

pentane at *ca.* 320, 340, 352 and 391 μ with inflections at *ca.* 368, 410 and 430–435 μ . These were chromatographed once more on 200 g. of alumina.

Typical fractions (50 cc. each), eluted with pentane-ether (4:1), were fraction 35 with $\lambda_{\text{max}}^{\text{pentane}}$ 319, 340, 352, 367(infl.), 391, 407(infl.) and 430 μ ; fraction 45 with $\lambda_{\text{max}}^{\text{pentane}}$ 322, 342(infl.), 354, 372, 393, 410(infl.) and 434(infl.) μ ; and fraction 50 with $\lambda_{\text{max}}^{\text{pentane}}$ 322, 343, 361(infl.), 374, 391, 414, 433(infl.) and 458 (infl.). All these fractions on evaporation gave yellow-brown oils which could not be crystallized.

Full Hydrogenations.—All the full hydrogenations of the crystalline polyacetylenes were carried out by shaking the substance dissolved in dioxane (freshly distilled over sodium) in hydrogen over a pre-reduced platinum catalyst at room temperature and atmospheric pressure. When no more gas was absorbed, the catalyst was removed, washed with hot dioxane, and the solvent was evaporated. The crystalline residue was dissolved in a little pentane or petroleum ether (b.p. 70–80°) and filtered through a short column of alumina. The solvent was again evaporated and the residue was crystallized from the specified solvent.

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N. C.]

Ring Closure *via* Aryne Intermediates: A General Principle of Synthesis^{1,2}

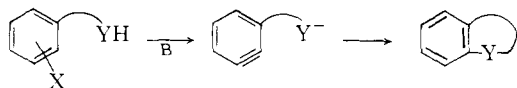
BY J. F. BUNNETT³ AND BJORN F. HRUTFIORD

RECEIVED SEPTEMBER 8, 1960

A novel general principle of ring closure, conceivably applicable to the synthesis of countless heterocyclic and homocyclic systems, is developed and explored. This principle involves the formation of an aryne (benzyne) intermediate having a side chain bearing a strong nucleophile which can add intramolecularly to the aryne structure. Such an intermediate is formed by treatment of a suitably constituted aryl halide with a strong base such as potassium amide in liquid ammonia. The principle is illustrated by new syntheses of benzothiazole, benzoxazole, phenothiazine and indole systems, mostly in yields of 60–90%. Several observations of interest with respect to reaction mechanisms are discussed.

Most anions having negative charge on carbon, nitrogen or sulfur are effective nucleophiles *versus* arynes (benzyne derivatives).^{4–8} Nucleophilic attack initiates an addition to the "triple bond," which is completed by acquisition of a proton from the medium. For example, thiophenoxide ion reacts with benzyne in liquid ammonia to form diphenyl sulfide.^{5,6}

It was therefore expected that compounds having (a) a halogenated aromatic ring as an aryne precursor plus (b) the conjugate acid of an active nucleophile in a suitably located side chain would, on treatment with a very strong base, furnish ring closure products representing intramolecular nucleophilic addition to the aryne structure. The principle is represented by the generalized equation



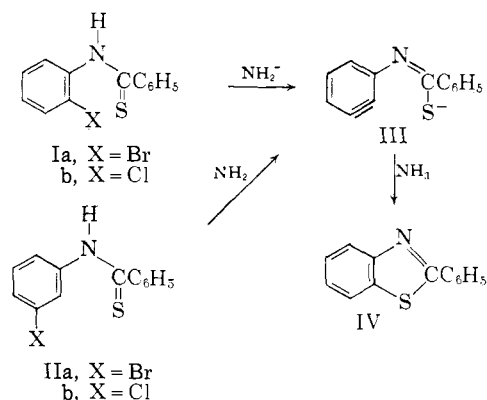
in which X is a halogen atom *ortho* or *meta*⁹ to the side chain and YH is a functional group which, upon loss of a proton, forms the nucleophilic group Y⁻.

In the laboratory, we discovered several ring closure reactions which fulfill the expectations from theory. These are described in this paper. While this work was in progress, Huisgen and König¹⁰

described some examples of this principle of ring closure in which YH was a primary or secondary amino group. Additional examples (nearly all involving amine side chains) and experiments bearing on the reaction mechanism are reported in three further papers from Huisgen's laboratory.^{11,12}

In our ring closure reactions, summarized in Table I, many classes of side-chain nucleophiles are represented. Intramolecular addition of sulfur anions, nitrogen anions, oxygen anions and a carbanion have been realized. In presenting this work, we first describe the experiments and discuss their significance in regard to reaction mechanism. Applications in synthesis are considered later in the paper.

Benzothiazoles.—Treatment of thiobenz(*o*-bromo)-anilide (Ia) with potassium amide in liquid ammonia gave, in the best experiment,



2-phenylbenzothiazole (IV) in 90% yield. A somewhat lower yield (62%) of the same product was obtained from the chlorine analog Ib. The presumed intermediate III should also be formed from the *meta* isomers IIa and IIb and indeed these compounds also gave IV on treatment with potas-

(1) Described in part in preliminary communications: B. F. Hrutfiord and J. F. Bunnett, *J. Am. Chem. Soc.*, **80**, 2021, 4745 (1958). Based on the Ph.D. thesis of B. F. H., April, 1959.

(2) Supported in part by the Office of Ordnance Research, U. S. Army.

(3) Brown University, Providence, Rhode Island.

(4) E. F. Jenny, M. C. Caserio and J. D. Roberts, *Experientia*, **14**, 349 (1958).

(5) F. Scardiglia and J. D. Roberts, *Tetrahedron*, **3**, 197 (1958).

(6) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **23**, 904 (1958).

(7) W. W. Leake and R. Levine, *J. Am. Chem. Soc.*, **81**, 1169, 1627 (1959).

(8) R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).

(9) If the side chain is long enough, the halogen may even be *para* to it.⁸

(10) R. Huisgen and H. König, *Angew. Chem.*, **69**, 268 (1957).

