TABLE I

ATTEMPTED OXYGENOLYSES OF HALIDE-$LiAlH_4$ AND NITRILE-$LiAlH_4$ COMPLEXES

Run	Substrate	Method	Molar Ratio of Hydride to Substrate	Reaction Temp., °C.	Oxygenolysis	Products, Yield %[a]	
						With O_2	Without O_2
1	Benzyl bromide	DA[b]; THF[c]	1.0	30–40[d]	conc.,[e] (7.5, 65)[f]	Toluene, 31	78[g]
2	Benzyl bromide	DA; Ether	1.1	35	after, (3, 35)	Toluene, 28	—
3	Benzyl bromide	DA; THF	0.72	35–50	after, (18, 65)	Toluene, 32	—
4	Benzyl bromide	DA; Ether	0.25	35	after, (2.5, 35)	Toluene, 15 Benzyl bromide, 42	—
5	Benzyl bromide	DA; THF	1.1	[h]	(17, 65)	Toluene, 38 Benzyl bromide, 58	—
6	*n*-Octyl bromide	DA; THF	2.0	65	conc., (7, 65)	*n*-Octane, 25	96[i]
7	*n*-Capronitrile	DA; THF	1.1	65	after, (6, 65)	*n*-Hexylamine, 24	36[j]
8	*n*-Capronitrile	RA[b]; Ether	1.1	35	after, (3, 35)	*n*-Hexylamine, 9[k]	32[j]
9	Phenylacetonitrile	RA; Ether	1.1	−75	conc., (6, 35)	Phenylacetonitrile, 50 Phenylacetaldehyde, 10[l]	—
10	Phenylacetonitrile	RA; Ether	1.1	35	conc., (2, 35)	Phenethylamine, 9	<40[j]
11[m]	Phenylacetonitrile	DA; Ether	0.8	35	after, (5.5, 35)	Phenethylamine, 35 α-Phenyl-β-aminoethanol, 7	—

[a] Identifying physical constants for products are not reported here because these reductions, exclusive of attempted oxygenolysis, have been amply documented (see Brown, *Org. Reactions, VI*, Chap. 10 (1951); Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, 1956; ref. (2). [b] Direct addition. RA means reverse addition. [c] Tetrahydrofuran. [d] Reaction times varied from 1–1.5 hr. [e] Concurrent. [f] The first figure in the bracket is the time of oxygenolysis in hours; the second is the temperature of attempted oxygenolysis after all the substrate had been added. [g] Trevoy and Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949). [h] See discussion in text. [i] Johnson, Blizzard, and Carhart, *J. Am. Chem. Soc.*, **70**, 3664 (1948). [j] Ref. 2. [k] Also dimers of usual type (Ref. 2). [l] M.p. of 2,4-dinitrophenylhydrazone, 239–240°; Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1953, reports 110° (240°). [m] Reported previously (ref. 2) and included here for purposes of comparison.

EXPERIMENTAL[5]

The reductions of halides and of nitriles were performed as described in the literature.[6] Oxygen was dried by passage through calcium chloride. No unusual difficulties were experienced with the attempted oxygenolyses but all precautions must be taken to avoid ignition of the mixtures of volatile solvent, hydrogen, and oxygen. In cases of doubt the presence of hydroxylic materials was sought by means of infra-red spectra and by attempted esterification (benzoylation and acetylation). In no case were esters obtained.

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[5] Appreciation is expressed to Manfred Katz for the performance of several runs.

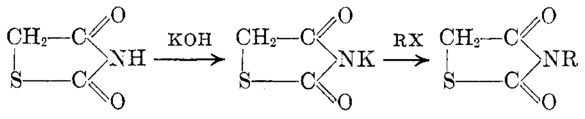
[6] Footnote *a* of the Table.

The Alkylation of 2,4-Thiazolidinedione

CHIEN-PEN LO AND ELWOOD Y. SHROPSHIRE

Received March 4, 1957

Although many 3-aryl-2,4-thiazolidinediones are known, until recently only three 3-alkyl-2,4-thiazolidinediones (namely, 3-methyl-,[1–4] 3-ethyl-,[5] and 3-allyl-[6]) have been reported in the literature. Just recently, Bradsher, Brown, and Sinclair[7] have synthesized 3-benzyl- and seven 3-substituted benzyl-2,4-thiazolidinediones. This paper reports the preparation of twelve 3-alkyl-2,4-thiazolidinediones (III), eight of which are new, by the alkylation of 2,4-thiazolidinedione (I).



I II III

The methylation of I has been achieved by (*1*) the reaction of I with methyl iodide in methanolic sodium methoxide,[1] (*2*) the reaction of the silver salt of I with methyl iodide,[2] and (*3*) the reaction of I with diazomethane.[4] In the work of Bradsher, Brown, and Sinclair, the benzylation was carried out in the presence of methanolic sodium methoxide and yields ranging from 15.5 to 46% were reported.

