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# An Interpretation of the Reaction of Aliphatic Primary Amines with Nitrous Acid

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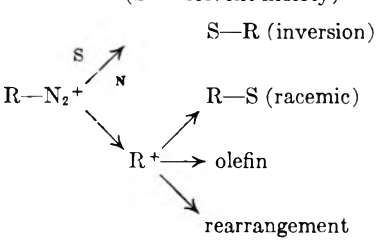
Although the reaction of aliphatic primary amines with nitrous acid has long been known to yield a variety of products including those resulting from solvolysis, elimination, and rearrangement, no comprehensive attempt has been made to account for all of these reactions in terms of a complete theory. By analogy with the reactions of aromatic primary amines with nitrous acid, an alkyldiazonium ion has been considered to be an important intermediate.[1] The mechanism of the reaction usually given in texts[2] is that of a solvolytic displacement reaction in which the diazonium ion decomposes into nitrogen and a carbonium ion which can subsequently react with solvent, eliminate a proton, or rearrange (Equation 1). To account for the partial inversion of configuration frequently observed when optically active amines are used[3,4] a competing reaction is considered to be a direct displacement ($S_N2$) by solvent.

(S = solvent moiety)




(1)

A major difficulty with this mechanism is that rearrangements are frequently observed which have no counterpart in related solvolytic reactions. For example, *n*-alkylamines yield substantial amounts of secondary alkyl products,[5] the results of a hydrogen rearrangement. Yet, solvolyses of *n*-alkyl halides or sulfonate esters give at most small amounts of rearranged products; *e.g.*, prolonged refluxing of *n*-propyl tosylate in acetic acid gives <3% of isopropyl acetate.[6] Rearrangements of *n*-alkyl halides to secondary alkyl derivatives generally occur only when the nucleophilic reagents available for reaction with the intermediate carbonium ion are so weak that such reaction is slower than the rearrangement. Such conditions are obtained, for example, in alkylations with aluminum chloride or boron fluoride.

Consequently, the hypothesis has been presented

(1) L. P. Hammett, *Physical Organic Chemistry*, p. 295, McGraw-Hill Book Company, Inc., New York, N. Y., 1940.

(2) (a) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, p. 397, Cornell University Press, Ithaca, N. Y., 1953. (b) M. J. S. Dewar, *Electronic Theory of Organic Chemistry*, p. 210, Oxford University Press, London, 1949. (c) P. H. Hermans, *Theoretical Organic Chemistry*, p. 246, Elsevier Publishing Co., Amsterdam, 1954. (d) E. E. Royals, *Advanced Organic Chemistry*, p. 226, Prentice-Hall Publishing Co., New York, N. Y., 1954. (e) E. R. Alexander, *Principles of Ionic Organic Reactions*, p. 49, J. Wiley and Sons, Inc., New York, 1950.

(3) P. Brewster, F. Hiron, E. O. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 179 (1950).

(4) K. B. Wiberg, Dissertation, Columbia University, July, 1950.

(5) (a) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 838 (1934). (b) V. Meyer and F. Forster, *Ber.*, **9**, 535 (1876). (c) V. Meyer, J. Barbieri, and F. Forster, *Ber.*, **10**, 130 (1877). (d) P. C. Ray and J. N. Rashkit, *J. Chem. Soc.*, **101**, 141 (1912). (e) F. C. Whitmore and D. P. Langlois, *J. Am. Chem. Soc.*, **54**, 3441 (1932). (f) F. C. Whitmore and R. S. Thorpe, *J. Am. Chem. Soc.*, **63**, 1118 (1941). (g) J. D. Roberts and M. Halmann, *J. Am. Chem. Soc.*, **75**, 5759 (1953).

(6) R. Huisgen and C. Rüchardt, *Ann.*, **601**, 1 (1956).

that the carbonium ion formed in the decomposition of an alkyldiazonium ion is a "hot", "high-energy", or "unsolvated" carbonium ion[5a,7-13] which has properties different from the carbonium ions formed in the solvolysis of a halide or sulfonate ester. However, this hypothesis fails to explain why diasteriomeric amines in cyclic systems generally yield different sets of products (*vide infra*). In terms of this mechanism diasteriomeric amines should yield the same carbonium ion.

The hypothesis has recently been proposed[14] that the diazonium ion rather than a carbonium ion is the branching point of the competing reactions. According to the theory presented, the great stability of the leaving nitrogen molecule implies that the activation energy required for the decomposition of an aliphatic diazonium ion is rather small—perhaps of the order of 3–5 kcal./mole. Consequently, the range of energies required for a number of competing reactions is compressed. To illustrate, if in the solvolysis of a halide two competing reactions of carbonium ion formation and a concerted rearrangement have activation energies of, respectively, 25 and 30 kcal./mole, in the corresponding amine-nitrous acid reaction the respective activation energies might be 5 and 6 kcal./mole. (In both cases the ratio of the activation energies is considered to be the same to a first approximation.) In the solvolysis reaction these values mean that rearrangement accounts for only 0.02% of the product; in the amine reaction, rearrangement would account for about 16% of the product. Consequently, a mode of reaction not observed in solvolyses may be important in amine-nitrous acid reactions.

In the present paper this theory and its corollaries are used to interpret many of the varied observations pertaining to the amine-nitrous acid reaction. The point of view of this presentation is to determine how well these observations are in accord with one unified theory, although, clearly, in individual cases alternative explanations are possible. In some of the relatively few cases which are not satisfactorily explained by this theory, the theory is probably deficient and may require future modification; in others, published data are contradictory.

(7) D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **79**, 2866 (1957).

(8) L. S. Ciereszko and J. G. Burr, *J. Am. Chem. Soc.*, **74**, 145 (1952).

(9) P. S. Bailey and J. G. Burr, *J. Am. Chem. Soc.*, **75**, 2591 (1953).

(10) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

(11) A. W. Fort and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 584 (1956).

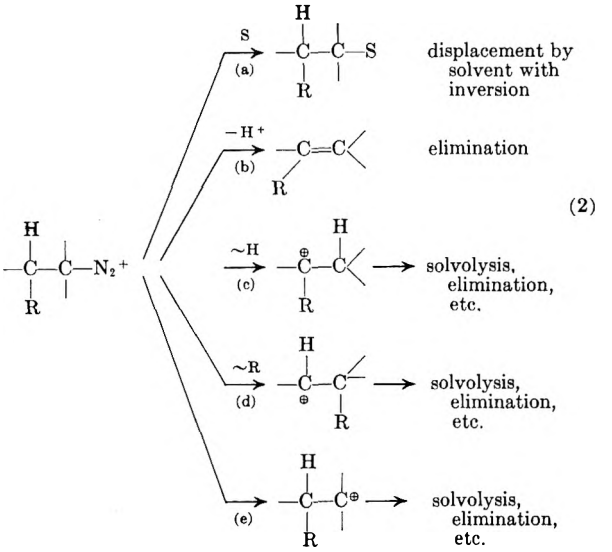
(12) J. G. Burr and L. S. Ciereszko, *J. Am. Chem. Soc.*, **74**, 5431 (1952).

(13) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **76**, 3719 (1954).

(14) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957).

It has been emphasized[14] that because the driving force for the decomposition of an alkyldiazonium ion is the elimination of nitrogen, the rearranging group should not be regarded as providing only anchimeric assistance in the reaction, i.e., a *push*, but also that it is being *pulled* over by the positive field being generated at the $\alpha$-carbon atom. A further implication of the facility with which nitrogen is lost is that the transition state of each of the various reactions may resemble the diazonium ion in important respects.[7,14,15]

The reactions which appear to compete more or less successfully in various systems are given in Equation 2.




(2)

ACYCLIC SYSTEMS

*Reaction 2a: Direct Displacement.* One of the reactions which can compete with normal carbonium ion formation is direct displacement by solvent. The hypothesis that the structure of the transition state resembles the reactants carries the implication that the bond to the attacking solvent molecule at transition state for displacement is long and weak. Steric hindrance effects are reduced and relatively small stereochemical differences are to be expected between various systems. The 1-butyl-1-*d* acetate obtained from the reaction of 1-aminobutane-1-*d* with nitrous acid in acetic acid is 69% inverted and 31% racemized.[14] The *sec*-butyl acetate similarly obtained from *sec*-butylamine is 28% inverted and 72% racemized.[4] Although *sec*-butyl and $\alpha$-phenylethyl cations differ markedly in stability, the stereochemical outcomes of the reactions of the corresponding amines with nitrous acid do not differ greatly. In aqueous media *sec*-butylamine gives *sec*-butyl alcohol with 22% net inversion;[4] $\alpha$-phenylethylamine gives $\alpha$-phen-

(15) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

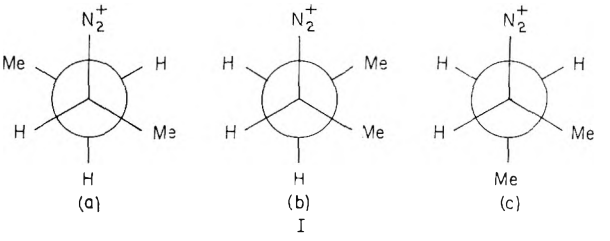
ylethyl alcohol with 6–12% net inversion.[16] The proportion of reaction by direct displacement decreases along the series, *n*-butyl > *sec*-butyl > α-phenylethyl, in agreement with theoretical expectations although the differences are comparatively small.

Since the bond to solvent at the transition state is weak, the nucleophilicity of the solvent would be expected to play a small role. Consequently, the stereochemical results with *sec*-butylamine in water and in the less nucleophilic acetic acid differ but little (and actually, in the wrong direction from a simple expectation).

The stereochemical results of racemization and inversion for the reactions of a number of secondary alkylamines have also been reported by Brewster, *et al.*[3] although complete details were not given. The partial net retention of configuration reported[17] for the reaction of α-phenylethylamine with nitrous acid in acetic acid requires an additional mode of reaction which may depend on ion-pair phenomena in acetic acid. However, additional results would be required to warrant further discussion.[18]

*Reaction 2b. Elimination.* The olefin obtained from *sec*-butylamine in aqueous nitrous acid consists of 25% 1-butene, 19% *cis*-2-butene and 56% *trans*-2-butene.[14] The composition of this mixture which would not be expected to change significantly in acetic acid differs greatly from that of the butene mixture obtained from the acetolysis of *sec*-butyl tosylate:[19] 10% 1-butene, 43% *cis*-2-butene, and 47% *trans*-2-butene. Not only does the amount of 1-butene differ considerably in the two reactions but the *cis*/*trans* ratios of the 2-butenes differ importantly. In the solvolysis reaction the olefin is considered to arise from an intermediate carbonium ion because in several such systems the olefin composition is independent of the nature of the leaving group.[20] The fact that a different olefin composition is obtained in the amine-nitrous acid reaction means that at least part of this olefin does not come from an intermediate carbonium ion.

An independent competing reaction, 2b, has been shown to explain the experimental results.[14] Generally such concerted eliminations result in the removal of hydrogens *trans* to the leaving group. Because the activation energy required for reaction 2b is presumed to be comparable to the energy required for rotation about a C—C bond (3–4 kilocalories per mole for the central bond in *n*-butane),[21] the decomposition of the diazonium ion will be of comparable rate to such rotation; *i.e.*, conformational effects will be important. In the case of 2-butylamine, three conformations are important, Ia, b, and c. Ib is expected to be less populated than Ia and Ic. Only Ia and Ib can eliminate a




I

*trans*-3-hydrogen; hence, consistent with the observed results, *cis*-2-butene which would arise from Ib is expected to be formed in smaller amount than *trans*-2-butene which arises from Ia. In elimination from a carbonium ion, the two types of hydrogen are conformationally equivalent and comparable amounts of the *cis* and *trans* olefins may be anticipated. Ic, which is relatively highly populated cannot give a 2-butene by *trans*-elimination. All three conformations (i.e., the entire population of diazonium ions) can give rise to 1-butene; only a fraction of the entire population of diazonium ions (that part in Ia and Ib) can generate 2-butene; therefore, even if the specific rate constant for formation of 1-butene is somewhat lower than that for the more stable 2-butenes, a relatively large amount of 1-butene is produced in the reaction.

*Reaction 2c: Migration of hydrogen.* Instead of eliminating, a *trans*-hydrogen may migrate instead in a 1,2-shift and generate a new carbonium ion as in reaction 3. The reaction apparently takes place to


an important extent, however, only when the resulting carbonium ion is more stable than that which would arise by elimination of nitrogen without rearrangement, hence the β-carbon must be distributing an important share of the positive charge. Ethylamine-1-$C^{14}$ gives ethanol which contains only 1.5% of the rearrangement product, ethanol-2-$C^{14}$.[22] although *n*-propyl-, *n*-butyl-, and *n*-amylamines, etc., yield important amounts of secondary carbinol.[5,6] 3-Aryl-1-propylamine gives 18–19% of 1-aryl-2-propyl alcohol.[11] Several cases are known in which no product of the rearrangement of a hydrogen is observed although such rearrangement would generate a more stable carbonium ion. For example, no diphenylmethylcarbinol is obtained

(16) Calculated from the data of W. Marckwald and R. Meth, *Ber.*, **38**, 801 (1905), and B. Holmberg, *Ber.*, **45**, 999 (1912).

(17) (a) E. Ott, *Ann.*, **488**, 186 (1931). (b) R. Huisgen and C. Rüchardt, *Ann.*, **601**, 21 (1956).

(18) However, see page 869.

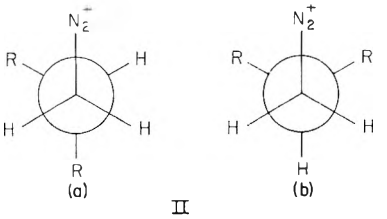
(19) H. C. Brown and M. Nakagawa, *J. Am. Chem. Soc.*, **77**, 3614 (1956).

(20) For a review, *cf.* A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571 (1956).

(21) K. S. Pitzer, *Discussions Faraday Soc.*, **10**, 66 (1951).

(22) J. D. Roberts and J. A. Yancey, *J. Am. Chem. Soc.*, **74**, 5943 (1952).

from 2,2-diphenylethylamine,[23] although more or less tertiary alcohol is obtained from isobutylamine,[24,25] 2-methyl-1-octylamine,[26] 2-phenyl-1-propylamine,[27] and cyclopentyl- and cyclohexylcarbinylamines.[28] An explanation for these apparently discordant results may again be found in reactions and populations of different conformations. The diazonium ions corresponding to these amines can exist in two types of conformation, IIa,




II

in which the diazonium function is *gauche* to only one of the carbon functions, R, and IIb, in which it is *gauche* to both R groups. Only IIb, the less populated conformation, can lead to rearrangement of a hydrogen. Consequently, as both R groups become more bulky, the population in IIb decreases and the amount of hydrogen-rearranged product (in these cases, $R_2COHCH_3$) decreases.

Although *n*-amylamine yields substantial amounts of 2-pentanol,[5a] no 3-pentanol is observed;[29] the 2-pentyl cation formed in the rearrangement does not further rearrange. Analogously, the acetolysis of 2-pentyl brosylate is reported to yield no observable amounts of 3-pentyl acetate.[19] Furthermore, 3-phenyl-1-propylamine gives no 1-phenyl-1-propyl derivatives.[11]

It should be mentioned that reactions 2b and 2c, elimination and rearrangement of a *trans*-hydrogen, may actually be a single reaction leading to a hydrogen-bridged intermediate which can subsequently eliminate a proton or complete the rearrangement.

*Reaction 2d: Rearrangement of a carbon function.* As in the rearrangement of hydrogen, the rearrangement of a carbon function has conformational requirements and is important only when the resulting carbonium ion is more stable than that which would arise without rearrangement;[28b,30a] hence, the rearranging group and the $\beta$-carbon atom are distributing an important share of the positive charge. In the reaction of *n*-butylamine, no ethyl group rearrangement is observed.[14] The 3,3-dimethyl-1-butanol obtained from the corresponding amine shows less than 1% of *t*-butyl group rearrangement.[30b] Similarly, the reactions of 3-phenyl-1-propylamine and 3-anisyl-1-propylamine give no rearrangement of a benzyl group or an anisylmethyl group, respectively.[11] It has been suggested[30b] that the 8.5% methyl rearrangement reported[6] in the *n*-propyl alcohol from *n*-propylamine is a high result due to experimental difficulties.

Halides and sulfonates which solvolyze with participation of a neighboring carbon function and consequent rearrangement also demonstrate analogous rearrangements when the corresponding amines are treated with nitrous acid provided that conformational requirements are met. Parallels of this sort in the rearrangemnt products obtained from solvolytic reactions and amine-nitrous acid reactions are given by neopentyl,[30a,31] $\beta,\beta$-diarylethyl,[8,23,32] and $\beta,\beta,\beta$-triarylethyl[23,32b,33] systems. The formation of some *sec*-butyl alcohol from isobutylamine[25] and the numerous[5] examples of the Demjanow ring expansion[34] and semipinacolic deaminations (Equation 4) are additional examples of this mode of reaction. In the latter cases, the rearrangement competes effectively because a relatively stable carbonium ion, a protonated carbonyl group, is produced.

$$R_2C(OH)C(NH_2)R_2 \longrightarrow RCOCR_3 \qquad (4)$$

The conformational requirements have been elegantly demonstrated by Cram and McCarty[7] by the reactions of *erythro*- and *threo*-3-phenyl-2-butylamine. Both diasteriomers gave evidence of phenyl group rearrangement, but the phenyl group rearrangement was much more prevalent in the *erythro* isomer. The population of that conformation in which the phenyl group is *trans* to the nitrogen function is expected to be greater than that in which the methyl group is *trans* for the *erythro* isomer. The reverse is expected to be true for the *threo* isomer.[7]

Studies of migration aptitudes are interesting. In the acetolysis of $\beta$-phenyl-$\beta$-tolylethyl tosylate, rearrangement of the *p*-tolyl group occurs three

(23) L. Hellerman, M. L. Cohn, and R. E. Hoen, *J. Am. Chem. Soc.*, **50**, 1716 (1928).

(24) (a) E. Linnemann, *Ann.*, **162**, 12 (1872). (b) L. Henry, *Compt. rend.*, **145**, 899 (1907).

(25) (a) L. G. Cannell and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **78**, 5812 (1956). (b) E. H. White, *J. Am. Chem. Soc.*, **77**, 6011 (1955).

(26) M. Freund and F. Schönfeld, *Ber.*, **24**, 3350 (1891).

(27) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **103**, 373 (1933).

(28) (a) P. A. S. Smith and D. R. Baer, *J. Am. Chem. Soc.*, **74**, 6135 (1952). (b) P. A. S. Smith, D. R. Baer, and S. N. Ege, *J. Am. Chem. Soc.*, **76**, 4564 (1954).

(29) A. Streitwieser, Jr., and D. van Sickle, unpublished results.

(30) (a) A. Brodhag and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 3024 (1955). (b) W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **78**, 6127 (1956).

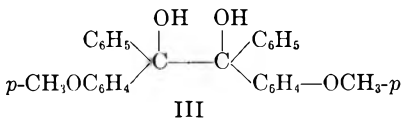
(31) (a) M. Freund and F. Lenze, *Ber.*, **23**, 2865 (1890); **24**, 2150 (1891). (b) M. L. Tissler, *Compt. rend.*, **112**, 1065 (1891). (c) F. C. Whitmore, E. C. Wittle, and A. H. Popkin, *J. Am. Chem. Soc.*, **61**, 1586 (1939). (d) I. Dostrovsky and E. D. Hughes, *J. Chem. Soc.*, 166 (1946).

(32) (a) J. G. Burr, *J. Am. Chem. Soc.*, **75**, 5008 (1953). (b) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1113 (1952).

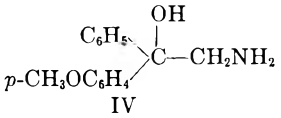
(33) J. C. Charlton, I. Dostrovsky, and E. D. Hughes, *Nature*, **167**, 986 (1951).

(34) For a review of N. J. Demjanow's results *cf. Uspekhi Khim.*, **3**, 493 (1934); for a recent comprehensive study *cf.* ref. 28.

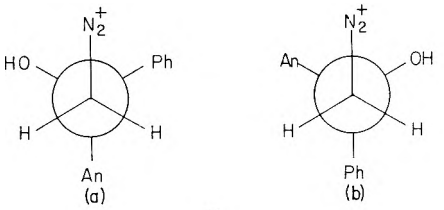
times as readily as the phenyl group.[32a] In the reaction of the corresponding amine with nitrous acid, the two groups rearrange almost equally.[8,35] More striking differences are observed in the comparison of the products of pinacol rearrangements with those of semipinacolic deaminations. For example, in the rearrangement of a 1,2-diphenyl-1,2-di-*p*-anisylethylene glycol, III, with acid the relative rate of anisyl to phenyl rearrangement is 500:1.[36] In the analogous reaction of 1-phenyl-1-*p*-anisyl-2-aminoethanol, IV, with nitrous acid, the anisyl:phenyl migration ratio is only 1.56:1.[13] On the basis of these results, Curtin and Crew[13] concluded that the rearranging group is not participating appreciably in the rearrangement in the amine reaction. Yet, the fact that the rearrangement occurs in this case to the virtual exclusion of other possible reactions demonstrates that the migrating group is participating to an important extent as far as the amount of positive charge distributed is concerned. However, the low activation required for decomposition of the intermediate diazonium ion which would exist almost entirely in only two conformations, Va and b, equally populated is hypothesized to be comparable to that required for rotation about




III

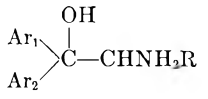



IV




V

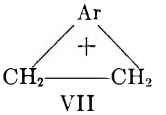
the carbon-carbon bond.[37] In the absence of any such rotation equal amounts of phenyl and anisyl rearrangement would be expected; because some rotation probably does occur, a small excess of anisyl rearrangement is observed. Correspondingly, both diastereomers of a number of amines of the type VI have been treated with nitrous acid. The ketone which is produced principally or exclusively, depending on the size of R, is that which results from migration of the group *trans* to the nitrogen




VI

function in the most stable conformation.[38] The stereospecificity of the rearrangement of the *trans* group has also been demonstrated in the reaction of several steroidal amines.[39]

The reactions of β-arylethylamines are particularly interesting. Rearrangement of the aryl group would produce a bridged ion, VII, which is probably




VII

more stable than the isomeric β-arylethyl cation.[20] From the reaction of 2-phenylethylamine-1-$C^{14}$ with nitrous acid in acetic acid, 2-phenylethyl-$C^{14}$ acetate is obtained in 70% yield[40] and is partially rearranged.[40,41] This product may be considered, to a first approximation, to arise from a competing displacement (reaction 2a) and phenyl rearrangement to a bridged ion. Because almost all of the diazonium salt is expected to be in that conformation in which the bulky phenyl ring is *trans* to the nitrogen function, hydrogen rearrangement and elimination are expected to be but minor reactions. In the corresponding saturated system, 2-cyclohexylethylamine, the bridged ion does not form, hence the other reactions, which require prior rotation about the carbon-carbon bond, are more important. Primary and secondary alcohol and olefin are isolated in this case.[42] The observation of 27% rearrangement from β phenylethylamine[41] would indicate that 54% of the reaction occurred by rearrangement to VII and 46% occurred directly with solvent.[43] The rate of rearrangement relative to displacement is 1.2. The corresponding relative rate for rearrangement of a *p*-anisyl group is 9.0. Since the rate for displacement on the diazonium salt from β-phenylethylamine is probably very similar to that on the diazonium salt from β-*p*-anisylethylamine, these

(35) P. S. Bailey and J. G. Burr, *J. Am. Chem. Soc.*, **75**, 2951 (1953); B. M. Benjamin and C. J. Collins, *J. Am. Chem. Soc.*, **78**, 4952 (1956).

(36) W. E. Bachman and F. H. Moser, *J. Am. Chem. Soc.*, **74**, 1124 (1932).

(37) Compare with J. Hine, *Physical Organic Chemistry*, p. 314, McGraw-Hill Book Co., New York, N. Y., 1956, and W. G. Dauben and K. S. Pitzer in *Steric Effects in Organic Chemistry*, M. S. Newman, Ed., p. 10, J. Wiley and Sons, Inc., New York, N. Y., 1956.

(38) (a) P. I. Pollack and D. Y. Curtin, *J. Am. Chem. Soc.*, **72**, 961 (1950). (b) D. Y. Curtin and P. I. Pollack, *J. Am. Chem. Soc.*, **73**, 992 (1951). (c) D. Y. Curtin, E. H. Harris, and P. I. Pollack, *J. Am. Chem. Soc.*, **73**, 3453 (1951). (d) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **77**, 354 (1955). (e) A. McKenzie and A. K. Mills, *Ber.*, **62**, 284 (1929). (f) A. McKenzie and A. D. Wood, *Ber.*, **71**, 358 (1938).

(39) F. Ramirez and S. Stafiej, *J. Am. Chem. Soc.*, **77**, 134 (1955); **78**, 644 (1956).

(40) C. C. Lee and J. W. T. Spinks, *Can. J. Chem.*, **31**, 761 (1953).

(41) J. D. Roberts and C. M. Regan, *J. Am. Chem. Soc.*, **75**, 2069 (1953).

(42) O. Wallach, *Ann.*, **359**, 312 (1899).

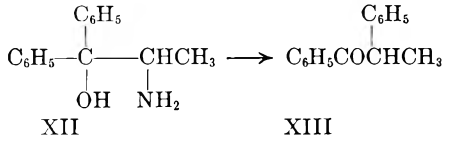
(43) This hypothesis is currently under stereochemical investigation.

relative rates indicate that the anisyl group tends to participate eight times as readily as a phenyl group. This "migratory aptitute" demonstrates that the migrating group bears a significant amount of positive charge[44] and reiterates the conclusion reached above that the *p*-anisyl:phenyl ratio of 1.56:1 measured directly from the reaction of 1-phenyl-1-*p*-anisyl-2-aminoethanol is due in large measure to the relative populations of different conformations. These conclusions are further supported by the observation that compounds VIII, IX, and X give a mixture of glycol and rearranged ketone in aqueous nitrous acid although XI and XII give only ketone.[46] In the former cases, displacement by solvent to form glycol apparently competes favorably with the rearrangement of an alkyl group or hydrogen but such displacement in the latter cases competes less effectively with rearrangement of an aryl group. In solvolytic displacements aryl groups generally give greater neighboring group participation than alkyl groups or hydrogen.

$C_6H_5CHOHCHNH_2C_6H_5$ (VIII) $(C_2H_5)_2COHCHNH_2C_6H_5$ (IX)

$(C_6H_5CH_2)_2COHCHNH_2C_6H_5$ (X) $(C_6H_5)_2COHCH_2NH_2$ (XI)

It should be mentioned that the present hypothesis which assumes a concerted rearrangement and expulsion of nitrogen is consistent with the stereochemical results of Bernstein and Whitmore[47] who found that optically active 1,1-diphenyl-2-aminopropanol, XII, gave optically active phenyl $\alpha$-phenylethyl ketone, XIII.



XII XIII

*Reaction 2e: Carbonium ion formation.* One of the competing modes of decomposition of the diazonium ion is the direct formation of a carbonium ion by loss of nitrogen. Unlike the "high energy" carbonium ion which has been postulated from such a reaction (*vide supra*) the carbonium ion is here considered to be "normal", *i.e.*, directly comparable to carbonium ions which are produced in other reactions such as solvolytic displacements of alkyl halides and sulfonates.

The *t*-butyl cation reacts with thiocyanate ion to give a mixture of *t*-butyl thiocyanate, XIV, and isothiocyanate, XV. The similarity of the ratio of

$(CH_3)_3CSCN$ (XIV) $(CH_3)_3CNCS$ (XV)

XIV to XV for the mixture obtained from different sources of the *t*-butyl cation, isobutylamine, 1.9, *t*-butylamine, 1.9, *t*-butyl chloride, 2.5, demonstrates that essentially the same cation is produced from the three sources.[48] The reactions with aqueous nitrous acid of crotylamine, $\alpha$-methylallylamine, $\alpha,\alpha$-dimethylallylamine, and $\gamma,\gamma$-dimethylallylamine yield, respectively, the same mixtures of isomeric allylic alcohols as the silver ion catalyzed aqueous solvolyses of the corresponding chlorides.[49,50] The reactions of cyclopropylcarbinylamine and cyclobutylamine with aqueous nitrous acid to give similar mixtures of cyclobutyl alcohol, cyclopropyl carbinol, and allyl carbinol have been interpreted on the basis of the same intermediate cation.[49]

The racemic portions of the 1-butyl-1-*d* acetate, 2-butyl acetate, 2-butyl alcohol, and $\alpha$-phenylethyl alcohol obtained from the reactions of the corresponding amines with nitrous acid in acetic acid or water (*vide supra*) undoubtedly result from the respective carbonium ions.

*Neighboring group participation.* To reactions 2a–e may be added a sixth competing reaction, reaction 5, when the $\beta$-carbon contains a suitable heteroatomic function. An example is found in the

reaction of $\alpha$-aminoacids with nitrous acid. Although the esters yield product with predominant inversion of configuration, the aminoacids produce a net retention of configuration[2a,3] presumably because of the formation of an $\alpha$-lactone by reaction 5 with one inversion followed by reaction of the $\alpha$-lactone with solvent water to yield the hydroxyacid with a second inversion. In suitable cyclic cases oxides have been obtained from $\beta$-aminoalcohols (*vide infra*).

### CYCLIC SYSTEMS

*Cyclohexyl systems.* Concerted rearrangements and eliminations with loss of nitrogen from diazonium ions in cyclohexyl systems have been proposed by several authors[51] but no attempt has previously been made to relate these proposals to a

(44) For comparison, the migratory aptitude of *p*-anisyl relative to phenyl in the acid-catalyzed rearrangement of $\beta,\beta$-diarylethanols is 21.[45]

(45) J. G. Burr and L. S. Ciereszko, *J. Am. Chem. Soc.*, **74**, 5426 (1952).

(46) H. Felkin, *Compt. rend.*, **226**, 819 (1948).

(47) H. I. Bernstein and F. C. Whitmore, *J. Am. Chem. Soc.*, **61**, 1324 (1939).

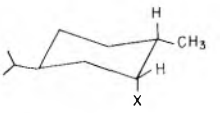
(48) L. G. Cannell and R. W. Taft, Jr., Abstracts of the 129th meeting of the AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 12, 1956, p. 46N.

(49) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).

(50) W. G. Young and C.-H. Shih, unpublished results reported in W. G. Young and R. H. DeWolfe, *Chem. Revs.*, **56**, 753 (1956).

(51) (a) M. Mousseron, *Bull. soc. chim. France*, 1008 (1956). (b) R. J. W. Cremlyn, D. L. Garmaise, and C. W. Shoppee, *J. Chem. Soc.*, 1847 (1953). (c) R. Anliker, O. Rohr, and H. Heuser, *Helv. Chim. Acta*, **38**, 1171 (1955).

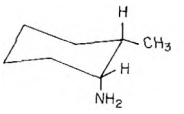
general theory. Cyclohexylamines have been shown to provide a striking demonstration of the importance of conformational considerations in the amine-nitrous acid reaction.[52,53] In general, equatorial amines yield equatorial (retained) alcohol with little or no olefin; axial amines yield large amounts of olefin together with a small amount of alcohol which is predominantly the equatorial (inverted) alcohol.[54] In terms of the present hypothesis, equatorial amines would undergo reaction 2e almost exclusively and the resulting carbonium ion would react with solvent along an equatorial path and may be expected to produce exclusively equatorial alcohol. This point has been discussed in greater detail by Dauben, *et al.*[53a,55] The axial diazonium ion can react by migration or elimination of a neighboring *trans*- (axial) hydrogen, by direct displacement by solvent, and in part by reaction 2e, carbonium ion formation. This carbonium ion, as in the equatorial case, should yield only equatorial alcohol. Other alcohols are generally also produced in small amount from axial amines but these have frequently been characterized either inadequately or not at all.[56] It seems clear, however, that in at least some of these cases, traces of the corresponding axial alcohols are formed.[57] According to the present hy-



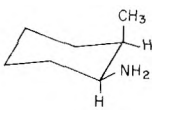

XVI

pothesis, these alcohols could not be formed from the carbonium ion from reaction 2e but could arise from the reaction with solvent of a hydrogen-bridged intermediate.[55] Cyclohexylamine, which gives 80% cyclohexanol and 16% cyclohexene,[56,58] would then be considered to be reacting about 80% as an equatorial amine and 20% as an axial.[59] Direct displacements are not expected to be important in cyclohexyl systems because typical SN2 reactions on cyclohexyl derivatives are about 100 times slower than on other secondary carbinyl systems.[20]

The 2-methylcyclohexylamine system is an important case. The *trans*-isomer, which exists almost exclusively in the conformation in which both the methyl group and the amino group are equatorial, yields, as expected, *trans*-2-methylcyclohexanol.[60] The *cis*-amine is expected to exist in comparable amounts in the equatorial-methyl, axial-amino (XVII) and axial-methyl, equatorial-amino (XVIII) conformations. The former should yield olefin, *trans*-2-methylcyclohexanol, and the product of the migration of the tertiary *trans* (axial) hydrogen, (reaction 2c), 1-methylcyclohexanol. The




XVII




XVIII

latter conformation, XVIII, should yield only 2-methylcyclohexyl cation which by rotation to the methyl-equatorial cation and equatorial reaction with solvent would lead to *trans*-2-methylcyclohexanol. Experimentally, the *cis*-amine yields mostly *trans*-2-methylcyclohexanol, some 1-methylcyclohexanol and olefin, and only a trace of *cis*-2-methylcyclohexanol,[60c] in complete accord with the present theory. A mechanism involving a frontside displacement of nitrogen by solvent has been proposed to explain the retention of configuration observed with equatorial amines.[52b] On this basis, XVIII should yield *cis*-2-methylcyclohexanol. The formation of only traces of this alcohol provides an argument against this mechanism. Similarly, these results are not consistent with the "hot" carbonium ion theory (*vide supra*).

In the case of equatorial amines, the *trans*-group is a ring carbon. As expected from the discussion developed in reaction 2d, rearrangement with ring contraction would be expected to be a significant competing reaction when a more stable carbonium ion would result from such rearrangement. Examples are the reaction of *trans*-2-phenylcyclohexylamine which gives a good yield of phenylcyclopen-

(52) (a) A. K. Bose, *Experientia*, 9, 256 (1953). (b) J. A. Mills, *J. Chem. Soc.*, 260 (1953).

(53) (a) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, 76, 4420 (1954). (b) W. G. Dauben and J. Jiu, *J. Am. Chem. Soc.*, 76, 4426 (1954). (c) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *J. Am. Chem. Soc.*, 77, 48 (1955).

(54) The recent report of C. W. Shoppee, D. E. Evans and G. H. R. Summers, *J. Chem. Soc.*, 97 (1957), that some axial steroid amines yield olefin and *axial* (retained) alcohol is in complete apparent contradiction to all of the other results cited with cyclohexyl systems. Clearly, additional work is required to determine why these amines differ from the others; no explanation can be offered at this time.

(55) *Cf.* also W. H. Saunders, Jr., in ref. 53a, footnote 36.

(56) For example, see the summary of other references cited in W. Hückel, *Ann.*, 533, 1 (1937).

(57) One of the best examples is the reaction of neocarvomenthylamine (XVI, X = $NH_2$) from which a small amount of neocarvomenthol (XVI, X = OH) was obtained and characterized *via* the 3,5-dinitrobenzoate. [R. G. Johnston and J. Read, *J. Chem. Soc.*, 1138 (1935)].

(58) W. Huckel and R. Kupka, *Ber.*, 89, 1694 (1956).

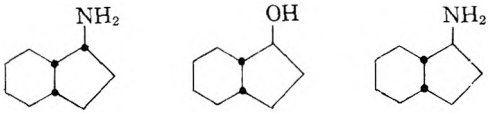
(59) These values correspond to an energy difference (A value) of the two conformations of the nitrogen function of 0.8 kcal./mole, a not unreasonable value inasmuch as the A value for the hydroxyl group is 0.8 kcal./mole [S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955)].

(60) (a) P. Anziani and R. Cornubert, *Compt. rend.*, 221, 103 (1945). (b) P. Anziani and R. Cornubert, *Bull. soc. chim. France*, 15, 857 (1948). (c) M. Claudon, P. Anziani and R. Cornubert, *Bull. soc. chim. France*, 150 (1956).

tylcarbinol[61] and the formation of phenyl cyclopentyl ketone from *trans*-2-amino-1-phenylcyclohexanol.[62] Analogous results are obtained with some steroidal amines.[51b,c]

*Trans*-2-aminocyclohexanol yields only cyclopentylaldehyde although the *cis*-aminoalcohol yields both cyclopentylaldehyde and cyclohexanone;[63] cyclohexyl systems in which an amino function and a hydroxyl function occupy adjacent axial positions yield epoxides.[51a,b] In these positions, neighboring group participation is geometrically most favorable (reaction 5). Similar reactions with other functions have been summarized by Mousseron.[51a]

*Cyclopentyl systems.* Both carbonium ion formation and direct displacement reactions are expected to be important with cyclopentyl amines. When *trans*-hydrogens are available, elimination and rearrangement are to be anticipated. Cyclopentylamine itself yields equal amounts of cyclopentene and cyclopentanol.[56,64a] The alcohol from *trans*-2-cyclopentyl-1-cyclopentylamine is almost pure *cis*-2-cyclopentyl-1-cyclopentanol and the alcohol from the *cis* amine is mostly *trans*. In both cases a net inversion of configuration predominates.[64b] Olefin is also obtained in both cases. Analogously, *cis*-1-amino-*cis*-hydrindane, XIX, yields more of the corresponding *trans*-alcohol, XX, than does the *trans*-amine, XXI.




XIX XX XXI

On the other hand, *cis*-2-methylcyclopentylamine is reported[64a] to yield an alcohol mixture of 70% *cis*-2-methylcyclopentanol and 30% *trans*-2-methylcyclopentanol and an olefin mixture consisting of about equal amounts of 1-methylcyclopentene and 2-methylcyclopentene although the *trans*-amine yields an alcohol mixture consisting of about equal parts of these *cis* and *trans* alcohols and olefin which is essentially pure 1-methylcyclopentene. These results are in direct contrast to those obtained in the other systems cited above and from those expected by the theory, and suggest further investigation.

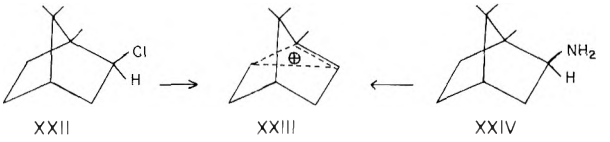
(61) (a) D. V. Nightingale and M. Maienthal, *J. Am. Chem. Soc.*, **72**, 4823 (1950). (b) D. V. Nightingale, J. D. Kerr, J. A. Gallagher, and M. Maienthal, *J. Org. Chem.*, **17**, 1017 (1952); *trans*-2-cyclohexylcyclohexylamine does not rearrange in this way probably because a secondary carbonium ion would result which is no more stable than that formed without rearrangement.

(62) D. Y. Curtin and S. Schmukler, *J. Am. Chem. Soc.*, **77**, 1105 (1955).

(63) G. E. McCasland, *J. Am. Chem. Soc.*, **73**, 2293 (1951).

(64) (a) W. Hückel and R. Kupka, *Ber.*, **89**, 1694 (1956). (b) W. Hückel, A. Gross, and W. Doll, *Rec. trav. chim.*, **57**, 555 (1938).

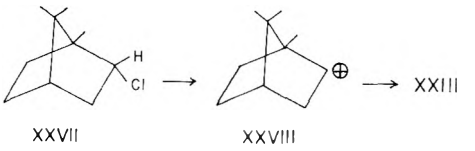
*Bridged bicyclic systems.* In the bicyclo[2.2.1]heptyl system a comparison of the amine-nitrous acid reaction with solvolytic displacement reactions is especially pertinent because nonclassical bridged ions have been shown to be important intermediates in the latter reactions.[20] The solvolysis of isobornyl chloride, XXII, to yield the bridged ion, XXIII, shows such substantial rate enhancement that in the reaction of the corresponding amine, XXIV, the decomposition of the diazonium salt to yield XXIII is expected to be the only important mode of reaction. In aqueous base, XXIII yields




XXII XXIII XXIV

camphene hydrate, XXV. The products of the reaction of XXIV with sodium nitrite in dilute acetic acid are camphene hydrate, XXV, and camphene, XXVI,[64a] consistent with expectations. On the other hand, bornyl chloride, XXVII, cannot yield XXIII by a concerted neighboring group rearrangement but does so in a comparatively slow reaction presumably by way of the bornyl cation, XXVIII. In the reaction of bornylamine, therefore, two modes of decomposition of the diazonium ion are important.

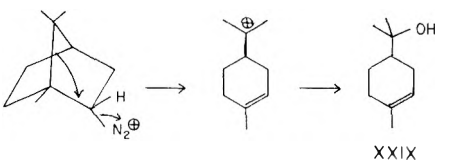

XXV XXVI




XXVII XXVIII

One is the formation of XXVIII, thence XXIII; the other is the elimination (or a rearrangement followed by elimination) of the *trans* group, the *gem*-dimethyl bridge (Equation 6). The products of the reaction in dilute acetic acid are not only camphene and camphene hydrate but also terpineol, XXIX.[65]

The reactions of the norbornylamines are directly comparable except that a reaction similar




XXIX

to reaction 6 does not occur because a primary carbonium ion would result. The *exo*-norborneol, XXX,

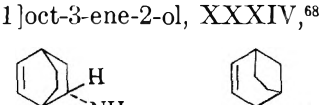
(65) W. Hückel and F. Nerdel, *Ann.*, **528**, 57 (1937).

which is obtained from *exo*-norbornylamine, XXXI, is about 50% rearranged,[10] apparently because of the almost exclusive direct formation of a bridged cation. The lesser amount of rearrangement[10] found in the case of the *endo*-amine, XXXII, is

XXX XXXI XXXII

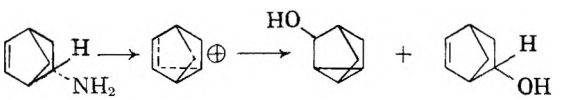
presumably due either to a reaction of the initial intermediate, the unbridged norbornyl cation, with solvent or by a competing direct displacement, or both. Similar arguments can be applied to the reaction products obtained from the epimeric fenchylamines[66] and from camphenylylamine.[67]

Although the reaction with nitrous acid of *endo*-2-aminobicyclo[2.2.2]octene-5, XXXIII, to yield bicyclo[3.2.1]oct-3-ene-2-ol, XXXIV,[68] is probably



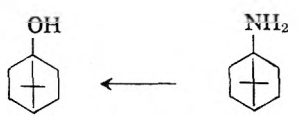
XXXIII XXXIV

best interpreted as a 2d reaction in which the ethylene bridge migrates as nitrogen is lost, the corresponding reaction of *endo*-2-amino-bicyclo[2.2.1]heptene-5, XXXV, on the basis of the present discussion probably occurs by way of the nonclassical ion, XXXVI.[69] The further rearrangement which the ion XXXVI can undergo has been detailed by Roberts, *et al.*[69a]



XXXV XXXVI

The formation of apocamphanol-1, XXXVII, from 1-amino-apocamphane, XXXVIII,[70] according to the present hypothesis is due to the formation of a carbonium ion at the bridgehead which in this case is the only mode of reaction available to the intermediate diazonium ion. Because of the higher energy of the tetrahedral carbonium ion[71] this reaction should occur less readily than the decomposition of other alkyldiazonium ions but should occur at least as readily as the decomposition of an aryldiazonium ion which yields a similarly unstable aryl cation.[72]



XXXVII XXXVIII

### OTHER SYSTEMS

The transannular 1,5- and 1,6-hydride shifts which have been found to occur during the reaction of cyclodecylamine with nitrous acid[73] are presumably directly analogous to the 1,2-shifts represented as reaction 2c.

Finally, mention should be made of the several reactions of the amine-nitrous acid type in inert solvents. The reaction of optically active $\alpha$-phenylethylamine with nitrosyl chloride in dioxane leads to the corresponding chloride with partial net retention of configuration.[74] The decomposition of 2-phenyl-2-*p*-tolylethylamine nitrite in dry ligroin or in dry butanol gave *carbinol*.[35] In both cases the results were attributed to an intramolecular reaction of the $S_Ni$[75] type. However, like other such reactions, these results are consistent with the intermediate formation of an "intimate ion pair" or "p$\sigma$-complex"which collapses with predominant retention of configuration, reaction 7.[76,77]

$$R{-}N{=}N{-}X \longrightarrow R^+ \ldots . X^- + N_2 \longrightarrow R{-}X + N_2 \quad (7)$$

Further work may demonstrate the necessity of including reactions of this type among the competing modes of decomposition of alkyldiazonium salts.

*Acknowledgment.* The author is indebted to Professor William G. Dauben for many stimulating discussions on this subject.

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(66) (a) W. Hückel and H. Wolowski, *Ber.*, **80**, 39 (1947). (b) W. Hückel and U. Ströle, *Ann.*, **585**, 182 (1954).

(67) S. Beckmann and R. Bamberger, *Ann.*, **574**, 65 (1951).

(68) W. C. Wildman and D. R. Saunders, *J. Am. Chem. Soc.*, **76**, 946 (1954).

(69) (a) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **77**, 3034 (1955). (b) W. E. Parham, W. T. Hunter, and R. Hanson, *J. Am. Chem. Soc.*, **73**, 5068 (1951).

(70) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939).

(71) *Cf.* W. E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, *J. Am. Chem. Soc.*, **75**, 1008 (1953).

(72) *Cf.* J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(73) V. Prelog, H. J. Urech, A. A. Bothner-by, and J. Würsch, *Helv. Chim. Acta*, **38**, 1095 (1955).

(74) H. Felkin, *Compt. rend.*, **236**, 298 (1953).

(75) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

(76) (a) C. E. Boozer and E. S. Lewis, *J. Am. Chem. Soc.*, **75**, 3182 (1953). (b) D. J. Cram, *J. Am. Chem. Soc.*, **75**, 332 (1953). (c) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 379 (1957). (d) A. Streitweiser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2893 (1957).

(77) The application of this explanation to the results of Bailey and Burr[35] is uncertain. Inadequate experimental details were given and one cannot tell if the first products were alkyl nitrites which hydrolyzed during work-up or whether an intermediate diazoalkane was formed.[76d]

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

# Rearrangement of 2,3-Bis(*p*-aminophenyl)-2,3-butanediol. Structure of Amphenone B*

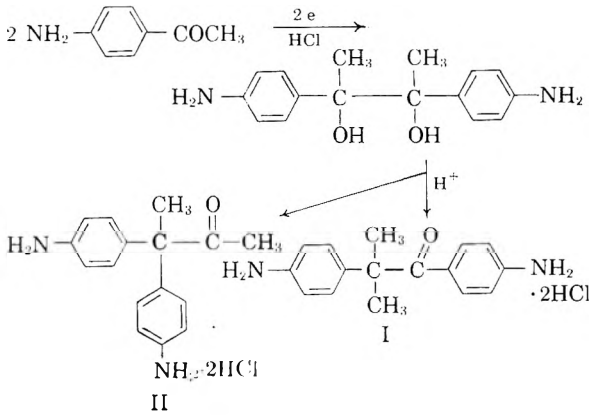
JEROME KORMAN AND EDWARD C. OLSON

*Received February 25, 1957*

The pinacolone obtained by the acid rearrangement of 2,3-bis(*p*-aminophenyl)-2,3-butanediol is shown to be 3,3-bis(*p*-aminophenyl)-2-butanone (II), rather than 1,2-bis(*p*-aminophenyl)-2-methylpropanone-1 (I) as previously formulated.

The substance called Amphenone B, which causes suppression of cortical hormone secretion with concurrent adrenal hypertrophy,[1] is a valuable tool for the clinical control of the symptoms evidenced by Cushing's Syndrome associated with adrenal carcinoma.[2]

Amphenone B was originally prepared by Allen and Corwin[3] who obtained the pinacol, 2,3-bis-(*p*-aminophenyl)-2,3-butanediol, from *p*-aminoacetophenone by electrolytic reduction at constant potential.[4,5] Treatment with dilute hydrochloric acid gave the pinacolone dihydrochloride, Amphenone B, which was assigned the structure I.[6] This structure was based upon the following evidence. (a) The substance gave a negative iodoform test.[7] (b) Methylation of the amino groups, followed by treatment of the product with potassium hydroxide solution, afforded a substance whose melting point compared favorably with that of *p*-dimethylaminobenzoic acid.[8] (c) No evidence was observed for the formation of acetic acid which was expected from II upon treatment with alkali.




Since the original paper by Fittig[9] in 1860, the pinacol rearrangement has received intensive study by numerous investigators. Among these, Bailar[10] and Bachmann and coworkers[11] determined the effect of substituents on the "migratory aptitude" of groups in a large number of symmetrical benzopinacols, and provided a numerical system for predicting relative mobility. Additional data were supplied by Tiffeneau and Levy[12] for glycols containing both aliphatic and aromatic groups, which also showed some order in migrating ability. In none of these studies is information available for any compounds possessing a *p*-aminophenyl grouping. It is impossible, therefore, to assign to this group any numerical value to indicate its migratory aptitude relative to any other group. In the rearrangement which proceeds *via* a carbonium ion mechanism as proposed by Whitmore[13,14] the migratory aptitude is associated with the electron donating ability of the various groups. Accordingly

* Subsequent to the receipt of this manuscript there appeared a communication to the Editor was published showing the corrected structure for Amphenone B [W. L. Bencze and M. J. Allen, *J. Org. Chem*, **22**, 352 (1957)].

(1) R. Hertz, M. J. Allen and W. W. Tullner, *Proc. Soc. Exptl. Biol. Med.*, **75**, 627 (1950); R. Hertz, W. W. Tullner and M. J. Allen, *Proc. Soc. Exptl. Biol. Med.*, **77**, 480 (1951); W. W. Tullner, M. M. Graff and R. Hertz, *Endocrinology*, **58**, 802 (1956).

(2) R. Hertz, J. A. Pittman and M. M. Graff, *J. Clin. Endocrinol. and Metabolism*, **16**, 705 (1956); G. W. Thorn, A. E. Renold, A. Goldfien, D. H. Nelson, W. J. Reddy and R. Hertz, *New Engl. J. Med.*, **254**, 547 (1956).

(3) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 117 (1950).

(4) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 114 (1950).

(5) N. J. Leonard, S. Swann, and G. Fuller, *J. Am. Chem. Soc.*, **75**, 5127 (1953).

(6) Subsequently M. J. Allen, *J. Chem. Soc.*, 1598 (1951), suggested a structure analogous to I for the pinacolone obtained from 2,3-bis(*p*-dimethylaminophenyl)-2,3-butanediol, which was prepared by the electrolytic reduction of *p*-dimethylaminoacetophenone. The assignment of structure was made entirely on the similarity of the infrared spectra.

(7) This cannot be used to support structure I. Pinacolone itself was shown by R. Poggi, *Atti soc. ital. progresso sci., XXI Reunione*, **2**, 376 (1933), to give a negative iodoform test. Similarly C. C. Price and G. R. Mueller, *J. Am. Chem. Soc.*, **66**, 634 (1944), observed the same result with 3,3-dianisyl-2-butanone.

(8) No mixed melting point or other evidence was provided.

(9) R. Fittig, *Ann.*, **114**, 54 (1860).

(10) J. C. Bailar, *J. Am. Chem. Soc.*, **52**, 3596 (1930).

(11) W. E. Bachmann and F. H. Moser, *J. Am. Chem. Soc.*, **54**, 1124 (1932); W. E. Bachmann and H. R. Steinberger, *J. Am. Chem. Soc.*, **55**, 3819 (1933); **56**, 170 (1934).

(12) M. Tiffeneau and J. Levy, *Bull. soc. chim. France*, [4] **49**, 1647, 1767, 1698 (1931).

(13) F. C. Whitmore, *J. Am. Chem. Soc.*, **54**, 3274 (1932).

(14) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, pp. 247–257. See also E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 45–49.

one might conclude that the amino group should supply tremendous impetus in effecting phenyl migration. In acid solution, however, $-NH_3^+$, which imparts electron attracting properties, would be expected to produce an opposite effect. The methyl group, which might now be considered as a competing electron donating group, could possibly displace phenyl as the migrating group. The conclusions arrived at by Allen and Corwin could be interpreted in conformance with this idea. This explanation is not, however, in accord with results obtained in these laboratories.

Physical data gathered on samples of Amphenone B, which were prepared according to the method described, are not in agreement with the structure I. The infrared spectrum in mineral oil mull shows only nonconjugated carbonyl absorption in the vicinity of 1705 cm.$^{-1}$ rather than a doublet at 1682 and 1665 cm.$^{-1}$ as determined for the conjugated carbonyl in *p*-aminoacetophenone hydrochloride. The carbonyl absorption for Amphenone free base is found at 1704 cm.$^{-1}$; for *p*-aminoacetophenone the carbonyl absorption occurs at 1636 cm.$^{-1}$ These differences in ketone absorption establish that Amphenone B cannot be structurally related to *p*-aminoacetophenone as was previously postulated. Furthermore, the substance in hexachlorobutadiene mull shows no absorption in the region which can be associated with the *gem*-dimethyl grouping which is required by structure I.

Differences in the ultraviolet spectra of Amphenone B and *p*-aminoacetophenone hydrochloride afford additional evidence for the nonconjugated carbonyl group in the former. *p*-Aminoacetophenone in 0.01 *N* ethanolic sulfuric acid shows absorption maxima at 233 and 318 m$\mu$ with molar absorbtivities ($a_M$) of 7075 and 19,325, respectively. Amphenone B in the same solvent has absorption maxima at 248 and 292 m$\mu$ with molar absorptivities of 3275 and 1075, respectively. It has been shown[15] that phenyl substitution on a saturated carbon atom $\alpha$ to a carbonyl group imparts enhanced absorption to that carbonyl in the region of 290 m$\mu$. In no case, however, was the intensity of the absorption greater than that which could be attributed to the phenyl group(s). On the other hand, when a ketone is conjugated with a phenyl group there is an even greater increase in the intensity of the absorption as well as a shift to longer wave lengths. Thus, the larger molar absorptivity of *p*-aminoacetophenone at 318 m$\mu$ indicates the presence of a conjugated carbonyl group, whereas the weak absorption of Amphenone B which lies at 292 m$\mu$ strongly suggests a nonconjugated ketone.

The polarographic behavior was studied in 75% ethyl alcohol–25% water containing 0.1*M* tetramethylammonium hydroxide as a supporting electrolyte. Half-wave potentials of $-2.05$ and $-2.12$ volts *vs.* a mercury pool anode were found for Amphenone and acetone, respectively. The half-wave potential observed for *p*-aminoacetophenone under identical conditions was $-1.67$ volts. This is additional support for the conclusions drawn from spectral data, since structure I would be expected to reduce in the same potential range as does *p*-aminoacetophenone, rather than at potentials normally found for nonconjugated ketones.[16]

From our material, prepared *via* electrolytic reduction, we obtained the analytically pure free base of Amphenone B and found it to have the same melting point as that reported by the previous authors. Moreover, all of the data described above agreed completely with that obtained from samples prepared at the National Cancer Institute.[17] Because of this overwhelming evidence and the equivalence in physiological activity, we feel that not only can there be no doubt as to the identity of our material with that of Allen and Corwin, but also that the previously assigned structure is incorrect.

From the data which have accumulated, the alternate structure II appeared more likely to be correct. Accordingly, 3,3-bis(*p*-aminophenyl)-2-butanone dihydrochloride was synthesized from acetophenone. The pinacol, 2,3-diphenyl-2,3-butanediol, was prepared according to Sisido and Nozaki[18] who employed the excellent method of Newman.[19] Treatment with acid[18] gave the pinacolone, 3,3-diphenyl-2-butanone, whose structure has been satisfactorily established.[20] Its infrared spectrum was in complete agreement with this structure and showed carbonyl absorption at 1707 cm.$^{-1}$ which was previously identified in the spectrum of Amphenone B. Nitration of the pinacolone with a mixture of nitric and sulfuric acids gave a gum from which was isolated a dinitrated product whose infrared spectrum carried a characteristic doublet at 850 and 855 cm.$^{-1}$, a fact indicating the presence of *p*-phenyl substituents. The 3,3-bis(*p*-nitrophenyl)-2-butanone was reduced catalytically at atmospheric pressure in the presence of 5% palladium charcoal, and the diamine which resulted was converted into the dihydrochloride salt. This material was identical in every respect with all previous samples of Amphenone B which we have examined. The fact that all of the infrared

(15) W. D. Kumler, L. A. Strait and E. L. Alpen, *J. Am. Chem. Soc.*, 72, 1463 (1950).

(16) I. M. Kolthoff and J. J. Lingane, *Polarography*, Interscience Publishers, New York, N. Y., 1952, 2nd ed., Vol. II, ch. XXXIX.

(17) Generously supplied by Dr. Roy Hertz and Dr. Bernard R. Landau, National Cancer Institute, Bethesda, Md.

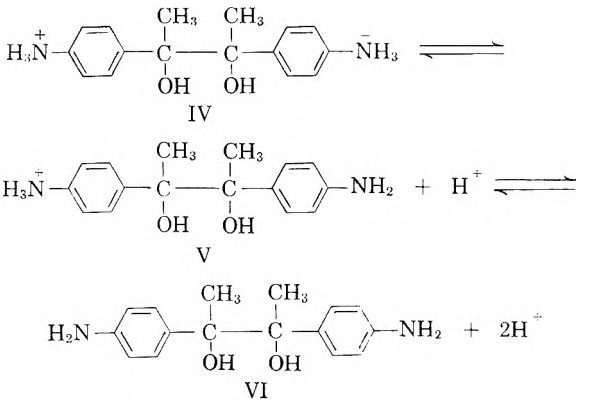
(18) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, 70, 776 (1948).

(19) M. S. Newman, *J. Am. Chem. Soc.*, 62, 1683 (1940).

(20) W. Thörne and T. Zinke, *Ber.*, 11, 1988 (1878).

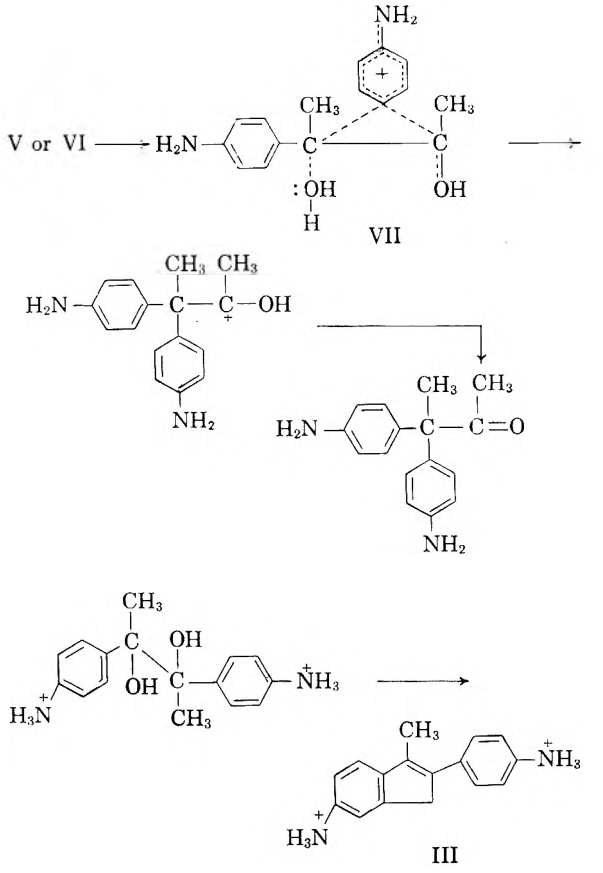
curves are superimposable is conclusive evidence for *para*-nitration of the starting pinacolone.[21]

In view of the mechanism discussed earlier one must conclude that in spite of salt formation in the acidic medium, the *p*-aminophenyl group still has a greater "migratory aptitude" than a methyl group. That the carbonium ion mechanism is applicable to this situation cannot be disputed, since the preponderance of evidence supports this concept.[14] We wish to suggest that the *para*-amino substituent on phenyl does indeed exert a powerful driving force by virtue of its electron donating character and that this substituted phenyl must be the group that migrates, but only when conditions are favorable. A proton might not approach the hydroxyl group of the pinacol unless either one or both of the amino groups are not protonated.[22] One can visualize an equilibrium between IV, V, and VI. When a proton approaches the hydroxyl



group of either V or VI, the phenyl group simultaneously migrates *via* the phenonium ion (VII)[23] under the influence of the *p*-amino substituent. In strong acid, on the other hand, the equilibrium represented by IV $\rightleftharpoons$ V $\rightleftharpoons$ VI is shifted to the left, and rearrangement occurs at a much slower rate.

Thus, the rate of rearrangement must be *p*H dependent, and available evidence suggests that this may be the case. It was shown[3] that treatment of the pinacol with concentrated hydrochloric acid gave only a 30% yield of pinacolone, the major product (61%) being 2-(*p*-aminophenyl)-3-methyl-6-aminoindene (III) which arises by cyclodehydration.[24] In dilute acid solution the only product isolated (67%) was the pinacolone. We feel that the acid concentration does not determine which group migrates but rather influences only the rate of reaction. If the amino groups remain protonated, two alternatives are presented. First, no reaction will take place and starting material will be recovered. Second, side reactions and the formation of by-products should occur. In this case the latter course is followed and the substituted indene (III) is obtained.[25,26] Just where the *p*-amino group lies with relation to other *para* phenyl substituents in migratory aptitude remains to be determined.



## EXPERIMENTAL[27]

*3,3-Bis(p-nitrophenyl)-2-butanone.* A solution of 22.4 g. (0.1 mole) of 3,3-diphenyl-2-butanone[18] in 65 g. of concentrated sulfuric acid was cooled to −10° and treated dropwise with a mixture of 29 g. of concentrated nitric acid (*d* 1.42) and 90 g. of concentrated sulfuric acid which was

(21) Dr. Bernard R. Landau has informed us that he has prepared the pinacolone from *p*-dimethylaminoacetophenone and has found the infrared spectrum to be similar to that of Amphenone B (*cf.* ref. 6). It follows therefore that this substance is the 3,3-bis(*p*-dimethylaminophenyl)-2-butanone.

(22) One can only speculate as to which condition is required. It can be argued on theoretical grounds that both amino groups must be free.

(23) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3863 (1949).

(24) W. Hausmann and A. E. W. Smith, *Nature*, **161**, 892 (1948). A diene may be the intermediate in the case of the amino compound, but is not required.

(25) A somewhat analogous situation exists in the case of 1,2-dimethyl-1,2-cyclopentanediol. The *cis* form rearranges normally to give 2,2-dimethylcyclopentanone, but the *trans* form, because of unfavorable stereochemistry, cannot participate in this type of reaction and gives only tar (*cf.* ref. 14).

(26) Although —$N(CH_3)_2$ of 2,3-*bis*(*p*-dimethylaminophenyl)-2,3-butanediol would be expected to have a stronger salt-forming tendency than —$NH_2$, the same mechanism applies. Here, however, *p*H is more critical and very dilute acid must be used if indene formation is to be avoided (*cf.* ref. 6, 21).

(27) Melting points are uncorrected.

cooled to 0°. The mixture was shaken during the addition, and the temperature was held at −5° by immersion in a freezing mixture when necessary. After standing at −5° for 20 min. longer it was poured onto crushed ice. The tan gummy solid which formed was filtered, washed with cold water, and dried. There was obtained 22.7 g. of material which failed to solidify completely, and which could not be crystallized. A portion (6.9 g.) was chromatographed over Florisil using various mixtures of Skellysolve B (b.p. 60–71°) and acetone as eluant. A fraction eluted with Skellysolve B containing 7.5% acetone gave a colorless solid which was recrystallized from 95% ethyl alcohol. There was obtained 2.1 g. of material which melted at 140–165°. An analytical sample melted at 165.5–167.5°.

*Anal.* Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.92. Found: C, 61.29; H, 4.14; N, 9.24.

*3,3-Bis(p-aminophenyl)-2-butanone dihydrochloride.* To a solution of 1.0 g. of 3,3-bis(*p*-nitrophenyl)-2-butanone in 50 ml. of purified dioxane was added 0.15 g. of 5% palladium charcoal and the mixture was shaken with hydrogen at atmospheric pressure until slightly more than the theoretical amount had been absorbed. The mixture was filtered and the solvent removed at 25° under reduced pressure. The residue was dissolved in 35 ml. of absolute ethyl alcohol and the solution was saturated with dry hydrogen chloride gas. It was evaporated to dryness under vacuum at room temperature to remove excess hydrogen chloride. The solid was suspended in 20 ml. of absolute ethyl alcohol, an equal volume of ethyl acetate added, and the mixture cooled overnight. The solid was filtered, washed with 20 ml. of a 1:1 mixture of absolute ethyl alcohol and ethyl acetate, and dried. There was obtained 0.86 g. of material melting at 252° (dec.).

The reported melting point is 272–275°.[3] We have found that this varies depending upon the rate of heating and the apparatus used. Our samples have melted between 250 and 282°; our most consistent results were obtained with a bath rather than a block.

*Anal.* Calcd. for $C_{16}H_{20}Cl_2N_2O$: C, 58.72; H, 6.16; N, 8.56; Cl, 21.67. Found: C, 58.44; H, 6.38; N, 8.49; Cl, 21.10.

The free base prepared by treatment of an aqueous solution of the salt with dilute ammonium hydroxide was purified by recrystallization from hot water. It melted at 137–138.5° (reported 137.5–138°[3]).

*Anal.* Calcd. for $C_{16}H_{16}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.44; H, 7.22; N, 10.94.

The infrared curves were obtained using a Perkin-Elmer model 21 Infrared Spectrophotometer equipped with sodium chloride optics and cells.

*Acknowledgments.* We wish to thank Prof. Melvin S. Newman and Dr. George Slomp for helpful suggestions. Our thanks also go to Dr. James L. Johnson, Mr. Marvin Grostic, and Mrs. Gunther Fonken for assistance in the preparation and interpretation of the infrared spectra, and Mr. James E. Stafford for the preparation of the ultraviolet spectra. Microanalyses were performed by Mr. William A. Struck and associates of the Analytical Chemistry Section of The Upjohn Co.

KALAMAZOO, MICH.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF STANFORD UNIVERSITY]

# Attempted Syntheses of Compounds Containing the 1,6-Diazacyclodecapentaene Ring

A. E. BLOOD[1] AND C. R. NOLLER

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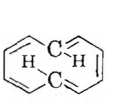
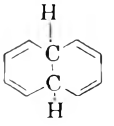
Attempts to prepare 2,3:4,5:8,9-tribenzo-1,6-diazacyclodecapentaene by the reaction of 2,2′-diaminobiphenyl with *o*-phthaldehyde gave only red polymeric compounds. Attempts to prepare the 7-methyl tribenzo derivative by the cyclization of *N*-benzylidene-*N*′-acetyl-2,2′-diaminobiphenyl with phosphorus oxychloride gave instead the cyclic amidine, *N*,*N*′-(2,2′-biphenylene)cinnamidine.

According to the calculations of Hückel,[2] completely conjugated, planar, monocyclic compounds having $(4n + 2)$ unsaturation $(\pi)$ electrons, where $n$ is any integer, should have aromatic properties. The only known examples of this rule are compounds for which $n = 1$. The simplest example where $n = 2$ would be cyclodecapentaene (I).

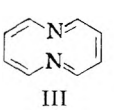
The steric interference of the internal hydrogen atoms in structure I is such, however, that the molecule cannot be planar. Although models indicate that the molecule probably is possible, at least in the *trans* conformation, it would not be expected to have aromatic properties. 9,10-Dihydronaphthalene (II), in either the *cis* or *trans* configuration, likewise appears to be only moderately strained but again would not be expected to be aromatic. 1,6-Diazacyclodecapentaene, on the other hand, appears to be reasonably strainless in the Fisher-Hirschfelder model, and even in the Briegleb model the unshared pairs of electrons on the nitro-



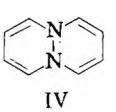
I



II



III



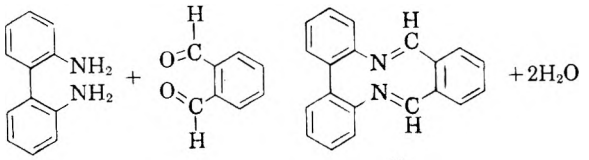
IV

(1) American Cyanamid Company Fellow, 1953–54, Eli Lilly Company Fellow, 1954–55, Eastman Kodak Fellow, 1955–56.

(2) E. Hückel, *Z. Physik*, 70, 204 (1931).

gen atoms do not appear to cause excessive strain. Moreover, the deviation from coplanarity does not appear to be sufficient to interfere seriously with conjugation and resonance. Structure IV also may contribute to the resonance hydrid.

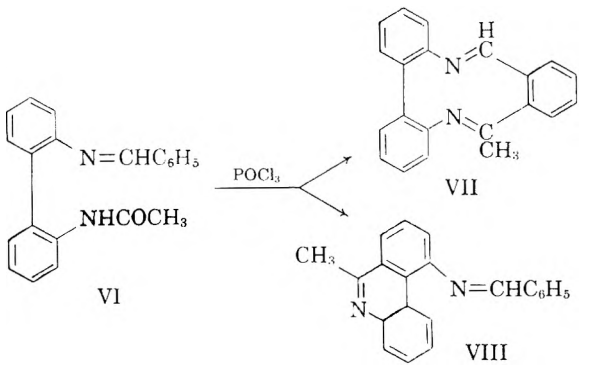
If structure III and IV are possible, it seemed that the simplest approach would be to attempt the synthesis 2,3:4,5:8,9-tribenzo-1,6-diazacyclodecapentaene (V) by the condensation of 2,2′-diaminobiphenyl with *p*-phthalaldehyde.



V

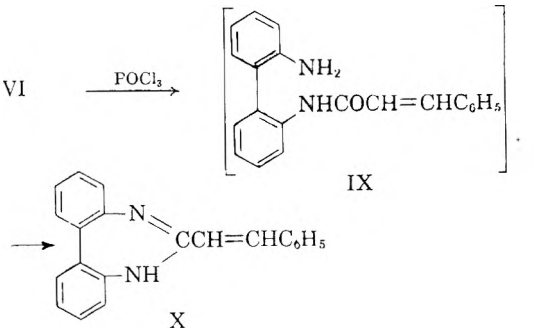
The diamine and dialdehyde reacted rapidly in boiling methanol. The products, however, always were complex mixtures which gave only resinous or amorphous fractions, even though the concentrations ranged from about 0.1 molar to extreme dilutions.

Because linear condensation apparently predominates in the bimolecular condensation, intramolecular ring closure was attempted. It was thought that the reaction of phosphorus oxychloride on *N*-benzylidene-*N*-acetyl-2,2′-diaminobiphenyl (VI) might cause a Bischler-Napieralski type of cyclization to give the diazacyclodecapentaene, VII, rather than or in addition to the phenanthridine, VIII.



Instead the reaction took an entirely different course, the product being *N*,*N*′-(2,2′-biphenylene)-cinnamidine (X). Presumably the reaction takes place by an inter- or intramolecular aldol-type addition followed by elimination to give the monocinnamyl derivative of 2,2′-diaminobiphenyl (IX), which cyclizes to the amidine (X).

The amidine absorbed in the infrared at 2.95$\mu$ (NH) and in the double bond region, and a strong band was present at 10.36$\mu$ (*trans* CH=CH). It formed a hydrochloride, a red sodium salt,[3] and a phenylthiourea derivative. On catalytic reduction



in the presence of Raney nickel, the amidine absorbed two moles of hydrogen rapidly and a third mole slowly, presumably with opening of the amidine ring.[4] Hydrolysis with aqueous sodium carbonate gave 2-amino-2′-cinnamidobiphenyl which on further hydrolysis with hydrochloric acid gave 2,2′-diaminobiphenyl and cinnamic acid. The structure of the amidine was confirmed by an independent synthesis. 2-Amino-2′-cinnamidobiphenyl, prepared from 2,2′-diaminobiphenyl and cinnamic anhydride, was cyclized with phosphorus oxychloride in benzene. The product was identical with that obtained by the action of phosphorus oxychloride on *N*-benzylidene-*N*′-acetyl-2,2′-diaminobiphenyl.

## EXPERIMENTAL

*Reaction of 2,2′-diaminobiphenyl with o-phthaldehyde.* The reaction of the diamine with the dialdehyde was very rapid in methanol or 95% ethanol and slower in 1-butanol or benzene. Thus 1 g. (0.0054 mole) of diamine and 0.7 g. (0.0052 mole) of dialdehyde in 50 cc. of ethanol gave a red solution. Evaporation to dryness gave an amorphous red solid which decomposed over the range 142–160°. When placed on a column of alumina and developed with methylene chloride, a series of orange, pink, and red bands formed, from which resins and other amorphous solids were obtained. When solutions of the diamine and the dialdehyde were added dropwise simultaneously into one liter of boiling methanol, essentially the same type of product was obtained.

In order to obtain even higher dilution an apparatus was devised whereby the two solutions could be added automatically at exactly the same slow rate. In this way 0.874 g. (0.0065 mole) of *o*-phthaldehyde[5] in 100 cc. of methanol and 1.2 g. (0.0065 mole) of 2,2′-diaminobiphenyl[6] in 100 cc. of methanol were added simultaneously to 500 cc. of boiling methanol at the rate of 0.52 cc. per hour (total time 192 hr.). The reaction mixture was concentrated to 80 cc., filtered to remove a very small amount of solid, and further concentrated to a dark red oil that weighed 2.0 g. The oil was dissolved in methylene chloride, put on a 2 × 30 cm. column of activated alumina, and eluted with methylene chloride. A large orange band was collected, leaving two small light brown bands and a small greenish band on the column. The solution containing the orange band was evaporated to a red oil which would not crystallize. Further washing of the column with 100 cc. of methylene chloride and evaporation of the solvent gave a red oil which deposited

(3) R. L. Shriner and F. W. Neumann, *Chem. Revs.*, **35**, 375, 385 (1944).

(4) G. Kubiczek, *Monatsh.*, **74**, 100 (1942).

(5) J. C. Bill and D. S. Tarbell, *Org. Syntheses*, **34**, 82 (1954).

(6) A. E. Blood and C. R. Noller, *J. Org. Chem.*, **22**, 711 (1957).

a solid on standing. When the oil was washed out with a small amount of ethanol, 0.006 g. of a yellow crystalline material melting at 233–236° was obtained. Infrared spectrum (KBr plate): maxima at 3.45, 6.03, 6.20, 6.30, 6.55, 6.74, 7.00, 7.33, 7.93, 9.15, 9.82, 10.52, 10.60, 11.30, 11.57, 11.90, 12.14, 12.50, 13.45, and 14.05 $\mu$.

Attempts to obtain more of this material were unsuccessful. In a larger run 2.18 g. (0.0163 mole) of *o*-phthaldehyde in 100 cc. of methanol and 3 g. (0.0163 mole) of 2,2′-diaminobiphenyl in 100 cc. methanol were added simultaneously to 3 l. of boiling methanol at the rate of 0.27 cc. per hour (total time 372 hr.). The product was separated on a column of alumina into six fractions, using methylene chloride as the eluting solvent. Each of the fractions was rechromatographed separately. Each gave a series of yellow, orange, or red oils or amorphous solids. The second of the original six fractions was the largest and was separated on alumina into seven fractions, the second of which was a bright red amorphous solid that decomposed over the range 123–205° and weighed 0.14 g. When rechromatographed it gave only one bright red main fraction that weighed 0.09 g.

*Anal.* Calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.37; H, 5.81; N, 7.49.

Infrared spectrum (KBr plate): maxima at 2.95, 3.44, 5.88, 6.12, 6.78, 6.95, 7.70, 8.44, 9.60, 10.22, 13.28, and 14.41 $\mu$.

*2-Amino-2′-acetamidobiphenyl.* When this compound was prepared by the partial acetylation of 2,2′-diaminobiphenyl,[7] the product melted at 99–100° instead of the reported 89–90°. In order to make certain that this material was the desired compound, an alternate synthesis was carried out in which 2-nitro-2′-acetamidobiphenyl[8] was reduced catalytically in ethanol over Raney nickel. This product likewise melted at 99–100°, and the melting point was not depressed when mixed with product from the partial acetylation of the diamine. The infrared spectra (KBr plate) also were identical: maxima at 3.01, 3.32, 5.22, 5.55, 5.98, 6.18, 6.32, 6.64, 6.94, 7.32, 7.68, 8.07, 8.65, 8.78, 9.00, 9.55, 9.65, 9.95, 10.64, 11.7 (broad), and 13.3 $\mu$ (broad).

The melting point of the 2-nitro-2′-acetamidobiphenyl was 156–158° compared to 151–152° as previously reported.[8] Infrared spectrum (KBr plate): maxima at 2.94, 3.15, 3.35, 6.01, 6.22, 6.32, 6.58, 6.67, 6.80, 6.98, 7.29, 7.40, 7.70, 7.80, 10.57, 11.65, 11.75, 12.68, 12.99, 13.24, 13.50, 14.20, and 15.20 $\mu$.

*N-Benzylidene-N′-acetyl-2,2′-diaminobiphenyl.* A solution of 13 g. (0.053 mole) of 2-amino-2′-acetamidobiphenyl and 12.6 g. (0.12 mole) of benzaldehyde in 50 cc. of benzene was refluxed for 19 hr. in a flask fitted with a Dean-Stark tube and condenser to remove the water. Removal of the benzene at reduced pressure and addition of 20 cc. of ether gave 15.3 g. (86%) of solid product. After crystallization from a mixture of 75 cc. of absolute ether and 20 cc. of absolute ethanol, it melted at 148–149°.

*Anal.* Calcd. for $C_{21}H_{18}N_2O$: C, 80.22; H, 5.77; N, 8.91. Found: C, 80.22; H, 5.58; N, 8.93.

Infrared spectrum (KBr plate): maxima at 3.12, 5.97, 6.14, 6.35, 6.64, 7.00, 7.35, 7.68, 7.78, 7.95, 8.14, 8.43, 8.56, 8.68, 9.13, 9.98, 10.28, 10.62, 10.92, 11.25, 11.51, 13.10, 13.55, and 14.54 $\mu$. Ultraviolet spectrum: maximum at 250 m$\mu$, log $\epsilon$ 4.43; inflection at 315 m$\mu$, log $\epsilon$ 3.79.

