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Studies of Ring Closure *via* Aryne Intermediates[1]

J. F. Bunnett,[2] Tetsuzo Kato,[3] Roland R. Flynn, and J. A. Skorcz

Venable Chemical Laboratory, University of North Carolina, Chapel Hill, North Carolina, and the Metcalf Chemical Laboratory, Brown University, Providence, Rhode Island

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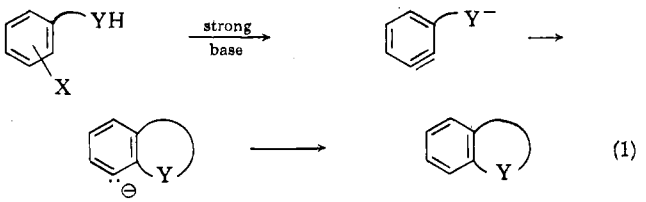
Several attempts, some successful, others not, to achieve ring closure *via* intramolecular nucleophilic addition to aryne intermediates are described. Cyclizations forming oxindole derivatives and the novel 2,1-benzisothiazoline 2,2-dioxide system are recorded. Instances in which ring closure was not realized owing to predominance of external addition of NH_2^- ion have been encountered, as has another case in which an initially formed substrate anion resisted aryne formation. Limitations of ring closure *via* aryne intermediates as a synthetic method are discussed.

It has recently been shown that an aryne[4,5] carrying a strong nucleophile in a side chain will often experience intramolecular addition of the nucleophile to the aryne "triple bond," forming a new ring fused to the original aromatic ring.[4-9] The process is illustrated in generalized notation by equation 1. As a principle

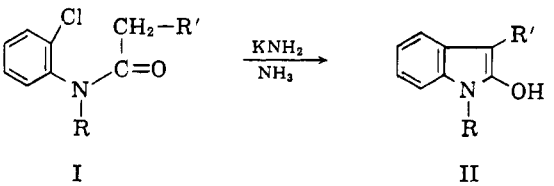


(1)

of synthesis, this reaction has wide applicability and considerable practical value. Studies of it also bring to light novel problems of reaction mechanism.

The present research continues our exploration of this type of reaction.

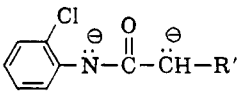
Experiments with N-acyl-*o*-Chloroanilines.—It was previously discovered[7,8] that acetoacet(*o*-chloro)anilide (Ia) afforded 3-acetyloxindole (IIa) in 78% yield on treatment with potassium amide in liquid ammonia. In the present work, phenylacet(N-methyl-*o*-chloro)-anilide (Ic) underwent ring closure to IIc in even better yield (91%). However phenylacet(*o*-chloro)anilide (Ib), which lacks the N-methyl group of Ic, was recovered unchanged almost quantitatively from exposure to the same reaction conditions.



I II

a. R = H; R′ = $COCH_3$
b. R = H; R′ = C_6H_5
c. R = CH_3; R′ = C_6H_5
d. R = H; R′ = H
e. R = CH_3; R′ = H

We believe that Ib resists aryne formation because it is rapidly and completely converted by potassium amide into dianion IIIb,[10] in which there is a large degree of localization of negative charge on the nitrogen atom. By mesomerism, the nitrogen atom



IIIa. R′ = $COCH_3$
b. R′ = C_6H_5

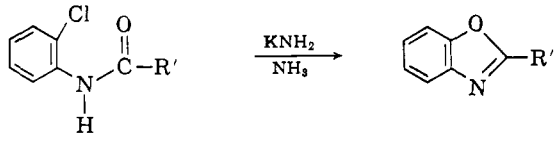
shares its negative charge with ring carbon atoms, thereby decreasing the acidity of ring hydrogens so much that they become unreactive with potassium amide. It has been noted in other instances that a high concentration of negative charge on an atom next to a benzene ring tends to protect halogens on that ring from being involved in aryne formation.[7,9,11]

In the case of dianion IIIa, an aryne is formed. Evidently the keto and amide carbonyl groups together sufficiently well accommodate the carbanion and

(1) Supported in part by the Army Research Office (Durham).
(2) To whom inquiries should be addressed, at Brown University.
(3) On leave from The Women's Department, Tokyo College of Pharmacy, 1957–1958.
(4) R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).
(5) J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961).
(6) R. Huisgen and co-workers, *Angew. Chem.*, **69**, 268 (1957); *Ber.*, **92**, 203, 424, 429 (1959); **93**, 1496 (1960).
(7) J. F. Bunnett and B. F. Hrutfiord, *J. Am. Chem. Soc.*, **80**, 2021 (1958); **83**, 1691 (1961).
(8) J. F. Bunnett, B. F. Hrutfiord, and S. M. Williamson, *Org. Syntheses*, **40**, 1 (1906).
(9) J. F. Bunnett and J. A. Skorcs, *J. Org. Chem.*, **27**, 3836 (1962).
(10) R. B. Meyer and C. R. Hauser, *ibid.*, **26**, 3696 (1961).
(11) C. R. Hauser and G. F. Morris, *ibid.*, **26**, 4740 (1961).

nitranion charges so that relatively little negative charge is forced onto ring carbon atoms.