(11) R. Huisgen and H. König, *Chem. Ber.*, **92**, 203, 429 (1959).

(12) R. Huisgen, H. König and N. Bleeker, *ibid.*, **92**, 424 (1959).

TABLE I
 RING CLOSURE REACTIONS (IN LIQUID AMMONIA)

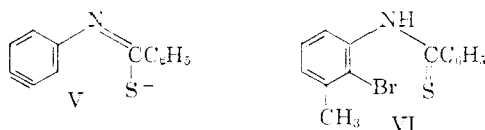
Reaction	Reactant	Moles KNH ₂ per mole reactant	Time, min.	Product	Yield, %
1	Thiobenz-(2-bromo)-anilide (Ia)	3.9	5	2-Phenylbenzothiazole (IV)	90
2	Thiobenz-(2-bromo)-anilide (Ia)	2.0	60	2-Phenylbenzothiazole (IV)	73
				+ recovd. Ia	20
3	Thiobenz-(2-chloro)-anilide (Ib)	3.0	120	2-Phenylbenzothiazole (IV)	62
				+ recovd. Ib	15
4	Thiobenz-(3-bromo)-anilide (IIa)	3.0	180	2-Phenylbenzothiazole (IV)	72
5	Thiobenz-(3-chloro)-anilide (IIb)	3.2	120	2-Phenylbenzothiazole (IV)	67
				+ recovd. IIb	2
6	Thiobenz-(2-bromo-4-methyl)-anilide	4.0	60	2-Phenyl-6-methylbenzothiazole	30
7	N-Phenyl-N'-(<i>o</i> -chlorophenyl)-thiourea	4.0	60	2-Anilinobenzothiazole	19
8	N-Phenyl-N'-(<i>o</i> -chlorophenyl)-thiourea	5.0	15	2-Anilinobenzothiazole	4
				+ recovd. reactant	12
9	Ammonium N-(<i>o</i> -chlorophenyl) dithiocarbamate	4.1	60	2-Mercaptobenzothiazole	17 ^a
				+ <i>o</i> -chloroaniline	82
10	Benz-(2-bromo)-anilide (VIIa)	5.0 ^c	90 ^c	2-Phenylbenzoxazole (IX)	72
11	Benz-(2-chloro)-anilide (VIIb)	4.0 ^b	150 ^b	2-Phenylbenzoxazole (IX)	69
12	Benz-(2-chloro)-anilide (VIIb)	2.3	90	2-Phenylbenzoxazole (IX)	31
				+ recovd. VIIb	42
13	2-Amino-2'-bromodiphenyl sulfide (X)	4.0	40	Phenothiazine (XI)	44
14	Acetoacet-(<i>o</i> -chloro)-anilide (XII)	4.0	30	3-Acetyloxindole (XIV)	78
15	<i>o</i> -Chlorophenylacetone (XV)	4.2 ^c	720 ^c	2-Methylindole (XIX)	31

^a Based on the *o*-chloroaniline used to prepare the reactant.
^c The solvent was about 20% ether-80% ammonia.

^b The solvent was a mixture of ammonia, ether and toluene.

sium amide, in 72 and 67% yields, respectively. The fact that IV is formed nearly as well from the *meta* compounds IIa and IIb as from the *ortho* isomers Ia and Ib is good support for the elimination-addition mechanism assigned to these reactions.

From the *meta* compounds, some of the isomeric aryne V might have been produced. No definite products derived from V were isolated, but appreci-



able amounts of inhomogeneous and possible polymeric product fractions from both IIa and IIb may have had this origin.¹³

If formation of IV from Ia had occurred *via* direct displacement of bromine by the sulfur anion, rather than *via* aryne III, any base strong enough to remove a proton from the thioamide structure should serve to bring about this transformation. In fact, when Ia was heated at reflux in ethanol with a fourfold excess of sodium ethoxide for five hours, 97% of it was recovered unchanged, and only 0.9% of IV was obtained. Since these conditions are far more strenuous with respect to temperature and time than those employed in the ring closure experiments, and since alkoxides in boiling alcohols are unable to generate arynes from aryl halides,^{6,14} this experiment is further support for the aryne mechanism assigned to reactions 1, 2 and 3 of Table I.

(13) It is noteworthy that the 2-hydrogens of IIa and IIb are more readily removed in aryne formation than the 4-hydrogens. We do not know the reason.

(14) F. Scardiglia and J. D. Roberts, *J. Org. Chem.*, **23**, 629 (1958).

Thiobenz-(2-bromo-3-methyl)-anilide (VI) should not form an aryne on treatment with potassium amide because it has no hydrogen *ortho* to bromine. After an hour's exposure of VI to a fourfold excess of potassium amide in ammonia, 69% was recovered unchanged. No well-defined product could be isolated. Since the isomer with methyl in the 4-position (reaction 6, Table I) and the parent compound lacking the methyl group (Ia) are both totally consumed on exposure to potassium amide under these conditions, with production of benzothiazoles, the unreactivity of VI is further evidence for the aryne mechanism. Were a direct displacement of bromine by the sulfur anion involved, the *ortho* methyl group should have little effect.¹⁵

Intermediate III is depicted with the *cis* configuration (of aryne to sulfur) about its carbon-nitrogen double bond. The *trans* configuration is also conceivable, but would not be expected to give ring closure products. The good yields of IV obtained indicate either that the *cis* and *trans* configurations are rapidly interconvertible or that the *cis* configuration is formed preferentially. Several conformations of III, from rotation about the carbon-nitrogen single bond, are conceivable, but only those approximating the conformation depicted should give ring closure. Presumably the lifetime of the aryne structure is much longer than the period of rotation.