The constitution of this product was confirmed by hydrolysis with 6*N* hydrochloric acid at room temperature to benzaldehyde and 2-amino-2′-acetamidobiphenyl. Further hydrolysis with boiling 6*N* acid gave 2,2′-diaminobiphenyl.

*2-Amino-2′-cinnamidobiphenyl and N,N′-dicinnamidobiphenyl.* To a solution of 2.1 g. (0.013 mole) of cinnamoyl chloride[9] in 25 cc. of absolute ether was added with stirring 2.4 g. (0.013 mole) of 2,2′-diaminobiphenyl in 25 cc. of absolute ether. After stirring for 30 min., the precipitate was filtered, suspended in benzene, saturated with dry hydrogen chloride, filtered, and washed with benzene. The solid was dissolved in water, neutralized with sodium carbonate and the precipitated base crystallized from ethanol. The product weighed 0.5 g. (11%) and melted at 117–119°. After chromatographing on Florisil and recrystallization from ethanol, the *2-amino-2′-cinnamidobiphenyl* melted at 123–124°.

*Anal.* Calcd. for $C_{21}H_{18}N_2O$: C, 80.22; H, 5.77; N, 8.91. Found: C, 79.78; H, 5.50; N, 9.19.

Infrared spectrum (in $CHCl_3$): maxima at 2.95, 5.96, 6.15, 6.32, 6.93, 7.71, 7.81, 8.55, 9.00, 9.92, 10.10, and 10.25 $\mu$. Ultraviolet maximum at 287 m$\mu$, log $\epsilon$ 4.43.

Concentration of the benzene solution containing the material not precipitated by hydrogen chloride gave needles of *2,2′-dicinnamidobiphenyl* melting at 188–191°. The melting point was unchanged on recrystallization.

*Anal.* Calcd. for $C_{30}H_{24}N_2O_2$: C, 81.06; H, 5.44; N, 6.30. Found: C, 80.68; H, 5.01; N, 6.48.

Ultraviolet absorption maximum at 285 m$\mu$, log $\epsilon$ 4.50.

Later a 68% yield of *2-amino-2′-cinnamidobiphenyl* was obtained by refluxing a solution of 2.0 g. (0.01 mole) of 2,2′-diaminobiphenyl and 3.1 g. (0.01 mole) of cinnamic anhydride[10] in 70 cc. of benzene for 3 hr.

*N,N′-(2,2′-Biphenylene)cinnamidine* (X) *from N-benzylidene-N′-acetyl-2,2′-diaminobiphenyl.* A solution of 20 g. (0.06 mole) of *N*-benzylidene-*N*′-acetyl-2,2′-diaminobiphenyl in 400 cc. of dry benzene and 10 cc. (0.11 mole) of phosphorus oxychloride was refluxed for 5 hr. A white solid first precipitated which redissolved. The solution then became orange in color and after the first hour an orange solid began to precipitate. The mixture was cooled and the orange solid filtered and washed with benzene. It weighed 23.4 g., melted with decomposition at 217–221°, and contained nitrogen, chlorine, and phosphorus.

When a solution of the phosphorus-containing product in methanol was neutralized with sodium methoxide and diluted with water, a compound free of phosphorus and chlorine precipitated. Crystallization from ethanol gave yellow needles, m.p. 148–151° (dec.), which proved to be *N,N′-(2,2′-biphenylene)cinnamidine.*

*Anal.* Calcd. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.68; mol. wt., 296. Found: C, 85.06; H, 5.19; N, 9.68; mol. wt.,[11] 257, 274, 346 in benzene.

Infrared spectrum (KBr plate): maxima at 2.96, 6.11, 6.20, 6.34, 6.81, 6.99, 7.79, 8.09, 8.29, 8.49, 8.64, 9.10, 10.36, 10.63, 11.19, 11.58, 11.76, 12.99, 13.14, 13.27, 13.77, and 14.42 $\mu$. Ultraviolet absorption in ethanol: maxima at 230 m$\mu$, log $\epsilon$ 4.40; 283 m$\mu$, log $\epsilon$ 4.20; 301 m$\mu$, log $\epsilon$ 4.30; inflection at 363 m$\mu$, log $\epsilon$ 3.58.

When the phosphorus-containing compound was crystallized from hot ethanol, the *hydrochloride,* m.p. 255–260° (dec.) was obtained; equivalent weight by titration 326, calculated 332.5. When the free base was crystallized from methanol the product contained one mole of methanol of crystallization. The *methanolate* melted at 81° with gas evolution, resolidified, and remelted at 148–149° with decomposition.

The free base reacted with sodium in boiling toluene or with a solution of sodium in liquid ammonia to give a red salt, indicating the presence of an imino group. The *phenylthiourea* derivative was prepared by heating equal amounts of the free base and phenyl isothiocyanate until the mixture was homogeneous. The resulting oil was chilled, triturated

(7) S. Sako, *Mem. Coll. Eng. Kyushu Imp. Univ.*, **6**, 283 (1932).

(8) L. Mascarelli, D. Gatti, and M. Pirona, *Gazz. chim. ital.*, **61**, 782 (1931); *Chem. Abstr.*, **26**, 1595 (1932).

(9) S. M. McElvain and T. P. Carney, *J. Am. Chem. Soc.*, **68**, 2599 (1946).

(10) E. Wedekind, *Ber.*, **34**, 2074 (1901).

(11) A. W. C. Menzies and S. L. Wright, *J. Am. Chem. Soc.*, **43**, 2314 (1921).

with petroleum solvent (80–110°) and with 50% aqueous ethanol, and dried by heating to 110° at 30 mm. for 4 hr. The resulting hard solid was triturated with ether to give a yellow solid melting at 175–184°. Repeated crystallization from chloroform gave a pale cream product, m.p. 215–216°.

*Anal.* Calcd. for $C_{28}H_{21}N_3S$: C, 77.94; H, 4.91; N, 9.74. Found: C, 77.81; H, 4.96; N, 9.87.

Infrared spectrum: maxima at 2.95, 6.01, 6.28, 6.71, 6.78, 7.07, 7.48, 7.71, 7.90, 8.41, 9.10, 9.75, 9.98, 10.40, 10.73, 11.50, 11.92, 12.60, 13.12, 13.28, 13.65, 13.82, and 14.40 $\mu$. Ultraviolet: maximum at 263 m$\mu$, log $\epsilon$ 4.35.

The free base decolorized bromine in carbon tetrachloride, but the only pure product isolated was the *hydrobromide*, m.p. 280–286° (dec.). When 0.07 g. of the free base was hydrogenated over Raney nickel in a semimicro hydrogenator, 2 moles of hydrogen was absorbed within 1 hr. and an additional mole over the next 24 hr. The chief product was a noncrystallizable oil. A small amount of solid melting at 55–59° could not be purified further. Oxidation of the free base with potassium permanganate in either acetone or pyridine gave benzoic acid as the only insolable product.

When 0.6 g. of the free base was refluxed with 40 cc. of 6*N* hydrochloric acid for 3 hr., it was recovered unchanged. Hydrolysis of 0.35 g. of the base by refluxing with 10 cc. of 6*N* sodium hydroxide in 30 cc. of methanol for 24 hr. gave a quantitative yield of 2,2′-diaminobiphenyl. Partial hydrolysis of the free base was accomplished by refluxing a suspension of 1 g. with 1 g. of sodium carbonate in 20 cc. of water and 30 cc. of methanol for 1 hr. The product was 2-amino-2′-cinnamidobiphenyl, m.p. 115–117° (76% yield). This compound was identified by further hydrolysis with 3*N* hydrochloric acid to 2,2′-diaminobiphenyl (77% yield) and cinnamic acid (85% yield) and by comparison with a sample synthesized from 2,2′-diaminobiphenyl and cinnamoyl chloride or cinnamic anhydride. 2-Amino-2′-cinnamidobiphenyl was formed also when the original phosphorus-containing precursor of the free base was boiled with water. On the basis of these results it was concluded that the free base is *N,N′*-(2,2′-biphenylene)cinnamidine. This conclusion was confirmed by direct comparison with the product from the cyclization of 2-amino-2-cinnamidobiphenyl with phosphorus oxychloride.

Attempts to cyclize *N*-benzylidene-*N′*-acetyl-2,2′-diaminobiphenyl with hydrogen fluoride or polyphosphoric acid resulted only in the isolation of 2-amino-2′-acetamidobiphenyl. When anhydrous zinc chloride was used, the starting material was recovered unchanged.

*N,N′-(2,2′-Biphenylene)cinnamidine from 2-amino-2′-cinnamidobiphenyl.* To a solution of 1.29 g. (0.0041 mole) of 2-amino-2′-cinnamidobiphenyl in 25 cc. of dry benzene was added 1.34 g. (0.0087 mole) of phosphorus oxychloride. A precipitate formed and the mixture was refluxed for 2 hr. The resulting orange solid, after filtering and washing with benzene, weighed 2.3 g.; m.p. 219–222° (dec.). When the solid was boiled with ethanol, it gave 1.3 g. (88%) of the hydrochloride, m.p. 253–256°, whose infrared absorption spectrum was identical with that of the hydrochloride obtained from *N*-benzylidene-*N′*-acetyl-2,2′-diaminobiphenyl. Neutralization of the hydrochloride in methanol with sodium methoxide gave 1 g. (83%) of the free base. Crystallization from a dilute solution in ethanol gave plates and from a concentrated solution needles, either of which melted at 148–150° (dec.). The infrared absorption spectrum was identical with that of the free base from the cyclization of *N*-benzylidene-*N′*-acetyl-2,2′-diaminobiphenyl, and a mixture of the two bases melted at 148–150° (dec.).

STANFORD, CALIF.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

# Studies in the Bicyclo[2.2.1]heptane Series.[1] IV. Brominative Bisdecarboxylation of Some Alicyclic Dicarboxylic Acids[2]

ANTHONY WINSTON,[3] GEORGE T. YOUNGBLOOD,[4] AND PELHAM WILDER, JR.

*Received August 20, 1956*

The Hunsdiecker reaction is suggested as a method for effecting the bisdecarboxylation of alicyclic dicarboxylic acids. The brominative bisdecarboxylation of *endo-cis*-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid (I), bicyclo[3.3.0]octane-2,4-dicarboxylic acid (II) and *cis*-cyclohexane-1,2-dicarboxylic acid is described, as are several attempts to prepare bicyclo-[2.2.1]-7-heptanone (III) by this method.

A good general method for the facile bisdecarboxylation of vicinal dicarboxylic acids of the type readily available through the diene synthesis of Diels and Alder would be a valuable contribution to organic chemistry.[5] Recently Doering and his collaborators reported a novel method for accomplishing just this by lead dioxide oxidation of the dicarboxylic acid or its anhydride to the corresponding $\alpha,\beta$-olefin and carbon dioxide,[5] but on further investigation it was found that the method was of very limited scope and not generally applicable.[6] It is interesting that the Hunsdiecker reaction,[7] which affords a method for the smooth decarboxylation of simple carboxylic acids and their derivatives, has not been extensively investigated as a means of effecting the bisdecarboxylation of alicyclic dicarboxylic acids. It is the purpose of

(1) For paper III in this series, see *J. Am. Chem. Soc.* **78**, 868 (1956).

(2) Taken in part from a thesis submitted by Anthony Winston to the Graduate School of Duke University in partial fulfillment of the requirements for the Ph.D. degree, October 1954.

(3) Du Pont Pre-doctoral Fellow, 1953–1954.

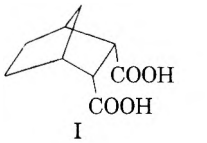
(4) American Cyanamid Pre-doctoral Fellow, 1955–1956.

(5) For a review of methods of bisdecarboxylation of vicinal dicarboxylic acids, see W. Doering, M. Farber, and A. Sayigh, *J. Am. Chem. Soc.*, **74**, 4370 (1952).

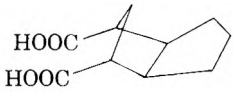
(6) M. Newman and R. Addor, *J. Am. Chem. Soc.*, **77**, 3789 (1955).

(7) R. G. Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956).

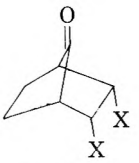
this communication to suggest that the Hunsdiecker reaction is a method for such bisdecarboxylations and to describe the brominative bisdecarboxylation of *endo-cis*-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid (I), bicyclo[3.3.0]octane-2,4-dicarboxylic acid (II), and *cis*-cyclohexane-1,2-dicarboxylic acid. Some attempts to prepare bicyclo-[2.2.1]-7-heptanone (III) from *endo-cis*-bicyclo-[2.2.1]-7-heptanone-2,3-dicarboxylic acid[1] (IV) under the same conditions are also discussed.




I




II

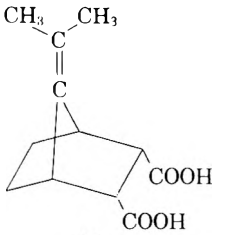



III X=H
IV X=COOH

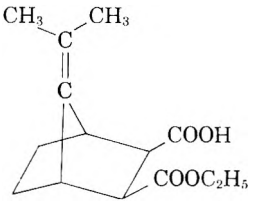

V

By the inverse technique of Conly,[8] the silver salt of *endo-cis*-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid (I) in carbon tetrachloride was converted into dibromide in 27% yield. The dibromide was found to be contaminated with a small amount (1.00%) of chlorine[9] and to have weak bands at 5.56 and 5.62 $\mu$ in the infrared, indicative of the presence of $\gamma$-lactonic impurities.[10,11] Reduction of the dibromide with sodium and alcohol gave an olefin which on hydrogenation over Adams' catalyst gave norbornane. By the same method bicyclo[3.3.0]octane-2,4-dicarboxylic acid (II), obtained by the nitric acid oxidation of 9-keto-tetrahydro-*exo*-dicyclopentadiene[12] (V), was converted in 32% yield into the corresponding dibromide. Also, *cis*-cyclohexane-1,2-dicarboxylic acid in like manner underwent bisdecarboxylation to the extent of 33%. No effort has been made to determine the stereochemistry of the resulting dibromides.

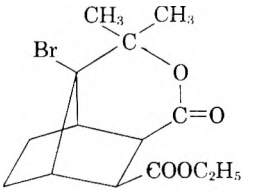
In a previous communication[1] the preparation of three bicyclo[2.2.1]-7-heptanones from adducts of 6,6-dimethylfulvene and maleic anhydride was reported; however, every effort to obtain the parent *endo*-carbonyl compound III from the keto-dicarboxylic acid IV by the Hunsdiecker method proved fruitless. From this reaction no appreciable amount of carbon dioxide was evolved and no neutral products were isolated. In the absence of an olefinic center it is surprising that decarboxylation did not occur to a greater extent since it has been observed that the presence of a carbonyl group in a molecule does not, in itself, prevent the occurrence of brominative decarboxylation.[7,10] In this connection neither the silver salt of *endo-cis*-7-isopropylidenebicyclo[2.2.1]heptane-2,3-dicarboxylic acid[1] (VI) nor that of the acidic ester of




VI




VII




VIII

the corresponding *exo*-isomer[11] (VII) underwent decarboxylation. Although no pure compound was isolated in the former reaction, the reaction mixture probably contained some intermolecular addition product of the acyl hyperbromite and the olefin. In the latter case only the intramolecular ("internal Simonini")[13] reaction product (VIII) was isolated. It seems that the rate of reaction of acyl hyperbromite with olefin is considerably greater than its decomposition into carbon dioxide and alkyl bromide.

On the basis of this investigation, even though bisdecarboxylation occurs in modest yield along with some lactonic impurities in the case of simple alicyclic dibasic acids, this method has been shown to offer both degradative and synthetic possibilities.

## EXPERIMENTAL[14]

*Silver salt of endo-cis-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid* (I). To a suspension in water of 29.4 g. (0.16 mole) of acid, prepared by the method of Diels and Alder,[15] was added 21.6 ml. of 28% ammonia solution (0.32 mole of $NH_3$). To this aqueous solution of the ammonium salt was then added dropwise with rapid stirring 54.4 g. (0.32 mole) of silver nitrate dissolved in 150 ml. of water. The silver salt

(8) J. C. Conly, *J. Am. Chem. Soc.*, **75**, 1148 (1953).

(9) P. Wilder, Jr., and A. Winston, *J. Am. Chem. Soc.*, **75**, 5370 (1953). See also reference 7, p. 253.

(10) J. W. H. Oldham, *J. Chem. Soc.*, 100 (1950). While a $\beta$-lactone is an expected by-product in this reaction, a $\gamma$-lactone could easily have arisen from a skeletal rearrangement of an intermediate bromo acid [*cf.* W. Doering and M. Farber, *J. Am. Chem. Soc.*, **71**, 1514 (1949)].

(11) For a discussion of the infrared absorption of tricyclic lactones, see P. Wilder, Jr., and A. Winston, *J. Am. Chem. Soc.*, **77**, 5598 (1955).

(12) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **67**, 723 (1945); **68**, 8 (1946).

(13) Reference 7, p. 255, 259.

(14) All melting points and boiling points are uncorrected. Except where otherwise indicated, microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(15) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

which was precipitated was collected and washed, first with water, then with alcohol, and finally with ether. The yield of silver salt, after drying in a vacuum desiccator over phosphorus pentoxide for three days, was 58.0 g. (91%).

*Anal.*[16] Calcd. for $C_9H_{10}O_4Ag_2$: Ag, 54.3. Found: Ag, 55.0.

*Bromination of the silver salt of acid I.* To a one-liter, three neck flask, fitted with a reflux condenser and a mechanical stirrer, was added 200 ml. of reagent grade carbon tetrachloride previously dried over phosphorus pentoxide and then 17 ml. (0.31 moles) of bromine, which had been previously dried over phosphorus pentoxide. The top of the condenser was connected through rubber tubing to a bubble counter and then to a trap containing barium hydroxide solution. By means of a rubber gasket 65.0 g. (0.173 mole) of silver salt was added to the bromine solution over a period of 2 hr. During this time the temperature was maintained at 15°. After 1 hr. carbon dioxide was detected by the precipitation of barium carbonate and after 2 hr. the evolution was vigorous. When the evolution of carbon dioxide had subsided, the cooling bath was removed and the reaction mixture was allowed to come to room temperature. Gentle heating then brought the reaction mixture to reflux temperature where it was held for 4 hr. The reaction mixture was then allowed to stand overnight. The amount of barium carbonate produced was 38 g. (56%).

Silver bromide was removed by filtration and the filtrate was washed with 5% sodium bisulfite solution, twice with 5% sodium carbonate solution, and finally with water. The carbon tetrachloride solution was dried over sodium sulfate and the solvent was removed under vacuum. After an initial distillation, a second yielded 4.91 g. of product, b.p. 78–90° (1 mm.), $n_D^{20}$ 1.5602, and 6.16 g., b.p. 90–94° (1 mm.), $n_D^{20}$ 1.5604[17] (27% total yield).

*Anal.* Calcd. for $C_7H_{10}Br_2$: Br, 62.9. Found: Br, 55.4; Cl, 1.00.

Weak bands at 5.56 $\mu$ and 5.62 $\mu$ in the infrared suggest the presence of a trace of $\gamma$-lactones.[10,11]

*Conversion of dibromide to norbornane.* Three grams of dibromide dissolved in 120 ml. of absolute ethanol was treated with 9 g. of sodium for 4 hr. The reaction mixture was diluted with 100 ml. of water and then distilled until the addition of a small amount of water to a sample of fresh distillate failed to produce turbidity. The distillate, which immediately decolorized bromine in $CCl_4$ solution, was hydrogenated over Adams' catalyst. Upon addition of water to the alcohol solution, there was obtained about 300 mg. of an extremely volatile solid, highly camphoraceous in odor. The solid was collected and sublimed three times, m.p. 83–85° (reported[18] for norbornane, 86–87°).

*The silver salt of bicyclo[3.3.0]octane-2,4-dicarboxylic acid* (II). This acid was obtained by the method of Bruson and Riener[12] by the nitric acid oxidation of 9-keto-tetrahydro-*exo*-dicyclopentadiene, which was in turn prepared by the reduction and subsequent oxidation of dicyclopentenyl alcohol.[19] The method described above for the preparation of the silver salt of acid I was utilized. From 24.2 g. (0.123 mole) of acid II the yield of silver salt was 49.3 g. (97%).

*Anal.*[16] Calcd. for $C_{10}H_{12}O_4Ag_2$: Ag, 52.4. Found: Ag, 51.9.

*Bromination of the silver salt of acid II.* The reaction was carried out in the manner described for the silver salt of acid I above with the following exceptions. When the evolution of carbon dioxide had subsided, the reaction mixture was heated under reflux for only 2 hr. and was then worked up in the usual manner. From 49.0 g. (0.119 mole) of silver salt, there was obtained 10.5 g. (32%) of dibromide, b.p. 111–114° (4 mm.). A second distillation afforded a colorless sample, b.p. 91° (1 mm.), $n_D^{25}$ 1.5561.

*Anal.* Calcd. for $C_8H_{12}Br_2$: Br, 59.70. Found: Br, 59.46.

*The silver salt of cis-cyclohexane-1,2-dicarboxylic acid.* The acid was prepared by catalytic hydrogenation and subsequent hydrolysis of *cis*-$\Delta^4$-tetrahydrophthalic anhydride. A yield of 44.6 g. (94%) of silver salt was realized from 20.5 g. (0.12 mole) of acid.

*Anal.*[16] Calcd. for $C_8H_{10}O_4Ag_2$: Ag, 56.0. Found: Ag, 55.7.

*Bromination of the silver salt of cis-cyclohexane-1,2-dicarboxylic acid.* This reaction was carried out in the manner described for the silver salt of acid II above. The decarboxylation of 44.0 g. (0.113 mole) of silver salt yielded 8.4 g. (33%) of dibromide,[20] b.p. 88–90° (5 mm.), $n_D^{25}$ 1.5465, which was contaminated with a trace of $\beta$-lactone, indicated by a weak band at 5.46 $\mu$ in the infrared.[11]

*Silver salt of bicyclo[2.2.1]-7-heptanone-2,3-dicarboxylic acid* (IV). The silver salt was prepared by the method described above. From 54 g. (0.27 mole) of the acid[1] IV was obtained 90 g. (82%) of silver salt.

*Anal.*[16] Calcd. for $C_9H_8O_5Ag_2$: Ag, 52.4. Found: Ag, 50.6.

*Bromination of the silver salt of acid IV.* Ten grams of the silver salt of acid IV was brominated by the method described above for acid I. Silver bromide was precipitated, but only a trace of carbon dioxide was evolved and no neutral reaction products were isolated.

*Acknowledgment.* This work was supported in part by a grant from the Duke University Research Council.

DURHAM, N. C.

(16) Analysis performed in this laboratory by the Volhard method.

(17) Reported for *trans*-2,3-dibromobicyclo[2.2.1]heptane, b.p. 62–63° (0.4 mm.), $n_D^{20}$ 1.5618 (H. Kwart and L. Kaplan, *J. Am. Chem. Soc.*, **76**, 4072 (1954)).

(18) G. Komppa and S. Beckmann, *Ann.*, **512**, 172 (1934).

(19) The authors are grateful to the Rohm & Haas Company, Philadelphia, Pa., for a sample of this compound.

(20) H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Am. Chem. Soc.*, **74**, 3588 (1952); S. Coffey, *Rec. trav. chim.*, **42**, 398 (1923); S. Winstein, *J. Am. Chem. Soc.*, **64**, 2792 (1942).

[CONTRIBUTION FROM THE CHEMICAL CENTRAL RESEARCH INSTITUTE OF THE HUNGARIAN ACADEMY OF SCIENCES]

# Synthesis and Investigation of Organic Fluorine Compounds. XXIII.* Preparation of Aromatic Fluorinated Esters as Local Anesthetics

GEORGE A. OLÁH, ATTILA E. PAVLÁTH, JUDITH A. OLÁH, AND FRANCIS HERR

*Received April 30, 1956*

A number of new fluorobenzoic and fluorophenylacetic acid esters have been prepared. The effect of these compounds as local anesthetics is similar to or greater than that of procaine; at the same time they do not cause tissue irritation.

Fosdick and coworkers[1-4] have been interested in the synthesis and pharmacological properties of fluorine compounds related to procaine (β-diethylaminoethyl *p*-aminobenzoate) for use in producing anesthesia. Several alkylaminoalkyl esters of *p*-fluorobenzoic acid were prepared. The anesthetic efficiency of these compounds was equal to, or slightly greater than, that of procaine and all possessed a low toxicity. Unfortunately tissue irritation was so pronounced that they could not be used for clinical work.

It appeared interesting therefore to examine some aminoalkyl esters of different aromatic fluorocarboxylic acids, in the hope of finding good local anesthetics without tissue-irritating properties.

In the present work some alkylaminoethyl esters of the isomeric fluorobenzoic and fluorophenylacetic acids have been investigated.

The hydrochlorides of the *o*-, *m*- and *p*-fluorobenzoic acid β-dimethylamino-, β-diethylamino-, β-piperidino-, and β-morpholino-ethyl esters were prepared. Among these compounds the dimethylamino and diethylaminoethyl esters of *p*-fluorobenzoic acid had already been reported. These compounds have proved in our experiments, in contrast to Fosdick's data, less active than procaine itself. The ten newly synthesized derivatives behave similarly. Among the esters of fluorobenzoic acids, the *m*-fluorobenzoic acid β-dimethylaminoethyl ester showed the greatest activity. Among the new derivatives the β-piperidinoethyl esters are of special interest, since with these compounds no tissue irritation could be observed.

The new fluorophenylacetic acid alkylaminoethyl esters now prepared have much more suitable properties. Löfgren and Lundquist[5] have described the local anesthetic activity of phenylacetic acid diethylaminoethyl ester hydrochloride. A similar effect for other phenylacetic acid derivatives has not yet been reported. The local anesthetic activity of *o*-, *m*- and *p*-fluorophenylacetic acid dimethylamino-, diethylamino-, and β-piperidinoethyl ester hydrochlorides is not far different from that of procaine itself. The effect of *o*-fluorophenylacetic acid β-piperidinoethyl ester is two times greater than that of procaine. The toxicities of these derivatives were found generally half as great as that of procaine. These compounds do not show tissue irritation in concentrations up to 2%, which is four times the therapeutical concentration.

The physical data, yields, analyses, and pharmacological data of the fluorobenzoic and fluorophenylacetic acid alkylaminoethyl esters prepared in this work are listed in Table I.

The local anesthetic activities of the compounds were examined by the method of Herr and coworkers[6] by determining the concentration of a 0.1 mole ester solution which caused anesthesia.

The isomeric fluorophenylacetic acids, of which *p*-fluorophenylacetic acid was already known,[7,8] were obtained from the corresponding fluorobenzyl bromides by the hydrolysis of the intermediate nitriles. The fluorophenylacetyl chlorides not described in the literature were prepared from the corresponding fluorophenylacetic acids by refluxing with thionyl chloride.

The fluorobenzoic acid, and the corresponding fluorophenylacetic acid alkylaminoethyl ester hydrochlorides were synthesized from the corresponding acid chlorides by reaction with amino alcohols in benzene solution.

## EXPERIMENTAL

The *o- and m-fluorobenzoic acids* were prepared by the method of Fosdick and Campaigne[1] for the synthesis of *p*-fluorobenzoic acid (from the Grignard derivative of the fluorobromobenzene by carbonation).

The *o-, m- and p-fluorobenzoyl chlorides* were obtained according to the procedures of Meyer and Hub,[9] and Cohen,[10] and Holleman and Slothouwer.[11]

* Paper XXII: G. A. Oláh, S. J. Kuhn, and G. Kovacs-Bruckner, *J. Org. Chem.* **22**, 979 (1957).

(1) L. S. Fosdick and E. E. Campaigne, *J. Am. Chem. Soc.*, **63**, 974 (1941).

(2) L. S. Fosdick and H. I. Barnes, *J. Am. Chem. Soc.*, **67**, 335 (1945).

(3) L. S. Fosdick and A. F. Dodds, *J. Am. Chem. Soc.*, **65**, 2305 (1943).

(4) L. S. Fosdick and R. Q. Blackwell, *J. Am. Chem. Soc.*, **66**, 1165 (1944).

(5) N. Löfgren and B. Lundquist, *Svensk. Kem. Tidskr.*, **58**, 206 (1946) [*Chem. Abstr.*, **43**, 1022 (1949)].

(6) F. Herr, *Arch. Exp. Path.*, **217**, 207 (1952).

(7) J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1466 (1934).

(8) G. Oláh, A. Pavláth, and S. Kuhn, *Acta Chim. Acad. Sci. Hung.*, **7**, 85 (1955).

(9) Meyer and Hub, *Monatsch.*, **31**, 934 (1910).

(10) Cohen, *J. Chem. Soc.*, **99**, 1063 (1911).

(11) Holleman and Slothouwer, *Zentrall.*, **I**, 91 (1911).

TABLE I

PROPERTIES, ANALYSES, AND PHARMACOLOGICAL DATA OF FLUORINE COMPOUNDS RELATED TO PROCAINE

| Ethyl Ester Hydrochloride | M.P., °C. | Yield, % | N Calcd. | N Found | C Calcd. | C Found | Effective Concentration, % | Toxicity, mg./kg. |
|---|---|---|---|---|---|---|---|---|
| *o*-Fluorobenzoic acid β-dimethylamino- | 92 | 83 | 6.66 | 6.51 | 16.62 | 16.71 | | 800 |
| *o*-Fluorobenzoic acid β-diethylamino- | 102 | 77 | 5.89 | 5.88 | 14.69 | 14.62 | 2 | 800 |
| *o*-Fluorobenzoic acid β-piperidino- | 104 | 70 | 5.60 | 5.79 | 13.96 | 13.80 | 2 | 800 |
| *o*-Fluorobenzoic acid β-morpholino | 102 | 76 | 5.56 | 5.61 | 13.88 | 13.76 | | 800 |
| *m*-Fluorobenzoic acid β-dimethylamino- | 111 | 69 | 6.66 | 6.38 | 16.62 | 16.54 | 1 | 800 |
| *m*-Fluorobenzoic acid β-diethylamino- | 98 | 72 | 5.89 | 5.99 | 14.69 | 14.60 | 2 | 600 |
| *m*-Fluorobenzoic acid β-piperidino- | 100 | 70 | 5.60 | 5.76 | 13.96 | 13.88 | 2 | 500 |
| *m*-Fluorobenzoic acid β-morpholino- | 90 | 80 | 5.56 | 5.55 | 13.88 | 13.80 | | 800 |
| *p*-Fluorobenzoic acid β-dimethylamino[a] | 107 | 74 | 6.66 | 6.71 | 16.62 | 16.52 | 2 | 500 |
| *p*-Fluorobenzoic acid β-diethylamino-[a] | 126 | 76 | 5.89 | 6.05 | 14.69 | 14.60 | 2 | 600 |
| *p*-Fluorobenzoic acid β-piperidino | 98 | 71 | 5.60 | 5.59 | 13.96 | 13.88 | 2 | 500 |
| *p*-Fluorobenzoic acid β-morpholino- | 90 | 81 | 5.56 | 5.40 | 13.88 | 13.71 | | 800 |
| *o*-Fluorophenylacetic acid β-dimethylamino- | 108 | 69 | 6.31 | 6.48 | 15.71 | 15.52 | | 800 |
| *o*-Fluorophenylacetic acid β-diethylamino- | 101 | 70 | 5.59 | 5.66 | 13.99 | 13.92 | 0.5 | 800 |
| *o*-Fluorophenylacetic acid β-piperidino- | 110 | 83 | 5.34 | 5.39 | 13.23 | 13.12 | 0.25 | 800 |
| *m*-Fluorophenylacetic acid β-dimethylamino- | 62 | 76 | 6.31 | 6.56 | 15.71 | 15.66 | | 800 |
| *m*-Fluorophenylacetic acid β-diethylamino- | 67 | 80 | 5.59 | 5.51 | 13.99 | 13.84 | 0.5 | 800 |
| *m*-Fluorophenylacetic acid β-piperidino- | 106 | 68 | 5.34 | 5.30 | 13.23 | 13.23 | 0.5 | 800 |
| *p*-Fluorophenylacetic acid β-dimethylamino | 103 | 73 | 6.31 | 6.42 | 15.71 | 15.64 | | 800 |
| *p*-Fluorophenylacetic acid β-diethylamino- | 71 | 89 | 5.59 | 5.70 | 13.99 | 13.90 | 1 | 800 |
| *p*-Fluorophenylacetic acid β-piperidino- | 100 | 83 | 5.34 | 5.48 | 13.23 | 13.06 | 1 | 800 |
| Procaine | | | | | | | 0.3–0.4 | 450 |

[a] Previously described by Fosdick and Campaigne, Footnote 1.

*o-, m- and p-Fluorobenzyl bromide.* Into a solution of 0.4 mole of fluorotoluene in 60 ml. of dry benzene was dropped 18 ml. (0.35 mole) of bromine over a period of 4 hr. under refluxing and ultraviolet irradiation. After completion of the reaction the product was purified by fractional distillation.

| | B.P., °C. | Yield, % | Br Calcd. | Br Found |
|---|---|---|---|---|
| *o*-Fluorobenzyl bromide | 195–202 | 71 | | 42.51 |
| *m*-Fluorobenzyl bromide | 196–200 | 75 | 42.32 | 42.44 |
| *p*-Fluorobenzyl bromide | 195–202 | 82 | | 42.49 |

*o-, m- and p-Fluorobenzyl cyanide.* A solution of 37 g. (0.2 mole) of fluorobenzyl bromide in 40 ml. of ethanol was dropped, over a period of 3 hr., into a solution of 10 g. of sodium cyanide in 15 ml. of water, contained in a three-neck, round-bottom flask, under maintenance of efficient stirring and heating on a water bath. The reaction mixture was refluxed for 4 hr. following the addition of the fluorobenzyl bromide. The cooled mixture was filtered from the inorganic salts and washed with a little alcohol. The alcohol was removed from the filtrate by distillation, and the residue was again filtered and washed with saturated aqueous sodium chloride solution. After drying, the organic layer was fractionated.

| | B.P., °C. | Yield, % | N Calcd. | N Found |
|---|---|---|---|---|
| *o*-Fluorobenzyl cyanide | 230–235 | 85 | | 10.31 |
| *m*-Fluorobenzyl cyanide | 229–230 | 82 | 10.37 | 10.46 |
| *p*-Fluorobenzyl cyanide | 228–230 | 90 | | 10.40 |

*o-, m- and p-Fluorophenylacetic acid.* Fluorobenzyl cyanide (27 g., 0.2 mole) was heated with 90 g. of aqueous sulfuric acid (diluted 3:2) until an exothermic reaction started. When the mixture began to boil, external heating was discontinued. After the cessation of boiling the solution was further heated for 2–3 min. The fluorophenylacetic acid which precipitated on cooling was filtered and recrystallized from chloroform.

| | M.P., °C. | Yield, % | C Calcd. | C Found | H Calcd. | H Found | F Calcd. | F Found |
|---|---|---|---|---|---|---|---|---|
| *o*-Fluorophenylacetic acid | 59 | 82 | | 62.39 | | 4.71 | | 12.17 |
| *m*-Fluorophenylacetic acid | 38 | 87 | 62.33 | 62.21 | 4.54 | 4.58 | 12.33 | 12.20 |
| *p*-Fluorophenylacetic acid | 85 | 79 | | 62.46 | | 4.41 | | 12.48 |

*o-, m- and p-Fluorophenylacetyl chloride.* To 23 g. (0.15 mole) of fluorophenylacetic acid in a round-bottom flask fitted with a reflux condenser was added 50 ml. of thionyl chloride. The ensuing exothermic reaction was allowed to go to completion. After removal of the excess thionyl chloride the product was fractionated.

| | B.P., °C. | Yield, % | Cl Calcd. | Cl Found |
|---|---|---|---|---|
| *o*-Fluorophenylacetyl chloride | 203–204 | 70 | | 20.52 |
| *m*-Fluorophenylacetyl chloride | 201–202 | 72 | 20.58 | 20.46 |
| *p*-Fluorophenylacetyl chloride | 202–204 | 85 | | 20.49 |

*Reaction of fluorobenzoyl and fluorophenylacetyl chlorides with alkylaminoethanols.* The amino alcohol (0.015 mole) was dissolved in 50 ml. of dry benzene and the solution was cooled with ice water. To this solution was added 0.015 mole of acyl chloride under efficient stirring. The white ester hydrochloride precipitated. After standing 1 hr. the reaction mixture was filtered and the precipitate was washed with a little benzene, recrystallized from ether-alcohol, and dried *in vacuo* (the products are strongly hygroscopic).

The properties of the compounds are listed in Table I.

BUDAPEST, HUNGARY

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

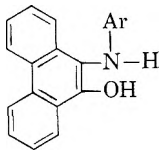
# Studies of Quinoid Structures. I. Action of Arylmagnesium Halides on Phenanthrenequinonimine

WILLIAM IBRAHIM AWAD AND ABDEL REHIM ABDEL RAOUF

*Received June 18, 1956*

Arylmagnesium halides react with phenanthrenequinonimine by 1,2-addition and not by 1,4-addition as described by Mustafa and Kamel.[1] The constitution of the Grignard products is discussed.

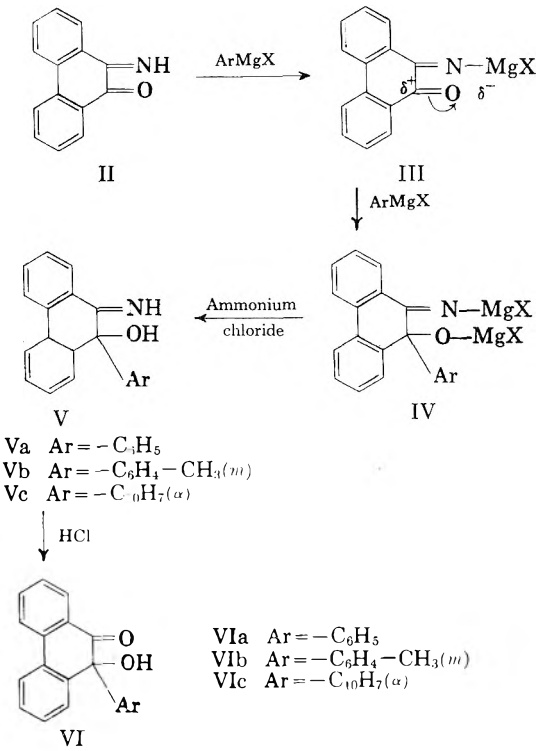
Mustafa and Kamel[1] stated that arylmagnesium halides react with phenanthrenequinonimine by 1,4-addition yielding 10-arylamino-9-phenanthrol (I). The main line of evidence was the identity of their product (from phenylmagnesium bromide and phenanthrenequinonimine) with the 10-phenylamino-9-phenanthrol obtained by Schmidt and Lumpp[2] from aniline and 9,10-dihydroxyphenanthrene. They claimed that a mixture melting point experiment gave no depression and hence structure I was assigned.




I

Ia Ar = $-C_6H_5$
Ib Ar = $-C_6H_4$-$CH_3(m)$
Ic Ar = $-C_{10}H_7(\alpha)$

In contrast to Mustafa and Kamel,[1] we found that the Grignard product (Va) gave a depression in melting point with Schmidt's compound (Ia). Also, the compounds gave different colors with concentrated sulfuric acid (Schmidt's compound, after purification, was orange-brown; the Grignard compound was green.) The benzoyl derivatives of the compounds gave different colors with concentrated sulfuric acid and a depression was noted in the mixture melting point.




Scheme A

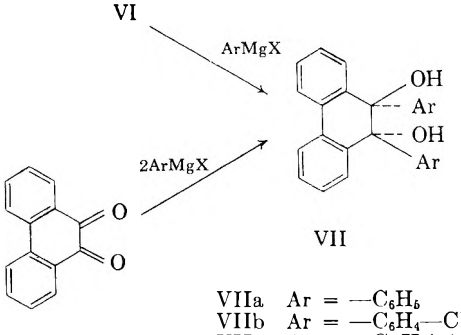
(1) Mustafa and Kamel, *J. Am. Chem. Soc.*, **76**, 124 (1954).

(2) Schmidt and Lumpp, *Ber.*, **43**, 787 (1910).

Phenanthrenequinonimine, like all other imines, was found to contain active hydrogen[3] (Zerewitinoff method). On the this basis, phenanthrenequinonimine should undergo a substitution reaction with a Grignard reagent to give a compound of the type III. The carbonyl group then is expected to react normally (1,2-addition) with an excess of the Grignard reagent to give IV. Hydrolysis of IV with ammonium chloride will then lead to 9-aryl-9,10-dihydro-10-imino-9-phenanthrol (V) according to Scheme A.

The constitution of the Grignard products was based on the fact that they are easily hydrolyzed in acid medium to give a ketonic nitrogen-free compound (VI) (compare the last step of Scheme A.) This hydrolysis is difficult to explain on the basis of the constitution given by Mustafa and Kamel, since 10-phenylamino-9-phenanthrol is stable to acid. (In its original method of preparation it is heated in a hydrochloric acid medium for one hour without change.)[2]

The constitution of the ketone VI is supported by (a) analytical data, (b) the formation of a 2,4-dinitrophenylhydrazone, (c) the reaction with arylmagnesium halide to yield *trans*-9,10-diaryl-9,10-dihydro-9,10-phenanthrenediol (VII), identified by melting point and mixture melting point determinations with an authentic sample prepared from phenanthrenequinone and the corresponding arylmagnesium halide[4] according to Scheme B.




VIIa Ar = $-C_6H_5$
VIIb Ar = $-C_6H_4-CH_3(m)$
VIIc Ar = $-C_{10}H_7(\alpha)$

Scheme B

Further confirmation of the differences in constitution of the Grignard product (Va) and Schmidt's compound (Ia) is observed by comparing the ultraviolet spectrograms (Fig. 1). From these curves it is clear that Va and Ia are different.

We have also compared the ultraviolet spectrograms of Va and the corresponding keto-compound (VIa) where the shape of the curves and the longest maxima are near to each other.[5]

(3) Compare Kharasch and Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 1169.

(4) *Elsevier's Encyclopaedia of Organic Chemistry*, Elsevier Publishing Company, Inc., New York, Amsterdam, **13**, (1946), pp. 852–3.

(5) Gillam and Stern, *An Introduction to Electronic Absorption in Organic Chemistry*, Edward Arnold, London, 1955, p. 44.

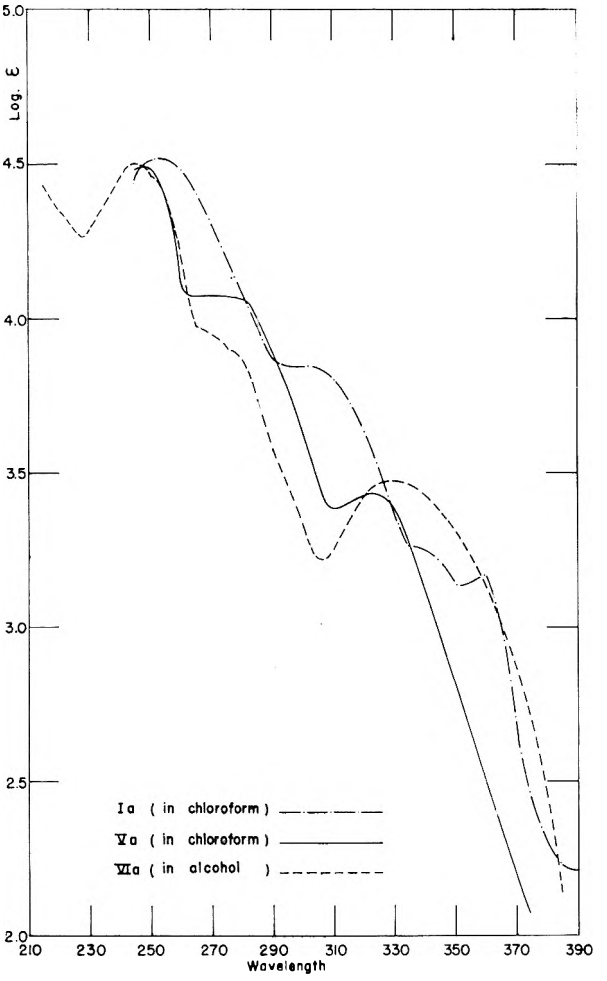



FIG. 1

## EXPERIMENTAL

Melting points are not corrected. Microanalyses were carried out by Alfred Bernhardt, Germany.

*Preparation of phenanthrenequinonimine.* This compound was prepared according to Schmidt and Junghans,[6] and was recrystallized from anhydrous benzene.

*Anal.* Calcd. for $C_{14}H_9NO$: Active hydrogen, 0.48. Found: Active hydrogen, 0.45.

*Action of phenylmagnesium bromide on phenanthrenequinonimine.* A solution of phenylmagnesium bromide (9 g. of bromobenzene and 0.9 g. of magnesium in 50 cc. of dry ether) was prepared in the usual way. A solution of 1 g. of phenanthrenequinonimine in 30 cc. of dry benzene was added to the above solution. The pale green reaction mixture was refluxed for 2 hr. on the water bath and left overnight at room temperature.

The Grignard product was hydrolyzed using a saturated solution of ammonium chloride. The ether-benzene layer was separated, washed with water, dehydrated over anhydrous sodium sulfate, filtered, and allowed to concentrate.

The product was precipitated by the addition of petroleum ether (40–60°) and was recrystallized from benzene–petroleum ether (40–60°), as pale yellow crystals m.p. 155°, yield 0.6 g. It gave an olive-green color with concentrated sulfuric acid; this color changed gradually to a reddish-brown and finally to brown on adding a crystal of potassium nitrate or a few drops of concentrated nitric acid.

The melting point was depressed on admixture with

(6) Schmidt and Junghans, *Ber.*, **37**, 3558 (1904).

Schmidt's compound (10-phenylamino-9-phenanthrol) (Ia).

*Anal.* Calcd. for $C_{20}H_{15}NO$: C, 84.2; H, 5.3; N, 4.9. Found: C, 84.1; H, 5.7; N, 4.6.

*Hydrolysis of* Va. A solution of 0.7 g. of Va, 50 cc. of ethyl alcohol, and 10 cc. of concentrated hydrochloric acid was refluxed for 2 hr. on the water bath. The addition of concentrated hydrochloric acid caused the substance to dissolve immediately and the solution acquired a dark brown color.

The product was precipitated after concentration and cooling and was recrystallized from methyl alcohol as colorless crystals m.p. 117–119°, yield 0.5 g. It gave a brown color with concentrated sulfuric acid, turning later to violet.

*Anal.* Calcd. for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9. Found: C, 84.6; H, 5.3.

*Preparation of the 2,4-dinitrophenylhydrazone derivative of* VIa. A solution of 0.2 g. of VIa in 20 cc. of hot methyl alcohol was prepared. A second solution, containing 0.4 g. of 2,4-dinitrophenylhydrazine in 30 cc. of hot methyl alcohol, also was prepared, a few drops of concentrated sulfuric acid were added and the two solutions were mixed together and heated on the water bath. The color darkened and heating was continued until crystals started to separate. The product was dissolved in benzene and allowed to pass through an alumina column. The benzene solution was concentrated and the precipitate was crystallized from benzene as violet-red needles, m.p. 224°, yield 0.1 g. It gave a green color with concentrated sulfuric acid.

*Anal.* Calcd. for $C_{26}H_{18}O_6N_4$: N, 12.0. Found: N, 11.4.

*Action of phenylmagnesium bromide on* VIa. Magnesium (0.1 g.) and bromobenzene (0.5 g.) were used in the preparation of phenylmagnesium bromide in the usual way. A solution of 0.5 g. of VIa in 10 cc. of dry benzene was added to the above reagent and the reaction was allowed to proceed to completion. The Grignard product was hydrolyzed in the usual way.

The ether-benzene mixture was evaporated and the residue was triturated with petroleum ether (40–60°) and recrystallized from a small amount of ethyl alcohol as colorless prisms, m.p. 179–180°, yield 0.3 g.

The melting point was not depressed on admixture with an authentic sample prepared as in Ref. 4. It gave an orange color with concentrated sulfuric acid.

*Anal.* Calcd. for $C_{26}H_{20}O_2$: C, 85.7; H, 5.5. Found: C, 85.5; H, 5.6.

*Benzoylation of* Va. Va (0.2 g.), 5 cc. of pyridine, and 3 cc. of benzoyl chloride were heated on the water bath for 2 hr. and then poured into 25 cc. of dilute hydrochloric acid. An oil separated out which was extracted with ether, washed with sodium carbonate solution, then with water, and then was dehydrated over anhydrous sodium sulfate. The ether was evaporated and the oily residue was triturated with benzene–petroleum ether (40–60°); it was recrystallized from benzene–petroleum ether (40–60°) to give pale yellow crystals m.p. 214°, yield 0.15 g. It gave an olive-green color with concentrated sulfuric acid. The m.p. was depressed on admixture with the benzoyl derivative of Schmidt's compound (Ia).

*Anal.* Calcd. (for monobenzoyl) $C_{27}H_{19}NO_2$: C, 83.3; H, 4.9; N, 3.6; (for dibenzoyl) $C_{34}H_{23}NO_3$: C, 82.8; H, 4.7; N, 2.8. Found: C, 83.5; H, 5.1; N, 3.1.

It is clear that the analytical data of the mono and the dibenzoyl derivatives are very similar. However, we believe that it is a dibenzoyl derivative, as is clear from the analytical data for the *o*-chlorobenzoyl derivative (shown below).

*Preparation of the o-chlorobenzoyl derivative of* Va. Va (0.2 g.), 5 cc. of pyridine and 3 cc. of *o*-chlorobenzoyl chloride were heated on the water bath for 2 hr. and treated as before. The product was recrystallized from benzene–petroleum ether (40–60°) as colorless crystals, m.p. 219°, yield 0.15 g. It gave an olive-green color with concentrated sulfuric acid.

*Anal.* Calcd. (for monobenzoyl) $C_{27}H_{18}ClNO_2$: C, 76.5; H, 4.3; N, 3.3; Cl, 8.4; (for dibenzoyl) $C_{34}H_{21}Cl_2NO_3$: C, 72.6; H, 3.7; N, 2.5; Cl, 12.6. Found: C, 73.0; H, 3.9; N, 2.6; Cl, 12.3.

*Comment on the purification of 10-phenylamino-9-phenathrol (Schmidt's compound)* (Ia).[2] Schmidt and Lumpp[2] obtained the above compound in green prisms from alcohol, m.p. 165°. This compound gave a green color with concentrated sulfuric acid; on adding a crystal of potassium nitrate or a few drops of concentrated nitric acid, it immediately changed to a persistent, intense red color.

In order to compare Schmidt's product (Ia) with the Grignard product (Va), Ia was recrystallized (using charcoal) from the same solvent as Va (benzene–petroleum ether, 40–60°) in grey crystals; the green color of the crystals completely disappeared, m.p. 169° (not depressed on admixture with the above sample). This pure compound gave an orange-brown color with concentrated sulfuric acid which changed rapidly to intense red on adding a crystal of potassium nitrate or a few drops of concentrated nitric acid.

It should be noted that on dissolving Ia in alcohol for the examination of the ultraviolet spectrum, the solution changed its color gradually from colorless to greenish-violet, a fact which forced us to carry out the examination of the ultraviolet spectrum of Ia in a nonhydroxylic solvent such as chloroform.

*Benzoylation of 10-phenylamino-9-phenanthrol [Schmidt's compound* (Ia)]. Ia (0.5 g.), 15 cc. of pyridine, and 8 cc. of benzoyl chloride were heated for 2 hr. on the water bath and treated as before. The product was recrystallized from benzene–petroleum ether (40–60°) as colorless crystals m.p. 217°, yield 0.3 g. It gave a pale lemon-yellow color with concentrated sulfuric acid. The melting point was depressed on admixture with the benzoyl derivative of Va.

*Anal.* Calcd. for $C_{34}H_{23}NO_3$: C, 82.8; H, 4.7; N, 2.8. Found: C, 82.9; H, 5.1; N, 2.97.

*Action of m-tolylmagnesium bromide on phenanthrenequinonimine.* Magnesium (0.7 g.) and *m*-bromotoluene (6 g.) were used in the preparation of *m*-tolylmagnesium bromide by the same procedure as in the preparation of phenylmagnesium bromide. A solution of 1.5 g. of phenanthrenequinonimine in 60 cc. of dry benzene was added and the reaction was allowed to proceed to completion as before. The product was recrystallized from benzene as pale yellow crystals m.p. 179°, yield 1.2 g. It gave a green color with concentrated sulfuric acid, rapidly changing to a brown-violet color.

*Anal.* Calcd. for $C_{21}H_{17}NO$: C, 84.3; H, 5.7; N, 4.7. Found: C, 84.4; H, 5.8; N, 4.5.

*Hydrolysis of* Vb. The compound (0.5 g.) in 50 cc. of ethyl alcohol was hydrolyzed with 10 cc. of concentrated hydrochloric acid in the same manner as before. The product was precipitated by the addition of water and was recrystallized from petroleum ether (40–60°) as colorless crystals m.p. 145°, yield 0.3 g. It gave a green color with concentrated sulfuric acid, changing to brown.

*Anal.* Calcd. for $C_{21}H_{16}O_2$: C, 84.0; H, 5.4. Found: C, 83.6; H, 5.4.

*Action of m-tolylmagnesium bromide on* VIb. Magnesium (0.1 g.) and *m*-bromotoluene (1 g.) were used in the preparation of *m*-tolylmagnesium bromide as before. A solution of 0.3 g. of VIb in 20 cc. of dry benzene was added and the reaction completed as before. The product in form of an oil was triturated with a chloroform–methyl alcohol mixture. The solid obtained was recrystallized by dissolving in hot methyl alcohol and adding a few drops of chloroform to help solution; it was filtered and left to evaporate slowly whereby colorless crystals came down, m.p. 149°, yield 0.2 g. It gave a yellow-orange color with concentrated sulfuric acid.

The melting point was not depressed on admixture with an authentic sample prepared as in Ref. 4.

*Action of α-naphthylmagnesium bromide on phenanthrenequinonimine.* Magnesium (1.2 g.) and α-bromonaphthalene (10 g.) were used in the preparation of α-naphthylmagnesium bromide in the usual way. A solution of 2 g. of phenanthrenequinonimine in 60 cc. of dry benzene was added to the

Grignard reagent and the reaction was completed as before. The product was recrystallized from benzene–petroleum ether (40–60°) as colorless crystals, m.p. 177°, yield 1.8 g. It gave a blue-violet color with concentrated sulfuric acid.

*Anal.* Calcd. for $C_{24}H_{17}NO$: C, 85.9; H, 5.1; N, 4.2. Found: C, 86.3; H, 5.3; N, 4.0.

*Hydrolysis of* Vc. The compound (0.5 g.) in 50 cc. of ethyl alcohol was hydrolyzed with 8 cc. of concentrated hydrochloric acid as before. The product was precipitated by the addition of water and recrystallized from petroleum ether (80–100°) as colorless crystals, m.p. 168°, yield 0.4 g. It gave a purple color with concentrated sulfuric acid.

*Anal.* Calcd. for $C_{24}H_{16}O_2$: C, 85.7; H, 4.8. Found: C, 85.2; H, 5.1.

*Action of α-naphthylmagnesium bromide on* VIc. Magnesium (0.3 g.) and α-bromonaphthalene (2 g.) were used in the preparation of α-naphthylmagnesium bromide as before. A solution of 1 g. of VIc in 30 cc. of dry benzene was added and the reaction was completed as before. The product was recrystallized from benzene as colorless crystals, m.p. 261°, yield 0.8 g. It gave a brown color with concentrated sulfuric acid.

The melting point was not depressed on admixture with an authentic sample prepared as in Ref. 4.

*Anal.* Calcd. for $C_{34}H_{24}O_2$: C, 87.9; H, 5.2. Found: C, 88.4; H, 5.5.

*Benzoylation of* Vc. Vc (0.5 g.), pyridine (10 cc.), and benzoyl chloride (8 cc.) were heated on the water bath for 2 hr., then poured into 60 cc. of dilute hydrochloric acid. The product was treated as in the case of benzoylation of Va.

The oily product was triturated with petroleum ether (40–60°), cooled in ice to solidify, and filtered from the oily part. It was recrystallized from benzene–petroleum ether (40–60°) in colorless crystals, m.p. 241°, yield 0.3 g. It gave an emerald-green color with concentrated sulfuric acid.

*Anal.* Calcd. (for monobenzoyl) $C_{31}H_{21}NO_2$: C, 86.7; H, 4.8; N, 3.2; (for dibenzoyl) $C_{38}H_{25}NO_3$: C, 84.0; H, 4.6; N, 2.6. Found: C, 84.2; H, 4.7; N, 2.6.

*Acknowledgment.* The authors are indebted to Dr. F. G. Baddar, Assistant Professor, Chemistry Department, Faculty of Science, Cairo University, for his valuable help in the determination of the ultraviolet spectrograms.

ABBASSIA, CAIRO, EGYPT

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, INSTITUTE OF SCIENCE]

# Substitution in the Benzopyrone Series. IV. Sulfonation of Coumarin Derivatives

J. R. MERCHANT AND R. C. SHAH

*Received November 19, 1956*

The sulfonation of 7-hydroxy-3,4-dimethylcoumarin, its methyl ether, 7-hydroxy-4-methyl-6-ethylcoumarin, its methyl ether, 7-hydroxy-3,4-dimethyl-6-ethylcoumarin and its methyl ether, with chlorosulfonic acid is described. The structures of the sulfonated products have been established, by oxidation, bromination, or nitration to give known compounds.

The present work was undertaken with a view to studying the reactivity of some substituted 7-hydroxycoumarins and their methyl ethers upon sulfonation.[1]

The products of sulfonation were characterized as described previously[2] by their conversion to crystalline derivatives. Table I describes the experimental conditions and the results obtained on the sulfonation of different coumarin derivatives with chlorosulfonic acid. From the results of the sulfonation, it is observed that in 7-hydroxycoumarins, the *6* position is the most reactive, positions *3* and *8* being next in order of reactivity. It is also interesting to note that the *8* position is not favorable for the formation of sulfonyl chlorides. In the case of 7-methoxycoumarins also, the order of reactivity is *6* > *3*. The substitution in the *8* position is always accompanied by demethylation.

It was observed that the sulfonation of 7-hydroxy-3,4-dimethylcoumarin at 100° or at lower temperatures gave monosulfonated products I and II, while the disulfonic acid III was obtained with excess of chlorosulfonic acid at higher temperatures. Experiments to prove the constitution of I by the hydrolysis, nitration, and methylation of its sodium salt failed to give definite products. Since the sulfonic acid I could be easily obtained by the hydrolysis of the sulfonyl chloride II, attempts were made to establish the structure of the latter. It is known[3] that halogenation and nitration of sulfonyl chlorides can be effected without modifying the sulfonyl chloride group. Consequently, the bromination of II was carried out and a bromo sulfonyl chloride was obtained. The chlorosulfonation of the known[4] 7-hydroxy-6-bromo-3,4-dimethylcoumarin was attempted under a variety of conditions; however, the product, in all cases, was a sulfonic acid (IV). This bromosulfonic acid was different from that obtained by hydrolysis of the bromo sulfonyl chloride and was assigned the structure, 7-hydroxy-6-bromo-3,4-dimethylcoumarin-8-sulfonic acid. The position of the sulfonyl chloride group in II, however, was determined by demethylation of

(1) C. M. Suter, *Organic Chemistry of Sulfur*, John Wiley and Sons, Inc., New York, 1948, p. 316.

(2) D. V. Joshi, J. R. Merchant, and R. C. Shah, *J. Org. Chem.*, 21, 1104 (1956); J. R. Merchant and R. C. Shah, *J. Ind. Chem. Soc.*, 34, 35 (1957).

(3) Reference 1, p. 512.

(4) D. Chakravarty and S. M. Mukherjee, *J. Ind. Chem. Soc.*, 14, 729 (1937).

TABLE I

SULFONATION OF 7-HYDROXYCOUMARINS

| Substance | Ref.[a] | Moles of Chlorosulfonic Acid | Temp., °C. | Time of Heating, Hr. | | Products |
|---|---|---|---|---|---|---|
| 7-Hydroxy-3,4-dimethylcoumarin | 9 | 4.3 | 80 | 3 | (I) | 6-Sulfonic acid and |
| | | | | | (II) | 6-sulfonyl chloride |
| | | 8.6 | 130–140 | 6 | (III) | 6,8-Disulfonic acid |
| 7-Hydroxy-6-bromo-3,4-dimethylcoumarin | 4 | Excess | 100 | 2 | (IV) | 8-Sulfonic acid |
| 7-Methoxy-3,4-dimethylcoumarin | 10 | 4.5 | 100 | 2 | (V) | 6-Sulfonic acid and |
| | | | | | (VI) | 6-sulfonyl chloride |
| | | Excess | 130–140 | 4 | (III) | (Complete demethylation) |
| 7-Hydroxy-4-methyl-6-ethylcoumarin | 11 | 2 | 100 | 2 | (VII) | 8-Sulfonic acid |
| | | Excess | 130–140 | 6 | (VIII) | 3,8-Disulfonic acid |
| 7-Methoxy-4-methyl-6-ethylcoumarin | 11 | 4 | 100 | 2 | (IX) | 3-Sulfonic acid and |
| | | | | | (X) | 3-sulfonyl chloride |
| | | Excess | 130–140 | | (VIII) | (Complete demethylation) |
| 7-Hydroxy-3,4-dimethyl-6-ethylcoumarin | 12 | Excess | 100 and above | 2 | (XI) | 8-Sulfonic acid |
| | | | | | (XII) | 8-Sulfonyl chloride |
| 7-Methoxy-3,4-dimethyl-6-ethylcoumarin | 13 | Small excess | 60 | 2 | (XI) | (Complete demethylation) |

[a] The numbers in this column indicate references for methods of preparation.

7-methoxy-3,4-dimethylcoumarin-6-sulfonyl chloride (V) with anhydrous aluminum chloride. The product of this reaction was identical to II.

The sulfonation of 7-hydroxy-3,4-dimethylcoumarin with excess of chlorosulfonic acid at 140° gave only the disulfonic acid. No disulfonyl chloride could be obtained even under different experimental conditions. 3,5-Dinitroresacetophenone was obtained when III was treated with nitric acid in acetic acid at 100°. The breaking up of the coumarin ring has also been observed by Naik and Jadhav[5] during the nitration of 7-hydroxy-3,4-dimethylcoumarin. The structure of the disulfonic acid III was proved by the bromination of its sodium salt which afforded 7-hydroxy-6,8-dibromo-3,4-dimethylcoumarin. The latter substance had been synthesized in our laboratory by the Pechmann condensation of 2,4-dibromoresorcinol with ethyl α-methylacetoacetate.

The sulfonation of 7-methoxy-3,4-dimethylcoumarin, at 100° or at lower temperatures, gave monosulfonated products V and VI. Attempts to prove the structures of V by nitration or hydrolysis failed to give definite results. Bromination of its sodium salt, however, gave a bromo compound free from sulfur which melted at 208–210°. The latter was not known, and attempts to prove its constitution by hydrolysis were unsuccessful. The position of the sulfonic acid group in V was established by the oxidation of its sodium salt with alkaline potassium permanganate. The product of this oxidation was 2-methoxy-4-hydroxy-benzenesulfonic acid, which did not give any coloration with alcoholic ferric chloride, but was easily converted to the known 2,4-dimethoxy-benzenesulfonic acid[6] by methylation. As a point of interest, the sulfonation of resorcinol mono methyl ether was carried out, affording a mono sulfonic acid different from the above. The product gives a violet coloration with alcoholic ferric chloride solution. It was therefore assigned the constitution 2-hydroxy-4-methoxy-benzenesulfonic acid.

At higher temperatures, and with excess of chlorosulfonic acid or with fuming sulfuric acid, 7-methoxy-3,4-dimethylcoumarin gave a disulfonic acid in which the methoxyl group was completely demethylated (III). The product gave a positive ferric chloride test and was converted to 7-hydroxy-6,8-dibromo-3,4-dimethylcoumarin by bromination of its disodium salt.

The sulfonation of 7-hydroxy-4-methyl-6-ethylcoumarin required controlled experimental conditions. Only mono- (VII) and di- (VIII) sulfonic acids were obtained. No sulfonyl chlorides, however, could be prepared.

The sulfonic acid (VII) gave a blue coloration with alcoholic ferric chloride solution. This color test indicated[7] that the sulfonic acid group in (VII) was in the position *ortho* to the hydroxyl group; that is, the sulfonation had taken place in the *8* position. The constitution of (VIII) was determined by bromination in acetic acid medium which afforded 7-hydroxy-3,8-dibromo-4-methyl-6-ethylcoumarin. The structure of the latter was confirmed by its conversion by alkaline hydrolysis, to a bromo coumarilic acid (A).

The sulfonation of 7-methoxy-4-methyl-6-ethylcoumarin at 100°, led to the formation of monosulfonated products (IX) and (X). At higher tempera-

(5) A. R. Naik and G. V. Jadhav, *J. Ind. Chem. Soc.*, 26, 245 (1945).

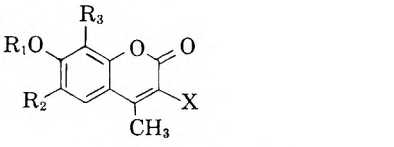
(6) C. M. Suter and H. L. Hansen, *J. Am. Chem. Soc.*, 55, 2080 (1933).

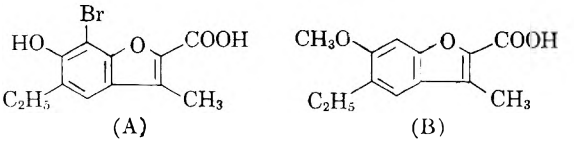
(7) S. Soloway and S. H. Wilen, *Anal. Chem.*, 24, 979 (1952).

tures, complete demethylation occurred as shown by the fact that the disulfonic acid formed gave upon bromination 7-hydroxy-3,8-dibromo-4-methyl-6-ethylcoumarin. The structure of (IX) was established by its conversion, by bromination to 7-methoxy-3-bromo-4-methyl-6-ethylcoumarin. The structure of the latter was determined by its conversion to the related coumarilic acid (B).

Only monosulfonated products (XI) and (XII) were obtained by the sulfonation of 7-hydroxy-3,4-dimethyl-6-ethylcoumarin. The sulfonic acid (XI) gave an intense coloration with alcoholic ferric chloride solution showing that the sulfonic acid group in (XI) had entered the *8* position. The bromination of (XI) gave 7-hydroxy-8-bromo-3,4-dimethyl-6-ethylcoumarin, the structure of the latter being confirmed by the fact that it was recovered unchanged on boiling with sodium carbonate.

The sulfonation of 7-methoxy-3,4-dimethyl-6-ethylcoumarin was accompanied by complete demethylation, and the corresponding hydroxy coumarin sulfonic acid XI was obtained.





(A) (B)

$R_1 = R_3 = H$; $X = CH_3$; $R_2 = HSO_3$, $SO_2Cl$ (I and II)
$R_1 = R_3 = H$; $X = CH_3$; $R_2 = R_3 = HSO_3$ (III)
$R_1 = H$; $X = CH_3$; $R_2 = Br$; $R_3 = HSO_3$ (IV)
$R_1 = OCH_3$; $R_3 = H$; $X = CH_3$; $R_2 = HSO_3$, $SO_2Cl$ (V and VI)
$R_1 = X = H$; $R_2 = C_2H_5$; $R_3 = HSO_3$ (VII)
$R_1 = H$; $R_2 = C_2H_5$; $R_3$, $X = HSO_3$ (VIII)
$R_1 = OCH_3$; $R_2 = C_2H_5$; $R_3 = H$; $X = HSO_3$, $SO_2Cl$ (IX and X)
$R_1 = H$; $R_2 = C_2H_5$; $X = CH_3$; $R_3 = HSO_3$, $SO_2Cl$ (XI and XII)

## EXPERIMENTAL

All melting points are corrected and were taken in a sulfuric acid bath. Freshly distilled chlorosulfonic acid was used for sulfonation.

*General method for sulfonation.* The general method is the same as that described in Part II of this series.[2]

*7-Hydroxy-8-bromo-3,4-dimethylcoumarin-6-sulfonyl chloride* ($R_1 = H$; $X = CH_3$; $R_2 = SO_2Cl$; $R_3 = Br$). To a solution of 500 mg. of the sulfonyl chloride (II) in 5 ml. of hot acetic acid, was added gradually with shaking, 5 ml. of a 10% solution of bromine in acetic acid. The mixture was heated on a water bath for 40 min. and kept overnight. The product which separated was filtered and crystallized from acetic acid, m.p. 195–196°.

*Anal.* Calcd. for $C_{11}H_8BrClO_5S$: S, 8.7. Found: S, 8.5.

*Demethylation of 7-methoxy-3,4-dimethylcoumarin-6-sulfonyl chloride* (VI). Three grams of the sulfonyl chloride was intimately mixed with 12 g. of powdered anhydrous aluminum chloride and the contents (protected from moisture) were heated at 165-170° for 4 hr. The mixture was cooled and ice and hydrochloric acid were added. The pasty residue, after repeated crystallizations from benzene, had a m.p. 193–195° (dec.). Its mixed melting point with the 7-hydroxy-3,4-dimethylcoumarin-6-sulfonyl chloride (II), obtained by direct sulfonation, showed no lowering.

*Nitration of 7-hydroxy-3,4-dimethylcoumarin-8,8-disulfonic acid* (III). To a solution of 500 mg. of the sulfonic acid obtained by decomposition of its barium salt, in 5 ml. of glacial acetic acid, was added dropwise 2 ml. of nitric acid (*d* 1.42). The mixture was heated on the water bath for 1.5 hr. and poured over ice. The yellow precipitate was crystallized from alcohol, m.p. 167–168°. Its mixed melting point with an authentic sample of 3,5-dinitroresacetophenone[5] showed no lowering.

*Bromination of sodium 7-hydroxy-3,4-dimethylcoumarin-6,8-disulfonate* (III). To a suspension of 2 g. of the sodium salt in 8 ml. of acetic acid, was added 8 ml. of a 25% solution of bromine in acetic acid, and the mixture heated at 100° for 1 hr. The mixture, on dilution, gave a precipitate which was crystallized from acetic acid as white needles melting at 238°.

*Anal.* Calcd. for $C_{11}H_3Br_2O_3$: Br, 46.0. Found: Br, 45.7.

Its mixed melting point with 7-hydroxy-6,8-dibromo-3,4-dimethylcoumarin prepared by Pechmann condensation of 2,4-dibromoresorcinol with ethyl $\alpha$-methylacetoacetate showed no lowering.

*Oxidation of sodium 7-methoxy-3,4-dimethylcoumarin-6-sulfonate* (V). To a solution of 3 g. of the salt in 50 ml. of 2*N* potassium hydroxide solution was added dropwise, with stirring and cooling, 100 ml. of a 4% solution of potassium permanganate. The mixture was heated on a water bath for an hour and filtered. The filtrate was concentrated and acidified with concentrated hydrochloric acid. When the mixture was cooled, a potassium salt separated which gave a crystalline derivative with benzylisothiourea hydrochloride, which melted at 226–228°. It did not give any coloration with alcoholic ferric chloride solution.

*Anal.* Calcd. for $C_{15}H_{18}N_2O_5S_2$: N, 7.6. Found: N, 7.2.

*Methylation of the above oxidation product.* One gram of potassium salt was dissolved in 6 ml. of a 10% potassium hydroxide solution and 1 ml. of dimethyl sulfate was added. The mixture was heated on a water bath for 2 hr. When the mixture was acidified, a precipitate was obtained which gave an *S*-benzylisothiouronium derivative (crystallized from dilute alcohol) melting at 183–185°.

*Anal.* Calcd. for $C_{16}H_{20}N_2O_5S_2$: N, 7.3. Found: N, 7.2.

The *p*-toluidine salt of the methylated product was crystallized from a mixture of alcohol and chloroform, m.p. 197°.

*Anal.* Calcd. for $C_{15}H_{13}NO_5S$: N, 4.3. Found: N, 4.2.

The mixed melting points of the *S*-benzylisothiouronium derivative and the *p*-toluidine salt with those of resorcinol dimethyl ether-4-sulfonic acid[6] showed no lowering.

*Sulfonation of resorcinol monomethyl ether.*[8] A mixture of 2.5 ml. of concentrated sulfuric acid and 5 g. of resorcinol monomethyl ether were heated at 90–100° for 30–40 min. The mixture was poured into saturated brine solution and the sodium salt separated. The derivative with benzylisothiourea hydrochloride was crystallized from dilute alcohol, m.p. 127°. It gave a violet coloration with alcoholic ferric chloride solution.

*Anal.* Calcd. for $C_{15}H_{18}N_2O_5S_2$: N, 7.6. Found: N, 7.8.

*7-Hydroxy-3,8-dibromo-4-methyl-6-ethylcoumarin* ($R_1 = H$; $X = R_3 = Br$; $R_2 = C_2H_5$). 7-Hydroxy-4-methyl-6-ethylcoumarin-3,8-disulfonic acid (VIII) was obtained by decomposition of the barium salt and had m.p. 185°. To a solution of 400 mg. of the acid in 2 ml. of acetic acid was added 5.3 ml. of a 10% solution of bromine in acetic acid, and the mixture was boiled for 30 min. The crystals which separated on cooling were crystallized in needles of m.p. 213–215°. The same product was also obtained by direct bromination of 7-hydroxy-6-ethyl-4-methylcoumarin.

*Anal.* Calcd. for $C_{12}H_{10}Br_2O_3$: Br, 44.2. Found: Br, 44.3.

(8) B. B. Dey, *J. Ind. Chem. Soc.*, 12, 685 (1935).

TABLE II

DERIVATIVES OF SULFONIC ACIDS AND SULFONYL CHLORIDES

| Sulfonation Product | M.P., °C. | Barium Salt or Sulfonyl Chloride | Analysis Barium Halogen Calcd. | Found | S-Benzylisothiouronium Derivative | Anilide | M.P., °C. | Analysis Nitrogen % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|
| I | — | $C_{22}H_{18}BaO_{12}S_2$ | 20.3 | 20.2 | $C_{19}H_{20}N_2O_6S_2$ | — | 222–224 | 6.4 | 6.4 |
| II | 193–195 (dec.) | $C_{11}H_9ClO_5S$ | 12.3 | 11.9 | — | $C_{17}H_{15}NO_5S$ | 198–200 | 4.1 | 4.3 |
| III | — | $C_{11}H_8BaO_9S_2$ | 28.3 | 27.8 | — | — | — | — | — |
| IV | — | — | — | — | $C_{19}H_{19}BrN_2O_6S_2$ | — | 191–192 | 5.4 | 5.4 |
| V[a] | — | $C_{24}H_{22}BaO_{12}S_2$ | 19.5 | 19.5 | $C_{20}H_{22}N_2O_6S_2$ | — | 266 | 6.2 | 6.5 |
| VI | 200–202 | $C_{12}H_{11}ClO_5S$ | 11.7 | 11.6 | — | $C_{18}H_{17}NO_5S$ | 241–243 | 3.9 | 4.1 |
| VII | — | $C_{24}H_{22}BaO_{12}S_2$ | 19.5 | 19.0 | $C_{20}H_{22}N_2O_6S_2$ | — | 159–161 | 6.2 | 6.4 |
| VIII | — | $C_{12}H_{10}BaO_9S_2$ | 27.5 | 27.3 | $C_{28}H_{32}N_4O_9S_4$ | — | 230–232 | 8.0 | 8.4 |
| IX | — | $C_{26}H_{26}BaO_{12}S_2$ | 18.8 | 18.1 | $C_{21}H_{24}N_2O_6S_2$ | — | 178 | 6.0 | 6.2 |
| X | 196–197 (dec.) | $C_{13}H_{13}ClO_5S$ | 11.2 | 11.0 | — | $C_{19}H_{19}NO_5S$ | 197 | 3.7 | 3.9 |
| XI | — | $C_{26}H_{26}BaO_{12}S_2$ | 18.8 | 18.2 | $C_{21}H_{24}N_2O_6S_2$ | — | 198–200 | 6.0 | 6.4 |
| XII[b] | 135–137 | $C_{13}H_{13}ClO_5S$ | 11.2 | 10.6 | — | $C_{19}H_{19}NO_5S$ | 260 | 3.7 | 3.3 |

[a] The free sulfonic acid crystallized from concentrated hydrochloric acid and had m.p. 186° (dec.) (Found: S, 11.6. $C_{12}H_{12}O_6S$ requires: S, 11.3%). [b] The free sulfonic acid crystallized from dilute hydrochloric acid and had m.p. 170–172° (Found: S, 10.1. $C_{13}H_{14}O_6S$ requires: S, 10.7%).

*6-Hydroxy-7-bromo-5-ethyl-3-methylcoumarilic acid* (A). Four hundred milligrams of the above dibromo coumarin was refluxed with 20 ml. of 1*N* potassium hydroxide solution for 2 hr. The filtrate, on acidification, deposited a violet substance which crystallized from dilute acetic acid, m.p. 186–188° (dec.). It dissolved in sodium bicarbonate readily.

*Anal.* Calcd. for $C_{12}H_{11}BrO_4$: Br, 26.7. Found: Br, 25.9.

*7-Hydroxy-8-bromo-4-methyl-6-ethylcoumarin* ($R_1$ = X = $CH_3$; $R_2$ = $C_2H_5$; $R_3$ = H). One gram of sodium 7-methoxy-4-methyl-6-ethylcoumarin-3-sulfonate (IX) was suspended in 5 ml. of acetic acid and a solution of bromine in acetic acid (2 equivalents) was added. The mixture was heated on a water bath for 15 min., filtered, and cooled. The crystals which separated were recrystallized from acetic acid affording white needles melting at 171–173°. The same compound was also obtained by the direct bromination of 7-methoxy-4-methyl-6-ethylcoumarin.

*Anal.* Calcd. for $C_{13}H_{13}BrO_3$: Br, 26.9. Found: Br, 26.7.

*6-Methoxy-5-ethyl-3-methylcoumarilic acid.* Five hundred milligrams of the above bromo compound was boiled with 20 ml. of 1*N* potassium hydroxide for 5 hr. The substance, which separated on acidification, was crystallized from acetic acid as needles of m.p. 220° (dec.). It gave a violet coloration with concentrated sulfuric acid.

*Anal.* Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.4. Found: C, 66.9; H, 6.8.