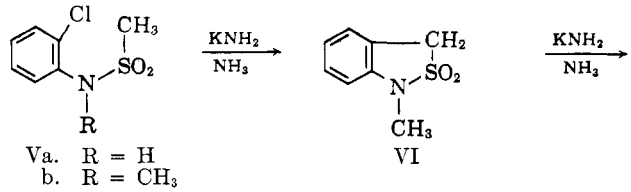
Acet(N-methyl-*o*-chloro)anilide (Ie) was converted into N-methyloxindole (IIe) in 16% yield by the action of potassium amide in ammonia. This shows that an amide carbonyl group is at least partially successful in activating carbanion formation at an otherwise unactivated α-carbon. Again the parent amide without the N-methyl group behaved differently. Id reacted with potassium amide in ammonia to form 2-methylbenzoxazole (IVd) in 37% yield. This resembles



Id. R′ = CH_3 IVd. R′ = CH_3
f. R′ = C_6H_5 f. R′ = C_6H_5

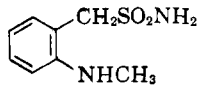
the transformation of benz(*o*-chloro)anilide (If) into 2-phenylbenzoxazole (IVf) in 69% yield under similar conditions.[7]

Experiments with N-Methanesulfonyl-*o*-chloro-anilines.—It seemed that the sulfonyl group of a sulfonamide should promote carbanion formation at an adjacent carbon atom. Methanesulfon(N-methyl-*o*-chloro)anilide (Vb) on treatment with potassium amide in ammonia (containing some ether) for one hour afforded,



Va. R = H
b. R = CH_3

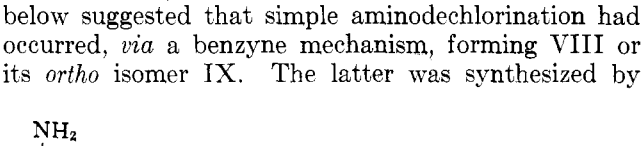
VI



VII

however, not the expected ring closure product VI, but rather a white compound, m.p. 137.5–138.5°, whose analysis was compatible with the formula $C_8H_{12}N_2O_2S$. Let us call this "compound A."

The solubility of compound A in dilute hydrochloric acid, its analysis, and analogy with cases described below suggested that simple aminodechlorination had occurred, *via* a benzyne mechanism, forming VIII or its *ortho* isomer IX. The latter was synthesized by



VIII IX X

an unequivocal route; though its melting point (137–138°) was nearly the same as that of compound A, the mixture melting point was depressed and the infrared spectra were different. Compound A also differed from authentic VIII.

Authentic VIII and IX were acquired by condensing the appropriate nitroanilines with methanesulfonyl chloride, methylating the resulting sulfonamides with methyl sulfate, and finally reducing the nitro groups with stannous chloride.

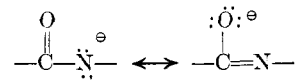
Reinvestigation of the reaction of Vb with potassium amide in ammonia revealed that the product formed in a short (15 min.) reaction time was not compound A, but rather a neutral substance, m.p. 91–92°, whose analysis and n.m.r. spectrum were consistent with structure VI. The yield was 66%. A repeated reaction of one hour's duration yielded a mixture of VI (37%) and compound A (43%). This suggested that potassium amide slowly acted upon VI to produce compound A. Indeed, it was found that 68% of VI was converted into compound A during an hour's exposure to ring closure conditions; 22% of VI was recovered unchanged.

Two modes of action of potassium amide upon VI were conceivable. Amide ion might initiate aryne formation by attacking the hydrogen *ortho* to nitrogen, with subsequent fission of the C_{Ar}—N bond and finally nucleophilic addition of amide ion, forming X or its *meta* isomer. Or it might effect nucleophilic displacement on sulfur, generating VII. Apart from the fact that the m.p. of compound A differs from that (110–111°) reported for X,[12] identification of compound A as VII was indicated by the observation that compound A did not give the diazotization–azo coupling test characteristic of aromatic primary amines and by its n.m.r. spectrum. The latter revealed, besides the aromatic protons, two protons (the methylene group) at the same field as the methylene group of VI and three protons at higher field than in VI.

The proper name of VI is 1-methyl-2,1-benzisothiazoline 2,2-dioxide. Although benz-2,1-isothiazole is known,[13] we have not found any record of previous synthesis of a derivative of 2,1-benzisothiazoline 2,2-dioxide.

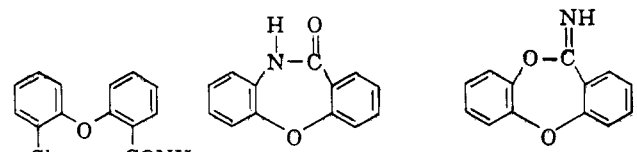
Methanesulfon(*o*-chloro)anilide (Va) reacted with four equivalents of potassium amide in ammonia (one-hour reaction time), but only basic, intractable oils were obtained.

Experiments with *o*-Chlorophenoxyacet- and Benzamides.—The action of strong base on a carboxamide carrying at least one hydrogen on nitrogen converts it to an anion in which the charge is shared between oxygen and nitrogen:



The reactions of Id and If, cited above, are testimony that such an anion can add via oxygen to an aryne "triple bond." Addition via nitrogen in an example of suitable geometry is also conceivable.