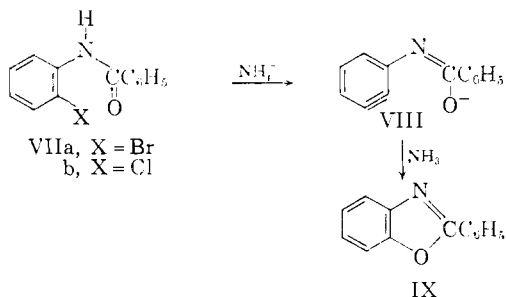
Reactions 6, 7, 8 and 9 of Table I represent further benzothiazole syntheses *via* aryne intermediates, albeit in poorer yields. The sharp decrease in yield on introduction of a 4-methyl group (reaction 6) is difficult to understand. Much tar was formed in this reaction.

Treatment of *o*-chlorophenylthiourea with potas-

(15) J. D. Reinbeiner and J. F. Bunnett, *J. Am. Chem. Soc.*, **81**, 315 (1959).

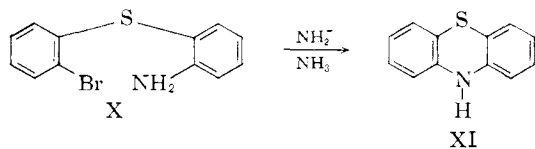
sium amide gave not 2-aminobenzothiazole, but rather *o*-chlorophenylcyanamide. Elimination of hydrogen sulfide occurred in preference to ring closure.

Benzoxazoles.—Benz-(2-bromo)-anilide (VIIa) and its chlorine analog VIIb were converted into 2-phenyl-benzoxazole (IX) in 72 and 69% yields, respectively, by the action of potassium amide in ammonia.



These reactions are analogous to the benzothiazole closures. The foregoing remarks about stereochemical considerations also apply here. A noteworthy feature of these reactions is that a product (IX) representing addition of an oxygen nucleophile to an aryne in competition with amide ion is obtained in high yield. Efforts to cause methoxide ion to add to benzyne in ammonia have failed,¹⁶ and only 4% of diphenyl ether was obtained when benzyne was generated in ammonia in the presence of phenoxide ion.⁵ Moreover, Huisgen, *et al.*,⁸ obtained meager yields (9 and 2%) of ring closure products from arynes bearing side-chain alkoxide ion functions. Possible reasons for the success of oxygen addition in the present case are a superb stereochemical situation in VIII and/or especially high nucleophilic reactivity in the type of oxygen anion derived from a carboxamide structure.

Phenothiazine.—Treatment of 2-amino-2'-bromo-diphenyl sulfide (X) with potassium amide gave phenothiazine (XI) in 44% yield. This was a single experiment; we believe the yield could be improved with practice. This reaction represents addition of a nitrogen anion to an aryne.

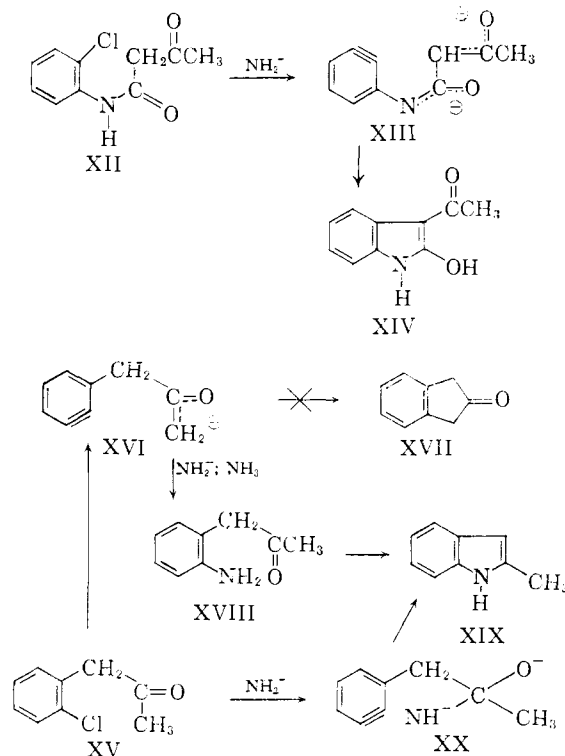


3-Acetyloxindole.—Treatment of acetoacet-(*o*-chloro)-anilide (XII) with potassium amide produced 3-acetyloxindole (XIV) in 78% yield (XII \rightarrow XX). This represents intramolecular addition of a carbanion (in XIII) to an aryne.

2-Methylindole.—We thought that treatment of *o*-chlorophenylacetone (XV) with potassium amide might produce 2-indanone (XVII) *via* aryne intermediate XVI. The product obtained was, however, 2-methylindole (XIX)¹⁷ in 31% yield.

(16) T. K. Brotherton, Thesis, University of North Carolina, 1956.

(17) Regrettably, the product was described as XVII in the first preliminary communication¹; the mistake was corrected in the second.¹



Two routes to this unexpected ring closure product are conceivable. One involves addition of external amide ion to aryne XVI, or to its isomer (not shown) representing loss of a proton from the α -position to the ring, or even to the related aryne-dianion resulting from loss of protons from both α - and γ -positions,¹⁸ to form XVIII or an anion thereof, which then closes with loss of water to form 2-methylindole. Addition of amide ion *ortho*, rather than *meta*, is reasonable with respect to Robert's rule of control by the inductive effect¹⁹ inasmuch as the anionic side chain would have an electron-releasing inductive effect.

The other route involves formation of intermediate XX, or a monoprotonated derivative thereof, which then closes intramolecularly to form XIX. Precedent for addition of amide ion to a carbonyl group has been furnished by Hamrick and Hauser,²⁰ who found that the adduct of potassium amide to benzophenone can be precipitated from liquid ammonia by addition of ether. At present, both routes to XIX appear feasible.

Compounds Unchanged by KNH₂ in Ammonia.—*o*-Chlorophenylacetamide was treated with potassium amide in ammonia in the hope of obtaining oxindole. The original reactant was, however, recovered unchanged. Recovery was 88% after exposure to 2.9 equivalents of potassium amide in ammonia for 15 minutes, and 80% after treatment with 5.2 equivalents of potassium amide in a homogeneous ammonia-toluene-tetrahydrofuran solution for six hours. Similarly, *o*-chlorophenylacetic acid was recovered to the extent of 95% from treat-

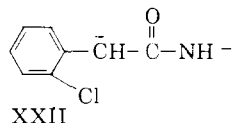
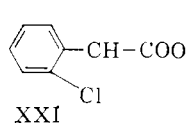
(18) Cf. T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 1100 (1959).