*7-Hydroxy-3,4-dimethyl-8-bromo-6-ethylcoumarin* ($R_1$ = H; X = $CH_3$; $R_3$ = Br; $R_2$ = $C_2H_5$). One gram of the sulfonic acid (XI) was suspended in 6 ml. of acetic acid and 6 ml. of a 10% solution of bromine in acetic acid was added. After heating the mixture at 100° the crystals which separated were recrystallized and the product was obtained as white needles of m.p. 226–228°.

*Anal.* Calcd for $C_{13}H_{13}BrO_3$: Br, 26.9. Found: Br, 27.4.

The same compound was also obtained by bromination of 7-hydroxy-3,4-dimethyl-6-ethylcoumarin.

BOMBAY 1, INDIA

(9) von H. Pechmann and C. Duisberg, *Ber.*, **16**, 2127 (1883).

(10) D. Chakravarti and S. M. Mukherjee, *J. Ind. Chem. Soc.*, **8**, 132 (1931).

(11) S. D. Limaye and D. B. Limaye, *Rasāyanam*, **1**, 204 (1941); *Chem. Abstr.*, **36**, 1038 (1942).

(12) R. D. Desai and C. K. Mavani, *Proc. Ind. Acad. Sci.*, **14A**, 100 (1941).

(13) V. M. Thakor and N. M. Shah, *J. Univ. Bombay*, **21A**, 14 (1947).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

# Dimerization Reactions in Sunlight. V.[1] Photodimerization of Substituted Coumarins

AHMED MUSTAFA, MOHAMED KAMEL, AND MOHAMED ALI ALLAM

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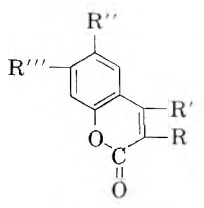
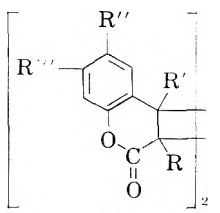
A study of the photodimerization of a large number of substituted coumarins in sunlight now has been undertaken. The colorless photodimers so obtained generally dissociate into their corresponding monomers on heating, a fact which is in favor of the proposed cyclobutane structure for the photodimers.

Coumarin (Ia),[2] and 3-phenylcoumarin (Ib)[3] undergo dimerization when exposed to light. It is now found that the coumarin derivatives Ic–e, Ig–h, and 7,8-benzocoumarin (IIIa) are completely converted by long exposure to sunlight into sparingly soluble crystalline dimers (IIc–e, IIg–h, and IV, respectively).

The photodimers, by analogy, are believed to be cyclobutane derivatives a fact which is favored by regeneration of monomer when a photodimer, e.g. IIc, is heated above its melting point. No molecular weight determination could be carried out as the dimers are difficultly soluble. Numerous photodimers from monomers containing the C=C—C=O group are believed to contain the cyclobutane ring.[4,5]

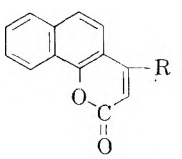


I

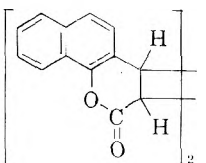


II

(a) R = R′ = R″ = R‴ = H
(b) R = $C_6H_5$; R′ = R″ = R‴ = H
(c) R = R′ = R‴ = H; R″ = $CH_3$
(d) R = R‴ = H; R′ = R″ = $CH_3$
(e) R = R″ = H; R′ = R‴ = $CH_3$
(f) R = R‴ = H; R′ = $CH_2COOCH_3$; R″ = $CH_3$
(g) R = R″ = H; R′ = $CH_2COOC_2H_5$; R‴ = $CH_3$
(h) R = R″ = H; R′ = $CH_2COOCH_3$; R‴ = $CH_3$
(i) R = R′ = R‴ = $CH_3$; R″ = H



III



IV

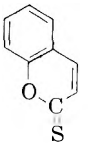
a, R = H
b, R = $CH_2COOCH_3$

III IV

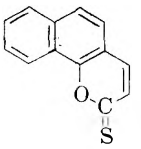
(a) R = H
(b) R = $CH_2COOCH_3$

Whereas 3-substituted coumarins, *e.g.* Ib, and 4-substituted coumarins, *e.g.* Id–e, undergo photodimerization in sunlight, 3,4-disubstituted coumarins, *e.g.* 3,4,7-trimethylcoumarin (Ii), are found to be stable or almost stable when their benzene solutions are exposed to sunlight under similar experimental conditions. The stability of Ii toward photodimerization and the ready photodimerization of Id and/or Ie parallel the stability of 2,3-dimethyl-1,4-naphthoquinone and the ready dimerization of 2-methyl-1,4-naphthoquinone in sunlight.[6]

When 6-methyl-(Ic) and 7-methylcoumarin-4-acetic acids (Ie) (R′ = $CH_2COOH$) were exposed to sunlight for one month, they were recovered unchanged.[7] The stability of these coumarin derivatives toward photodimerization may be attributed to their insolubility. We were unable to prepare the photodimer of thioncoumarin (V); the crystals were recovered unchanged when exposed to sunlight, and no photoreaction could be detected when a benzene solution of V was irradiated. However, when benzene solution of 7,8-benzothioncoumarin (VI) was exposed to sunlight, the orange-yellow solution turned into dark brown with the separation of brownish crystals which gave the same analytical values for VI. The product is not soluble and for this reason no molecular weight determination could be carried out. The structure of the photoproduct, which may be considered by analogy to IV as a dimer, is under further investigation.



V

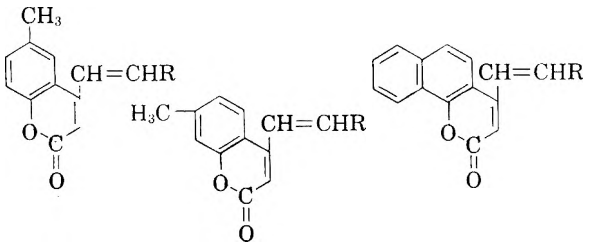


VI

4-Styrylcoumarin, which may be considered as the inner lactone of β-(*o*-hydroxyphenyl)cinnamylideneacetic acid, contains two ethylenic linkages,

(1) Part IV, A. Mustafa and S. A. E. D. Zayed, *J. Am. Chem. Soc.*, 6174 (1956).
(2) A. W. K. de Jong, *Rec. trav. chim.*, **43**, 316 (1924).
(3) A. Schönberg, *et al.*, *J. Chem. Soc.*, 374 (1950).
(4) Cf. A. Mustafa, *Chem. Revs.*, **51**, 1 (1952).
(5) W. Davies and F. C. James, *J. Chem. Soc.*, 314 (1955).
(6) A. Schönberg, *et al.*, *J. Chem. Soc.*, 2126 (1948).
(7) Exposure of phenylacetic acid alone in benzene to sunlight for a long period (six months) caused the formation of a little carbon dioxide and a little yellow oil [R. de Fazi, *Atti accad. naz Lincei* [6], **6**, 266 (1925); *Chem. Abstr.*, **20**, 594 (1926); *atti congr. naz. chim. pura ed appl.* 1926 1287; *Chem. Abstr.*, **22**, 2154 (1928)].

one of which constitutes a part of the heterocyclic ring. In the similarly constituted cinnamylideneacetic acid and its derivatives, photodimerization occurring through the double bond with the formation of a four-membered ring involves the $\gamma,\delta$ —C=C— bond in the case of cinnamylidene malonic acid,[8] and of $\alpha$-phenylcinnamylideneacetonitrile[9] and the $\alpha,\beta$—C=C— double bond together with the $\gamma,\delta$—C=C— double bond in the case of cinnamylideneacetic acid.[10] When solutions of the colored 4-styrylcoumarins (VIIa–c, VIIIa–c and IXa–c) in benzene are exposed to sunlight, colorless photodimers are separated during irradiation.



VII

(a) R = $C_6H_5$
(b) R = $C_6H_4OCH_3$-*p*
(c) R = $C_6H_4OCH_3$-*o*



VIII

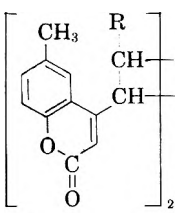
(a) R = $C_6H_5$
(b) R = $C_6H_4OCH_3$-*p*
(c) R = $C_6H_4Cl$-*o*



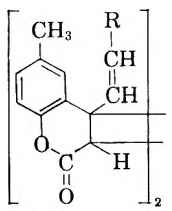
IX

(a) R = $C_6H_4OCH_3$-*p*
(b) R = $C_6H_4OCH_3$-*o*
(c) R = $C_6H_4Cl$-*o*

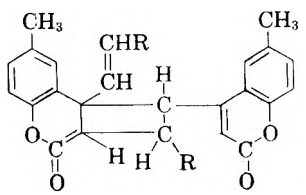
The photodimers are all crystalline substances and were obtained in good yields. The dimer of VIIb is taken as an example of the photodimers, and which are obviously of analogous structure. Whereas VIIb is deep yellow in color, the dimer is colorless. It is insoluble in aqueous sodium hydroxide solution and gives no color with ferric chloride. On heating, the dimer dissociates above its melting point, yielding the monomer almost quantitatively, a fact which favors the cyclobutane structure. By analogy, structures like X and XI are advanced, but we do not wish to exclude a structure like XII.[10]



X



XI



XII (or its stereo-isomers

(8) E. P. Kohler, *Am. Chem. J.*, **28**, 233 (1902); C. N. Riiber, *Ber.*, **35**, 2411 (1902); *cf.* ref. 4.

(9) H. Stobbe and Barbaschinow, *Ber.*, **45**, 3396 (1912); H. Stobbe and F. Kuhrmann, *Ber.*, **58**, 85 (1925).

(10) C. N. Riiber, *Ber.*, **46**, 335 (1913); H. Stobbe, A. Hensel, and W. Simon, *J. prakt. Chim.*, 110, 129 (1925).

## EXPERIMENTAL

The photochemical reactions were carried out in Pyrex glass Schlenk tubes,[11] from which the air was displaced by dry carbon dioxide prior to sealing by fusion. The benzene was thiophen-free (Kahlbaum), dried over sodium. Control experiments in the dark, but otherwise under identical conditions, showed no reaction.

*Preparation of methyl esters of coumarin-4-acetic acids.* For the preparation of methyl coumarin-4-acetates (If, Ih, and IIIb), a procedure identical to that described by Bhatt and Shah[12] for the preparation of the methyl esters of 6-alkylcoumarin-4-acetic acids, was followed. The new esters (listed in Table I) are colorless crystalline compounds, readily soluble in ordinary organic solvents. If and Ih remain colorless in concentrated sulfuric acid; while IIIb gives a pale yellow color.

*Photodimerization of coumarin derivatives. General procedure.* A solution of 0.5 g. of each of the coumarins (Ic–e) in 30 ml. of dry benzene was exposed to sunlight for one month (March–April). In the case of Ig and Ih photodimerization was carried out in the presence of eosin (0.005 g.) as a photosensitizer.[13] The reaction mixtures were worked up either by filtration of the separated photodimer or by concentration of the benzene solution to a small volume (*ca.* 5 ml.), followed by cooling. The photodimers, so obtained, were then crystallized from the proper solvent (cf. Table II).

The photodimers IIc–e, IIg,h, are colorless crystalline compounds. They dissolve in hot benzene, dioxan; and acetic acid, but are sparingly soluble in light petroleum (b.p. 60–80°).

A benzene solution of 0.5 g. of 3,4,7-trimethylcoumarin (Ii) proved to be stable toward the action of sunlight under the above experimental conditions.

*Pyrolysis of the photodimers of coumarin derivatives* (IIc and IIh). The pyrolysis was carried out at 195–200° (metal bath) for 20 min. in Pyrex glass test tubes, containing 0.1 g. of the dimer in the case of IIc and at 250–258° in the case of IIh. Cooling the reaction mixture, followed by crystallization from a suitable solvent, yielded the corresponding monomers (Ic and Ih), respectively, in an almost quantitative yield.

*Photodimerization of 7,8-benzocoumarin* (IIIa). A solution of 1 g. of IIIa[14] in 25 ml. of glacial acetic acid was exposed to sunlight for 6 months (January–July). The colorless solution became deep brown and deposited a brown solid (*ca.* 0.5 g.) which gave, upon filtration followed by crystallization from acetone, colorless crystals, m.p. 225° (brown melt).

*Anal.* Calcd. for $C_{26}H_{16}O_4$: C, 79.59; H, 4.08. Found: C, 79.58; H, 4.36.

(11) W. Schlenk and A. Thal, *Ber.*, **46**, 2840 (1913).

(12) M. R. Bhatt and N. M. Shah, *J. Indian Chem. Soc.*, **32**, 322 (1955).

(13) C. Kögel and A. Steigmann, *Phot. Ind.*, 1169 (1925); *Chem. Abstr.*, **20**, 544 (1926).

(14) K. Bartsch, *Ber.*, **36**, 1966 (1903).

TABLE I

LIST OF NEW METHYLCOUMARIN-4-ACETATES

| Ester | M.P.[a] °C. | Solvent for Cryst.[b] | Yield, % | Formula | Analysis, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|
| If | 157 | A | 95 | $C_{13}H_{12}O_4$ | 67.24 | 67.32 | 5.17 | 5.46 |
| Ih | 122 | B | 90 | $C_{13}H_{12}O_4$ | 67.24 | 67.31 | 5.17 | 5.53 |
| IIIb | 130 | B | 93 | $C_{16}H_{12}O_4$ | 71.64 | 71.74 | 4.48 | 4.42 |

[a] Melting points are uncorrected. [b] A– petroleum ether (b.p. 80–100°). B– a mixture of benzene and light petroleum (b.p. 60–80°).

TABLE II

PHOTODIMERS OF COUMARIN DERIVATIVES

| Coumarin Derivative | Photodimer | M.P.[a] °C. | Solvent for Cryst.[b] | Color with $H_2SO_4$ | Yield, % | Formula | Analysis, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| Ic[c] | IIc[d] | 194 | A | Orange | 78 | $C_{20}H_{16}O_4$ | 75.00 | 74.89 | 5.00 | 4.77 |
| Id[e] | IId | 220 | B | Nil | 65 | $C_{22}H_{20}O_4$ | 75.85 | 76.10 | 5.75 | 5.71 |
| Ie[f] | IIe | 211 | C | Nil | 70 | $C_{22}H_{20}O_4$ | 75.85 | 75.99 | 5.75 | 5.99 |
| Ig[g] | IIg | 259–260 | B | Nil | 61 | $C_{28}H_{28}O_8$ | 68.29 | 67.68 | 5.69 | 5.54 |
| Ih | IIh | 253 | B | Pale yellow | 42 | $C_{26}H_{24}O_8$ | 67.24 | 66.95 | 5.17 | 5.07 |

[a] Melting points are uncorrected. [b] A– benzene. B– a mixture of dioxane and light petroleum (b.p. 40–60°). C– benzene and petroleum ether (b.p. 60–80°) mixture. [c] T. J. Thompson and R. H. Edke, *J. Am. Soc.*, **47**, 2557 (1925). [d] This experiment was carried out with A. H. E. Harhash. [e] K. Fries and W. Klostermann, *Ann.*, **362**, 23 (1908). [f] K. Fries and W. Klostermann, *Ber.*, *39*, 871 (1906). [g] B. B. Dey, *J. Chem. Soc.*, 1606 (1915).

TABLE III

PHOTODIMERS OF 4-STYRYLCOUMARINS

| Photodimer of | M.P.[a] °C. | Solvent[b] for Cryst. | Color with $H_2SO_4$ | Yield, % | Formula | Analysis, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VIIa[c] | 246 | A | Yellow | 80 | $C_{36}H_{28}O_4$ | 82.44 | 82.31 | 5.35 | 5.12 | | |
| VIIb[c] | 328 | B | Yellow | 92 | $C_{38}H_{32}O_6$ | 78.08 | 77.78 | 5.48 | 5.24 | | |
| VIIc[c] | 327 | C | Yellow | 40 | $C_{38}H_{32}O_6$ | 78.08 | 77.93 | 5.48 | 5.13 | | |
| VIIIa[d] | 251 | A | Yellow | 70 | $C_{36}H_{28}O_4$ | 82.44 | 82.29 | 5.35 | 4.97 | | |
| VIIIb[e] | 217 | D | Yellow-orange | 81 | $C_{38}H_{32}O_6$ | 78.08 | 77.94 | 5.48 | 5.32 | | |
| VIIIc[c] | 322 | E | Yellowish green | 60 | $C_{36}H_{26}Cl_2O_4$ | 72.85 | 72.65 | 4.38 | 4.16 | 11.96 | 11.52 |
| Xa[e] | 290[f] | F | Yellow | 53 | $C_{44}H_{32}O_6$ | 80.48 | 80.27 | 4.87 | 4.67 | | |
| Xb[c] | above 350 | [g] | Yellow[h] | 75 | $C_{44}H_{32}O_6$ | 80.48 | 80.31 | 4.87 | 4.77 | | |
| Xc[c] | 245 | H | Yellow | 85 | $C_{42}H_{26}Cl_2O_4$ | 75.78 | 75.46 | 3.90 | 3.78 | 10.67 | 10.46 |

[a] Melting points are uncorrected. [b] A– xylene. B– glacial acetic acid. C– a mixture of chloroform and ether. D– toluene. E– a mixture of chloroform and petroleum ether. F– benzene. [c] A. Mustafa, M. Kamel, and M. A. Allam, *J. Am. Chem. Soc.*, **78**, 4692 (1956). [d] A. Mustafa and M. Kamel, *J. Am. Chem. Soc.*, **77**, 1828 (1955). [e] B. B. Dey and K. K. Row, *J. Indian Chem. Soc.*, **1**, 107; 277 (1924). [f] The dimer begins to darken at 290°. [g] The dimer was proved to be pure enough for analytical determination after washing with hot xylene; it is insoluble in most organic solvents. G– phenetole. [h] The solution in sulfuric acid acquires deep green fluorescence.

The photodimer (IVa)[15] is difficultly soluble in benzene, alcohol, acetic acid, and light petroleum, but dissolves in hot acetone. It dissolves in concentrated sulfuric acid with a yellow color.

*Photodimerization of 7,8-benzothioncoumarin* (VI).[15] A solution of 1 g. of VI in 20 ml. of dry benzene was exposed for 20 days (January). By the end of the exposure period, the benzene solution had turned dark brown and had deposited a brownish black solid (*ca.* 0.3 g.) which was filtered off and crystallized from the minimum of benzene.

*Anal.* Calcd. for $C_{26}H_{16}O_2S_2$: C, 73.58; H, 3.70. Found: C, 73.39; H, 3.61.

The photoproduct was soluble in benzene, but difficultly soluble in light petroleum.

(15) This experiment was carried out with Sayed Mohamed Abdel Rahman Omran.

*Exposure of thioncoumarin* (V). When V, in the solid state or in dry benzene solution, was exposed to sunlight for 1 month, no reaction took place and V was recovered unchanged.

*Photodimerization of 4-styrylcoumarins. General procedure.* A solution or a suspension of 0.5 g. of the 4-styrylcoumarin in 30 ml. of benzene was exposed to sunlight for a period varying from 15 to 30 days (January). At the end of the exposure period, the yellow color of the styrylcoumarin had almost disappeared and colorless crystals of the photodimer usually separated out. The separated photodimers were collected by filtration and crystallized from a suitable solvent.

Generally, the dimers are moderately soluble in benzene, alcohol, and acetic acid, but difficultly soluble in ether and light petroleum ether. The properties of the dimers are recorded in Table III.

*Pyrolysis of the photodimer of* VIIIb. The dimer of VIIIb (0.3g.) was heated at 180–185° (metal bath) in a Pyrex test tube for 10 min. The colorless dimer melted with yellow color, and upon cooling the reaction mixture, followed by crystallization, VIIIb was obtained in almost quantitative yield.

GIZA, CAIRO, EGYPT.

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[CONTRIBUTION OF THE CENTRAL EXPERIMENT STATION, BUREAU OF MINES, DIVISION OF SOLID FUELS TECHNOLOGY]

# Lithium in Ethylenediamine: A New Reducing System for Organic Compounds[1]

LESLIE REGGEL, R. A. FRIEDEL, AND IRVING WENDER

*Received January 11, 1957*

A new metal-amine reducing system, lithium in ethylenediamine, is described. It reduces aromatic rings to monoölefins and to cycloparaffins; reduces phenols; cleaves ethers; reduces ketones to alcohols; and reduces acetylenes and both terminal and internal olefins to alkanes. It appears to be the most powerful, and perhaps the least selective, of the metal-amine systems.

The present investigation deals with the reduction of organic compounds by the lithium-ethylenediamine system. Most studies with metal-ammonia and metal-amine systems have been carried out using liquid ammonia. Although Kraus[2] predicted in 1953 that methylamine, ethylamine, and ethylenediamine would be valuable solvents for studying the physico-chemical properties of solutions of metals in amines at higher temperatures, ethylenediamine has not hitherto been used in a metal-amine reducing system. The first use of the lower aliphatic amines for metal-amine reductions was recently reported by Benkeser *et al.*,[3] who showed that aromatic rings are reduced to monoölefins by lithium-ethylamine. However, their attempt to replace ethylamine by higher primary amines gave poor yields, perhaps because lithium becomes progressively less soluble in these monofunctional amines as the ratio of nitrogen to carbon decreases. Since ethylenediamine contains one amine group per carbon atom, and since its relatively high boiling point (117°) is a potential advantage, we decided to investigate its use in a metal-amine system. Our results show that the lithium-ethylenediamine system, at 90–100°, is a convenient and effective metal-amine combination for carrying out reductions and cleavage reactions of organic compounds.[4]

(1) I. Wender and L. Reggel, Abstracts of Papers, 127th Meeting, AMERICAN CHEMICAL SOCIETY, Cincinnati, Ohio, April 1955, page 22N. See also *Chem. Eng. News*, **33**, 1525 (1955).

(2) C. A. Kraus, *J. Chem. Ed.*, **30**, 83 (1953).

(3) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **76**, 631 (1954); **77**, 3230 (1955). A preliminary investigation of this topic was mentioned in a paper by R. A. Benkeser, R. E. Robinson, and H. Landesman, *J. Am. Chem. Soc.*, **74**, 5699 (1952).

(4) Recent work in these laboratories has shown that coal, which is difficult to hydrogenate at temperatures below 300°, can be reduced by the lithium-ethylenediamine system.

## EXPERIMENTAL

*Materials.* Lithium, obtained from the Lithium Corp. of America, was used in the form of one-eighth inch wire.

Anhydrous ethylenediamine (Union Carbide Chemical Co. and Eastman) was purified by heating with sodium for a few days and then distilling; the reaction of sodium with the amine is slow. This once-distilled material was poured directly into the reaction flask without any special precautions to avoid exposure to the atmosphere. (In some experiments, the once-distilled amine was distilled from sodium a second time directly into the dropping funnel on the reaction apparatus; where this material was used, it is referred to as twice-distilled ethylenediamine.)

Diethylenetriamine (Eastman) was purified by distilling it once from a solution of sodium in the amine.

*General Procedure.* A four-neck flask, or a three-neck flask with a suitable adapter, was fitted with a mercury-sealed double Hershberg stirrer, a thermometer dipping below the surface of the liquid, a spiral reflux condenser with a nitrogen inlet and mercury-sealed outlet, and a straight reflux condenser, 6 to 8 inches long, which was stoppered at the top. (In some experiments, a graduated dropping funnel was so arranged that ethylenediamine could be distilled into the funnel and then added to the flask without exposure to air.) After the apparatus was flushed with nitrogen, the substrate to be reduced and the ethylenediamine were added, the stirrer was started, and the mixture was heated to 90–100°. The lithium was then added in portions through the short reflux condenser; it was added in pieces about 1.5 in. long, about 4 to 8 pieces (0.5–1.0 g.) being added in each portion. The rate of addition of the lithium was controlled by two factors, the hydrogen evolution and the persistence of the dark blue color. Usually the gas evolution was the determining factor, the metal being added during 1.5 to 3 hr., without waiting for discharge of the blue color between portions. The mixture was maintained at 90–100° during addition of the lithium. After all of the metal had been added, the mixture was heated at or just below a gentle reflux for 1 or 2 hr. The mixture was then cooled in ice, and water was added slowly; considerable heat was evolved, and after a little water had been added the mixture usually became almost solid, requiring efficient stirring. After enough water had been added to dissolve most of the solids, the mixture was transferred to a separatory funnel with the aid of water and benzene or ether. The aqueous layer was extracted with the solvent, and the combined organic layers washed with dilute hydrochloric acid, then with saturated sodium chloride solution, dried, and dis-

TABLE I

REDUCTION OF TETRALIN[a]

| Experiment | Moles of lithium per mole tetralin | Percent excess lithium[b] | Amine used[c] | Amine, ml. | Yield, percent | | |
|---|---|---|---|---|---|---|---|
| | | | | | Octalin | *Trans*-decalin[d] | Tetralin |
| 1 | 4.4[e] | 10 | II | 150 | 32.1 | — | 46.0 |
| 2 | 8.0[e] | 100 | II | 150 | 68.0 | — | 31.4 |
| 3 | 4.4 | 10 | II | 150 | 40.0 | — | 65.2 |
| 4 | 8.0 | 100 | II | 375 | 54.2 | 32.6 | — |
| 5 | 8.0 | 100 | III | 375 | 96.9 | — | — |
| 6 | 12.2 | 200 | III | 375 | 54.9 | 34.7 | — |
| 7 | 8.0 | 100 | I | 375 | 57.5 | 31.9 | — |
| 8 | 8.0[f] | 100 | I | 375 | 81.8 | 4.5 | — |
| 9 | 8.0 | 100 | IV[g,h] | 375 | 24.3 | — | 60.3 |
| 10 | 8.0 | 100 | IV[g,i] | 375 | 27.6 | — | 56.8 |
| 11 | 8.0[j] | 100 | I | 375 | 5.7 | — | 89.4 |
| 12 | 8.0[k] | 100 | I | 375 | 68.7 | 18.5 | — |

[a] In all experiments, 0.20 mole of tetralin was used. Unless otherwise noted, the lithium was added fairly rapidly, during 1 to 2 hr. [b] Percent excess over amount theoretically needed to reduce tetralin to octalin. [c] I, ethylenediamine distilled from sodium and poured into reaction flask; II, ethylenediamine distilled from sodium and then redistilled from sodium directly into apparatus; III, ethylenediamine as received; IV, diethylenetriamine. [d] No *cis*-decalin was formed in any reaction. [e] In these experiments, the tetralin, lithium, and ethylenediamine were mixed and allowed to react. In the other experiments, the lithium was added in portions, as given in the general procedure. [f] Lithium added in small portions during 5 hr.; each portion was allowed to react completely before the next was added. In experiment 7, which is otherwise identical, the lithium was added during 1 hr. [g] Reaction much slower than with ethylenediamine. Solution becomes dark red and then dark brown, but is never blue. [h] Reduction at a temperature of 130–140°. [i] Reduction at a temperature of 155–168°. [j] Sodium, 6–8 mm. shot. The reaction is much slower with sodium than with lithium, and the solution becomes dark brown and quite viscous. [k] In presence of 2.5 moles of ethanol per mole of tetralin.

tilled. (The reaction mixtures from the reductions of phenol and anisole were acidified to prevent any acidic organic materials from being lost in the alkaline aqueous portion.) The products were analyzed by infrared spectroscopy, supplemented in a few cases by ultraviolet or mass spectra.

Convenient quantities were found to be about 375 ml. (5.6 moles) of ethylenediamine,[5] 0.40 mole of a compound containing one double bond, or 0.20 mole of a compound containing two double bonds, and 1.60 moles of lithium, *i.e.*, twice as much lithium as is theoretically needed for the reduction. Since the reaction of lithium with amine to form hydrogen is competitive with the reduction, a better yield from a difficultly reducible compound might be obtained by increasing the amount of lithium still further; in such a case, more amine would probably be needed to prevent the mixture from becoming too viscous.

## RESULTS AND DISCUSSION

A study has been made of the reduction of tetralin by lithium in ethylenediamine in an attempt to find the best general conditions for the reaction, and also throw some light on the course of the reaction. The results are shown in Table 1 and the conclusions are summarized below:

1. The extent of reduction increases with an increase in the amount of lithium used. The reaction[6] between a mixture of tetralin, ethylenediamine, and lithium (in 10% excess over the amount theoretically required to reduce tetralin to the octalin stage) gives a 32.1 percent yield of $\Delta^{9,10}$-octalin.[7] Increasing the amount of lithium to 100% excess gives a 68.0 percent yield of octalin.

2. Addition of the lithium in portions increases the amount of reduction, giving both octalin and *trans*-decalin.[8] It seems probable that the increased amount of reduction in the portionwise addition of lithium is due to the metal having a better chance to react with the tetralin, rather than to become lost by reaction with the amine.

(5) Because of the corrosive nature and toxicity of ethylenediamine, all operations with it are carried out in a hood. The operator wears rubber gloves, at least up to the point where the ethylenediamine has been diluted with a large quantity of water. Since ethylenediamine will penetrate rubber, the gloves should be rinsed off frequently. These precautions are considered absolutely necessary.

(6) When tetralin and lithium are placed in ethylenediamine and the mixture stirred at room temperature, a very slow evolution of gas takes place at the surface of the lithium. When the mixture is heated to about 85°, however, a violent reaction takes place, with evolution of a considerable amount of hydrogen. It is apparently not possible to prepare a solution of lithium in ethylenediamine, because of the rapid formation of amide.

(7) For simplicity, these samples were analyzed (infrared spectra) as three component mixtures of tetralin, $\Delta^{9,10}$-octalin, and *trans*-decalin. Other octalins were present only in small amounts. We wish to thank Dr. R. A. Benkeser for a copy of the infrared spectrum of pure $\Delta^{9,10}$-octalin.

(8) No *cis*-decalin is found in any of the tetralin reductions. It is known that sodium-ammonia[9] and lithium-ethylamine[10] reduce acetylenes exclusively to *trans*-olefins. Lithium-ethylamine also can reduce tetralin to decalin, although in lower yield than does lithium-ethylenediamine; the configuration of the decalin formed was not reported.[3]

(9) G. W. Watt, *Chem. Revs.*, 46, 317 (1950).

(10) R. A. Benkeser, G. Schroll, and D. M. Sauve, Abstracts of Papers, 127th meeting, AMERICAN CHEMICAL SOCIETY, Cincinnati, Ohio, April 1955, page 21N; *J. Am. Chem. Soc.*, 77, 3378 (1955).

3. Addition of lithium at a very slow rate causes a decrease in the yield of reduced material.[11]

4. The yield of reduced material is decreased by the presence of impurities (water and carbonate) in the ethylenediamine. Thus, the use of twice-distilled amine, with complete exclusion of moisture, gives essentially the same results as does the use of once-distilled amine, with some exposure to atmospheric moisture. However, the use of one sample of unpurified amine (as received from the supplier), which may have contained as much as 5% of moisture and carbonate, gave a high yield of octalin, but no decalin. This loss of reductive power is thought to be due to loss of lithium by its reaction with water in the amine. (The use of a very large excess of lithium results in the formation of both octalin and decalin, even with unpurified amine.) Similarly, the presence of added ethanol reduces the proportion of decalin; this is probably caused by the ethanol using up some of the lithium, but having no other effect on the course of the reaction. It is known that in the case of the sodium-liquid ammonia system, addition of a material that can furnish protons, such as water or an alcohol, may materially change the course of the reaction.[9,13] With lithium in ethylenediamine, however, any protons needed for the reduction are probably supplied by the amine, in the absence of any added proton donor; addition of ethanol merely reduces the total amount of reduction by using up some of the lithium.

5. Diethylenetriamine is a poorer reagent for these reductions than is ethylenediamine. Increasing the reaction temperature from 130° to 155° appears to have little effect on the yield obtained with diethylenetriamine.

6. The sodium-ethylenediamine system is a much poorer reagent for reductions than is the lithium-ethylenediamine system. This parallels the findings of Wilds and Nelson,[14] who have shown that lithium in liquid ammonia is a better reducing system than sodium in liquid ammonia; it is also in accord with the work of Benkeser *et al.*,[3] who found that naphthalene gave only polymeric materials when treated with sodium-ethylamine.

Table II reports the reduction of a variety of compounds. It is noteworthy that phenol is reduced to a mixture of cyclohexanone and cyclohexanol.[15]

Anisole reacts vigorously, with gas evolution; the main product is phenol, together with small amounts of $\Delta^2$-cyclohexenone, cyclohexanone, cyclohexanol, cyclohexene, and cyclohexane. The primary reaction is apparently a rapid cleavage of the ether linkage to give methane and phenol; this is followed by a slower reduction of the phenol. Undoubtedly, the phenol would react further if more lithium were used. Similarly, the reaction of lithium and ethylenediamine with di-*n*-hexyl ether gives small amounts of hexanol and hexenes.[17]

Terminal acetylenes and both terminal and internal olefins are reduced to alkanes by lithium and ethylenediamine. In contrast, sodium in liquid ammonia reduces acetylenes to olefins,[9] does not reduce nonconjugated internal olefins at all,[9] and reduces terminal olefins only in the presence of a proton donor.[18] On the basis of the present work, the authors believe that it will be possible to reduce any double or triple carbon to carbon bond with lithium in ethylenediamine. Under conditions where a terminal olefin is not completely reduced, it is largely or entirely isomerized to internal olefins. Subsequent work[19] has shown that this isomerization is catalyzed by the amide $H_2NCH_2$-$CH_2\bar{N}HLi^+$. These reactions, and the corresponding lithium-ethylamine reactions,[10] are the first examples of chemical reduction of a nonconjugated internal olefin.

The other reductions shown in Table II require no comment, except to point out that each is the result of a single experiment.

It seems likely that lithium-ethylamine will prove useful for reduction of aromatic compounds to monoölefins, while lithium-ethylenediamine will be useful for complete saturation of ring systems and for reduction of difficultly reducible materials. Compared to other metal-amine systems, lithium-ethylenediamine appears to be the most powerful and the least selective. However, the high yield of octalin obtained in one experiment (Table 1) does suggest that it may be possible to find conditions under which lithium-ethylenediamine is selective in its action.

The metal-amine reactions with aromatic sys-

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(11) It has recently been shown[12] that some sodium-ammonia and lithium-ammonia reductions, which fail when the usual procedures are used, can be carried out successfully if the metal is added at a rate rapid enough to cause the separation of a bronze layer.

(12) W. F. Short, unpublished work; W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956). We wish to thank Professor Johnson for sending us a copy of his manuscript in advance of publication.

(13) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950).

(14) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

(15) The present work[1] is thought to be the first report of chemical reduction of a phenol. In subsequent work, Benkeser has found that phenol is reduced by the lithium-ethylamine system.[16]

(16) R. A. Benkeser, C. Arnold, R. F. Lambert, and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 6042 (1955).

(17) The ether cleavage is probably an elimination reaction catalyzed by the base $H_2NCH_2CH_2\bar{N}HLi^+$, which is formed by the reaction of lithium with the amine.

(18) H. Greenfield, R. A. Friedel, and M. Orchin, *J. Am. Chem. Soc.*, **76**, 1258 (1954).

(19) L. Reggel, S. Friedman, and I. Wender, Abstracts of Papers, 129th Meeting, AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 1956, page 10N.

TABLE II

REDUCTION OF VARIOUS COMPOUNDS BY LITHIUM IN ETHYLENEDIAMINE

| | Compound, Moles | Li per Mole Compound, Moles | Ethylenediamine, Ml. | Products | Yield Percent | Yield Recovered Starting Material |
|---|---|---|---|---|---|---|
| $\Delta^{9,10}$-Octalin[a] | 0.20 | 4.0 | 375 | *trans*-Decalin[b] | 36.9 | 55.4 |
| Phenanthrene | 0.05 | 14.4[c] | 200 | Decahydro- and dodecahydrophenanthrenes[d] | *ca.* 90 | 1.7 |
| Anthracene | 0.05 | 28.0 | 300 | Dodecahydro- and tetradecahydroanthracenes[e] | *ca.* 95 | — |
| Benzene | 0.30 | 4.8 | 375 | Cyclohexene | 51.0 | 21.6 |
| | | | | Cyclohexane | 1.4 | |
| Benzyl alcohol | 0.20 | 16.0 | 400 | Hexahydrobenzyl alcohol | 38.5 | — |
| Phenol | 0.30 | 14.0 | 400 | Cyclohexanone | 50.0 | 21.3 |
| | | | | Cyclohexanol | 5.5 | |
| | | | | Cyclohexane | Absent | |
| Anisole | 0.40 | 4.4 | 375 | Phenol | 53.9 | 0.2 |
| | | | | $\Delta^2$-Cyclohexenone | 6.5 | |
| | | | | Cyclohexanone | 1.6 | |
| | | | | Cyclohexanol | 1.1 | |
| | | | | Cyclohexene | 1.5 | |
| | | | | Cyclohexane | 1.6 | |
| Heptanone-3 | 0.30 | 4.0 | 375 | Heptanol-3 | 29.6 | 15.1 |
| Di-*n*-hexyl ether | 0.20 | 8.0 | 400 | Hexene-2 or -3 | 0.5 | 78.8 |
| | | | | Hexanol[f] | 8.4 | |
| Heptene-1 | 0.32 | 1.0 | 300 | Heptane | 41 | 32 |
| | | | | Heptene-2 | 13 | |
| Decene-1 | 0.30 | 2.4[c] | 150 | Decane | 47.2 | Absent |
| | | | | Decenes with internal double bond | 13.8 | |
| Heptene-2 | 0.40 | 4.0 | 375 | Heptane | 81.8 | |
| | | | | Heptene-1 | Absent | |
| | | | | Heptenes with internal double bond | 2.6 | |
| Heptyne-1 | 0.20 | 10.0 | 300 | Heptane | 50.9 | |
| | | | | Heptenes | Absent | |
| | | | | Heptyne | Absent | |
| Octene-1 | 0.40 | 3.0[g] | 375 | Octane | 84.8 | |
| | | | | Octenes with internal double bond | 3.4 | |
| Octene-1 | 0.40 | 3.0[h] | 375 | Octane | 76.5 | |
| | | | | Octenes with internal double bond | 12.5 | |

[a] Obtained by lithium reduction of tetralin and purified by distillation. Analyses (mass and infrared spectra) indicated 2.1 percent *trans*-decalin, 0.8 percent tetralin, and 97.1 percent octalins, primarily the $\Delta^{9,10}$-isomer. [b] No *cis*-decalin was formed. [c] In these experiments, the substrate, lithium, and ethylenediamine were mixed and allowed to react. In the other experiments, the lithium was added in portions, as given in the general procedure. [d] *Anal.* Calcd. for $C_{14}H_{20}$: C, 89.29; H, 10.71. Calcd. for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.29; H, 10.61. [e] *Anal.* Calcd. for $C_{14}H_{22}$: C, 88.35; H, 11.65. Calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.97; H, 11.87. [f] Isomer not determined. [g] Lithium added during 32 min. [h] Lithium added in small portions, during 5 hr. Each portion was allowed to react completely before the next was added.

tems have usually been regarded as taking place via 1,4-additions;[13] further reaction occurs only after the initial product has rearranged to a conjugated system. The reduction of the last remaining double bond, which can only be a 1,2-addition, either does not take place (metal-ammonia) or is slow (lithium-ethylamine). Reduction of an isolated double bond with lithium and ethylenediamine is a fast reaction. It is possible that 1,2- and 1,4-additions may take place concurrently in the initial stages. Since high yields of alkanes are obtained from straight chain olefins, the relatively low yield in the reduction of octalin may be due to the presence of a steric factor.

Wilds and Nelson[14] have discussed the superiority of lithium in liquid ammonia to sodium in liquid ammonia for the reduction of various compounds. Benkeser *et al.*[3] have pointed out "the potency and uniqueness" of the lithium-ethylamine combination in the reduction of aromatic hydrocarbons. In a similar way, lithium-ethylenediamine is superior to sodium-ethylenediamine.

*Acknowledgments.* We wish to thank Leonard Shufler and John Queiser for infrared analyses and Raphael Raymond for some of the reduction experiments.

BRUCETON, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

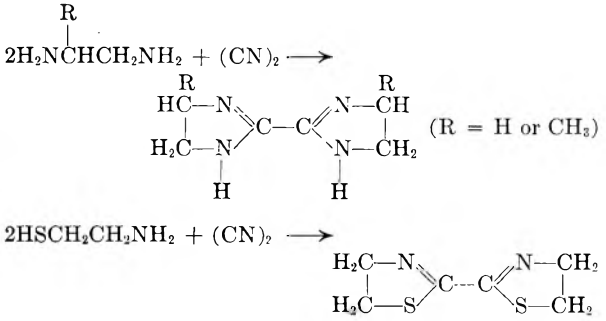
# Reaction of Cyanogen with Organic Compounds. X. Aliphatic and Aromatic Diamines[1]

HENRY M. WOODBURN AND JOHN R. FISHER[2]

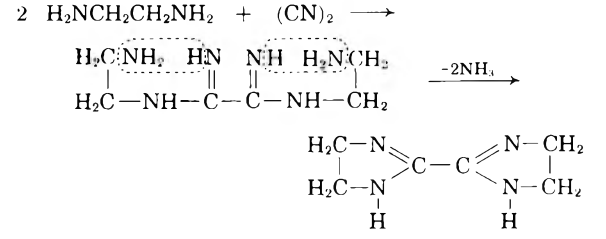
*Received January 14, 1957*

The cyanogenation of aliphatic and *para*-oriented aromatic diamines proceeds through an unstable oxamidine intermediate. This is followed by intramolecular loss of ammonia with the formation of a bicyclic product in those cases where the potential ring contains five or six members, and by intermolecular loss of ammonia to form a condensation polymer when the potential ring contains more than six members.

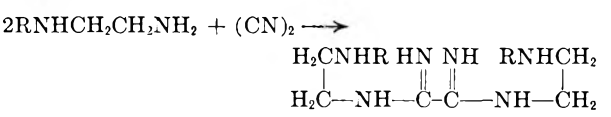
Several years ago, in the first papers resulting from a series of researches on the behavior of bifunctional compounds with cyanogen[3,4] we reported the formation of bicyclic products from ethylenediamine, 1,2-propanediamine and 2-mercaptoethylamine:




Since, with cyanogen, primary amines and mercaptans normally form oxamidines[5] and dithiooxaldiimidates[6] it seemed reasonable that the reaction might have proceeded by way of such an intermediate which then lost ammonia:




Support for this view was found in the fact that *N*-alkylethylenediamines produced symmetrically disubstituted oxamidines.[3] Here the structure precludes the loss of ammonia:




If this hypothesis is correct, from the series $H_2N(CH_2)_nNH_2$ only those compounds in which $n$ is 2 or 3 should form bicyclic products since from that point on all rings would exceed the stable five- or six-member type.

With the object of establishing the mechanism of the reaction we have, therefore, studied, or restudied, the reaction of cyanogen with the following compounds: ethylenediamine, 1,2-propanediamine, 1,3-propanediamine, 1,4-butanediamine, 1,5-pentanediamine, and 1,6-hexanediamine, and have established these facts:

(1) The formation of a bicyclic product from the cyanogenation of a diamine proceeds by the mechanism of an oxamidine intermediate.

(2) These intermediates are, in general, unstable as free bases but can be isolated as hydrochloride salts.

(3) When the oxamidine intermediate is such that the potential cyclic structure would have more than six atoms per ring, the reaction proceeds by intermolecular loss of ammonia with the formation of an insoluble polymer.

To facilitate isolation of the intermediate, the reaction conditions used by Woodburn and O'Gee[3] were altered to include a solvent for the diamine in which the potential oxamidine would probably be insoluble (usually ethyl ether or an ether-methanol mixture). As cyanogen was passed through the cold solution, an oil or white solid formed which settled to the bottom of the reaction flask. This was the oxamidine. The reaction could be terminated at this point by adding a solvent which would dissolve the oxamidine and passing in dry hydrogen chloride to precipitate the stable salt.

If the oxamidine was isolated as the free base, or if the original reaction mixture was allowed to stand, ammonia was evolved and either a bicyclic endproduct or a condensation polymer resulted.

A summary of the reactions and products follows:

(1) From the thesis submitted by John R. Fisher in partial fulfillment of the requirements for the Ph.D. degree, June 1956.

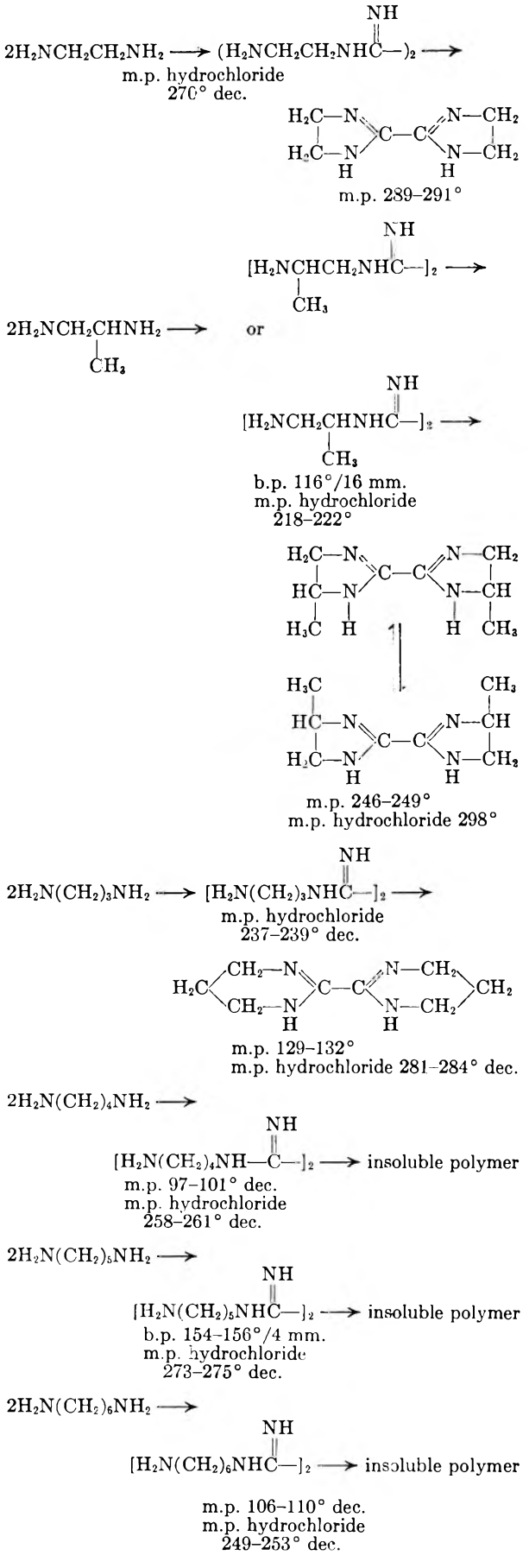
(2) Present address: Film Department, E. I. du Pont de Nemours and Co., Buffalo, N. Y.

(3) H. M. Woodburn and R. C. O'Gee, *J. Org. Chem.*, **17**, 1235 (1952).

(4) H. M. Woodburn and B. G. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

(5) H. M. Woodburn, B. A. Morehead and M. C. Chen, *J. Org. Chem.*, **15**, 535 (1950).

(6) H. M. Woodburn and C. E. Sroog, *J. Org. Chem.*, **17**, 371 (1952).

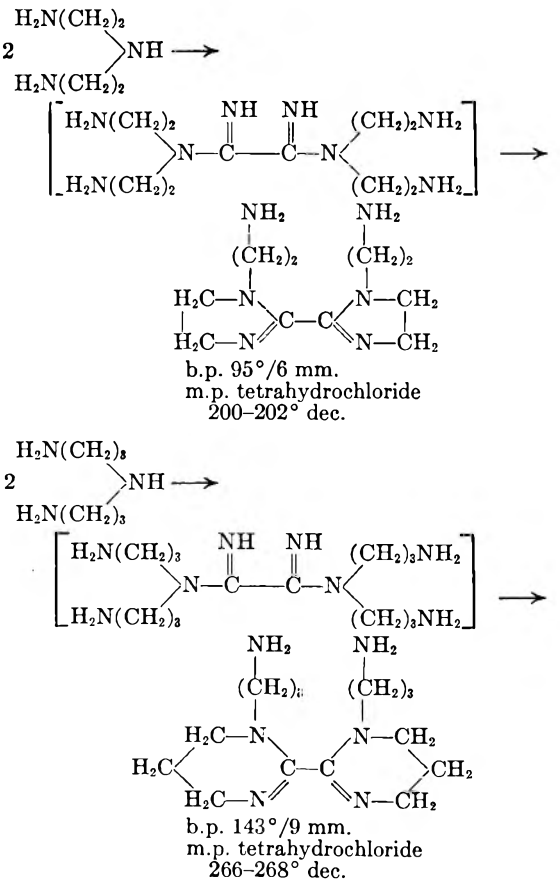



The insolubility of the polymers suggests that intermolecular loss of ammonia involved the $-NH_2$ group of one molecule and the $=NH$ group of a second since this would lead to crosslinking, rather than only $-NH_2$ groups of separate molecules which should produce a linear polymer.

Because of obvious relationships to the series above, four additional amines were investigated:

| | |
|---|---|
| (a) diethylenetriamine | $H_2N(CH_2)_2NH(CH_2)_2NH_2$ |
| (b) 3,3′-iminobispropylamine | $H_2N(CH_2)_3NH(CH_2)_3NH_2$ |
| (c) *p*-phenylenediamine | $H_2NC_6H_4NH_2$ |
| (d) benzidine | $H_2NC_6H_4C_6H_4NH_2$ |

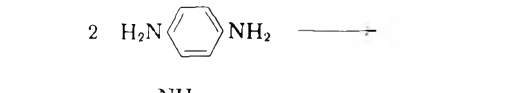
While the intermediates were too unstable to isolate, even as hydrochlorides, compounds (a) and (b) produced well defined products whose analyses corresponded to bicyclic structures. The odor of ammonia was noticeable during cyanogenation. Loss of ammonia and the formation of bicyclic compounds with stable rings could come about only by the following mechanism:




The formation of tetrahydrochlorides is in accord with results obtained previously[3] with bis-[$\Delta^2$-2-imidazolinyl]. Under the more rigorous conditions of heat and prolonged introduction of hydrogen chloride, however, hexachlorides were formed for which we have no plausible explanation although analyses leave no doubt of their composition.

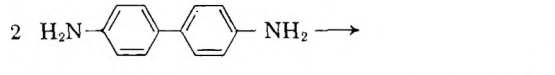
*p*-Phenylenediamine reacted with cyanogen in

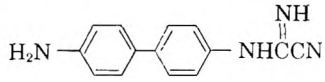
the manner of putrescine, cadaverine, and 1,6-hexanediamine. *Sym*-bis(4-aminophenyl)oxamidine was isolated. If the compound or its solution was heated, ammonia was evolved and a dark red solid soluble only in nitric or sulfuric acid resulted.



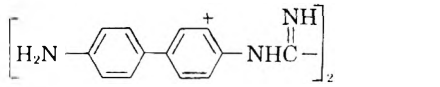
m.p. decomposes above 170°
hydrochloride and picrate
dec. on drying

Benzidine was unique among the amines investigated, in that both oxamidine and cyanoformamidine could be isolated.





m.p. decomposes 200°
m.p. hydrochloride
above 320°



m.p. decomposes 180°
hydrochloride and picrate
dec. on drying

While the oxamidine appeared to be stable at 105°, a solution in dimethylformamide heated to reflux slowly changed to a tarry mass.

## EXPERIMENTAL

*Reagents.* Cyanogen, prepared and purified by the method of Janz,[7] was frozen to a solid by passing the exit gas through a glass trap immersed in Dry-Ice-acetone mixture. When the trap was removed from the cooling bath the solid melted and vaporized at about the proper rate for cyanogenation. 1,3-Propanediamine and 1,5-pentanediamine (cadaverine) were prepared from the dibromo analogues by the method of Fischer and Koch.[8] 1,4-Butanediamine (putrescine) was prepared by the reduction of succinonitrile supplied by the American Cyanamid Company. Either sodium and ethanol or zinc and hydrochloric acid were used as the reducing mixture.[9] Ethylenediamine, 1,2-propanediamine, 1,6-hexanediamine, *p*-phenylenediamine and benzidine were purchased from Distillation Products Industries and purified by appropriate means. Diethylenetriamine was supplied by Union Carbide Chemicals Co. 3,3′-Iminobispropylamine was supplied by the American Cyanamid Company.

Melting and boiling points are uncorrected. Molecular weight determinations were made cryoscopically in glacial acetic acid, or ebullioscopically in ethanol using a modified Cottrell boiling point apparatus.

*Reactions with cyanogen.* With a few exceptions noted at the proper place, cyanogenations were carried out as follows: An appropriate weight of diamine, dissolved in ether or ether-methanol mixture was cooled to 0°. Cyanogen, vaporized from the cold trap, was passed through the solution until a cloudy, white mixture resulted which slowly became a light yellow oil layer at the bottom of the reaction vessel. To prevent tar formation, care was taken that the incoming cyanogen did not travel through the oil layer. When it appeared that the volume of oil was no longer increasing, cyanogenation was stopped.

*Reaction with ethylenediamine.* (a) *sym-Bis(2-aminoethyl)-oxamidine.* Since ethylenediamine is not very soluble in ethyl ether, the compound was first dissolved in methanol, cooled to 0°, and cold ether added until a slight cloudiness persisted. Methanol was then added dropwise until the mixture was again clear.

A solution approximately 20% in strength containing 19 g. of ethylenediamine was thus prepared and cyanogenated at 0°. A cloudy mixture formed immediately which separated into a light yellow oil at the bottom of the reaction vessel. The mixture was allowed to stand for 2 hr. at room temperature during which time a small amount of solid, later identified as bis($\Delta^2$-2-imidazolinyl), formed. The oil was then isolated by decantation and filtration and diluted to five times its volume with cold methanol. Dry hydrogen chloride was passed into the solution producing a white precipitate immediately.

The precipitated salt was filtered off periodically, six filter cakes of approximately the same size being obtained before salt formation was complete. The first three were combined as product; the last three were discarded because analysis for chlorine indicated an increasing amount of ethylenediamine dihydrochloride in successive filter cakes.

The product was recrystallized twice from ethanol giving white crystals melting at 207° with decomposition. Because of the method of recovery, no estimate of yield was made.

*Anal.* Calcd. for $C_6H_{16}N_6 \cdot 4HCl$: C, 22.7; H, 6.3; N, 26.4; Cl, 44.6. Found: C, 22.9; H, 6.3; N, 26.1; Cl, 44.8.

(b) *Bis($\Delta^2$-2-imidazolinyl).* Cyanogenation was carried out as above and the mixture allowed to stand 2 days. The solid which separated represented a 17% yield.

*Reaction with 1,2-propanediamine.* (a) *sym-Bis(2-aminopropyl)oxamidine* or *sym-bis(1-methyl-2-aminoethyl)oxamidine.* A solution of 20 g. of 1,2-propanediamine dissolved in 100 ml. of diethyl ether was cooled to 0° and cyanogenated as above. When the reaction mixture had stood for 1 day at room temperature, the oil was separated and distilled from a Claisen flask. The fraction boiling at 166°/16 mm. weighed 0.9 g., a 3.3% yield.

*Anal.* Calcd. for $C_8H_{20}N_6$: C, 48.0; H, 10.1; N, 41.9; mol. wt., 200.3. Found: C, 48.4; H, 9.7; N, 42.2; mol. wt. (Cryoscopic) 194.

The *tetrahydrochloride* was made by cyanogenating as above, dissolving the separated oil in methanol, and saturating with dry hydrogen chloride. The product, recrystallized from ethanol, was a white solid melting at 218–222° with decomposition.

*Anal.* Calcd. for $C_8H_{20}N_6 \cdot 4HCl$: C, 27.7; H, 7.0; N, 24.3; Cl, 41.0. Found: C, 27.4; H, 7.3; N, 24.1; Cl, 40.9.

(b) *Bis[$\Delta^2$-2-(4-methylimidazolinyl)].* Cyanogenation of 1,2-propanediamine was carried out as above and the mixture of the two layers was allowed to stand at room temperature in a closed flask.

At the end of 1 week a small amount of white solid had formed at the layer interface. This was filtered off and recrystallized from ethanol. It melted at 246–249° with decomposition, contained 33.4% nitrogen, and had a molecular weight of 169. Woodburn and O'Gee[3] reported a melting point of 246–250°, nitrogen 33.8%, and molecular weight 166.2 for bis[$\Delta^2$-2-(4-methylimidazolinyl)].

During seven months' standing the white solid which continued to form was filtered off periodically, ultimately representing a yield of 22%. It was converted to the *dihydrochloride* by dissolving it in an ether-ethanol mixture and saturating with dry hydrogen chloride. The white salt darkened at 194° and melted with decomposition at 298°.

*Anal.* Calcd. for $C_8H_{14}N_4 \cdot 2HCl$: C, 40.2; H, 6.7; N, 23.4; Cl, 29.7. Found: C, 40.0; H, 7.2; N, 23.5; Cl, 29.7.

(7) G. J. Janz, *Inorganic Synthesis*, **V**, in press.
(8) E. Fischer and H. Koch, *Ber.*, **17**, 1799 (1884).
(9) T. Fairley, *Ann.*, **Supplement 3**, 371 (1864).

The pure oxamidine resulting from a cyanogenation similar to (a) was allowed to stand at room temperature for 4 months. A small amount (0.04 g.) of white solid formed which was filtered, recrystallized from methanol, and analyzed for nitrogen. It contained 33.6% (theory, 33.8%) and melted at 244–249°.

*Reaction with 1,3-propanediamine.* (a) *sym-Bis(3-aminopropyl)oxamidine.* A solution of 20 g. of 1,3-propanediamine in 50 ml. of diethyl ether was cyanogenated as above. The reaction mixture was allowed to stand until a slight cloudiness appeared in the oil layer (25 min.). Hydrogen chloride was then passed in, the white precipitate filtered and recrystallized twice from ethanol. The yield was 11%.

*Anal.* Calcd. for $C_8H_{20}N_6 \cdot 4HCl$: C, 27.8; H, 7.0; N, 24.3; Cl, 41.0. Found: C, 27.5; H, 6.8; N, 24.5; Cl, 41.3.

(b) *Bis($\Delta^2$-2-pyrimidinyl).* Twenty grams of 1,3-propanediamine in 100 ml. of diethyl ether was cooled to 0° and cyanogenated. The mixture was placed in an ice bath and allowed to warm up slowly overnight. Ammonia was evolved and the lower layer changed from an oil to a light yellow solid. This was filtered and recrystallized from ethanol giving a white product melting at 129–132° with decomposition. The yield was 15%.

*Anal.* Calcd. for $C_8H_{14}N_4$: C, 57.8; H, 8.5; N, 33.7; mol. wt. 166.2. Found: C, 57.5; H, 8.8; N, 33.5; mol. wt. (ebullioscopic) 169.

The *dihydrochloride* was prepared by passing dry hydrogen chloride through a methanol solution of the free base. Recrystallization from ethanol gave a white solid melting at 281–284° with decomposition.

*Anal.* Calcd. for $C_8H_{14}N_4 \cdot 2HCl$: C, 40.2; H, 6.7; N, 23.4; Cl, 29.7. Found: C, 40.6; H, 6.8; N, 23.3; Cl, 29.4.

*Reaction with 1,4-butanediamine (putrescine). sym-Bis(4-aminobutyl)oxamidine.* This material decomposed so rapidly that a special method had to be devised to allow its isolation. An ether solution of cyanogen was prepared at 0° from 100 ml. of ether and 6.4 g. of cyanogen and placed in a cold buret. In a second buret was placed 100 ml. of a 5% ether solution of 1,4-butanediamine which had been cooled to −10° in a Dry-Ice chest. The two burets were arranged so as to deliver drops onto a glass rod which carried the liquid to a Buchner funnel. Where drops from the two solutions met, a white precipitate formed, which by this arrangement was almost immediately filtered from the solution. Throughout the reaction the precipitate was washed constantly with ether cooled to −40°. The entire process took 7 min.

The white solid was recrystallized from methanol, 0.6 g. being recovered (9% yield). It was unstable at room temperature and gave off ammonia. It melted between 97° and 101°.

*Anal.* Calcd. for $C_{10}H_{24}N_6$: C, 52.6; H, 10.6; N, 36.8. Found: C, 52.9; H, 10.1; N, 36.3.

The *tetrahydrochloride* was prepared by repeating the cyanogenation, dissolving the precipitate in cold methanol, and passing in dry hydrogen chloride. The salt was recrystallized twice from ethanol and melted at 258–261° with decomposition.

*Anal.* Calcd. for $C_{10}H_{24}N_6 \cdot 4HCl$: C, 32.1; H, 7.5; N, 22.5; Cl, 37.9. Found: C, 32.6; H, 7.8; N, 22.0; Cl, 38.0.

*Reactions with 1,5-pentanediamine (cadaverine). sym-Bis(5-aminoamyl)oxamidine.* A solution of 17 g. of 1,5-pentanediamine in 100 ml. of a 65–35 ether-methanol mixture was saturated with cyanogen at 0°. Since the oil layer did not separate after standing overnight, the mixture was distilled. A light yellow oil which boiled at 154–156°/4 mm. was recovered. The yield was only 1%. On standing the product decomposed with the evolution of ammonia.

*Anal.* Calcd. for $C_{12}H_{28}N_6$: C, 56.2; H, 11.0; N, 32.8; mol. wt. 256.4. Found: C, 55.9; H, 11.4; N, 33.3; mol. wt. (cryoscopic) 248.

The *tetrahydrochloride* was prepared by passing dry hydrogen chloride through the cyanogenation mixture which had stood overnight. The white precipitate was recrystallized from glacial acetic acid. It melted at 273–275° with decomposition.

*Anal.* Calcd. for $C_{12}H_{28}N_6 \cdot 4HCl$: C, 36.0; H, 8.0; N, 20.9; Cl, 35.3. Found: C, 36.0; H, 8.4; N, 20.5; Cl, 35.7.

*Reaction with 1,6-hexanediamine. sym-Bis(6-aminohexyl)oxamidine.* A solution of 50 ml. of 1,6-hexanediamine in 100 ml. of a 65–35 ether-methanol mixture was saturated with cyanogen at room temperature. The reaction mixture contained no oil layer; however, after standing overnight a tan-colored solid had precipitated. The yield was 38%.

Because of the relatively high yield, careful study could be made of the decomposition of this compound. When it was heated above 60° or, in solution, above 50°, it decomposed in a few hours into a reddish, resinous material, insoluble in organic solvents.

Twelve grams of the oxamidine was dissolved in 55 ml. of methanol by heating to boiling for less than 1 min. The solution was cooled, filtered and allowed to stand. After 3 weeks the solution had become a clear, firm gel which did not liquefy when heated.

Placed in an oven at 110° for three weeks, the oxamidine was converted to a shiny, black, very hard solid. The polymer was insoluble in water, methanol, ethanol, dioxane, ethyl acetate, acetonitrile, ligroin, petroleum ether, benzene, toluene, aqueous ammonia, acetic acid, concentrated hydrochloric acid, and strong sodium hydroxide solution. It was attacked by concentrated nitric and concentrated sulfuric acids.

Measurements were made of the ammonia evolved when the oxamidine was refluxed in methanol solution. The evolution was greatest during the first day, about half of that on the second day and one fourth as much on the third. Insoluble material began to appear on the second day.

To obtain a sample for analysis the crude oxamidine was dissolved in ethanol without allowing the temperature to rise above 40° and precipitated by the addition of acetone. After three reprecipitations it was dried overnight in a vacuum desiccator. The white solid melted at 106–110° with decomposition. A sample closed in a tube for several weeks had developed a distinct odor of ammonia when reopened.

*Anal.* Calcd. for $C_{14}H_{32}N_6$: C, 59.1; H, 11.3; N, 29.6; mol. wt., 284.4. Found: C, 59.0; H, 11.5; N, 29.2; mol. wt. (cryoscopic), 296.

The *tetrahydrochloride* was prepared by dissolving the free base in methanol and passing in dry hydrogen chloride. The white salt melted with decomposition at 249–253°. It appeared to be completely stable at room temperature.

*Anal.* Calcd. for $C_{14}H_{32}N_6 \cdot 4HCl$: C, 39.1; H, 8.4; N, 19.5; Cl, 33.0. Found: C, 38.8; H, 9.0; N, 19.0; Cl, 32.5.

*Reaction with diethylenetriamine. Bis[$\Delta^3$-1-(2-aminoethyl)-2-imidazolinyl].* Twenty grams of diethylenetriamine was dissolved in 100 ml. of diethyl ether and cyanogenated at 0°. A white solid formed immediately and at once began to decompose into a reddish, viscous oil which settled to the bottom of the reaction vessel. Fractionation under reduced pressure gave a 12% yield of almost colorless liquid boiling at 95°/6 mm.

*Anal.* Calcd. for $C_{10}H_{20}N_6$: C, 53.5; H, 9.0; N, 37.5; mol. wt., 224.3. Found: C, 53.1; H, 9.5; N, 37.3; mol. wt. (ebullioscopic), 231.

The *tetrahydrochloride* was produced by dissolving the oil in 60–40 methanol-ether mixture and passing dry hydrogen chloride into the cooled solution. The white salt melted at 200–202°.

*Anal.* Calcd. for $C_{10}H_{20}N_6 \cdot 4HCl$: C, 32.4; H, 6.5; N, 22.7; Cl, 38.3. Found: C, 32.4; H, 7.1; N, 22.8; Cl, 38.0.

By dissolving the oil in ethanol and passing in dry hydrogen chloride without cooling, the mixture became very warm and no precipitate formed until the hydrogen chloride had been passed in for 30 min. The white, solid product corresponded in analysis to a *hexahydrochloride.*

*Anal.* Calcd. for $C_{10}H_{20}N_6 \cdot 6HCl$: C, 27.1; H, 5.9; N, 19.0; Cl, 48.0. Found: C, 27.1; H, 6.3; N, 19.1; Cl, 47.8.

*Reaction with 3,3'-iminobispropylamine.* (a) *Bis[$\Delta^3$-1-(3-aminopropyl)-2-pyrimidinyl].* A solution of 10 g. of 3,3'-iminobispropylamine in 100 ml. of diethyl ether was cyanogenated at 0°. A white solid immediately formed and at once changed to a viscous oil. Fractionation gave a 30% yield of a liquid boiling at 143°/9 mm. which changed upon cooling to a pale yellow waxy solid.

*Anal.* Calcd. for $C_{14}H_{28}N_6$: C, 60.0; H, 10.1; N, 30.0; mol. wt. 280.2. Found: C, 59.8; H, 10.4; N, 29.9; mol. wt. (ebullioscopic) 270.

The *tetrahydrochloride* was prepared by dissolving the product from the reaction above in 70–30 methanol-ether mixture and passing in dry hydrogen chloride, keeping the solution in an ice bath during the precipitation. The white solid melted at 266–268° with decomposition.

*Anal.* Calcd. for $C_{14}H_{28}N_6 \cdot 4HCl$: C, 39.4; H, 7.6; N, 19.7; Cl, 33.3. Found: C 39.7; H, 7.1; N, 19.2; Cl, 33.4.

By dissolving the bispyrimidinyl in ethanol and allowing the temperature to rise while dry hydrogen chloride was passed in for 30 min., a white solid *hexachloride* was produced.

*Anal.* Calcd. for $C_{14}H_{28}N_6 \cdot 6HCl$: C, 33.7; H, 6.9; N, 16.8; Cl, 42.6. Found: C, 33.7; H, 7.2; N, 16.7; Cl, 42.9.

*Reaction with p-phenylenediamine. sym-Bis(p-aminophenyl)oxamidine.* A solution of 20 g. of *p*-phenylenediamine in 20 ml. of ethanol was cyanogenated at 0° with excess cyanogen. While standing overnight in the ice box a large amount of red, tarry material separated from the reaction mixture. This was filtered off and the filtrate mixed with water until a red precipitate formed. After filtration and drying in a vacuum desiccator, the solid was recrystallized from dimethylformamide, care being taken to keep the temperature below 40°. The yield was 28%. The solid was slightly soluble in ethanol, acetone, chloroform, diethyl ether, ethyl acetate, and dilute hydrochloric acid, very soluble in dimethylformamide, nitrobenzene, and dioxane, and insoluble in water, carbon disulfide, toluene, ligroin, and carbon tetrachloride.

It was kept in a vacuum desiccator for a week to rid it of traces of dimethylformamide before analysis.

*Anal.* Calcd. for $C_{14}H_{16}N_6$: C, 62.7; H, 6.0; N, 31.3; mol. wt. 268.3. Found: C, 62.8; H, 6.5; N, 31.1; mol. wt. (cryoscopic) 279.

The *hydrochloride* was prepared by dissolving the oxamidine in 1:1 dimethylformamide-ethanol mixture and passing in dry hydrogen chloride. The product decomposed on drying. This was also true of the *picrate.*

*Reaction with benzidine.* (a) *N-(cyanoformimino)benzidine.* Twenty grams of benzidine was dissolved in 100 ml. of methanol and the solution was cyanogenated at 0° (4.9 g. of cyanogen was absorbed). During 24 hr. standing in the ice chest a large amount of dark red solid had precipitated from the reaction mixture. This was filtered off [see (b) below] and the orange-colored filtrate mixed with water until a solid precipitated. This was recovered, dried in a vacuum desiccator, and recrystallized from methanol. The yield was 34%. The solid was soluble in methanol, ethanol, acetonitrile, dioxane, and dimethylformamide, insoluble in water, ligroin, petroleum ether, and dilute sodium hydroxide solution. It decomposed at about 200°.

*Anal.* Calcd. for $C_{14}H_{12}N_4$: C, 71.2; H, 5.1; N, 23.7; mol. wt., 236.3. Found: C, 70.9; H, 5.8; N, 23.9; mol. wt. (cryoscopic) 239.

The *dihydrochloride* was prepared by passing dry hydrogen chloride through a methanol solution of the base. It was a red solid melting at 315–317°.

*Anal.* Calcd. for $C_{14}H_{12}N_4 \cdot 2HCl$: C, 54.4; H, 4.6; N, 18.1; Cl, 22.9. Found: C, 54.0; H, 4.9; N, 18.6; Cl, 22.9.

(b) *sym-Bis-4-(4'-aminobiphenylyl)oxamidine.* The dark red solid filtered off from the original cyanogenation [see (a) above] was recrystallized twice from dimethylformamide without allowing the temperature to rise above 40°. The dark red, solid product was freed of solvent by storing it in a vacuum desiccator. It decomposed at 182°. It was slightly soluble in dilute hydrochloric acid, ethanol, ethyl acetate, acetic acid, acetone, acetonitrile, and dimethylformamide. It was insoluble in water, dilute sodium hydroxide solution, ether, and carbon tetrachloride. The yield of this product was 38%.

*Anal.* Calcd. for $C_{26}H_{24}N_6$: C, 74.3; H, 5.8; N, 20.0; mol. wt., 420.5. Found: C, 73.5; H, 6.0; N, 20.1; mol. wt. (cryoscopic), 440.

A *hydrochloride* and a *picrate* prepared from the dimethylformamide solution decomposed on drying.

A 5% methanol solution of the cyanoformamidine prepared above (a), was mixed with a 5% solution of benzidine in methanol and allowed to stand at room temperature for 2 weeks. A red-brown precipitate formed which was filtered and recrystallized twice from dimethylformamide without allowing the temperature to rise above 40°. The product corresponded to *sym-bis*-4-(4'-aminobiphenylyl)oxamidine in solubility and nitrogen analysis (19.6% found; 20.0% theory). Its hydrochloride was unstable.

BUFFALO, N. Y.

[CONTRIBUTION FROM MATERIALS LABORATORY, WRIGHT AIR DEVELOPMENT CENTER]

# Derivatives of Ferrocene. I. The Metalation of Ferrocene

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The metalation of ferrocene by means of *n*-butyllithium and mercuric acetate has been further investigated. The lithiation reaction has been extended for the preparation of trimethylsilylferrocene and 1,1′-di(trimethylsilyl)ferrocene. In the mercuration reaction, the ratio of starting materials has been varied in order to obtain optimum yields of either chloromercuriferrocene or 1,1′-dichloromercuriferrocene. Chloromercuriferrocene has been converted to diferrocenylmercury by means of dispersed sodium, sodium stannite, and sodium iodide in ethanol.

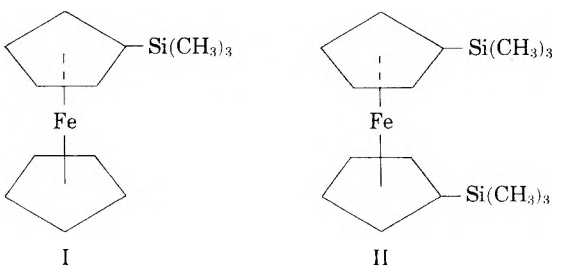
Since the discovery of ferrocene[1-3] in 1951, over one hundred technical publications have appeared in the literature concerning cyclopentadienylmetal compounds.[4] In this and subsequent papers we wish to report some new derivatives of ferrocene, as well as discuss the various synthetic methods by which substituted ferrocenes can be made.

One method for the preparation of ferrocene derivatives is by metalated intermediates. Benkeser, Goggin, and Schroll,[5] and Nesmeyanov *et al.*[6] have lithiated ferrocene using *n*-butyllithium to produce a mixture of mono- and dilithioferrocene. These metalated intermediates have been converted to carboxy,[5,6] triphenylsilyl,[5] and amino[7] derivatives. Nesmeyanov *et al.* have also mercurated ferrocene[6] and have converted the mercurated intermediates to bromo and iodo derivatives.[8]

The present investigation was undertaken to determine the usefulness of these two reactions as practical methods for the preparation of mono- and disubstituted derivatives of ferrocene; part of our results are discussed herein. Initial experiments were directed toward improving the yields of mono- and dilithioferrocene, these metalated derivatives being characterized by carbonation to the mixed mono- and dicarboxyferrocenes. In numerous experiments in which experimental conditions were varied, however, the total yield of mixed acids could not be increased to more than about 30%. These yields are consistent with the yields of ferrocene acids reported by the other investigators.[5,6]

Benkeser *et al.*[5] have also reported that the mixture of mono- and dilithioferrocene obtained from the reaction of ferrocene and *n*-butyllithium in ether reacts with triphenylchlorosilane to produce triphenylsilylferrocene and 1,1′-di(triphenylsilyl)-ferrocene. These two compounds were obtained in yields of 27% and 7%, respectively, or a total yield of 34%.

We have found that this reaction can also be applied to the synthesis of trialkylsilylferrocenes, and wish to report here the synthesis of trimethylsilylferrocene (I)[9] and 1,1′-di(trimethylsilyl)ferrocene (II). Both I and II were isolated as mobile, distillable, orange-red liquids, possessing mild odors. Both appeared to be completely stable in light and in air, in contrast to several low molecular weight alkyl derivatives of ferrocene.[10-12] The yields of I and II obtained were somewhat higher than the yields of carboxy- and triphenylsilylferrocenes obtained by this method. It is also interesting to note that more disubstituted product was obtained than monosubstituted product, in contrast to the above results.




I II

The infrared spectra of I and II were very

(1) T. J. Kealy and P. L. Pauson, *Nature*, **168**, 1039 (1951).

(2) S. A. Miller, J. A. Tebboth, and J. F. Tremaine, *J. Chem. Soc.*, 632 (1952).

(3) In this and subsequent papers from this laboratory, the generic name ferrocene will be used instead of the more formal dicyclopentadienyliron (II). Furthermore, the system of nomenclature as outlined by Rosenblum[10] has been adopted.

(4) For excellent reviews on the subject, see: E. O. Fischer, *Angew. Chem.*, **67**, 475 (1955); P. L. Pauson, *Quart. Revs. (London)*, **9**, 391 (1955).

(5) R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954).

(6) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Doklady Akad. Nauk SSSR*, **97**, 459 (1954).

(7) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and L. S. Shilovtseva, *Doklady Akad. Nauk SSSR*, **102**, 535 (1955).

(8) A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Doklady Akad. Nauk SSSR*, **100**, 1099 (1955).

(9) The structural configuration which is shown for ferrocene is used for convenience only; the exact nature of the bonding is still in dispute.[4]

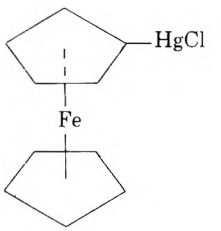
(10) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953.

(11) A. N. Nesmeyanov and N. A. Vol'kenau, *Doklady Akad. Nauk SSSR*, **107**, 262 (1956).

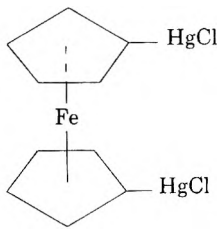
(12) M. Vogel, M. D. Rausch, and H. Rosenberg, unpublished results.

similar, the only notable difference being strong absorption bands at 9.00 and 9.95 $\mu$ in the spectrum of I. Both bands were totally absent in the spectrum of II. These results are in good accord with the data of Rosenblum[10] and of Pauson[13] who have found that the bands at 9.00 and 9.95 $\mu$ are present in both ferrocene itself and in derivatives in which only one cyclopentadienyl ring is substituted, but are absent in derivatives in which both rings are substituted. Among the absorption bands in both spectra were strong bands at 8.0 $\mu$, 13.2 $\mu$, and strong absorption from 11.6 to 12.4 $\mu$. These three regions of absorption may be assigned to $CH_3$—Si stretching and rocking vibrations.[14]

The mercuration of ferrocene in either ether-alcohol or benzene-alcohol has been reported by Nesmeyanov *et al.* to produce a mixture of both chloromercuriferrocene (III) and 1,1′-dichloromercuriferrocene (IV).[6] A study of this reaction indicates that the relative proportions of III and IV




III




IV

produced can be conveniently controlled by varying the ratio of the starting materials. Table I summarizes these results.

TABLE I

MERCURATION OF FERROCENE

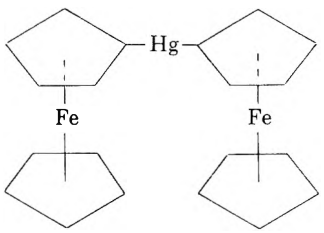
| $FeC_{10}H_{10}$, Moles | $Hg(OAc)_2$, Moles | MCl,[a,b] Moles | Yield of III, % | Yield of IV, % |
|---|---|---|---|---|
| 0.100[a] | 0.050 | 0.055 | 14 | 14 |
| 0.500[b] | 0.500 | 0.520 | 19 | 64 |
| 0.200[b] | 0.100 | 0.105 | 32 | 39 |
| 0.500[b,c] | 0.100 | 0.105 | 50 | 11 |

[a] Glacial acetic acid used as the solvent, M = K. [b] Ethyl ether-methanol used as the solvent, M = Li. [c] Extensive extraction with hot methanol was required to completely remove the unreacted ferrocene.