Accordingly 2-(*o*-chlorophenoxy)benzamide (XI) was exposed to potassium amide in ammonia in the hope

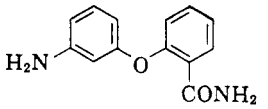


XI XII XIII

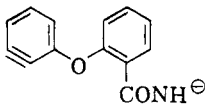
(12) U. M. Teotino and G. Cignarella, *J. Am. Chem. Soc.*, **81**, 4935 (1959).

(13) S. Gabriel and T. Posner, *Ber.*, **28**, 1025 (1895); J. Goerdeler and J. Kandler, *ibid.*, **92**, 1679 (1959).

of obtaining XII or XIII. The product isolated in 55% yield was, however, 2-(*m*-aminophenoxy)benzamide (XIV), identical with a sample procured by an unequivocal synthesis. Evidently aryne intermediate



XIV

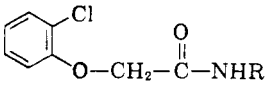


XV

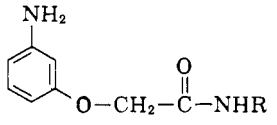
XV exists to such a large extent in conformations with —CONH⁻ so remote from the aryne bond that external addition of amide ion prevails over intramolecular addition. That a cine-substitution product of *meta* orientation was formed is reasonable by analogy with the directing effect of the methoxy group in similar reactions.[14,15]

2-(*o*-Chlorophenoxy)benzoic acid was synthesized by the copper-catalyzed condensation of sodium *o*-chlorophenoxide with sodium *o*-iodobenzoate or *o*-chlorobenzoate. Both variations of this method were satisfactory. 2-(*o*-Chlorophenoxy)benzoic acid was then converted to its amide (XI) via the acid chloride. We got authentic XIV by copper-catalyzed reaction of sodium *m*-nitrophenoxide with sodium *o*-chlorobenzoate in 1-pentanol,[16] transformation of the resulting 2-(*m*-nitrophenoxy)benzoic acid to its amide, and finally stannous chloride reduction of the nitro group.

o-Chlorophenoxyacetamide (XVIa) and *o*-chlorophenoxyacetanilide (XVIb) were also submitted to the action of potassium amide in ammonia. None of the anticipated six-ring cyclization products was obtained. In both cases the presumed aryne intermediates added external amide ion preferentially, forming *m*-amino compounds XVIIa and XVIIb, respectively. Both were identical with authentic samples.



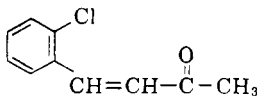
XVIa. R = H
b. R = C_6H_5



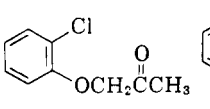
XVIIa. R = H
b. R = C_6H_5

Authentic XVIIa and XVIIb were synthesized by condensation of sodium *m*-nitrophenoxide with sodium chloroacetate to *m*-nitrophenoxyacetic acid, reaction of the acid chloride with ammonia as well as aniline, and finally stannous chloride reduction of the nitroamides.

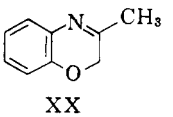
Experiments with Ketones.—It was hoped that potassium amide in ammonia would act upon *o*-chlorobenzalacetone (XVIII) to generate β-naphthol. However, only tars were produced. The products from exposure of *o*-chlorophenoxyacetone (XIX) to ring closure conditions were also tarry, but a small amount of an unstable, pale yellow liquid whose properties resemble those reported for 2-methyl-2H-1,4-benzoxazine (XX)[17] was isolated. Formation of XX from XIX would parallel transformation of *o*-chlorophenylacetone to 2-methylindole as reported by Bunnett and Hrutfiord.[7]



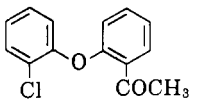
XVIII



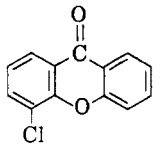
XIX



XX



XXI



XXII

2-(*o*-Chlorophenoxy)acetophenone (XXI) was made in 55% yield by treatment of 2-(*o*-chlorophenoxy)benzoyl chloride with dimethylcadmium.[18] A lesser amount of 4-chloroxanthone (XXII) was obtained as a by-product. The latter was at first mistaken to be XXI, and was submitted to ring closure conditions. The product isolated in 26% yield was 3-aminoxanthone, representing aminodechlorination with rearrangement as might have been expected.[14,15] No well defined products were gained from exposure of XXI to potassium amide in ammonia.

Discussion.—Although the present research records further successes in formation of oxindole derivatives and a facile synthesis of the 2,1-benzisothiazoline 2,2-dioxide ring system, its principal contribution is toward defining the limitations of ring closure via aryne intermediates.

When cyclization does not occur according to the pattern of equation 1, the reason may be one of the following:

1. The substance subjected to the action of strong base may be converted into an anion with such a high concentration of negative charge on an atom next the ring that aryne formation is prevented.[7,9] In the present work, the unreactivity of Ib compared to the satisfactory cyclizations realized with Ia and Ic is an excellent illustration.

2. The side chain nucleophile may not be an effective competitor with the external strong base (in this work, potassium amide) in adding to the aryne bond. It may have inherently low nucleophilicity, or it may have an unfavorable steric relationship to the aryne function. In our experience, the occurrence of aminodechlorination in the reactions of XI, XVIa, and XVIb is illustrative. We tentatively conclude that carboxamide anions are relatively poor nucleophiles towards arynes, although we recognize that this disadvantage can be overcome by a superb steric relationship as in the arynes from Id and If. Clearly, reduction of the potassium amide concentration should favor intramolecular nucleophilic addition. We have not probed this variable systematically.

