were treated with 20 ml. of 10% sodium hydroxide solution and ether and transferred to a separatory funnel. After shaking vigorously, the aqueous layer was removed and the ether washed twice with water (and then with a buffered solution[15] for Runs 18–20, to remove the N^1,N^1-diethyl-N^4,N^4-dimethyl-1,4-pentanediamine). After drying and removing the ether by distillation an oil was obtained which was a mixture of 4,7-dichloroquinoline and 7-chloro-4-phenoxyquinoline. In Runs 18 and 21 the oil consisted mainly of the former and solidified on standing.

The amount of unchanged 4,7-dichloroquinoline present in the mixture was determined by its conversion to 7-chloro-4-hydroxyquinoline. In each case, the mixture was heated with 3 ml. of acetic acid and 1 ml. of triethylamine at 125° for seventy-five minutes. The reaction mixture was then treated with 80 ml. of 10% sodium hydroxide solution and ether, shaken thoroughly and the layers separated. The ether was washed twice with water and the washings combined with the alkaline solution. Acidification with acetic acid gave 7-chloro-4-hydroxyquinoline.

The 7-chloro-4-phenoxyquinoline was obtained from the ether layer after removal of the ether by distillation.

In order to check the accuracy of the above method of analysis, a mixture containing known amounts of 4,7-dichloroquinoline, 7-chloro-4-phenoxyquinoline and N^1,N^1-diethyl-N^4,N^4-dimethyl-1,4-pentanediamine was assayed. This work indicated that although the results tabulated in Table II are reasonably precise, the values for the phenoxy compound probably should be about 5% lower and that for the dichloroquinoline about 10–15% higher.

RENSSELAER, N. Y. RECEIVED DECEMBER 22, 1950

(14) The compound apparently loses hydrogen chloride very easily.

(15) Prepared by treating dilute ammonium hydroxide with acetic acid until just acid to litmus.

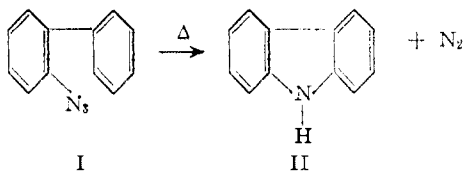
[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

The Synthesis of Heterocyclic Compounds from Aryl Azides. II. Carbolines and Thienoindole[1]

BY P. A. S. SMITH AND J. H. BOYER

o-(α-Pyridyl) and *o*-(β-pyridyl)-phenyl azide have been prepared from the corresponding anilines by diazotization and coupling with sodium azide. The former is converted to *o*-(α-pyridyl)-aniline (XII) when heated in "inert" solvents, but the latter cyclizes to a mixture of α- and γ-carboline (VIII, IX) in good yield. *o*-(α-Thienyl)-aniline was prepared by coupling diazotized *o*-nitroaniline with thiophene followed by reduction. The product was then converted to the corresponding azide, which was cyclized in good yield to 4-thieno[3,2-b]indole (VI).

Since the thermal decomposition of *o*-azidobiphenyl (I) and certain substituted derivatives proved a convenient synthesis of carbazole (II) and corresponding derivatives,[1b] an investigation of the application of the reaction for the synthesis of compounds isosteric with carbazole was undertaken. The investigation of *o*-(α-thienyl)-phenyl azide and *o*-(α-pyridyl)-phenyl azide and its β-isomer are reported here.



I II

o-(α-Thienyl)-phenyl azide (V) was readily prepared by a three-step process from diazotized *o*-nitroaniline and thiophene. Several examples of the coupling of diazonium derivatives with thiophene to give arylthiophenes have been reported,[2,3] but only in the case of *m*-cyanophenyldiazonium acetate, which gave α-(*m*-cyanophenyl)-thiophene,[4] has the position taken by the entering aryl group been clearly determined. The product formed in our experiment was shown to be α-(*o*-nitrophenyl)-thiophene (III) by reducing the nitro group and deaminating the resulting aminophenylthiophene to the known α-phenylthiophene (IV).

After reduction of the nitro group using sodium sulfide according to a general procedure developed by Hodgson,[5] the diazotized amine was treated with sodium azide and hydrochloric acid. *o*-(α-Thienyl)-phenyl azide (V) separated immediately. Thermal decomposition of this compound in one per cent. solutions in decalin (preferred), kerosene, or trichlorobenzene at 170–180° brought about the loss of nitrogen accompanied by ring closure to the carbazole analog, 4-thieno(3,2-b)indole (VI). The numbering system used here is that recommended by the Ring Index,[5a] in place of those previously reported.[6,7]

Whereas 4-thieno(3,2-b)indole itself has not before been reported, several derivatives of it have been prepared in different ways. Benary and Baravian[6] reported that 3-hydroxy-4-carbethoxy-5-methylthiophene undergoes the Fischer indole synthesis to form 3-carbethoxy-2-methyl-4-thieno-(3,2-b)indole, which was saponified and decarboxyl-

(1) (a) Presented at the National Meeting of the Am. Chem. Soc., Chicago, Ill., Sept., 1950; (b) Part I of this series: P. A. S. Smith and B. B. Brown, THIS JOURNAL, **73**, 2435 (1951).

(2) M. Gomberg and W. E. Bachmann, *ibid.*, **46**, 2339 (1924).

(3) E. Bamberger, *Ber.*, **30**, 3666 (1897).

(4) W. E. Bachmann and R. A. Hoffman, Chap. 6 in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York City, N. Y., 1944.

(5) H. H. Hodgson and S. Birtwell, *J. Chem. Soc.*, 75 (1944) (for leading references).

(5a) A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publ. Corp., New York, N. Y., 1940, p. 198.

(6) E. Benary and A. Baravian, *Ber.*, **48**, 593 (1915).

(7) Ng. Ph. Buü-Hoi, Ng. Hoan, Ng. H. Khoi and Ng. D. Xuong, *J. Org. Chem.*, **14**, 802 (1949).