The mercuration of ferrocene to form III and IV can likewise be carried out in glacial acetic acid. This reaction requires no pressure vessel or additional high boiling solvent as does the well-known mercuration of benzene.[15,16] Under these conditions, however, some oxidation of ferrocene to the ferricinium ion, $(FeC_{10}H_{10})^+$, occurred, and the combined yield of III and IV was low. The use of ether-methanol as the solvent offers many advantages, avoiding oxidation of ferrocene and producing an excellent combined yield of III and IV. The facile formation and separation of these mercurated derivatives suggest them as useful intermediates in the preparation of additional ferrocene compounds in which either one or both cyclopentadienyl rings are substituted. Further studies along these lines are currently in progress in this laboratory.

The direct reaction of organomercury compounds with active halogen compounds such as alkyl halides, acid halides, *etc.*, has been reported in only a few instances to yield the desired derivatives,[17] these compounds being among the least reactive organometallics known.[18,19] Attempts to react III with acetyl chloride and trimethylchlorosilane in toluene solution were likewise not successful and considerable oxidation occurred. In both instances, insoluble blue solids separated which were identified as ferricinium salts by means of their solubility characteristics, reactions, and ultraviolet spectra.

In an attempt to *trans*-metalate III using dispersed sodium, several unexpected results were obtained. When III was reacted with a 10-molar excess of dispersed sodium (40% in *n*-nonane) diluted with benzene and the reaction mixture hydrolyzed at room temperature, quantitative yields of ferrocene were obtained. In a similar experiment in which the reaction mixture was first carbonated with a Dry Ice-ether mixture and then hydrolyzed, a 70% yield of diferrocenylmercury (V) was isolated. This result is not entirely anomalous, since both sodium and sodium amalgam have been reported to convert compounds of the type RHgX to the symmetrical $R_2Hg$ derivatives.[18] It was subsequently found that contact of the reaction mixture with Dry Ice ether was not necessary to obtain V; direct hydrolysis at the low temperatures afforded by this refrigerant produced comparable results. No carboxyferrocene was isolated from




V

(13) P. L. Pauson, *J. Am. Chem. Soc.*, 76, 2187 (1954).
(14) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, pp. 274–277, John Wiley and Sons, Inc., New York (1954).
(15) F. C. Whitmore, *Organic Compounds of Mercury*, pp. 35, 171, Chemical Catalog Co., New York (1921).
(16) K. A. Kobe and P. F. Lueth, *Ind. Eng. Chem.*, 34, 309 (1942).
(17) For example, see W. D. Schroeder and R. Q. Brewster, *J. Am. Chem. Soc.*, 60, 751 (1938).
(18) F. C. Whitmore, *Organic Compounds of Mercury*, pp. 38–84, Chemical Catalog Co., New York (1921).
(19) H. Gilman, *Organic Chemistry*, Vol. I, p. 550, John Wiley and Sons, Inc., New York (1943).

these reactions, indicating that probably *trans*-metalation did not occur.

In a manner analogous to other compounds of the type RHgX,[18,20] III reacted readily with a solution of sodium stannite to produce V in good yield. III also reacted rapidly with sodium iodide in ethanol, another reagent which is frequently used to convert RHgX compounds to $R_2Hg$ compounds.[18] In this reaction, two stable forms of V with different melting points were isolated.

Attempts to metalate ferrocene directly using either lithium metal in *n*-butyl ether or dispersed sodium in tetrahydrofuran were unsuccessful. In the latter reaction considerable destruction of ferrocene occurred, and small amounts of ferric oxide were isolated.

## EXPERIMENTAL[21]

*Lithiation of ferrocene and subsequent carbonation.* In general, the procedure followed was similar to that described by Benkeser, Goggin, and Schroll.[5] For example, in a typical experiment in which 0.123 mole of *n*-butyllithium in 175 ml. of anhydrous ethyl ether was reacted with 17.7 g. (0.095 mole) of ferrocene in 200 ml. of ether, 11.0 g. of ferrocene and 5.0 g. of the crude acid were obtained. The neutralization equivalent of the crude acid, determined potentiometrically in aqueous ethanol solution, was 196, indicating a mixture of about 3 parts carboxyferrocene to 1 part dicarboxyferrocene, assuming these are the only two acids present.

*Trimethylsilylferrocene* (I) *and 1,1'-di(trimethylsilyl)ferrocene* (II). A suspension of 139.5 g. (0.75 mole) of ferrocene in 1200 ml. of anhydrous ethyl ether (dried and distilled over sodium) was placed in a 3-liter, 3-necked flask, fitted with a stirrer, reflux condenser, addition funnel, and nitrogen inlet. Over a 1-hr. period was added 1000 ml. of a 1.55-molar solution of *n*-butyllithium in anhydrous ether. Following the addition, all the ferrocene appeared to be dissolved. The reaction mixture was then stirred under a nitrogen atmosphere for 44 hr. at room temperature, during which time an orange precipitate separated from the ether solution. With stirring, 163.0 g. (1.50 moles) of trimethylchlorosilane was added over a period of about 5 hr., in order to maintain gentle reflux. The reaction mixture was then refluxed for 15 hr., hydrolyzed with ice, and the aqueous and ether phases separated. The aqueous layer was extracted once with ether and the combined ether phase washed repeatedly with water to neutrality and dried over Drierite.

The ether was evaporated leaving a dark orange-red liquid and precipitated ferrocene. This mixture was chilled in a Dry Ice-acetone bath in order to freeze out as much ferrocene as possible, filtered, and the ferrocene washed with a little ether. After drying the ferrocene weighed 35.1 g., m.p. 173–174°. The filtrate was placed in a 500-ml. flask fitted with a 12-inch Vigreux column and warmed under a pressure of 0.1 to 0.2 mm. of mercury. After about 1 hr. additional unreacted ferrocene had sublimed onto the column. Atmospheric pressure was then restored and the column was removed, rinsed with acetone, dried, and replaced. This procedure was repeated several times until all the ferrocene appeared to have sublimed, and only refluxing liquid was observed. From the acetone washings an additional 6.5 g. of ferrocene was isolated, for a total recovery of 41.6 g.

The remaining liquid was fractionally distilled using a packed column and a distillation head equipped for total reflux. After initial separation into low and high boiling fractions, both fractions were redistilled through a 12-inch Vigreux column equipped with a straight take-off head.

Following redistillation, 36.9 g. (19% yield) of I was obtained as a dark orange-red mobile liquid possessing a mild cedar-like odor, b.p. 64–65° (uncorr.) at 0.045 mm. of mercury, m.p. 23°, $n_D^{25}$ 1.5696.

*Anal.* Calcd. for $C_{13}H_{18}SiFe$: C, 60.47; H, 7.03; Fe, 21.63; Si, 10.88. Found: C, 60.58, 60.69; H, 7.17, 7.17; Fe, 21.95, 21.69; Si, 10.64, 10.89.

The higher boiling fraction produced 66.5 g. (27% yield) of II, b.p. 87–88° (uncorr.) at 0.060 to 0.070 mm. of mercury, m.p. 16°, $n_D^{25}$ 1.5454. II was similar in appearance to I, although its odor was very faint.

*Anal.* Calcd. for $C_{16}H_{26}Si_2Fe$: C, 58.16; H, 7.93; Fe, 16.90; Si, 17.00. Found: C, 58.50, 58.13; H, 7.97, 7.98; Fe, 16.63, 16.60; Si, 16.80, 16.82.

*Chloromercuriferrocene* (III) *and 1,1'-di(chloromercuri)ferrocene* (IV). (*A*) *Methanol-ethyl ether as the solvent.* In general, modifications of the procedure described by Nesmeyanov *et al.*[6] were used, by varying the ratio of the reactants as illustrated in Table I. III was obtained in the form of golden-yellow leaflets, m.p. 193–194°, with decomp. (lit.[6] m.p. 194–196°). IV was isolated as a yellow powdery solid which did not melt at temperatures up to 300°. When heated at elevated temperatures over a period of time, however, slow decomposition was observed with ferrocene subliming on the tube.

(*B*) *Glacial acetic acid as the solvent.* A solution of 18.6 g. (0.10 mole) of ferrocene in 400 ml. of glacial acetic acid was heated to reflux, and a solution of 15.9 g. (0.05 mole) of mercuric acetate in 100 ml. of hot glacial acetic acid was added with stirring over a period of 1.25 hr. Following the addition the reaction mixture was refluxed for 0.5 hr. and then stirred for 16 hr. at room temperature. After filtering from a small amount of metallic mercury which had separated (0.4 g.), the filtrate was mixed with a solution of 4.1 g. (0.055 mole) of potassium chloride in 100 ml. of a 1:1 mixture of ethanol and water. A brown solid separated (A), which was washed with benzene to remove ferrocene; after drying the solid weighed 9.5 g.

The blue acidic filtrate was diluted with 500 ml. of water and a yellow solid separated, which after filtering, washing with water, and recrystallizing from cyclohexane produced a small amount of ferrocene. The filtrate was stirred with 50 g. of powdered zinc for about 2 hr. during which time the blue color was discharged. Extraction with benzene and removal of the solvent produced an additional 1.4 g. of ferrocene. From A, both III and IV were obtained by recrystallization from hot 1-butanol. The total amount of III isolated was 3.0 g., m.p. 192–193°, with decomp., or a yield of 14%. The total amount of IV isolated was 2.2 g., or a total yield of 14%.

*Attempted reaction of III with trimethylchlorosilane.* To a warm solution of 2.1 g. (0.005 mole) of III in 100 ml. of toluene (dried over sodium) was added 5.4 g. (0.05 mole) of trimethylchlorosilane. The reaction mixture was stirred under a nitrogen atmosphere for 3 hr. at 70°. During this period the solution darkened and a blue solid separated. The reaction mixture was diluted with 100 ml. of cold water and filtered. The light blue solid which was collected was washed with water and with toluene and dried, weighing 1.2 g. This solid was insoluble in common organic solvents, only slightly soluble in water, and was moderately soluble in dilute hydrochloric acid, forming a blue solution. The blue color was readily discharged upon addition of an excess of sodium hydroxide solution. The ultraviolet spectrum of a small sample in dilute hydrochloric acid was similar to that reported for the ferricinium ion.[10] From the toluene layer 0.7 g. of ferrocene was recovered.

A similar experiment was carried out using acetyl chloride in place of trimethylchlorosilane. In this reaction also,

(20) J. L. Maynard, *J. Am. Chem. Soc.*, **46**, 1510 (1924).

(21) All melting points and boiling points are corrected unless otherwise noted. Analyses were made by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

a similar blue solid was isolated and ferrocene was recovered.

*Reaction of III with dispersed sodium. (A). Isolation of ferrocene.* In a 3-necked 250-ml. flask was placed 2.9 g. (0.05 mole) of sodium dispersion (40% in *n*-nonane), and the dispersion diluted with 50 ml. of benzene (dried over sodium). With stirring and under a nitrogen atmosphere, 2.1 g. (0.005 mole) of III in 100 ml. of warm dried benzene was added over a period of 15 min., and the reaction mixture stirred at 25° for 3.5 hr At the end of this period 35 ml. of 95% ethanol was cautiously added, followed by 50 ml. of water. The hydrolyzed mixture was filtered with suction and washed thoroughly with hot water and with benzene. The residue which remained (0.82 g.) appeared to be a gray powder containing small globules of mercury. The filtrate was separated into layers, the aqueous phase extracted with benzene, the combined benzene portion washed with water, and then the benzene solution dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent left 0.92 g. (99% yield) of ferrocene, m.p. 171–174° (uncorr.).

(*B*). *Isolation of diferrocenylmercury* (V). The apparatus and quantities of reactants were the same as outlined in (A). After stirring at 25° for 3.5 hr., the reaction mixture was poured onto a mixture of Dry Ice and ether. After cautious hydrolysis with 95% ethanol and with water, the mixture was vacuum-filtered. The aqueous and benzene phases were separated, and the benzene phase washed and dried over anhydrous magnesium sulfate. Removal of the solvent by evaporation left a yellow-orange solid. This solid and the initially insoluble material were extracted with a small quantity of boiling xylene, filtered, and the filtrate cooled to produce 1.0 g. (70% yield) of orange crystals of V, m.p. 235–236°, with decomp. (lit.[6] m.p. 233–234°). Acidification of the basic aqueous phase produced no trace of solid acidic material.

When the above reaction was carried out at 50° instead of 25°, carbonation and hydrolysis produced some V and some light yellow powdery solid which was insoluble in hot xylene and in dilute potassium hydroxide solution, but which did react with hydrochloric acid to give a blue solution. Acidification of the aqueous layer produced a trace of insoluble yellow material.

*Reaction of III with sodium stannite.* To a suspension of 2.1 g. (0.005 mole) of III in 20 ml. of 95% ethanol and 50 ml. of water was added a solution of sodium stannite, previously prepared by mixing 5.0 g. of sodium hydroxide in 25 ml. of water with 1.8 g. of stannous chloride dihydrate in 25 ml. of water. The yellow-orange color was immediately discharged and a gray-black solid separated. After stirring for 3 hr., the mixture was vacuum filtered, the solid washed well with water, dried, and digested with a little boiling xylene. The residue consisted of a dark gray solid containing globules of mercury. Upon cooling the xylene solution, 1.0 g. (70% yield) of V separated as yellow-orange crystals, m.p. 230–233° (uncorr.). Recrystallization from xylene raised the melting point to 234–235°, with decomp.

*Reaction of III with sodium iodide in ethanol.* A mixture of 600 ml. of 95% ethanol, 10.5 g. of sodium iodide, and 2.1 g. (0.005 mole) of III was refluxed for 2 hr. After filtering the hot mixture a yellow-orange solid separated, m.p. 215–225° (uncorr.). Two recrystallizations from xylene produced 0.9 g. (64% yield) of V, m.p. 235–236°, with decomp. Upon cooling and concentrating the ethanolic filtrate there was obtained 0.5 g. (35% yield) of an orange crystalline solid, m.p. 245–248°. Recrystallization from xylene produced a second form of V, m.p. 248–249°, with decomp.

*Anal.* Calcd. for $C_{20}H_{18}Fe_2Hg$: C, 42.09; H, 3.18; Fe, 19.57; Hg, 35.16. Found: C, 42.01, 41.99; H, 3.28, 3.15; Fe, 19.46, 19.41; Hg, 35.10, 35.24.

In two additional experiments both forms of V were obtained in each case. The infrared spectra of both forms of V (mulls in Nujol) were completely identical.

*Acknowledgment.* The authors wish to express their appreciation to Mr. F. F. Bentley and Mrs. N. E. Srp for the infrared spectra. We are also very grateful to Dr. Eric Barthel of the E. I. du Pont de Nemours and Co., Inc., and to Dr. Roy Pruett of the Linde Co., for generous samples of ferrocene which have been used in our research program.

WRIGHT-PATTERSON AIR FORCE BASE, OHIO

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[CONTRIBUTION FROM MATERIALS LABORATORY, WRIGHT AIR DEVELOPMENT CENTER]

# Derivatives of Ferrocene. II. Some Reduction Products of Benzoylferrocene and 1,1′-Dibenzoylferrocene[1]

MARVIN RAUSCH, MARTIN VOGEL, AND HAROLD ROSENBERG

*Received January 15, 1957*

The reduction of benzoyl- and 1,1′-dibenzoylferrocene to benzyl- and 1,1′-dibenzylferrocene has been accomplished by either catalytic hydrogenation or by reduction with sodium and ethanol. 1-Hydroxybenzylferrocene has been prepared by the sodium borohydride reduction of benzoylferrocene, while the reduction of 1,1′-dibenzoylferrocene with lithium aluminum hydride has produced 1,1′-di(1-hydroxybenzyl)ferrocene. The action of a number of other reducing agents on these aryl ferrocenyl ketones is discussed.

In the Friedel-Crafts reaction of ferrocene, benzoyl chloride, and aluminum chloride, both benzoylferrocene (I)[2,3] and 1,1′-dibenzoylferrocene (II)[2,4,5] have been reported to be formed. We have further investigated this reaction and have found that by varying the method of addition and the molar ratio of the reactants, both I and II can be prepared in

(1) Presented in part at the 131st Meeting of the AMERICAN CHEMICAL SOCIETY, Miami, Fla., April 7 to 12, 1957; see Abstracts of Papers, p. 47-O.

(2) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953 (see Appendix).

(3) N. Weliky and E. S. Gould, New York Section, AMERICAN CHEMICAL SOCIETY, Meeting in Miniature, March 16, 1956.

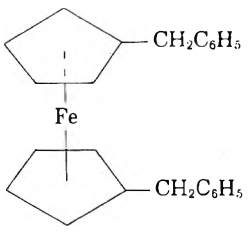
(4) R. Riemschneider and D. Helm, *Ber.*, 89, 155 (1956).

(5) A. N. Nesmeyanov and N. A. Vol'kenau, *Doklady Akad. Nauk SSSR*, 107, 262 (1956).

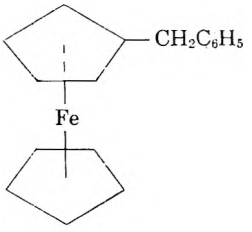
yields more satisfactory than any thus far reported.

Although Csendes[2] has reported the preparation of benzoylferrocene oxime, our attempts to prepare oximes, phenylhydrazones, and *p*-nitrophenylhydrazones by the usual methods were not successful. By resorting to more drastic conditions, however, both benzoylferrocene oxime and 1,1′-dibenzoylferrocene dioxime were obtained.

The Clemmensen reduction has successfully been applied to the preparation of ethyl-,[5,6] *n*-propyl-,[5] *n*-butyl-,[5] and long chain alkylferrocenes[7] from the corresponding ketones, as well as to the preparation of 1,1′-dibenzylferrocene (III)[5] from II. The reduction of I by the Clemmensen method proceeded anomalously, however. Upon extensive refluxing, a small yield of the expected product, benzylferrocene (IV), was obtained, although the




III




IV

primary reduction product was an as yet unidentified high melting orange-red solid (V). In several experiments V was the only product isolated from the reaction.

The reaction of I with the binary mixture, magnesium–magnesium iodide, has been carried out in this laboratory and elsewhere[3] to produce small yields of a reduction product (VI) similar in appearance and properties to V. The ultraviolet and visible spectra of V and VI are completely identical, while the infrared spectra are very nearly identical.

It was initially suspected that the reduction products V and VI were the *sym*-pinacol, since the magnesium–magnesium iodide mixture is commonly used for the preparation of pinacols from aromatic ketones[8,9] and the Clemmensen reduction of aromatic ketones occasionally produces pinacols rather than hydrocarbons.[10] Numerous elemental analyses of both V and VI have indicated, however, that only carbon, hydrogen, and iron are present, eliminating the possibility of a pinacol or other oxygen-containing compound. The structures of V and VI are currently being investigated and detailed information will be published later.

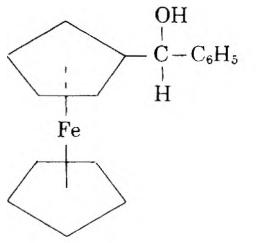
Attempts to reduce II using magnesium–magnesium iodide in ethyl ether–benzene solution either at room temperature or at reflux resulted in the formation of an insoluble complex, and after hydrolysis only starting ketone could be recovered. Preliminary experiments indicate that reduction of II does occur when solvents capable of producing higher temperatures are used.

While I did react with magnesium–magnesium iodide, it failed to undergo two other reactions which are commonly used to reduce aromatic ketones to bimolecular derivatives.[11–13] When I was stirred several days at 25° with powdered zinc and glacial acetic acid, only starting ketone was recovered. In an attempted photochemical reduction of I in 2-propanol, nearly all the ketone was recovered after 10 days exposure to sunlight, and only a very small amount of insoluble material resulted. This appeared to contain mostly iron oxide together with a trace of carbonaceous material. It has since been observed in this laboratory that certain derivatives of ferrocene in hydroxylic solvents are subject to photochemical decomposition. In a control photochemical experiment using benzophenone, a 97% yield of benzopinacol was obtained.

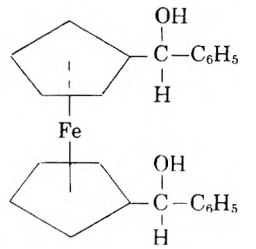
Both I and II could be reduced to the corresponding hydrocarbons IV and III by either catalytic hydrogenation or by "chemical" hydrogenation using sodium and ethanol. Although both reactions proceeded smoothly, the latter was more rapid and produced much better yields.

It has been reported[3] that the reaction of I with aluminum isopropoxide in isopropanol produced 1-propoxybenzylferrocene. In a similar experiment in which the reaction was carried out at higher temperatures using xylene as the solvent, we isolated a small yield of IV. In only one other case has the reduction of a ketone by aluminum isopropoxide been reported to yield a hydrocarbon, namely, the reduction of 9,9-dimethylanthrone-10 in xylene solution to 9,9-dimethyl-10,10-dihydroanthracene.[14]

The reduction of I with sodium borohydride in aqueous methanolic solution proceeded smoothly to produce the expected carbinol, 1-hydroxybenzylferrocene (VII). II was likewise reduced readily




VII




VIII

(6) F. S. Arimoto and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **77**, 6295 (1955).

(7) M. Vogel, M. D. Rausch, and H. Rosenberg, unpublished results.

(8) M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

(9) M. D. Rausch, W. E. McEwen, and J. Kleinberg, *Chem. Revs.*, in press.

(10) R. C. Fuson, *Advanced Organic Chemistry*, John Wiley and Sons, Inc., New York (1950), p. 361.

(11) W. E. Bachmann and F. H. Moser, *J. Am. Chem. Soc.*, **54**, 1124 (1932).

(12) R. P. Zelinski and M. Jurisch, *J. Am. Chem. Soc.*, **78**, 1015 (1956).

(13) W. E. Bachmann, *Org. Syntheses*, **Coll. Vol. II**, 71 (1943).

(14) A. L. Wilds, *Org. Reactions* **II**, 178 (1944).

with lithium aluminum hydride in ether-benzene solution, and the tarry residue which resulted was purified to yield 1,1′-di(1-hydroxybenzyl)ferrocene (VIII).

## EXPERIMENTAL[15]

*Benzoylferrocene* (I). I was best prepared by the dropwise addition of a solution of equimolar quantities of benzoyl chloride and aluminum chloride to an equimolar quantity of ferrocene, using methylene chloride as the solvent. After hydrolysis and product workup, 70–75% yields of dark red needles of I were obtained by recrystallization from methanol, m.p. 108.1–108.3° (lit.[2] 111.5–112.0°). Extensive refluxing following the addition usually resulted in lower yields of I accompanied by increased amounts of tars.

*1,1′-Dibenzoylferrocene* (II). A modification of the procedure already reported[4] was adopted by adding the ferrocene in methylene chloride solution to slightly greater than two equivalents each of benzoyl chloride and aluminum chloride in the same solvent. In this manner, 81–91% yields of II were obtained in the form of purple needles, m.p. 106.5–106.7° (lit.[4] 105–106°).

*1,1′-Dibenzoylferrocene dioxime.* A solution of 2.0 g. of II, 4.0 g. of hydroxylamine hydrochloride, and 16.0 g. of potassium hydroxide in 100 ml. of 95% ethanol was refluxed for 4 hr. The reaction mixture was poured into 400 ml. of water and acidified with dilute hydrochloric acid. A yellow solid weighing 1.8 g. separated, m.p. 164–165° (uncorr.), with decomp. After several recrystallizations from methanol and water, the dioxime was collected in the form of golden-yellow crystals, m.p. 172–173°, with dec.

*Anal.* Calcd. for $C_{24}H_{20}FeN_2O_2$: C, 67.94; H, 4.75; Fe, 13.16; N, 6.60. Found: C, 68.12, 68.07; H, 4.65, 4.75; Fe, 12.86, 12.90; N, 6.36, 6.48.

*Benzoylferrocene oxime.* In a manner similar to the preparation of the dioxime, benzoylferrocene oxime was obtained as golden-yellow crystals, m.p. 159.6–160.0° (lit.[2] 160°).

*Reduction of I by the Clemmensen method.* A mixture of 60 g. of zinc dust, 4.5 g. of mercuric chloride, 3 ml. of concentrated hydrochloric acid and 75 ml. of water were stirred for 10 min. in a 1000-ml., 3-necked flask fitted with stirrer and reflux condenser. The aqueous phase was removed by a pipet and the amalgamated zinc was covered with 30 ml. of water, 60 ml. of concentrated hydrochloric acid and 100 ml. of toluene. There was then added 17.4 g. (0.06 mole) of I and the mixture was stirred under reflux for 72 hr. During this period, five 25-ml. portions of concentrated hydrochloric acid were added occasionally in order to replenish the concentration of acid. Upon cooling to room temperature an appreciable amount of yellow solid had separated, and the reaction mixture was filtered and extracted with hot toluene. The combined toluene portion was washed to neutrality with water and dried over anhydrous magnesium sulfate. The solid which remained after evaporation of the solvent was extracted with 200 ml. of hot methanol, the methanol solution was concentrated, and water was added to the cloud point. Upon cooling, 3.7 g. of benzylferrocene (IV) separated. IV was recrystallized from ethanol and water and was isolated as yellow crystals, m.p. 73–74° (lit.[16] 76°).

The methanol insoluble portion was recrystallized several times from either xylene and heptane, cyclohexane, or *n*-heptane to produce 5.0 g. of an orange-red solid (V). V did not melt when a melting point determination was made in the usual manner, but did slowly decompose when heated above 250°.

*Anal.* Found: C, 74.26, 74.38; H, 5.35, 5.13; Fe, 19.88, 19.92.

When the above reaction was carried out using less ketone and a shorter time of reaction, V was the only reduction product isolated.

*Reduction of I by the binary mixture, magnesium–magnesium iodide.* To a mixture of 1.7 g. (0.070 g. atom) of powdered magnesium in 50 ml. of ethyl ether and 50 ml. of dried benzene was added 5.6 g. (0.022 mole) of iodine with stirring. After the first few iodine crystals had been added the reaction mixture was warmed to initiate the reaction, which proceeded exothermically thereafter. After about 30 min. the reaction was complete and the mixture was nearly colorless. To this mixture was added 9.3 g. (0.032 mole) of I in 50 ml. of benzene. A deep violet color formed immediately upon contact of the ketone with the mixture, reminiscent of the color of the metal ketyls reported by Gomberg and Bachmann[3] and later workers. After shaking on a mechanical shaker overnight, the reaction mixture was hydrolyzed with 300 g. of ice containing 25 ml. of concentrated hydrochloric acid. The ether-benzene layer was washed with dilute sodium bicarbonate solution, dilute sodium bisulfite solution, water, and dried overnight over Drierite. The solvent was evaporated and the solid residue was extracted with 150 ml. of hot methanol. From the methanol extracts, 7.3 g. of crude I was obtained, m.p. 102–108° (uncorr.).

The methanol insoluble material was recrystallized several times from hot *n*-heptane to produce 0.7 g. of VI. VI was obtained as fine orange-red crystals, which did not melt but slowly decomposed at elevated temperatures.

*Anal.* Found: C, 74.35, 74.28; H, 5.08, 5.25; Fe, 19.92, 20.06.

*Catalytic hydrogenation of I.* In a 500-ml. hydrogenation bottle were placed 8.70 g. (0.03 mole) of I, 1.0 g. of 5% platinum on charcoal, and 250 ml. of redistilled 1-butanol. The mixture was placed on a Parr hydrogenation apparatus under a pressure of 35 psi.; after about 30 hr. a theoretical uptake of hydrogen was noted. The catalyst was filtered and the butanol solution was concentrated almost to dryness. Several recrystallizations of the residue from ethanol and water produced 5.8 g. (70% yield) of IV in the form of yellow leaflets, m.p. 72–73°.

*Catalytic hydrogenation of II.* A mixture of 11.8 g. (0.03 mole) of II, 2.0 g. of 5% platinum on charcoal and 250 ml. of redistilled 1-butanol was hydrogenated as described above under a pressure of 65 psi. After 17 hr. a theoretical hydrogen uptake was noted and the catalyst was filtered. Removal of the solvent and several recrystallizations of the residue from hot methanol produced long yellow needles of III weighing 5.4 g. (68% yield), m.p. 97–98° (lit.[16] 102°).

*Reduction of I by sodium and ethanol.* A mixture of 1.50 g. (0.0052 mole) of I and 50 ml. of absolute ethanol was warmed to about 60° during which time all the ketone dissolved. With stirring, about 5 g. of small clean chunks of sodium metal was added at such a rate as to maintain the reaction temperature between 60° and 70°. During the addition the reaction mixture changed from a red color characteristic of the ketone to a thick yellow-orange solution. Following addition of all of the sodium, 25 ml. of additional ethanol was added and the solution was stirred at room temperature for an additional hour. Water was then added until the solution became cloudy, and the solution was cooled. After filtering and drying, 1.40 g. (98% yield) of yellow leaflets of IV was collected, m.p. 72–73°. One recrystallization from ethanol and water raised the melting point to 73.5–74.0°.

*Anal.* Calcd. for $C_{17}H_{16}Fe$: C, 73.93; H, 5.85; Fe, 20.22. Found: C, 74.07, 74.01; H, 6.06, 6.08; Fe, 20.11, 20.36.

In another experiment, a 95% yield of IV was obtained by this procedure.

*Reduction of II by sodium and ethanol.* In a manner similar

(15) All melting points are corrected unless otherwise noted. Analyses were made by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(16) B. F. Hallam and P. L. Pauson, *J. Chem. Soc.*, 3030 (1956).

to that described for the reduction of I, about 7.5 g. of sodium was added to a solution of 2.00 g. (0.0051 mole) of II in 75 ml. of absolute ethanol at 60–70°. Following addition of the sodium, 25 ml. of additional ethanol was added to the thick yellow solution and the mixture was stirred for 1 hr. at room temperature. Water was added and the yellow crystals which separated were dried and recrystallized from hot ethanol. Long yellow needles of III were obtained weighing 1.00 g., m.p. 105–106°. From the methanol mother liquor an additional 0.49 g. of III was recovered, for a total yield of 80%.

*Anal.* Calcd. for $C_{24}H_{22}Fe$: C, 78.70; H, 6.06; Fe, 15.24. Found: C, 78.40, 78.35; H, 6.16, 6.16; Fe, 15.05, 15.02.

A mixed melting point test of a sample of III prepared above and a sample obtained by means of catalytic hydrogenation melted intermediate between the two melting points. The infrared spectra of the two samples were identical.

In another experiment, a 72% yield of III was obtained by this procedure.

*Reduction of II by lithium aluminum hydride.* To a slurry of 1.52 g. (0.04 mole) of powdered lithium aluminum hydride in 250 ml. of ether was added 11.8 g. (0.030 mole) of II in 150 ml. of benzene and 50 ml. of ether over a 1 hr. period. The reaction mixture was refluxed with stirring for 16 hr., cooled, and moist ether followed by dilute ammonium chloride solution was added. After filtering, the ether phase was washed with water and dried over Drierite. The solvent was evaporated leaving a dark viscous oil which was induced to crystallize by dissolving it in hot methanol and rapidly cooling in a Dry Ice-acetone bath. Seven g. of a yellow solid was thus obtained, m.p. 115–125° (uncorr.). After repeated crystallization from either methanol or ethanol, 5.0 g. of VIII was obtained in the form of yellow leaflets, m.p. 136–137°.

*Anal.* Calcd. for $C_{24}H_{22}FeO_2$: C, 72.37; H, 5.57; Fe, 14.02. Found: C, 72.42, 72.62; H, 5.85, 5.86; Fe, 14.04, 14.04.

*Reduction of I by sodium borohydride.* To a solution of 2.90 g. (0.01 mole) of I in 80 ml. of methanol was added 3.8 g. (0.10 mole) of sodium borohydride in 20 ml. of water. The mixture was stirred for 2 hr. and then filtered. The filtrate was cooled in ice and the excess sodium borohydride was decomposed with acetone. Following the addition of 50 ml. of water and 100 ml. of ether, the ether portion was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent and two recrystallizations from ether–petroleum ether produced 1.9 g. (66% yield) of yellow crystals of VII, m.p. 80.3–80.5°.

*Anal.* Calcd. for $C_{17}H_{16}FeO$: C, 69.88; H, 5.52; Fe, 19.12. Found: C, 70.10, 69.92; H, 5.57, 5.67; Fe, 19.18, 19.22.

*Reduction of I by aluminum isopropoxide.* A solution of 4.37 g. (0.015 mole) of I and 7.4 g. (0.036 mole) of aluminum isopropoxide in 150 ml. of redistilled isopropyl alcohol was slowly distilled for 1 hr.; however, the presence of acetone in the distillate could not be detected. In order to raise the reaction temperature, 300 ml. of xylene was added and the isopropyl alcohol was removed by distillation. Continued slow distillation at 134–135° produced a distillate containing acetone. After hydrolysis with 150 ml. of 10% hydrochloric acid, the organic phase was washed with water and the solvent evaporated. Recrystallization of the residue produced 0.6 g. of benzylferrocene (IV), m.p. 73–74°. A mixed melting point test with an authentic sample was not depressed.

*Acknowledgment.* The authors wish to express their appreciation to Mr. F. F. Bentley and Mrs. N. E. Srp for the infrared spectra. We are also very grateful to Dr. Roy Pruett of the Linde Co., and to Dr. Eric Barthel of the E. I. du Pont de Nemours & Co., Inc., for generous samples of ferrocene used in our research program.

WRIGHT-PATTERSON AIR FORCE BASE, OHIO

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# Some Typical Aldehyde Addition and Condensation Reactions of Formylferrocene[1]

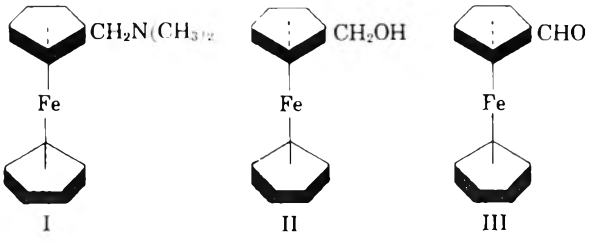
CHARLES R. HAUSER AND JACQUE K. LINDSAY

*Received February 8, 1957*

Formylferrocene was found to undergo typical addition and condensation reactions with methylmagnesium iodide, dimethylamine and sodium cyanide, lithio *t*-butyl acetate, and acetophenone and alkali. These processes together with further reactions of certain of the products illustrate useful methods for the synthesis of a number of ferrocene derivatives. Formylferrocene failed to condense with acetophenone in the presence of boron fluoride.

Recently[2] *N*,*N*-dimethylaminomethylferrocene (I) was prepared from ferrocene and the methiodide of this tertiary amine converted to the corresponding alcohol and aldehyde, II and III, respectively.

In the present investigation aldehyde III (formylferrocene) was shown to undergo the addition and condensation reactions represented in Chart I. The crude aldehyde, which was obtained by the oxidation of alcohol II with manganese dioxide,

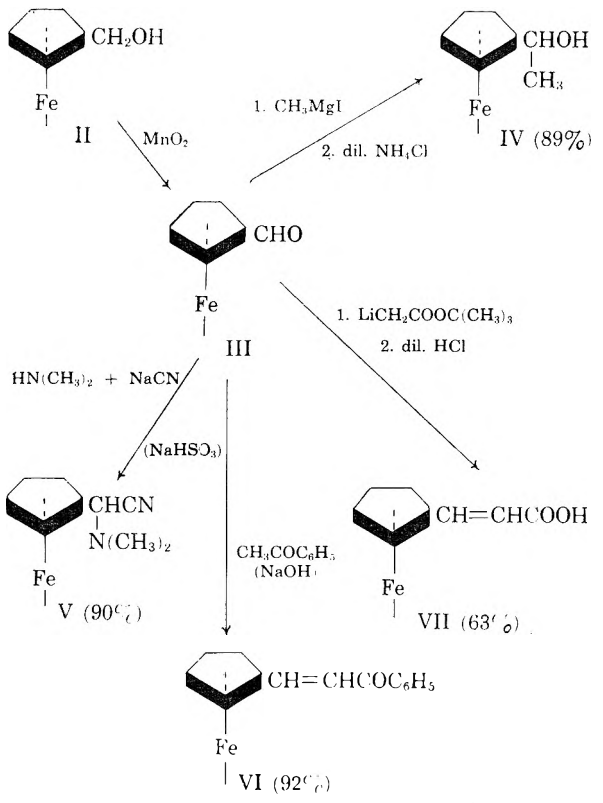



was employed in these reactions, the yields being based on the alcohol.

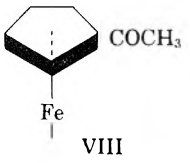
It can be seen from Chart I that the yields of the products (IV–VII) were good to excellent (63–

(1) Supported by the Office of Ordnance Research, U. S. Army.

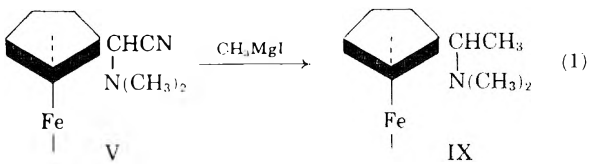
(2) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, 22, 355 (1957).



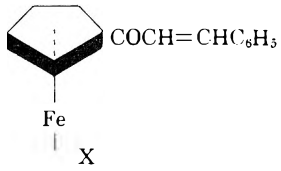

92%). The carbinol (IV) from the addition reaction of aldehyde III with methylmagnesium iodide was shown to be identical with that obtained by the lithium aluminum hydride reduction of acetylferrocene (VIII). This ketone was prepared by the Friedel-Crafts type of acetylation of ferrocene with acetic anhydride by means of boron fluoride.[3]




The reaction of aldehyde III with dimethylamine and sodium cyanide to form aminonitrile V was effected through the sodium bisulfite addition compound of the aldehyde similar to that described for benzaldehyde.[4] The aminonitrile (V) was shown to react with methylmagnesium iodide to form tertiary amine IX (Equation 1). Such a substitution of the cyanide group by the alkyl or aryl group of a Grignard reagent is known to be characteristic of $\alpha$-aminonitriles.[5]




The condensation of aldehyde III with acetophenone by means of alkali produced an $\alpha,\beta$-unsaturated ketone (VI) that was isomeric with another $\alpha,\beta$-unsaturated ketone (X) prepared recently[3] from benzaldehyde and acetylferrocene (VII). Both of these $\alpha,\beta$-unsaturated ketones are purple although of different shades.




The condensation of aldehyde III with lithio *t*-butyl acetate was effected by a modification of the method developed recently[6] for that of certain aldehydes and ketones with this metallo ester which was prepared from lithium amide and *t*-butyl acetate. The intermediate $\beta$-hydroxy ester was dehydrated and hydrolyzed by means of hydrochloric acid in dioxane to form $\alpha,\beta$-unsaturated acid VII which is an analog of cinnamic acid.

The reactions represented in Chart I together with that of aminonitrile V with the Grignard reagent (Equation 1) illustrate useful methods for the synthesis of a number of new ferrocene derivatives. Although carbinol IV would usually be prepared by the reduction of acetylferrocene, certain other carbinols could probably be synthesized more conveniently through formylferrocene.

Although the condensation of aldehyde III with acetophenone to form $\alpha,\beta$-unsaturated ketone VI was realized with alkali, the reaction failed with boron fluoride which is known to bring about the corresponding condensation between benzaldehyde and acetophenone.[7] Similarly the condensation of acetylferrocene (VIII) with benzaldehyde to form $\alpha,\beta$-unsaturated ketone X was realized recently[3] with alkali but not with boron fluoride. Evidently the iron in aldehyde III and ketone VIII hinders this Lewis acid from serving as catalyst, the function of which would presumably involve the conversion of the aldehyde group to a carbonium ion and the ketone group, to an enol type intermediate.[8]

## EXPERIMENTAL[9]

*Hydroxymethylferrocene* (II). This alcohol was prepared in

(3) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 482 (1957).

(4) E. Knoevenagel and E. Mercklin, *Ber.*, **37**, 4087 (1904); D. B. Luten, Jr., *J. Org. Chem.*, **3**, 588 (1938).

(5) See L. H. Goodson and H. Christopher, *J. Am. Chem. Soc.*, **72**, 358 (1950).

(6) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **75**, 1068 (1953).

(7) D. S. Breslow and C. R. Hauser, *J. Am. Chem. Soc.*, **62**, 2385 (1940).

(8) In this connection see C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 99 (1954).

(9) Melting points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn.

three steps from ferrocene[10] as described previously.[2] Ferrocene was aminomethylated to form dimethylaminomethylferrocene (I) in 50% yield (80% conversion yield), and the methiodide of this tertiary amine (obtained in 95% yield) was treated with alkali to give hydroxymethylferrocene (II), m.p. 81–82°, in 94% yield.

*Oxidation of alcohol II to aldehyde III and its reactions. Chart I.* Alcohol II (10.7 g., 0.05 mole) was oxidized with manganese dioxide in chloroform to form aldehyde III as described previously.[2] The crude solid aldehyde, which was obtained quantitatively (10.8 g., 0.05 mole), was used in the reactions described below, the yields being based on alcohol II. Freshly prepared aldehyde was generally employed, although it was sometimes kept several hours under nitrogen before usage.

*A. Reaction with methylmagnesium iodide to form carbinol IV.* To a stirred ethereal solution of methylmagnesium iodide (prepared from 0.075 moles each of methyl iodide and magnesium) was added dropwise a solution of 0.05 mole of crude aldehyde III in 100 ml. of anhydrous ether. After 2 hr. stirring and refluxing, the yellow suspension was cooled in an ice bath, decomposed with excess ammonium chloride solution, and the ether layer of the product dried over magnesium sulfate. The solvent was removed to leave 10.2 g. (89%) of yellow powder of α-hydroxyethylferrocene (IV), m.p. 72–75°. Recrystallization from *n*-hexane gave large tan crystals, m.p. 78–79°; reported[11] m.p. 73–75°.

*Anal.* Calcd. for $C_{12}H_{14}OFe$: C, 62.64; H, 6.13; Fe, 24.27. Found: C, 62.73; H, 6.30; Fe, 24.22.

The melting point was not depressed by admixture with a sample of α-hydroxyethylferrocene (IV), m.p. 78–79°, prepared by the lithium aluminum hydride reduction of acetylferrocene (VIII) essentially as described by Arimoto and Haven.[11] The melting point of IV reported by these workers was 73–75° after recrystallization from a mixture of ether and petroleum ether. We obtained large tan crystals, m.p. 78–79°, after recrystallization from *n*-hexane.

*B. Reaction with dimethylamine and sodium cyanide to form aminonitrile V.* To a stirred solution of 5.2 g. (0.05 mole) of sodium bisulfite in 50 ml. of water was added 10.8 g. (0.05 mole) of crude aldehyde III in 30 ml. of methanol followed, after 5 min., by a solution of 3.0 g. (0.07 mole) of dimethylamine in 10 ml. of 50% methanol. The mixture was cooled in an ice bath, and a solution of 2.45 g. (0.05 mole) of sodium cyanide in 10 ml. of water was added dropwise with stirring. The color changed from red to orange. Ether (25 ml.) was added and the reaction mixture stirred at room temperature for 4 hr., then extracted three times with ether. The combined ethereal extract was dried over magnesium sulfate, and the solvent removed. The residual amber oil crystallized on adding petroleum ether to give 12.0 g. (90%) of (aminonitrile V), m.p. 83–86°. Recrystallization from *n*-hexane gave light brown plates, m.p. 86–88°.

*Anal.* Calcd. for $C_{14}H_{16}N_2Fe$: C, 62.71; H, 6.01; N, 10.45; Fe, 20.83. Found: C, 63.07; H, 5.75; N, 10.46; Fe, 20.74.

A solution of 26.0 g. (0.1 mole) of aminonitrile V (m.p. 83–86°) in 100 ml. of dry ether was added dropwise to a stirred solution of methylmagnesium iodide prepared from 0.2 mole each of methyl iodide and magnesium in 150 ml. of dry ether. After stirring one hour and standing overnight, the reaction mixture was cooled and decomposed with ammonium chloride solution to give 23.0 g. (89%) of tertiary amine IX (clear amber oil) which distilled with partial decomposition at 111° at 0.65 mm., $n_D^{25}$ 1.5883.

*Anal.* Calcd. for $C_{14}H_{19}NFe$: C, 65.38; H, 7.45; N, 5.45; Fe, 21.72. Found: C, 65.12; H, 7.50; N, 5.27; Fe, 21.53.

The amine was converted to a picrate which was recrystallized from 95% ethanol to give red plates, m.p. 136–137°.

*Anal.* Calcd. for $C_{20}H_{22}O_7N_4Fe$: C, 49.40; H, 4.56; N, 11.52; Fe, 11.49. Found: C, 49.55; H, 4.55; N, 11.68; Fe, 11.23.

*C. Condensation with acetophenone to form α,β-unsaturated ketone VI.* To a stirred solution of 2.56 g. (0.064 mole) of sodium hydroxide in 20 ml. of water (cooled to 15°) was added, successively, solutions of 6.0 g. (0.05 mole) of acetophenone in 10 ml. of 95% ethanol and 10.8 g. (0.05 mole) of crude aldehyde III in 30 ml. of 95% ethanol. The mixture was stirred at room temperature for 3 hr. and allowed to stand overnight. The thick purple suspension was filtered, and the solid washed thoroughly with water, followed by a small portion of ice-cold 95% ethanol. After drying, there was obtained 14.5 g. (92%) of α,β-unsaturated ketone VI (purple solid), m.p. 123–126°. Recrystallization from 95% ethanol gave deep purple needles, m.p. 126–128°.

*Anal.* Calcd. for $C_{19}H_{16}OFe$: C, 72.17; H, 5.10; Fe, 17.66. Found: C, 72.05; H, 5.23; Fe, 17.43.

*D. Condensation with t-butyl acetate to form α,β-unsaturated acid VII.* This reaction was effected by a modification of the general method developed previously in this laboratory.[6]

To a stirred suspension of 0.05 mole of lithium amide in 200 ml. of liquid ammonia was added a solution of 5.7 g. (0.05 mole) of *t*-butyl acetate in 10 ml. of anhydrous ether. To the resulting lithio ester was added, after 30 min., a solution of 10.8 g. (0.05 mole) of crude aldehyde III in 20 ml. of anhydrous ether. The yellow-green suspension was stirred for 2 hr., and excess solid ammonium chloride then added. The liquid ammonia was allowed to evaporate and, after the addition of 200 ml. of ether, the mixture was heated under reflux for 10 min., cooled slightly, and filtered. Removal of the solvent left 14 g. of the β-hydroxy ester as an amber oil. Samples of this oil failed to yield satisfactory crystals on treatment with *n*-hexane or benzene. A solution of 5 g. of this oil in 40 ml. of dioxane and 10 ml. of concentrated hydrochloric acid was refluxed for 1.5 hr.[6] After dilution with five volumes of water, the mixture was extracted with ether. The combined ethereal solution was extracted with 20 ml. portions of 1*N* sodium hydroxide. The combined alkaline solution (after extracting with ether) was chilled and acidified with 6*N* hydrochloric acid to precipitate acid VII which was collected on a funnel, washed with water, and dried. The bright red powder (2.9 g., 63%) melted at 176–178° dec., and at 177–179° dec. after careful sublimation at 130° at 0.1 mm.

*Anal.*[12] Calcd. for $C_{13}H_{12}O_2Fe$: C, 60.97; H, 4.72; Fe, 21.81. Found: C, 61.23; H, 4.74; Fe, 21.43.

*Attempt to effect aldol condensation by boron fluoride.* A solution of 0.5 mole of crude formylferrocene (III) and 0.10 mole of acetophenone in 100 ml. of methylene chloride was saturated with boron fluoride at 0°. After standing at room temperature for 3 hr. the reaction mixture was stirred with excess sodium acetate solution. Aldehyde III was recovered through its sodium bisulfite addition compound and converted to its semicarbazone, m.p. 217–219°.[2]

DURHAM, N. C.

(10) We are indebted to Linde Co., Tonawanda, N. Y. (Dr. R. L. Pruett) for a generous sample of this compound.

(11) F. S. Arimoto and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **77**, 6295 (1955).

(12) Galbraith Laboratories reported that acid VII was too insoluble for a satisfactory neutral equivalent.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

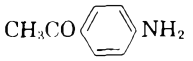
# *N*- and *C*-Benzoylation of *p*-Aminoacetophenone with Methyl Benzoate by Sodium Amide. Synthesis of β-Diketones Having *p*-Acylamino and *p*-Hydroxy Groups[1]

CHARLES R. HAUSER AND CHARLES J. EBY

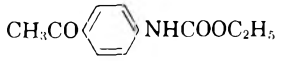
*Received February 12, 1957*

*p*-Aminoacetophenone underwent *N*-benzoylation with sodium amide and methyl benzoate to form *p*-benzoylaminoacetophenone which then underwent *C*-benzoylation with these reagents to give the corresponding β-diketone amide. This β-diketone was cyclized with hydrazine and urea to produce a pyrazole and pyrimidol, respectively. Other acylations of ketone amides and the benzoylation of *p*-hydroxyacetophenone were effected to form the corresponding β-diketones. These condensations furnish a significant extension of the Claisen method of synthesis of β-diketones. The mechanism is considered to involve intermediate dianions.

Broadbent and Chu[2] have observed that *p*-aminoacetophenone (I) undergoes *N*-carbethoxylation on treatment with sodium amide followed by ethyl carbonate to form II which, however, fails to undergo further carbethoxylation in the presence of excess of these reagents. These workers had hoped to effect the *C*-carbethoxylation of I or II to produce the corresponding β-keto ester.

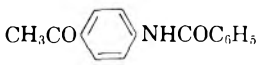


I

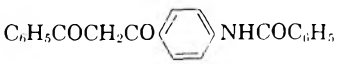


II

We have found that ketone amine I undergoes *N*-benzoylation with sodium amide and methyl benzoate to form ketone amide III which, in addition, undergoes *C*-benzoylation in the presence of excess of these reagents to give β-diketone amide IV. The reaction was carried out by adding I to sodium amide in liquid ammonia followed by the ester in ether.



III



IV

In Table I are summarized the yields of III and IV obtained from I with various equivalent amounts of sodium amide and methyl benzoate. It can be seen from this table that only III was obtained with equivalents of the base and ester but that IV was also produced with excesses of these reagents. Moreover the ratio of IV to III increased as the excess of reagents was increased. These two products were separated by converting the β-diketone amide (IV) to its copper chelate which was relatively insoluble in methanol. The β-diketone amide was regenerated by treatment of the chelate with acid. The yields of III and IV given in Table I are based on essentially pure compounds.

TABLE I

YIELDS OF III AND IV FROM I WITH VARIOUS EQUIVALENTS OF REAGENTS

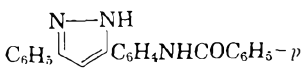
| Reagents[a] | | Products | |
|---|---|---|---|
| Sodium amide, equiv. | Methyl benzoate, equiv. | III, yield % | IV, yield % |
| 1 | 1 | 89[b] | 0 |
| 3 | 2 | 46 | 32 |
| 4 | 3 | 21 | 54 |

[a] One equivalent of ketone amine I was used in each experiment. [b] Some (10%) of ketone amine I was recovered.

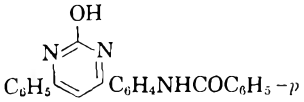
The monobenzoylated product was shown to be *p*-benzoylaminoacetophenone (III) by a mixed melting point with an authentic sample of this compound prepared from I and benzoyl chloride by the usual Schotten-Baumann reaction.

The structure of the dibenzoylated product was established as IV by a positive ferric chloride enol test and by the formation of a copper chelate, both of which are characteristic of β-diketones. The presence of the —CONH— group in IV was indicated[3] by an infrared absorption band at 3330 cm.$^{-1}$

The β-diketone structure of IV was confirmed by characteristic cyclizations with hydrazine[4] and urea[5] to form pyrazole V (96%) and pyrimidol VI (58%), respectively. The latter product was isolated as its monohydrochloride salt. An unstable



V



VI (as HCl salt)

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) H. Broadbent and C. Chu, *J. Am. Chem. Soc.*, **75**, 226 (1953).

(3) See R. Richards and H. Thompson, *J. Chem. Soc.*, 1248 (1947).

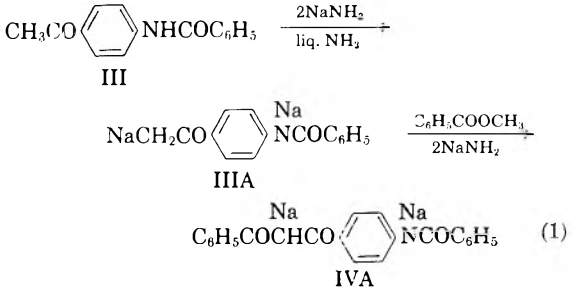
(4) See E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1954, p. 658.

(5) See C. Hauser and R. Manyik, *J. Org. Chem.*, **18**, 588 (1953).

dihydrochloride salt also appeared to form (see Experimental).

β-Diketone amide IV was prepared not only by treating ketone amine I with excess sodium amide and methyl benzoate (Table I) but also by the action of these reagents on ketone amide III the disodium salt of which is presumably an intermediate under the former conditions. Indeed the yield of IV from ketone amide III in the presence of three equivalents of sodium amide and two of methyl benzoate was approximately the same (52%) as that (54%) obtained from ketone amine I employing four equivalents of the base and three of the ester. This was anticipitated on the basis that one equivalent each of the base and ester was required to convert the amine group of I to the amide group of III (see Table I).

The mechanism of formation of IV from III evidently involves the *C*-benzoylation of the dianion of disodium salt IIIA which is presumably first formed from III in the presence of two or more equivalents of sodium amide (Equation 1). The α-hydrogen of the resulting β-diketone[6] would be ionized to form disodium salt IVA from which β-diketone amide IV was subsequently liberated by acidification of the reaction mixture.

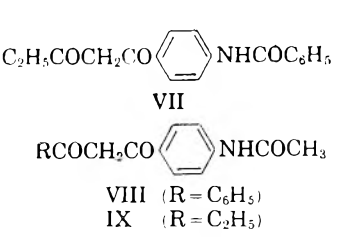



(1)

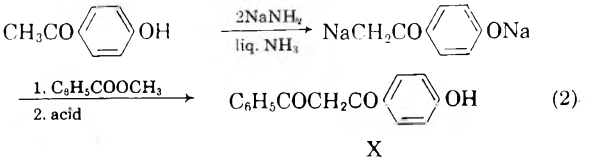
It is not surprising that disodium salt IIIA did not exhibit *N*-benzoylation to form *p*-dibenzoylaminoacetophenone since sodio benzanilide (prepared by means of sodium amide)[7] failed to undergo *N*-benzoylation with methyl benzoate under similar conditions to give dibenzanilide.

Similarly *p*-benzoylaminoacetophenone (III) was propionylated to form β-diketone-amide VII (20%), and the corresponding *p*-acetylaminoacetophenone was benzoylated and propionylated to give β-diketone amides VIII (20%) and IX (13%), respectively. The yields of these β-diketones could probably be improved. The possible acyl exchange was not observed under the conditions employed.

Also, *p*-hydroxyacetophenone was benzoylated to form β-diketone phenol X (37%). This product was isolated through its copper chelate. Similar to the acylations of the dianions of ketone-amides




such as IIIA (Equation 1), the formation of X evidently involves the *C*-acylation of the intermediate dianion (equation 2).




(2)

These condensations of ketones having hydrogens more acidic than their α-hydrogens furnish a significant extension of the well known Claisen method of acylation of ketones to form β-diketones.[6] Actually, relatively few such acylations of ketones involving intermediate dianions appear to have been realized previously.[6] A number of acylations of *o*-hydroxyacetophenone and its derivatives have been accomplished but at least certain of these might have involved the preferential *O*-acylation, of the intermediate dianion followed by intramolecular *C*-acylation.[8] Such a cyclic mechanism would not be possible for the present acylations of the dianions of *para*-substituted ketones. These reactions might have involved preferential *O*- or *N*-acylation followed by intermolecular *C*-acylation but this seems unlikely in view of the failure of sodio benzanilide to undergo acylation under similar conditions (see above).

An attempt to employ the present method for the acylation of diacetone alcohol resulted in the formation of benzoylacetone. Apparently this β-hydroxy ketone[9] underwent a reversed aldol condensation to form sodio acetone which then was benzoylated, or the reversed aldol condensation might have occurred after benzoylation.

It should be mentioned that sodio acetophenone failed to undergo acylation with methyl *p*-benzoylaminobenzoate or *p*-hydroxybenzoate in the presence of excess sodium amide under the conditions employed with ketone amide III. Apparently the active hydrogens in these esters was ionized by the sodium amide, thereby deactivating the carbonyl groups of the esters.

## EXPERIMENTAL[10]

*N- and C-benzoylation of p-aminoacetophenone* (I) *to form*

(6) See C. Hauser, F. Swamer, and J. Adams, *Org. Reactions*, VIII, Chapter 3 (1954).

(7) That sodium amide converts amides of the type $RCONHC_6H_5$ to their sodium salts is shown by their alkylation with alkyl halides by means of this base; V. Wolf, *Ann.*, **576**, 35 (1952).

(8) See ref. 6, p. 91.

(9) The α-hydroxyketone, butyroin, has evidently been acylated with ethyl acetate by means of sodium ethoxide; see ref. 6, pp. 72–73, and R. Woodward and E. Blout, *J. Am. Chem. Soc.*, **65**, 562 (1943).

(10) Melting points are uncorrected. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

III *and* IV. *Table I.* To a stirred suspension of 0.10, 0.30, or 0.40 mole of sodium amide in 350 ml. of liquid ammonia[11] was added 13.5 g. (0.10 mole) of *p*-aminoacetophenone, followed after 30 min. by 0.10, 0.20, or 0.30 mole of methyl benzoate in an equal volume of dry ether during about 5 min. After stirring for 1.5 hr. more, the liquid ammonia was removed on the steam bath while dry ether was being added to maintain constant volume. The resulting ether suspension was stirred overnight.

In the experiment with equivalent amounts of the three reactants, the reaction mixture was filtered, and the solid triturated with 6*N* hydrochloric acid and dried to give 21.15 g. (89%) of *p*-benzoylaminoacetophenone (III), m.p. 199–201° (204–206° on Kofler Micro Hot Stage); reported m.p. 205°.[12] The melting point of this product was not depressed upon admixture with an authentic sample of III prepared from *p*-aminoacetophenone and benzoyl chloride by the Schotten-Baumann procedure.[12] From the hydrochloric acid wash there was recovered 1.4 g. (10%) of *p*-aminoacetophenone, m.p. 104–105°; reported m.p. 105°.[13]

In the experiments with excesses of sodium amide and methyl benzoate, the reaction mixture was filtered, and the solid washed with ether. The solid then was added to ice water, and the mixture acidified with acetic acid. The crude product was dissolved in 2 l. of hot methanol and an excess of a saturated aqueous solution of copper acetate was added.[11] The resulting precipitate was collected on a funnel and washed thoroughly with hot methanol to give the copper chelate of β-diketone IV, m.p. 362° (dec.). The copper salt was dissolved in concentrated sulfuric acid and the solution poured onto excess ice. The liberated β-diketone was taken up in chloroform, and the solution washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent (water aspirator) gave 1-*p*-*N*-benzoylaminophenyl-3-phenylpropane-1,3-dione (IV), m.p. 181–183°. One recrystallization from 95% ethanol gave light yellow needles, m.p. 184.5–186°.

*Anal.* Calcd. for $C_{22}H_{17}O_3N$: C, 76.95; H, 4.99; N, 4.08. Found: C, 77.01; H, 4.71; N, 3.85.

The product (IV) gave a red enol test with ferric chloride.

Evaporation of the methanol mother liquor from the copper chelate precipitation gave a solid which, after being washed with water, yielded *p*-*N*-benzoylaminoacetophenone (III), m.p. and mixed m.p. 199–201° (204–206° on Kofler Micro Hot Stage). The yields of products are summarized in Table I.

*Benzoylation of p-benzoylaminoacetophenone* (III) *to form β-diketone* IV. To a stirred suspension of 0.15 mole of sodium amide in 350 ml. of liquid ammonia was added through a powder funnel 12 g. (0.05 mole) of *p*-benzoylaminoacetophenone (III), followed after 15 min. by 13.6 g. (0.10 mole) of methyl benzoate in an equal volume of dry ether during 20 min. After stirring for one hour more, the liquid ammonia was replaced by dry ether, and the resulting ether suspension was stirred at room temperature for 24 hr. The reaction mixture was added to ice water, and acidified with iced 6*N* hydrochloric acid. The precipitate (pink) was collected on a funnel, and dissolved in ethanol. To the ethanolic solution was added an aqueous solution of sufficient copper acetate to precipitate completely the copper chelate of the β-diketone.[11] The copper chelate was collected on a funnel, washed with hot ethanol, and decomposed with 10% sulfuric acid.[11] The liberated β-diketone was taken up in chloroform, washed with saturated sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed to give 8.9 g. (52%) of β-diketone IV, m.p. 179–182° and 184.5–186° after recrystallization from 95% ethanol.

*Cyclization of β-diketone* IV *with hydrazine to form pyrazole* V. To a solution of 1.7 g. (0.005 mole) of β-diketone IV in 250 ml. of methyl alcohol was added dropwise with swirling and heating on the steam bath 4.8 g. (0.15 mole) of 95% hydrazine. The heating was continued for 30 min. To the clear yellow solution was added gradually with swirling 100 ml. of water. The solution was then cooled in a dry ice–acetone bath to precipitate a white solid which was collected on a funnel and washed with water. There was obtained 1.5 g. (89%) of 3-*p*-*N*-benzoylaminophenyl-5-phenylpyrazole (V), m.p. 253–254.5°, and 0.1 g. of this product, m.p. 247–250°; total yield 96%.

*Anal.* Calcd. for $C_{22}H_{17}ON_3$: C, 77.85; H, 5.05; N, 12.38. Found: C, 77.60; H, 4.91; N, 12.10.

As expected, the product (V) gave a negative enol test with ferric chloride.

*Cyclization of β-diketone* IV *with urea to form pyrimidol* VI. To a mixture of 3.43 g. (0.01 mole) of β-diketone IV, 70 ml. of absolute ethanol, and 0.96 g. (0.016 mole) of urea was added 11 ml. of an absolute ethanol solution of 2.1*N* (0.024 mole) hydrogen chloride. The mixture was refluxed 8 days (protected from moisture by a drying tube). A clear orange solution resulted after 1 day, and an orange solid was present after the 8-day refluxing period. The mixture was cooled and filtered. The orange-yellow solid was washed with ether to give 1.15 g. of the monohydrochloride salt of 4-*p*-benzoylamino-6-phenylpyrimidol (VI), m.p. 283–293°. Addition of dry ether to the filtrate and washings precipitated more orange solid (apparently the dihydrochloride of VI) which started to decompose (turned red). This solid was immediately washed with saturated sodium bicarbonate solution to produce more (1.2 g.) of yellow salt VI, m.p. 260–280°. A mixed melting point of this sample with that melting at 283–293° was 268–276°. The total yield of the crude monohydrochloride of VI was 58%. Two recrystallizations from methanol raised the melting point to 297–299°.

*Anal.* Calcd. for $C_{23}H_{18}O_2N_3Cl$: C, 68.40; H, 4.49; N, 10.40. Found: C, 68.62; H, 4.51; N, 10.33.

*1-p-N-Benzoylaminophenylpentane-1,3-dione* (VII). This β-diketone was prepared essentially as described for IV employing 0.15 mole of sodium amide in 350 ml. of liquid ammonia, 11.9 g. (0.05 mole) of ketone III, and 10.2 g. (0.10 mole) of methyl propionate in 50 ml. of dry ether. After adding the solution of the ester during 20 min., the ammonia was immediately replaced by ether, and the resulting ether suspension stirred at room temperature for 24 hr. The reaction mixture was added to ice water and filtered. The solid consisted of 9.35 g. (79%) of recovered ketone III. Acidification of the filtrate precipitated 2.9 g. (20%) of 1-*p*-*N*-benzoylaminophenylpentane-1,3-dione (VII), m.p. 164–170°. One recrystallization from 95% ethanol raised the melting point (white needles) to 170.5–172°.

*Anal.* Calcd. for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.28; H, 5.98; N, 4.89.

*1-p-N-Acetylaminophenyl-3-phenylpropane-1,3-dione* (VIII). To a stirred suspension of 0.15 mole of sodium amide in 350 ml. of liquid ammonia was added 8.85 g. (0.05 mole) of *p*-*N*-acetylaminoacetophenone[14] followed 35 min. later by 13.6 g. (0.10 mole) of methyl benzoate in 50 ml. of dry ether over a period of 20 min. After replacing the ammonia by ether and refluxing the ether suspension for 24 hr., the reaction mixture was added to ice water, the ether layer separated and the water layer acidified. The β-diketone was collected in chloroform and isolated through its copper chelate (m.p. 313° dec.). There was obtained 2.85 g. (20%) of β-diketone VIII, m.p. 157–162°. One recrystallization from benzene raised the melting point (yellow needles) to 162–164°.

*Anal.* Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.58; H, 5.58; N, 5.03.

*1-p-N-Acetylaminophenylpentane-1,3-dione* (IX). This β-diketone was prepared essentially as described for VIII

(11) See ref. 6, p. 122.

(12) F. Chattaway, *J. Chem. Soc.*, **85**, 390 (1904).

(13) V. Drewsen, *Ann.*, **212**, 162 (1882).

(14) See L. Fieser, *Experiments in Organic Chemistry*, Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 165; and C. Derick and J. Bornmann, *J. Am. Chem. Soc.*, **35**, 1281 (1913).

employing methyl propionate instead of methyl benzoate. The copper chelate (m.p. 292° dec.) was acidified to give after recrystallization from benzene, 1.5 g. (13%) of β-diketone IX, m.p. 132–134°. One more recrystallization raised the melting point of IX to 135–136.5°.

*Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.76; H, 6.36; N, 5.92.

*Benzoylation of p-hydroxyacetophenone to form β-diketone* X. To a stirred suspension of 0.19 mole of sodium amide in 300 ml. of liquid ammonia[11] was added through a powder funnel 8.65 g. (0.063 mole) of *p*-hydroxyacetophenone. After 1 hr., 17.3 g. (0.127 mole) of methyl benzoate in an equal volume of dry ether was added over 15 min., and the liquid ammonia replaced by dry ether. The resulting ether suspension was stirred and refluxed for 2.5 hr. Dry benzene (250 ml.) was then added, and most of the ether distilled off. The resulting benzene suspension was refluxed for 24 hr. The mixture was added to crushed ice. After the ice had melted, the water layer was separated and filtered through Amend hyflo supercell (on a filter paper in a Büchner funnel) and then acidified with iced 6*N* hydrochloric acid. The precipitated oil was taken up in ether and dried over magnesium sulfate. The solvent was removed to give 13.3 g. of golden oil which gave, on recrystallization from benzene, 3.30 g. of 1-*p*-hydroxyphenyl-3-phenylpropane-1,3-dione (X), m.p. 146–153°. More (2.3 g.) of β-diketone X was isolated from the mother liquor through the copper chelate; total yield, 37%. Two recrystallizations from benzene raised the melting point of X to 154–156°.

*Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.33; H, 5.05.

DURHAM, N. C.

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[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

# Orientation in Friedel-Crafts Reactions with 2-Methoxy-1-methylnaphthalene

NG. PH. BUU-HOÏ AND DENISE LAVIT

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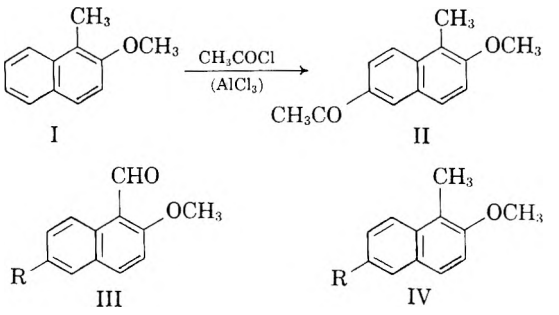
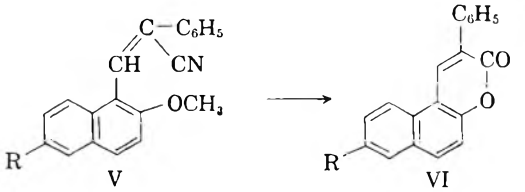
The acyl group in the Friedel-Crafts acetylation product (II) of 2-methoxy-1-methylnaphthalene in nitrobenzene is shown to enter position 6. The proof is based on the identity of the Kishner-Wolff reduction product of II and that of 1-formyl-2-methoxy-6-ethylnaphthalene, prepared by formylation of 2-methoxy-6-ethylnaphthalene. In the course of this work, a number of new homologs of 6-substituted naphthols, naphthaldehydes, naphthalene ketones, and their derivatives were prepared.

2-Methoxynaphthalene is known to undergo Friedel-Crafts acylations with aliphatic acid chlorides in nitrobenzene medium to give, as the isolated products, primarily the 6-acyl derivative, and some of the 8-acyl isomer; with carbon disulfide as solvent, substitution takes place predominantly in position 1.[1] It was of interest to investigate the behavior of 1-alkyl-2-naphthols in similar Friedel-Crafts reactions.

A convenient intermediate was 2-methoxy-1-methylnaphthalene (I), readily prepared by Kishner-Wolff reduction of 2-methoxy-1-naphthaldehyde. Acetylation of compound I, effected in nitrobenzene medium by Robinson and Weygand,[2] afforded a reaction product which, without proof of constitution, they considered to be 6-methoxy-5-methylacetonaphthone (II). Such a proof was now provided, by Kishner-Wolff reduction of this ketone to 6-ethyl-2-methoxy-1-methylnaphthalene (IV; R = $C_2H_5$), which was found to be identical with a sample prepared by Kishner-Wolff reduction of 6-ethyl-2-methoxy-1-naphthaldehyde (III; R = $C_2H_5$). The latter aldehyde was




readily prepared by formylation[3] of 6-ethyl-2-methoxynaphthalene with dimethylformamide in the presence of phosphorus oxychloride. The position taken by the formyl group in this reaction was ascertained by condensation of the aldehyde (III; R = $C_2H_5$) with benzyl cyanide to give the diarylacrylonitrile (V; R = $C_2H_5$), which yielded on




demethylation with pyridine hydrochloride 3′-

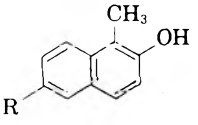
(1) L. Gattermann, R. Ehrhardt, and H. Maisch, *Ber.*, 23, 1199 (1890); M. L. Rousset, *Bull. soc. chim. Belges*, [3] 15, 633 (1896); R. R. Galle, *J. Gen. Chem. U.S.S.R.*, 8, 402 (1938).

(2) R. Robinson and F. Weygand, *J. Chem. Soc.*, 389 (1941).

(3) For similar formylations of naphthol ethers with dimethylformamide, see N. P. Buu-Hoï and D. Lavit, *J. Chem. Soc.*, 2776 (1955).

ethyl-3-phenyl-5,6-benzocoumarin (VI; R = $C_2H_5$); this coumarin cyclization of diarylacrylonitriles derived from methoxy aldehydes has often been used as proof of the position *ortho* to a methoxy radical occupied by the formyl group.[4] 6-*n*-Propyl-2-methoxynaphthalene was similarly formylated to 2-methoxy-6-*n*-propyl-1-naphthaldehyde (III; R = *n*-$C_3H_7$), which underwent condensation with benzyl cyanide to a diarylacrylonitrile (V; R = *n*-$C_3H_7$), and this in turn was demethylated to3-phenyl-3′-*n*-propyl-5,6-benzocoumarin (VI; R = *n*-$C_3H_7$). Kishner-Wolff reduction of the aldehyde (III; R = *n*-$C_3H_7$) yielded 2-methoxy-1-methyl-6-*n*-propylnaphthalene (IV; R = $C_3H_7$), a product identical with that obtained by similar reduction of the propionylation product of 2-methoxy-1-methylnaphthalene.

The ready accessibility of 6-alkyl-2-methoxy-1-methylnaphthalenes provided a convenient route to 6-alkyl-1-methyl-2-naphthols, which were obtained by demethylation with pyridine hydrochloride; 6-ethyl-1-methyl-2-naphthol (VII; R =



(VII, R = $C_2H_5$ or *n*-$C_3H_7$)

$C_2H_5$) and 1-methyl-6-*n*-propyl-2-naphthol (VII; R = *n*-$C_3H_7$) were thus prepared in excellent yield.

The fact that the Friedel-Crafts acetylation of 2-methoxy-1-methylnaphthalene occurred only at position 6, whereas under the same experimental conditions 2-methoxynaphthalene would yield a mixture of the 6- and 8-acetyl derivatives, could possibly be explained on the grounds of steric hindrance exerted on position 8 by the *peri*-methyl group.

In the course of this work, a number of further new derivatives, including several chalcones, in the naphthalene series were prepared, and are reported below.

## EXPERIMENTAL[5]

*Preparation of 6-ethyl-2-methoxynaphthalene.* The following method, which was found more satisfactory than Lévy's procedure,[6] gave a much purer product: A solution of 66.5 g. of recrystallized 2-methoxy-6-acetonaphthone (m.p. 111°) and 67 g. of 98% hydrazine hydrate in 400 ml. of diethylene glycol was heated at 120° for a few minutes to allow the hydrazone to form. After cooling, 55 g. of potassium hydroxide was added, and the mixture refluxed for 90 min., with removal of water. Water was added on cooling, the reduction product taken up in benzene, the benzene solution washed first with dilute hydrochloric acid, then with water, dried over calcium chloride, and the solvent distilled. Fractionation of the residue *in vacuo* yielded 50 g. of 6-ethyl-2-methoxynaphthalene, b.p. 160–161°/14 mm., crystallizing from ethanol in lustrous leaflets, m.p. 62°; Lévy[6] gave m.p. 58° for a less pure product.

*6-Ethyl-2-methoxy-1-naphthaldehyde* (III; R = $C_2H_5$). To 48.5 g. of the foregoing ether and 22.8 g. of dimethylformamide, 48.5 g. of phosphorus oxychloride was carefully added, and the mixture refluxed for 5 hr. on the water bath. To the reaction product, a saturated aqueous solution of sodium acetate was added, and refluxing was resumed for a further 30 min. The aldehyde formed was taken up in benzene, the benzene layer washed with dilute hydrochloric acid, then with water, dried over calcium chloride, and the solvent removed. Vacuum fractionation of the residue yielded 47 g. of a product, b.p. 210–211°/12 mm., crystallizing from ethanol in shiny colorless needles, m.p. 61°. The halochromy in sulfuric acid was deep yellow.

*Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 78.5; H, 6.6. Found: C, 78.4; H, 6.6.

*6-Ethyl-2-methoxy-1-methylnaphthalene* (IV; R = $C_2H_5$). (a) Forty-four grams of the foregoing aldehyde dissolved in 260 ml. of diethylene glycol was reduced with 44 g. of hydrazine hydrate and 39 g. of potassium hydroxide in the usual way. Yield: 32.5 g. of a product, b.p. 178–180°/17 mm., crystallizing from ethanol in lustrous colorless leaflets, m.p. 41°.

*Anal.* Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.1. Found: C, 83.7; H, 8.2.

(b) A similar reduction, performed with 20 g. of the acetylation product of 2-methoxy-1-methylnaphthalene (m.p. 97–98°, prepared according to Robinson and Weygand[2]), yielded 16 g. of the same product.

*6-Ethyl-1-methyl-2-naphthol* (VII; R = $C_2H_5$). A mixture of 5 g. of 6-ethyl-2-methoxy-1-methylnaphthalene and 20 g. of redistilled pyridine hydrochloride was refluxed for 20 min.; after cooling, dilute hydrochloric acid was added, and the solid formed taken up in chloroform. The chloroform solution was then washed with water and dried over sodium sulfate, and the solvent removed. Recrystallization of the residue from cyclohexane yielded 3.5 g. of colorless prisms, m.p. 102°.

*Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.8; H, 7.6. Found: C, 83.6; H, 7.6.

*1-Phenyl-2-(6-ethyl-2-methoxy-1-naphthyl)acrylonitrile* (V; R = $C_2H_5$). A solution of 0.8 g. of 6-ethyl-2-methoxy-1-naphthaldehyde and 0.48 g. of benzyl cyanide in warm ethanol was treated with a few drops of a 20% aqueous solution of sodium hydroxide. The solid precipitate which formed almost immediately, crystallized from ethanol in yellowish needles (0.7 g.), m.p. 136°. The solutions in sulfuric acid were yellow.

*Anal.* Calcd. for $C_{22}H_{19}NO$: C, 84.3; H, 6.1. Found: C, 84.0; H, 6.2.

*3′-Ethyl-3-phenyl-5,6-benzocoumarin* (VI, R = $C_2H_5$). A mixture of 0.5 g. of the foregoing acrylonitrile and 5 g. of pyridine hydrochloride was refluxed for 10 min.; on cooling, dilute hydrochloric acid was added, the mixture then boiled, and the precipitate collected after cooling. Recrystallization from ethanol afforded 0.3 g. of pale yellow needles, m.p. 141°; the ethanol solutions gave a violet-blue fluorescence.

*Anal.* Calcd. for $C_{21}H_{16}O_2$: C, 84.0; H, 5.4. Found: C, 83.9; H, 5.5.

*2-Methoxy-6-n-propylnaphthalene.* This ether[7] was prepared from 100 g. of 2-methoxy-6-propionaphthone (m.p. 111°), 100 g. of hydrazine hydrate, and 83 g. of potassium hydroxide in 600 ml. of diethylene glycol. Yield: 79 g. of a product, b.p. 171–172°/13 mm., which crystallized from ethanol in lustrous colorless leaflets, m.p. 56°.

*Anal.* Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.1. Found: C, 84.0; H, 8.0.

(4) N. P. Buu-Hoï, B. Eckert, and R. Royer, *J. Org. Chem.*, 19, 1548 (1954); N. P. Buu-Hoï and D. Lavit, *J. Org. Chem.*, 21, 21 (1956); *J. Chem. Soc.*, 1743 (1956).