3. The expected ring closure product may itself react with the strong base reagent. This subsequent reaction may be fast, as in the example of diethyl 1,2,3,4 - tetrahydronaphthalene - 1,1 - dicarboxylate,[9] or recognizably slow as in the case of VI. In instances of the latter sort, complications can be avoided by employing a short reaction time.

(14) H. Gilman and S. Avakian, *J. Am. Chem. Soc.*, **67**, 349 (1945).
(15) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenow, *ibid.*, **78**, 611 (1956).
(16) C. F. Koelsch and F. J. Lucht, *ibid.*, **71**, 3556 (1949).
(17) R. Stoermer and H. Brockerhof, *Ber.*, **30**, 1631 (1897).
(18) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

4. Reaction of the strong base with a side chain function may generate a different side chain nucleophile than anticipated. The reactions of *o*-chlorophenylacetone[7] and *o*-chlorophenoxyacetone (XIX) with potassium amide in ammonia are possible examples.

5. The substance submitted to the action of strong base may undergo some entirely different reaction in preference to ring closure. The cleavage of 2-chloro-2′,5′-dimethylbenzophenone by potassium amide in ammonia is an illustration.[19]

6. Intermolecular addition of side chain nucleophile to aryne "triple bond" may occur, giving rise to dimers, oligomers, or polymers. No certain example can be cited from experiments in liquid ammonia solvent.

7. Tars may be formed. This catch-all category, which is not foreign to our experience, can in principle include complications 2, 3, 5, and 6 as well as others, in various combinations.

With an understanding of the kinds of complications which can intrude, one is able to plan ring closure experiments with greater assurance. But he is handicapped by the imperfection of our knowledge of how strong bases such as potassium amide in ammonia react with various functional groups. Fortunately, this situation is gradually improving, in part by virtue of experimentation on ring closure reactions.

Experimental[20]

Preparation of Starting Materials. Phenylacet(*o*-chloro)anilide (Ib) was prepared by reaction of *o*-chloroaniline (7.0 g.) with phenylacetyl chloride (8.5 g.) in 75 cc. of carbon tetrachloride containing 4.3 g. of pyridine for 1.5 hr. The product (12 g.; 88%), crystallized from benzene as colorless needles, had m.p. 129–130° and was insoluble in water, difficultly soluble in ether, and carbon tetrachloride, and rather soluble in benzene and ethanol.

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.43; H, 4.88; N, 5.70; Cl, 14.46. Found: C, 69.12; H, 4.72; N, 5.97; Cl, 14.63.

Phenylacet(N-methyl-*o*-chloro)anilide (Ic).—A mixture of 7.0 g. of N-methyl-*o*-chloroaniline, 8.3 g. of phenylacetyl chloride, 4.0 g. of dry sodium bicarbonate, and 50 cc. of benzene was heated 5 hr. at reflux. The cooled mixture was extracted with concentrated aqueous sodium hydroxide, and the benzene layer was dried over solid potassium hydroxide, concentrated, and distilled at reduced pressure. The distillate, b.p. 178–185°/5 mm., weighed 7.0 g. (51%); it crystallized from petroleum ether, furnishing pale yellow prisms, m.p. 78–82°.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.39; N, 5.39. Found: C, 69.50; H, 5.15; N, 5.13.

Acet(*o*-chloro)anilide (Id), m.p. 86–87° (lit.[21] 86.7°), acet(N-methyl-*o*-chloro)anilide (Ie), b.p. 126–132°/6 mm. (lit.[22] 142°/14 mm.), and methanesulfon(*o*-chloro)anilide (Va), m.p. 89–90° (lit.[23] 90.5°) were made substantially as described in the references.

Methanesulfon(N-methyl-*o*-chloro)anilide (Vb), m.p. 75–76°, was made by methylation of Va by methyl sulfate and aqueous alkali, and was crystallized from dilute ethanol.

Anal. Calcd. for $C_8H_{10}ClNO_2S$: C, 43.73; H, 4.55. Found: C, 43.76; H, 4.63.

2-(*o*-Chlorophenoxy)benzoic Acid. A. From *o*-Iodobenzoic Acid.—*o*-Iodobenzoic acid (25 g.) and potassium carbonate (7 g.) were combined in water, and the mixture was evaporated to dryness. Sodium metal (2.3 g.) was dissolved in 25 cc. of methanol, 38 g. of *o*-chloropenol was added, and the mixture was evaporated to dryness. The two residues were combined with 1 g. of copper powder and heated for 5 hr. at 170–180°. The cooled mixture was taken up in aqueous sodium carbonate solution, and the resulting mixture was treated with charcoal, filtered and acidified. The precipitated solid was extracted with hot water to remove *o*-iodobenzoic acid, and the residue was crystallized from dilute acetone, furnishing white needles, m.p. 128° (lit.[24] 123–124°).

Anal. Calcd. for $C_{13}H_9ClO$: C, 62.77; H 3.62. Found: C, 62.60; H, 3.66.

B. From *o*-Chlorobenzoic Acid.—To a solution of 9 g. of sodium metal in 300 cc. of methanol 25 g. of *o*-chlorophenol and 31 g. of *o*-chlorobenzoic acid were added, the solvent was evaporated, 1 g. of copper powder was added, and the mixture was heated at 180° (it melted) and finally to 220° (it solidified). The yield of 2-(*o*-chlorophenoxy)benzoic acid of m.p. 125–128° (128° after crystallization from methanol) was 35 g. (72%).