(19) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenov, *ibid.*, **78**, 611 (1956).

(20) P. J. Hamrick, Jr., and C. R. Hauser, *ibid.*, **81**, 2096 (1959).

ment with four equivalents of potassium amide for 12 hours.

The resistance of these compounds to aryne formation is remarkable. We believe it stems from the protective effect, toward aryne formation, of a negative charge concentrated on the α -carbon of a side-chain. The initial product of the action of potassium amide on *o*-chlorophenylacetic acid is undoubtedly dianion XXI.²¹ Likewise, XXII is no doubt obtained from *o*-chlorophenylacetamide.



In each of these dianions, the negative charge on the α -carbon cannot be shared to any considerable extent with the adjacent carbonyl group which is already part of a negatively charged function. In consequence, sharing of the charge of the α -carbon atom with ring positions by resonance is strong. The resulting negative charge on the ring decreases the acidity of ring hydrogens so that they are not attacked by amide ion. The same protective effect is evident in the resistance of halogenated anilines^{22,23} and of *o*-chlorophenylcyanamide (*cf.* Experimental) to aryne formation.

One of our best ring closures, of XII to XIV, must involve aryne formation from a chlorobenzene bearing a dianion side chain, inasmuch as the amide and active methylene hydrogens of XII are much more acidic than ring hydrogens. The principle stated above is not violated, though, because of the capacity of this particular side chain to diffuse the negative charge through resonance. Negative charge is not concentrated on the atom next to the ring.

Application in Synthetic Work.—Described above are new syntheses of four ring systems, all heterocyclic. The principal interest in this work lies, however, not so much in the syntheses that have been achieved as in the potentialities for synthesis of countless other systems, heterocyclic and homocyclic, by the general principle of synthesis developed in this paper. Ring closure by intramolecular nucleophilic addition to an aryne structure is as general in principle as ring closure by intramolecular electrophilic aromatic substitution, and perhaps may be just as useful.

With regard to specific syntheses described in this paper, only that of 3-acetyloxindole is superior to methods previously known. This synthesis has additional interest as a route to oxindole itself, since the acetyl group is easily removed by refluxing with dilute sodium hydroxide (92% yield).²⁴ Further synthetically useful transformations utilizing 3-acetyloxindole and related compounds have recently been described by Wenkert and co-workers.²⁴

Our benzothiazole, benzoxazole and phenothiazine syntheses have potential value for preparation of specific derivatives of these systems. Thus,

(21) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956).

(22) R. A. Benkeser and G. Schroll, *ibid.*, **75**, 3196 (1953).

(23) J. H. Wotiz and F. Huba, *J. Org. Chem.*, **24**, 595 (1959).

(24) E. Wenkert, B. S. Bernstein and J. H. Udelhofen, *J. Am. Chem. Soc.*, **80**, 4899 (1958).

synthesis of substituted benzoxozoles by action of alkali amides on acyl derivatives of haloanilines may prove, in certain applications, to be more convenient than common benzoxazole syntheses requiring *o*-aminophenols. For synthesis of benzothiazoles and phenothiazines, ring closure *via* arynes has the advantage of giving products of definite structure in contrast to other methods which may give either of two isomers. It therefore has value for proof of structure. Roe and Tucker²⁵ have recently used this method to confirm the structure of 2-phenyl-5-fluorobenzothiazole obtained by another route.

Experimental²⁶

Benzanilides were prepared by reaction of benzoyl chloride with the appropriate aniline derivative in pyridine and benzene.²⁷ Yields were 83–95%, and melting points were all within one degree of literature values. Benz-(2-bromo)-anilide (VIIa),²⁸ m.p. 116°; benz-(2-chloro)-anilide (VIIb),²⁹ m.p. 99°; benz-(3-bromo)-anilide,³⁰ m.p. 134°; benz-(3-chloro)-anilide,²⁹ m.p. 120–121°; benz-(2-bromo-4-methyl)-anilide,³¹ m.p. 147–148°.

Thiobenzanilides were prepared from the corresponding benzanilides by thiation with phosphorus pentasulfide in refluxing pyridine.³² Best yields were obtained when purified phosphorus pentasulfide, extracted from the commercial product by carbon disulfide in a Soxhlet extractor, and strictly anhydrous pyridine were used. Recrystallization was from dilute ethanol or from cyclohexane.

Thiobenz-(2-bromo)-anilide (Ia), m.p. 85–86°, was obtained in 90% yield. *Anal.* Calcd. for C₁₃H₁₀BrNS: Br, 27.35; N, 4.79. Found: Br, 27.50; N, 4.78.

Thiobenz-(2-chloro)-anilide (Ib), m.p. 73–74°, was obtained in 92% yield. *Anal.* Calcd. for C₁₃H₁₀ClNS: C, 63.02; H, 4.07. Found: C, 63.08; H, 4.15.

Thiobenz-(3-bromo)-anilide (IIa), m.p. 106–108°, was obtained in 66% yield. *Anal.* Calcd. for C₁₃H₁₀BrNS: Br, 27.35; N, 4.79. Found: Br, 27.50; N, 4.78.

Thiobenz-(3-chloro)-anilide (IIb), m.p. 97–98°, was obtained in 95% yield. *Anal.* Calcd. for C₁₃H₁₀ClNS: C, 63.02; H, 4.07. Found: C, 62.84; H, 4.15.

Thiobenz-(2-bromo-4-methyl)-anilide, m.p. 131–132°, was obtained in 94% yield. *Anal.* Calcd. for C₁₄H₁₂BrNS: C, 54.91; H, 3.95. Found: C, 55.00; H, 4.08.