(5) With Miss J. Collard.

(6) G. Lévy, *Compt. rend.*, 202, 1679 (1936).

(7) R. D. Desai and W. S. Waravdekar [*Proc. Indian Acad. Sci.*, **24A**, 382 (1946)] gave m.p. 49–50° for an impure sample of this substance.

As a by-product of the reduction, the corresponding *azine* was obtained; it crystallized from benzene in silky yellow needles, m.p. 241°.

*2-Methoxy-6-n-propyl-1-naphthaldehyde* (III; R = *n*-$C_3H_7$). This was prepared from 78 g. of the foregoing ether, 37 g. of dimethylformamide, and 78 g. of phosphorus oxychloride in the usual way. Yield: 75 g. of an *aldehyde*, b.p. 216–218°/13 mm., crystallizing from ethanol in shiny colorless prisms, m.p. 49°.

*Anal.* Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 78.7; H, 7.2.

The corresponding *thiosemicarbazone* crystallized from ethanol in shiny yellowish leaflets, melting with decomposition around 258°.

*Anal.* Calcd. for $C_{16}H_{19}N_3OS$: N, 14.0. Found: N, 13.7.

*2-Methoxy-1-methyl-6-n-propylnaphthalene* (IV; R = *n*-$C_3H_7$) was prepared from 67 g. of the foregoing aldehyde, 67 g. of hydrazine hydrate, and 60 g. of potassium hydroxide in 400 ml. of diethylene glycol. Yield, 56 g. of an *ether*, b.p. 183–185°/15 mm., crystallizing from ethanol in lustrous colorless leaflets, m.p. 35°.

*Anal.* Calcd. for $C_{15}H_{18}O$: C, 84.1; H, 8.5. Found: C, 84.0; H, 8.5.

*1-Methyl-6-n-propyl-2-naphthol* (VII; R = *n*-$C_3H_7$). Demethylation of 53 g. of the foregoing ether with 200 g. of pyridine hydrochloride yielded 44 g. of a *naphthol*, b.p. 194–195°/15 mm., crystallizing from cyclohexane in colorless leaflets, m.p. 99°.

*Anal.* Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.1. Found: C, 83.7; H, 8.3.

*1-Phenyl-2-(2-methoxy-6-n-propyl-1-naphthyl)acrylonitrile* (V; R = *n*-$C_3H_7$) was obtained from 1 g. of 2-methoxy-6-*n*-propyl-1-naphthaldehyde and 0.56 g. of benzyl cyanide with a few drops of 20% aqueous sodium hydroxide. This *nitrile* crystallized from ethanol in silky yellowish needles (0.9 g.), m.p. 126°.

*Anal.* Calcd. for $C_{23}H_{21}NO$: C, 84.4; H, 6.5. Found: C, 84.1; H, 6.6.

*3-Phenyl-3'-n-propyl-5,6-benzocoumarin* (VI; R = *n*-$C_3H_7$). A mixture of 0.5 g. of the foregoing nitrile and 5 g. of pyridine hydrochloride was treated as for the lower homolog, to give 0.3 g. of a *coumarin*, crystallizing from ethanol in long yellowish needles, m.p. 136°. The solutions in ethanol or acetone showed a strong violet-blue fluorescence, and the halochromy in sulfuric acid was greenish-yellow.

*Anal.* Calcd. for $C_{22}H_{18}O_2$: C, 84.1; H, 5.8. Found: C, 84.0; H, 5.7.

*Chalcones derived from 2-methoxy-6-acetonaphthone.* These compounds were readily prepared by adding a few drops of a 20% aqueous solution of sodium hydroxide to a warm ethanolic solution of equimolar amounts of 2-methoxy-6-acetonaphthone and the appropriate aldehyde. The *2-furylidene derivative* crystallized from ethanol in fine yellowish needles, m.p. 112°, giving a crimson halochromy in sulfuric acid.

*Anal.* Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.1. Found: C, 77.5; H, 5.4.

The *p-anisal derivative* crystallized from ethanol in shiny, pale yellow leaflets, m.p. 131°; deep red halochromy in sulfuric acid.

*Anal.* Calcd. for $C_{21}H_{18}O_3$: C, 79.2; H, 5.7. Found: C, 79.1; H, 5.9.

The *α-naphthylidene* derivative crystallized from a mixture of ethanol and benzene in pale yellow leaflets, m.p. 173°; violet halochromy in sulfuric acid.

*Anal.* Calcd. for $C_{24}H_{18}O_2$: C, 85.2; H, 5.4. Found: C, 84.9; H, 5.3.

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[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

# Physical Properties of the Aminoazobenzene Dyes. VII. Absorption Spectra of 4-Aminoazobenzene Dyes in Ethanol[1]

EUGENE SAWICKI[2]

*Received February 6, 1957*

The visible absorption spectra of approximately sixty azobenzene derivatives in 95% ethanol have been investigated. Of particular interest was the effect of various substituents on the long wave length band associated with a zwitterionic resonance structure. An increasing shift toward the visible is shown by 4-substituted azobenzenes with the following substituents: H < Me < NHAc < OH < SMe < $NH_2$ < $N(CH_2CH_2Cl)_2$ < NHMe < NHEt < $NMe_2$ < $NEt_2$. Substitution of electron acceptor groups in the 4′-position of the 4-aminoazobenzene dyes causes an increasing shift toward the visible in the order: H < $C_6H_5$ < SCN < $CH{=}CH_2$ < Ac < $N{=}N{-}C_6H_5$ < $NO_2$. For the 4-dialkylaminoazobenzene dyes containing either a nitro or acetyl group at the negative end of the molecule there is a gradual shift toward the visible in the order 3′ < 2′ ≪ 4′. The presence of alkoxy, methylthio, or amino groups at the negative end of the molecule has very little effect on the wave length maximum in 95% ethanol. In naphthalene dyes such as 4-phenylazo-1-naphthol, $\lambda_{max}$ 409 mμ, as compared to 4-hydroxyazobenzene, $\lambda_{max}$ 349 mμ, the bathochromic shift is postulated as due to the relatively lower energy of the α-naphthoquinone excited state structure as compared to the *p*-benzoquinone excited state structure of 4-hydroxyazobenzene.

The relative intensity of two adjacent bands in chloro-, methoxy-, methylthio-, and amino derivatives of 4-dialkylaminoazobenzenes is shown to be solvent dependent. In aqueous alcohol 2′-amino-4-dimethylaminoazobenzene shows evidence of spectral fine structure that appears to be absent in the other compounds. On the basis of the spectra it is suggested that this compound exists mainly in a structure which contains a five membered ring involving an intramolecular hydrogen bond between the amino hydrogen and the β-azo nitrogen. The structure involving a six membered ring containing an intramolecular hydrogen bond between the amino hydrogen and the α-azo nitrogen is believed to be present also.

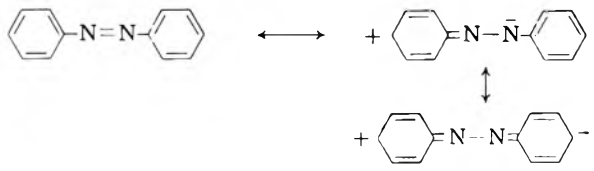
Ten new azo dyes have been prepared.

In previous papers of the series[3] the relation of the basicity of the various basic centers of an aminoazobenzene dye to tautomerism, resonance, inductive and steric effects, and inter- and intramolecular hydrogen bonding was discussed. In this paper the ultraviolet-visible absorption spectra of some 4-dimethylaminoazobenzene, DAB, derivatives is investigated.

The spectra of aromatic azo compounds show at least three regions of absorption in alcoholic solution. In the absence of a 2- or 4-amino group a weak absorption band is usually found at about 440–470 mμ. This band is believed to be derived from a transition involving the free non-bonding electrons of the –N=N– group. This type of transition has been symbolized variously as n—V,[4] n→π*[5] and N→ A.[6] The band has been thoroughly investigated by Burawoy, who believes it is due to a radical transition in the azo group and consequently has named it the R- band.[7]

The bands of moderate intensity at 210–290 mμ are believed to arise from electronic transitions in the aromatic rings.[8,9] As these bands are believed to arise from the E band of benzene at 205 mμ, they have been called E- bands.[10,11]

In azobenzene an intense band is found at 318 mμ which has been ascribed to the conjugation between the azo group and the aromatic ring system.[7] Some of the structures which contribute to the electronic transition involved in this band system are of a varying degree of importance depending upon the type of substituent and the environment. Substitution of electron-acceptor and/or electron-donor groups in positions of conjugation on the benzene rings decreases the energy of the zwitterionic structures. With such substitutions the change in energy involved in the transition from ground to excited state is decreased and the wave length maximum of this band system shows the expected bathochromic shift, Table I. This type of band structure where zwitterionic resonance structures



(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Present address: Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio.

(3) E. Sawicki and F. Ray, *J. Org. Chem.*, **19**, 1686 (1954); E. Sawicki and D. Gerber, *J. Org. Chem.*, **21**, 410 (1956); E. Sawicki, *J. Org. Chem.*, **22**, 365 (1957).

(4) P. Birnbaum, J. Linford, and D. Style, *Trans. Faraday Soc.*, **49**, 735 (1953).

(5) M. Kasha, *Discussions Faraday Soc.*, No. 9, 14, 72, 74, 75 (1950).

(6) G. Wheland, *Resonance in Organic Chemistry*, p. 307, John Wiley and Sons, Inc., New York, 1955.

(7) A. Burawoy, *J. Chem. Soc.*, 1177 (1939); and previous work.

(8) G. Badger and R. Buttery, *J. Chem. Soc.*, 2156 (1953).

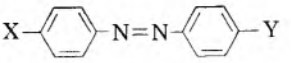
(9) A. Burawoy, *J. Chem. Soc.*, 1865 (1937).

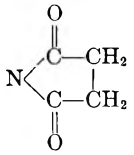
(10) P. Gore and O. Wheeler, *J. Am. Chem. Soc.*, **78**, 2160 (1956).

(11) K. Bowden and E. A. Braude, *J. Chem. Soc.*, 1068 (1952).

TABLE I

ABSORPTION SPECTRAL DATA OF Z BAND IN 95% ETHANOL[a]



| X | Y | $\lambda_{max}$ (log $\epsilon$) | X | Y | $\lambda_{max}$ (log $\epsilon$) |
|---|---|---|---|---|---|
| H | $NO_2$ | 332[2] (4.38) | NHEt | H | 405 (4.42) |
| H | COOMe | 330[4] (4.47) | $NMe_2$ | H | 408 (4.44) |
| H | H | 318 (4.33) | NMeEt | H | 411 (4.45) |
|  | H | 323[13] (4.34) | $NEt_2$ | H | 415 (4.47) |
| Me | H | 333 (4.37) | $NMe_2$ | SCN | 433 (4.51) |
| NMeCHO | H | 338 (4.39) | $N(CH_2CH_2Cl)_2$ | Ac | 435[14] (4.53) |
| NHTos[b] | H | 346 (4.41) | $NMe_2$ | $CH=CH_2$ | 435[15] (4.33) |
| NHCHO | H | 347 (4.44) | $N(CH_2CH_2Cl)_2$ | $NO_2$ | 446[14] (4.33) |
| NHAc | H | 347[13] (4.37) | $NMe_2$ | Ac | 447 (4.50) |
| OH | H | 349 (4.42) | NMeEt | Ac | 454 (4.52) |
| NHCOOEt | H | 352 (4.42) | $NEt_2$ | Ac | 462 (4.54) |
| SMe | H | 362 (4.38) | $NMe_2$ | $-N=N-C_6H_5$ | 473 (4.55) |
| $NH_2$ | H | 385 (4.39) | $NHC_6H_5$ | $NO_2$ | 475 (4.52) |
| OH | $NO_2$ | 386[16] (4.47) | $NMe_2$ | $NO_2$ | 478 (4.52) |
| $N(CH_2CH_2Cl)_2$ | H | 397[14] (4.41) | NMeEt | $NO_2$ | 485 (4.52) |
| NHMe | H | 402 (4.41) | $NEt_2$ | $NO_2$ | 490 (4.56) |

[a] An R-band at 430–450 m$\mu$, log $\epsilon$ 2.9–3.2 is found for all compounds in the table from 4-nitroazobenzene to 4-hydroxy-4′-nitroazobenzene, except for 4-aminoazobenzene. In this compound and the *N*-alkylated aminoazo compounds, the R-band is hidden, but a fairly intense shoulder is found at the long wavelength slope of the main band which has been attributed to hydration of the azo dye.[17] [b] Tos is *p*-toluenesulfonyl.

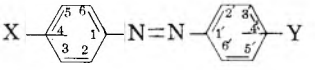
are involved has been called a zwitterionic resonance, or Z, band.[18]

In the 4-substituted azo dyes in Table I there is an increasing shift toward the visible with the following substituents H < Me < NHAc < OH < SMe < $NH_2$ < $N(CH_2CH_2Cl)_2$ < NHMe < NHEt < $NMe_2$ < NMeEt < $NEt_2$. Essentially with an increase in the electron-donor properties of the substituent there is a definite bathochromic shift in the absorption spectra. This same order has been found for 5-substituted 2,1,3-benzoselenadiazoles,[19] *para*-substituted nitrobenzene derivatives,[19] and *para*-substituted triphenylmethane dyes.[20] In the 4-aminoazobenzene dyes, substitution of electron-acceptor groups in the 4′-position causes an increasing shift toward the visible in the order –H < $C_6H_5$ < SCN < $CH=CH_2$ < $COCH_3$ < $N=N-C_6H_5$ < $NO_2$.

For some fifteen 4-dialkylaminoazobenzene dyes containing either a nitro or acetyl group at the negative end of the molecule the position of substitution affected the $\lambda_{max}$ values in that the $\lambda_{max}$ increased in the order 3′ < 2′ << 4′, Table II. This has also been shown for the nitro-4-di(2-

TABLE II

Z BAND OF MISCELLANEOUS AZO DYES IN 95% ETHANOL



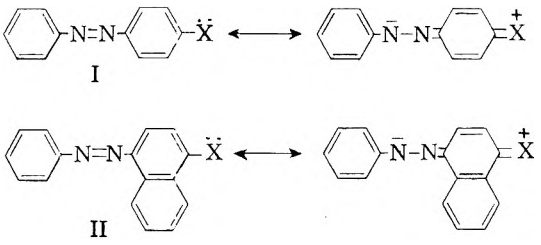
| X | Y | $\lambda_{max}$ (log $\epsilon$) |
|---|---|---|
| 4-EtS-2-Me | H | 367 (4.18) |
| 4-MeS | 4′-MeS | 380 (4.39) |
| $4-Me_2N$ | $4'-C_6H_5$ | 422 (4.53)[21] |
| $4-Me_2N$ | $3'-CF_3$ | 423 (4.47) |
| 4-MeEtN | $3'-CF_3$ | 426 (4.47) |
| $4-Me_2N-2-Me$ | $2'-COOCH_3$ | 420 (4.41) |
| $4-Me_2N$ | 3′-Ac | 420 (4.45) |
| $4-Me_2N-2-Me$ | 3′-Ac | 424 (4.45) |
| $4-Me_2N-2-Me$ | 4′-Ac | 452 (4.50) |
| $4-Me_2N$ | $2'-NO_2$ | 440 (4.43) |
| $4-Me_2N$ | $3'-NO_2$ | 431 (4.46) |
| $4-Me_2N-2-Me$ | $2'-NO_2$ | 447 (4.43) |
| $4-Me_2N-2-Me$ | $3'-NO_2$ | 441 (4.46) |
| $4-Me_2N-2-Me$ | $4'-NO_2$ | 489 (4.49) |
| 4-MeEtN | $2'-NO_2$ | 449 (4.43) |
| 4-MeEtN | $3'-NO_2$ | 445 (4.47) |
| $4-Et_2N$ | $3'-NO_2$ | 450 (4.50) |

(12) H. Dahn and H. Castelmur, *Helv. Chim. Acta*, **36**, 638 (1953).
(13) H. Henbest and T. Owen, *J. Chem. Soc.*, 2968 (1955).
(14) W. Ross and G. Warwick, *J. Chem. Soc.*, 1719 (1956).
(15) M. Martynoff, *Bull. soc. chim. France*, 374 (1955).
(16) A. Pongratz, G. Markgraf, and E. Mayer-Pitsch, *Ber.*, **71**, 1287 (1938).
(17) W. Brode, I. Seldin, P. Spoerri, and G. Wyman, *J. Am. Chem. Soc.*, **77**, 2762 (1955).
(18) E. Sawicki, *J. Org. Chem.*, **21**, 605 (1956).
(19) E. Sawicki and A. Carr, *J. Org. Chem.*, **22**, 503 (1957).
(20) N. Deno, J. Jaruzelski, and A. Schriesheim, *J. Org. Chem.*, **19**, 155 (1954).

chloroethyl)aminoazobenzenes where the 2′, 3′-, and 4′-nitro derivatives have $\lambda_{max}$ 420, 416, and 446 mμ, respectively.[14] Apparently the conjugation of the electronegative group with the amino group is of importance in bringing about the bathochromic shift.

A phenyl group can act as an electron donor or an electron acceptor. Substitution of the electron acceptor 4′-phenyl group in 4-dimethylaminoazobenzene causes a shift to 422 mμ.[21] The same phenomenon is seen in 2-4′-dimethylaminophenylazofluorene where a wave length maximum is found at 423 mμ. In 2-4′-dimethylaminophenylazo-7-nitrofluorene the electron acceptor properties of the fluorene group is materially increased. This causes a wave length shift to 460 mμ.

In both 4-phenylazo-1-naphthol (II, X = OH), $\lambda_{max}$ 409 mμ, as compared to 4-hydroxyazobenzene (I, X = OH), $\lambda_{max}$ 349 mμ, and 4-phenylazo-1-naphthylamine (II, X = $NH_2$), $\lambda_{max}$ 430 mμ, as compared to 4-aminoazobenzene (I, X = $NH_2$), $\lambda_{max}$ 385 mμ, there is a strong spectral shift. An important excited state structure of I involves a



I



II

*p*-benzoquinone ring. The analogous structure in II involves an α-naphthoquinone ring system. The relatively lower energy of the α-naphthoquinone structures would help to account for the strong bathochromic shift shown in II as compared to I. The presence of alkoxy, methylthio, or amino groups at the negative end of the molecule has very little effect on the wave length maximum in 95% ethanol.

On the other hand the addition of water to alcoholic solutions of 4-amino-, 4-dimethylamino-, 4-hydroxy and 4-methoxy substituted azobenzene gives rise to a new absorption band in the visible region. This new band is attributed to the formation of a hydrogen bond between the β azo nitrogen and water.[17] Examination of the visible absorption spectrum in 95% ethanol of a large number of chloro, methyl, methoxy, methylthio, and amino derivatives of 4-aminoazobenzene dyes indicates the presence of a strong unsymmetrical band sloping more gradually at the long wave-length side. This band system appears to consist of two bands. Increasing the amount of water in the solvent increases the intensity of the longer wave-length band while decreasing the intensity of the shorter wave length band, Table III, Fig. 1. An exception

(21) W. Brode, J. Gould, and G. Wyman, *J. Am. Chem. Soc.*, 75, 1856 (1953).

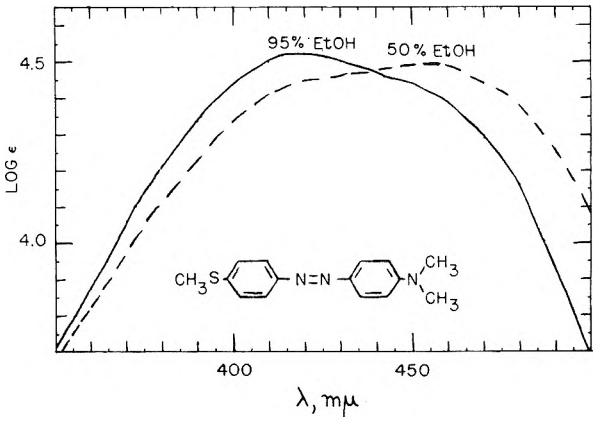



FIG. 1. ABSORPTION SPECTRA: 4′-METHYLTHIO-4-DIMETHYLAMINOAZOBENZENE; in 95% ethanol (——), in 50% ethanol (- - -).

to this rule appears to be 2′-amino-4-dimethylaminoazobenzene which absorbs most strongly at 450 to 470 mμ in 95% and 25% alcohol, Table III, Fig. 2. In the visible spectrum this compound shows fine structure that appears to be absent in the other compounds. It is suggested that intermolecular hydrogen bonding between both alcohol and water with the azo nitrogens and intramolecular hydrogen bonding between the α- and β-azo nitrogens with the amino hydrogen probably account for the fine structure. The intramolecular hydrogen bond between the amino hydrogen and the β-azo nitrogen (see III) could account for the

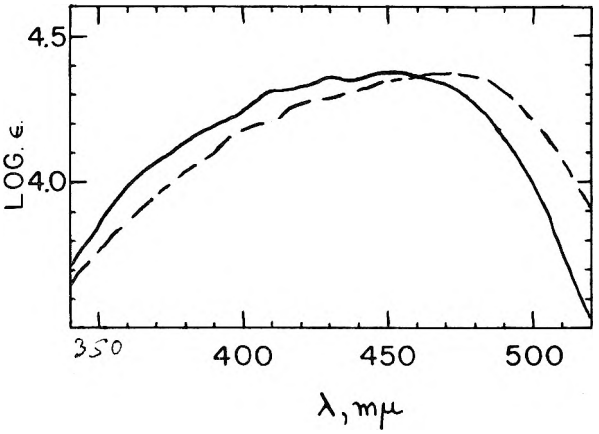
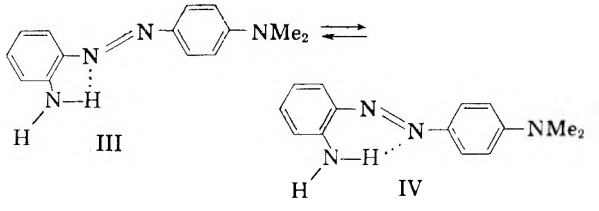



FIG. 2. ABSORPTION SPECTRA: 2′-AMINO-4-DIMETHYLAMINOAZOBENZENE; in 95% ethanol (——), in 25% ethanol (- - -)

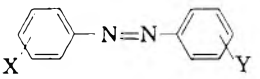
long wave length absorption even in 95% ethanol; the intramolecular hydrogen bond between the amino hydrogen and the α-azo nitrogen (see IV) could account for the absorption at approximately 360 mμ. III is stabilized by the attraction of the



III IV

TABLE III

VISIBLE SPECTRAL DATA IN AQUEOUS ALCOHOL



| X | Y | $\lambda_{max}$ (log $\epsilon$) 95% EtOH | 50% EtOH | X | Y | $\lambda_{max}$ (log $\epsilon$) 95% EtOH | 50% EtOH |
|---|---|---|---|---|---|---|---|
| 4-$NMe_2$ | 2′-OMe | 413 (4.42) | 425 (4.38) | 4-$NHC_6H_5$ | 4′-SMe | 423 (4.56) | 425 (4.49) |
| | | ~450s (4.29)[a] | ~450s (4.36) | | | ~445s (4.52) | 442 (4.52) |
| 4-$NMe_2$ | 3′-OEt | 410 (4.45) | 425 (4.40) | 4-$NMe_2$ | 2′-$NH_2$ | [b] | [b] |
| | | ~440s (4.33) | ~440s (4.39) | | | 452 (4.36) | 468 (4.37)[c] |
| 4-$NMe_2$ | 4′-OMe | 405 (4.46) | 420s (4.40) | 4-$NMe_2$ | 3′-$NH_2$ | 410 (4.39) | ~410s (4.26)[c] |
| | | ~440s (4.34) | 440 (4.41) | | | ~445s (4.20) | 455 (4.36)[c] |
| 4-$NMe_2$ | 4′-OEt | 405 (4.47) | 420s (4.41) | 2-Me-4-$NMe_2$ | 4′-$NH_2$ | 413 (4.48) | 420s (4.36)[c] |
| | | ~440s (4.36) | 440 (4.42) | | | ~460s (4.39) | 460 (4.43)[c] |
| 4-$NMe_2$ | 4′-SMe | 419 (4.52) | 422s (4.45) | 4-$NMe_2$ | 4′-$NH_2$ | 410 (4.48) | ~418s (4.36)[c] |
| | | ~455s (4.41) | 455 (4.49) | | | 440 (4.46) | 458 (4.48)[c] |
| 2-Me-4-$NMe_2$ | 4′-SMe | 422 (4.54) | 432 (4.48) | | | | |
| | | ~460s (4.43) | ~460s (4.48) | | | | |

[a] s = shoulder. [b] Fine structure is found at the short wave length side of the main band. [c] In 25% ethanol.

amino hydrogen for the β-nitrogen because of the high electron density at the β-nitrogen. On the other hand the five membered ring involved in the hydrogen bond of III is more strained than is the comparable six membered ring in IV.

## EXPERIMENTAL[22]

*Preparations.* Most of the dyes were available from other investigations[3] in this laboratory and had been purified by crystallization to a constant melting point 4′-Phenylazo-4-dimethylaminoazobenzene,[23] m.p. 198–199°, 4′-nitro-4-phenylaminoazobenzene,[24] m.p. 158–159°, 4,4′-bismethylthioazobenzene,[25] m.p. 170–171°, 4′-amino-4-dimethylaminoazobenzene,[26] m.p. 186–187°, 3′-amino-4-dimethylaminoazobenzene,[27] m.p. 168–169°, and 2′-amino-4-dimethylaminoazobenzene,[28] m.p. 105–106°, were prepared and purified by the procedures in the literature.

*4′-Acetylamino-2-methyl-4-dimethylaminoazobenzene.* Coupling of diazotized *N*-acetyl-*p*-phenylenediamine with *N,N*-dimethyl-*m*-toluidine by a standard procedure, followed by crystallization from benzene, gave orange crystals, m.p. 189–190°.

*Anal.* Calcd. for $C_{17}H_{20}N_4O$: N, 18.9. Found: N, 18.7.

*4′-Amino-2-methyl-4-dimethylaminoazobenzene.* Hydrolysis of the *N*-acetyl derivative was accomplished by refluxing for 0.5 hr. in Methyl Cellosolve[29]–25% aqueous sulfuric acid solution. Neutralization followed by several crystallizations from heptane gave red-gold plates, m.p. 128–129°.

*Anal.* Calcd. for $C_{15}H_{18}N_4$: N, 22.0. Found: N, 22.1.

*2-4′-Dimethylaminophenylazo-7-nitrofluorene.* Coupling of diazotized 2-amino-7-nitrofluorene with dimethylaniline followed by two crystallizations of the precipitate from nitrobenzene gave glistening black-brown plates, m.p. 270–271°.

*Anal.* Calcd. for $C_{21}H_{18}N_4O_2$: N, 15.6. Found: N, 15.2.

*2-Methyl-4-thiocyanoazobenzene.* To a solution of 1.07 g. of nitrosobenzene in 2 ml. of acetic acid and 6 ml. of alcohol was added 1.64 g. of 2-methyl-4-thiocyanoaniline,[30] m.p. 69–70°, in 2 ml. acetic acid and 4 ml. alcohol. The mixture was kept at 0–10° over 12 hr. The solid was collected and crystallized from hexane to give a 70–80% yield of gleaming orange needles, m.p. 88–89°.

*Anal.* Calcd. for $C_{14}H_{11}N_3S$: C, 66.4; H, 4.35; N, 16.6. Found: C, 66.3; H, 4.28; N, 16.5.

*2-Methyl-4-methylthioazobenzene.* A solution of 0.25 g. of 2-methyl-4-thiocyanoazobenzene and 0.11 g. of potassium hydroxide in 10 ml. of methanol was refluxed for 20 min., cooled, and then 0.1 ml. of methyl iodide was added. An hour later 15 ml. of water was added. Crystallization from hexane gave an 80% yield of orange rods, m.p. 76–77°.

*Anal.* Calcd. for $C_{14}H_{14}N_2S$: C, 69.4; H, 5.78; N, 11.6. Found: C, 69.6; H, 5.84; N, 11.4.

*4′-Methylthio-4-dimethylaminoazobenzene.* To a solution of 2.82 g. of 4′-thiocyano-4-dimethylaminoazobenzene,[31] m.p. 154°, in 40 ml. of methanol was added 1.23 g. of potassium hydroxide in 10 ml. of methanol. The mixture was refluxed 15 min., cooled to 0° and treated with 0.8 ml. of methyl iodide. After standing overnight at 0–10° excess water was added. The precipitate was crystallized from hexane to give a 70% yield of yellow crystals, m.p. 177–178°.

*Anal.* Calcd. for $C_{15}H_{17}N_3S$: N, 15.5. Found: N, 15.2.

*4′-Methylthio-2-methyl-4-dimethylaminoazobenzene.* The coupling of diazotized *p*-thiocyanoaniline[32] with *N,N*-dimethyl-*m*-toluidine by standard procedure gave the crude 4′-thiocyano-2-methyl-4-dimethylaminoazobenzene.

A solution of this crude product in methanol was treated with a solution of 12.3 g. of potassium hydroxide in 20 ml. of methanol. The mixture was refluxed 15 min., cooled to 0°, and filtered. The residue was crystallized from Methyl Cellosolve to give red crystals of 4,4′-bis(*p*-dimethylamino-*o*-tolylazo)diphenyl disulfide, m.p. 200°.

*Anal.* Calcd. for $C_{30}H_{32}N_6S_2$: N, 15.6. Found: N, 15.7.

The cold filtrate was treated with 8 ml. of methyl iodide. After several hours standing at 0–10°, excess water was added. Two crystallizations from heptane gave bulky red crystals, m.p. 120–122°.

*Anal.* Calcd. for $C_{16}H_{19}N_3S$: N, 14.7. Found: N, 14.6.

*4′-Thiocyano-4-phenylaminoazobenzene.* Coupling of diazotized *p*-thiocyano aniline with diphenylamine gave brown-yellow plates, m.p. 151–152°, after several crystallizations from alcohol.

(22) All melting points are uncorrected.

(23) J. Hewitt and F. Thole, *J. Chem. Soc.*, **95**, 1393 (1909).

(24) R. Meldola, *J. Chem. Soc.*, **43**, 425 (1883).

(25) K. Brand and A. Wirsing, *Ber.*, **45**, 1757 (1912).

(26) R. Meldola, *J. Chem. Soc.*, **45**, 106 (1884).

(27) O. Wallach, *Ann.*, **234**, 350 (1886).

(28) W. Ross and G. Warwick, *J. Chem. Soc.*, 1724 (1956).

(29) Trade name for β-methoxyethanol.

(30) M. Likhosherstov and A. Petrov, *J. Gen. Chem. U.S.S.R.*, **3**, 759 (1933); *Chem. Abstr.*, **28**, 2690 (1934).

(31) T. Campbell, D. Young, and M. Rogers, *J. Am. Chem. Soc.*, **73**, 5789 (1951).

(32) H. Kaufmann, *Ber.*, **62**, 390 (1929).

*Anal.* Calcd. for $C_{19}H_{14}N_4S$: N, 17.0. Found: N, 16.7.

*4'-Methylthio-4-phenylaminoazobenzene.* This was prepared by the standard procedure. Crystallization from aqueous alcohol and heptane gave glistening orange crystals, m.p. 126–127°.

*Anal.* Calcd. for $C_{19}H_{17}N_3S$: N, 13.2. Found: N, 13.0.

*Absorption spectral data.* The intense long wavelength band of all compounds was measured with a Beckman Model DU Spectrophotometer in commercial 95% ethanol. The spectra of some of the compounds was determined in 50% and 25% aqueous alcohol. By 50% aqueous alcohol is meant a solution containing 50 ml. of water diluted to 100 ml. with 95% ethanol; by 25% aqueous alcohol is meant a solution containing 75 ml. of water diluted to 100 ml. with 95% ethanol.

GAINESVILLE, FLA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KANSAS STATE COLLEGE]

# Reaction of Sodium Methoxide with 2-Alkyl-2,3-dichloroaldehydes[1]

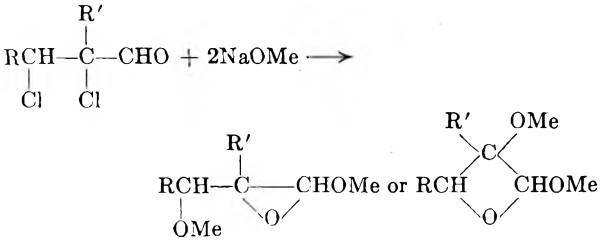
SCOTT SEARLES, JR., EDWIN K. IVES, AND HARRISON M. KASH

*Received February 7, 1957*

The reactions of sodium methoxide with 2-methyl-2,3-dichlorovaleraldehyde and 2-ethyl-2,3-dichlorohexanal in dry methanol and in dry ether have been investigated. The previous report that 4-membered cyclic acetals were formed in methanol solution was found to be incorrect, the products actually being $\alpha,\beta$-epoxy dimethyl acetals. In ether, the products are 2-methoxy-3-chloroaldehydes. The effect of solvent differs from that observed for the reactions of various $\alpha$-chlorocarbonyl compounds with sodium methoxide, apparently due to the large electrical effect of chlorine in the $\beta$-position.

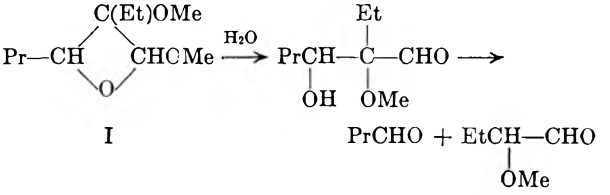
2-Alkyl-2,3-dichloroaldehydes undergo smooth substitution of both chlorine atoms when treated with alcoholic sodium methoxide (2 moles), whereas 2,3-dichloroaldehydes possessing $\alpha$-hydrogen undergo dehydrohalogenation to unsaturated aldehydes.[2] The products from the former, however, are not the corresponding dimethoxyaldehydes, as they possess neither the chemical properties of aldehydes[2] nor the bond characteristic of the carbonyl group in the Raman spectrum.[3]

Since these compounds give the usual aldehyde reactions after they have been treated with aqueous acids, Lichtenberger and his coworkers considered them to be cyclic acetals possessing either the oxirane or the oxetane ring. More recently these products have been reinvestigated by Krausz,[4] who believed that he had definitely established the oxetane structure.



Negatively substituted oxetanes of this type appeared to be completely unknown[5–7] and would be of great interest in connection with current studies on substituted oxetanes.[8]

Krausz's argument for the presence of the oxetane ring in these compounds is based on his study of their hydrolysis products. After dilute sulfuric acid hydrolysis of the dimethoxy compound (I) obtained from 2-ethyl-2,3-dichlorohexanal (II), butyraldehyde was identified. This might have formed by a retrograde-aldol cleavage of a $\beta$-hydroxyaldehyde, formed as follows:



This would not be possible if (I) were a cyclic acetal with the oxirane structure and cleaved to a hydroxymethoxyaldehyde.

For additional evidence on the structure of these compounds, Krausz subjected the dimethoxy compound (III) from 2-methyl-2,3-dichloropentanal (IV) to mild acid hydrolysis, obtained the prod-

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(1) Abstracted in part from the Ph.D. thesis of Edwin K. Ives, Kansas State College, 1957.

(2) J. Lichtenberger and M. Naftali, *Bull. soc. chim. France*, [5], **4**, 325 (1937).

(3) R. Kirmann and J. Lichtenberger, *Compt. rend.*, **206**, 1259 (1939).

(4) F. Krausz, *Ann. chim.*, [12], **4**, 811 (1949).

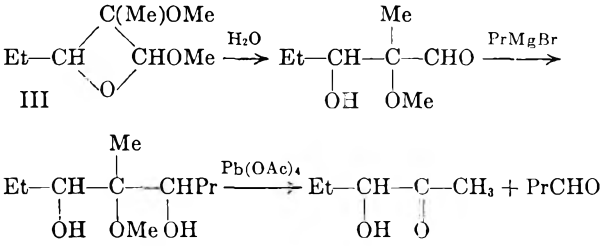
(5) The report of 2-acetoxyoxetane from the reaction of 3-hydroxypropionaldehyde with acetic anhydride (M. Bergmann, A. Mickley, and E. O. Lippmann, *Ber.*, **62**, 1467 (1929)) has been shown to be incorrect by E. Spath and L. Pallam-Raschik (*Monatsh.*, **79**, 447 (1948)).

(6) "3-Chlorooxetane," reported by H. Bigot [*Ann. Chim. phys.*, [6], **22**, 433 (1891)], has been shown by W. E. Noland and B. N. Bastian [*J. Am. Chem. Soc.*, **77**, 3395 (1955)] to be actually 2-chloroallyl alcohol.

(7) Recently 2-phenyloxetane [S. Searles, K. A. Pollart, and E. F. Lutz, *J. Am. Chem. Soc.*, **79**, 948 (1957)] and a steroid derivative having a 3,3-ethylenedioxyoxetane structure [W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955)] have been reported.

(8) S. Searles, K. A. Pollart, and F. Block, *J. Am. Chem. Soc.*, **79**, 952 (1957) and preceding papers.

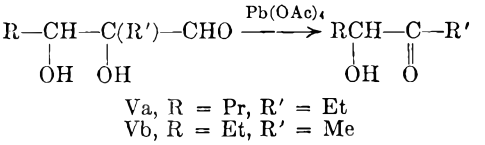
uct as a crude sirup, which he added to excess propylmagnesium bromide. The Grignard product also was obtained as a sirup which was not purified, but after it was treated with lead tetraacetate in benzene, butyraldehyde and 3-hydroxy-2-pentanone were isolated and characterized. This sequence was interpreted as supporting the oxetane structure by the following reasoning. The hydrolysis product of the cyclic acetal with an oxirane ring would be expected to be a 2-hydroxy-3-methoxyaldehyde, and the Grignard product from such would be a *vic*-diol, which on oxidative cleavage would have given 3-methoxy-2-pentanone rather than 3-hydroxy-2-pentanone. Krausz considered that this sequence of reactions confirmed the oxetane structure for III, even though the lead tetraacetate cleavage involved seemed most unusual:



Two intrinsic weaknesses of this proof of the oxetane structure are the assumption that the dimethoxy compounds hydrolyze only to hydroxymethoxyaldehydes, and the failure to consider the isomeric 2,3-epoxy dimethyl acetals as possible structures. These would be expected to hydrolyze easily to 2,3-dihydroxyaldehydes, which would lead to all the reactions reported. Furthermore, since the yields of identified degradation products were quite low, the reactions reported might have been caused by formation of a small amount of 2,3-dihydroxyaldehydes during the hydrolysis of either type of cyclic acetal structure.

Recent data on the infrared spectra of cyclic ethers suggested that the oxetane structures favored by Krausz might be readily confirmed or possibly rejected on a spectral basis. Oxetanes have characteristic strong absorption bands at 970–980 and 1200–1240 cm.$^{-1}$,[9] while oxiranes are characterized by a medium to strong band at 1240–1260 cm.$^{-1}$ as well as a band near 900 cm.$^{-1}$ (sometimes found around 830 cm.$^{-1}$).[10,11] The spectra of I and III, however, possessed bands characteristic of both structures. Although they confirmed the absence of carbonyl and hydroxyl and indicated the presence of an ordinary ether linkage, no conclusion could be drawn regarding the size of the epoxide ring.

Chemical evidence on the structures of these compounds was then sought by studying the structures of their hydrolysis products. Dilute acid hydrolysis of I and III, as carried out by Krausz, was found to give only dihydroxyaldehydes. Assignment of structures Va and Vb to these aldehydes is supported by the isolation of 4-hydroxy-3-heptanone and 3-hydroxy-2-pentanone after lead tetraacetate oxidation.



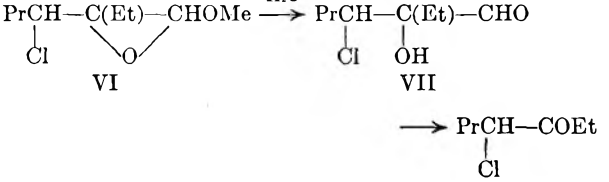
Va, R = Pr, R′ = Et
Vb, R = Et, R′ = Me

No success was realized in finding conditions suitable for hydrolysis of I and III to monomethoxy compounds. This may be significant, as such would be the expected behavior of 2,3-epoxy dimethyl acetals.

Of considerable help in the problem at this point was the isolation in moderate yield of a methoxychloro compound (VI) from the reaction of 2-ethyl-2,3-dichlorohexanal (II) and one equivalent of sodium methoxide. This was apparently an intermediate in the formation of the dimethoxy compound (I), since it reacted with an additional mole of methoxide to form I. It was a neutral compound, analyzing as $C_8H_{14}OCl(OCH_3)$, which was not an aldehyde, since it gave Tollen's and Schiff's tests only after long standing and the infrared spectrum did not contain a carbonyl group.

Hydrolysis of VI with dilute sulfuric acid gave a chlorohydroxy aldehyde, analyzing as $C_8H_{14}O_2Cl$. This was cleaved readily by lead tetraacetate, forming 4-chloro-3-heptanone, indicating it to be the $\alpha$-hydroxy aldehyde, VII.

It follows that VI has the oxirane structure, shown below. Thus, the reaction of the $\alpha,\beta$-dichloroaldehyde with the first mole of methoxide follows the same course as the reaction of various $\alpha$-chlorocarbonyl compounds with sodium methoxide.[12] In the latter cases, however, the $\alpha$-methoxyoxiranes react with methanol solvent to give $\alpha$-hydroxy acetals and $\alpha$-hydroxy ketals.[12]



Apparently compound VI is less reactive than simple $\alpha$-methoxyoxiranes towards methanol though it is reactive towards sodium methoxide,

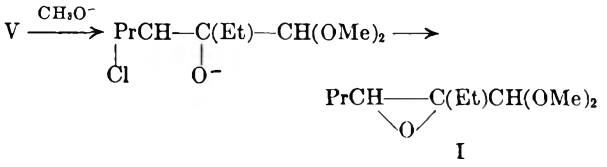
(9) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(10) J. E. Fields, J. O. Cole, and D. E. Woodford, *J. Phys. Chem.*, **18**, 1298 (1950); O. D. Shreve, *et al.*, *Anal. Chem.*, **53**, 282 (1951).

(11) The infrared spectrum of a cyclic acetal with an oxirane ring, 1-methoxy-1,2-epoxybutane, has been published by C. L. Stevens, E. Farkas, and Bernard Gillis, Ref. 12. Strong bands were observed at 1270 and 890 cm.$^{-1}$ and a medium band at 950 cm.$^{-1}$; there were no bands between 950 and 1020 cm.$^{-1}$

(12) C. L. Stevens, E. Farkas, and B. Gillis, *J. Am. Chem. Soc.*, **76**, 2695 (1954) and previous papers.

as seen above. Attack of the second mole of sodium methoxide might reasonably be expected to cleave the oxirane ring, resulting in an acetal intermediate, in which another oxirane ring can form.[13] This would give 2-ethyl-2,3-epoxyhexa-

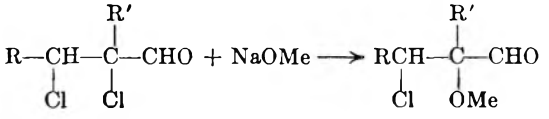


I

nal dimethyl acetal as the structure of the dimethoxy product (I), which is in complete agreement with all the hydrolysis studies. By analogy, the dimethoxy compound (III) must be 2-methyl-2,3-epoxypentanal dimethyl acetal because of the close similarity of mode of formation, spectra, and chemical properties.

Stevens has found the solvent to be a very important factor in the reaction of sodium methoxide with $\alpha$-chlorocarbonyl compounds. In dry ether $\alpha$-methoxyoxiranes (epoxy ethers) were formed, while in methanol $\alpha$-hydroxy acetals (or ketals) were the products, due to the reaction of the oxiranes with the solvent. Therefore, it seemed likely that excellent yields of chloromethoxy compounds, such as VI, would be obtained from the dichloro aldehydes in dry ether.

To our surprise, however, the reaction took a different course in ether, forming 3-chloro-2-methoxyaldehydes, rather than epoxides. The same results



were obtained when up to 2.3 molecular equivalents of sodium methoxide was used in ether and also when toluene was used as the solvent.[14] The evidence for the free aldehyde group in each of these compounds is the strong infrared absorption band at 1740 cm.$^{-1}$ and the immediate rendering of positive Tollens' and Schiff's tests. The presence of one chlorine atom and one methoxyl group was indicated by the elemental and Zeisel analyses, and their positions were shown by hydrolysis of the compounds to chlorohydroxyaldehydes which were cleaved by means of lead tetraacetate to the corresponding $\alpha$-chloroketones.

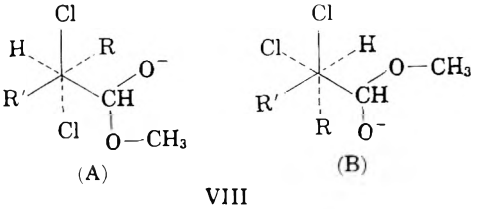
The reason for the solvent being able to alter the course of the reaction of sodium methoxide with $\alpha,\beta$-dichloroaldehydes may be ascribed to one or both of the following two factors: (1) ability of methanol to aid the attack of methoxide ion at the carbonyl carbon and (2) solvation of a possible subsequent dipolar reaction intermediate.

(13) Originally suggested by Dr. B. Gillis and Dr. C. L. Stevens.

(14) It was claimed by Krausz (Ref. 4) that II gave the same dimethoxy product with toluene as with methanol as solvent.

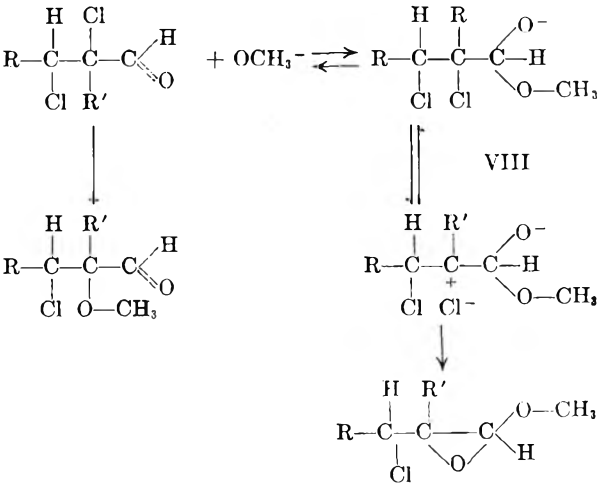
Inspection of molecular models of these aldehydes indicates that when the chlorine atoms are *anti* to each other, the $\beta$-chlorine atom shields the carbonyl carbon (as do also the $\alpha$-chlorine and the $\alpha$-alkyl group). Since this would be expected to be the most stable conformation, it seems likely that attack of methoxide at the carbonyl carbon is sterically hindered in $\alpha,\beta$-dichloroaldehydes. As a result, polarization of the carbonyl group by hydrogen bonding may be a deciding factor as to the principal sites of attack by methoxide.

Attack by the methoxide ion on the carbon atom of the carbonyl group would produce a methoxydichloroalkoxide ion (VIII), which would be highly strained. Examination of molecular models of this intermediate show that when the chlorine atoms are in the *anti* conformation (VIIIA), one or the other of them has to lie extremely close to one of the oxygen atoms. The only way the chlorine-oxygen distances can be reduced is to have the chlorines *syn* to each other (VIIIB).



VIII

In either case there will be considerable direct repulsive force on the $\alpha$-chlorine, while displacement of it by the negatively charged oxygen is greatly inhibited, since the back face of the $\alpha$-carbon is largely covered by the $\beta$-chlorine or the alkyl groups. The strain in this intermediate, however, could be relieved by ionization of the $\alpha$-chlorine, to give a transitory dipolar intermediate, which would cyclize by a front-side attack.



Such ionization of $\alpha$-chlorine would be an $S_N1$ process, requiring a polar solvent. In a non-polar solvent VIII might merely revert to dichloro aldehyde and methoxide. A molecular model shows that the back-side displacement of the $\alpha$-chlorine is much

less hindered in the dichloro aldehyde than in VIII. In ether or toluene apparently attack of methoxide at that sight predominates over attack at the carbonyl.

## EXPERIMENTAL

*2,3-Dichloro-2-methylvaleraldehyde* (IV) was prepared in 60% yield by bubbling chlorine into a dry chloroform solution of 2-methyl-2-pentenal at 5–15°, b.p. 78° (20 mm.) $n_D^{20}$ 1.4540 [literature[2,4] b.p. 68° (14 mm.), $n_D^{23}$ 1.4563].

*2,3-Dichloro-2-ethylhexanal* (II) was prepared in like manner, 80% yield, b.p. 110–112° (20 mm.), $n_D^{20}$ 1.4523 [lit.[2,4] b.p. 95° (14 mm.), $n_D^{22}$ 1.4518].

*2,3-Epoxy-2-methylvaleraldehyde dimethyl acetal* (III) was obtained from the reaction of IV and 2.3 molecular equivalents of sodium methoxide in dry methanol by the literature procedure.[2,5] After a reaction time of 12 hr. at 25°, the yield was 73%. The properties of the product were: b.p. 84–85° (20 mm.), $n_D^{20}$ 1.4192 (lit.[2,4] 70° (15 mm.), $n_D^{18.5}$ 1.4196). Strong infrared bands were observed at 950, 980, 1220, and 1270 cm.$^{-1}$ and a medium band at 890 cm.$^{-1}$

*2-Ethyl-3-chloro-1-methoxy-1,2-epoxyhexane* (VI). A mixture of 50 g. of II and 15 g. of sodium methoxide in 400 ml. of anhydrous methanol was heated at 40° for 30 hr. and then processed in the usual manner,[2,4] giving 29 g. (60%) of a colorless liquid, b.p. 123–125° (30 mm.), $n_D^{20}$ 1.4470. This product gave a positive test for chlorine after sodium fusion and gave Schiff's and Tollens' tests only after heating and standing for 30 min. The infrared spectrum possessed strong bands at 900, 950, 980, 1270, and 1310 cm.$^{-1}$, medium bands at 1120 and 1300 cm.$^{-1}$, and a weak band at 1210 cm.$^{-1}$

*Anal.* Calcd. for $C_9H_{17}O_2Cl$: C, 56.1; H, 8.8; Cl, 17.8; $OCH_3$, 17.1. Found[15]: C, 56.7; H, 8.8; Cl, 17.8; $OCH_3$, 16.1.

*2,3-Epoxy-2-ethylhexanal dimethyl acetal* (I). (*A*) From a mixture of 50 g. of II and 31.5 g. of sodium methoxide in 600 ml. of dry methanol, heated under reflux for 3 days and then processed as usual, was obtained 30 g. (63%) of a colorless liquid, b.p. 107–108° (25 mm.), $n_D^{20}$ 1.4285 (lit.,[2,4] b.p. 95° (17 mm.), $n_D^{16}$ 1.4304).

(*B*) A mixture of 20 g. of VI and 6 g. of sodium methoxide in 200 ml. of anhydrous methanol was heated at 40° for 3 days. After the usual isolation procedure, 12.5 g. (59%) of a product identical to that in A was obtained, b.p. 104° (24 mm.), $n_D^{20}$ 1.4280. The compound gave a negative test for halogen and positive Schiff's and Tollens' tests after heating and standing 30 min. Strong infrared bands were observed at 900, 890, 1000, 1170, 1270, and 1310 cm.$^{-1}$

*Anal.* Calcd. for $C_{10}H_{20}O_3$: $OCH_3$, 32.9. Found: $OCH_3$, 32.1.

*3-Chloro-2-methoxy-2-methylvaleraldehyde.* A solution of 169 g. of IV in 400 ml. of dry ether was added dropwise to a stirred suspension of 124 g. of sodium methoxide in 1.5 l. of dry ether at 0–5°. The reaction mixture was allowed to warm to room temperature and to stand overnight and was then filtered. Distillation of the filtrate gave 111 g. (68%) of a colorless oil, b.p. 85–90° (23 mm.), $n_D^{20}$ 1.4400. It gave the usual aldehyde tests and had infrared bands at 1070 (m) and 1740 (s) cm.$^{-1}$

*Anal.* Calcd. for $C_7H_{13}O_2Cl$: C, 51.1; H, 7.9; Cl, 21.6; $OCH_3$, 18.8. Found: C, 50.9; H, 7.5; Cl, 21.5; $OCH_3$, 18.8.

*3-Chloro-2-methoxy-2-ethylhexanal* (VI). The reaction of 198 g. (1 mole) of II and 124 g. (2.3 moles) of sodium methoxide in ether was carried out in the same manner as described above to give 118 g. (60%) of a colorless oil, b.p. 95–100° (20 mm.), $n_D^{20}$ 1.4250. Titration of the inorganic precipitate dissolved in water indicated that only 1.1 moles of sodium methoxide had been consumed in the reaction. The organic product gave a positive chlorine test and positive Tollens' and Schiff's tests; it had infrared bands at 1170 (m) and 1740 (s) cm.$^{-1}$

*Anal.* Calcd. for $C_9H_{17}O_2Cl$: C, 56.1; H, 8.8; Cl, 17.8; $OCH_3$, 16.1. Found: C, 56.3; H, 8.8; Cl, 17.7; $OCH_3$, 16.2.

By the same procedure except for using dry toluene as solvent, this compound was obtained in 63% yie d.

*Hydrolysis of cyclic acetals and methoxy aldehyd s.* Twenty g. of the compound to be hydrolyzed was heated on the steam bath for 30 min. with 100 ml. of 1*N* sulfuric acid with frequent shaking. The mixture was then cooled, neutralized with saturated sodium bicarbonate and extracted with ether. The product was isolated by distillation of the dried extracts. The infrared spectrum of each indicated hydroxyl and aldehyde carbonyl groups but no ether function. Each gave positive Tollens' and Schiff's tests and Zeisel analysis showed a methoxyl content of 0.7% or less in each case.

The lead tetraacetate oxidations of these products were carried out by dissolving in dry benzene (75 ml. for 10 g. of hydroxyaldehyde) and adding a 10% excess of lead tetraacetate in several portions. After heating on the steam bath 2 hr., the reaction mixture was filtered. The filtrate was shaken with dilute sulfuric acid, dried and distilled. The infrared spectra of the products were in agreement with the structures assigned.

From compound VI was obtained *3-chloro-2-hydroxy-2-ethylhexanal* (VII) in 55% yield, b.p. 105–110° (16 mm.), $n_D^{20}$ 1.4370, m.p. of 2,4-DNP 203–204°.

*Anal.* Calcd. for $C_{18}H_{15}O_2Cl$: C, 53.8; H, 8.4; Cl, 19.9. Found: C, 53.7; H, 8.5; Cl, 19.9.

Lead tetraacetate cleavage of VII gave a 56% yield of *4-chloro-3-heptanone*, b.p. 85–87° (16 mm.), $n_D^{20}$ 1.4408.

*Anal.* Calcd. for $C_7H_{13}OCl$: C, 56.6; H, 8.7; Cl, 23.2. Found: C, 56.8; H, 8.7; Cl, 23.0.

The 2,4-DNP melted at 204°.

*Anal.* Calcd. for $C_{13}H_{17}O_4N_4Cl$: C, 46.86; H, 5.3; Cl, 9.9; N, 15.6. Found: C, 46.53; H, 5.2; Cl, 9.5; N, 15.9.

Hydrolysis of compound I produced 2,3-dihydroxy-2-ethylhexanal (Va) (46% yield), b.p. 130–135° (15 mm.), $n_D^{20}$ 1.5206.

*Anal.* Calcd. for $C_8H_{16}O_3$: C, 60.0; H, 10.1. Found: C, 60.0; H, 10.7. Lead tetraacetate oxidation of Va gave *4-hydroxy-3-heptanone*, (37%), b.p. 71–73° (16 mm.), $n_D^{20}$ 1.4620 [lit.[16] b.p. 74–75° (18 mm.)], m.p. of semicarbazone 120–122° (lit.[16] 121–122°).

Hydrolysis of compound III lead to *2-methyl-2,3-dihydroxyvaleraldehyde* (Vb) in 53% yield, b.p. 130–135° (30 mm.), $n_D^{20}$ 1.4447, m.p. of 2,4-DNP 222–223°.

*Anal.* Calcd. for $C_6H_{12}O_3$: C, 54.5; H, 9.1. Found: C, 54.8; H, 9.3. Lead tetraacetate oxidation of Vb gave *3-hydroxy-2-pentanone*, b.p. 105–107° (50 mm.), [lit.[17] b.p. 77° (35 mm.)], $n_D^{20}$ 1.4350, which forms a *bis*-2,4-DNP melting at 226–228° (mixed m.p. with 2,4-DNP of the aldehyde 215–219°).

*Anal.* Calcd. for $C_{17}H_{16}O_8N_8$: C, 43.9; H, 3.4; N, 24.2. Found: C, 44.4; H, 3.5; N, 24.4.

Hydrolysis of VI gave 66% yield of 2-ethyl-2-hydroxy-3-chlorohexanal, identical to the compound obtained by hydrolysis of compound III.

From 3-chloro-2-methoxy-2-methylvaleraldehyde was obtained 2-methyl-2-hydroxy-3-chlorovaleraldehyde (55%), b.p. 95–97° (27 mm.), $n_D^{20}$ 1.4581.

*Anal.* Calcd. for $C_6H_{11}O_2Cl$: C, 47.4; H, 7.3. Found: C, 47.4; H, 7.2.

(15) Carbon-hydrogen microanalyses reported in this paper were done by Geller Laboratories, Hackensack, N. J. The chlorine and methoxyl analyses were done by the Carius and Zeisel methods, respectively.

(16) E. D. Venus-Danilova, *Bull. soc. chim. France* [4], **43**, 479 (1928).

(17) H. von Peckmann and F. Dahl, *Ber.*, **23**, 2425 (1890).

Lead tetraacetate oxidation of the above gave 3-chloro-2-pentanone (38%), b.p. 123–125° (730 mm.) (lit. b.p. 130°[18]), $n_D^{20}$ 1.4280, which formed a 2,4-DNP melting at 106–107°.

*Anal.* Calcd. for $C_{11}H_{13}O_4N_4Cl$: C, 43.8; H, 4.3; Cl, 11.8; N, 18.7. Found: C, 43.9; H, 4.3; Cl, 11.5; N, 18.6.

(18) M. Conrad, *Ann.*, **186**, 241 (1877).

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MANHATTAN, KAN.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

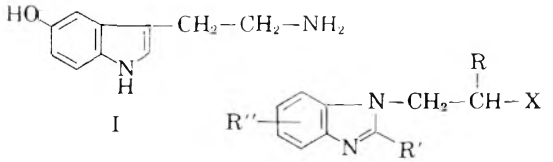
# 1-(β-Aminoalkyl)benzimidazoles[1a]

WILLIAM B. WHEATLEY AND GERALD F. STINER[1b]

*Received February 6, 1957*

A series of 1-(β-aminoalkyl)benzimidazoles has been synthesized by a reaction sequence involving the base-catalyzed addition of acrylamide or methacrylamide to benzimidazoles and subsequent Hofmann rearrangement of the amides thus obtained.

During the past few years, the role of serotonin (I), 5-hydroxytryptamine, in certain physiological functions has been the subject of much investigation. Of particular interest have been its effect on the cardiovascular system and its place in mental processes, neither of which is completely understood as yet. It does indeed have a powerful vasoconstrictor action, and the hypothesis that an excess of serotonin is a significant factor in essential



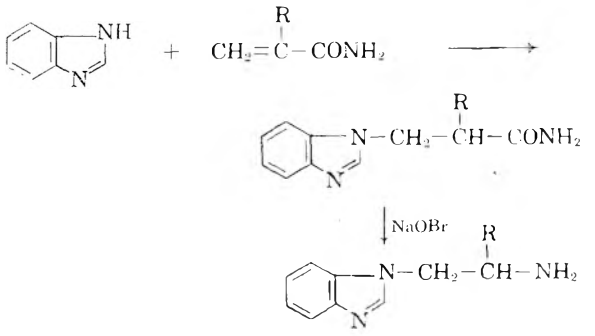
I



II, X = $NH_2$
III, X = $CONH_2$

hypertension has been proposed.[2] This hypothesis has prompted the synthesis of a number of indoles related to serotonin which might be antagonists.[3] The authors became interested in this problem and decided to attack it by replacing the indole nucleus of serotonin with the isosteric benzimidazole nucleus. At this time the authors wish to report the synthesis of a series of compounds, the simplest of which is 1-(β-aminoethyl)benzimidazole (II, R, R′, R″ = H).

Since benzimidazoles are readily obtained from *o*-phenylenediamine and organic acids,[4] it was felt that introduction of the β-aminoethyl group into a preformed benzimidazole would be the best synthetic approach. A sequence involving cyanomethylation of benzimidazole, followed by reduction to the primary amine, was attempted first, with quite unpromising results. Recalling that acrylonitrile adds to benzimidazole,[5] we tried the addition of acrylamide, to be followed if successful by a Hofmann rearrangement.



This synthesis proved to be acceptable, and could be adapted to the preparation of β-aminopropyl (R = $CH_3$) benzimidazoles by the use of methacrylamide. The synthesis of β-aminopropyl compounds had been contemplated, since it is known that the methyl group adjacent to the amine function is effective in inhibiting *in vitro* enzymatic degradation of many primary amines.[6]

Acrylamide and methacrylamide add to benzimidazoles, on boiling several hours in pyridine solution with Triton B as catalyst, to yield β-(1-benzimidazole)propionamides and β-(1-benzimidazole)-isobutyramides in reasonably good yields. In Table I are summarized a number of such amides; benzimidazoles substituted in the 2 and 5 positions were used. In the case of those benzimidazoles having a substituent in the benzene ring, the expected

(1) (a) Presented before the Division of Medicinal Chemistry, AMERICAN CHEMICAL SOCIETY, Atlantic City, September, 1956. (b) Present address: State University of New York, College of Medicine, Syracuse, N. Y.

(2) D. W. Woolley and E. N. Shaw, *J. Am. Chem. Soc.*, **74**, 2948 (1952).

(3) D. W. Woolley and E. N. Shaw, *Science*, **124**, 34 (1956).

(4) J. B. Wright, *Chem. Revs.*, **48**, 397 (1951).

(5) (a) British patent **457,621** [*Chem. Abstr.*, **31**, 3068 (1937)]; (b) L. S. Efros and B. A. Poraĭ-Koshits, *Zhur. Obshchei Khim.*, **23**, 697 (1953)[*Chem. Abstr.*, **48**, 7603 (1954)].

(6) W. H. Hartung, *Ann. Rev. Biochem.*, **15**, 593 (1946).

TABLE I

SUBSTITUTED β-(1-BENZIMIDAZOLE)PROPIONAMIDES (III)

| R | R′ | R″ | Yield, % | M.P., °C.[a] | Formula | Analyses: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|---|
| H | H | H | 78 | 173.5–175.0 | $C_{10}H_{11}N_3O$ | 63.5 | 63.6 | 5.9 | 6.1 |
| | $CH_3$ | | 67 | 195.5–197.0 | $C_{11}H_{13}N_3O$ | 65.0 | 64.7 | 6.4 | 6.5 |
| | $C_3H_7$ | | 50 | 198.5–200.0 | $C_{13}H_{17}N_3O$ | 67.5 | 67.8 | 7.4 | 7.4 |
| | $i$-$C_3H_7$ | | 61 | 213.5–215.0 | $C_{13}H_{17}N_3O$ | 67.5 | 67.3 | 7.4 | 7.4 |
| | $C_6H_5CH_2$ | | 57[b] | 192.5–194.5 | $C_{17}H_{17}N_3O$ | 73.1 | 73.8 | 6.1 | 6.1 |
| | H | $CH_3$ | 60 | 162–186 | $C_{11}H_{13}N_3O$ | 65.0 | 65.1 | 6.4 | 6.4 |
| | | $CH_3O$ | 57 | 159–164 | $C_{11}H_{13}N_3O_2$ | 60.3 | 60.1 | 6.0 | 6.2 |
| | | Cl | 44 | 159–200 | $C_{10}H_{10}ClN_3O$ | 53.7 | 54.0 | 4.5 | 4.5 |
| $CH_3$ | | H | 59 | 183.0–185.5 | $C_{11}H_{13}N_3O$ | 65.0 | 65.1 | 6.4 | 6.4 |
| | $CH_3$ | | 48 | 227.5–231.0 | $C_{12}H_{15}N_3O$ | 66.3 | 66.6 | 7.0 | 7.1 |

[a] All amides were recrystallized from water, except when R′ = $C_6H_5CH_2$ which was recrystallized from isopropyl alcohol. [b] It is reported that 2-benzylbenzimidazole does not add acrylonitrile.[5b]

TABLE II

SUBSTITUTED 1-(β-AMINOALKYL)BENZIMIDAZOLES II

| R | R′ | R″ | Yield, % | M.P., °C.[a] | Formula | Analyses: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|---|
| H | H | H | 27 | 271–277[b] | $C_9H_{11}N_3 \cdot 2HCl$ | 46.2 | 46.2 | 5.6 | 5.6 |
| | $CH_3$ | | 59 | 286–289 | $C_{10}H_{13}N_3 \cdot 2HCl$ | 48.4 | 48.2 | 6.1 | 6.3 |
| | $i$-$C_3H_7$ | | 22 | 140–143 | $C_{12}H_{17}N_3 \cdot 2HCl \cdot H_2O$ | 49.0 | 48.5 | 7.2 | 7.5 |
| | $C_6H_5CH_2$ | | 31 | 251.5–254 | $C_{16}H_{17}N_3 \cdot 2HCl$ | 59.2 | 59.3 | 5.9 | 6.1 |
| | H | $CH_3$ | 57 | 210–218 | $C_{10}H_{13}N_3 \cdot 2HCl \cdot {}^1/_2H_2O$ | 46.7 | 47.0 | 6.4 | 6.3 |
| | | $CH_3O$ | 47 | 230–240 | $C_{10}H_{13}N_3O \cdot 2HCl$ | 45.4 | 44.7 | 5.7 | 5.8 |
| | | Cl | 44 | 243–247 | $C_9H_{10}ClN_3 \cdot 2HCl$ | 40.3 | 40.2 | 4.5 | 4.6 |
| $CH_3$ | | H | 44 | 71.5–74.5[c] | $C_{10}H_{13}N_3$ | 68.5 | 68.1 | 7.5 | 7.2 |
| | $CH_3$ | | 64 | 268.5–275 | $C_{11}H_{15}N_3 \cdot 2HCl$ | 50.3 | 50.1 | 6.5 | 6.9 |

[a] The dihydrochlorides were recrystallized from methanol-ether. [b] See ref. 9. [c] Recrystallized from benzene-cyclohexane.

mixtures of 5- and 6-isomeric amides were obtained. The Hofmann rearrangement proceeds in fair yields with the amides, giving the amines which are described in Table II.

It is probable that this sequence of reactions could be applied to other compounds, provided of course that a sufficiently activated position is available for addition of the unsaturated amide, and that other portions of the molecule are inert towards hypobromite. This might prove more satisfactory than methods hitherto used for introduction of the β-aminoalkyl group, many of which are quite lengthy.

## EXPERIMENTAL[7]

*β-(1-Benzimidazole)propionamide. Method A.* Benzimidazole (59.0 g., 0.5 mole) and acrylamide (35.6 g., 0.5 mole) were suspended in 150 ml. of pyridine and 4.0 ml. of Triton B[8] was added. Heat was gradually applied to the stirred reaction mixture, bringing it to reflux, where it was maintained for 7 hr. On cooling, crystals separated and were collected by filtration. Recrystallization of the crude solid from water afforded 74.0 g. of β-(1-benzimidazole)propionamide, m.p. 173.5–175.0°.

(7) Melting points are uncorrected.

(8) A 2.5*N* aqueous solution of benzyltrimethylammonium hydroxide supplied by Rohm & Haas was used.

*Method B.* A solution of 1.71 g. (0.01 mole) of β-(1-benzimidazole)propionitrile[5] in 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 24 hr. The reaction mixture was poured onto ice and made basic with ammonium hydroxide. Chilling and scratching induced crystallization, giving on filtration 1.67 g. (88%) of β-(1-benzimidazole)propionamide, m.p. 174.0–175.5°. A mixture of the amides prepared by the two different routes showed no depression in melting point.

The reaction of substituted benzimidazoles with acrylamide or methacrylamide yielded, as described in Method A, the amides listed in Table I. Those benzimidazoles containing substituents in the benzene ring gave mixtures of isomeric 5- and 6-substituted amides, as indicated by the wide melting ranges. These mixtures could not be separated reasily by crystallization and were not investigated further.

*1-(β-Aminoethyl)benzimidazole.* To an ice-cold, stirred solution of 24.0 g. (0.6 mole) of sodium hydroxide in 200 ml. of water was added 6.0 ml. (0.12 mole) of bromine. When all of the bromine had dissolved, 18.9 g. (0.10 mole) of β-(1-benzimidazole)propionamide was added all at once. The ice bath was removed and external heat applied, causing the amide to dissolve rapidly. The clear yellow solution was refluxed for 6 hr., then cooled and extracted with four 50-ml. portions of methylene chloride. Evaporation of the solvent from the combined extracts left a residual oil of 11.5 g., which could be crystallized with difficulty on scratching under ether. The oil was dissolved in 100 ml. of methanol, treated with an excess of dry hydrogen chloride and the acidic solution was diluted with 300 ml. of ether. There was thus obtained 12.7 g. of crude solid, which after several recrystallizations from methanol-ether afforded 6.3

g. of 1-(β-aminoethyl)benzimidazole dihydrochloride, m.p. 271–277° dec.[9]

In a similar manner the β-aminoalkylbenzimidazoles in Table II were prepared. One was isolated as the free base, the others as the dihydrochlorides. Even after several recrystallizations, these salts decomposed over a rather wide range at the melting point. In order to obtain material for preliminary pharmacological testing, the mixtures of isomeric 5- and 6-substituted amides (Table I, R″ ≠ H) were treated as above with hypobromite. No attempt other than ordinary recrystallization was made to separate the mixtures of products.

*Acknowledgment.* The authors wish to acknowledge the continued interest of Dr. Lee C. Cheney throughout this work. Microanalyses were performed by Richard M. Downing.

SYRACUSE, N. Y.

(9) This compound has also been prepared by a different synthesis, starting with *N*-(2-phthalimidoethyl)-*o*-phenylenediamine [P. Mamalis, V. Petrow, and B. Sturgeon, *J. Chem. Soc.*, 1600 (1950).

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

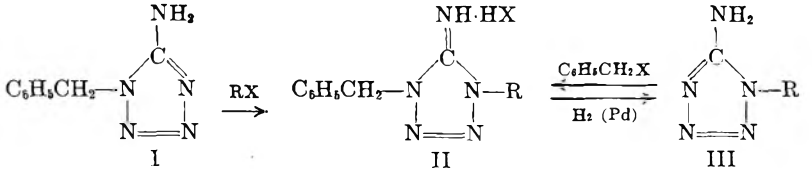
# Alkylated 5-Aminotetrazoles, Their Preparation and Properties[1]

DOUGLAS F. PERCIVAL[2] AND ROBERT M. HERBST

*Received February 13, 1957*

A group of 1,4-benzylalkyl-5-iminotetrazolines was prepared both by alkylation of 1-benzyl-5-aminotetrazole and by benzylation of 1-alkyl-5-aminotetrazoles. In each instance both processes gave identical pairs of compounds. Furthermore, catalytic hydrogenolysis removed the benzyl group from both products and in each case a 1-alkyl-5-aminotetrazole was recovered. These observations confirm the conclusion that the alkylation of 1-alkyl-5-aminotetrazoles takes place in the 4-position. A group of 1,4-dialkyl-5-iminotetrazolines in which both alkyl groups were the same was prepared by similar procedures. A comparable group of 1-alkyl-5-alkylaminotetrazoles was prepared both by addition of hydrazoic acid to the appropriate carbodiimides and from suitable aminoguanidines. The marked differences between comparably substituted 1,4-dialkyl-5-iminotetrazolines and 1-alkyl-5-alkylaminotetrazoles further substantiates the conclusion that alkylation of 1-alkyl-5-aminotetrazoles leads primarily to the 1,4-dialkyl-5-iminotetrazolines with the alkylating agents and conditions employed. An attempt has been made to correlate the physical and chemical properties of the alkylated 5-aminotetrazoles with the tautomeric and resonance possibilities inherent in the several groups.

Many years ago Thiele and Ingle[3] showed that benzylation of 5-aminotetrazole led to several mono- and dibenzylated products whose structures were not established at that time. More recently the alkylation of a number of 1-alkyl-5-aminotetrazoles was studied[4] and it was noted that the introduction of a second alkyl group caused marked changes in the physical and chemical properties of the compounds. Although structures were assigned to the dialkylated aminotetrazoles, it was recognized that further work was required to establish the true structure of these compounds. Subsequently, based on a comparison of the physical properties of several dialkylated aminotetrazoles and their derivatives in which the same pair of alkyl groups had been introduced in different order, it was suggested that the compounds were actually 1,4-dialkyl-5-iminotetrazolines.[5] This conclusion was supported by the ethylation of 1-benzyl-5-aminotetrazole (I) with ethyl sulfate followed by removal of the benzyl group by hydrogenolysis and isolation of 1-ethyl-5-aminotetrazole (III, R = ethyl).[5] A similar conclusion was reached by Henry *et al.*, as the result of methylation of I and isolation of 1-methyl-5-aminotetrazole (III, R = methyl) after hydrogenolytic removal of the benzyl group.[6] In both cases the conclusions were further supported by the fact that the benzylethyl(or methyl-)iminotetrazolines (II, R = ethyl or methyl, were identical whether prepared by ethylation (or methylation) of I or by benzylation of III (R = ethyl or methyl).




I II III

In this report further studies of the alkylation of 1-substituted 5-aminotetrazoles with a variety of alkylating agents are described from which it may

(1) Based on a thesis submitted to the School for Advanced Graduate Studies at Michigan State University in 1955 by Douglas F. Percival in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: California Research Corp., Richmond, Calif.

(3) J. Thiele and H. Ingle, *Ann.*, **287**, 233 (1895).

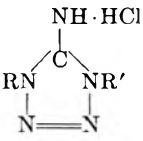
(4) R. M. Herbst, C. W. Roberts, and E. J. Harvill, *J. Org. Chem.*, **16**, 139 (1951).

(5) R. M. Herbst and D. F. Percival, *J. Org. Chem.*, **19**, 439 (1954).

(6) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).

TABLE I

1,4-DIALKYL-5-IMINOTETRAZOLINE HYDROCHLORIDES



| R | R'[a] | Yield % | M.P.° C.[b] | Formula | Analyses Calculated C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| Methyl | Benzyl[c] | 47 | 216 | $C_9H_{12}ClN_5$ | 47.9 | 5.4 | 31.0 | 48.1 | 5.5 | 30.4 |
| Benzyl | Methyl | 50 | 216 | $C_9H_{12}ClN_5$ | 47.9 | 5.4 | 31.0 | 48.2 | 5.5 | 30.9 |
| Ethyl | Benzyl[c] | 55 | 225 | $C_{10}H_{14}ClN_5$ | 50.1 | 5.9 | 29.2 | | | 29.2 |
| Benzyl | Ethyl | 49 | 224 | $C_{10}H_{14}ClN_5$ | 50.1 | 5.9 | 29.2 | | | 29.2 |
| *n*-Propyl | Benzyl | 74 | 199 | $C_{11}H_{16}ClN_5$ | 52.1 | 6.3 | 27.6 | 52.2 | 6.1 | 27.5 |
| Benzyl | *n*-Propyl | 58 | 198 | $C_{11}H_{16}ClN_5$ | 52.1 | 6.3 | 27.6 | 52.0 | 6.7 | 27.5 |
| *n*-Butyl | Benzyl | 79 | 196 | $C_{12}H_{18}ClN_5$ | 53.8 | 6.8 | 26.2 | 53.8 | 6.9 | 26.0 |
| Benzyl | *n*-Butyl | 62 | 195 | $C_{12}H_{18}ClN_5$ | 53.8 | 6.8 | 26.2 | 54.3 | 6.7 | 26.0 |
| β-Phenylethyl | Benzyl | 80 | 221 | $C_{16}H_{18}ClN_5$ | 60.9 | 5.7 | 22.2 | 61.0 | 6.0 | 22.0 |
| Benzyl | β-Phenylethyl | 49 | 220 | $C_{16}H_{18}ClN_5$ | 60.9 | 5.7 | 22.2 | 60.7 | 5.6 | 22.5 |
| Methyl | Methyl[d] | 56 | 241 | $C_3H_8ClN_5$ | 24.1 | 5.4 | 46.8 | 24.0 | 5.5 | 47.1 |
| Ethyl | Ethyl[d] | 45 | 228 | $C_5H_{12}ClN_5$ | 33.8 | 6.8 | 39.4 | 34.0 | 6.9 | 39.1 |
| *n*-Propyl | *n*-Propyl | 54 | 193 | $C_7H_{16}ClN_5$ | 40.9 | 7.8 | 34.0 | 41.0 | 8.0 | 33.6 |
| *n*-Butyl | *n*-Butyl | 46 | 203 | $C_9H_{20}ClN_5$ | 46.2 | 8.6 | 30.0 | 46.2 | 8.5 | 29.9 |
| Benzyl | Benzyl[d] | 65 | 214 | $C_{15}H_{16}ClN_5$ | 59.7 | 5.3 | 23.2 | 59.9 | 5.5 | 23.1 |

[a] R' is the group introduced by alkylation. [b] All compounds melted with decomposition; mixtures of the respective pairs showed no depression of the melting points. [c] Ref. 4. [d] Ref. 3.

be concluded that the nature of the alkylated products is not greatly influenced by the character of the alkylating agents. For this purpose I was alkylated with alkyl sulfates, alkyl benzene- and toluenesulfonates, and a number of alkyl halides. Furthermore, the corresponding 1-alkyl-5-aminotetrazoles (III) were prepared from alkylcyanamides[7] and benzylated with benzyl chloride. In each instance identical 1,4-benzylalkyl-5-iminotetrazolines (II) were formed by both routes as evidenced by comparison of the melting points and mixture melting points of their hydrochlorides, phenylthioureas, and benzenesulfonyl derivatives (Tables I and III) and infrared absorption spectra of their hydrochlorides. Identity of the products was also substantiated by removal of the benzyl group by hydrogenolysis and isolation of the anticipated 1-alkyl-5-aminotetrazole (III).