2-(*o*-Chlorophenoxy)benzamide (XI).—The above acid was converted to the acid chloride with thionyl chloride, and the latter was treated with aqueous ammonia. The product was crystallized from dilute methanol; m.p. 145°.

Anal. Calcd. for $C_{13}H_{10}ClNO_2$: C, 63.03; H, 4.04. Found: C, 62.90; H, 4.20.

o-Chlorophenoxyacetamide (XVIa), m.p. 149–150° (lit.[25] 149.5°), and *o*-chlorophenoxyacetanilide (XVIb), m.p. 125–127° (lit.[25] 121°), were prepared after Minton and Stephen.[25] Our XVIb was analyzed.

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.24; H, 4.58. Found: C, 64.37; H, 4.76.

o-Chlorobenzalacetone (XVIII), b.p. 133–134°/6 mm. (lit.[26] 154–155°/17 mm.), was made after Vorländer.[26]

o-Chlorophenoxyacetone (XIX), b.p. 180–181°/65 mm. (lit.[27] 110–115°/4 mm.), was made after Bokarev and Mel'nikov,[27] except that chloroacetone was used instead of bromoacetone.

2-(*o*-Chlorophenoxy)acetophenone (XXI).—A Grignard reagent was prepared from magnesium metal (2.4 g.) and methyl iodide (14.2 g.) in ether, and to it 9.8 g. of anhydrous cadmium chloride was added and the mixture was heated at reflux for 70 min. The ether was removed, 50 cc. of benzene was added, and the mixture was vigorously stirred at reflux. The flask was cooled. The acid chloride obtained from 20 g. of 2-(*o*-chlorophenoxy)benzoic acid and 50 cc. of thionyl chloride in 50 cc. of benzene, with subsequent vacuum evaporation, was dissolved in 50 cc. of benzene and added dropwise with stirring. This caused active refluxing. The mixture was heated at reflux 1 hr. after completion of addition. By standard separation procedures, 3.0 g. (16%) of XXII, m.p. 135–136° (not depressed on admixture with an authentic sample[28]) and 11 g. (55%) of colorless XXI, b.p. 155–156°/3 mm., were isolated.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.15; H, 4.46. Found: C, 68.28; H, 4.43.

Preparation of Authentic Products (Actual or Conceivable). 2-Methylbenzoxazole (IVd), b.p. 95–96°/25 mm. or 197–199°/1 atm. (lit.[29] 200–201°/1 atm.), was made after Ladenburg.[29]

Methanesulfon(*m*-nitro)anilide was synthesized by condensation of *m*-nitroaniline (10.0 g.) with methanesulfonyl chloride (8.3 g.) in 56 cc. of pyridine on the steam bath for 2.5 hr. The product was isolated conventionally, and was crystallized from 95% ethanol. Cream-colored crystals, m.p. 161.5–163.5° (lit.[30] 164°), weighing 14.9 g. (95%), were obtained.

Anal. Calcd. for $C_7H_8N_2O_4S$: C, 38.88; H, 3.73. Found: C, 39.01; H, 3.84.

Methanesulfon(N-methyl-*m*-nitro)anilide was made by heating a solution of 6.48 g. of the above product in 46 cc. of 16% aqueous sodium hydroxide with 16.0 g. of methyl sulfate 3 hr. at reflux, was isolated conventionally, and finally crystallized from 95% ethanol. It was obtained as colorless crystals (3.7 g.; 53%), m.p. 94–95°.

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.38. Found: C, 41.65; H, 4.35.

(19) J. F. Bunnett and B. F. Hrutfiord, Abstracts, 135th National Meeting of the American Chemical Society, Boston, April, 1959, p. 94-O; *J. Org. Chem.*, in press.

(20) Analyses for carbon and hydrogen by Micro-Tech Laboratories, Skokie, Ill. Melting points are uncorrected.

(21) A. F. H. Lobry de Bruyn, *Rec. trav. chim.*, **36**, 135 (1916).

(22) P. Grammaticakis, *Bull. soc. chim.*, 761 (1949).

(23) C. S. Marvell, M. D. Helfrick, and J. P. Belsley, *J. Am. Chem. Soc.*, **51**, 1272 (1929).

(24) C. N. Deshpande, P. B. Sattur, and K. S. Nargund, *J. Karnatak Univ.*, **2**, 33 (1957); *Chem. Abstr.*, **53**, 14100 (1959).

(25) T. H. Minton and H. Stephen, *J. Chem. Soc.*, 121, 1598 (1922).

(26) D. Vorländer, *Ann.*, **294**, 291 (1897).

(27) K. S. Bokarev and N. N. Mel'nikov, *Zh. Obshch. Khim.*, **24**, 2014 (1954); *Chem. Abstr.*, **49**, 14678 (1955).

(28) S. N. Dhar, *J. Chem. Soc.*, 117, 1068 (1920).

(29) A. Ladenburg, *Ber.*, **9**, 1524 (1876).

(30) A. G. Kostsova, *Zh. Obshch. Khim.*, **24**, 618 (1954); *Chem. Abstr.*, **48**, 10537 (1954).