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(1) L. Arapides, *Ann.*, **249**, 28 (1888).

(2) H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **24**, 73 (1900).

(3) B. Weibull, *Arkiv kemi, Mineral. Geol.*, **25A**, No. 9, 1 (1947).

(4) K. Iwaya, S. Mitsuhashi, K. Yoshida, and K. Kijima, *J. Pharm. Soc. Japan*, **68**, 245 (1948).

(5) F. B. Dains, L. M. Kinsett, C. O. Holmberg, and C. C. Robinson, *Univ. Kansas Sci. Bull.*, **24**, 15 (1936).

(6) F. A. Eberly and F. B. Dains, *J. Am. Chem. Soc.*, **58**, 2544 (1936).

(7) C. K. Bradsher, F. C. Brown, and E. F. Sinclair, *J. Am. Chem. Soc.*, **78**, 6189 (1956).

TABLE I

3-ALKYL-2,4-THIAZOLIDINEDIONES (III)

Alkylating Agent (RX)	Yield, %	M.P., °C. or B.P., °C. (Mm)	Formula	N Calcd.	N Found	S Calcd.	S Found
i-C_4H_9Br	67.5	150–153 (17)[a]	$C_7H_{11}NO_2S$	8.1	8.4	18.5	18.7
n-$C_8H_{17}Br$	75	118–120 (0.2)[b]	$C_{11}H_{19}NO_2S$	6.1	6.2	14.0[c]	14.0[c]
$C_{12}H_{23}Cl$[d]	58	135–138 (0.2)[e]	$C_{15}H_{25}NO_2S$	4.9	4.7	11.3	11.0
$ClCH_2COOC_2H_5$	60	107–110 (0.15)[f]	$C_7H_9NO_4S$	6.9	7.0	15.8	16.0
$C_6H_5CH_2Cl$	80	62–63[g]	$C_{10}H_9NO_2S$	6.8	6.8	15.5	15.3
o-$ClC_6H_4CH_2Cl$	70	49.5–51.5[h]	$C_{10}H_8ClNO_2S$	5.8	5.7	13.2	12.8
p-$ClC_6H_4CH_2Cl$	76	97–98[i]	$C_{10}H_8ClNO_2S$	5.8	5.8	13.2[j]	13.1[j]
2,4-$Cl_2C_6H_3CH_2Cl$	60	68.5–70.5	$C_{10}H_7Cl_2NO_2S$	5.1	5.0	11.6	11.5
3,4-$Cl_2C_6H_3CH_2Cl$	78	91–92.5	$C_{10}H_7Cl_2NO_2S$	5.1	5.1	11.6[k]	11.2[k]
p-$NO_2C_6H_4CH_2Cl$	78	117–118[l]	$C_{10}H_8N_2O_4S$	11.0	11.0	12.7	12.5
2,4-$Cl_2C_6H_3OCH_2CH_2Br$	52	78–80	$C_{11}H_9Cl_2NO_3S$	4.6	4.5	10.5	10.3
2,4-$Cl_2C_6H_3(OCH_2CH_2)_2Cl$	66.5	92–93	$C_{13}H_{13}Cl_2NO_4S$	4.0	3.9	9.1	8.8

[a] n_D^{20} 1.5128. [b] n_D^{21} 1.4980. [c] Calcd.: C, 57.59; H, 8.37. Found: C, 57.79, H, 8.28. [d] 5,5,7,7-Tetramethyl-2-octenyl chloride [e] n_D^{20} 1.5083. [f] n_D^{21} 1.5130. [g] Ref. 8 reports m.p. 60.3–61°. [h] Ref. 8 reports m.p. 49–51°. [i] Ref. 8 reports m.p. 96.5–97.5°. [j] Calcd.: Cl, 14.7; Found: 14.5. [k] Calcd.: Cl, 25.6; Found: 25.4. [l] Ref. 8 reports m.p. 119.8–121°.

In the present work, the potassium salt of I was prepared and allowed to react with various reactive halogen compounds in dimethylformamide.[8] The latter reaction is smooth and clean and the yields of the 3-alkyl-2,4-thiazolidinediones are generally good, serving as another example of the superiority of dimethylformamide as a medium for the alkylation of imide type of compounds.[9] Table I gives the pertinent information of the 3-alkyl-2,4-thiazolidinediones thus prepared including four of the benzyl compounds reported by Bradsher, Brown, and Sinclair for comparison. Because of the simplicity, good yield, and general applicability of the present method, it is to be recommended as a preparative method for the 3-alkyl-2,4-thiazolidinediones.