2-Bromo-3-methylaniline, b.p. 108° (10 mm.), was prepared by the action of hydrazoic acid (from 6.5 g. of sodium azide) on 2-bromo-3-methylbenzoic acid³³ (17.7 g.) in concentrated sulfuric acid (80 cc.) at 50° for 2 hours and then at room temperature for 6 hours. The yield was 82%.

Benz-(2-bromo-3-methyl)-anilide, m.p. 116–117°, was obtained as described above in 90% yield. *Anal.* Calcd. for C₁₄H₁₂BrNO: C, 57.95; N, 4.17. Found: C, 57.84; H, 4.34.

Thiobenz-(2-bromo-3-methyl)-anilide (VI), m.p. 76–77°, was obtained by treatment of this amide with phosphorus pentasulfide, as described above, in 80% yield. *Anal.* Calcd. for C₁₄H₁₂BrNS: C, 54.91; H, 3.95. Found: C, 55.15; H, 4.04.

(25) A. Roe and W. P. Tucker, Univ. of North Carolina, unpublished work.

(26) Analyses for carbon and hydrogen by Micro-Tech Laboratories, Skokie, Ill.; for nitrogen and bromine by Miss Betty Jean Pegram, Venereal Disease Experimental Laboratory, U. S. Public Health Service, through the courtesy of Dr. Leon Freedman.

(27) R. L. Shriner and R. C. Fuson, "The Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 177.

(28) F. D. Chattaway and J. M. Wadmore, *J. Chem. Soc.*, **81**, 986 (1902).

(29) R. von Walther and A. Groesmann, *J. prakt. Chem.*, [2] **78**, 486 (1908).

(30) F. B. Dains and R. N. Harger, *J. Am. Chem. Soc.*, **40**, 562 (1918).

(31) J. Pinnow, *Ber.*, **24**, 4170 (1891).

(32) E. Klingsberg and D. Papa, *J. Am. Chem. Soc.*, **73**, 4988 (1951).

(33) J. F. Bunnett and M. M. Rauhut, *Org. Syntheses*, **38**, 11 (1958).

o-Chlorophenylthiourea,³⁴ m.p. 144–146°, and *N*-phenyl-*N'*-(*o*-chlorophenyl)-thiourea,³⁵ m.p. 157–158°, were obtained by standard methods.

2-Bromo-2'-nitrodiphenyl sulfide, m.p. 116–117°, was obtained from condensation of *o*-bromothiophenol with *o*-chloronitrobenzene by the method of Tarbell and Fukushima³⁶ in 90% yield. Recrystallization was from ethanol.

Anal. Calcd. for C₁₂H₉BrNO₂S: C, 46.45; H, 2.60. Found: C, 46.41; H, 2.70.

2-Amino-2'-bromodiphenyl Sulfide (X).—Six grains of 2-bromo-2'-nitrodiphenyl sulfide was placed in a 200-cc. round-bottom flask with about 5 g. of iron metal powder, 40 cc. of water and 1 cc. of concentrated hydrochloric acid. The mixture was heated at reflux for 3 hours. The mixture was extracted twice with ether and once with hot benzene, and the combined extracts were dried over anhydrous potassium carbonate. The amine was precipitated as its hydrochloride by treatment with dry hydrogen chloride. The hydrochloride was treated with aqueous sodium hydroxide, the mixture was extracted twice with benzene, and the benzene was evaporated. The residue was crystallized from ethanol; white crystals (3.09 g., 57%), m.p. 62–63°, were obtained.

Anal. Calcd. for C₁₂H₁₀BrNS: C, 51.44; H, 3.60. Found: C, 51.00; H, 3.63.

A sample of the hydrochloride (from another preparation) was crystallized from ethanol. When pure, it melted at 132–134°.

Anal. Calcd. for C₁₂H₁₁BrClNS: C, 45.51; H, 3.50. Found: C, 45.57; H, 3.79.

o-Chlorophenylacetonitrile.—In a 1-liter 3-neck flask, 100 g. of powdered sodium cyanide was dissolved in 100 cc. of water with heating by a water-bath. A solution of 250 g. (1.55 moles) of *o*-chlorobenzyl chloride in 250 cc. of 95% ethanol was slowly added from a dropping funnel. The mixture was then heated under a condenser overnight on the steam-bath. The flask was cooled and the precipitated sodium chloride was collected and washed with ethanol, the washings being combined with the main filtrate. The filtrate was evaporated as much as possible on the steam-bath, a second crop of sodium chloride was collected, and the filtrate was concentrated under water-pump vacuum and then distilled. The yield of *o*-chlorophenylacetonitrile b.p. 101–104° (4 mm.), was 202 g. (86%).

o-Chlorophenylacetamide.—The above nitrile (28.8 g.) was mixed with 50 cc. of concentrated sulfuric acid and 10 cc. of water, and the mixture was allowed to stand at room temperature for 30 min. before being poured onto ice. The resulting white crystals of *o*-chlorophenylacetamide were recrystallized from dilute ethanol. The yield was 24.5 g. (76%), m.p. 171–174° (lit.³⁷ 175°).

o-Chlorophenylacetic acid, m.p. 93–95° (lit.³⁸ 93–95°), was obtained in 71% yield by refluxing 115 g. of *o*-chlorophenylacetonitrile with a mixture of 100 cc. each of glacial acetic acid, water and concentrated sulfuric acid for 1 hour. Crystallization was from dilute ethanol.

o-Chlorophenylacetone (XV).—A mixture of 57 g. of *o*-chlorophenylacetic acid, 80 g. of acetic anhydride and 24 g. of sodium acetate was maintained at 145°, under an air-cooled condenser, for 18 hours. The solution was poured into water, and the resulting mixture was made basic and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, concentrated and distilled; 33 g. (59%) of *o*-chlorophenylacetone, b.p. 123–128° (13 mm.), was obtained. The oxime had m.p. 121–122° (lit.³⁹ 120°).