In addition, a series of 1,4-dialkyl-5-iminotetrazolines with identical alkyl groups in both positions was prepared by interaction of the 1-alkyl-5-aminotetrazoles with similar alkyl benzene- or toluenesulfonates. The properties of the 1,4-dialkyl-5-iminotetrazolines obtained in this way were similar to those of the benzyl alkyl compounds. They were characterized as hydrochlorides, phenylthioureas, and benzenesulfonyl derivatives (Tables I and III). As a result it is now possible to identify the dimethyl, diethyl, and *alpha* dibenzyl 5-aminotetrazoles of Thiele and Ingle[3] as the 1,4-dialkyl-5-iminotetrazolines. Furthermore, all of the compounds described by Herbst, Harvill, and Roberts[4] as 1-alkyl-5-alkylaminotetrazoles should be formulated as 1,4-dialkyl-5-iminotetrazolines.

For comparative purposes a group of 1-alkyl-5-alkylaminotetrazoles (VI) with identical alkyl substituents in both positions was prepared (Table II). Two procedures were used for the synthesis of these compounds. Symmetrically substituted dialkylthioureas (IV) were converted into dialkylcarbodiimides (V) by treatment with mercuric oxide,[8] followed by interaction of the carbodiimides with hydrazoic acid in benzene or xylene solution to form the tetrazoles (VI). Although it is likely that the procedures developed by Stollé[9] for the preparation of 1-aryl-5-arylaminotetrazoles from symmetrical diarylthioureas by interaction with sodium azide in the presence of lead carbonate or oxide involve the transitory formation of diarylcarbodiimides, we have found no record of the synthesis of tetrazoles from previously formed carbodiimides. To support the identity of the products formed in this reaction sequence the same group of 1-alkyl-5-alkylaminotetrazoles was prepared from appropriately substituted aminoguanidines (VIII) by the procedure developed by Finnegan *et al.*[10] The compounds prepared by both procedures were identical in every respect (Table II) and differed markedly from the correspondingly substituted 1,4-dialkyl-5-iminotetrazolines. The

(7) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1014 (1953).

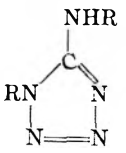
(8) E. Schmidt, F. Hitzler, and E. Lahde, *Ber.*, 71, 1933 (1938). E. Schmidt and W. Striewsky, *Ber.*, **73**, 286 (1940); *Ber.*, **74**, 1285 (1941).

(9) R. Stollé, *Ber.*, **55**, 1289 (1922); *Ber.*, 62, 1118 (1929); *J. prakt. Chem.*, **134**, 282 (1932).

(10) W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

TABLE II

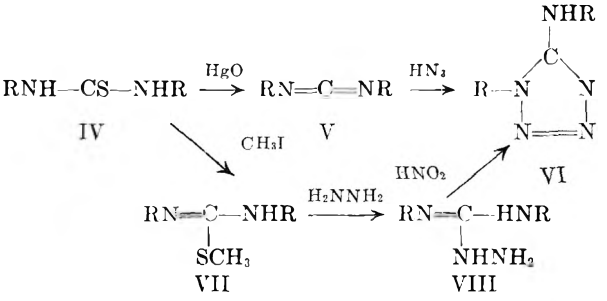
1-ALKYL-5-ALKYLAMINOTETRAZOLES



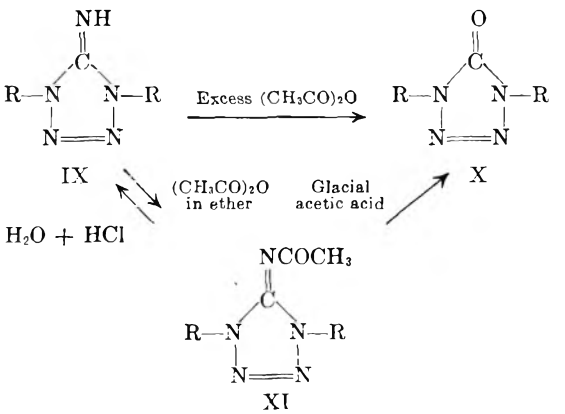
| R | M.P., °C.[a] | Method | Yield, %[b] | Formula | Analyses Calculated C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| Methyl | 171–172 | A-1 | 32 | $C_3H_7N_5$ | 31.9 | 6.2 | 61.9 | 32.0 | 6.3 | 62.2 |
| Ethyl[c] | 92–93 | A-1 | 57 | $C_5H_{11}N_5$ | 42.5 | 7.9 | 49.6 | 42.9 | 7.8 | 49.1 |
| | 92–93 | B | 59 | | | | | | | |
| *n*-Propyl | 70–71 | A-1 | 69 | $C_7H_{15}N_5$ | 49.7 | 8.9 | 41.4 | 50.1 | 9.1 | 41.0 |
| | 71–72 | B | 50 | | | | | | | |
| Isopropyl | 160–161 | A-2 | 78 | $C_7H_{15}N_5$ | 49.7 | 8.9 | 41.4 | 49.5 | 8.9 | 41.5 |
| | 160–161 | B | 62 | | | | | 49.8 | 8.7 | 41.3 |
| *n*-Butyl | 73–74 | A-1 | 61 | $C_9H_{19}N_5$ | 54.8 | 9.7 | 35.5 | 54.9 | 9.6 | 35.1 |
| | 72–73 | A-2 | 73 | | | | | | | |
| | 73–74 | B | 48 | | | | | | | |
| Benzyl[d] | 167–168 | A-1 | 50 | $C_{15}H_{15}N_5$ | 67.9 | 5.7 | 26.4 | 68.1 | 5.9 | 26.3 |
| | 167–168 | A-2 | 68 | | | | | | | |

[a] Mixture melting points of products made by different methods showed no depression. [b] Yields are based on amount of thiourea employed in methods A-1 and A-2, or aminoguanidine hydriodide in method B. [c] Ref. 10. [d] Ref. 3.

*beta* dibenzyl 5-aminotetrazole of Thiele and Ingle[3] is identical with VI (R = benzyl) prepared by either of these methods.



During attempts to prepare an acetyl derivative of 1,4-dibenzyl-5-iminotetrazoline (IX, R = benzyl) by treatment with excess hot acetic anhydride, a compound was obtained in which the imino group had apparently been replaced by oxygen, possibly by acetolysis. The product, 1,4-dibenzyl-4-ketotetrazoline (X, R = benzyl), was identical with the material obtained according to Thiele and Ingle[3] from the nitroso derivative of IX (R = benzyl) upon warming with glacial acetic acid. It is interesting to note that Thiele's nitroso derivative can be hydrolyzed to the iminotetrazoline (IX) with hot, dilute hydrochloric acid. In order to determine whether these reactions involved acetolysis, IX (R = benzyl) was acetylated with acetic anhydride in ether solution. Under these conditions the hydrate of an acetyl derivative, XI (R = benzyl) was obtained which on hydrogenolysis over palladium oxide gave 5-acetylaminotetrazole. Whether the water was chemically bound by addition to the C=N linkage, or whether by complex formation has not been determined. However, heating the acetyl derivative with glacial acetic acid caused conversion to X (R = benzyl), while heating with dilute hydrochloric acid led back to IX (R = benzyl).



In extending these observations to other iminotetrazolines it was found that 1,4-diethyl-5-iminotetrazoline (IX, R = ethyl) on heating with excess acetic anhydride gave a mixture of the acetyl derivative, XI (R = ethyl), and the ketotetrazoline, X (R = ethyl). The acetyl derivative, which was not hydrated, gave X (R = ethyl) and acetamide on boiling with glacial acetic acid, and was hydrolyzed to IX (R = ethyl) with boiling, dilute hydrochloric acid. The acetolysis apparently requires the intermediate formation of the acetyl derivatives of the 1,4-dialkyl-5-iminotetrazolines; IX (R = benzyl) was recovered unchanged after boiling with glacial acetic acid for 0.5 hr. and the hydrochloride of IX (R = benzyl) showed no change upon boiling with either glacial acetic acid or acetic anhydride. Attempts to acetolyze the benzoyl or benzenesulfonyl derivatives of IX (R = benzyl)

with acetic acid or anhydride were unsuccessful, although the former could be hydrolyzed easily with boiling hydrochloric acid. 5-Acetylaminotetrazole, although it can be hydrolyzed easily with concentrated hydrochloric acid, was recovered unchanged after boiling for several hours with glacial acetic acid. Similarly, the acetyl derivatives of 1-alkyl- and 1-aryl-5-aminotetrazoles are easily hydrolyzed with hydrochloric acid but stable toward glacial acetic acid.[11] Apparently the 1,4-dialkyl-5-iminotetrazoline structure, IX, is essential and acetolysis under the conditions studied is limited to the acetyl and nitroso derivatives of IX.

The marked increase in basicity of the 1,4-dialkyl-5-iminotetrazolines as compared with the 1-alkyl-5-aminotetrazoles is striking. Although the 1-alkyl-5-alkylaminotetrazoles also exhibit distinctly basic character, the increase does not seem to be as marked. It has long been recognized that the 1-alkyl-5-aminotetrazoles do not exhibit the characteristics usually associated with primary amines; even those of low molecular weight have rather high melting points and their basic properties are apparent only under anhydrous conditions in the presence of strong proton donors, as recently confirmed by titrations with perchloric acid in glacial acetic acid.[12a] Murphy and Picard[12b] have suggested, on the basis of spectrographic studies, that the 1-alkyl-5-aminotetrazoles have polymolecular structures involving intermolecular hydrogen bonding. We would suggest that a resonance hybrid derived from a series of dipolar contributing forms could explain not only the high melting points but the lack of basic character as well. In such structures (Figure 1*a*), the immonium ion state would deprive the amino group of its ability to donate a pair of electrons to the reagents with which it usually reacts. The dipolar character of the resonance hybrid could also account for the preferential alkylation in the 4 position.

The marked increase in basic properties of the 1,4-dialkyl-5-iminotetrazolines appears to be associated with the change from tetrazole to tetrazoline ring system where formation of dipolar structures of the type postulated in Figure 1 is unlikely. Furthermore, the 5-iminotetrazolines present structural features closely analogous to the guanidine structure which may account for their

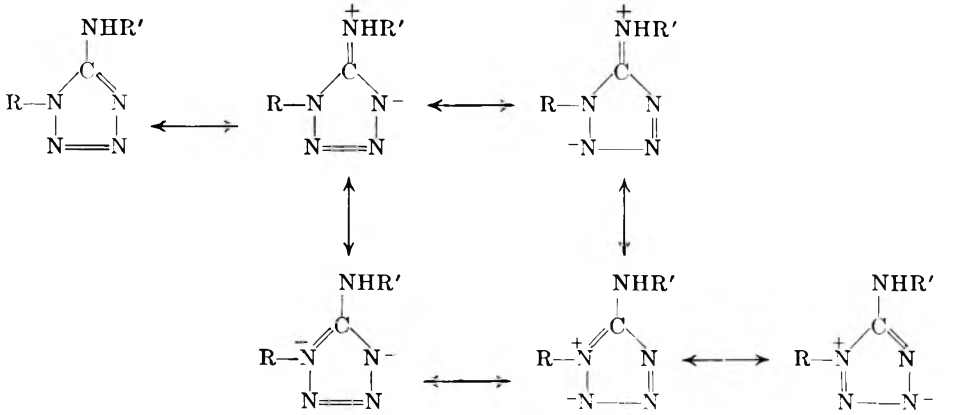


FIG. 1. (a), R = ALKYL, R′ = H; (b), R, R′ = ALKYL

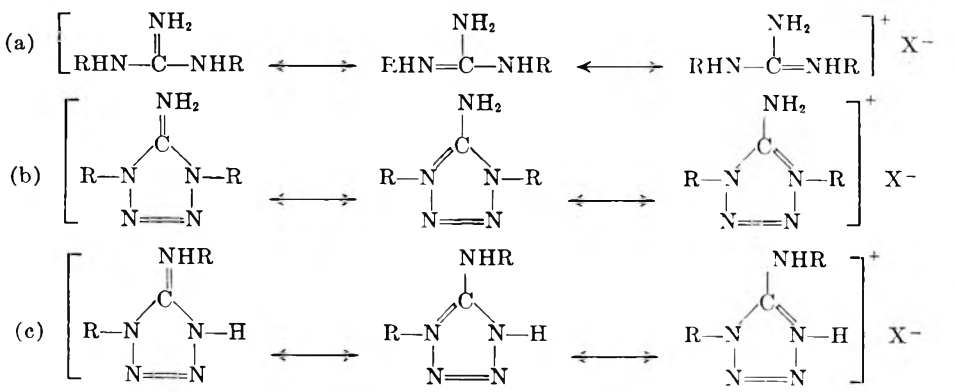


FIG. 2. (R = ALKYL)

physical and chemical characteristics. Thus, the imino group retains its ability to donate a pair of electrons so that stable salts can be formed with acids in which the cation (Fig. 2b) is stabilized by resonance of the guanidinium ion type (Fig. 2a).

(11) R. M. Herbst and W. L. Garbrecht, *J. Org. Chem.*, 18, 1283 (1953).

(12) (*a*) P. Rochlin, D. B. Murphy, and S. Helf, *J. Am. Chem. Soc.*, **76**, 1451 (1954). (*b*) D. B. Murphy and J. P. Picard, *J. Org. Chem.*, 19, 1807 (1954).

The 1-alkyl-5-alkylaminotetrazoles are generally solids with melting points intermediate between those of the isomeric 1,4-dialkyl-5-iminotetrazolines (usually liquids) and the related 1-alkyl-5-aminotetrazoles. The solid character of the 1-alkyl-5-alkylaminotetrazoles may also be attributed to the possibility of a resonance hybrid involving dipolar contributing forms (Fig. 1b) while their basicity could derive from guanidinium type resonance of the cation formed by reaction with acids (Fig. 2c). Since ring substitution in the 1,4- positions produces a somewhat greater degree of symmetry in the structure than alkylation of the amino group, it should not be surprising to find appreciable differences in the basicity of the two isomeric dialkylated 5-aminotetrazoles.

Infrared spectra of a series of 1-alkyl-5-aminotetrazoles, 5-alkylaminotetrazoles, 5-dialkylaminotetrazoles, 1,4-dialkyl-5-iminotetrazoline hydrochlorides, and 1-alkyl-5-alkylaminotetrazoles and their hydrochlorides have been recorded.[13]

## EXPERIMENTAL[14]

*1-Alkyl-5-aminotetrazoles.* 1-Methyl-,[4] 1-ethyl-,[7] 1-*n*-propyl-,[4] 1-isopropyl-,[4] 1-*n*-butyl-,[4] 1-benzyl-,[7] and 1-β-phenylethyl-5-aminotetrazole[4] were prepared by a slight modification of the method of Garbrecht and Herbst.[7]

*1,4-Dialkyl-5-iminotetrazolines.* These compounds were prepared by heating a mixture of the 1-alkyl-5-aminotetrazole and the alkylating agent without diluent in an oil bath until an exothermic reaction was initiated.[4] The temperature of the oil bath was kept constant for 0.5–1.0 hr. after cessation of the exothermic reaction. The products remained as thick viscous masses in the case of the benzene- or toluenesulfonates, and solidified during the reaction period or on cooling in the case of the hydrochlorides. The alkylating agents employed were either alkyl halides, alkyl sulfates, alkyl benzene- or toluenesulfonates. The 1,4-dialkyl-5-iminotetrazolines were isolated as hydrochlorides (Table I) and characterized as phenylthioureas and as benzenesulfonyl derivatives (Table III). Several typical preparations are described.

*1-Benzyl-4-n-propyl-5-iminotetrazoline hydrochloride. Method A, from 1-n-propyl-5-aminotetrazole.* A mixture of 25.4 g. (0.2 mole) of 1-*n*-propyl-5-aminotetrazole and 25.4 g. (0.2 mole) of benzyl chloride was heated in an oil bath. At a bath temperature of 135° a homogeneous melt formed, followed by an exothermic reaction and resolidification of the mixture. Heating was continued at 145° for 0.5 hr. The product was crystallized first from 95%, then from 90% isopropyl alcohol; colorless lustrous needles, m.p. 199–200° with decomposition, yield 37.6 g.

*Method B, from 1-benzyl-5-aminotetrazole.* A mixture of 8.75 g. (0.05 mole) of 1-benzyl-5-aminotetrazole and 10.8 g. (0.05 mole) of *n*-propyl *p*-toluenesulfonate was heated to 160–165° in an oil bath. A homogeneous melt formed and the bath was maintained at this temperature 0.5 hr. After cooling, the reaction mixture was dissolved in 20 ml. of isopropyl alcohol and treated with 20 ml. of 5*N* sodium hydroxide. The organic base was extracted with ether, the ethereal solution was dried over sodium carbonate, and then treated with 10 ml. of concentrated hydrochloric acid to pre-

TABLE III

1,4-DIALKYL-5-IMINOTETRAZOLINE DERIVATIVES

| R | R′[a] | Phenylthioureas | | | | | | Benzenesulfonyl Derivatives | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | M.P., °C. | Formula | Analyses | | | | M.P., °C. | Formula | Analyses | | | |
| | | | | Caled. | | Found | | | | Caled. | | Found | |
| | | | | N | S | N | S | | | N | S | N | S |
| Methyl | Benzyl | 124–125 | $C_{16}H_{16}N_6S$ | 25.9 | | 26.1 | | 82–84 | $C_{15}H_{15}N_5O_2S$ | 21.3 | | 21.2 | |
| Benzyl | Methyl | 123–124 | $C_{16}H_{16}N_6S$ | 25.9 | | 25.8 | | 82–84 | $C_{15}H_{15}N_5O_2S$ | 21.3 | | 20.7 | |
| Ethyl | Benzyl | 117–118 | | Ref. 4 | | | | | | | | | |
| Benzyl | Ethyl | 117–118 | | Ref. 4 | | | | | | | | | |
| *n*-Propyl | Benzyl | 134–135 | $C_{18}H_{20}N_6S$ | 23.9 | | 24.0 | | 80–82[b] | $C_{16}H_{21}N_5O_2S$ | 18.9 | | 18.9 | |
| Benzyl | *n*-Propyl | 134–135 | $C_{18}H_{20}N_6S$ | 23.9 | | 23.8 | | 80–81[b] | $C_{16}H_{21}N_5O_2S$ | 18.9 | | 18.9 | |
| *n*-Butyl | Benzyl | 114–115 | $C_{19}H_{22}N_6S$ | 22.9 | | 23.0 | | 67–68 | $C_{17}H_{23}N_5O_2S$ | 18.9 | | 18.8 | |
| Benzyl | *n*-Butyl | 113–114 | $C_{19}H_{22}N_6S$ | 22.9 | | 22.7 | | 67–68 | $C_{17}H_{23}N_5O_2S$ | 18.9 | | 18.8 | |
| β-Phenylethyl | Benzyl | 125–126 | $C_{23}H_{22}N_6S$ | 20.3 | | 20.5 | | 98–99 | $C_{22}H_{23}N_5O_2S$ | 16.7 | | 16.9 | |
| Benzyl | β-Phenylethyl | 123–124 | $C_{23}H_{22}N_6S$ | 20.3 | | 20.7 | | 97–98 | $C_{22}H_{23}N_5O_2S$ | 16.7 | | 16.9 | |
| Methyl | Ethyl | 210–211 | $C_{10}H_{12}N_6S$ | 33.8 | 12.9 | 33.7 | 13.3 | 125–126 | $C_9H_{11}N_5O_2S$ | 27.7 | 12.9 | 27.7 | 13.2 |
| Ethyl | Methyl | 108–109 | $C_{12}H_{16}N_6S$ | 30.4 | 11.6 | 30.6 | 11.8 | 67–68 | $C_{11}H_{15}N_5O_2S$ | 24.9 | 11.4 | 24.4 | 11.4 |
| *n*-Propyl | *n*-Propyl | 95–96 | $C_{14}H_{20}N_6S$ | 27.6 | 10.5 | 27.1 | 10.6 | 46–47 | $C_{13}H_{19}N_5O_2S$ | 22.6 | 10.5 | 22.7 | 10.5 |
| *n*-Butyl | *n*-Butyl | 92–93 | $C_{16}H_{24}N_6S$ | 25.3 | 9.6 | 25.6 | 9.6 | 41–42 | $C_{15}H_{23}N_5O_2S$ | 20.8 | 9.6 | 20.9 | 9.7 |
| Benzyl | Benzyl | 140–141 | $C_{22}H_{20}N_6S$ | 21.0 | 8.0 | 21.2 | 8.3 | 89–90 | $C_{21}H_{19}N_5O_2S$ | 17.3 | 7.9 | 17.3 | 8.1 |

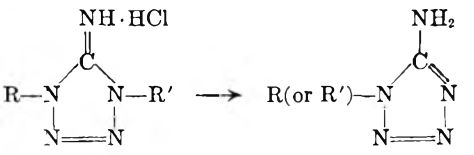
[a] R′ is the group introduced by alkylation. [b] Toluenesulfonyl derivatives.

(13) D. F. Percival, *Alkylated 5-Aminotetrazoles, Their Preparation and Properties.* Ph.D. Thesis, Michigan State University, 1955.

(14) Analyses were done by Micro-Tech Laboratories, Skokie, Ill.

TABLE IV

DEBENZYLATION OF 1,4-ALKYLBENZYL-5-IMINOTETRAZOLINES




| 1,4-Alkyl-benzyl-5-imino-tetrazoline hydrochloride | | 1-Alkyl-5-aminotetrazole | | |
|---|---|---|---|---|
| R | R′[a] | R or R′ | M.P.°C. | Yield, % |
| Methyl | Benzyl | Methyl | 227–228 | 82 |
| Benzyl | Methyl | Methyl | 226–227 | 86 |
| *n*-Propyl | Benzyl | *n*-Propyl | 150–152 | 76 |
| Benzyl | *n*-Propyl | *n*-Propyl | 151–152 | 87 |
| *n*-Butyl | Benzyl | *n*-Butyl | 148–149.5 | 77 |
| Benzyl | *n*-Butyl | *n*-Butyl | 148–149 | 75 |
| β-Phenylethyl | Benzyl | β-Phenylethyl | 175–177 | 81 |
| Benzyl | β-Phenylethyl | β-Phenylethyl | 176–177 | 79 |

[a] R′ is the group introduced by alkylation

cipitate the hydrochloride which was recrystallized from isopropyl alcohol, yield 7.3 g., m.p. 198–199° with decomposition.

*1,4-Di-n-butyl-5-iminotetrazoline hydrochloride.* A mixture of 7.1 g. (0.05 mole) of 1-*n*-butyl-5-aminotetrazole and 11.4 g. (0.05 mole) of *n*-butyl *p*-toluenesulfonate was heated in an oil bath. At 155–160° a homogeneous melt had formed and the bath was kept at this temperature for 0.5 hr. The solid which formed on cooling the reaction mixture was dissolved in 20 ml. of isopropyl alcohol, treated with 20 ml. of 5*N* sodium hydroxide and the organic base extracted with ether. The ethereal solution was dried over sodium carbonate and treated with 10 ml. of concentrated hydrochloric acid. On evaporation of the solvent the hydrochloride remained as a solid and was crystallized from isopropyl alcohol–ether mixture, yield 5.4 g., m.p. 203–204° with decomposition.

*Phenylthioureas derived from the 1,4-diakyl-5-iminotetrazolines.* The base was liberated by treatment of the 1,4-dialkyl-5-iminotetrazoline hydrochloride with 5*N* sodium hydroxide and extracted with ether. After drying the ethereal solution over sodium carbonate and evaporating the solvent, the residual base was warmed with phenyl isothiocyanate. The phenylthioureas so formed were washed with petroleum ether and 50% isopropyl alcohol and crystallized, usually from aqueous isopropyl alcohol or ligroin. Physical constants and analytical data are collected in Table III.

*Benzenesulfonyl derivatives.* Approximately 0.5 g. of the 1,4-dialkyl-5-iminotetrazoline hydrochloride and 0.5 ml. of benzenesulfonyl chloride were suspended in 10 ml. of 10% sodium hydroxide and shaken. The benzenesulfonyl derivatives solidified on cooling the mixture and were crystallized from aqueous isopropyl alcohol. In one instance, 1,4-benzyl-*n*-propyl-5-iminotetrazoline, the *p*-toluenesulfonyl derivative was prepared in the same manner because the benzenesulfonyl derivative could not be induced to crystallize. Physical constants and analytical data are collected in Table III.

*Hydrogenolysis of 1,4-alkylbenzyl-5-iminotetrazolines.* A solution of about 0.01 mole of the 1,4-alkylbenzyl-5-iminotetrazoline hydrochloride in 80 ml. of 75% isopropyl alcohol was shaken with 0.1 g. of palladium oxide catalyst at 50 p.s.i. hydrogen pressure. The calculated amount of hydrogen was taken up in about 2 hr. The catalyst was filtered off, washed with hot isopropyl alcohol and the combined filtrate and washings neutralized with sodium carbonate. After concentration of the solution the 1-alkyl-5-aminotetrazole crystallized. All the 1,4-alkylbenzyl-5-iminotetrazolines were debenzylated in this way and in each instance the anticipated 1-alkyl-5-aminotetrazole could be isolated in yields of 70–90%. Identity of the products was established by melting point and mixture melting point. Pertinent data are collected in Table IV.

*Acetolysis of 1,4-dialkyl-5-iminotetrazolines. 1,4-Dibenzyl-5-ketotetrazoline* (X, R = benzyl). *A.* Two grams of 1,4-dibenzyl-5-iminotetrazoline, obtained from the hydrochloride by treatment with sodium hydroxide and extraction with ether, was heated under reflux with 10 ml. of acetic anhydride for 0.5 hr. The solution was diluted with 20 ml. of isopropyl alcohol, evaporated to a small volume, treated with water until permanent turbidity developed, and chilled. The product separated and was recrystallized from cyclohexane; colorless needles, yield 1.6 g. (79%), m.p. 105–106°.

*Anal.* Calcd. for $C_{15}H_{14}N_4O$: C, 67.4; H, 5.3; N, 21.1. Found: C, 67.7; H, 5.3; N, 20.8.

*B.* One gram of 1,4-dibenzyl-5-iminotetrazoline hydrochloride was suspended in 10 ml. of water and treated with 10 ml. of 5*M* sodium nitrite. The mixture was warmed and water added until a clear solution formed. On cooling the nitrite separated as needles, m.p. 109° with decomposition[3] after recrystallization from ether. The nitrite was dissolved in glacial acetic acid and diluted with water to turbidity. On cooling the nitroso derivative separated, m.p. 105° with decomposition.[3] The nitroso derivative was dissolved in 3 ml. of glacial acetic acid and heated for 40 min. on a steam bath. During the first 10 min. the yellow color disappeared. The hot solution was diluted with 40 ml. of 50% isopropyl alcohol and the product that separated on cooling was recrystallized from cyclohexane; colorless needles, m.p. 104–106°, no depression on admixture of the material prepared in *A*. The same product was also obtained by heating the nitrite in glacial acetic acid for 0.5 hr.

*1,4-Dibenzyl-5-acetyliminotetrazoline hydrate.* The base from 9 g. (0.03 mole) of 1,4-dibenzyl-5-iminotetrazoline hydrochloride was treated in ether solution with 5.4 g. (0.05 mole) of acetic anhydride. The residue left on evaporation of the ether was suspended in 20 ml. of water and treated with small portions of sodium carbonate until gas evolution ceased. The solid obtained by cooling the mixture was crystallized from 50% isopropyl alcohol; yield 7.1 g., m.p. 61–62°. No water lost on drying in a vacuum at 40°.

*Anal.* Calcd. for $C_{17}H_{17}N_5O.H_2O$: C, 62.8; H, 5.9; N, 21.5. Found: C, 62.8; H, 5.8; N, 21.3.

*Acetolysis of 1,4-dibenzyl-5-acetyliminotetrazoline hydrate.* A solution of 2 g. of the acetyliminotetrazoline in 10 ml. of glacial acetic acid was boiled under reflux for 0.5 hr. Dilution of the hot solution with water to turbidity and cooling gave a product which was crystallized from cyclohexane; yield 1.5 g., m.p. 105–106°, no depression on admixture of 1,4-dibenzyl-5-ketotetrazoline.

*Hydrolysis of 1,4-dibenzyl-5-acetyliminotetrazoline hydrate.*

About 1 g. of the acetyliminotetrazoline was boiled under reflux with 10 ml. of concentrated hydrochloric acid for about 3 min. The product which separated from the hot solution was filtered and washed with 50% isopropyl alcohol; yield quantitative, m.p. 213–214° with decomposition, no depression on admixture of 1,4-dibenzyl-5-iminotetrazoline hydrochloride. The nitroso derivative of 1,4-dibenzyl-5-iminotetrazoline likewise was hydrolyzed to the iminotetrazoline on boiling with concentrated hydrochloric acid.

*Hydrogenolysis of 1,4-dibenzyl-5-acetyliminotetrazoline hydrate.* A solution of 6.1 g. (0.02 mole) of the acetyliminotetrazoline in 150 ml. of absolute ethanol was shaken at room temperature with hydrogen at 50 p.s.i. in the presence of 0.1 g. of palladium oxide catalyst. After 3.5 hr. the reaction was interrupted, the mixture filtered, and the residue washed with 20 ml. of boiling water. The colorless solid that separated from the aqueous washings on cooling was recrystallized from water, yield 1.65 g., m.p. 263° with decomposition, no depression on admixture of 5-acetylaminotetrazole.[11]

*1,4-Diethyl-5-acetyliminotetrazoline* (XI, R = ethyl). A solution of 20 g. of 1,4-diethyl-5-iminotetrazoline, obtained from the hydrochloride by treatment with sodium hydroxide, extraction with ether and distillation under reduced pressure (b.p. 121–122° at 20 mm.), in 40 g. of acetic anhydride was distilled slowly at atmospheric pressure until most of the acetic anhydride had been removed. After removing from the residual liquid the forerun of acetic acid and anhydride the following fractions were collected at 2 mm.: (*a*) 3.4 g., b.p. 94–95°, $n_D^{25}$ 1.45857; (*b*) 15.2 g., b.p. 95°, $n_D^{25}$ 1.4896; (c) 5.7 g., b.p. 95–97°, $n_D^{25}$ 1.4850. Fraction *b* was redistilled at 2 mm. and fractions were collected as follows: (*i*) 2.1 g., b.p. 94–95°, $n_D^{25}$ 1.4901; (*ii*) 2.3 g., b.p. 95°, $n_D^{25}$ 1.4909; (*iii*) 3.2 g., b.p. 95°, $n_D^{25}$ 1.4910; (*iv*) 1.9 g., b.p. 95°, $n_D^{25}$ 1.4910; *v* 3.5 g., b.p. 95–96°, $n_D^{25}$ 1.4916. Fractions *ii–iv* were apparently identical; a sample of fraction *iii* was submitted for elemental analysis.

*Anal.* Calcd. for $C_7H_{13}N_5O$: C, 46.0; H, 7.1; N, 38.2. Found: C, 45.9; H, 7.2; N, 38.1.

*Acetolysis of 1,4-diethyl-5-acetyliminotetrazoline.* A solution of 15 g. of the crude acetyl derivative in 20 ml. of glacial acetic acid was boiled under reflux for 2 hr., after which the solution was distilled under reduced pressure. The forerun of acetic acid was discarded and the following fractions were collected at 2 mm.: (*a*) 4.3 g., b.p. 55–60°, $n_D^{25}$ 1.4514; (*b*) 5.2 g., b.p. 60–61°, $n_D^{25}$ 1.4586; (c) 2.4 g., b.p. 62°, $n_D^{25}$ 1.4606; (*d*) 1.7 g., b.p. 62–64°, $n_D^{25}$ 1.4634. Fraction *d* solidified at room temperature and could be shown to be acetamide; recrystallized from isopropyl alcohol–cyclohexane, m.p. 81–82°, mixture m.p. with acetamide not depressed. The other fractions were recombined and dissolved in cyclohexane. After filtering off a small amount of acetamide that separated slowly, the material was again fractionated at 12 mm. A fraction, b.p. 94°, $n_D^{25}$ 1.4531, was submitted for analysis.

*Anal.* Calcd. for $C_5H_{10}N_4O$: C, 42.2; H, 7.1; N, 39.4. Found: C, 42.3, 42.2; H, 7.2, 7.0; N, 38.1, 38.0.

The low nitrogen values could be due to a trace of acetamide which would not affect the carbon-hydrogen values greatly, or they might be due to an idiosyncrasy of the compound. A similar fraction was heated with 1*N* sodium hydroxide to hydrolyze any acetamide present. Distillation gave a product, b.p. 94° at 12 mm., $n_D^{25}$ 1.4530, but the nitrogen analysis was not improved.

*Hydrolysis of 1,4-diethyl-5-acetyliminotetrazoline.* One gram of the acetyliminotetrazoline was boiled for 2 hr. with 5 ml. of concentrated hydrochloric acid. The solution was diluted with 15 ml. of acetone and treated with ether until turbid. 1,4-Diethyl-5-iminotetrazoline hydrochloride crystallized on cooling, m.p. and mixture m.p. 227–228° with decomposition.

*1,4-Dibenzyl-5-benzoyliminotetrazoline.* 1,4-Dibenzyl-5-iminotetrazoline hydrochloride (1 g.) was shaken with 1 ml. of benzoyl chloride and 20 ml. of 10% sodium hydroxide. The benzoyl derivative was crystallized from isopropyl alcohol, m.p. 85–86°.

*Anal.* Calcd. for $C_{22}H_{19}N_5O$: C, 71.5; H, 5.2; N, 19.0. Found: C, 71.4; H, 5.3; N, 18.8.

*Hydrolysis* of the benzoyl derivative was accomplished by boiling under reflux for 0.5 hr. with a mixture of concentrated hydrochloric and glacial acetic acids. On diluting with water and cooling 1,4-dibenzyl-5-iminotetrazoline hydrochloride crystallized, m.p. and mixture m.p. 213–214° with decomposition.

*Acetolysis* of the benzoyl derivative was attempted by boiling in glacial acetic acid for 0.5 hr. and by boiling with acetic anhydride for 0.5 hr. In both instances only unchanged benzoyl derivative was recovered.

*1,4-Dibenzyl-5-benzenesulfonyliminotetrazoline* was refluxed in separate experiments with 3*N* and 6*N* hydrochloric acid, glacial acetic acid, and 10% aqueous potassium hydroxide. In each instance the benzenesulfonyl derivative was recovered. There was no evidence of hydrolysis or acetolysis.

*1,4-Dibenzyl-5-iminotetrazoline* was boiled under reflux in glacial acetic acid for 0.5 hr.; the hydrochloride was subjected to similar treatment with both glacial acetic acid and acetic anhydride. In all cases the starting material was recovered unchanged as hydrochloride.

*5-Acetylaminotetrazole*[11] (2 g.) was recovered unchanged after boiling for 2.5 hr. in 10 ml. of glacial acetic acid; hydrolysis was accomplished easily by evaporating a mixture of 1 g. of 5-acetylaminotetrazole and 5 ml. of concentrated hydrochloric acid on the steam bath. The residue of 5-aminotetrazole crystallized from water, m.p. and mixture m.p. 203–204°.[9]

*N,N'-Dialkylthioureas.* *N,N'*-Diethyl-, diisopropyl-, di-*n*-butyl, and diphenylthiourea were commercial products. *N,N'*-Di-*n*-propylthiourea, m.p. 71–72°,[15] yield 94%, and *N,N'*-dibenzylthiourea, m.p. 146–147°,[16] yield 97%, were prepared from the primary amine and carbon bisulfide in toluene solution according to Strakosch.[17] *N,N'*-Dimethylthiourea was prepared by interaction of methyl isothiocyanate and methylamine,[18] yield 85%, m.p. 52–53°.

*S-Methyl-N,N'-dialkylisothiuronium iodides* were prepared by interaction of the *N,N'*-dialkylthioureas and methyl iodide in isopropyl alcohol solution, an adaptation of the procedure of Braun and Randall.[19] Only *S*-methyl-*N,N'*-di-*n*-butylisothiuronium iodide failed to crystallize. Physical constants and analytical data for the remaining compounds are given in Table V.

TABLE V

*S*-METHYL-*N,N'*-DIALKYLISOTHIURONIUM IODIDES

RHN—C(SCH$_3$)=NR·HI

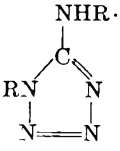
| R | M.P., °C. | Yield, % | Analysis | | | |
|---|---|---|---|---|---|---|
| | | | Calculated | | Found | |
| | | | N | S | N | S |
| Ethyl | 75–76 | 91 | 10.2 | 11.7 | 9.8 | 12.0 |
| *n*-Propyl | 61.5–63 | 94 | 9.3 | 10.6 | 8.7 | 11.0 |
| Isopropyl | 122–123 | 98 | 9.3 | 10.6 | 9.1 | 10.7 |
| Benzyl | 119.5–120.5 | 98 | 7.0 | 8.1 | 7.2 | 8.5 |

*N,N'-Dialkyl-N"-aminoguanidine hydriodides* were prepared by an adaptation of the procedure of Kerstin and Smith[20] involving interaction of the *S*-methyl isothiuro-

(15) O. Hecht, *Ber.*, **23**, 281 (1890).
(16) E. A. Werner, *J. Chem. Soc.*, **59**, 406 (1891).
(17) J. Strakosch, *Ber.*, **5**, 692 (1872).
(18) A. E. Dixon, *J. Chem. Soc.*, **63**, 328 (1893).
(19) C. E. Braun and W. M. Randall, *J. Am. Chem. Soc.*, **56**, 2134 (1934).
(20) G. W. Kerstin and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936).

TABLE VI

1-ALKYL-5-ALKYLAMINOTETRAZOLE HYDROCHLORIDES



| R | M.P., °C.[a] | Method | Formula | Analyses | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Calculated | | | Found | | |
| | | | | C | H | N | C | H | N |
| Methyl | 209 dec. | A-1 | $C_3H_8ClN_5$ | [b] | | 46.8 | | | 46.5 |
| Ethyl | 162–163 | A-1 | $C_6H_{12}ClN_5$ | 33.8 | 6.8 | 39.4 | 34.1 | 6.7 | 39.6 |
| | 161–163 | B | | | | | 33.7 | 6.8 | 39.5 |
| *n*-Propyl | 141–142 | A-1 | $C_7H_{16}ClN_5$ | 40.9 | 7.3 | 34.1 | 41.1 | 7.6 | 34.1 |
| | 141–142 | B | | | | | 40.9 | 7.8 | 34.0 |
| Isopropyl | 192–193 | A-2 | $C_7H_{16}ClN_5$ | | | | | | |
| | 193–194 | B | | [c] | | 34.1 | | | 34.0 |
| *n*-Butyl | 156–157 | A-1 | $C_9H_{20}ClN_5$ | 46.2 | 8.6 | 30.0 | 46.0 | 8.5 | 30.1 |
| | 156–157 | A-2 | | | | | | | |
| | 156–157 | B | | | | | 46.1 | 8.7 | 30.1 |
| Benzyl | 160–161 | A-1 | $C_{15}H_{16}ClN_5$ | [d] | | 23.2 | | | 23.5 |

[a] Mixture melting points of the respective pairs showed no depression. [b] Calcd. Cl, 23.7. Found: Cl, 23.9. [c] Calcd. Cl, 17.2. Found: Cl, 17.0. [d] Calcd. Cl, 11.8. Found: Cl, 11.9.

nium iodides and hydrazine in isopropyl alcohol solution. Difficulty in crystallizing the hydriodides made it necessary to purify samples of the products for analysis as benzal derivatives or as picrates.

*Benzal N,N'-diethyl-N"-aminoguanidine hydriodide*, m.p. 204–206°, crystallized from isopropyl alcohol.

*Anal.* Calcd. for $C_{12}H_{19}IN_4$: I, 36.7; N, 16.2. Found: I, 36.6; N, 16.2.

*N,N'-Di-n-propyl-N"-aminoguanidine picrate*, yellow crystals from water, m.p. 105–106°.

*Anal.* Calcd. for $C_{13}H_{21}N_7O_7$: C, 40.4; H, 5.4; N, 25.3. Found: C, 40.5; H, 5.6; N, 25.5.

*N,N'-Di-isopropyl-N"-aminoguanidine picrate*, yellow crystals from water, m.p. 93–94°.

*Anal.* Calcd. for $C_{13}H_{21}N_7O_7$: C, 40.4; H, 5.4; N, 25.3. Found: C, 40.6; H, 5.7; N, 25.7.

*Benzal N,N'-di-n-butyl-N"-aminoguanidine hydriodide*, crystallized from ethylene chloride, m.p. 123–124°.

*Anal.* Calcd. for $C_{16}H_{27}IN_4$: I, 31.5; N, 14.0. Found: I, 31.3; N, 14.0.

*1-Alkyl-5-alkylaminotetrazoles* (VI) *from carbodiimides.* The method involved conversion of *N,N'*-dialkylthioureas into *N,N'*-dialkylcarbodiimides according to Schmidt *et al.*,[8] and subsequent interaction of the carbodiimides with hydrazoic acid. Two techniques were used; *Method A-1* using ether-water mixtures as solvents, and *Method A-2* using benzene-chloroform mixtures as solvents for the reactants. The preparation of 1-*n*-butyl-5-*n*-butylaminotetrazole affords an example of both techniques.

*Method A-1.* A mixture of 37.6 g. (0.2 mole) of *N,N'*-di-*n*-butylthiourea, 300 ml. of ether, and 400 ml. of water was stirred vigorously while 54 g. (0.25 mole) of yellow mercuric oxide was added slowly during 10 min. The mercuric oxide turned black as fast as it was added. Stirring was continued for 5 min. before the mixture was filtered by suction. The mercuric sulfide was washed with ether and the ether layers were separated and dried for 10–15 min. over calcium chloride. The ether solution was decanted from the drying agent, 100 ml. of a benzene solution containing 15 g. of hydrazoic acid[21] was added and the resulting solution boiled under reflux for 1.5 hr. The solvents and excess hydrazoic acid were removed by distillation. The oily residue solidified when washed with petroleum ether. The 1-*n*-butyl-5-*n*-butylaminotetrazole was recrystallized from ether–petroleum ether, m.p. 73–74°, yield 61% based on thiourea. The hydrochloride was prepared in ether with dry hydrogen chloride and recrystallized from ether–isopropyl alcohol, m.p. 156–157°.

*Method A-2.* A mixture of 18.8 g. (0.1 mole) of *N,N'*-di-*n*-butylthiourea, 43.2 g. (0.2 mole) of yellow mercuric oxide, 100 ml. of benzene, 100 ml. of chloroform and 15 g. of anhydrous calcium chloride was heated under reflux for an hour. The mercuric sulfide was filtered by suction and washed with 50 ml. of hot chloroform. To the combined filtrate and washings 50 ml. of a xylene solution containing 8 g. of hydrazoic acid[21] were added and the mixture boiled under reflux for 1.5 hr. The volume of the reaction mixture was reduced to 100 ml. by distillation, the residual solution cooled, diluted with 100 ml. of ether and treated with dry hydrogen chloride until precipitation of the hydrochloride was complete. The hydrochloride was recrystallized from ether–isopropyl alcohol, m.p. 156–157°, yield 73% based on the thiourea.

Other 1-alkyl-5-alkylaminotetrazoles prepared by these techniques and their hydrochlorides are listed in Tables II and VI, respectively. 1-Phenyl-5-phenylaminotetrazole was prepared by method A-1; recrystallized from isopropyl alcohol, m.p. 161–162°,[9] yield 67%.

*Anal.* Calcd. for $C_{13}H_{11}N_5$: N, 29.6. Found: N, 30.0.

*1-Alkyl-5-alkylaminotetrazoles* (VI) *from aminoguanidines. Method B.* The procedure of Finnegan *et al.*,[10] was used. The preparation of 1-*n*-butyl-5-*n*-butylaminotetrazole serves as an example. A solution of 0.1 mole of crude *N,N'*-di-*n*-butyl-*N"*-aminoguanidine hydriodide in 100 ml. of water was acidified with 1.3 ml. of concentrated nitric acid. Silver nitrate (17.2 g., 0.1 mole) dissolved in 22 ml. of water was added with continued stirring. After 0.5 hr. any excess of silver ion was precipitated by addition of 1.2 ml. of concentrated hydrochloric acid, the silver halide was filtered off and washed with two 20-ml. portions of hot water. The combined filtrate and washings were cooled in an ice bath, 7.3 ml. of concentrated hydrochloric acid were added followed by a solution of 0.1 mole of sodium nitrite in 22 ml. of water, the latter dropwise with stirring and cooling so that the temperature remained below 10° until a faint starch-iodide test was obtained. Careful addition of 12.1 g. (0.11 mole) of sodium carbonate caused an oil to separate which solidified on standing overnight. The 1-*n*-butyl-5-*n*-butylaminotetra-

(21) All operations involving hydrazoic acid must be done in a well ventilated hood.

zole was recrystallized from ether-petroleum ether, m.p. 73–74°. Admixture of the same product prepared by method A-1 or A-2 caused no depression of the melting point; yield 48% based on crude aminoguanidine hydriodide.

The hydrochloride was prepared in ether solution with dry hydrogen chloride and recrystallized from ether–isopropyl alcohol, m.p. and mixture m.p. 156–157°.

All the 1-alkyl-5-alkylaminotetrazoles and their hydrochlorides prepared by this procedure are listed in Tables II and VI, respectively. In all cases the products were identical with the materials prepared by Method A-1 or A-2.

EAST LANSING, MICH.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

# Synthesis of 1-Substituted Tetrazoles[1]

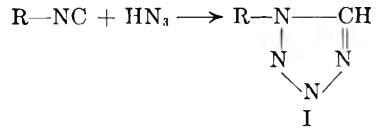
FRANCES G. FALLON[2] AND ROBERT M. HERBST

*Received March 8, 1957*

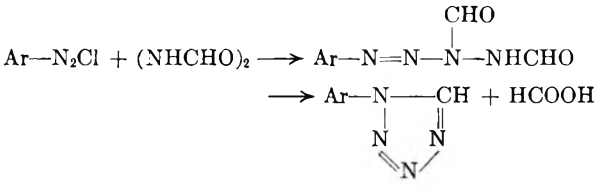
A group of seven 1-alkyltetrazoles was prepared by interaction of alkyl isocyanides and hydrazoic acid in benzene solution. The same method was applied to the synthesis of 1-phenyltetrazole but the yield was very poor. The Dimroth procedure for preparation of 1-aryltetrazoles by coupling diformyl hydrazide and diazonium salts also gave very poor yields of 1-phenyltetrazole. A new procedure involving an adaptation of the von Braun synthesis of 1,5-disubstituted tetrazoles was developed. Interaction of formanilides successively with phosphorus pentachloride and hydrazoic acid in toluene gave fair yields of the desired 1-aryltetrazoles. A group of eight 1-aryltetrazoles was prepared in this way. Their ultraviolet absorption spectra were determined and compared with those of comparable 5-aryltetrazoles.

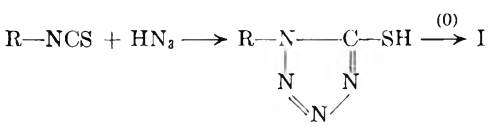
Although many 5-substituted tetrazoles are known, only very few 1-substituted tetrazoles have been described. Benson,[3] in his review of tetrazole chemistry, listed only seven examples including the questionable 1-hydroxytetrazole. It was the purpose of this study to investigate the preparation and properties of a larger group of 1-substituted tetrazoles.

Of the known methods for synthesis of 1-substituted tetrazoles three appeared to offer possibilities of rather general application. Oliveri-Mandalà and Alagna[4] obtained 1-methyl-, 1-ethyl-, and 1-phenyltetrazole by addition of hydrazoic acid to the appropriate isocyanide in ether solution. 1-Aryltetrazoles were prepared by Dimroth and de



Montmollin[5] by coupling aryl diazonium salts with diformyl hydrazide in aqueous alkaline medium and cyclizing the resulting diazohydrazide with warm aqueous alkali. Freund and Paradies[6] and later Stollé and Henke-Stark[7] oxidized 1-substituted-5-mercaptotetrazoles which had been prepared by interaction of isothiocyanates and hydrazoic acid or sodium azide. Although only 1-methyl- and 1-phenyltetrazole have been prepared this way, a variety of 1-substituted 5-mercaptotetrazoles have been described.[3]





For the preparation of 1-alkyltetrazoles the addition of hydrazoic acid to alkyl isocyanides[4] appeared to be the most generally applicable procedure. A series of seven 1-alkyltetrazoles was prepared in this way (Table I) but the method leaves much to be desired because of the disagreeable character of the requisite alkyl isocyanides. The latter were best prepared by the technique of Guillemard[8] by interaction of alkyl iodides and silver cyanide at steam bath temperature under reflux. Crude yields of the isocyanides were generally satisfactory, although the products were probably contaminated with dimerized or polymerized material in increasing quantity on standing which necessitated immediate use of the crude products in the next step of the synthesis. An attempt to estimate the isocyanide content of the crude products by a bromide-bromate titration in-

(1) Based on a thesis submitted by Frances G. Fallon to the School for Advanced Graduate Studies at Michigan State University in 1956, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) F. R. Benson, *Chem. Revs.*, **41**, 1 (1947).

(4) E. Oliveri-Mandalà and B. Alagna, *Gazz. chim. ital.*, **40**, II, 441 (1910).

(5) O. Dimroth and G. de Montmollin, *Ber.*, **43**, 2904 (1910).

(6) M. Freund and T. Paradies, *Ber.*, **34**, 3110 (1901).

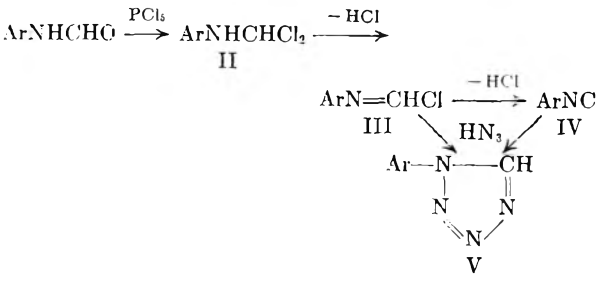
(7) R. Stollé and F. Henke-Stark, *J. prakt. Chem.*, **124**, 261 (1930).

(8) H. Guillemard, *Ann. chim. et phys.*, (8) **14**, 311 (1908).

dicated a marked decrease of titratable material during 24 hr., but it was not possible to standardize the procedure for lack of a standard of known purity. The crude alkyl isocyanides were added immediately to a benzene solution of hydrazoic acid and heated under reflux on a steam bath for periods of 1–5 hr. The 1-alkyltetrazoles were subsequently isolated by fractionation under reduced pressure. 1-Phenyltetrazole was also prepared from phenyl isocyanide and hydrazoic acid, but the unsatisfactory yield of tetrazole coupled with poor yields of the isocyanide in the carbylamine reaction prompted investigation of other methods of synthesis for 1-aryltetrazoles.

Application of the Dimroth procedure for the synthesis of 1-phenyltetrazole[5] gave only a very small yield of the desired product in our hands although the technique had been applied with considerable success to other diacyl hydrazides in the preparation of 1-aryl-5-alkyltetrazoles.[5,9]

In view of these difficulties an attempt was made to extend the von Braun technique[10] for the preparation of 1,5-disubstituted tetrazoles to *N*-substituted formamides. Wallach[11] had reported the formation of *N,N'*-diphenylformamidine by interaction of formanilide and phosphorus pentachloride. Since Wallach worked without solvent and without temperature control of the exothermic reaction and isolated the product by distilling the reaction mixture at atmospheric pressure, the formation of formimidyl chlorides under more moderate conditions was not precluded. Experiments in which formanilide was treated in toluene solution with phosphorus pentachloride at or below room temperature led to the formation of an intermediate that reacted with hydrazoic acid in the same solvent to give moderate quantities of 1-phenyltetrazole. The procedure was extended successfully to substituted formanilides and *N*-isobutylformamide; however, the yield of 1-isobutyltetrazole from the latter was poor and the process does not appear promising for the synthesis of 1-alkyltetrazoles under the conditions studied.




During the reaction of phosphorus pentachloride with the formanilides at ice bath temperature a heavy oil ranging from yellow to bright red in color separated without evolution of hydrogen chloride. When the reaction mixture was allowed to come to room temperature, hydrogen chloride was evolved. These observations could be interpreted as initial formation of an unstable amide chloride (II) which subsequently lost hydrogen chloride with formation of the formimidyl chloride (III) or possibly the aryl isocyanide (IV), either of which could react with hydrazoic acid to form the tetrazole (V). Since hydrogen chloride is also evolved during the reaction with hydrazoic acid, II would appear to be the more likely intermediate. The 1-aryltetrazoles prepared in this way are listed in Table I. They are all solids of considerably lower melting point than the corresponding 5-aryltetrazoles.[12] The product from the reaction with *o*-formotoluidide could not be made to crystallize nor could it be purified by distillation.

Ultraviolet absorption spectra of a number of 1-alkyl- and 1-aryltetrazoles were examined in the region of 210–300 mμ. Neither tetrazole nor the 1-alkyl- or 5-alkyltetrazoles exhibited appreciable absorption in this range, a pattern also shown by 5-cyclohexyltetrazole.[13] All the 1-aryltetrazoles showed strong absorption bands with maxima and extinction coefficients as noted in Table II. It is interesting that substitution on the benzene ring of the 1-phenyl- and the 5-phenyltetrazole systems has similar effects. In both instances *meta* and *para* substituents cause a progressively greater shift of the maximum toward longer wave lengths, while *ortho* substituents cause a shift of the maximum toward shorter wave lengths. Just as in the 5-aryltetrazole series[12] the strong absorption band of the 1-aryltetrazoles may be attributed to the resonance interaction of the phenyl and tetrazole rings (Figure 1). The shift of the maximum to much shorter wave lengths in the *ortho* substituted compounds may similarly be attributed to interference with the attainment of a coplanar configuration by the two rings due to a bulky group in the *ortho* position.

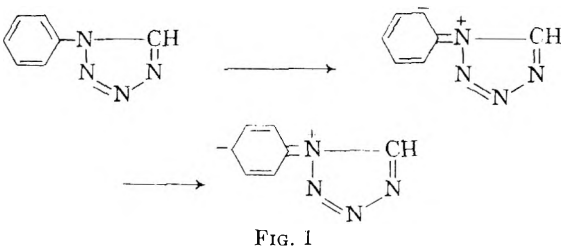


FIG. 1

Infrared spectra for the 1-substituted tetrazoles here described as well as comparable 5-substituted and 1,5-disubstituted tetrazoles have been recorded.[14]

(9) D.-Y. Wu and R. M. Herbst, *J. Org. Chem.*, **17**, 1216 (1952).

(10) J. von Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).

(11) O. Wallach, *Ann.*, **214**, 193 (1882).

(12) R. M. Herbst and K. R. Wilson, unpublished results.

(13) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950).

(14) F. G. Fallon, *The Synthesis of 1-Substituted Tetrazoles and Spectrographic Studies with Tetrazoles.* Ph.D. Thesis, Michigan State University, 1956.

## EXPERIMENTAL[15]

*Alkyl isocyanides* were prepared from alkyl iodides and silver cyanide under the conditions recommended by Guillemard.[8] The normal alkyl isocyanides from ethyl to heptyl as well as isobutyl and isoamyl isocyanide were prepared in this way. Phenyl isocyanide was prepared by the carbylamine reaction under the conditions recommended by Malatesta.[16] An attempt was made to estimate the amount of isocyanide in the crude products by treatment of their benzene solutions with excess standard bromide-bromate solution, addition of potassium iodide, and back-titration with standard thiosulfate. Bromide-bromate solution was used up in decreasing amounts as the isocyanides were kept for a day or two. Lack of a pure standard prevented further exploration of this procedure.

*Diformyl hydrazide* was prepared from sodium formate and hydrazine sulfate according to Pellizzari.[17]

*Formanilides and N-alkylformamides* were prepared by heating the appropriate amines with excess formic acid. Most of the formanilides were purified by crystallization; the *N*-alkylformamides, formanilide, and *m*-formotoluidide were distilled.

*1-Alkyltetrazoles* were prepared from the alkyl isocyanides and hydrazoic acid in benzene solution. The preparation of *n*-hexyltetrazole serves as a typical example. A mixture of 8.0 g. of crude *n*-hexyl isocyanide and 100 ml. of a 16% solution of hydrazoic acid in benzene was heated under reflux in a well-ventilated hood for 3 hr. The solvent was removed under reduced pressure and the residue was boiled under reflux for an hour with 20% hydrochloric acid. After making the cooled solution alkaline with sodium hydroxide, the crude tetrazole layer was separated and the aqueous layer was shaken with ether. The combined tetrazole layer and ether solution were dried over sodium sulfate before the ether was removed by distillation and the residue fractionated under reduced pressure. Physical constants and analytical data are given in Table I. The 1-alkyltetrazoles are sparingly soluble in water, soluble in concentrated aqueous acids, and most of the common organic solvents except petroleum ether. Their aqueous suspensions are neutral or weakly basic to litmus.

*1-Aryltetrazoles* were prepared from the formanilides by reaction successively with phosphorus pentachloride and hydrazoic acid in toluene. The preparation of 1-*m*-tolyltetrazole serves as a typical example. A solution of 33.8 g. (0.25 mole) of *m*-formotoluidide in 100 ml. of toluene was stirred and cooled in an ice bath during the portion-wise addition of 52 g. (0.25 mole) of phosphorus pentachloride. Upon complete reaction with the phosphorus pentachloride the resulting bright yellow solution was treated with 100 ml. of a 16% solution of hydrazoic acid in toluene, stirred at room temperature for 24 hr., poured over ice, made alkaline with sodium hydroxide, and filtered. The filter cake was washed by resuspension first in 4% sodium hydroxide and then in water. A further quantity of the crude product was obtained by separating the toluene layer from the filtrate and evaporating the toluene. The two crops were combined and recrystallized from aqueous isopropyl alcohol. Final purification was accomplished by repeated extraction with warm cyclohexane from which the tetrazole separated as colorless crystals. Physical constants and analytical data are given in Table I. 1-Phenyltetrazole and 1-*o*-methoxyphenyltetrazole were also crystallized from cyclohexane. All the other 1-aryltetrazoles were crystallized from isopropyl alcohol. In some instances the formanilide was insoluble and was used as a suspension in toluene. The product of reaction with phosphorus pentachloride varied

TABLE I

1-SUBSTITUTED TETRAZOLES (I)

| R | B.P. (M.P.),[a] °C. at mm. | $n_D^{20}$ | Yield, % | Formula | Analyses | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Calculated | | | Found | | |
| | | | | | C | H | N | C | H | N |
| $C_6H_5$ | 147–148/14 | 1.4601 | 30 | $C_7H_6N_4$ | 36.7 | 6.2 | 57.1 | 36.8 | 6.3 | 56.9 |
| *n*-$C_4H_9$ | 143–145/2 | 1.4604 | 63 | $C_5H_{10}N_4$ | 47.6 | 7.9 | 44.4 | 47.9 | 7.7 | 44.3 |
| *iso*-$C_4H_9$ | 121–123/1 | 1.4590 | 18 | $C_5H_{10}N_4$ | 47.6 | 7.9 | 44.4 | 47.9 | 8.2 | 44.6 |
| *n*-$C_6H_{11}$ | 138–139/1 | 1.4608 | 57 | $C_6H_{12}N_4$ | 51.4 | 8.6 | 40.0 | 51.4 | 8.7 | 40.0 |
| *iso*-$C_5H_{11}$ | 143–145/1 | 1.4607 | 37 | $C_6H_{12}N_4$ | 51.4 | 8.6 | 40.0 | 51.8 | 8.8 | 39.4 |
| *n*-$C_6H_{13}$ | 144–146/1 | 1.4610 | 57 | $C_7H_{14}N_4$ | 54.6 | 9.1 | 36.4 | 54.7 | 9.2 | 36.2 |
| *n*-$C_7H_{15}$ | 150–152/1 | 1.4613 | 9 | $C_8H_{16}N_4$ | 57.1 | 9.5 | 33.3 | 57.5 | 9.3 | 32.6 |
| $C_6H_5$ | (65–66) | *b* | 16 | $C_7H_6N_4$ | 57.5 | 4.1 | 38.3 | 57.5 | 3.9 | 38.6 |
| *m*-$CH_3C_6H_4$ | (53–54) | *b* | 34 | $C_8H_8N_4$ | 60.0 | 5.0 | 35.0 | 60.1 | 5.0 | 34.9 |
| *p*-$CH_3C_6H_4$ | (93–94) | *c* | 28 | $C_8H_8N_4$ | 60.0 | 5.0 | 35.0 | 59.8 | 4.9 | 34.9 |
| *o*-$ClC_6H_4$[d] | (86–87) | *c* | 41 | $C_7H_5N_4Cl$ | 46.6 | 2.8 | 31.0 | 46.6 | 2.9 | 31.1 |
| *m*-$ClC_6H_4$[e] | (101–102) | *c* | 43 | $C_7H_5N_4Cl$ | 46.6 | 2.8 | 31.0 | 46.5 | 2.9 | 31.2 |
| *p*-$ClC_6H_4$[f] | (155–156) | *c* | 32 | $C_7H_5N_4Cl$ | 46.6 | 2.8 | 31.0 | 46.6 | 2.9 | 31.0 |
| *o*-$CH_3OC_6H_4$ | (48–49) | *b* | 32 | $C_8H_8N_4O$ | 54.5 | 4.6 | 31.8 | 54.8 | 4.6 | 32.0 |
| *p*-$CH_3OC_6H_4$ | (116–117) | *c* | 35 | $C_8H_8N_4O$ | 54.5 | 4.6 | 31.8 | 54.7 | 4.6 | 32.1 |

[a] Parentheses indicate m.p. [b] Crystallized from cyclohexane. [c] Crystallized from isopropyl alcohol. [d] Calcd.: Cl, 19.6. Found: Cl, 19.7. [e] Calcd.: Cl, 19.6. Found: Cl, 19.7. [f] Calcd.: Cl, 19.6. Found: Cl, 19.7.

(15) Microanalyses were done by Micro-Tech Laboratories, Skokie, Ill.

(16) L. Malatesta, *Gazz. chim. ital.*, **77**, 238 (1947); *Chem. Abstr.*, **42**, 869 (1948).

(17) G. Pellizzari, *Gazz. chim. ital.*, **39**, I, 520 (1909).

in color from bright yellow to bright red and in some instances separated as a pasty mass or an oil without interference in the subsequent reaction with hydrazoic acid.

1-Phenyltetrazole was also prepared from phenyl isocyanide and hydrazoic acid[4] in benzene solution and by Dimroth's method from benzene diazonium chloride and diformyl hydrazide. In both instances the yields were poor but the products were identical with the material prepared from formanilide.

*1-Isobutyltetrazole* was prepared by interaction of 17.9 g. (0.18 mole) of *N*-isobutylformamide in 100 ml. of toluene with 37 g. (0.18 mole) of phosphorus pentachloride followed by treatment with 100 ml. of a 16% solution of hydrazoic acid in toluene. After addition of the hydrazoic acid solution the reaction mixture was stirred for 1 hr. at room temperature and then for 3 hr. under reflux on a steam bath. The mixture was poured onto ice and made alkaline with sodium hydroxide. After separation of the toluene layer the aqueous layer was shaken once with toluene and then discarded. The combined toluene solutions were dried and the residue left after removal of the solvent was fractionated. 1-Isobutyltetrazole was collected at 121–123° at 1 mm., $n_D^{20}$ 1.4590, yield 4.0 g. (18%). This product and the material prepared from isobutyl isocyanide gave identical infrared spectra.

*Ultraviolet absorption spectra* were determined with $1 \times 10^{-4}M$ solutions in 95% ethanol using a Beckman Model DU spectrophotometer. Readings were made with 1-cm. cells with 95% ethanol as the blank. The region 210–300 mμ was scanned at 5-mμ intervals and near the maxima readings were taken at 1-mμ intervals. Tetrazole and the 1-alkyltetrazoles showed only little absorption and no maxima in the region examined although in these cases concentrations as high as $1 \times 10^{-2}M$ were used. All the 1-aryltetrazoles exhibited a broad absorption band; maxima and extinction coefficients are recorded in Table II.

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA OF SOME 1- AND 5-ARYLTETRAZOLES

| Aryl | 1-Aryltetrazoles Max. (mμ) | ε | 5-Aryltetrazoles Max. (mμ) | ε |
|---|---|---|---|---|
| Phenyl | 236 | 9,300 | 241[a] | 15,900 |
| *m*-Tolyl | 239 | 8,700 | 243 | 13,600 |
| *p*-Tolyl | 243 | 10,100 | 246 | 16,700 |
| *o*-Chlorophenyl | (215)[b] | (10,400) | 234[a] | 9,600 |
| *m*-Chlorophenyl | 239 | 8,800 | 242[a] | 14,000 |
| *p*-Chlorophenyl | 242 | 14,000 | 247[a] | 20,400 |
| *o*-Methoxyphenyl | 235 | 5,800 | 246[a] | 11,600 |
| | 282 | 3,800 | 294 | 4,900 |
| *p*-Methoxyphenyl | 255 | 10,900 | 259[a] | 16,900 |

[a] Ref. 12. [b] Shoulder.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

# Catalytic Synthesis of Heterocycles. IX.[1] Dehydrocyclization of 2-Methyl-5-ethyl-4-pyridinethiol to 6-Methyl-5-azathianaphthene

CORWIN HANSCH AND WAYNE CARPENTER

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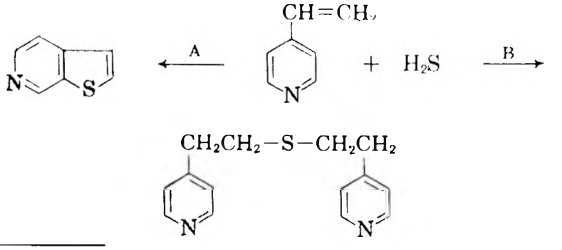
A procedure for the synthesis of 2-methyl-5-ethyl-4-pyridinethiol from 2-methyl-5-ethylpyridine has been developed. The dehydrogenation of this *o*-ethylthiol to 6-methyl-5-azathianaphthene is discussed.

After considering suitable systems in which to extend the use of the dehydrocyclization reaction it was decided that the pyridine ring offered a highly stable and interesting structure for such a study. In particular this ring system offers an approach to the synthesis of heterocycles containing two hetero atoms. The fact that ethylpyridines are available commercially and that improved methods have been worked out for the introduction of substituents into the pyridine ring[2,3] indicated that the necessary starting materials should be relatively easy to prepare. Formation of the thiophene ring was chosen for the first of these experiments because previous work[1] had shown that the dehydrocyclization reaction is particularly useful in its formation.

It was first expected that azathianaphthenes could be obtained by the reaction of hydrogen sulfide with vinyl pyridines. It is known[4] that styrene and hydrogen sulfide react at 600° to give thianaphthene. A number of runs were made using the catalyst of Moore and Greensfelder,[4] as well as with the catalyst used in the dehydrocyclization of *o*-ethylthiophenol.[1] The products from the reaction of 4-vinylpyridine and hydrogen sulfide at 600° were separated into two fractions: one was a red, tarry material soluble in water, but insoluble in ether, and the other was a yellow oil which was soluble in ether and insoluble in water. Of two possible paths which the reaction might take, A or B, a work-up of the ether soluble fraction indicated that this material was formed *via* path B as follows:




(1) For the previous paper in this series see *J. Org. Chem.*, 21, 265 (1956).

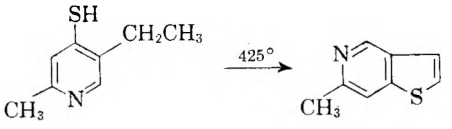
(2) Den Hertog and Combe, *Rec. trav. chim.*, 70, 581 (1951).

(3) Ochiai, *J. Org. Chem.*, 18, 534 (1953).

(4) Moore and Greensfelder, *J. Am. Chem. Soc.*, 69, 2008 (1947).

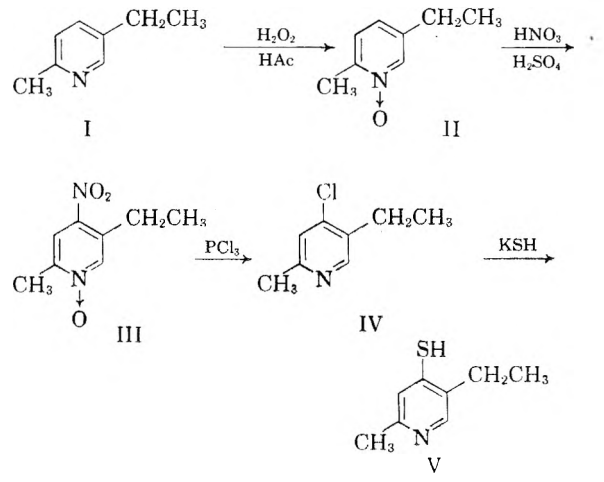
The ether soluble fraction was subjected to chromatographic analysis in an attempt to determine its composition and discover any azathianaphthene which might have formed. No azathianaphthene was isolated. A yellow oil which gave analytical data corresponding to that expected for the addition of two molecules of pyridine to one of hydrogen sulfide was the only pure substance which could be isolated from the ether soluble fraction.

Another approach to the synthesis of the azathianaphthenes is the possible dehydrogenation of an *ortho* ethylarylthiol. Previous work[1] has shown that this procedure worked well with benzenethiols and therefore we decided to apply this approach to a pyridinethiol according to the following equation:




VI

2-Methyl-5-ethyl-4-pyridinethiol was used as a model compound since it is relatively easily made from 2-methyl-5-ethylpyridine, an inexpensive commercial product.[5] The following procedure was used for its synthesis:




The 4-pyridinethiol was chosen partly because of its relative ease of synthesis, and partly because it was of interest to determine whether a 4-pyridinethiol which would be in equilibrium with thione would undergo the dehydrocyclization reaction as well as a benzenethiol. It was expected that the thione might not give as good results, and indeed, this was found to be true.

In the synthesis of the 2-methyl-5-ethyl-4-pyridinethiol commercial grade 2-methyl-5-ethylpyridine was oxidized to the oxide by the procedure of Ochiai[3] in yields of better than 95%. The nitration of the oxide to the nitro compound III did not give high yields. Experiments were carried out using various strengths of nitric acid and various reaction times and temperatures; however, yields of 40 to 45% were the best obtained. The main cause for the low yields was the oxidation of the molecule which occurs much more readily with an ethylpyridine than with a methylpyridine. Preliminary work on the nitration of 3-ethylpyridine oxide indicates that this molecule is also very easily oxidized by a mixture of nitric and sulfuric acid. Compound III was smoothly converted to IV in yields of 70–75% by refluxing with $PCl_3$ in chloroform. The conversion of IV to the thiol V proceeded poorly. Refluxing IV in ethylene glycol with potassium hydrogen sulfide gave about 50% of crude V, which could be purified with some difficulty by recrystallization from either acetone or ethanol-benzene.

The dehydrocyclization of V to 6-methyl-5-azathianaphthene gave yields of 20–25% on runs of 10 g. On larger runs it is likely that the yields would be lower since the activity of the catalyst decreases with use. One of the most important causes of the low yield is the hydrogenolysis of the thiol to give hydrogen sulfide. Analysis of the $H_2S$ evolved indicated that 35–40% of compound V underwent hydrogenolysis. About 10–15% of the thiol was recovered leaving about 20–35% of the starting material unaccounted for. A certain amount of charring in the catalyst tube and dark material in the product indicated that some of the starting material was lost by thermal decomposition.

The identity of the 6-methyl-5-azathianaphthene was confirmed by carbon and hydrogen analysis, and by the fact that the methiodide con-

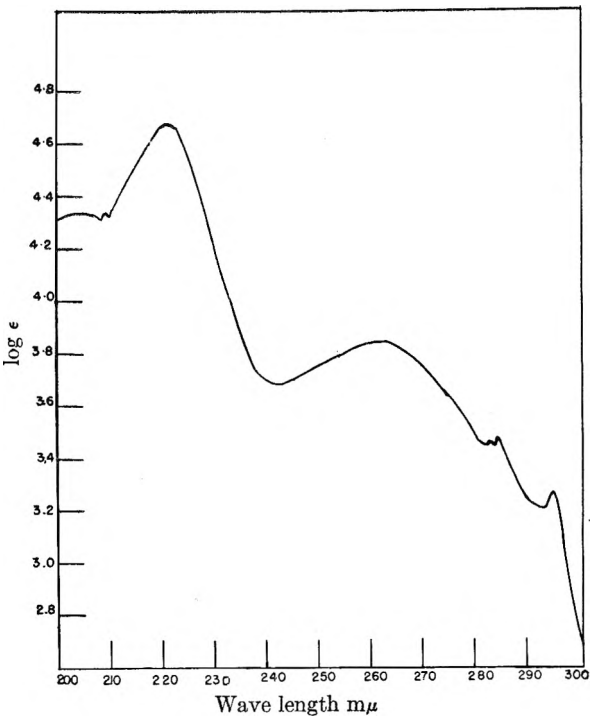



FIG. 1. ULTRAVIOLET SPECTRUM OF 6-METHYL-5-AZATHIANAPHTHENE.

(5) Purchased from Union Carbide Chemicals Co., South Charleston, W. Va.

densed readily with benzaldehyde indicating an active methyl group. Its ultraviolet absorption spectrum (Fig. 1) is similar to that obtained for 5-azathianaphthene by Herz and Tsai.[6]

## EXPERIMENTAL[7]

*Reaction of 4-vinylpyridine with hydrogen sulfide.* After 10 ml. of iron oxide on alumina catalyst was reduced according to the procedure of Moore and Greensfelder[4] hydrogen sulfide was started over it at the rate of 1000 ml./ml. catalyst/hour, the temperature being held at 600°. Then 30 g. of 4-vinylpyridine was processed over the catalyst in the hydrogen sulfide stream during the course of 135 min. A liquid condensate was removed from the effluent gas stream by means of an ice trap, after which the hydrogen sulfide was removed by passing the gases through two dry ice traps. The red condensate from the ice cooled receiver was extracted with ether. Evaporation of the ether gave 10.8 g. of yellow oil. The red oil not soluble in ether amounted to 8.2 g. Of the ether soluble material 8.7 g. was chromatographed over 200 g. of alumina. The effluent solvents from the elution of the column were collected in 27 100-ml. fractions. The column was first eluted with benzene (7 fractions), then ether (16 fractions), and finally methanol (4 fractions). The oil obtained from the evaporation of the eleventh ether fraction yielded a picrate of m.p. 185–186°. Ether fractions 6 through 12 were combined and evaporated to give 6.9 g. of light yellow oil. This material was converted to the picrate which after five recrystallizations from 1:1 water-methanol gave a product which melted at 180–182°. Decomposition of the picrate gave 1.2 g. of oil, a small sample of which was distilled under high vacuum prior to analysis.

*Anal.* Calcd. for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60. Found: C, 68.47; H, 7.02.

The picrate appeared to contain two molecules of picric acid.

*Anal.* Calcd. for $C_{26}H_{22}N_8O_{14}S$: C, 44.45; H, 3.16. Found: C, 44.70; H, 3.36.

The benzene fractions contained 0.8 g. of material which may have contained some azathionaphthene, but attempts to isolate it were unsuccessful. The methanol fractions contained 0.36 g. of crude material.

*2-Methyl-5-ethylpyridine oxide* (II). 2-Methyl-5-ethylpyridine (240 g.) was dissolved in 1200 ml. of glacial acetic acid and to this solution was added 160 ml. of 30% hydrogen peroxide. After heating the mixture on a water bath for 4 hr. at 60–70°, 160 ml. more hydrogen peroxide was added and the heating continued for 5 hr. The reaction mixture was then evaporated as far as possible by means of an aspirator and a steam bath; 300 ml. of water was added and the process was repeated. Excess anhydrous potassium carbonate was added to remove small amounts of acetic acid still present, and the product was separated from the carbonate with chloroform. Evaporating the chloroform and distillating the resulting oil gave 252.5 g. of oxide, b.p. 102°/0.7 mm., $n_D^{25}$ 1.5591.

*Anal.* Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 69.69; H, 8.41.

*2-Methyl-5-ethyl-4-nitropyridine oxide* (III). Compound II (120 g.) was added with cooling to 100 ml. of concd. sulfuric acid. This solution was added slowly from a dropping funnel to a mixture of 200 ml. of concd. sulfuric acid and 130 ml. of nitric acid (sp. gr. 1.49) held at 105–110°. About 1.5 hr. were required for the addition, after which the mixture was heated at 130° for 2.5 hr. Then the solution was poured onto crushed ice, neutralized with ammonium hydroxide, cooled, and extracted four times with chloroform. The chloroform solution was evaporated to a small volume and poured into ether where, upon cooling, 74 g. of crystals of m.p. 74–78° separated. Recrystallization from ether gave 61.9 g., m.p. 78–79°.

*Anal.* Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53. Found: C, 52.97; H, 5.83.

*2-Methyl-5-ethyl-4-chloropyridine* (IV). Compound III (23 g.) was dissolved in 300 ml. of chloroform and 40 ml. of phosphorus trichloride was added slowly with cooling. After the initial exothermic reaction had subsided the solution was refluxed for 5 hr. Then it was poured onto crushed ice, neutralized with ammonium hydroxide, and the product extracted with chloroform. The chloroform was evaporated from the extracts and the residue was distilled to give 16 g. of yellow oil of b.p. 70–71°/5 mm., $n_D^{25}$ 1.5170.

*Anal.* Calcd. for $C_8H_{10}ClN$: C, 61.74; H, 6.48. Found: C, 61.99; H, 6.69.

Preparation of the picrate gave a substance which melted at 129.5–132.5° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{14}H_{13}ClN_4O_7$: C, 43.70; H, 3.40. Found: C, 44.24; H, 3.63.

If insufficient phosphorus trichloride was used, or if the reflux time was too short, a second substance was obtained in the distillation of the 2-methyl-5-ethyl-4-chloropyridine. This material boiled at 95–100°/5 mm. and on treatment with phosphorus trichloride in chloroform was converted into 2-methyl-5-ethyl-4-chloropyridine. A picrate was made which, after recrystallization from ethanol, melted at 116–118°. The nitrogen analysis of the picrate would indicate that this higher boiling material is 2-methyl-5-ethyl-4-chloropyridine oxide.