The 3-alkyl-2,4-thiazolidinediones were synthesized for evaluation as fungicides. In the preliminary laboratory test,[12] these compounds were found to have low fungitoxicity, their ED_{50} values being greater than 100 p.p.m. against both *Stemphylium sarcinaeforme* and *Monilinia fructicola.* These results bear out the finding of Bradsher, Brown, and Sinclair on the low fungistatic activity of the 3-benzyl-2,4-thiazolidinediones toward *Aspergillus niger.*

EXPERIMENTAL[13]

Potassium salt of 2,4-thiazolidinedione. 2,4-Thiazolidinedione (m.p. 122–124°) (160 g.) was dissolved in 250 ml. of ethanol. To this hot solution was added a solution of potassium hydroxide (84 g.) in ethanol (200 ml.). The mixture was stirred without cooling for 2 hr. and then cooled in an ice-bath. The crystalline solid was collected on a filter, washed with ethanol, and air-dried. The potassium salt of 2,4-thiazolidinedione thus obtained weighed 176 g. (83%), decomposed at 247–250°, and was analytically pure.

Anal. Calcd. for $C_3H_2NO_2SK$: N, 9.0; S, 20.6. Found: N, 8.7; S, 20.5.

The potassuim salt was used in the subsequent alkylation reaction without further purification. However, it could be recrystallized from ethanol if so desired.

Alkylation of 2,4-thiazolidinedione. (General procedure). To a suspension of the above potassium salt of 2,4-thiazolidinedione (46.5 g., 0.3 mole) in dimethylformamide (150 ml.) was slowly added the alkyl halide (0.3 mole). After the addition was complete, the mixture was stirred and heated under reflux on a steam bath for 4 hr. The reaction mixture was then poured into water (500 ml.). The 3-alkyl-2,4-thiazolidinedione which separated either as a solid or an oil was purified accordingly. When the product was a solid, it was separated by filtration or by decantation (in the case of low melting solid) and recrystallized from ethanol. In case where the product was a liquid, the oil was taken up in a suitable solvent such as chloroform or ethylene chloride, washed with water, and dried over calcium sulfate. After the removal of the solvent under reduced pressure, the residual oil was distilled *in vacuo.*

The yields, physical properties, and analyses of the twelve compounds prepared are given in Table I. The yield of the purified products reported therein was based on the result of one or two runs. Because the compounds were prepared by a standard procedure which does not necessarily represent the optimum conditions for each compound, it is reasonable to believe that the yield of an individual compound can be improved by properly adjusting the experimental conditions such as time and temperature.

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(8) The isobutylation of 5-aralkylidene-2,4-thiazolidinediones by a similar method has been reported before, see C. P. Lo, E. Y. Shropshire, and W. J. Croxall, *J. Am. Chem. Soc.*, **75**, 4845 (1953).

(9) The use of dimethylformamide as a medium for the Gabriel condensation was first reported by J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2787 (1950). For later work on related subject, see, for example, references 8, 10, and 11.

(10) J. H. Billman and R. V. Cash, *J. Am. Chem. Soc.*, **75**, 2499 (1953).

(11) H. L. Rice and G. R. Pettit, *J. Am. Chem. Soc.*, **76**, 302 (1954).

(12) Tested by the slide-germination method published by the American Phytopathological Society, *Phytopathology*, **33**, 627 (1943).

(13) All melting points and boiling points are uncorrected.

Acknowledgment. We wish to thank Mr. W. S. Zawacki for technical assistance, Messrs. T. P. Callan, C. W. Nash and their staffs for analyses, and Dr. H. L. Keil for fungicidal data.

RESEARCH LABORATORIES
ROHM & HAAS CO.
BRISTOL, PA.

Simple Procedure for the Conversion of Aryl Halides to the Corresponding Phenols

M. FREDERICK HAWTHORNE

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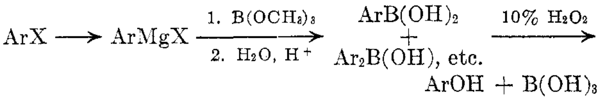
The use of two well known reactions in series has afforded a relatively rapid and efficient route from aryl halides to the corresponding phenols. The overall reaction sequence employed is illustrated in the following formulation.



$$\mathrm{ArX} \longrightarrow \mathrm{ArMgX} \xrightarrow[\text{2. } H_2O,\ H^+]{\text{1. } B(OCH_3)_3} \begin{matrix} ArB(OH)_2 \\ + \\ Ar_2B(OH), \text{ etc.} \end{matrix} \xrightarrow{10\%\ H_2O_2} ArOH + B(OH)_3$$

The simplicity of the method lies in the fact that the arylboronic acid, which is produced along with varying amounts of other materials having aryl-boron bonds, need not be isolated. Treatment of the crude product (in ethereal solution) with 10% hydrogen peroxide readily degrades the product mixture to the corresponding phenol in 60–80% overall yield (based on aryl halide). The method has been applied to the preparation of phenol, α-naphthol and *p*-cresol which were obtained in 78, 75, and 60% yields, respectively.