Ring Closure Reactions. General Procedure.—The apparatus sketched in Fig. 1, which resembles that of Scardiglia and Roberts,⁵ was used. Two 1000-cc. 3 necked flasks were mounted side by side. Each was equipped with a Dry Ice condenser in the outermost neck, and each condenser outlet was protected by a soda lime drying tube. Each flask was fitted in the center neck with a ball-joint-bearing mechanical stirrer, the right stirrer having a small propeller

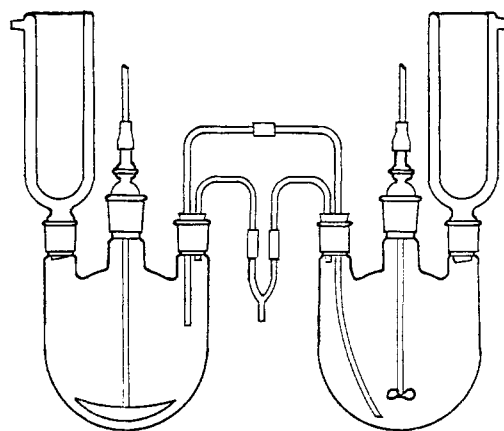


Fig. 1.—Apparatus for ring closure reactions.

blade and the left a large sweep blade. The innermost neck of each flask was fitted with a 2-hole rubber stopper. One hole in each stopper was for nitrogen supply, through a short piece of glass tubing inserted through each stopper and connected by rubber tubes, which could be closed by pinch clamps, to a Y-tube which in turn was connected to a dry nitrogen source. The other hole in each stopper was for transfer of liquid from the right flask to the left via a glass tube extending to the bottom of the right flask, inserted through the right stopper and connected by a piece of rubber fitted with a pinch clamp to a short glass tube inserted through the left stopper.

The first step in using this apparatus was to dry it by flaming while dry nitrogen was passed through. The compound to be treated with potassium amide was then placed in the left flask; occasionally sodium-dried ethyl ether or toluene was also added to increase solubility. The condensers were charged with solid carbon dioxide and isopropyl alcohol, and liquid ammonia (from a commercial cylinder) was placed in the right flask. Usually about 600 cc. of ammonia was used. Small pieces of potassium metal were added to the ammonia, to destroy water, until a blue color in the ammonia persisted for several minutes. About 200 cc. of the ammonia was then transferred to the left flask by nitrogen pressure; nitrogen supply to the left flask was temporarily shut off and pressure was generated (cautiously) in the right flask by blocking egress from the right soda lime tube with a finger. Potassium amide was prepared in the right flask by adding the required weight of potassium metal and a small amount of crushed ferric nitrate. As soon as the blue color had disappeared, the potassium amide solution was forced over into the left flask by nitrogen pressure. (As soon as possible, with nitrogen flowing into the left flask and both connections to the right flask shut by pinch clamps, the right flask was removed from the apparatus and rinsed with ethanol from a wash bottle to destroy traces of potassium metal or potassium amide which are a fire hazard.)

After the chosen reaction time, the theoretical amount of solid ammonium nitrate was added to the reaction mixture. Ethyl ether was added and the ammonia was allowed to evaporate, usually overnight. The residue is referred to as "the crude reaction product" in the following paragraphs.

2-Phenylbenzothiazole (IV). A. From Thiobenz-(2-bromo)-anilide (Ia).—In reaction 1, Table I, 2.9 g. of Ia was used with 100 cc. of liquid ammonia and other quantities as indicated in Table I. In reaction 2, 11.0 g. of Ia was used. In isolating products, unreacted Ia was obtained from an alkaline aqueous layer and IV from a benzene extract. Compound IV, crystallized from ethanol, had m.p. 114°, not depressed on admixture with an authentic sample, and gave an infrared spectrum identical with that of authentic IV.

B. From Thiobenz-(2-chloro)-anilide (Ib).—In reaction 3, 10.0 g. of Ib was used. Unreacted Ib was recovered from an alkaline aqueous layer, and IV from an ether extract; IV had m.p. 112–113°.

C. From Thiobenz-(3-bromo)-anilide (IIa).—In reaction 4, 10.0 g. of IIa was used. The crude reaction product was treated with water and benzene. From the

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benzene layer, 4.9 g. of IV, m.p. 112°, was crystallized directly. The benzene liquors were evaporated and the residue was extracted with concentrated hydrochloric acid. From the hydrochloric acid solution, another 0.4 g. of IV, m.p. 112–114°, was obtained. Remaining insoluble in hydrochloric acid was 1.3 g. of foul smelling tar. The mixture melting point of this IV with authentic IV was not depressed.

D. From Thiobenz-(3-chloro)-anilide (IIb).—In reaction 5, 10.0 g. of IIb was used. The crude reaction product was extracted with water and ether. Acidification of the water layer precipitated 0.20 g. of IIb, m.p. 96–97°. The ether layer was extracted with dilute mineral acid and then evaporated, and the residue was crystallized from petroleum ether. White crystals of IV, m.p. 112–113°, weighing 5.68 g. were so obtained. By basification of the acidic solution (from extraction of the ether layer), extraction with ether, evaporation of the ether and crystallization from ethanol, 1.05 g. of a substance which sintered at 95° and melted completely at 165° was obtained. An attempt to prepare a benzoyl derivative, by treatment with benzoyl chloride, was unsuccessful. This material was not further investigated.

2-Phenyl-6-methylbenzothiazole.—In reaction 6, 8.4 g. of thiobenz-(2-bromo-4-methyl)-anilide was used. The reaction solution (in ammonia) had a deep blue-violet color. The color changed to red upon addition of ammonium nitrate. The crude reaction product was extracted with ether and water. No unreacted thioanilide could be recovered from the water layer. By sublimation of the residue from evaporation of the ether layer, 1.89 g. of white crystals, m.p. 123–125°, was obtained. The mixture melting point with authentic 2-phenyl-6-methylbenzothiazole⁴⁰ was not depressed. The residue from the sublimation was 4.4 g. of tar, soluble only in acetone.