Methanesulfon(N-methyl-*m*-amino)anilide (VIII).—The above product (2.30 g.) was heated with stirring 60 min. on the steam bath with 8.4 g. of hydrated stannous chloride and 10 cc. of concentrated hydrochloric acid. The cooled mixture was basified, the precipitated tin hydroxides were removed by filtration, the filtrate was extracted with ether, and VIII was gained from the extract with ultimate crystallization from 95% ethanol. Pale yellow crystals (0.5 g.; 29%), m.p. 87.5–88.5°, were obtained.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04. Found: C, 47.93; H, 6.03.

Methanesulfon(*o*-nitro)anilide.—The method used for the *meta* isomer was unsuccessful. *o*-Nitroaniline (5.25 g.), 21 cc. of triethylamine, 15 g. of methanesulfonyl chloride, and 200 cc. of toluene were combined and heated 4 hr. at reflux. By conventional methods, 2.95 g. (36%) of pale yellow crystals (from 95% ethanol), m.p. 101–103°, were isolated.

Anal. Calcd. for $C_7H_8N_2O_4S$: C, 38.88; H, 3.73. Found: C, 38.95; H, 3.89.

Methanesulfon(N-methyl-*o*-nitro)anilide, pale yellow crystals of m.p. 142–143°, was prepared in 88% yield by the procedure used for the *meta* isomer.

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.38. Found: C, 41.58; H, 4.40.

Methanesulfon(N-methyl-*o*-amino)anilide (IX), pale yellow crystals of m.p. 137–138°, was prepared in 65% yield by the procedure used for VIII, with the exception that the precipitated tin hydroxide as well as the filtrate was extracted with ether.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 48.19; H, 6.01; N, 13.82.

2-(*m*-Nitrophenoxy)benzamide was prepared by treating 2-(*m*-nitrophenoxy)benzoic acid[16] with thionyl chloride, and the resulting acid chloride with aqueous ammonia. The amide formed pale yellow prisms, m.p. 116–117°, on crystallization from ethanol.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.87. Found: C, 60.54; H, 3.98.

2-(*m*-Aminophenoxy)benzamide (XIV) was obtained by stannous chloride reduction of the nitro amide. XIV formed colorless prisms (from benzene), m.p. 140–142°.

m-Nitrophenoxyacetamide, m.p. 179.5–182.5° (lit.[31] 178.5°), was prepared after Minton and Stephen.[31] It was reduced to *m*-aminophenoxyacetamide (XVIIa) by brief exposure to stannous chloride in hydrochloric acid on the steam bath; XVIIa was obtained as colorless crystals (from benzene), m.p. 118.5–119.5° (lit.[32] 123.5–124°).

***m*-Nitrophenoxyacetanilide**, m.p. 124–125° (lit.[31] 125°), was prepared after Minton and Stephen.[31]

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.79; H, 4.45. Found: C, 61.59; H, 4.53.

***m*-Aminophenoxyacetanilide (XVIIb)** was secured by reduction of the above nitro anilide with stannous chloride and hydrochloric acid on the steam bath for 1 hr. XVIIb was obtained as colorless crystals (from 95% ethanol), m.p. 123–124°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.34; H, 5.82; N, 11.55. Found: C, 69.31; H, 6.01; N, 11.70.

Reactions with Potassium Amide in Ammonia.—Except as otherwise stated, reactions were performed as described by Bunnett and Hrutfiord.[7]

Of Phenylacet(N-methyl-*o*-chloro)anilide (Ic).—Ic (1.5 g.) in 50 cc. of dry ether was treated with a solution of potassium amide (from 1.0 g. of potassium metal) in 500 cc. of liquid ammonia. Reaction time was 30 min. By standard procedures, 1.1 g. (91%) of IIc, m.p. 118–119° (lit.[33] 118–119°), was isolated as colorless leaflets (from diethyl ether and petroleum ether).

Of Acet(N-methyl-*o*-chloro)anilide (Ie).—Ie (5.4 g.) in 100 cc. of ammonia was treated for 60 min. with a solution of potassium amide (from 3.5 g. of potassium metal) in 400 cc. of ammonia. By standard procedures, 0.7 g. (16%) of IIe, m.p. 87–89° (lit.[34] 89°), was isolated as white needles (from petroleum ether).

Of Acet(*o*-chloro)anilide (Id).—To 5 g. of Id in 100 cc. of ammonia, a solution of potassium amide (from 4.7 g. of potassium metal) in 400 cc. of ammonia was added. Reaction time was 40 min. By standard procedures, 1.5 g. (37%) of IVd was isolated as a colorless liquid of b.p. 67–69°/6 mm. or 98°/26 mm. The infrared spectrum was identical to that of the authentic sample of 2-methylbenzoxazole (above).

Of Methanesulfon(N-methyl-*o*-chloro)anilide (Vb). First Run.—To 5.3 g. of Vb in 50 cc. of ether and 150 cc. of ammonia, a solution of potassium amide (from 4.4 g. of potassium metal) in ammonia was added. Reaction time was 60 min. The crude reaction product was fractionated by customary extraction procedures. From the fraction soluble in dilute hydrochloric acid, 1.8 g. (38%) of white needles, (from ethanol), m.p. 136–137°, was isolated. A negative test for chlorine and positive tests for nitrogen and sulfur were obtained.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 48.00; H, 6.00. Found: C, 47.82; H, 6.06.