*Anal.* Calcd. for $C_{14}H_{13}ClN_4O_8$: N, 13.98. Found: N, 13.99.

*2-Methyl-5-ethyl-4-pyridinethiol* (V). The procedure used in the preparation of this compound is a modification of that described by Thirtle.[8] Potassium hydroxide (198 g.) was dissolved in 600 ml. of ethylene glycol and then hydrogen sulfide was bubbled into the solution until a gain in weight of 102 g. was obtained. This mixture was then distilled until the temperature of the material distilling reached 190° to remove the water. To this solution was added 136 g. of compound IV after which the mixture was refluxed for 8 hr. Then it was cooled, diluted with ethanol, and the potassium chloride which separated was removed by filtration. The ethylene glycol and ethanol were then distilled under vacuum. The semi-solid residue which resulted was dissolved in water and carefully neutralized with acetic acid. The solid product which separated was crystallized from acetone to give 71 g. of product, m.p. 141–149°. Recrystallization from acetone gave 53 g., m.p. 154–158°. The pure substance obtained by another crystallization melted at 159–161°.

*Anal.* Calcd. for $C_8H_{11}NS$: C, 62.70; H, 7.24. Found: C, 62.83; H, 7.38.

*6-Methyl-5-azathianaphthene* (VI). In the dehydrogenation of V to VI 10 ml. of the previously described[1] catalyst was used. Compound V (10 g.) was dissolved in 35 ml. of pyridine. In several experiments phenol was substituted for pyridine; the yields, however, were 10–20% lower using this solvent. This solution was then processed over the catalyst at 425° during the course of 100 min. The liquid condensate was collected in an ice bath and the effluent gases were passed through an Ascarite tube. The gain in weight of this tube was considered to be hydrogen sulfide formed from the hydrogenolysis of the thiol group. Hydrogenolysis calculated this way amounted to 30–35% of the starting material. The liquid condensate was transferred to an efficient distilling column and all but traces of the pyridine removed by fractionation. Petroleum ether was added to the residue in the distilling pot whereupon some of the starting thiol separated. Washing the petroleum ether solution with dilute sodium hydroxide solution extracted a small additional amount to give in all 1–1.5 g. of crude V.

(6) Herz and Tsai, *J. Am. Chem. Soc.*, 75, 5122 (1953).

(7) Microanalyses by C. F. Geiger, Chaffey College, Ontario, Calif.

(8) Thirtle, *J. Am. Chem. Soc.*, 68, 342 (1946).

The petroleum ether solution was then poured over a column of activated alumina (30 g.) and the azathianaphthene eluted with a solution of 25% ether-petroleum ether. This treatment removed tarry material which was difficult to remove by crystallization. The solvent was then evaporated and the residue vacuum sublimed at 60°/0.1 mm. to give 2.2 g. of product of m.p. 71.5–72.5°.

*Anal.* Calcd. for $C_8H_7NS$: C, 64.39; H, 4.73. Found: C, 64.58; H, 5.11.

The picrate was prepared and crystallized from ethanol to give a product which melted at 222–224°.

*Anal.* Calcd. for $C_{14}H_{10}N_4O_7S$: C, 44.45; H, 2.66. Found: C, 44.85; H, 2.96.

*6-Methyl-5-azathianaphthene methiodide* (VII). Compound VI was refluxed for a few minutes with excess methyl iodide and the mixture then was diluted with ether. The solid product which separated was removed by filtration and recrystallized from methanol to give a substance of m.p. 240–242°.

*Anal.* Calcd. for $C_9H_{10}INS$: C, 37.09; H, 3.46. Found: C, 37.18; H, 3.77.

*1-Phenyl-2-[6-(5-azathianaphthenyl)]ethene methiodide* (VIII). Compound VII (1.5 g.), 2 ml. of benzaldehyde, and 1 ml. of piperidine were placed in 20 ml. of methanol and refluxed for 12 hr. Cooling the mixture caused 1.03 g. of yellow solid m.p. 290–292° (decomp.) to separate. The filtrate from which the yellow solid separated was refluxed for 12 hr. more and then cooled, whereupon 0.27 g. more of the product crystallized. Recrystallization of these two fractions did not raise the melting point.

*Anal.* Calcd. for $C_{16}H_{14}INS$: C, 50.28; H, 3.69. Found: C, 50.97; H, 3.98.

*1-Phenyl-2-[6-(5-azathianaphthenyl)]ethene* (IX). Compound VIII (526 mg.) was heated at 280°/0.25 mm. which caused it to decompose and sublime. The 318 mg. of product melted at 118–120°. After recrystallization from ligroin it melted at 126–127°.

*Anal.* Calcd. for $C_{15}H_{11}NS$: C, 75.91; H, 4.67. Found: C, 76.08; H, 5.13.

CLAREMONT, CALIF.

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[CONTRIBUTION NO. 1007 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# The Synthesis of Nitrogen-Containing Ketones. VII. A Study of the Acylation of 4-Picoline[1,2]

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The lateral metalation of 4-picoline cannot be effected by means of phenylmagnesium bromide, methylmagnesium iodide, or ethylmagnesium bromide. However, its reaction with phenyllithium by either the Standard Addition method (S.A.) or the Reverse Addition method (R.A.) followed by the addition of an acylating ester gives mixtures of the desired 4-picolyl ketone and the azomethine addition products, 2-phenyl-4-methylpyridine and 2,6-diphenyl-4-methylpyridine. Although the reaction of 4-picoline, *n*-butyllithium, and methyl benzoate by the S.A. method gives a mixture of 2-*n*-butyl-4-methylpyridine, A, (36%) and 4,4′-dimethyl-2,2′-dipyridyl and none of the desired 4-phenacylpyridine, B, repeating this reaction by the R.A. method gave a 15.5% yield of A and a 39.8% yield of B. Furthermore, 4-picoline may be acylated with esters in acceptable yields by using both methyllithium and sodium amide as the condensing agents.

The previous papers in this series have been concerned with the synthesis of ketones containing pyridine and quinoline rings by the side-chain acylation of 2-picoline,[4,5] 3-picoline,[6] quinaldine,[5] and certain related compounds.[2,5,7] The present report deals with the acylation of 4-picoline and certain of its derivatives.

A survey of the literature indicated that a general method for the synthesis of ketones of the type, $4\text{-}C_5H_4NCH_2COR$ (I), has apparently not been devised. In the aromatic series (I, R = aryl) the following results have been reported. Chichibabin[8] obtained 4-phenacylpyridine, II (I, R = $C_6H_5$), in unreported yield by the reaction of sodium amide, 4-picoline, and benzonitrile followed by hydrolysis of the resulting ketimine. Although only a low yield of this ketone was also obtained by Smith *et al.*[9] from the reaction of 4-picoline, phenyllithium, and benzonitrile, these workers obtained fair to good yields of II and related ketones by applying, in the 4-picoline series, the multi-stage method developed by Scheuing and Winterhalder[10] for the synthesis of aryl 2-picolyl ketones. This route involves the following steps: $4\text{-}C_5H_4NCH_3 + ArCHO \rightarrow 4\text{-}C_5H_4NCH{=}CHAr \rightarrow 4\text{-}C_5H_4NCHBrCHBrAr \rightarrow 4\text{-}C_5H_4NC{\equiv}CAr \rightarrow 4\text{-}C_5H_4NCH_2COAr$

(1) This work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) For paper VI in this series, see C. Osuch and R. Levine, *J. Org. Chem.*, 21, 1099 (1956).

(3) This paper is based on part of the thesis presented by Carl Osuch to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree; present address: Monsanto Chemical Co., St. Louis, Mo.

(4) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(5) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(6) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

(7) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **77**, 3647 (1955).

(8) A. E. Chichibabin, *Rec. trav. chim.*, **57**, 582 (1938).

(9) J. M. Smith, H. W. Stewart, B. Roth, and E. H. Northey, *J. Am. Chem. Soc.*, **70**, 3997 (1948).

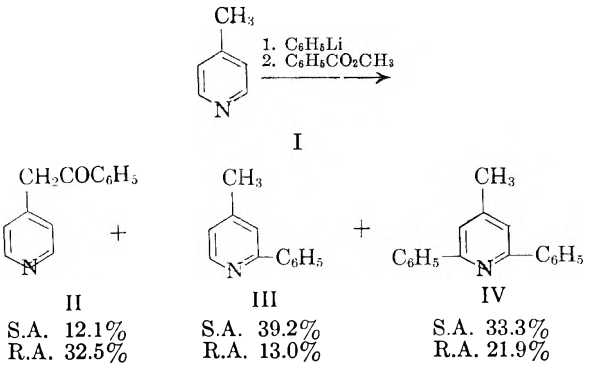
(10) G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929); German Patent 594,849, March 22, 1934 [*Chem. Abstr.*, **28**, 4542 (1934)].

Previous attempts to prepare alkyl 4-pyridyl ketones (I, R = alkyl) have also met with only moderate success. Although Burger and Ullyot[11] obtained none of the desired 4-acetonylpyridine (I, R = $CH_3$) from the reaction of 4-picoline, phenyllithium, and acetyl chloride or acetonitrile, this ketone was subsequently obtained in 50% yield by Burger *et al.*[12] by the interaction of the difficultly accessible 4-pyridylacetic acid with acetic anhydride and sodium acetate. During the course of the present investigation, Hey and Wibaut[13] published a report in which they claim to have obtained a 34% yield of this ketone by the reaction of ethyl acetate with 4-picolyllithium, which was prepared by the slow *addition of phenyllithium to 4-picoline (Reverse Addition Method)* rather than by *adding the tar base to the organolithium compound (Standard Addition Method)*.

Based on our previous success in the 2-picoline series,[2,4,5,7] it appeared reasonable to expect that 4-picoline could also be acylated with a variety of esters provided that it could first be metalated at its side chain. Therefore, attempts were made to metalate this tar base by treating it with several Grignard reagents, organolithium compounds, and sodium amide.

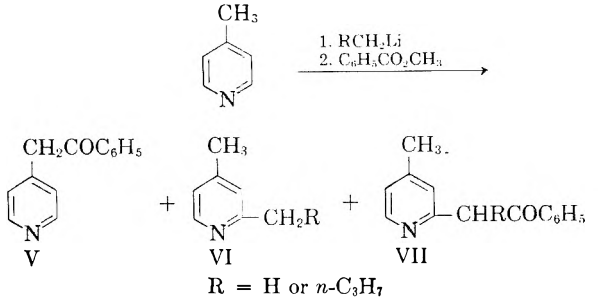
We first attempted the acylation of 4-picoline with methyl benzoate using ether solutions of phenylmagnesium bromide, methylmagnesium iodide, and ethylmagnesium bromide as the condensing agents. None of the desired 4-phenacylpyridine was obtained. Instead, the following neutral materials were isolated: triphenylcarbinol (58.8%); a mixture of dimethylphenylcarbinol and $\alpha$-methylstyrene; and diethylphenylcarbinol (86.6%), respectively.[14]

We next investigated the acylation of 4-picoline with methyl benzoate using phenyllithium as the metalating agent and employing both the Standard Addition (S.A.) and the Reverse Addition (R.A.) methods. Both of these procedures gave mixtures of 4-phenacylpyridine, II, and the azomethine addition products, 2-phenyl-4-methylpyridine, III, and 2,6-diphenyl-4-methylpyridine, IV. Apparently, as shown in the accompanying scheme, the use of the R.A. method greatly decreases the extent of azomethine addition and increases the extent of lateral metalation.




Because of the above results and the claim by Hey and Wibaut[13] that the reaction of phenyllithium with 4-picoline and ethyl acetate by the R.A. method gave a 34% yield of 4-acetonylpyridine, V, (I, R = $CH_3$) and apparently none of the azomethine addition products, we reinvestigated the acetylation of 4-picoline by the R.A. method. In contrast with the previously reported[13] results we obtained a mixture of 4-acetonylpyridine, V, (22%) and 2-phenyl-4-methylpyridine, III, (6%).[15]

We next attempted to effect the lateral metalation of 4-picoline by means of the aliphatic organolithium compounds, *n*-butyllithium and methyllithium. Theoretically, some or all of the following products might be formed by the addition of an acylating ester such as methyl benzoate to these reaction mixtures: (*1*) the desired ketone, 4-phenacylpyridine, II, (by lateral metalation of 4-picoline followed by acylation); (*2*) the azomethine addition products, VI, and (*3*) the ketones, VII, (from VI by lateral metalation at the substituent in the 2-position of the pyridine ring followed by acylation[16]).




When 4-picoline was added to *n*-butyllithium (S.A.) followed by the addition of methyl benzoate,

(11) A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 342 (1947).

(12) A. Burger, J. R. Rector, and A. C. Schmalz, *J. Am. Chem. Soc.*, **74**, 3175 (1952).

(13) J. W. Hey and J. P. Wibaut, *Rec. trav. chim.*, **72**, 522 (1953).

(14) During the addition of the 4-picoline to the Grignard reagents, white precipitates are formed. These precipitates, which appear to be complexes between the Grignard reagents and 4-picoline, then probably react with the ester to give the observed products. These observations parallel those of B. Oddo [*Gazz. chim. ital.*, **37**, 356 (1907)], who found that pyridine reacts with methylmagnesium iodide and phenylmagnesium bromide to form ether-insoluble complexes, which on treatment with benzaldehyde give methylphenylcarbinol and diphenylcarbinol, respectively.

(15) Since, in our hands, the mixture of III and V could not be separated by distillation, it was converted to a mixture of picrates, which was separated into its components by fractional crystallization. Therefore, it seems possible that Hey and Wibaut[13] had a mixture of III and V.

(16) Another possible product would be an isomer of VII, which might conceivably be formed by the lateral metalation of VI at its 4-methyl group followed by acylation. However, the formation of this isomer is unlikely since the preferred reaction between an organolithium compound and a 2,4-dialkylpyridine appears to be at the 2-position of the pyridine ring (see ref. 7).

none of the desired 4-phenacylpyridine was isolated. However, there was obtained a mixture of 36% of 2-*n*-butyl-4-methylpyridine (VI, R = *n*-$C_3H_7$),[17] a small amount of 4,4′-dimethyl-2,2′-dipyridyl,[18] and an unidentified, viscous, high-boiling nitrogenous oil.[19] When this reaction was repeated, except that the R.A. method was used, a mixture of 15.5% of 2-*n*-butyl-4-methylpyridine and 39.8% of 4-phenacylpyridine was obtained.

With the idea in mind that it might be possible to increase the extent of lateral metalation and decrease the extent of azomethine addition by changing the organolithium compound, the acylation of 4-picoline with both methyl benzoate and methyl acetate was attempted by the R.A. method using methyllithium as the condensing agent. From these reactions, none of the azomethine addition product was isolated and 4-phenacylpyridine and 4-acetonylpyridine were obtained in yields of 48.7% and 27.0% respectively. Since azomethine addition did not occur by the R.A. method, it was of interest to repeat these reactions by the much more convenient, less time-consuming S.A. method. By this procedure, 4-phenacylpyridine (50.8%) and 4-acetonylpyridine (22.6%) as well as trace amounts of 2,4-lutidine and 4,4′-dimethyl-2,2′-dipyridyl[20] were obtained. The methyllithium-S.A. method was then used to effect three more acylations with the results listed in Table I.

Finally it was of interest to determine whether sodium amide in liquid ammonia could be used as the condensing agent. As may be seen in Table I, this base gave acceptable yields of ketones with all the esters used except methyl acetate. It should also be noted that although it was not possible to acylate 4-ethylpyridine with methyl benzoate using methyllithium as the condensing agent, an 85% yield of the desired product, α-(4-pyridyl)propiophenone was obtained by the sodium amide method.

The properties of the ketones which were prepared are found in Table II.

TABLE I

4-PICOLYL KETONES, 4-$C_5H_4NCH_2COR$, BY ACYLATING 4-PICOLINE WITH METHYL ESTERS IN THE PRESENCE OF VARIOUS CONDENSING AGENTS

| R | Condensing Agent[a] | Yield, % |
|---|---|---|
| $C_6H_5$ | $C_6H_5Li$ | 12.1(S.A.)[b,c]; 32.5(R.A.)[b,d] |
| | $CH_3Li$ | 50.8(S.A.)[b,e]; 48.7(R.A.)[b] |
| | *n*-$C_4H_9Li$ | 0.0(S.A.)[b,f]; 39.8(R.A.)[b,g] |
| | $NaNH_2$ | 73.8 |
| 4-$C_5H_4N$[h] | $NaNH_2$ | 56.0 |
| $CH_3$ | $C_6H_5Li$ | 22.0(R.A.)[b,i] |
| | $CH_3Li$ | 22.6(S.A.)[b,e]; 27.0(R.A.)[b] |
| | $NaNH_2$ | 6.3 |
| $C_2H_5$ | $CH_3Li$ | 54.8(S.A.)[b] |
| | $NaNH_2$ | 50.0 |
| *i*-$C_3H_7$[j] | $CH_3Li$ | 65.6(S.A.)[b] |
| | $NaNH_2$ | 79.1 |
| *t*-$C_4H_9$ | $CH_3Li$ | 70.6(S.A.)[b] |
| | $NaNH_2$ | 63.3 |

[a] In all reactions a 2:2:1 molar ratio of condensing agent: 4-picoline:ester was used. [b] S.A. = Standard Addition Method, i.e., tar base was added to the organolithium compound. R.A. = Reverse Addition Method, i.e., the organolithium compound was added to the tar base. [c] A 39.2% yield of 2-phenyl-4-methylpyridine, A, and a 33.3% yield of 2,6-diphenyl-4-methylpyridine, B, were also isolated. [d] A 13.0% yield of A and a 21.9% yield of B were also isolated. [e] Traces of 2,4-lutidine, C, and 4,4′-dimethyl-2,2′-dipyridyl, D, were also isolated. [f] A 36% yield of 2-*n*-butyl-4-methylpyridine, E, and a trace of D were also isolated. [g] A 15.5% yield of E was also obtained. [h] 4-$C_5H_4N$ = 4-pyridyl radical. [i] A 6% yield of A was also obtained. [j] Ethyl ester was used.

## EXPERIMENTAL[21]

In this reaction several typical experiments are described.

I. *Reaction of phenylmagnesium bromide, 4-picoline and methyl benzoate.* 4-Picoline (0.2 mole, 18.6 g.), diluted with an equal volume of anhydrous ether, was added to phenylmagnesium bromide (0.2 mole in 250 ml. of anhydrous ether). During the addition of the 4-picoline a greyish-white precipitate formed. After the addition of the tar base was completed, methyl benzoate (0.1 mole, 13.6 g.), diluted with an equal volume of ether, was added at such a rate that the solvent gently refluxed. The reaction was refluxed for an additional 30 min. and was then poured onto a mixture of crushed ice and 25 ml. of concentrated hydrochloric acid. Processing the mixture in the customary fashion[2,4] gave 9.3 g. of recovered 4-picoline, b.p. 140–146°, and 15.3

(17) H. Gilman and H. S. Broadbent [*J. Am. Chem. Soc.*, **70**, 2809 (1948)] have apparently prepared this compound in 13.4% yield by the reaction of 4-picoline and *n*-butyllithium at −10°. They report that its picrate melts at 88.5–90.5° while the picrate of our material melts at 98.6–99.0°. Therefore, we prepared an authentic sample of VI (R = *n*-$C_3H_7$) in 78.8% yield by alkylating 2,4-lutidine with *n*-propyl bromide using phenyllithium as the condensing agent [for the procedure used, see C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956)]. A mixed melting point between the picrate of the authentic sample and that obtained in the reaction of 4-picoline with *n*-butyllithium showed no depression.

(18) This compound probably arises from the nuclear metalation of 4-picoline by *n*-butyllithium to give 2-lithio-4-methylpyridine, which then undergoes azomethine addition to a second molecule of 4-picoline followed by the elimination of lithium hydride. Evidence in support of this argument was obtained by repeating this reaction in the absence of the ester and isolating 39.8% of VI (R = *n*-$C_3H_7$) and 0.7 g. of the dipyridyl.

(19) We have found that most ketones which have the grouping, —CHRCOR′, at the 2-position of the pyridine ring produce a blue-green color when treated with alcoholic iron (III) chloride solution. Apparently this oil does not contain an appreciable amount of α-(4-methyl-2-pyridyl)-valerophenone (VII, R = *n*-$C_3H_7$) since it does not give the iron (III) chloride color reaction, while an authentic sample of this ketone, which was prepared in 60% yield from the reaction of 2-*n*-butyl-4-methylpyridine, phenyllithium, and methyl benzoate, gives a positive test.

(20) That this compound probably arises from the reaction of 4-picoline and methyllithium (also see footnote 18) was shown by the fact that it was obtained in 5% yield by the interaction of these reagents in the absence of an acylating ester.

(21) The 4-picoline used in this study was supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

TABLE II

PROPERTIES OF THE KETONES, 4-$C_5H_4NCHRCOR'$

| R | R' | M.P., °C. | B.P. °C. | B.P. mm. | Formula | Analysis Caled. C | Analysis Caled. H | Analysis Found C | Analysis Found H | M.P., °C. | Picrate Formula | Picrate Nitrogen Caled. | Picrate Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | $C_6H_5$ | 112–113 4[a] | | | | | | | | 167.5–168.1[b] | $C_{19}H_{14}N_4O_8$ | 13.14 | 12.97 |
| H | 4-$C_5H_4N$[c] | 116–116.8[d] | | | $C_{12}H_{10}N_2O$ | 72.71 | 5.08 | 72.84 | 5.18 | [e] | | | |
| H | $CH_3$[f] | | 110–115 | 3–4 | | | | | | 155–155.4[b,g] | | | |
| H | $C_2H_5$ | | 86–88.5 | 1.0 | $C_9H_{11}NO$ | 72.45 | 7.43 | 72.00 | 7.38 | 163.2–164[b] | $C_{15}H_{14}N_4O_8$ | [h] | |
| H | i-$C_3H_7$ | | 95.97 | 1.0 | $C_{10}H_{13}NO$ | 73.58 | 8.03 | 73.10 | 7.80 | 121.0–121.7[b] | $C_{16}H_{16}N_4O_8$ | 14.28 | 14.07 |
| H | t-$C_4H_9$ | 41.8–42.4[i] | 98–102 | 1.0 | $C_{11}H_{15}NO$ | 74.54 | 8.53 | 74.36 | 8.38 | 157.3–157.8[b] | $C_{17}H_{18}N_4O_8$[j] | 13.79 | 14.26 |
| $CH_3$ | $C_6H_5$ | 62.4–63.0[i] | | | $C_{14}H_{13}NO$[k] | 75.59 | 6.20 | 75.57 | 5.75 | 150.1–150.9[b,l] | $C_{20}H_{16}N_4O_8$ | 12.72 | 13.08 |

[a] See reference 9. [b] Recrystallized from 95% ethanol. [c] 4-$C_5H_4N$ = 4-pyridyl radical. [d] Recrystallized from 75–90° petroleum ether. [e] Attempts to prepare an analytically pure picrate or trinitrocresolate failed. [f] Reference 13 gives a b.p. of 75.5° at 0.1 mm. [g] See reference 13. [h] Caled.: C, 47.62; H, 3.73. Found: C, 47.72; H, 3.84. [i] Recrystallized from 30–60° petroleum ether. [j] Caled.: C, 50.25; H, 4.46. Found: C, 49.93; H, 4.38. [k] Caled.: N, 6.63. Found: N, 6.82; obtained in 84.8% yield. [l] Darkens on standing.

g. (58.8%) of triphenylcarbinol, m.p. 161–162° alone and when mixed with an authentic sample.

II. *Reaction of phenyllithium and methyllithium with 4-picoline and methyl benzoate.* (a) *Phenyllithium and the Standard Addition (S.A.) Method.* By using the previously described procedures for the acylation of 2-picoline[4] and its homologues,[2] the interaction of phenyllithium (0.4 mole), 4-picoline (0.4 mole, 37.2 g.), and methyl benzoate (0.2 mole, 27.2 g.) gave 23.2 g. (39.2%) of 2-phenyl-4-methylpyridine, b.p. 113–114° at 2.0 mm. (picrate, m.p. 187.5–188.5°[22]); 16.4 g. (33.3%) of 2,6-diphenyl-4-methylpyridine, b.p. 188–190° at 1.5 mm.,[22] and 4.8 g. (12.1%) of 4-phenacylpyridine, m.p. 112–113.4° (lit.[9] 113–115°), picrate, m.p. 167.5–168.1°.

*Anal.* Caled. for $C_{19}H_{14}N_4O_8$: N, 13.14. Found: N, 12.97.

(b) *Phenyllithium and the Reverse Addition (R.A.) Method.* Phenyllithium (0.4 mole in 400 ml. of anhydrous ether) was added to 4-picoline (0.4 mole, 37.2 g., in 250 ml. of anhydrous ether) at such a rate that the ether did not reflux (2.5 to 3 hr.). To the dark, brownish-red suspension thus obtained, methyl benzoate (0.2 mole, 27.2 g.), dissolved in 50 ml. of anhydrous ether, was added at such a rate that the solvent refluxed gently. The mixture was refluxed for an additional 30 min. and processed in the regular manner[2,4] to give 8.8 g. (13.0%) of 2-phenyl-4-methylpyridine, 12.8 g. (32.5%) of 4-phenacylpyridine, and 10.8 g. (21.9%) of 2,6-diphenyl-4-methylpyridine.

(c) *Methyllithium and the Standard Addition (S.A.) Method.* When reaction IIa was repeated, except that the phenyllithium was replaced by methyllithium (0.4 mole), there were obtained 17.4 g. of basic material (fraction A, b.p. 138.5–160°) and 20.0 g. (50.8%, b.p. 140–160° at 1.0 mm., m.p. 112.5–113.4° from 60–70° petroleum ether) of 4-phenacylpyridine. The small amount of oil, which remained in the column after the distillation of the above materials, was shown to contain some 4,4′-dimethyl-2,2′-dipyridyl since it gave a red color when treated with aqueous iron (II) sulfate solution and formed a picrate, m.p. 202–203° alone and when mixed with an authentic sample. Redistillation of fraction A gave 15.0 g. of material, b.p. 140–150° (predominantly 4-picoline) and less than one gram of residue, which was shown to contain some 2,4-lutidine since it gave a picrate, m.p. 179.5–180.5° alone and when mixed with an authentic sample.

III. *Reaction of n-butyllithium with 4-picoline by the S.A. Method.* (a) *In the presence of methyl benzoate.* From 0.292 mole of *n*-butyllithium [prepared in 73% yield from 0.8 mole (5.6 g.) of lithium and 0.4 mole (54.8 g.) of *n*-butyl bromide], 0.292 mole (27.2 g.) of 4-picoline, and 0.146 mole (19.8 g.) of methyl benzoate there was obtained a mixture of 15.8 g. (36.3%) of 2-*n*-butyl-4-methylpyridine (b.p. 205–208°; picrate, m.p. 98.6–99.0° alone and when mixed with an authentic sample, see below), 0.1 g. of 4,4′-dimethyl-2,2′-dipyridyl (m.p. 169.5–170.3°[23] from 60–70° petroleum ether), and 10.8 g. of a viscous, nitrogenous oil (b.p. 148–180° at 1.5 mm.) from which it was not possible to isolate any pure compounds. The dipyridyl gave a bright red color when treated with aqueous iron (II) sulfate solution and formed a monopicrate, m.p. 202–203°, from 95% ethanol.

*Anal.* Caled. for $C_{18}H_{15}N_5O_7$: C, 52.30; H, 3.62. Found: C, 52.33; H, 3.48.

(b) *In the absence of methyl benzoate.* From the interaction of 0.278 mole of *n*-butyllithium and 0.278 mole (25.9 g.) of 4-picoline, there was obtained 16.5 g. (39.8%) of 2-*n*-butyl-4-methylpyridine, b.p. 205–208°, and 0.7 g. of 4,4′-dimethyl-2,2′-dipyridyl, m.p. 169.6–170.4°.

IV. *Synthesis of an authentic sample of 2-n-butyl-4-methylpyridine.* The interaction of phenyllithium (0.4 mole), 2,4-lutidine (0.4 mole, 42.9 g.), and *n*-propyl bromide (0.2 mole,

(22) C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956).

(23) F. H. Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).

24.6 g.), using the previously described procedure[22] for similar alkylations, gave 23.5 g. (78.8%) of 2-*n*-butyl-4-methylpyridine, b.p. 205–208°, which gave a picrate, m.p. 98.6–99.0° (lit. 88.5–90.5°[17]).

*Anal.* Calcd. for $C_{16}H_{18}N_4O_7$: N, 14.81. Found: N, 14.85.

V. *Synthesis of an authentic sample of α-(4-methyl-2-pyridyl)valerophenone.* The interaction of phenyllithium (0.2 mole), 2-*n*-butyl-4-methylpyridine (0.2 mole, 29.8 g.), and methyl benzoate (0.1 mole, 13.6 g.), using the previously described procedure for similar acylations,[2,4] gave 15.1 g. (59.7%) of α-(4-methyl-2-pyridyl)valerophenone, b.p. 168–170° at 1.5 mm.

*Anal.* Calcd. for $C_{17}H_{19}NO$: N, 5.53. Found: N, 6.05.

This ketone gave a dark, blue-green color with iron(III) chloride solution and gave a picrate, m.p. 109.2–109.6° (from 95% ethanol).

*Anal.* Calcd. for $C_{23}H_{22}N_4O_8$: N, 11.61. Found: N, 11.56.

VI. *The use of sodium amide to effect the benzoylation of 4-alkylpyridines.* (a) *4-Picoline.* Undiluted 4-picoline (0.4 mole, 37.2 g.) was added to a suspension of sodium amide [prepared from 0.4 mole (9.2 g.) of sodium in 300 ml. of anhydrous liquid ammonia] and the mixture was stirred for 15 to 20 min. To the suspension of 4-picolylsodium thus obtained, methyl benzoate (0.2 mole, 27.2 g.), dissolved in 30 ml. of anhydrous ether, was added over a period of 25 to 35 min. and stirring was continued for one more hour. The reaction was quenched by the addition of excess solid ammonium chloride and the liquid ammonia was replaced by adding ether and warming on a water bath. When the liquid ammonia had evaporated, as indicated by the refluxing of the ether, the reaction mixture was poured onto a mixture of ice and hydrochloric acid and processed in the regular fashion.[2,4] The solvent was distilled from the dried ether extracts and on cooling a semi-solid mass was obtained. This was filtered and gave 26.4 g. of 4-phenacylpyridine, m.p. 112–113.4°. The mother liquor was distilled to give 4.0 g. of 4-picoline, b.p. 140–145°, and 6.9 g. of a solid mixture of benzamide and 4-phenacylpyridine, b.p. 135–160° at 1.1 mm. This mixture was washed with several portions of cold anhydrous ether and filtered to separate the ketone from the amide. On the funnel there remained 3.6 g. of benzamide, m.p. 126.4–127.6° alone and when mixed with an authentic sample. The combined ether washings were distilled to given an additional 2.7 g. of 4-phenacylpyridine, b.p. 135–150° at 1.1 mm., m.p. 112–113.5°. The total yield of the ketone was 29.1 g. (73.8%).

(b) *4-Ethylpyridine.* The last reaction was repeated except that sodium amide (0.2 mole), 4-ethylpyridine (0.2 mole, 21.5 g.), and methyl benzoate (0.1 mole, 13.6 g.) were used. On processing the reaction mixture there was obtained 18.8 g. of crude product, b.p. 130–147° at 1 mm. This material, which crystallized on standing, was filtered and washed with several portions of anhydrous ether. Benzamide (0.5 g., m.p. 126.5–127.5°) remained on the funnel. The solvent was removed from the combined ether washings to give 17.9 g. (84.8%) of α-(4-pyridyl)propiophenone, m.p. 62.4–63.0° (from 30–60° petroleum ether).

*Anal.* Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.57; H, 5.75; N, 6.82.

The ketone gave a picrate, m.p. 150.1–150.9° (from 95% ethanol).

*Anal.* Calcd. for $C_{20}H_{16}N_4O_8$: N, 12.72. Found: N, 13.08.

PITTSBURGH 13, PA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

# Thiazolidine Chemistry. II. The Preparation of 2-Substituted Thiazolidine-4-carboxylic Acids[1,2]

IRVING R. SCHMOLKA[3] AND PAUL E. SPOERRI[4]

*Received March 21, 1957*

Twenty-two 2-substituted thiazolidine-4-carboxylic acids have been prepared by the condensation of cysteine with aliphatic and aromatic aldehydes. Attempts to synthesize similar compounds from some α,β-unsaturated aldehydes were unsuccessful. An explanation of this failure of the reaction is discussed.

In the course of an investigation directed towards the preparation of water-soluble thiazolidine salts, the scope of the reaction of cysteine with aldehydes has been extended and an attempt made to explain its limitations. Twenty-two new (L)-2-substituted thiazolidine-4-carboxylic acids,[5] listed in Table I, were prepared using the method of Schubert.[6]

The preparation of the thiazolidines from the saturated aliphatic aldehydes indicated that increasing the chain length does not hinder the reaction. All these compounds crystallize in shining white platelets and are soluble in boiling isopropyl alcohol. The melting points decrease with increasing molecular weight. This was to be expected, since the compounds change from essentially heterocyclic carboxylic acids with a small aliphatic side chain to hydrocarbons with a small heterocyclic acid at one end.

The potassium salts of 2-undecyl and 2-hexadecylthiazolidine-4-carboxylic acids were prepared. The former was found to be soluble in water at a concentration of 0.1%, but the latter was insoluble at a 0.02% concentration, at 25°. The potassium salts were unstable and slowly decomposed on aging. This is in agreement with the reported findings

(1) Previous paper in series: H. Soloway, F. Kipnis, J. Ornfelt, and P. E. Spoerri, *J. Am. Chem. Soc.*, **70**, 1667 (1948).

(2) Abstracted in part from the M.S. thesis of Irving R. Schmolka, Polytechnic Institute of Brooklyn, June 1950. Presented in part at the first Meeting in Miniature, Metropolitan Long Island Subsection of the AMERICAN CHEMICAL SOCIETY's New York Section, March 17, 1950.

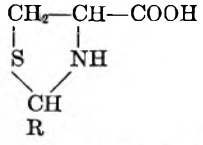
(3) Current address, Wyandotte Chemicals Corp., Wyandotte, Mich.

(4) To whom inquiries should be sent.

(5) Y. Kashida, *J. Pharm. Soc. Japan*, **69**, 185 (1949), has since reported No. 15 and No. 19, Table I.

(6) M. P. Schubert, *J. Biol. Chem.*, **111**, 671 (1935); **114**, 341 (1936); **121**, 539 (1937); **130**, 601 (1939).

TABLE I



2-SUBSTITUTED THIAZOLIDINE-4-CARBOXYLIC ACIDS

| No. | R | Emp. Form. | M.P., °C.[a] | Yield | Rec. Solvent | Analyses[b] C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *n*-Pentyl | $C_9H_{17}O_2NS$ | 162 163 dec. | 64 | Isopr. Alc. | 53.17 | 53.07 | 8.43 | 8.54 | — | — |
| 2 | *n*-Heptyl | $C_{11}H_{21}O_2NS$ | 159–160 dec. | 75 | Isopr. Alc. | 57.10 | 57.17 | 9.15 | 9.42 | — | — |
| 3 | *n*-Octyl | $C_{12}H_{23}O_2NS$ | 158–159 dec. | 45 | Isopr. Alc. | — | — | — | — | 5.71 | 5.54 |
| 4 | *n*-Nonyl | $C_{13}H_{25}O_2NS$ | 156–157 dec. | 46 | Isopr. Alc. | — | — | — | — | 5.40 | 5.39 |
| 5 | *n*-Decyl | $C_{14}H_{27}O_2NS$ | 153–154 dec. | 57 | Isopr. Alc. | — | — | — | — | 5.12 | 5.22 |
| 6 | *n*-Undecyl | $C_{15}H_{29}O_2NS$ | 151–152 dec. | 72 | Isopr. Alc. | — | — | — | — | 4.87 | 4.92 |
| 7 | *n*-Tridecyl | $C_{17}H_{33}O_2NS$ | 148–149 dec. | 65 | Isopr. Alc. | — | — | — | — | 4.44 | 4.20 |
| 8 | *n*-Hexadecyl | $C_{20}H_{39}O_2NS$ | 142–143 dec. | 76 | Isopr. Alc. | 67.17 | 67.16 | 10.99 | 10.61 | 3.92 | 4.23 |
| 9 | 2′-Chlorophenyl | $C_{10}H_{10}O_2NSCl$ | 145–146 dec. | 77 | 50% Acetone | 49.28 | 49.49 | 4.14 | 4.37 | 5.75 | 5.68 |
| 10 | 4′-Chlorophenyl | $C_{10}H_{10}O_2NSCl$ | 150–151 dec. | 83 | 50% Acetone | 49.28 | 49.61 | 4.14 | 4.12 | — | — |
| 11 | 3′,4′-Dichlorophenyl | $C_{10}H_9O_2NSCl_2$ | 160–161 dec. | 83 | 50% Acetone | 43.18 | 43.49 | 3.26 | 3.41 | — | — |
| 12 | 2′,6′-Dichlorophenyl | $C_{10}H_9O_2NSCl_2$ | 159–160 dec. | 89 | [c] | — | — | — | — | 5.04 | 5.06 |
| 13 | 2′-Hydroxy-5′-chlorophenyl | $C_{10}H_{10}O_3NSCl$ | 160–161 dec. | 77 | [c] | — | — | — | — | 5.40 | 5.25 |
| 14 | 2′-Nitrophenyl | $C_{10}H_{10}O_4N_2S \cdot 1^1/_2H_2O$ | 103–104 dec. | 76 | [c] | 42.70 | 42.10 | 4.66 | 4.80 | 9.96 | 10.02 |
| 14 | 2′-Nitrophenyl | $C_{10}H_{10}O_4N_2S \cdot HCl$ | 158–159 | 90 | [c] | — | — | — | — | 9.64 | 9.77 |
| 15 | 3′-Nitrophenyl | $C_{10}H_{10}O_4N_2S$ | 151–153 dec.[d] | 83 | [c] | — | — | — | — | 11.02 | 10.73 |
| 16 | 4′-Nitrophenyl | $C_{10}H_{10}O_4N_2S$ | 131–133 dec. | 73 | [e] | — | — | — | — | 11.02 | 11.18 |
| 17 | 1′-Naphthyl | $C_{14}H_{13}O_2NS$ | 152–153 dec. | 68 | [c] | — | — | — | — | 5.40 | 5.26 |
| 18 | 4′-(2′-Thiazolidine-4′-carboxylic acid)-phenyl | $C_{14}H_{16}O_4N_2S_2$ | 162–163 dec. | 85 | [c] | — | — | — | — | 8 23 | 8 00 |
| 19 | 4′-Dimethylaminophenyl | $C_{12}H_{16}O_2N_2S$ | 198–199 dec.[d] | 73 | 50% Isopr. Alc. | — | — | — | — | 11.11 | 11.01 |
| 20 | 4′-Isopropyl-α-methylphenethyl | $C_{16}H_{23}O_2NS$ | 152–153 dec. | 69 | 50% Isopr. Alc. | — | — | — | — | 4.78 | 4.72 |
| 21 | 2′-Hydroxy-3′-methoxyphenyl | $C_{11}H_{13}O_4NS$ | 142–143 dec. | 33 | [f] | — | — | — | — | 5.49 | 5.20 |
| 22 | 3′-Ethoxy-4′-hydroxyphenyl | $C_{12}H_{15}O_4NS$ | 176–177 dec. | 88 | Ethyl Alc. | — | — | — | — | 5.20 | 5.10 |

[a] Melting points are uncorrected. [b] Microanalyses by R. Schachat and H. Biletch of the Polytechnic Institute of Brooklyn. [c] No recrystallizing solvent found other than alkali. Therefore the material was washed and thoroughly dried. [d] Ref. (5) reports 154–156° for No. 15 and 195–197° for No. 19. [e] Dissolved in hot ethyl alcohol and reprecipitated with carbon tetrachloride. [f] Dissolved in hot diethyl ether and reprecipitated with *n*-heptane.

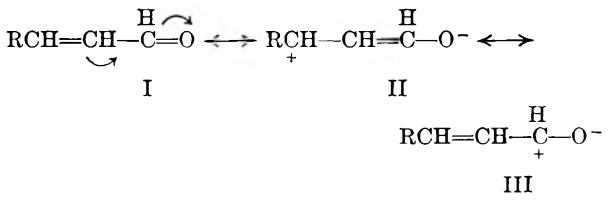
concerning the sodium salt of a similar compound.[7]

The formation of thiazolidine carboxylic acids from aromatic aldehydes containing nitro or chloro substituents demonstrated that these groups do not hinder the cyclization. The chlorinated products are stable, white, crystalline materials, whereas the nitrophenyl substituted thiazolidines are colored and exhibit a great affinity for water. The existence of the dihydrate of the condensation product of cysteine and nitrosalicylaldehyde has been reported[8] and other thiazolidine carboxylic acid hydrates have been previously described.[9] Only the *o*-nitro isomer gives a positive nitroprusside test in 5% sodium bicarbonate solution.

The reaction between cysteine and naphthaldehyde shows that the cyclization proceeds equally well with a naphthalene ring as with a benzene ring. From terephthaldehyde it can be inferred that the reaction takes place equally well with a dialdehyde as with a monoaldehyde. The thiazolidine carboxylic acid formed from *p*-dimethylaminobenzaldehyde and cysteine is water soluble.

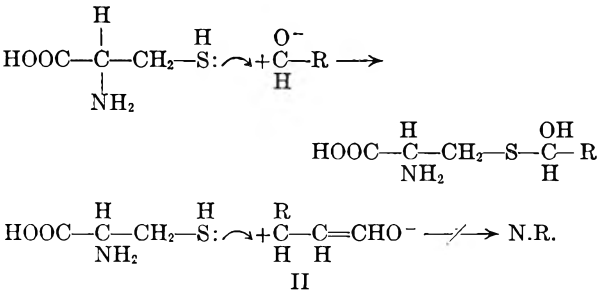
The following aldehydes did not give the normal reaction product, when using the customary method: citral, crotonaldehyde, acrolein, 2-ethyl-2-hexenal, $\alpha$-amyl cinnamaldehyde, $\alpha$-hexyl cinnamaldehyde, and 2,2,4,8,10,10-hexamethylundecene-5-al-5. This is in agreement with other findings[5,9-11] that an unsaturated bond $\alpha$, $\beta$ to the carbonyl group influences the reaction with cysteine.

The mechanism for thiazolidine carboxylic acid reaction has been shown[12] to consist in hemimercaptal formation, followed by dehydration and cyclization. In the case of unsaturated carbonyl compounds, the following structures can be written:



I II III

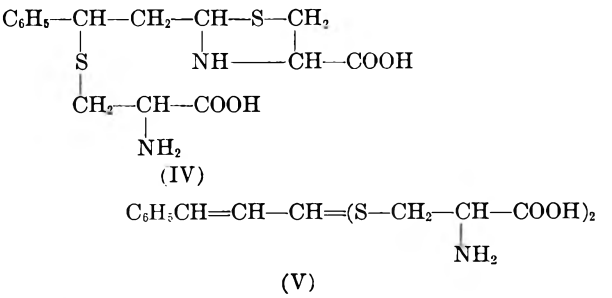
It is suggested that condensation fails to occur due to the low contribution of III, the active species necessary for hemimercaptal formation, as follows:



II

Cinnamaldehyde and *p*-chlorocinnamaldehyde did form a precipitate with cysteine hydrochloride. This phenomenon agrees with the observation made by Lieberman *et al.*[10] Since microanalyses of product from the initial experiment indicated a ratio of two moles of cysteine to one mole of aldehyde, this molar ratio was used subsequently.

Only two products appeared possible from the condensation of two moles of cysteine with one mole of cinnamaldehyde. One would be 5′-carboxy-4′-amino-2′-phenyl-3′-thiapentylthiazolidine-4-carboxylic acid (IV), formed by a 1,4 addition of one mole of cysteine to the double bond of cinnamaldehyde, followed by a reaction of this product with a second mole of cysteine to form the thiazolidine. The other would be the cinnamaldehyde mercaptal (V).



(IV)



(V)

The formation of IV would be in agreement with the postulation made by Geiger and Conn,[13] that some simple $\alpha$, $\beta$ unsaturated ketones react with sulfhydryl compounds by means of a 1,4 addition to produce $\beta$ alkyl thioketones. The formation of V would be in agreement with the work of Holmberg,[14] who reported that cinnamaldehyde condensed with $\beta$ mercaptopropionic acid to form the corresponding mercaptal. Examination of the ultraviolet and infrared absorption spectra revealed the presence of a conjugated double bond, ruling out compound (IV), and served to establish the unknown condensation product as a mercaptal.

## EXPERIMENTAL

*L-2-Hexadecylthiazolidine-4-carboxylic acid.* The conditions employed for the preparation of this compound are essentially the same as those of Schubert.[6] The heptadecanal was

(7) I. T. Strukov, *J. Gen. Chem.* (*U.S.S.R.*), **22**, 521 (1952).

(8) M. Ikawa and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 653 (1954).

(9) H. T. Clarke, J. R. Johnson, and R. Robinson, *The Chemistry of Penicillin*, pp. 940–963, Princeton University Press, Princeton, N. J., 1949. The book describes the extensive studies of thiazolidines made on the Penicillin program.

(10) S. Lieberman, P. Brazeau, and L. B. Hariton, *J. Am. Chem. Soc.*, **70**, 3094 (1948).

(11) D. Todd and S. Reich, *J. Am. Chem. Soc.*, **75**, 1895 (1953).

(12) S. Ratner and H. T. Clarke, *J. Am. Chem. Soc.*, **59**, 200 (1937).

(13) W. B. Geiger and J. E. Conn, *J. Am. Chem. Soc.*, **67**, 112 (1945).

(14) B. Holmberg, *Arkiv. Kemi., Mineral. Geol.*, **15A**, No. 8, 1 (1942).

prepared from hexadecanol *via* the chloride, the Grignard, and ethyl orthoformate. A solution of 1.7 g. (0.0067 mole) of freshly prepared heptadecanal (m.p. 36°) in 25 ml. of 95% ethanol was added to a solution of 1.0 g. (0.0057 mole) of L-cysteine hydrochloride monohydrate[15] and 0.6 g. (0.007 mole) of potassium acetate in 25 ml. of water. Upon vigorous agitation for a few minutes, precipitation occurred. After standing at room temperature for an hour the mixture was refrigerated overnight. Following filtration by gentle suction, the precipitated thiazolidine carboxylic acid was thoroughly washed with water, cold 95% ethanol, ether, and air-dried. Upon recrystallization from boiling isopropyl alcohol, there were obtained 1.54 g. (76%) of product melting at 142–143°, dec.

(15) Purchased from Mann Fine Chemicals Inc., New York, N. Y.

*Cysteinyl cinnamyl mercaptal.* This was prepared similarly, using a 2:1 ration of water to ethanol. The product, for which no recrystallization solvent was found, is a white powder, melting at 179.3–180.5°, dec., obtained in 81% yield.

*Anal.* Calcd. for $C_{15}H_{20}O_4N_2S_2$: C, 50.54; H, 5.66; N, 7.86. Found: C, 50.45; H, 5.75; N, 7.55.

*Acknowledgment.* Thanks are due to Monsanto Chemical Co. for samples of *o*-vanillin and bourbonal, to Heyden Chemical Corp. for 2,6-dichlorobenzaldehyde, to Shell Chemical Corp. for 2-ethyl-2-hexenal, and to Rohm & Haas Co. for 2,2,4,8,10,10-hexamethylundecene-5-al-5.

BROOKLYN 1, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

# Flavonoid Petal Constituents of *Chrysanthemum segetum* L.

T. A. GEISSMAN AND CORNELIUS STEELINK

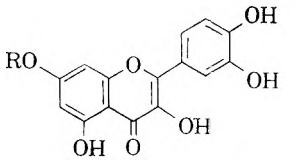
*Received February 11, 1957*

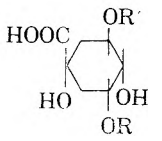
The petals of *Chrysanthemum segetum* L. contain gossypitrin (3,3′,4′,5,7,8-hexamethoxyflavone-7-glucoside), quercimeritrin, and chlorogenic and isochlorogenic acids. This is the first recorded occurrence of gossypitrin in a plant family other than the Malvaceae. The co-occurrence of gossypitrin and quercimeritrin is observed in both *C. segetum* and in *Gossypium* species, and appears to be of significance in the problem of the biogenesis of the flavonoid pigments.

Chromatographic examination on paper of the methanol extract of the bright yellow petals of *Chrysanthemum segetum* L. disclosed the presence of five distinct substances. Three of these were readily identified as quercimeritrin (quercetin-7-glucoside) (I), chlorogenic acid (II), and isochlorogenic acid (III). A fourth was isolated by methanol extraction of the fresh or dried petals and concentration of the extract, when it separated as a bright yellow crystalline substance in an amount constituting six per cent of the weight of the dried petals. Spectral and $R_f$ data suggested that this compound was a derivative of a hexahydroxyflavone, and analyses of the glucoside, the aglucon, and their acetates were in agreement with the formulation of the pigment as a monoglucoside of a hexahydroxyflavone. The melting point of the aglucon hexaacetate was in agreement with that reported for gossypetin (IV, R = H) hexaacetate,[1] but since spectral data for gossypetin derivatives were lacking, and authentic samples were not at hand for direct comparison, the structure of the glycoside was established by degradative and synthetic procedures.

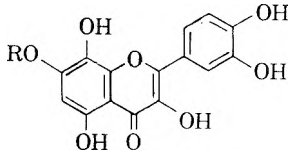
The presence of a free hydroxyl group in the 3-position of the glycoside was indicated by the characteristic shift of 60 mμ in the long wavelength absorption maximum (from 388 to 448 mμ) induced by the addition of aluminum chloride.[2] Methylation of the aglycon yielded gossypetin hexamethyl ether, identical with an authentic sample prepared by synthesis from quercetin 3,3′,4′,7-tetramethyl ether.[3]

Alkaline cleavage of the fully methylated aglycon yielded veratric acid and 2′-hydroxy-2,3′,4′,6′-tetramethoxyacetophenone.[4]




I, R = $C_6H_{11}O_5$ (glucosyl)
II, R = H, R′ = 3,4-dihydroxycinnamoyl
III, R′ = H, R = 3,4-dihydroxycinnamoyl




IV, R = H
V, R = $C_6H_{11}O_5$ (glucosyl)

The determination of the position of the sugar residue in the glycoside, and thus the establishment of the identity of the latter with gossypitrin (V),

(1) A. G. Perkin, *J. Chem. Soc.*, **95**, 2181 (1909).
(2) T. A. Geissman and L. Jurd, unpublished results.
(3) P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **25A**, 379 (1946).
(4) A. G. Perkin, *J. Chem. Soc.*, **103**, 653 (1913)

was accomplished by methylation of the glycoside and subsequent removal of the sugar residue. The product had the properties reported for 7-hydroxy-3,3′,4′,5,8-pentamethoxyflavone.[5] Identity of the sugar as glucose was established by paper chromatographic methods.

Quercimeritrin (I) was identified by direct comparison with an authentic sample on paper chromatograms, and by hydrolysis and chromatographic identification of quercetin and glucose. Quercimeritrin, a 7-glucoside, is readily distinguished from quercetin-3-glycosides on paper chromatograms: It shows a bright yellow fluorescence in ultraviolet light, changing to a vivid yellow-green when sprayed with aluminum chloride; 3-glucosides are, respectively, brown to purple, and yellow under these conditions.

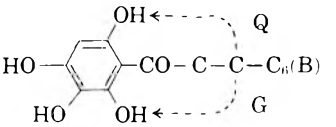
Chlorogenic and isochlorogenic acids were identified by their characteristic color (blue, changing to bright blue-green with ammonia vapor) on paper under ultraviolet light, by their absorption spectra, by the formation of caffeic acid (identified by comparison with authentic material on paper) upon alkaline hydrolysis, and by chromatographic comparison with authentic samples.

The fifth substance was neither strongly visible nor well differentiated on a paper chromatogram. Its spectral behavior was that of a flavonol, but it has not yet been identified.

The presence of gossypitrin, quercimeritrin, and the two caffeic acid esters in *C. segetum* emphasizes several biogenetic relationships that have been recognized in other cases. Their common possession of the 3,4-dihydroxyphenyl grouping parallels numerous observations already recorded,[6,7] and suggests the biogenetic importance of the 3,4-dihydroxyphenylpropane unit.[8,9]

The co-occurrence of gossypitrin (V) and quercimeritrin (I) may have a special significance. The members of this pair of glucosides differ only in the presence of the 8-hydroxyl group in gossypitrin. The occurrence in the same plant of these two compounds has heretofore been known only in two species of Malvaceae,[1,10,11] although the respective aglycons have been found in other species of this family.[12,13] The presence in a single species of pairs of flavonoid compounds differing only by a single hydroxyl group has been observed in other cases,[7,14] and has been offered by Seshadri[14] as evidence to support a theory of biogenesis that includes a direct hydroxylation step (*e.g.*, I → V).

It is of interest to note that flavones with the related 3,3′,4′,5,6,7-hydroxylation pattern (*i.e.*, that of quercetagetin) have been observed in other compositae.[15,16] This arrangement of hydroxyl groups is uniquely related to that present in IV and V by the common relationship of both quercetagetin (containing hydroxyl groups at 5,6,7) and gossypetin (containing hydroxyl groups at 5,7,8) to the hypothetical open-chain precursor VI, in which ring closure according to VI-G would lead to the gossypetin arrangement (5,7,8), and according to VI-Q to the quercetagetin arrangement (5,6,7). Moreover, the rutaceous species *Melicope ternata* contains (*O*-alkylated) flavones belonging to *both* the quercetagetin and the




VI

gossypetin classes.[17] It is clear that much remains to be learned of the biogenetic origin of flavonoid hydroxyl groups, for while the examples of quercimeritrin and gossypitrin, herbacitrin and populnin, and sulfurein and maritimein support the hypothesis of hydroxylation of the fully constituted flavone or aurone, the presence of both gossypetin and quercetagetin derivatives in *Melicope* species can better be accounted for by supposing that the hydroxylation occurs before the heterocyclic ring is formed (VI).

## EXPERIMENTAL

*Isolation of gossypitrin. Chrysanthemum segetum* L. flowers were collected in August near Caspar, Calif. Rays and disks were separated and immersed in methanol. The methanol and ray flowers were slurried in a Waring Blendor, filtered, and the marc extracted further with hot methanol. The total filtered extract (2.5 l.) was evaporated under reduced pressure to 175 ml. A fine, yellow crystalline solid separated. The filtrate was washed with petroleum ether and with ether, concentrated further to 50 ml. and retained for chromatographic study.

The yellow solid, crystallized from dilute acetic acid, melted at 237–241°. It proved to be identical with the most prominent component observed on paper chromatograms.

The plant material remaining after the extraction weighed 65 g. (dry), and the total extractives amounted to 25 g.

(5) T. R. Seshadri, *Proc. Indian Acad. Sci.*, **24A**, 375 (1946).

(6) P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **18A**, 222 (1943).

(7) T. A. Geissman, J. B. Harborne and M. K. Seikel, *J. Am. Chem. Soc.*, **78**, 825 (1956).

(8) T. A. Geissman and E. H. Hinreiner, *Botan. Rev.*, **18**, 77 (1952).

(9) R. Robinson, "Structural Relations of Natural Products," Oxford University Press, 1955.

(10) K. Neelakantam, T. R. Seshadri, and R. H. Rao, *Proc. Indian Acad. Sci.*, **2A**, 490 (1953).

(11) K. Neelakantam and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **4A**, 54 (1937).

(12) K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **24A**, 352 (1946).

(13) A. G. Perkin, *J. Chem. Soc.*, **95**, 1855 (1909).

(14) T. R. Seshadri, *Proc. Indian Acad. Sci.*, **30A**, 333 (1939).

(15) P. S. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **14A**, 289 (1941).

(16) Z. Čékan and V. Herout, *Chem. Listy*, **49**, 1053 (1955).

(17) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3131 (1951) and earlier papers cited therein.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF GOSSYPETIN AND MYRICETIN DERIVATIVES

| Compound | 95% Ethanol | | Ethanol-$AlCl_3$ | Ethanol-NaOEt |
|---|---|---|---|---|
| | $\lambda_{max}$ | log $\epsilon$ | $\lambda_{max}$ | $\lambda_{max}$ |
| Gossypitrin | 262, 278, 350,[a] 388 | 4.33, —, —, 4.20 | 272, 377, 448 | — |
| Gossypetin | 262, 278, 341,[a] 386 | 4.26, 4.23, —, 4.15 | 272, 370, 446 | — |
| Gossypetin hexaacetate | 255, 295, 320[a] | — | — | — |
| Gossypetin hexamethyl ether | 252, 273, 351 | 4.34, 4.33, 4.34 | — | — |
| 5-OH-3,3′,4′,7,8-penta OMe[b] | 255, 272, 360 | 4.34, 4.33, 4.18 | 282, 360, 420 | 285, 395 |
| 7-OH-3,3′,4′,5,8-penta OMe[b] | 251, 270,[a] 351 | — | No shift | 280, 368 |
| 5,8-diOH-3,3′,4′,7-tetra OMe[b] | 255, 280, 330 | — | 290, 365 | — |
| Myricetin | 255, 378 | 4.21, 4.29 | 270, 435 | — |
| Myricetin hexamethyl ethyl | 262, 332 | — | — | — |
| 5-OH-3,3′,4′,5′,7-penta OMe[b] | 265, 305,[a] 345 | — | 280, 345, 395 | 285, 380 |

[a] Inflection. [b] Flavone.

The crude gossypitrin weighed 6.0 g., thus constituting about 6% of the dry weight of the petal material.

*Anal.* Calcd. for a hexahydroxyflavone monoglucoside, $C_{21}H_{20}O_{12}$: C, 50.60; H, 4.40. Found: C, 50.40; H, 4.53.

*Gossypitrin acetate* was prepared by heating a mixture of 300 mg. of the glucoside, 150 mg. of dry sodium acetate, and 2.5 ml. of acetic anhydride for 90 min. on the steam bath. The white solid that separated when the solution was poured onto ice was recrystallized from aqueous ethanol. The colorless needles melted at 232–236°.

*Anal.* Calcd. for the nona-acetate of gossypitrin, $C_{39}H_{37}O_{22}$: C, 54.50; H, 4.40. Found: C, 54.51; H, 4.36.

*Gossypetin.* Hydrolysis of the glucoside with boiling 2*N* sulfuric acid afforded the aglucon. Recrystallized from aqueous acetic acid, it had m.p. 299–304°. Gossypetin has been reported to melt at 304°, 305°, and 310–14° with composition.[13,18,19] The sugar released in the hydrolysis was identified as glucose by means of paper chromatography.

*Gossypetin hexaacetate* formed colorless needles, m.p. 226–28°, in agreement with the value reported by Perkin.[1]

*Anal.* Calcd. for $C_{27}H_{22}O_{14}$: C, 56.87; H, 4.11. Found: C, 57.15; H, 4.09.

*Gossypetin hexamethyl ether* was prepared by the methylation of gossypetin with dimethyl sulfate in acetone in the presence of potassium carbonate. The product melted at 171–172.5°, in agreement with the reported value.[2] There was no depression in the melting point when it was mixed with an authentic sample.

*Alkaline cleavage* of gossypetin hexamethyl ether with 10% methanolic potassium hydroxide yielded veratric acid and 2′-hydroxy-2,3′,4′,6′-tetramethoxyacetophenone, m.p. 114.5–115.5°, in agreement with the value reported by Perkin.[4]

*Position of the sugar residue.* Methylation of the glucoside according to Murti and Seshadri,[20] and hydrolysis of the product with dilute sulfuric acid yielded 7-hydroxy-3,3′,4′,-5,8-pentamethoxyflavone,[20] m.p. 250–251°, the *acetate* of which melted at 164–168°.

*Gossypetin hexamethyl ether* was prepared by the nuclear oxidation of quercetin 3,3′,4′,7-tetramethyl ether and methylation of the resulting 5,8-diol.[2]

*Identification of quercimeritrin, chlorogenic acid, and isochlorogenic acid.* Paper chromatograms of the solution from which gossypitrin had crystallized showed, in addition to gossypitrin, four clearly defined substances. Three of these were identified as follows:

*1. Quercimeritrin.* The component having $R_f$ 0.50 in butanol–27% acetic acid (1:1) was separated by chromatography on Whatman No. 1 paper, purified by rechromatography on paper, and eluted. Its ultraviolet spectrum corresponded with that of quercimeritrin, and the expected shift of the long wave maximum (377 to 427 m$\mu$) was observed when aluminum chloride was added to the alcoholic solution. Hydrolysis yielded quercetin, identified by chromatographic methods. Finally, chromatographic comparison with an authentic sample of quercimeritrin[21] in three solvent systems showed complete agreement in appearance, reaction to spray reagents, and $R_f$ values.

*2. Chlorogenic and isochlorogenic acids.* Two components visible on the chromatograms of extracts of *C. segetum* petals showed the characteristic behavior of chlorogenic and isochlorogenic acids; they had $R_f$ of 0.72 and 0.89, respectively; they showed the typical color reactions under ultraviolet light (blue, changing to bright greenish blue on fuming with ammonia); and they reacted quickly to an ammoniacal silver nitrate spray, giving dark brown spots. They were separated and isolated by chromatography on paper, and the eluted bands were hydrolyzed (under nitrogen) with alkali. Caffeic acid was formed in both cases; it was identified by its behavior on paper ($R_f$ and reaction to Tollen's reagent and ferric chloride), in comparison with that of a synthetic specimen of the authentic substance. Confirmation of the identities of these bands was carried out by chromatographic comparison with authentic specimens of chlorogenic and isochlorogenic acids,[22] with which they agreed in all respects.

*Absorption spectra.* The ultraviolet absorption spectra of many of the compounds prepared in the course of this study have not been recorded. In Table I are gathered together the spectral data for several gossypetin derivatives and several model substances of related structures.

LOS ANGELES 24, CALIF.

(18) T. R. Seshadri and N. Viswanadham, *Current Sci.*, 16, 343 (1947).

(19) W. Baker, R. Nodzu and R. Robinson, *J. Chem. Soc.*, 80 (1929).

(20) V. V. S. Murti and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 4A, 258 (1948).

(21) We are indebted to Professor T. R. Seshadri for a specimen of this glucoside.

(22) These were kindly supplied by Dr. H. M. Barnes, who isolated them from coffee beans. [See H. M. Barnes, J. R. Feldman, and W. V. White, *J. Am. Chem. Soc.*, **72**, 4178 (1950).]

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, BECCO CHEMICAL DIVISION, FOOD MACHINERY AND CHEMICAL CORP.]

# Reactions of Limonene Monoxide. The Synthesis of Carvone

SEYMOUR M. LINDER AND FRANK P. GREENSPAN[1]

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An extensive study was made of the conversion of D-limonene into L-carvone. Two successful methods were developed, one by the pyrolysis of limonene glycol diacetate, and the other the oxidation of limonene glycol with *tert*-butyl chromate.

The first step in each synthesis was the same, the epoxidation of limonene, which proceeded in 90% yield. The basic approach involved the dehydration and oxidation of the ring-opened epoxide. In the first group of syntheses attempted the oxidation was performed before the dehydration.

On oxidation with *tert*-butyl chromate, limonene glycol could be converted to the keto alcohol. The keto alcohol could not be dehydrated directly. When the oxime or semicarbazone of the keto alcohol was steam distilled with acid, simultaneous hydrolysis and dehydration took place. The yield of carvone from limonene glycol was 9.2%.

In the second group of syntheses, the dehydration (alternately the dehydrochlorination or deacylation of ester) was performed before the oxidation. Pyrolysis of the glycol diacetate (deacylation) gave carveol acetate which was then saponified to carveol, and in turn oxidized to carvone. The overall yield of carvone from limonene epoxide was 7%.

Attempts to dehydrate limonene glycol to carveol led generally to dihydrocarvone. Limonene chlorohydrin formed by the ring opening of limonene oxide with hydrogen chloride could not be dehydrated. Limonene chlorohydrin, formed by the reaction of limonene glycol with thionyl chloride, dehydrochlorinated in the wrong direction, forming dihydrocarvone rather than the desired carveol.

The synthesis of L-carvone from D-limonene has been previously studied[2] but in each case limonene nitrosochloride was involved as the intermediate. The synthesis involved the conversion of D-limonene into the nitrosochloride which was then dehydrochlorinated to L-carvoxime and hydrolyzed to L-carvone. It was of interest to develop a method of synthesis which did not involve the use of nitrosyl chloride.

The basic approach used involved the conversion of limonene to limonene monoxide, ring opening to the glycol (alternately the acetate or chlorohydrin), followed by dehydration and oxidation of the ring-opened intermediate. The various attempted syntheses can be divided into two groups, (A) in which the oxidation was performed first, and (B) in which the dehydration (or dehydrochlorination) of the ring-opened intermediate was performed first.

Two successful syntheses were accomplished. One proceeded from the epoxide which was ring-opened to the glycol, then oxidized to the keto alcohol and dehydrated to carvone. In the other synthesis, the epoxide was converted to the glycol diacetate, which was pyrolyzed to carveol acetate, saponified to carveol, then oxidized to carvone.

While the yields are low in comparison to the previously reported syntheses of carvone, the reactions studied are of interest since they shed considerable light on the chemistry of terpene epoxides and their derivatives.

Limonene oxide for all the reactions described was prepared using a solution of peracetic acid in chloroform as the epoxidizing reagent. The yields were 90%, substantially greater than that previously reported for perbenzoic acid,[3,4] monoperphthalic acid[5] (71%), and peracetic acid.[6]

*Synthesis through the oxidation of limonene glycol.* One of the syntheses attempted involved the hydrolysis of limonene oxide to limonene glycol, followed by the oxidation of the glycol to the ketol, which was then to be dehydrated to carvone. Limonene glycol was prepared by the hydrolysis of the oxide with 1% sulfuric acid at 0°C.[3,4,7]

An extensive study was made of the oxidation of limonene glycol to the corresponding keto alcohol. The results in all cases except one were unsuccessful, probably due to glycol cleavage and oxidation of the exocyclic double bond. Tertiary butyl chromate,[8] a selective oxidizing agent which does not attack double bonds, has been found to accomplish the desired oxidation, although only in 44% yield. This represents the first successful synthesis of 1-hydroxydihydrocarvone to be reported.

As in the case of 1-methyl-1-cyclohexene-6-one,[9] the dehydration of the keto alcohol presented difficulties due to the interaction of the hydroxyl and carbonyl groups. The direct dehydration of the ketol could not be accomplished. It was necessary first to convert it into the oxime or semicarbazone and then simultaneously dehydrate and hydrolyze

(1) New Address: FMC Organic Chemicals Division, Food Machinery and Chemical Corporation, New York 17, New York.

(2) E. E. Royals and S. E. Horne, Jr., *J. Am. Chem. Soc.*, **73**, 5856 (1951). Other references to previous work will be found in the above reference.

(3) N. Prileschajew, *Ber.*, **42**, 4811 (1909) and German Patent **230,723**.

(4) H. Meerwein, A. Ogait, W. Prang, and A. Serini, *J. prakt. Chem.*, **113**, 9 (1926).

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(7) H. Schmidt, *Ber.*, **82**, 11 (1949).

(8) R. V. Oppenauer and H. Oberrauch, *Anales asoc. quím. argentina*, **37**, 246 (1949).

(9) L. W. Butz, B. L. Davis, and A. M. Gaddis, *J. Org. Chem.*, **12**, 130 (1947).

the derivative. An interfering reaction is the acid-catalyzed isomerization of carvone to carvacrol.

Using a *p*H of 0.9 to 1.0, previously optimum for the hydrolysis of carvoxime,[10] we obtained a 21% yield of carvone. A 9% yield was obtained when oxalic acid was used as dehydrating agent. The best overall yield was 6%.

*Attempted synthesis through dehydration of limonene glycol.* An attempt was made to dehydrate limonene glycol to carveol, which could then be oxidized to carvone. The dehydrating agents used were iodine, anhydrous oxalic acid, sulfuric acid in formic acid, 10% sulfuric acid, and anhydrous zinc chloride. In all cases, dihydrocarvone was obtained rather than the desired carveol. After this work had been completed, Royals and Harrell similarly reported the formation of ketone, rather than carveol, for the dehydration of limonene glycol.[5]

*Synthesis through pyrolysis of limonene glycol diacetate.* An attempt was made to convert the glycol diacetate to carveol acetate which could be hydrolyzed to carveol and oxidized to carvone. This approach had previously been studied by Blumann and Wood,[11] who report that they obtained a material similar to carvone in chemical properties, but having a different odor. It was of interest, nevertheless, to study the reactions and to determine whether it was possible, by varying the conditions, to obtain the desired carvone.

The monoacetate was converted to the diacetate by treatment with acetic anhydride. The overall yield from the epoxide was 70%. The crude diacetate, which contained 17% dihydrocarvone, was pyrolyzed by dropping it through a column packed with glass helices. (Alumina caused isomerization to carvacrol and stainless steel caused reduction of the double bond.) The temperature proved to be very critical. If it were too low, no reaction took place; if too high, removal of both acetoxy groups took place, as evidenced by the high bromine number and low ester value. The hydrocarbon and the unreacted diacetate were separated from the carveol acetate by distillation. The conversion to carveol acetate in the pyrolysis was 25%.

The yield on the saponification of the carveol acetate was 55%. Infrared evidence indicated that the product contained a high concentration of carveol with dihydrocarvone as an impurity.

The carveol, so obtained, was oxidized with chromium trioxide in acetic acid at low temperatures.[11-13] The resultant carvone was separated from the unreacted carveol by extraction with neutral sodium sulfite. The yield of carvone was 75% on the basis of the carveol reacted. The material prepared from the pyrolysis had an off-odor, but had the correct bromine number, carbonyl content, and formed a crystalline hydrogen sulfide addition compound.[14]

The overall yield from limonene oxide to carvone for this synthesis was 7%.

*Attempted synthesis through dehydration of limonene chlorohydrin.* Limonene oxide was converted into the chlorohydrin by reaction with hydrogen chloride in ether. Limonene chlorohydrin, which has not previously been described, was found to be a mixture of two isomers, one of which, when dehydrated, would be expected to give carvyl chloride, which could then be hydrolyzed to carveol and oxidized to carvone.

The results of all dehydration experiments attempted were unsuccessful. In no case was there any appreciable increase in bromine number, indicating that little dehydration took place. The dehydrating agents used were aqueous oxalic acid, anhydrous oxalic acid, anhydrous formic acid, phosphorus pentoxide, acetic anhydride, potassium acid sulfate, aqueous sulfuric acid, and iodine.

*Attempted synthesis through dehydrochlorination of limonene chlorohydrin.* This synthesis was dependent on conversion of the tertiary hydroxyl to a chloro group and dehydrochlorination of the resultant limonene chlorohydrin to carveol. Treatment of the glycol with concentrated hydrochloric acid under mild conditions did not give the desired chloro compound. Addition to the double bond appeared to take place. Under more vigorous conditions, isomerization to dihydrocarvone was the dominant reaction. The tertiary hydroxyl group of limonene glycol appears to be fairly unreactive toward substitution by chlorine. Ethereal hydrogen chloride also appears to add to the double bond.

When the glycol was treated with thionyl chloride, substitution by chlorine took place. The hydrogen chloride was removed only on prolonged refluxing with pyridine and large amounts of dihydrocarvone were formed, indicating that the dehydration took place in the wrong direction.

## EXPERIMENTAL

*Oxidation of limonene glycol to the keto alcohol. tert*-Butyl chromate was prepared by adding 59 g. of chromium trioxide in small portions to 168 ml. of *tert*-butyl alcohol with slight cooling.[15] The solution was diluted with 220 ml. of dry benzene and dried over anhydrous magnesium sulfate. To the above solution was added a solution of 100 g. of anhydrous limonene glycol in 800 ml. of dry benzene, keeping the temperature between 25° and 30°. Infrared evidence indicated that the reaction was complete in 2 hr. The complex was hydrolyzed by the addition in succession of 600 ml. of water, 120 g. of hydrated oxalic acid, then 600 ml. of 20% sulfuric acid with stirring, keeping the temperature below 25°. After 3 hr., the mixture was separated and the organic layer washed with alkali and dried. A 44% yield of oil was obtained.

(10) C. Bordenca, R. K. Allison, and P. H. Dirstine, *Ind. Eng. Chem.*, **43**, 1196 (1951).

(11) A. Blumann and W. R. Wood, *J. Chem. Soc.*, 4420 (1952).

(12) R. H. Reitsema, *J. Am. Chem. Soc.*, **75**, 1996 (1953).

(13) A. Blumann and O. Zeitschel, *Ber.*, **47**, 2623 (1914).

(14) O. Wallach, *Ann.*, **305**, 224 (1899).

(15) It is stated[7] that *tert*-butyl chromate explodes violently when heated above 60°.

*Anal.* Calcd. for $C_{10}H_{16}O_2$: Carbonyl oxygen, 9.5%, bromine number, 94; hydroxyl, 10.10. Found: Carbonyl oxygen, 8.6; bromine number, 102.8; hydroxyl, 10.25%.

Infrared evidence indicated the presence of an $\alpha$-hydroxy ketone.

*Dehydration of the keto alcohol.* The keto alcohol was converted to the semicarbazone which could not be crystallized. The semicarbazone was steam-distilled, the *p*H being kept at 0.9 to 1.0 by the addition of 25% sulfuric acid. The product was isolated from the distillate and purified by conversion to the sodium sulfite derivative. A 15% yield of oil having a spearmint-like odor was obtained.

*Anal.* Calcd. for $C_{10}H_{14}O$: Carbonyl oxygen, 10.7%; bromine number, 211. Found: Carbonyl oxygen, 10.3%; bromine number, 210.8.

The keto alcohol was converted to the oxime which could not be crystallized. The oxime was refluxed for an hour with 5% oxalic acid, then the mixture was steam-distilled. The product which was isolated from the distillate in 20% yield was shown by infrared analysis to consist of approximately 50% carvone.

*Preparation of limonene glycol monoacetate.* A solution of 463.7 g. of limonene monoxide in 1400 ml. of acetic acid was refluxed for 4 hr. and allowed to stand at room temperature for 72 hr. On removal of the acetic acid, 561.5 g. (93%) of oil was obtained which had an ester value of 275.2. A sample was steam-distilled.

*Anal.* Calcd. for $C_{12}H_{20}O_3$: Ester value, 264; bromine number, 75.5; carbonyl, 0. Found: Ester value, 274.9; bromine number, 76.8; carbonyl, 17.4% as dihydrocarvone.

*Preparation of limonene glycol diacetate.* A solution of 633.8 g. of limonene glycol monoacetate in 1265 ml. of acetic anhydride was refluxed for 7 hr. and allowed to stand at room temperature for 50 hr. On removal of the acetic anhydride and acetic acid, 688 g. (88.4%) of oil was obtained. A steam-distilled sample was submitted for analysis.

*Anal.* Calcd. for $C_{14}H_{22}O_4$: Ester value, 442; bromine number, 63; carbonyl, 0. Found: Ester value, 413.4; bromine number, 64.7; carbonyl, 6.6% as dihydrocarvone.

A solution of 50 g. of anhydrous limonene glycol in 250 ml. of acetic anhydride was refluxed for 2.5 hr., then poured into water. After the acetic anhydride had hydrolyzed, the product was isolated by extraction with ether. On removal of the ether, a residue of 69 g. (92.5%) of oil was obtained.

*Anal.* Found: Ester value, 420.7; bromine number, 65.2.

*Pyrolysis of limonene glycol diacetate.* The pyrolysis was conducted by dropping 544 g. of limonene glycol diacetate (77% pure by ester value, 10% dihydrocarvone) through an electrically-heated column packed with glass helices. It was run at 347–361° over a period of 2.5 hr., being preheated to 190°. The material which came through the column was treated with sodium bicarbonate solution to remove the acid, a yield of 318 g. of oil being obtained.

*Anal.* Calcd. for $C_{12}H_{18}O_2$: Ester value, 290; bromine number, 164; carbonyl, 0. Found: Ester value, 244.2; bromine number, 118.1; carbonyl, 16.4% as dihydrocarvone.

After two treatments with sodium bisulfite, 257.2 g. of material, which was free of carbonyl was obtained.

*Anal.* Found: Ester value, 249.0; bromine number, 117.0; glycol, 9.12% as limonene glycol.

The product resulting was distilled *in vacuo*, the main fraction, 92 g., boiling at 83–90°/3.5 mm.

*Anal.* Found: Ester value, 275.3; bromine number, 145.1; glycol, 5.48% as limonene glycol; carbonyl, 2.45% as dihydrocarvone.

*Saponification of carveol acetate to carveol.* A solution of 29.1 g. (0.15 mole) of carveol acetate (distilled) in a solution of 20 g. potassium hydroxide (100% excess) in 300 ml. of methanol was refluxed for 1.5 hr. After neutralization of the excess alkali and removal of the solvents and salts, 12 g. of oil was obtained. Infrared evidence indicated that it contained a high concentration of carveol. It contained 32% of dihydrocarvone as an impurity.

*Preparation of limonene chlorohydrin.* To 550 ml. of 1.9*N* hydrogen chloride in ether was added slowly 150 g. of limonene monoxide (92% pure) and the mixture allowed to stand at room temperature for 3 hr. The solution was then washed with water and dried over anhydrous magnesium sulfate. After removal of the ether, 170 g. (91%) of oil was obtained.

*Anal.* Calcd. for $C_{10}H_{17}OCl$: Cl, 18.83; bromine number, 85; sapon. number, 282; glycol, 0; oxirane oxygen, 0. Found: Cl, 17.81; bromine number, 80.5; sapon. number, 274; glycol, 0; oxirane oxygen, 0.

*Analytical methods.* 1. Bromine number: W. W. Scott and N. H. Furman; *Standard Methods of Chemical Analysis*, Fifth Edition, Vol. 2, p. 1770, Van Nostrand Co., Inc., New York, 1944. 2. Epoxy (ether HCl Method): D. Swern, T. W. Findley, G. N. Billen, and J. T. Scanlan, *Anal. Chem.*, **19**, 414 (1947). 3. Hydroxyl (acetic anhydride-pyridine): C. L. Ogg, W. L. Porter, and C. O. Willits, *Ind. Eng. Chem., Anal. Ed.*, **17**, 394 (1945). 4. Carbonyl (hydroxylamine hydrochloride-pyridine): W. M. D. Bryant and D. M. Smith, *J. Am. Chem. Soc*, **57**, 57 (1935). 5. Glycol (periodic acid): W. D. Pohle, V. C. Mehlenbacher, and J. H. Cook, *Oil and Soap*, **22**, 115 (1945), or S. Siggia, *Quantitative Organic Analysis via Functional Groups*, First Edition, John Wiley & Sons, New York, 1949, p. 8.