2-Anilinobenzothiazole.—In reaction 7, 13.1 g. of N-phenyl-N'-(*o*-chlorophenyl)-thiourea was used. The ether layer from extraction of the crude reaction product yielded, on evaporation, a solid which was extracted for 5 days with petroleum ether (b.p. 60–90°) in a Soxhlet extractor. The yellow solid obtained by evaporation of the extract was shaken with dilute hydrochloric acid, from which 2.0 g. of a white solid was obtained upon neutralization. After several recrystallizations from ethanol, the m.p. was 157–158°. This is the m.p. of both 2-anilinobenzothiazole⁴¹ and the starting thiourea. Identification as 2-anilinobenzothiazole was supported by the facts that (a) the m.p. after admixture with the starting thiourea was below 145°, (b) the acetyl derivative melted at 162–163° and depressed the m.p. of the starting thiourea, and (c) the picrate melted at 228°. Literature melting points for the acetyl and picrate derivatives of 2-anilinobenzothiazole are 167° and 222°, respectively.⁴¹ A further 0.15 g. of 2-anilinobenzothiazole was obtained from the residue of the hydrochloric acid extraction.

In reaction 8, 10.0 g. of N-phenyl-N'-(*o*-chlorophenyl)-thiourea was used. The crude reaction product was extracted with ether and dilute sodium hydroxide, and 1.21 g. of white crystals, m.p. 156° not depressed on admixture with the starting thiourea, was recovered from the alkaline layer. The ether layer was evaporated and the residue was extracted with benzene and dilute sulfuric acid, and 0.35 g. of crystals of m.p. 157°, not depressed on admixture with authentic 2-anilinobenzothiazole, was obtained from the acidic layer. Evaporation of the benzene layer gave 5.8 g. of a gummy solid from which no pure compound could be isolated.

2-Mercaptobenzothiazole.—In reaction 9, *o*-chloroaniline (5.7 g.), carbon disulfide (4 cc.) and dry ether (100 cc.) were placed in the standard reaction flask. Ammonia gas was bubbled into the constantly stirred solution for 30 minutes. Then 100 cc. of anhydrous ammonia was added, followed by a solution of potassium amide (from 7.2 g. of potassium metal) in ammonia. Water and ether were added to the crude reaction product. Acidification of the water layer gave a precipitate which, after crystallization from methanol, had m.p. 172–176° and weighed 1.26 g. This melting point was not depressed on admixture with authentic 2-mercaptobenzothiazole. Treatment of the ether layer with dry hydrogen chloride precipitated 6.25 g. of white

crystals. By the Schotten-Baumann method, these were converted to the benzoyl derivative, m.p. 97–99°, which is in agreement with the m.p. (99°) reported for benz-(2-chloro)-anilide.²⁹

2-Phenylbenzoxazole (IX). **A. From Benz-(2-bromo)-anilide (VIIa).**—In reaction 10, 10.0 g. of VIIa was used. A green color appeared on addition of potassium amide in ammonia to VIIa in ammonia and ether, and after about 5 minutes a white precipitate formed. The crude reaction product was extracted with water and ether. The pH of the water layer was carefully adjusted to 7.0, and the 0.4 g. of crystals which separated was added to the ether layer which was then evaporated. By recrystallization of the residue from ethanol and then sublimation of the solid recovered from the mother liquors, two crops of crystals of m.p. 99–101° were obtained. The m.p. was not depressed on admixture with authentic 2-phenylbenzoxazole prepared by distilling a mixture of *o*-aminophenol and benzoyl chloride.

B. From Benz-(2-chloro)-anilide (VIIb).—In reaction 12, 10.0 g. of VIIb was used. The crude reaction product was extracted with benzene and water, and 4.15 g. of unreacted VIIb was recovered from the benzene layer. The water layer was carefully neutralized and on long standing 2.57 g. of crystals, m.p. 101°, separated. The mixture m.p. with authentic 2-phenylbenzoxazole was 99–102° and the infrared spectra were identical. In contrast, a mixture of the crystals of m.p. 101° with VIIb melted at 76–79°.

In reaction 11, 5.0 g. of VIIb was used. The ether layer from extraction of the crude product left no residue on evaporation. The water layer deposited a dark precipitate, which was discarded, on neutralization to pH 8. The pH was then adjusted to 7.0; 2.31 g. of crystals, m.p. 99–101° not depressed on admixture with authentic 2-phenylbenzoxazole (IX), separated on standing overnight. From the mother liquors, a further 0.45 g. of IX and 0.26 g. of VIIb were recovered.

Phenothiazine (XI).—In reaction 13, 3.09 g. of X was used. The aqueous layer from extraction of the crude reaction product did not give any oil or precipitate on neutralization. The benzene layer was filtered, concentrated and cooled; 0.97 g. of blue-white crystals, m.p. 182–184°, separated. The mixture m.p. with authentic XI was 181–183°.

3-Acetyloxindole (XIV).⁴²—In reaction 14, 5-l. flasks were used in an apparatus otherwise of the standard type. The quantities used were: liquid ammonia, 4 l.; XII,⁴³ 105.8 g. (0.5 mole); potassium metal, 78 g. (2.0 mole); reaction time was 30 minutes. After addition of ammonium nitrate, 500 cc. of ethyl ether was added and the ammonia was evaporated. The residue was extracted with 1.5 l. of water, and the water layer, after being extracted three times with ether (which removed a purple impurity), was made acidic by addition of hydrochloric acid. The resulting light tan precipitate weighed 68.5 g., had m.p. 204–206°. Recrystallization from chloroform with use of charcoal gave white needles of m.p. 204–205.5°.

This product did not depress the m.p. of authentic XIV prepared by the method of Horner,⁴⁴ gave an identical infrared spectrum. The oxime had m.p. 178°, literature value²⁴ 180–181°.

2-Methylindole (XIX).—In reaction 15, 31 g. of XV was used. A deep red color and the formation of a precipitate were observed immediately after addition of the potassium amide (in ammonia) to XV (in ammonia and ether). The crude reaction product was extracted with water and ether. The ether layer was extracted with aqueous mineral acid and with aqueous alkali, and the residue from evaporation of the ether was steam distilled. A white solid, 7.40 g., m.p. 59°, was obtained from the distillate. The distillation residue was 3.2 g. of tar.