Second Run. By the "one pot" technique of Bunnett and Skorcz,[9] 4.5 g. of Vb was allowed to react 15 min. with potassium amide (0.082 mole) in 300 cc. of ammonia. From the neutral fraction, 2.53 g. (66%) of VI was isolated as colorless crystals (from chloroform-petroleum ether), m.p. 91–92°.

Anal. Calcd. for $C_8H_9NO_2S$: C, 52.44; H, 4.95. Found: C, 52.38; H, 4.96.

Third Run. Quantities and technique were as in the second run, but reaction time was 60 min. From the neutral fraction, 1.63 g. (43%) of VI, m.p. 90–92°, was isolated. The acid-soluble fraction yielded 1.5 g. (37%) of a compound, m.p. 137–138.5°, whose mixture m.p. with the substance of m.p. 136–137° from the first run was not depressed. For reasons stated in the text, this was taken to be VII.

The n.m.r. spectra of VI and VII were run at 60 Mc. in deuteriochloroform.[35] For VI, an unsplit three proton peak (the N-methyl group) showed a chemical shift of −3.1 p.p.m. relative to tetramethylsilane, and an unsplit two proton peak (the CH_2 group) showed a shift of −4.3 p.p.m. For VII, the peaks were again unsplit and the shifts were −2.8 p.p.m. and −4.35 p.p.m., respectively.

Of 1-Methyl-2,1-benzisothiazoline 2,2-Dioxide (VI).—A 2.5 g. sample of VI was treated with potassium amide (0.062 mole) in 300 cc. of ammonia for 60 min. by the technique of Bunnett and Skorcz.[9] Recovered VI, m.p. 89–91°, weighed 0.55 g. (22%), and 1.45 g. (68%) of sulfonamide VII, m.p. 136–138°, was isolated.

Of 2-(*o*-Chlorophenoxy)benzamide (XI).—To 3.5 g. of XI in 50 cc. of ether and 150 cc. of ammonia, a solution of potassium amide (from 2.2 g. of potassium metal) in ammonia was added. Reaction time was 60 min. Besides a small amount of recovered XI, 2.7 g. (77%) of XIV was isolated (from the acid-soluble fraction) as white prisms (from benzene), m.p. 144°. A positive diazotization–azo coupling test was obtained. The mixture m.p. with authentic XIV (above) was not depressed.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26. Found: C, 68.28; H, 5.19.

Of *o*-Chlorophenoxyacetamide (XVIa).—To 4.5 g. of XVIa in 200 cc. of ammonia, a solution of potassium amide (from 3.9 g. of potassium metal) in ammonia was added. Reaction time was 30 min. By standard procedures, 0.6 g. (15%) of XVIIa, m.p. 122–123°, was isolated as white needles. The identity of this with authentic XVIIa (above) was established by mixture m.p. and the identity of the infrared spectra of the two samples.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.12; H, 6.10; N, 16.82.

Of *o*-Chlorophenoxyacetanilide (XVIb).—To 5.2 g. of XVIb in 50 cc. of ether and 150 cc. of ammonia, a solution of potassium amide (from 3.2 g. of potassium metal) in ammonia was added. Reaction time was 70 min. By standard procedures, 3.5 g. (79%) of XVIIb, m.p. 125°, was isolated as prisms (from benzene) or needles (from dilute ethanol). The identity of this with authentic XVIIb (above) was established by mixture m.p. and identity of infrared spectra.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.64; H, 5.88.

Of *o*-Chlorophenoxyacetone (XIX).—To 6.5 g. of XIX in 100 cc. of ammonia a solution of potassium amide (from 4.5 g. of potassium metal) in ammonia was added. Reaction time was 60 min. The product was largely brown tarry substances soluble in dilute hydrochloric acid. By chromatography on alumina and distillation at reduced pressure (b.p. 145°/6 mm.),

(31) T. H. Minton and H. Stephen, *J. Chem. Soc.*, 121, 1591 (1922).

(32) W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.*, **39**, 2423 (1917).

(33) G. Palazzo and V. Rosnati, *Gazz. chim. ital.*, **82**, 584 (1952).

(34) O. Hinsberg and J. Rosenzweig, *Ber.*, **27**, 3253 (1894); R. Stolle, D. R. P. 335,763 (June 14, 1914); P. Friedlaender, "Fortschritte der Teerfarbenfabrikation," Vol. 13, 1923 p. 446.

(35) The n.m.r. spectra were obtained through the courtesy of Dr. H. Agahigian of Olin Mathieson Chemical Co., New Haven, Conn.

a small amount of pale yellow liquid with an amine-like odor was obtained. This turned brown on exposure to the air, gave a positive ferric chloride test, a negative test for chlorine and a positive test for nitrogen, and with chloroplatinic acid formed a salt melting above 250°. These properties match those reported by Stoermer and Brockerhof[17] for 2-methyl-2H-1,4-benzoxazine (XX).

Anal. Calcd. for $(C_9H_9NO)_2 \cdot 2HCl \cdot PtCl_4$: C, 30.68; H, 2.84; N, 3.98. Found: C, 30.63; H, 3.41; N, 4.03.

Results from a run with a 10-min. reaction time were similar.

Of 4-Chloroxanthone (XXII).—To 1.7 g. of XXII in 100 cc. of ether and 100 cc. of ammonia a solution of potassium amide (from 1.1 g. of potassium metal) was added. Reaction time was 30 min. By standard procedures, 3-aminoxanthone, m.p. 233–234° (lit. 232° for 3-aminoxanthone,[36] 199–200° for 4-aminoxanthone[37]), was isolated in 26% yield.