EXPERIMENTAL

The experimental procedure is illustrated by the preparation of phenol. To a one-liter three-neck flask equipped with a stopcock on its bottom and carrying a reflux condenser, dropping funnel, stirrer, nitrogen inlet, and drying tube, was added 31 g. (0.33 mole) of pure methyl borate and 400 ml. of dry ether. The apparatus was flushed with dry nitrogen and 200 ml. of 1.5*M* phenylmagnesium bromide was added dropwise over a period of 1 hr. while the contents of the flask were cooled to −80° and rigorously stirred. After the addition the reaction mixture was warmed to room temperature and 200 ml. of 10% hydrochloric acid slowly run in with stirring under nitrogen. The stirrer was stopped and the lower aqueous phase separated by use of the stopcock in the flask bottom. The ether layer was washed twice more with water in this fashion. Two hundred milliliters of 10% hydrogen peroxide was slowly added from the dropping funnel with stirring at such a rate as to maintain gentle reflux. After the addition the mixture was stirred for 15 min. and the layers separated as before. The ether layer was washed with 10% ferrous ammonium sulfate and the phenol extracted by two portions of 10% sodium hydroxide solution. Acidification of the alkaline extract followed by extraction with ether and distillation afforded 22.0 g. (78% theory) of pure phenol, melting at 40–41°.

ROHM & HAAS COMPANY
REDSTONE ARSENAL RESEARCH DIVISION
HUNTSVILLE, ALA.

Rauwolfia Alkaloids. V.[1] Stereochemical Correlation of Some Indole Alkaloids from the Infrared Spectra

NORBERT NEUSS AND HAROLD E. BOAZ

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In a series of publications on Rauwolfia[2] alkaloids from these laboratories, we have used spectral data for deduction of structural features of reserpine,[3] reserpinine,[4] and deserpidine (recanescine).[5]

Our technique consisted of comparing the infrared spectrum of the naturally occurring alkaloid in chloroform solution[3] with the spectrum of an equimolar solution of a substituted methoxyindole and suitable component, bearing the remaining functional groups of the alkaloid. In the case of reserpinine, for example, it was pointed out that the identity of the wave lengths and intensities of most of the corresponding bands in the spectra of reserpinine and summation of 2,3-dimethyl-6-methoxyindole and tetrahydroalstonine strongly suggests the same steric configuration in these two alkaloids.[4]

After the compilation of the physical data of indole and dihydroindole alkaloids[6] we had on hand the infrared spectra of several heteroyohimbane derivatives in chloroform solution.

A close examination of these spectra permits the assignment of a methoxylated derivative to the tetrahydroserpentine or tetrahydroalstonine series.[7] The present paper deals with our observations in this class of indole alkaloids.

In our studies we have used the following indole alkaloids, derivatives of the heteroyohimbane ring system: aricine (VI),[8] reserpinine (III),[4] isoreserpiline (VIII),[8] raumitorine (VII),[9] tetra-

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[1] For paper IV of this series, see S. C. Pakrashi, Carl Djerassi, Richard Wasicky, and N. Neuss, *J. Am. Chem. Soc.*, **77**, 6687 (1955).

[2] In strict usage and in compliance with the International Code of Botanical Nomenclature, the name should be spelled Rauvolfia, J. Monachino, *Economic Botany*, **8**, 349 (1954).

[3] N. Neuss *et al.*, *J. Am. Chem. Soc.*, **76**, 2463 (1954).

[4] N. Neuss *et al.*, *J. Am. Chem. Soc.*, **76**, 3234 (1954) and references cited therein.

[5] N. Neuss *et al.*, *J. Am. Chem. Soc.*, **77**, 4087 (1955).

[6] Lilly collection of Physical Data of Indole and Dihydroindole Alkaloids, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis 6, Ind., 1954 and 1956.

[7] E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956), have just classified different indole alkaloids into normal and allo compounds and pseudo or epiallo compounds on the basis of presence or absence of certain bands in the 3.4–3.7 μ region. We would like to thank Dr. Wenkert for sending us the paper prior to its publication.

[8] A. Stoll, A. Hofmann, and R. Brunner, *Helv. Chim. Acta*, **38**, 270 (1955).

[9] Janot, Goutarel, Le Hir, and Poisson, *Compt. rend.*, **239**, 302 (1954).