This white solid was at first thought to be 2-indanone (XVII), m.p. 58–59°,⁴⁵ and was so described in the first

(42) This procedure represents optimum conditions developed by Mr. S. M. Williamson. Using these conditions but a smaller scale of operation, Mr. Williamson obtained yields as high as 86%.

(43) Acetoacet-(*o*-chloro)-anilide (XII) is a product of Union Carbide Chemicals Co. We are grateful for their gift of a generous sample.

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preliminary Communication.¹⁷ However, it strongly depressed the m.p. of authentic XVII prepared by the method of Leven, *et al.*,⁴⁶ and was found to contain nitrogen. The product of m.p. 59° did not depress the m.p. of authentic XIX, m.p. 57–59°, prepared by the Fischer indole synthesis.⁴⁷ Also, it formed a picrate, m.p. 137–138°, and a styphnate, m.p. 142–144°; the reported melting points of the picrate and styphnate of XIX are 139° and 147°, respectively.⁴⁸ The product is thus 2-methylindole (XIX).¹⁷

In other runs, XIX was obtained in 10% yield from treatment of XV with potassium amide (3 equivalents) in liquid ammonia (without ether being present). No XIX was obtained by treatment of XV with potassium amide in dry ether (without ammonia) or with lithium diethylamide in ether. In no case was any XVII or any 2-methylbenzofuran (another conceivable product) isolated.

Other Experiments. Action of Potassium Amide on *o*-Chlorophenylthiourea.—The standard ring closure procedure was employed, with 10.0 g. of *o*-chlorophenylthiourea and 8.4 g. of potassium metal being used. A white precipitate appeared three minutes after the potassium amide solution was added to the thiourea in ammonia, and soon turned yellow. When ammonium nitrate was added after 1 hour, the precipitate dissolved. Ether was added, the ammonia was evaporated, water was added, and the resulting suspension was filtered. The solid collected would neither melt nor burn. After evaporation of the ether layer, only a trace of pleasant smelling substance remained. The water layer was treated with decolorizing charcoal; upon neutralization of the resulting solution a precipitate formed and hydrogen sulfide was evident by odor. The precipitate when dried was a brown powder; 4.2 g. Recrystallization from ethanol and then from benzene-pe-

troleum ether gave 3.47 g. of white crystals, m.p. 105–106°. Elemental analysis was positive for chlorine and nitrogen but negative for sulfur. The infrared spectrum showed strong absorption peaks at 3340, 3190 and 2250 cm.⁻¹ but no absorption between 1615 and 2100 cm.⁻¹. The bands observed are typical of N—H, aromatic C—H and C≡N, respectively. The substance is believed to be *o*-chlorophenylcyanamide,³⁴ m.p. 104–105°.

Action of Potassium Amide on Thiobenz-(2-bromo-3-methyl)-anilide (VI).—The potassium amide from 5.1 g. (0.13 mole) of potassium metal was allowed to act for 1 hour upon 10.0 g. (0.033 mole) of VI by the standard ring closure procedure. The crude reaction product was treated with ether and aqueous alkali. The aqueous layer was acidified and extracted with ether. Recrystallization from cyclohexane of the residue from evaporation of the ether furnished yellow crystals of VI, weight 6.91 g., m.p. 73–75° not depressed on admixture with the original VI. Efforts to isolate other pure substances from the product mixture were fruitless. A fraction expected to contain basic compounds was chromatographed on alumina and several fractions of indefinite melting point around 40° were obtained. These fractions were combined in benzene and dry hydrogen chloride was introduced; 0.65 g. of a precipitate melting about 130–140° separated. The basic material recovered from this hydrochloride was impure, and no crystalline sublimate was obtained.

Action of Sodium Ethoxide in Ethanol on Ia.—Sodium metal (4.6 g.) was "dissolved" in 100 cc. of absolute ethanol, and 14.6 g. of Ia was added. The mixture was refluxed 5 hours, during which the color was constantly pale yellow. The mixture was then poured into water which was acidified with sulfuric acid. From the heavy yellow precipitate which formed, 14.13 g. of Ia, m.p. 83–85° not depressed on admixture with the original Ia, and 0.16 g. of pale yellow crystals of m.p. 60–65° (presumably impure Ia) were obtained by standard procedures. From the acidic solution, 0.09 g. of white crystals m.p. 110° not depressed on admixture with authentic IV, was isolated by standard methods. The latter depressed the melting point of Ia.

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Polymerization of Non-conjugated Diynes by Complex Metal Catalysts^{1,2}

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The polymerization of 1,6-heptadiyne by Ziegler type catalysts leads to soluble, highly colored polymers of 10,000–20,000 molecular weight, which contain alternating double and single bonds along the backbone of the polymer chain and a cyclic recurring unit as the main structural features. Polymerization of 1,7-octadiyne and 1,8-nonadiyne under the same conditions, however, affords mostly crosslinked polymers.

Recently, it has been established that non-conjugated diolefinic monomers can polymerize to yield linear, high molecular weight polymers.³ An alternating intramolecular–intermolecular propagation mechanism has been postulated to account for the absence of crosslinking and the cyclic recurring units. The monomers 1,6-heptadiene, biallyl and bimethallyl have been shown to form

cyclic recurring units by this mechanism when initiated by an aluminum triisobutyl–titanium tetrachloride catalyst.⁴ An X-ray investigation of polybiallyl has shown it contains the methylenecyclopentane recurring units.⁵ Polymerization of the higher members in the α -diolefin series gives greater amounts of non-cyclic crosslinked polymers.⁶

Since acetylene and various substituted monoacetylenes have recently been polymerized by complex metal catalysts to olefinic polymers,⁷

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(2) Presented in part at the April, 1959, Meeting of the American Chemical Society, Boston, Mass.

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