(36) F. Ullmann and C. Wagner, *Ann.*, **355**, 395 (1907).

(37) S. Akagi and T. Iwashige, *J. Pharm. Soc. Japan*, **74**, 610 (1954); *Chem. Abstr.*, **48**, 10742 (1954).

Experiments Directed toward the Total Synthesis of Terpenes. IV. The Synthesis of (±)-Sandaracopimaradiene and (±)-Pimaradiene[1,2]

ROBERT E. IRELAND AND PETER W. SCHIESS

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan

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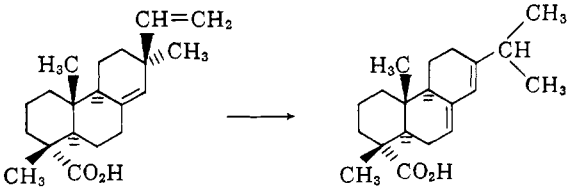
Two synthetic sequences for the conversion of (±)-14-podocarpanone (11) to (±)-sandaracopimaradiene (2) and (±)-pimaradiene (3) are described. The first route involves the methylation of (±)-13-ethylidene-14-podocarpanone (23), while a second, milder pathway proceeds through (±)-13-podocarpen-13-carboxaldehyde (31).

The synthetic challenge presented by the diterpenoid resin acids, such as abietic acid and the pimaric acids, while similar to that of the steroids, has been overlooked until recently because of the lack of any significant therapeutic effect associated with the diterpenes. The solution to the synthetic problems associated with the steroids has not only brought about renewed interest[3] in the resin acids, but also laid an experimental foundation of incalculable value to one rising to the challenge of these acids. As a part of this resurgence of interest in the diterpenes, we began an integrated program directed toward elaborating methods suitable to the total synthesis of the pimaric acids. The pimaric acids, rather than the more common abietic acid, were chosen as a goal since it appeared reasonable to expect that acid catalyzed rearrangement of these acids would ultimately lead to abietic acid. That such was indeed the case was later shown by Wenkert and co-workers[6a] when they effected the isomerization of (+)-pimaric acid to (−)-abietic acid by treatment with sulfuric acid.

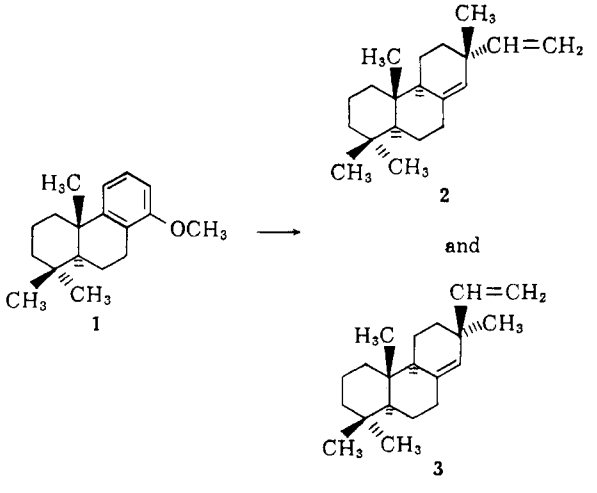


(+)-Pimaric acid (−)-Abietic acid

As a result, a total synthesis of the synthetically more complex pimaric acid would represent a formal total synthesis of abietic acid.

Much as has been done by previous workers,[3] our program was divided into two main phases: one directed toward the construction of a tricyclic acid possessing the appropriate substituents on the *trans*-fused A and B rings and an aromatic C-ring[4]; coupled with this, a program was initiated to investigate methods suitable for the conversion of a model aromatic system to a compound having the ring C substitution pattern of the pimaric acids. In this manner, the procedures developed in the latter phase would be available for application to the intermediate that resulted from the former phase, and hence lead to a scheme for the total synthesis of the pimaric acids.

The work described herein is concerned with the methods that we were able to develop for the construction of the ring C substitution pattern of the pimaric acids. The first choice to be made was that of an appropriate model for this work, and while in principle a simple monocyclic system could serve as such a model, we chose instead the tricyclic ether 1.[5] The rationale behind this choice was that a tricyclic model, lacking only the asymmetry at C-4, would more closely approximate the tricyclic acid resulting from the other phase of the program. An equally important factor was that a stereorational route for the conversion of the ether 1 to the dienes 2 and 3 offered the opportunity to test the earlier stereochemical assignments[6] of the pimaric acids



(1) For a preliminary report of this work, see R. E. Ireland and R. W. Schiess, *Tetrahedron Letters*, No. **25**, 37 (1960).

(2) This investigation was supported by the National Science Foundation through a research grant (G-5912).

(3) For a recent review, see N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.*, **16**, 117 (1962).

(4) R. E. Ireland and R. C. Kierstead, *J. Org. Chem.*, **27**, 703 (1962).

(5) Steroid numbering is used throughout, and although formulas of only one enantiomer are drawn, they are taken to represent a racemate except where indicated.

(6) (a) E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.*, **81**, 688 (1959); (b) O. E. Edwards and R. Howe, *Can. J. Chem.*, **37**, 760 (1959); (c) B. Green, A. Harris, and W. B. Whalley, *J. Chem. Soc.*, 4715 (1958).