BUFFALO 7, N. Y.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE HEYDEN NEWPORT CHEMICAL CORP.]

# Local Anesthetics. I. Dialkylaminoalkyl Ethers of Benzaldoximes and Benzophenone Oximes

GEORGE M. SIEGER[1] AND DAVID X. KLEIN

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A number of dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes have been prepared and characterized. In preliminary physiological screening studies the $\beta$-diethylaminoethyl ether of $\alpha$-benzaldoxime (as the hydrochloride) appeared to be the most interesting of all the compounds tested for local anesthetic activity; it offered good anesthetic action and was the least irritating.

As part of a synthetic medicinals program started in these laboratories several years ago a search was made for new and improved local anesthetics. In these studies attention was focused on the dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes, two previously unreported types

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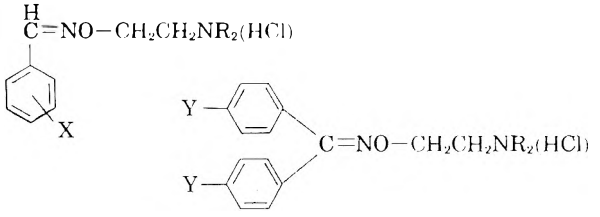
TABLE I

DIALKYLAMINOALKYL ETHERS OF OXIMES (HYDROCHLORIDES)

| No. | Oxime | Dialkylaminoalkyl Radical | Yield, % | Solvents Used for Crystallization | M.P., °C. (Corrected) | Formula | Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|---|---|
| VI | α-Benzaldoxime | β-Diethylaminoethyl | 56.8 | Chloroform-Ether; Acetone | 124–126 | $C_{13}H_{21}ClN_2O$ | 10.9 | 10.9 | 13.9 | 14.3 |
| VII | α-Benzaldoxime | β-Dimethylaminoethyl | 49.3 | Ethanol-Ether | 123–126.1 | $C_{11}H_{17}ClN_2O$ | 12.3 | 12.2 | 15.5 | 15.6 |
| VIII | α-Anisaldoxime | β-Diethylaminoethyl | 73 | Ether | 142–146 | $C_{14}H_{23}ClN_2O_2$ | 9.8 | 9.6 | 12.4 | 12.7 |
| IX | 3,4-Dichlorobenzaldoxime | β-Diethylaminoethyl | 56.8 | Chloroform-Ether | 159.9–162 | $C_{13}H_{19}Cl_3N_2O$ | 8.6 | 8.5 | 10.9[a] | 11.2[a] |
| X | 3,4-Dichlorobenzaldoxime | β-Dimethylaminoethyl | 62.2 | Chloroform-Ether | 156–158.8 | $C_{11}H_{15}Cl_3N_2O$ | 9.2 | 9.1 | 11.9[a] | 12.2[a] |
| XI | Benzophenone oxime | β-Diethylaminoethyl | 36.6 | Chloroform-Ether | 132.1–133.8 | $C_{19}H_{25}ClN_2O$ | 8.4 | 8.2 | 10.7[a] | 10.8[a] |
| XII | p,p'-Dichlorobenzophenone oxime | β-Diethylaminoethyl | 62.2 | Chloroform-Ether | 156.5–158.5 | $C_{19}H_{24}Cl_3N_2O$ | 7.0 | 7.1 | 26.4 | 26.6 |
| XIII | p,p'-Dichlorobenzophenone oxime | β-Dimethylaminoethyl | 32.8 | Chloroform-Ether | 188.1–191 | $C_{17}H_{19}Cl_3N_2O$ | 7.7 | 7.6 | 9.8[a] | 10.1[a] |

[a] Ionizable chlorine only.

of compounds represented by formulas A and B, which were found to possess significant anesthetic activity.




R is methyl or ethyl
X is H, methoxy, dichloro, β-diethylaminoethoxy

A

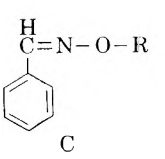
R is methyl or ethyl
Y is hydrogen, chloro

B

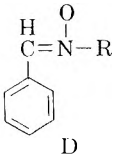
Inspection of these general formulas, A and B, will readily suggest structural similarities found in portions of well known physiologically and chemotherapeutically active compounds such as Procaine, Tetracaine, Benadryl, Trasentine, 929F of Forneau and Bovet, Tibione, and the like.

The synthesis of these dialkylaminoalkyl ethers was accomplished by a modification of a method described by Cheney, Smith, and Binkley[2] for preparing dialkylaminoalkyl ethers of benzylphenols. A toluene suspension of the sodium salt of the oxime was treated with a toluene solution of the free base of the various dialkylaminoalkyl chlorides to yield the dialkylaminoalkyl ethers.

The benzaldoximes (I, II, III) reported in this paper are the anti (α) oximes, which are more stable than the syn (β) forms.[3,4,5] The dialkylaminoalkyl ethers of the benzaldoximes have been assigned the benzaldoxime-*O*-ether structure, C, in preference to the isomeric benzaldoxime-*N*-ether,




C




D

D. Although both oxygen and nitrogen ethers are theoretically possible reaction products, the *O*-ethers are much more likely to be the main products and very little of the *N*-ethers is obtained.[2]

In preliminary studies it was observed that in general representative compounds of the series of dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes (as hydrochloride salts) tested in the cornea of a rabbit produced a marked anesthesia but in some cases also caused irritation. Compound VI, the β-diethylaminoethyl ether of α-benzaldoxime, was found to be the most promising local anesthetic of the compounds tested, showing the greatest degree of activity and the least irritation. It appears that the presence of halogen

(2) Cheney, Smith, and Binkley, *J. Am. Chem. Soc.*, **71**, 60 (1949).

(3) Beckmann, *Ber.*, **23**, 1684 (1890).
(4) Bamberger and Scheutz, *Ber.*, **34**, 2024 (1901).
(5) Hodgson and Beard, *J. Chem. Soc.*, 25 (1927).

substituents in the nuclei of these compounds enhances the irritation effect.

In general representative types of the dialkylaminoalkyl ethers in series A and B showed very little antibacterial or antifungal activity in preliminary *in vitro* tests. Benzaldoxime, anisaldoxime, benzophenone oxime, and *p,p'*-dichlorobenzophenone oxime (compounds I, II, IV, and V) failed to show any significant bacteriological activity, while compound III, the 3,4-dichlorobenzaldoxime, demonstrated sufficient activity to warrant further testing.

## EXPERIMENTAL

*Synthesis of benzaldehyde and benzophenone oximes. α-Benzaldoxime, sodium salt* (I).[6] To 140 g. (3.5 moles) of sodium hydroxide dissolved in 400 ml. of water was added 210 g. (1.98 moles) of benzaldehyde. To this mixture was added, while stirring, 150 g. (2.16 moles) of hydroxylamine hydrochloride. During the mixing the mixture became warm and the oily layer dissolved to form a homogeneous yellow solution which crystallized on cooling. Sufficient water (*ca.* 300 ml.) was added with stirring to form a clear solution. Sufficient carbon dioxide gas was then passed through the solution to cause a colorless emulsion of the *anti*-benzaldoxime to separate on the surface of the solution. The insoluble oil was extracted with two 1-l. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was distilled off leaving an oily residue, the crude α-benzaldoxime. The crude product was treated with 700 ml. of a solution of sodium methoxide [235 g. (4.37 moles) in 1500 ml. of anhydrous alcohol] to form its sodium salt. The mixture was stirred well, filtered, and washed with alcoholic sodium methoxide solution and dried.[8] It was then triturated and washed with three 500-ml. portions of benzene, refiltered and dried at 70°. Weight, 125 g. An additional 62 g. of product was obtained by concentration of the filtrate plus washes. Total yield, 187 g. (65.8%).

The other benzaldoximes were prepared by similar methods. α-Anisaldehyde (II) was obtained in a 45% yield by the procedure of Bamberger and Scheutz[4]; m.p. 60°. The oxime of 3,4-dichlorobenzaldehyde (III) was isolated in an 86.5% yield by the method of Hodgson and Beard[5]; m.p. 116.3–119°.

*Benzophenone oxime* IV. Starting with 100 g. (0.55 mole) of benzophenone, the oxime was prepared essentially by the method described by Lachman and Noller[9] with the exception that powdered potassium hydroxide was used in place of sodium hydroxide. The crude product was recrystallized from methanol to give 90 g. (83% yield) of product melting at 143–144°.

*p,p'-Dichlorobenzophenone oxime* V. The oxime of *p,p'*-dichlorobenzophenone was prepared starting with 138 g. (0.55 mole) of the ketone by the method used for benzophenone oxime. Yield, 110 g. (75.3%); m.p. 135.2–136.9°. Newton and Groggins[10] reported 136° as the melting point for this compound.

*Synthesis of dialkylaminoalkyl chlorides.* Most of the required β-dialkylaminoalkyl chlorides were commercially available as the hydrochloride salts. The preparation of the unavailable β-dialkylaminoalkyl chlorides was effected by the method of Slotta and Benisch.[11]

*Synthesis of dialkylaminoalkyl ethers of benzaldoximes and benzophenone oximes. Procedure A.* This procedure is illustrated by the synthesis of compound VI. *β-Diethylaminoethyl ether of α-benzaldoxime (hydrochloride)* (VI). A suspension of 42.9 g. (0.3 mole) of the sodium salt of α-benzaldoxime in 1 l. of toluene was stirred while a dried toluene solution of the free base of β-diethylaminoethyl chloride was slowly added by means of a dropping funnel. When the addition was complete, stirring was continued for 1 hr. without any external heating. The mixture was then heated at reflux temperature (*ca.* 71–92°) for 12 hr. At the end of this period the reaction mixture was cooled to room temperature and filtered to remove salt and insoluble impurities. The filtrate was distilled *in vacuo* to remove excess free amine chloride and toluene.

To the residue was added 2 l. of dry ether, and after filtration the ethereal solution was treated with dry hydrogen chloride until precipitation of a crude oily hydrochloride salt was complete. The gummy precipitate was purified by dissolving it in 200 ml. of chloroform, filtering to remove cloudiness, and then slowly pouring the filtrate into an excess of fresh, dry ether (1500 ml.). The product, which separated as a pale yellowish oil that crystallized on standing, was filtered, washed with two 100-ml. portions of fresh, dry ether, and dried. The dried material was ground, triturated well with 500 ml. of dry ether, filtered, and redried to rid it of a benzaldehyde-like odor. The weight of this product melting at 120 to 125° was 46.4 g. (60.3% yield). Further purification was effected by recrystallization from dry acetone. The pure product melted at 124–126° and weighed 43.8 g. (56.8% yield). Analytical data are given in the table.

*Procedure B.* This procedure is illustrated with the synthesis of compound IX. *β-Diethylaminoethyl ether of 3,4-dichlorobenzaldoxime (hydrochloride)* (IX). To a freshly prepared sodium methoxide solution obtained by dissolving 7 g. (0.3 mole) of sodium in 120 ml. of dry methanol was added 57 g. (0.3 mole) of 3,4-dichlorobenzaldoxime. After the mixture had been stirred 1 hr. to effect solution, the excess methanol was removed by vacuum distillation. The residual mass, the sodium salt of the oxime, was suspended in 1 l. of toluene. To the toluene suspension of the sodium salt of 3,4-dichlorobenzaldoxime was added about 1 l. of dried toluene solution of the free base of β-dicthylaminoethyl chloride prepared from 72.2 g. (0.42 mole) of the corresponding hydrochloride salt. The mixture was heated at reflux temperature (95–97°) for 12 hr. and then worked up as described in Procedure A. The crude hydrochloride salt was purified by recrystallizing it from chloroform by the addition of dry ether. The white crystalline product melting 159.9–162° weighed 65 g. (66.8% yield). Analytical data are given in the table.

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(6) Procedures used for alkylating the α-oximes were essentially the same as those reported in the literature to give the *O*-ethers.[7] Studies of the ultraviolet spectra of *N*- and *O*-methyl and *N*- and *O*-benzyl ethers of benzaldoxime [Meisenheimer and Dorner, *Ann.*, **499**, 161 (1933) and Ramart-Lucus and Martynoff, *Bull. soc. chim.*, 916 (1949)] have shown that the *O*-ethers have spectra similar to that of the parent oxime, whereas the spectra of the *N*-ethers are quite different. The similarity between the ultraviolet absorption curves of the diethylaminoethyl ethers of 3,4-dichlorobenzaldoxime and *p,p'*-dichlorobenzophenoneoxime and those of the parent oxime offered confirmation that these compounds are *O*-ethers.

(7) Richter-Anschütz, *The Chemistry of the Carbon Compounds*, Vol. III, 3rd ed., Elsevier, New York, 1946, pp. 273–274.

(8) Beckmann[3] noted that an alkaline wash removes virtually all of the small amount of the β-oxime present.

(9) Lachman and Noller, *Org. Syntheses*, **Coll. Vol. II** 70 (1944).

(10) Newton and Groggins, *Ind. Eng. Chem.*, **27**, 1397 (1935).

(11) Slotta and Benisch, *Ber.*, **68**, 754 (1935).

*Acknowledgment.* The authors wish to thank Mr. Joseph Marrus for the physiological tests, Mr. Hilding Johnson and members of his staff for the microanalyses, Mr. Irving Wakeman for ultraviolet analyses, and Messrs. Firman and Abbey for the bacteriological tests. The authors also wish to thank Dr. William M. Ziegler, Dr. Neil E. Rigler, and Dr. Herman Sokol for their valuable assistance and cooperation.

GARFIELD, N. J.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

# Synthesis of Potential Anticancer Agents. VI.[2] Use of *O*-Benzoyl Blocking Group for Synthesis of 6-Chloropurine Nucleosides

B. R. BAKER,[3] KATHLEEN HEWSON, H. JEANETTE THOMAS, AND JAMES A. JOHNSON, JR.

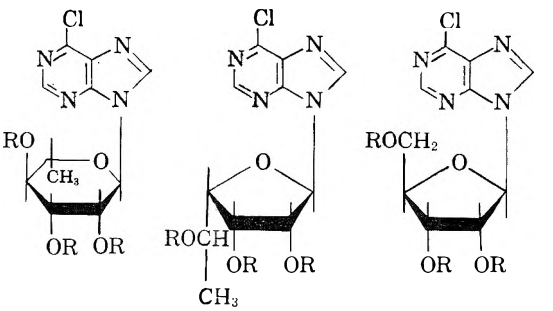
*Received February 11, 1957*

A general method for the synthesis of 6-chloropurine nucleosides, particularly valuable as intermediary nucleosides, is described. Condensation of chloromercuri-6-chloropurine with the proper *O*-benzoylated glycosyl chloride has afforded 9-α-L-rhamnopyranosyl-, 9-α-L-rhamnofuranosyl-, and 9-β-D-ribofuranosyl-6-chloropurines in 28–41% yields.

Since Fischer and Helferich[4] synthesized the first nucleoside, 7-glucopyranosyltheophylline, by condensation of silver theophylline with tetra-*O*-acetyl-α-D-glucopyranosyl bromide there have been only three improvements in the procedure. Davoll, Lythgoe, and Todd[5] observed that tri-*O*-acetylpentofuranosyl chlorides, due to their increased stability, gave higher yields of nucleosides than the corresponding furanosyl bromides. Another major improvement was the introduction of the use of chloromercuri derivatives of purines, rather than silver purines, by Davoll and Lowy.[6] The third major improvement was the introduction of *O*-benzoyl blocking groups, rather than *O*-acetyl for the sugar moiety by Kissman, Pidacks, and Baker[7]; that higher yields are obtained has been verified several times.[8–10] In certain cases, the use of the more hydrolytically stable *O*-benzoyl group is essential for transformation work necessary during synthesis of the blocked sugars.[7,11,12]

The use of *O*-benzoyl blocking groups for the synthesis of nucleosides may have the serious drawback that base-catalyzed removal of the group from base-labile nucleosides, such as those derived from 6-chloropurine, may not be feasible. The finding that 6-chloropurine nucleosides can be made from poly-*O*-benzoyl glycosyl halides in satisfactory yield is the subject of this paper.

The only example of a 6-chloropurine nucleoside described in the literature is the 9-β-D-ribofuranoside (VII). Brown and Weliky[13] synthesized this nucleoside (VII) from 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride and chloromercuri-6-chloropurine. They obtained a 26% yield of crude, colored nucleoside; recrystallization was attended by a considerable loss and the yield of pure material was not specified.



I, R = $C_6H_5CO$—
II, R = H

III, R = $C_6H_5CO$—
IV, R = H

V, R = $CH_3CO$—
VI, R = $C_6H_5CO$—
VII, R = H

(1) Affiliated with Sloan-Kettering Institute.

(2) This work was supported in part by the Kettering Foundation and by the Lasker Foundation. For paper V of this series see L. L. Bennett, Jr. and H. T. Baker, *J. Org. Chem.*, **22**, 707 (1957).

(3) Present address: Stanford Research Institute, Menlo Park, Calif.

(4) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).

(5) (a) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948). (b) An apparent exception that furanosyl chlorides can be expected to give higher yields of nucleosides than furanosyl bromides has been observed with the 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl halides.[9]

(6) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

(7) H. M. Kissman, C. Pidacks and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

(8) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).

(9) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(10) J. A. Johnson and H. J. Thomas, Southern Research Institute, to be published.

(11) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 7 (1955).

(12) B. R. Baker and K. Hewson, Paper VIII of this series, *J. Org. Chem.*, **22**, 966 (1957).

(13) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

In order to employ the Brown-Weliky approach to nucleosides from a 6-chloropurine blocked nucleoside such as I, it was essential to establish whether or not the benzoyl groups of I could be removed preferentially without seriously affecting the base-labile 6-chloro group. This posed a serious problem since benzoates[3] react with basic reagents at about 10% of the rate of acetates.[14] If the benzoyl groups could not be removed from I without affecting the 6-chloro group, then it would be necessary to transform the 6-chloro group of the crude blocked nucleoside first to such groups as 6 —H, 6 —SH, etc., before hydrolyzing the benzoates. This latter approach has the serious drawback that each new nucleoside would still have the accumulated sugar decomposition products from the coupling reaction formed during synthesis of I. Since nucleosides can be notoriously difficult to purify when the sugar decomposition products are still present, this would lead to a difficult purification for each nucleoside. On the other hand if the benzoyl groups can be removed selectively from the blocked nucleoside, I, to give the 6-chloropurine nucleoside, II, in reasonable yield, then only one difficult purification, that of II, is necessary since the transformations on a pure 6-chloropurine nucleoside would appear to proceed smoothly.[13]

Brown and Weliky,[13] for preparation of 6-chloropurine riboside, used the standard conditions[4,5a,6,7,15,16] for removing *O*-acetyl groups from blocked nucleosides, namely methanol saturated with ammonia at 0° for 15–20 hr., even though there has been no time study made for this reaction. If one assumes that the benzoates will require ten times as long a reaction period,[14] then 6–8 days at 0° would be required to cleave the benzoates. This lengthy reaction time could seriously impair the yield of 6-chloro-9-α-L-rhamnopyranosylpurine (II) since the quantities of the corresponding adenine nucleoside could become appreciable, thus not only lowering the yield but aggravating the purification problem.

The blocked 6-chloropurine rhamnoside (I) was allowed to react with methanolic ammonia at 0° for 5 days. The products were partitioned between chloroform and water. The latter contained a nearly theoretical weight of debenzoylated nucleosides. Both fractions were subjected to paper chromatography with a water-saturated butanol system using an ultraviolet lamp to locate the spots and using 6-chloropurine ($R_{Ad}$ 1.60, pink), adenine ($R_{Ad}$ 1.00, purple), and 9-α-L-rhamnopyranosyladenine[17] ($R_{Ad}$ 0.46, purple) as standards.[18] The water solution showed the presence of a spot corresponding to 9-α-L-rhamnopyranosyladenine ($R_{Ad}$ 0.46) and a spot with $R_{Ad}$ 1.46 which was purple at the back side shading into pink at the front side. There were also several strongly fluorescent spots, which when eluted, had no absorption in the ultraviolet and were not considered further. The pink to purple spot with $R_{Ad}$, 1.46 was considered the one most likely to be the desired 6-chloropurine nucleoside (II). Elution of this spot with water and determination of the ultraviolet maximum indicated 6-chloropurine nucleoside could be present, although the peak was broader toward the shorter wave lengths than it should have been. When the spot with $R_{Ad}$ 1.46 was split in half to give mostly a pink front half and purple back half, then eluted, the ultraviolet peak of the pink spot was sharper at 262 mμ. Thus the pink spot was mostly the chloropurine nucleoside and the purple half of the spot was an impurity with a broad absorption peak about 240 mμ. The chloroform fraction of the debenzoylation reaction contained no purines of interest since there were no spots with $R_{Ad}$ values less than that of 6-chloropurine.

A second methanolic ammonia debenzoylation was carried out at 0° for only 23 hr. The yield of debenzoylated nucleosides in the aqueous fraction was again quantitative showing that the reaction was more rapid than could be anticipated by the conditions described in the literature for removal of *O*-acetates. Paper chromatography of the same concentration of this material gave a strip very similar to the five-day run. The spots from both runs with $R_{Ad}$ 0.46 corresponding to 9-α-L-rhamnopyranosyladenine were eluted with water. Determination of the ultraviolet spectrum of the eluates showed that there was about three times as much adenine nucleoside in the longer run. In addition, elution of the spot with $R_{Ad}$ 1.46 corresponding to the 6-chloropurine nucleoside (II) showed that the peak at 262 mμ was sharper and higher in the one-day run than in the five-day run. Thus, it is quite clear that even at 0° the 6-chloro group is being replaced with ammonia and that the yield of 6-chloropurine nucleoside (II) is considerably higher after one day.

With a more optimum time established for the debenzoylation of the blocked 6-chloropurine nucleoside (I) and with some knowledge of the type of impurities established by paper chromatography, purification of the crude 6-chloropurine nucleoside (II) by column chromatography, since the crude material failed to crystallize, was then investigated. The first column was run with powdered cellulose using water-saturated butanol as the moving phase in order to approach the condi-

(14) K. Kindler, *Ann.*, **452**, 90 (1927); *Ber.*, **69B**, 2792 (1936).

(15) P. A. Levene and J. Compton, *J. Biol. Chem.*, **117**, 37 (1937).

(16) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1780 (1954).

(17) B. R. Baker and K. Hewson, *J. Org. Chem.*, Paper VII of this series, *J. Org. Chem.*, **22**, 959 (1957).

(18) Adenine was used as a standard and the $R_{Ad}$ values were calculated by assigning the adenine spot $R_{Ad}$ 1.00. The chromatograms were run with water-saturated butanol by the descending technic on Whatman No. 1 paper.

tions of the paper chromatography. Although some useful data were obtained in this column, purification was not completely satisfactory. The main difficulty was that almost all the material were moved through the column with less than one holdback volume (h.b.v.) of solvent. Fractions of about 0.03 h.b.v. were collected after the front moved off the column. These were examined by ultraviolet absorption. Some of the fractions showing purines absorbing the vicinity of 260 mμ were also examined by paper chromatography. The results indicated that the purple spot with $R_{Ad}$ about 1.46 traveled most rapidly on the column. This compound is an impurity, probably a sugar decomposition product. The next fractions were richer in 6-chloropurine nucleoside (II). However, these were still somewhat contaminated with the brown pigment of the earliest fraction. However, the fraction richest in II, when evaporated, crystallized on standing. A somewhat more efficient separation occurred using a Celite partition column with water as the stationary phase and butanol as the mobile phase.[7] Again most of the material was eluted in the first h.b.v. following the front. However, purer fractions of II were obtained than from the cellulose column. The main fraction should have a distribution coefficient of 0.1–0.2 (mobile phase to stationary phase) to obtain good results.[7] It has now been found that the purest fraction of 6-chloropurine rhamnoside (II), which crystallized on standing, has a distribution coefficient in ethyl acetate–water of 0.22. Thus a Celite partition column with a stationary water phase and mobile ethyl acetate phase should give more efficient purification. This indeed proved to be the case, pure crystalline 6-chloro-9-α-L-rhamnopyranosylpurine (II)[19] being obtained in 41% over-all yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide.[20]

The fact that butanol moved the 6-chloro-9-α-L-rhamnopyranosylpurine rapidly through a cellulose column suggested that simple butanol extraction might effect sufficient purification for crystallization without preliminary column purification, particularly in view of the fact that seed crystals were then available. Evaporation of the butanol extracts and crystallization of the residue from methyl ethyl ketone afforded the crystalline nucleoside (II) in 41% over-all yield. However, without preliminary butanol extraction, the crude nucleoside still could not be crystallized even with seeding.

Before the ammonia-methanol debenzoylation of I was studied, the Zemplen debenzoylation with methanolic sodium methoxide was investigated. Normally about 20–30 mole % of sodium methoxide is necessary to keep the solution alkaline enough to debenzoylate a crude nucleoside obtained in a chloromercuri coupling.[7] It was observed, however, that during debenzoylation of I, the solution continued to consume a total of 130 mole % of sodium methoxide before remaining alkaline. This experiment clearly demonstrated that the 6-chloro group was being replaced by 6-methoxy at room temperature. A run was then made allowing I to react in methanol with 130 mole % of sodium methoxide for 4 hr. The water-soluble fraction containing debenzoylated nucleosides was examined by ultraviolet absorption. The major peak was at 250 mμ in acidic, basic, or neutral solution with an inflection at about 260 mμ. The inflection shows the presence of some of the 6-chloropurine nucleoside (II). The major peak at 250 mμ could be compatible with that of a 6-methoxypurine nucleoside, but not compatible with a hypoxanthine nucleoside which gives shifts in ultraviolet maxima with changing *p*H. This approach to debenzoylation of a 6-chloropurine nucleoside was not considered worthy of further study.

In order to demonstrate that *O*-debenzoylation of blocked 6-chloropurine nucleosides with methanolic ammonia at 0° was a general reaction, two more 6-chloropurine nucleosides were investigated.

Condensation of crude 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride, obtained from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose,[12] with chloromercuri-6-chloropurine gave a crude blocked nucleoside (III) in 94% yield which had a maximum purity of 65% based on nitrogen analysis. Treatment of the blocked nucleoside (III) with methanolic ammonia at 0° for one day gave crude 6-chloro-9-α-L-rhamnofuranosylpurine (IV)[19] relatively free of 9-α-L-rhamnofuranosyladenine[12] as demonstrated by paper chromatography. The pure nucleoside (IV) was readily obtained by Celite partition chromatography using a stationary water phase and mobile ethyl acetate phase. Separation was quite sharp. The over-all yield of IV from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose was 33%. The nucleoside (IV) was obtained as a glass with the expected ultraviolet and infrared spectra. This glass traveled as a single spot on paper ($R_{Ad}$ 1.49).[18]

Since Brown and Weliky[13] obtained unspecified, but probably poor yields of pure 6-chloro-9-β-D-ribofuranosylpurine (VII) by condensation of chloromercuri 6-chloropurine with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride, the synthesis of VII with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[7] was investigated. The crude blocked nucleoside (VI) was treated with methanolic ammonia at 3° for 18 hr. Crystalline 6-chloro-9-β-D-ribofuranosylpurine (VII) was readily isolated from methanol. Recrystallization from water afforded a 28% yield of pure nucleoside (VII).

Concomitant with this work, a thorough study of the variables in the synthesis of adenosine from 6-acylaminopurines and 2,3,5-tri-*O*-acyl-D-ribofu-

(19) For a discussion of the configuration of rhamnose nucleoside, *cf.* refs. 12, 17.

(20) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 296 (1951).

ranosyl chloride was being made in these laboratories.[10] One of the most important conclusions reached was that traces of mercuric oxide in the chloromercuri purines had a very deleterious effect on the nucleoside coupling reaction, this effect being greater on 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride than on the corresponding tribenzoate.[21] In fact, with good quality chloromercuri derivative there was little difference in over-all yield of adenosine using either the *O*-acetyl or *O*-benzoyl blocking groups. Since the chloromercuri-6-chloropurine used in all the experiments described in this paper was obtained in almost quantitative yield by the Fox modification[21] and was free of mercuric oxide, the condensation of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride with this mercuric oxide-free chloromercuri-6-chloropurine was reinvestigated. No difficulty was encountered in crystallizing and purifying the resultant 6-chloro-9-β-D-ribofuranosylpurine (VII), a 29% over-all yield of pure nucleoside being obtained.

Thus, there is little difference in yield of 6-chloro-9-β-D-ribofuranosylpurine (VII) prepared from either 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose[23] or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose.[7] However, since the benzoylated D-ribofuranose[7] is easier to obtain in quantity than the acetylated D-ribofuranose,[23] the *O*-benzoyl blocking group is still the blocking group of choice for synthesis of VII.[24]

## EXPERIMENTAL[25]

*Chloromercuri-6-chloropurine.* To a solution of 7.38 g. of mercuric chloride in 100 ml. of 50% alcohol was added 4.20 g. of 6-chloropurine.[27] Then 10 ml. of 10% sodium hydroxide was added dropwise with good stirring at such a rate (10–15 min.) that the yellowish mercuric oxide color disappeared before the next drop was added. The addition was stopped if the solution acquired a yellow color. During this time, the reaction mixture thickened. After being stirred an additional 30 min., the mixture was filtered. The white product was washed successively with water, alcohol, and ether, then dried; yield, 10.12 g. (97%).

The amount of alkali necessary may vary slightly depending upon the extent of hydration in the 6-chloropurine used[28,29]; the production of a permanent slight yellow color is a good end point for the addition. If the crystal size of the 6-chloropurine is large, the 6-chloropurine should be dissolved in the 50% alcohol by warming, then the mercuric chloride added and finally the alkali. This last procedure was found particularly effective for 6-chloropurine-8-$C^{14}$ where the crystal size was large and powdering of the crystals was not expedient. In large batches or in radioactive runs, filtration of the chloromercuri derivatives was aided considerably by addition of 1 g. of analytical grade Celite[30] per gram of 6-chloropurine to the reaction mixture just prior to addition of the base.

*6-Chloro-9-α-L-rhamnopyranosylpurine* (II). (A) *Preparation:* A stirred mixture of 7.4 g. of chloromercuri-6-chloropurine, 3.5 g. of Celite,[30] and 350 ml. of xylene was distilled until all moisture was removed. After the addition of a warm solution of 9.4 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide[20] in 100 ml. of xylene, the mixture was refluxed and stirred for 2 hr., then filtered hot. The filter cake was washed with two 50-ml. portions of hot chloroform. The xylene filtrate was evaporated to dryness *in vacuo* and the residue dissolved in the chloroform washes. Washed with 100 ml. of 30% aqueous potassium iodide and with water, the chloroform solution was dried with magnesium sulfate, clarified with decolorizing carbon, and evaporated to dryness *in vacuo;* yield, 11.2 g. (105%) of crude, blocked nucleoside (I).

A mixture of 6.2 g. of crude blocked nucleoside (I) and 200 ml. of methanol saturated with ammonia at 0° was stirred in an ice bath until solution was complete (4 hr.). After standing at 3° in a stoppered flask for an additional 20 hr., the solution was filtered from a little brown solid and evaporated to a sirup *in vacuo* (bath 40°). The residue was partitioned between 25 ml. each of water and chloroform. The aqueous layer, washed twice more with chloroform, was evaporated to dryness *in vacuo* (bath 40°) leaving 3.08 g. (101%) of crude nucleoside (II) as a glass.

(B) *Purification by Celite partition chromatography.*[7] To 22.5 ml. of water saturated with ethyl acetate was added 45 g. of acid washed Celite 545[30] in portions. After each addition the paste was thoroughly mixed to give eventually a dry powder. A column with 2.1 cm. inside diameter was dry packed in 1–2 cm. layers to a height of 35 cm. A solution of 108 mg. of the above crude 6-chloro-9-α-L-rhamnopyranosylpurine (II) in 1.5 ml. of water saturated with ethyl acetate was mixed with 3 g. of Celite 545 and packed on top of the column. The column was developed with ethyl acetate saturated with water. A peak ultraviolet fraction of pigmented material was eluted with the first 15 ml. The ultraviolet absorption was then zero for the next 8.5 ml. The next main fraction appeared over the next 200 ml. of eluate; this solution was evaporated to dryness *in vacuo.* A solution of the residue in water was washed several times with chloro-

(21) Several years ago it was observed that condensation of 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranosyl chloride with chloromercuri-2-methylmercapto-6-dimethylaminopurine was quite sensitive to impurities in the chloromercuri derivative, no nucleoside[16] being obtained if the chloromercuri derivative was off color.[22] J. J. Fox and coworkers of Sloan-Kettering Institute independently made the observation that yields of nucleosides were poor if the chloromercuri derivative of a purine or pyrimidine was not obtained in nearly quantitative yield. Fox *et al.* devised an inverse procedure for preparation of chloromercuripurines which gave pure products in nearly quantitative yield (*cf.* Experimental).

(22) B. R. Baker and F. J. McEvoy, American Cyanamid Company, unpublished results.

(23) G. B. Brown, J. Davoll, and B. A. Lowy, *Biochemical Preparations,* 4, 70 (1955).

(24) H. M. Kissman and M. J. Weiss, *J. Org. Chem.,* 21, 1053 (1956), have recently published an alternate method for use of 6-chloro-9-β-D-ribofuranosylpurine (VII) as an intermediate. They purified the blocked nucleoside (VI) by chromatography on acid-washed alumina. The 6-chloro group of VI was then replaced by other groups followed by *O*-debenzoylation.

(25) The ultraviolet spectra were determined with a Beckman Model DK-2 spectrophotometer, the infrared spectra with a Perkin-Elmer Model 21 spectrophotometer and the optical rotations with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[26] Melting points were determined in capillary tubes in a stirred oil bath and are uncorrected.

(26) A. S. Keston, Abstracts of 125th Meeting, AMERICAN CHEMICAL SOCIETY, p. 18 C (1955).

(27) Purchased from Francis Earle Laboratories, Inc., Peekskill, N. Y.

(28) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.,* 76, 6073 (1954).

(29) J. A. Montgomery, Paper I of this series, *J. Am. Chem. Soc.,* 78, 1928 (1956).

(30) Johns-Manville Co.

form. The aqueous solution was evaporated to dryness *in vacuo* leaving 42 mg. of II as a glass. An acetone solution of this material was allowed to evaporate in air. The residue consisted of white crystals, m.p. 164–165° (dec.). Its infrared spectrum was identical with preparation (C). Thus the recovery of II was 39% and the over-all yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide was 41%. On paper[16] this material traveled as a major spot which was pink in ultraviolet light and which had $R_{Ad}$ 1.40. A trace of fluorescent material, previously shown to be negligible in the crude material, traveled at a slower rate.

(C) *Butanol purification:* A solution of 2.89 g. of crude nucleoside (II) in 15 ml. of water was extracted with four 15-ml. portions of redistilled butanol. The combined extracts were evaporated to dryness *in vacuo*. The residue was dissolved in about 20 ml. of warm methyl ethyl ketone by addition of a little alcohol and water. The solution was clarified with 0.5 g. of Norit. The solution was evaporated to a sirup in an air stream, then seeded. Crystals began to separate within 2 hr. After standing overnight, the mixture of crystals and oil was triturated with methyl ethyl ketone. The crystalline product was collected on a filter and washed with methyl ethyl ketone; yield, 0.761 g., m.p. 170–172° (dec.).

The filtrate was evaporated to a sirup under an air stream and seeded. After standing overnight, the mixture of crystals and oil was again triturated with methyl ethyl ketone; yield, 0.328 g. of white crystals, m.p. 172–174° (dec.). This material had $\lambda_{max}^{H_2O}$ 264 mμ ($a_M$ 9300); $\nu_{max}^{KBr}$ 3410 cm.$^{-1}$ (OH), 1598, 1570 cm.$^{-1}$ (C=C and C=N), 1097, 1080, 1070 (C—O—). The infrared spectrum is in excellent agreement with the expected key peaks. The recovery of II in crystalline form was 38% and the overall yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide was 40%. No solvent could be found for direct recrystallization of this material. It would only crystallize as the solution reached near dryness. A sample of the second crop was dried in high vacuum at room temperature and analyzed; $[\alpha]_D^{26}$ −62° (1.27% in $H_2O$).

*Anal.* Calcd. for $C_{11}H_{13}ClN_4O_4$: C, 44.0; H, 4.37; N, 18.7. Found: C, 44.3; H, 4.81; N, 17.9.

This compound traveled on paper in a butanol-water system as one major spot, pink in ultraviolet light, with $R_{Ad}$ 1.40 and a negligible fluorescent spot with $R_{Ad}$ 1.07.

*6-Chloro-9-α-L-rhamnofuranosylpurine* (IV). A solution of 9.79 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose[12] in 8 ml. of acetyl chloride[31] was treated with 300 ml. of reagent ether saturated with hydrogen chloride at 0°. After 3 days at 3° in a glass-stoppered container, the solution was evaporated to dryness *in vacuo* (bath 40°). The residue was dissolved in 50 ml. of reagent benzene and the evaporation repeated. The evaporation was repeated once more with 25 ml. of fresh reagent benzene. The crude 2,3,5-tri-*O*-benzoyl-α-L-rhamnofuranosyl chloride was immediately dissolved in 70 ml. of xylene and added to a mixture of 7.4 g. of chloromercuri-6 chloropurine, 3.7 g. of Celite[30] and 350 ml. of xylene previously dried by azeotropic distillation. After being refluxed and stirred for 2 hr., the mixture was processed as described for the corresponding pyranose (I). The chloroform residue was dissolved in 150 ml. of ether and the solution was washed with four 30-ml. portions of ice cold 3% sodium hydroxide. Dried with magnesium sulfate, clarified with Norit and filtered through Celite, the solution was evaporated to dryness *in vacuo;* yield, 10.8 g. (94%) of crude blocked nucleoside (III) which had a maximum purity of 65% based on nitrogen analysis and had $\nu_{max}^{Chf}$ 1730, 1285 cm.$^{-1}$ (C=O and C—O—C of benzoate); 1610, 1570 cm.$^{-1}$ (C=C and C=N).

The crude blocked nucleoside (III) (4.1 g.) was debenzoylated with 70 ml. of methanol saturated with ammonia of 0° as described for the pyranose (I), except that only 1 hr. stirring was required to effect solution; yield, 1.62 g. (82%) of crude IV.

For purification 111 mg. of crude nucleoside (IV) was chromatographed[7] on 46 g. of Celite 545[30] in a 2.1 cm. diameter column as described for the corresponding pyranose (II) using a stationary aqueous phase and mobile ethyl acetate phase. After elution of pigmented material at 0–40 ml., the product was eluted as a sharp peak at 56–104 ml. Evaporation of the latter solution to dryness *in vacuo* (bath 40°) afforded 48 mg. (33% based on 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose) of product as a glass. After being dried at 60° in high vacuum over $P_2O_5$ for several hours, the product still contained solvent. This compound traveled as a single spot ($R_{Ad}$ 1.49)[18] on paper. $\lambda_{max}^{H_2O}$ 263 mμ ($a_M$ 7,920 corrected for ethyl acetate); $\nu_{max}^{KBr}$ 3360 cm.$^{-1}$ (OH); 1557, 1587 cm.$^{-1}$ (C=C and C=N); 1020–1080 cm.$^{-1}$ (broad C—O—); $[\alpha]_D^{26}$ −42° (0.21% in $H_2O$).

*Anal.* Calcd. for $C_{11}H_{13}ClN_4O_4 \cdot {}^1/_4C_4H_8O_2$: C, 45.0; H, 4.72; N, 17.5. Found: C, 45.4; H, 5.22; N, 17.5.

The solvent could not be removed any more completely from this heat-sensitive compound, since at higher temperatures the compound darkened badly.

Although several smaller fractions were eluted from the column after the major peak, no attempt was made to identify them.

*6-Chloro-9-β-D-ribofuranosylpurine* (VII). (A) To 50 ml. of reagent ether saturated with hydrogen chloride at 0° were added 1.8 ml. of acetyl chloride[31] and 1.80 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose.[7] After 4 days at 3° in a stoppered flask, the solution was evaporated to dryness *in vacuo*. The evaporation was repeated with two 10-ml. portions of reagent benzene. The resultant chloro sugar was dissolved in 10 ml. of xylene and reacted with 1.51 g. of chloromercuri-6-chloropurine suspended in xylene as described for the corresponding rhamnopyranoside (II); yield, 2.47 g. of crude blocked nucleoside (VI).

This material was treated with methanolic ammonia as described for the debenzoylation of I and II. During concentration of the methanolic ammonia solution to a sirup *in vacuo*, the product crystallized. Trituration with methanol gave 334 mg. (33%) of product as cream-colored crystals, m.p. 180–182° (dec.); $\lambda_{max}^{H_2O}$ 263 mμ ($a_M$ 9200); $\nu_{max}^{KBr}$ 3360 cm.$^{-1}$ (broad OH); 1560, 1595 cm.$^{-1}$ (C=C and C=N); 1047, 1090 cm.$^{-1}$ (C—O—). This compound traveled as a major spot ($R_{Ad}$ 1.46) on paper[18]; also present was a fluorescent spot ($R_{Ad}$ 0.63) of a trace impurity. The analysis also indicated that this compound was not quite pure; however, this material was suitable for further transformation work.

*Anal.* Calcd. for $C_{10}H_{11}ClN_4O_4$: C, 42.0; H, 3.88; N, 19.6. Found: C, 42.5; H, 4.18; N, 19.4.

A second crop (6%) of less pure material was obtained from the mother liquor.

(B) A larger run with 7.77 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[7] gave the crude crystalline nucleoside (VII) in 43% yield, which was less pure than preparation A. Recrystallization from water with the aid of Norit afforded a 28% yield of pure material as light yellow crystals.

(C) By condensation of the 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride[5a] from 18 g. of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose[23] with 22 g. of chloromercuri-6-chloropurine in 500 ml. of xylene in the presence of 22 g. of Celite,[30] followed by deacylation of the blocked nucleoside (V), with methanolic ammonia (600 ml. saturated at 0°) as described in Part (A) was obtained 5.6 g. (35%) of crystalline nucleoside. One recrystallization from water with the aid of Norit gave 4.70 g. (29%) of pure nucleoside (VII) as nearly colorless needles, m.p. 179–180° (dec.), $\lambda_{max}^{Ph.\ 7}$ 264 mμ ($a_M$ 8900); $[\alpha]_D^{26}$ −45° (0.79% in $H_2O$).

Brown and Weliky[13] have recorded m.p. 170–171° (dec.), varying considerably with the rate of heating. They also recorded $\lambda_{max}^{pH\ 6}$ 264 mμ ($a_M$ 8800).

(31) The use of acetyl chloride for keeping such a preparation anhydrous has been described by B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, 77, 5900 (1955).

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

# Synthesis of Potential Anticancer Agents. VII.[2] Nucleosides Derived from L-Rhamnopyranose

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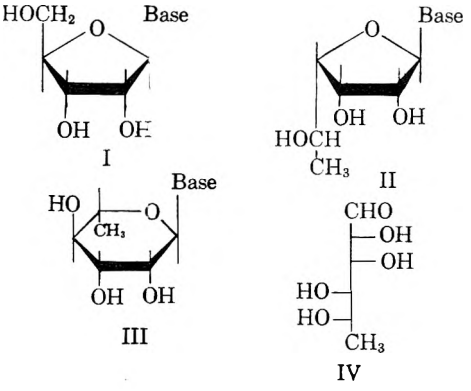
The syntheses of six nucleosides derived from L-rhamnopyranose have been accomplished by proper modification of standard procedures.

The most commonly available sugar, besides D-ribose, that has $C_2$-$C_3$-*cis*-hydroxyls of D-configuration is L-rhamnose (IV, 6-deoxy-L-mannose). From L-rhamnose, it should be possible to synthesize L-rhamnofuranosyl nucleosides (II) as well as L-rhamnopyranosyl nucleosides (III). Since L-*rhamno*-nucleosides with structures II and III have certain structural features in common with natural D-*ribo*-nucleosides (I) derived from nucleic acids, these L-rhamnonucleosides may inhibit some stage of nucleotide metabolism in the cell. The L-rhamnofuranosyl nucleosides (II) differ from the natural ribosides only in the size and configuration of the group at $C_4$ of the sugar moeity. The L-rhamnopyranosyl nucleosides (III) are similar to the natural nucleosides (I) in the configurations at $C_1$, $C_2$, $C_3$ and $C_4$ of the sugar moeity; however, the group at $C_4$ is hydroxyl in place of hydroxymethyl and, in addition, III has a pyranose ring rather than the natural furanose ring. This communication describes the synthesis of several nucleosides (III) derived from L-rhamnopyranose. An accompanying paper describes the synthesis of nucleosides (II) derived from L-rhamnofuranose.




A search of the literature revealed that only one nucleoside has been synthesized from L-rhamnopyranose, namely 7-L-rhamnopyranosyltheophylline.[4] Although the anomeric configuration was unknown, it is highly probable that an $\alpha$-nucleoside was obtained. The formation of an $\alpha$-nucleoside (III) would conform with the rule[5-7] that a nucleoside with $C_1$-$C_2$-*trans*-configuration will be obtained when a heavy metal salt of a purine (such as theophylline[4]) is condensed with an *O*-acylated glycosyl halide (such as 2,3,4-tri-*O*-acetyl-L-rhamnopyranosyl bromide[4]).

Since past experience has shown that *O*-benzoyl blocking groups for the glycosyl halide generally give higher yields of nucleosides than *O*-acetyl blocking groups,[8,9] 2,3,4-tri-*O*-benzoyl-$\alpha$-L-rhamnopyranosyl bromide (VI)[10] was employed for synthesis of these nucleosides.

*9-α-L-Rhamnopyranosyladenine* (XI). This nucleoside (XI) was synthesized by two routes. Condensation of chloromercuri-6-chloropurine (V) with 2,3,4-tri-*O*-benzoyl-$\alpha$-L-rhamnopyranosyl bromide (VI) afforded the blocked chloropurine nucleoside (VII), as previously described.[11] The crude blocked nucleoside was treated at 100° with

(1) Affiliated with The Sloan-Kettering Institute for Cancer Research.

(2) This work was supported in part by the C. F. Kettering Foundation.

(3) Present address: Stanford Research Institute, Menlo Park, Calif.

(4) E. Fischer and K. Fodor, *Ber.*, **47**, 1058 (1914).

(5) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(6) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 2396 (1955).

(7) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).

(8) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

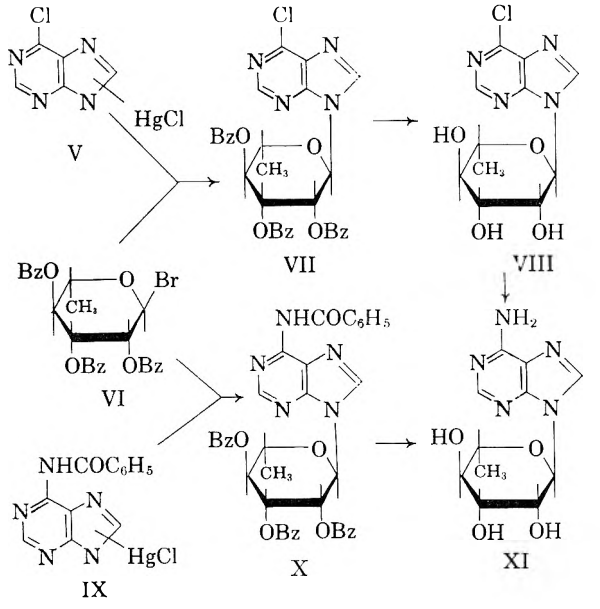
(9) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(10) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 296 (1951).

(11) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., Paper VI of this series, *J. Org. Chem.*, **22**, 954 (1957).

methanolic ammonia, which caused replacement of the chloro by amino as well as *O*-debenzoylation. The adenine nucleoside (XI) was isolated as its picrate. Higher yields of XI picrate were obtained if the blocked nucleoside (VII) was *O*-debenzoylated at 0° with methanolic ammonia to VIII,[11] then the solution heated at 100° to replace the 6-chloro group of the purine moiety with the amino group.[12]

Regeneration of the base (XI) from its picrate was accomplished by treatment of the picrate with Dowex I (Cl)[13] in aqueous suspension. Evaporation of the solution and crystallization from alcohol gave crystalline 9-α-L-rhamnopyranosyladenine (XI) in 46% overall yield from the sugar bromide (VI).[14]




The 9-α-L-rhamnopyranosyladenine (XI) could also be synthesized in good yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide and chloromercuri-6-benzamidopurine (IX) by the standard method for syntheses of adenosine[13] as modified by Johnson and Thomas.[15] Isolation of the product *via* the picrate and regeneration with Dowex 1 (Cl) gave XI hydrochloride identical with that obtained by the 6-chloropurine method. The overall yield from VI was 51%. However, examination by paper chromatography showed that XI was contaminated with a small amount of adenine. Since the aqueous solution of the nucleoside (XI) from which the picrate was prepared contained no detectable adenine by paper chromatography, the presence of adenine must have arisen by hydrolysis either during preparation of the picrate or during regeneration of the nucleoside from the picrate or both.

The original procedure of Davoll and Lowy[13] for regeneration of adenosine from its picrate with Dowex 1 (Cl) called for neutralization of the generated hydrochloric acid with sodium hydroxide before evaporation. Adenosine is sufficiently insoluble in water to be readily separable from salt. However, 9-α-L-rhamnopyranosyladenine (XI) was extremely water soluble, a characteristic of all the rhamnopyranosyl nucleosides described in this paper. An attempt to regenerate XI from its picrate with freshly prepared Dowex 1 (OH) gave poor results since about half of the nucleoside was lost by adsorption on the resin. Two less basic forms of the resin were then considered, namely the carbonate and the acetate forms. The carbonate form of Dowex 1, which forms carbon dioxide during regeneration was found satisfactory. Although there was more adsorption than with Dowex 1 (Cl), the carbonate form was quite satisfactory provided the final solution of nucleoside was no more concentrated than about 0.001 molar. Thus, 9-α-L-rhamnopyranosyladenine (XI) was obtained as the crystalline free base in 43% overall yield based on the sugar bromide (VI). This nucleoside was free of adenine as shown by paper chromatography. An additional 7% of the nucleoside (XI) could be isolated from the alcoholic mother liquor as the hydrochloride, but was contaminated with a small amount of adenine. The use of Dowex 1 (Ac) was not investigated with this nucleoside since the Dowex 1 ($CO_3$) was considered satisfactory.[16]

The 9-α-L-rhamnopyranosyladenine (XI) failed to have any activity against Adenocarcinoma 755,[17] Sarcoma 180,[18] or *in vitro* against Endamoeba histolytica.[19]

At this point the question arose, "What are the minimum number of purines and pyrimidines that should be converted to a nucleoside with a given unnatural sugar in order to establish whether or not any biological activity will be obtained?" The lack of examples in the literature leaves this problem still unsolved. Nevertheless, consideration of what biological factors are known led to a more or less arbitrary selection of the following pyrimidine and purine nucleosides as a representative cross-sec-

(12) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(13) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

(14) That the nucleoside has a $C_1$-$C_2$-*trans*-configuration is highly probable in view of the rule postulated for the stereochemistry of nucleoside formation.[5] The formation of this α-nucleoside would require a double Walden inversion during nucleoside condensation, a previously observed phenomenon (*cf.* ref. 6, footnote 16).

(15) J. A. Johnson, Jr., and H. J. Thomas, Southern Research Institute, to be published.

(16) Later work on nucleosides has shown that Dowex 1 in the acetate form is also satisfactory for regeneration of a nucleoside from its picrate.

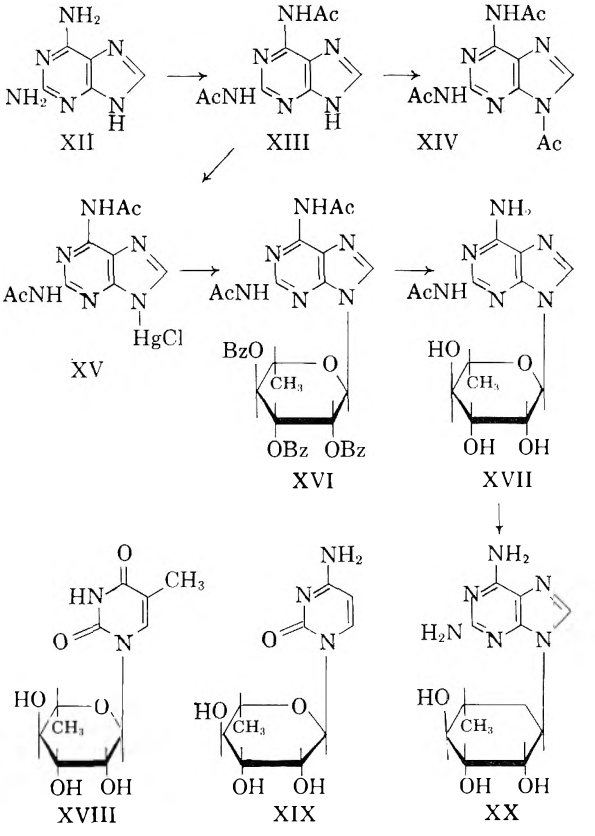
(17) Private communication from Dr. H. E. Skipper, Southern Research Institute.

(18) Private communication from Dr. C. C. Stock, Sloan-Kettering Institute.

(19) Private communication from Dr. E. F. Elslager, Parke, Davis & Co.

tion: (*1*) Adenine, (*2*) 2,6-Diaminopurine, (*3*) Thymine, (*4*) Cytosine or uracil.

*2,6-Diamino-9-α-L-rhamnopyranosylpurine* (XX). An apparently general method for the synthesis of 2,6-diaminopurine-9-glycosides has been described by Davoll and Lowy.[13] They acetylated 2,6-diaminopurine (XII) with acetic anhydride to form 2,6-diacetamidopurine (XIII), m.p. 295–300° (dec.), in 83% yield. Repetition of their procedure gave a mixture of XIII and its 9-acetyl derivative (XIV). That the 9-acetyl group was present was clearly shown by the C=O infrared absorption of an "active" *N*-acetyl at 1745 cm.$^{-1}$ and by the diminished acidic 9-N-H absorption at 2400–3000 cm.$^{-1}$. Recrystallization of the mixture from water served to hydrolyze the 9-acetyl group of XIV, thus forming pure 2,6-diacetamidopurine (XIII) in 59% yield. The lability of the 9-acetyl group on a purine nucleus was observed earlier in our laboratories.[20]




Reacetylation of the mixed products in the mother liquors raised the yield to 77%. Similar results were obtained by acetylation with acetic anhydride containing 20% acetic acid. The data of Davoll and Lowy[13] indicate that they obtained no 9-acetylation. The reason for this discrepancy is still unknown.

Conversion to chloromercuri-2,6-diacetamidopurine (XV) was effected in 100% yield by adding one equivalent of sodium hydroxide slowly to a solution of mercuric chloride containing the purine XII in suspension.[21] Condensation of the chloromercuri purine (XV) with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) gave crystalline 2,6-diacetamido-9-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl) purine (XVI) in 32% yield. Treatment of XVI with excess methanolic sodium methoxide at the boiling point[13] removed both the *O*-benzoyl and *N*-acetyl blocking groups.[22] The 2,6-diaminopurine rhamnopyranoside (XX) was isolated as its beautifully crystalline picrate in 96% yield. Regeneration of the nucleoside from the picrate with Dowex 1 ($CO_3$) afforded crystalline XX with 74% recovery.

In order to try to avoid isolation of XX *via* the picrate, a method was sought which would not introduce inorganic material. Deacylation with boiling methanolic butylamine[24] was investigated. The major product, isolated in 55% yield, was 2-acetamido-6-amino-9-α-L-rhamnopyranosylpurine (XVII) and was readily differentiated from the 2,6-diaminopurine rhamnoside by paper chromatography or infrared analysis. The 2-acetamidopurine nucleoside could be prepared in 94% yield by use of methanolic ammonia, a reagent used by Davoll and Lowy[13] for synthesis of 2-acetamido-6-amino-9-β-D-ribofuranosylpurine.

*1-α-L-Rhamnopyranosylthymine* (XVIII). A new synthesis of thymine nucleosides has recently been discovered by Fox *et al.*[9] Coupling of dithyminyl mercury with *O*-acylglycosyl halides gave excellent results. This method has now been applied to the synthesis of 1-α-L-rhamnopyranosylthymine (XVIII).

Condensation of dithyminyl mercury with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) afforded the crude blocked nucleoside in quantitative yield which had a maximum purity of 53% based on nitrogen content. Debenzoylation with methanolic sodium methoxide gave a water soluble product. The by-product methyl benzoate was removed by extraction of an aqueous solution of crude XVIII with chloroform. The residue from evaporation of the aqueous solution was extracted with acetone. The acetone solution of XVIII was separated from insoluble inorganic materials. Evaporation gave a 58% yield of XVIII with a maximum purity of 85% based on ultraviolet analysis. The entire separation to this point was followed by ultraviolet examination of the various fractions. The nucleoside XVIII was further purified by Celite partition chromatography[8] using a

(20) J. A. Montgomery, Paper I of this series, *J. Am. Chem. Soc.*, **78**, 1928 (1956).

(21) We wish to thank Dr. J. J. Fox of Sloan-Kettering Institute for suggesting this inverse procedure for preparation of chloromercuri derivatives in quantitative yield.

(22) The use of the usual catalytic amounts of sodium methoxide[5,7,8,23] was not satisfactory since the 2-acetamido group did not undergo methanolysis at an appreciable rate.

(23) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1780 (1954).

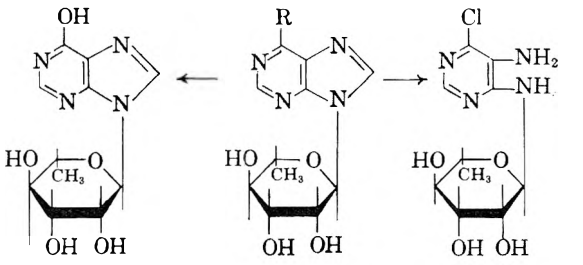
(24) L. Goldman, J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, **78**, 4173 (1956).

stationary aqueous phase and mobile butanol phase. The peak fractions were characterized by ultraviolet absorption and paper chromatography. The major fraction was a colorless glass which showed $\lambda_{max}^{H_2O}$ 265 m$\mu$ ($a_M$ 9930) and traveled on paper as a single ultraviolet absorbing spot in a butanol-water system. The ultraviolet spectrum compared favorably with that of a pure sample of thymidine. Although the nucleoside XVIII is apparently pure, it has not been obtained in crystalline form. The overall yield from 2,3,5-tri-*O*-benzoyl-$\alpha$-L-rhamnopyranosyl bromide (VI) was 53%.

*1-$\alpha$-L-Rhamnopyranosylcytosine* (XIX). The outstanding research of J. J. Fox and coworkers on new syntheses of pyrimidine nucleosides has also led to a new method for synthesis of cytosine nucleosides.[25] They found that *N*-acetylcytosine formed a 1:1 complex with mercuric ion which contained no halogen. This mercuri derivative, $C_6H_5HgN_3O_2$, could be condensed with *O*-acylglycosyl halides to form cytosine nucleosides; two moles of sugar halide were necessary for the reaction and one mole was not coupled.

Condensation of mercuri-*N*-acetylcytosine with two moles of 2,3,4-tri-*O*-benzoyl-$\alpha$-L-rhamnopyranosyl bromide (VI) gave a blocked nucleoside which was deacylated with methanolic sodium methoxide. The most difficult problem in this synthesis, as in the case of thymine rhamnoside (XVIII), was the isolation of the pure cytosine nucleoside (XIX) since the compound could not be crystallized. Again Celite partition chromatography[8] with a stationary water phase and mobile butanol phase was successful in giving the pure, although amorphous, nucleoside (XIX). The overall yield was 24% based on mercuri-*N*-acetylcytosine.

*9-$\alpha$-L-Rhamnopyranosylhypoxanthine* (XXI). The synthesis of 6-chloro-9-$\alpha$-L-rhamnopyranosylpurine (VIII) has previously been described.[11] Since Bendich, Russell, and Fox[26] have shown that treatment of 6-chloropurine with boiling 0.1 *N* sodium hydroxide gave a quantitative yield of hypoxanthine, the conversion of VII to XXI was investigated. Unfortunately, the action of 0.1*N* sodium hydroxide on 6-chloro-9-$\alpha$-L-rhamnopyranosylpurine (VIII) followed a different course, and did not give 9-$\alpha$-L-rhamnopyranosylhypoxanthine (XXI). That XXI was not formed was readily demonstrated by examination of the change in ultraviolet absorption spectrum of the chloropurine nucleoside (VIII) in 0.1*N* sodium hydroxide as a function of time at 100°. After each time interval, the solution was acidified to *p*H 1 and the absorption spectrum determined. The starting material has $\lambda_{max}$ 263 m$\mu$ at *p*H 1,[11] whereas the hypoxanthine nucleoside




XXI VIII R = Cl XI R = $NH_2$ XXII

(XXI) should have $\lambda_{max}$ about 247 m$\mu$, about the same as inosine. The observed results were quite unexpectedly different. A new peak rapidly appeared at 307 m$\mu$ and there were slower changes in the 260 m$\mu$ region. This spectrum could best be explained by a cleavage of the imidazole ring of the 6-chloropurine nucleoside (VIII) with formation of 4,5-diamino-6-chloropyrimidine-N$^5$-rhamnoside (XXII) since 4,5-diamino-6-chloropyrimidine[27] was found to have $\lambda_{max}$ 268 m$\mu$ ($a_M$ 7380) and 305 m$\mu$ ($a_M$ 10,100).[28]

A similar rupture of the imidazole ring of 9-$\beta$-D-ribofuranosylpurine with 0.1*N* base had been observed by Brown and Gordon.[29] These workers concurred with our interpretation of the base cleavage and informed us[29a] that they had observed earlier the same base cleavage with 6-chloro-9-$\beta$-D-ribofuranosylpurine.

The 6-amino group of adenosine and 2-chloroadenosine has been replaced by hydroxyl by use of nitrous acid.[30-33] When adenine-free 9-$\alpha$-L-rhamnopyranosyladenine (XI) was treated with sodium nitrite and dilute acetic acid,[33] the resultant 9-$\alpha$-L-rhamnopyranosylhypoxanthine (XXI), isolated *via* its lead salt, was obtained as an amorphous solid in 71% yield; this material was chromatographically pure, traveling as a single spot ($R_{Ad}$ 0.39)[34] on paper.

(25) We wish to thank Dr. J. J. Fox of the Sloan-Kettering Institute for allowing us to use this procedure prior to publication.

(26) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(27) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).

(28) Private communication from Dr. J. A. Montgomery, Southern Research Institute.

(29) (a) Private communication from Drs. G. B. Brown and M. P. Gordon, Sloan-Kettering Institute; (b) G. B. Brown, Ciba Foundation Symposium on "Chemistry and Biology of Purines," in London, England, May, 1956.

(30) P. A. Levene and W. A. Jacobs, *Ber.*, **43**, 3150 (1910).

(31) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **111**, 313 (1935).

(32) J. M. Gulland and E. R. Holiday, *J. Chem. Soc.*, 765 (1936).

(33) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 1685 (1948).

(34) Paper chromatograms were run with water-saturated butanol by the descending procedure on 7″ × 17″ strips of Whatman No. 1 paper with spots 1″ apart. The spots were located by visual examination with an ultraviolet lamp. Adenine was used as a control spot in all cases and was arbitrarily assigned $R_{Ad}$ 1.00. The distances moved by other spots were assigned $R_{Ad}$ values with reference to adenine. Melting points were determined in capillary tubes in a stirred oil-bath and are uncorrected.

*9-α-L-Rhamnopyranosylpurine.* Brown and Weliky[12] have described the conversion of 6-chloro-9-β-D-ribofuranosylpurine to 9-β-D-ribofuranosyl-purine by hydrogenolysis with a palladium-charcoal catalyst in the presence of magnesium oxide as the acid acceptor. These conditions have now been applied to 6-chloro-9-α-L-rhamnopyranosylpurine (VIII). Hydrogenation proceeded smoothly. However, the product was soluble in alcohol and insoluble in acetone, the same as the by-product, magnesium chloride. Separation of the purine rhamnoside from magnesium chloride was effected smoothly by Celite partition chromatography[8] in a short column using water as the stationary phase and butanol as the mobile phase. The purine rhamnopyranoside was obtained as a glass in 83% yield from the chloropurine nucleoside (VII). Examination of this product with the aid of paper chromatography showed that there was no contamination with any other materials in the ultraviolet absorbing such as purines. A single spot with $R_{Ad}$ 0.89 was obtained.[34] The starting material (VIII) had $R_{Ad}$ 1.46 in the same solvent system.

*Biological activity.* None of these nucleosides had any effect on Adenocarcinoma 755 at 200 mg. per kg. (mouse) per day.[17]

## EXPERIMENTAL[34,35]

*9-α-L-Rhamnopyranosyladenine* (XI). *A.* To 2.00 g. of the blocked nucleoside (VII), obtained by condensing chloromercuri-6-chloropurine (V) with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide[10] as previously described,[11] was added 70 ml. of methanol saturated with ammonia at 5°. The mixture was stirred in a closed flask until solution was complete (about 2–4 hr.). The solution was heated in a steel bomb at 100° for 10 hr. The bomb contents were evaporated to dryness *in vacuo* and the residue partitioned between 25 ml. of water and 25 ml. of chloroform. The separated aqueous phase, washed several more times with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 10 ml. of methanol was added 10 ml. of 10% methanolic picric acid. After 90 min. the picrate was collected on a filter and washed with small amounts of cold methanol; yield, 0.96 g. of yellow solid, which charred and partially melted at 210–225°. This crude picrate contained 5–10% of adenine picrate. The pure picrate was readily prepared from the pure base (described below) with methanolic picric acid and melted at 214–216° (dec.). This picrate showed broad OH–NH at 3400 cm.$^{-1}$ and C=NH$^+$ at 1710 cm.$^{-1}$ in the infrared (KBr); $[\alpha]_D^{26}$ −32° (0.66% in 50% $H_2O$-dimethyl formamide).

*Anal.* Calcd. for $C_{17}H_{18}N_8O_{11}$: C, 40.0; H, 3.57; N, 21.9. Found: C, 39.7; H, 3.67; N, 21.2.

The 0.96 g. of crude picrate was dissolved in 200 ml. of hot water with magnetic stirring. The solution was treated with portions of Dowex 1 (Cl) until the solution was colorless. Evaporation of the aqueous solution to dryness *in vacuo* left 0.61 g. of a gum. The gum was triturated with 5 ml. of absolute alcohol when the product crystallized. The mixture was allowed to stand overnight at room temperature. The product was collected and washed with absolute alcohol; yield, 414 mg. of XI hydrochloride (44% based on 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide), m.p. 170–171° dec.). The combined filtrate and washings were evaporated to dryness *in vacuo*. A solution of the residue in 1 ml. of absolute alcohol was treated with 0.1 ml. of 5% hydrogen chloride in methanol. An additional 15 mg. (total 47%) of product, m.p. 160–165° (dec.) was obtained. Two recrystallizations of 58 mg. of the first crop by solution in about 0.1 ml. of water, addition of about 5 ml. of acetone, then about 0.5 ml. of absolute alcohol afforded beautiful white crystals, m.p. 169–170° (dec.); $\nu_{max}^{KBr}$ 3000–3400 cm.$^{-1}$ (broad OH–NH), 1675 cm.$^{-1}$ (C=NH$^+$), 1605, 1500 cm.$^{-1}$ (C=N and C=C), 1120, 1015 cm.$^{-1}$ (OH and C—O—C).

*Anal.* Calcd. for $C_{11}H_{15}N_5O_4$·HCl: C, 41.6; H, 5.09; N, 22.1. Found: C, 42.0; H, 5.40; N, 21.8.

This compound traveled on paper as a single spot with water-saturated butanol ($R_{Ad}$ 0.56) and with butanol-water-acetic acid (4:5:1) ($R_{Ad}$ 0.72).[34]

*B.* To a stirred mixture of 3.94 g. of chloromercuri-6-benzamidopurine (IX), 3.82 g. of Celite,[37] and 170 ml. of xylene previously dried by distillation was added a warm solution of 4.12 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) in 50 ml. of xylene. After being refluxed and stirred for 2 hr., the reaction mixture was processed as in Part A; yield, 5.82 g. (109%) of crude blocked nucleoside (X).

A mixture of 5.82 g. of crude blocked nucleoside (X), 50 ml. of methanol, and 5 ml. of 1*N* methanolic sodium methoxide was refluxed for 30 min., solution taking place at the boiling point. At the end of the reflux period, the solution still had the necessary *p*H 9 when spotted on moist indicator paper.[8] After being neutralized with 0.25 ml. of acetic acid, the solution was evaporated to dryness *in vacuo*. The residue was partitioned between about 20 ml. each of chloroform and water. The separated aqueous layer, washed once more with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 15 ml. of methanol was added 30 ml. of 10% methanolic picric acid. After 90 min. in an ice-bath, the mixture was filtered. The picrate was washed with 10 ml. of methanol, then two 15-ml. portions of water to remove sodium picrate.

The moist picrate was dissolved in about 200 ml. of warm water and treated with Dowex 1 ($CO_3$) until the solution was colorless (about 15 g. of wet resin required). The filtered solution was evaporated to dryness *in vacuo*. The residue was heated in a mixture of 1 ml. of water and 15 ml. of absolute alcohol. The gum dissolved and crystals began to separate from the hot solution. The mixture was allowed to stand at room temperature overnight. The crystals were collected and washed with absolute alcohol; yield, 918 mg. (43% based on VI), m.p. 209–210°. Since a second crop could not be isolated from the solution, the solution was treated with a little methanol containing excess hydrogen chloride. The solution was concentrated to about 1 ml. under an air stream, then diluted with about 5 ml. of acetone. The hydrochloride salt was collected and washed with acetone; yield, 150 mg. (7%).

A sample of the 918 mg. was dissolved in hot absolute alcohol by addition of sufficient water to cause solution. The cooled solution deposited white crystals, m.p. 210–211°; $\lambda_{max}^{pH\ 1}$ 257 mμ ($a_M$ 13,800), $\lambda_{max}^{pH\ 7.14}$ 259 mμ ($a_M$ 13,800); $\nu_{max}^{KBr}$ 3460, 3360, 3200 cm.$^{-1}$ (OH, NH), 1635 cm.$^{-1}$ ($NH_2$ of $NH_2$—C=N), 1597, 1575 cm.$^{-1}$ (C=N and C=C), 1115, 1083, 1075, 1055 cm.$^{-1}$ (OH and C—O—C); $[\alpha]_D^{26}$ −54° (0.44% in $H_2O$); $R_{Ad}$ 0.56. The analysis and $a_M$ values showed that the compound was slightly hydrated.

*Anal.* Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.9; H, 5.41; N, 24.9. Found: C, 46.1; H, 5.44; N, 24.5.

Paper chromatography with water-saturated butanol

(35) The ultraviolet spectra were determined with a Beckman Model DK-2 spectrophotometer, the infrared spectra with a Perkin-Elmer Model 21 spectrophotometer, and optical rotations with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[36]

(36) A. S. Keston, Abstracts, 125th Meeting, AMERICAN CHEMICAL SOCIETY, 18C (1955).

(37) Johns-Manville Co.

showed that a sample of the 918 mg. was homogeneous ($R_{Ad}$ 0.54).[34] The 150 mg. of hydrochloride contained a trace of adenine.

*Chloromercuri-2,6-diacetamidopurine* (XV). 2,6-Diaminopurine was acetylated with boiling acetic anhydride with stirring as described by Davoll and Lowy.[13] The acetic anhydride deposited white crystals which were mainly 2,6-diacetamido-9(or 7)-acetylpurine, m.p. 243–245° (dec.). Examination of the infrared spectrum of this material showed that the characteristic broad acidic NH absorption of a purine at 2400–3000 cm.$^{-1}$ was missing. In addition, an "active" 9(or 7)-acetyl C=O band[20] was present at 1745 cm.$^{-1}$.

Recrystallization of the solid from water caused loss of the 9(or 7)-acetyl group with formation of 2,6-diacetamidopurine in 59% yield, m.p. 285–289° (dec.); $\nu_{max}^{KBr}$ 3190 cm.$^{-1}$ (amide NH), 2400–3000 cm.$^{-1}$ (broad acidic NH), 1700, 1660 cm.$^{-1}$ (amid C=O), 1625, 1568 cm.$^{-1}$ (C=C and C=N), 1500 cm.$^{-1}$ (amide NH), 1370 cm.$^{-1}$ (C—Me).

The aqueous mother liquor from the recrystallization was evaporated to dryness *in vacuo*. Reacetylation and recrystallization from water, as above, gave additional 2,6-diacetamidopurine; total yield, 77%.

Davoll and Lowy[13] record a melting point of 305° (dec.) for the recrystallized product and a melting point of 295–300° (dec.) for the crude product obtained in 83% yield.

To a solution of 5.45 g. of mercuric chloride in 80 ml. of 50% alcohol was added 4.72 g. of recrystallized 2,6-diacetamidopurine. Then 8.04 ml. of 10% sodium hydroxide was added dropwise with stirring to the mixture over a period of 30 min. The mixture was diluted with an equal volume of water, then chilled at 0° for 30 min. After the addition of 10.00 g. of Celite (analytical grade)[37] the mixture was well slurried, then filtered. The product was washed with water, alcohol, and ether, then dried; yield 19.4 g. or 9.4 g. (100%) of XV corrected for Celite.[37]

With larger batches, it is expedient to add the Celite before the base in order to obtain homogeneity.

*2,6-Diacetamido-9-(2′,3′,4′-tri-O-benzoyl-α-L-rhamnopyranosyl)purine* (XVI). A mixture of 2.00 g. of chloromercuri-2,6-diacetamidopurine (XV) and 2.14 g. of Celite suspended in 100 ml. of xylene was distilled with stirring until no more water was removed from the mixture (30 ml. of distillate). After the addition of a warm solution of 2.06 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) in 40 ml. of xylene, the mixture was refluxed for 2 hr. protected from moisture. The mixture was filtered hot and the filtrate evaporated to dryness *in vacuo*. The filter cake was washed with two 50-ml. portions of hot chloroform. The xylene residue was dissolved in the combined chloroform washings. Washed with 30% potassium iodide solution and water, the chloroform solution was dried with magnesium sulfate. The drying agent was washed with several portions of boiling chloroform. The combined filtrate and chloroform washings were evaporated to about 20 ml. *in vacuo*. After standing overnight, the mixture was filtered and the white crystals washed with small amounts of cold chloroform; yield, 0.854 g. (32%), m.p. 239–242°. Recrystallization of a similar preparation (from a pilot run, m.p. 239–242°) from absolute alcohol gave white crystals, m.p. 204°, with shrinking at about 170°, resolidification and remelting at 224°; $\nu_{max}^{KBr}$ 3170 cm.$^{-1}$ (NH), 1730 cm.$^{-1}$ (benzoate C=O), 1640, 1630 cm.$^{-1}$ (amide C=O), 1605 (purine and phenyl) 1500 cm.$^{-1}$ (phenyl), 1515 cm.$^{-1}$ (NH of amide), 1265, 1110 cm.$^{-1}$ (C—O—C of benzoate), 1100, 1075, 1030 cm.$^{-1}$ (C—O—C of sugar), and 710 cm.$^{-1}$ (monosubstituted phenyl); $[\alpha]_D^{26}$ +33° (1% in $CHCl_3$). Apparently isomorphic crystals are obtained from chloroform or alcohol.

*Anal.* Calcd. for $C_{36}H_{32}N_6O_9$: C, 62.4; H, 4.66; N, 12.1. Found: C, 62.4; H, 4.61; N, 12.3.

*2,6-Diamino-9-α-L-rhamnopyranosylpurine* (X) *picrate*. A mixture of 770 mg. of crystalline 2,6-diacetamido-9-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl)purine (XI), 15 ml. of reagent methanol, and 1.36 ml. of 1*N* methanolic sodium methoxide was refluxed for 2 hr., solution taking place at the boiling point. The solution was neutralized with acetic acid, then evaporated to dryness *in vacuo*. The residue was partitioned between 10 ml. of water and 10 ml. of chloroform. The separated aqueous layer, washed again with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 10 ml. of hot water was added 5 ml. of 10% methanolic picric acid. The picrate separated immediately. After several hours at 3°, the mixture was filtered and the picrate washed with several small portions of water; yield, 572 mg. (95%). The compound gradually decomposed from 215–230° without melting.

A similar preparation was recrystallized from water giving yellow leaflets which decomposed at 223–234° without melting.

*Anal.* Calcd for $C_{17}H_{19}N_9O_{11}$: C, 38.2; H, 3.59; N, 23.6. Found: C, 38.4; H, 3.85; N, 23.2.

This compound showed bands in the infrared at 3200–3500 cm.$^{-1}$ (broad OH and NH); 1683 cm.$^{-1}$ (C=NH$^+$); 1640 cm.$^{-1}$ (NH); 1610 cm.$^{-1}$ (C=N); 1555, 1315 cm.$^{-1}$ ($NO_2$); 1085, 1060, 1030 cm.$^{-1}$ (OH and C—O—C).

*2,6-Diamino-9-α-L-rhamnopyranosylpurine* (XX). Regeneration of the nucleoside from 572 mg. of XX picrate with Dowex 1 ($CO_3$), as described for the adenine rhamnoside (XI), afforded 252 mg. of a glass on evaporation of the aqueous solution. This glass was dissolved in 0.5 ml. of water, diluted with 2 ml. of acetone, filtered from a trace of insolubles, then diluted with 2 ml. more of acetone and seeded. After standing overnight, the mixture was filtered and the crystals washed with 80% acetone; yield, 127 mg. of solvated crystals which partially melted at 120–160° and completely melted at 198°. Evaporation of the combined mother liquor and washings to dryness *in vacuo* and trituration of the residue with acetone gave an additional 105 mg. of solvated crystals with the same m.p.; total yield, 232 mg. (74%). Both fractions had identical infrared spectra and each traveled on paper as a single blue-fluorescing spot with $R_{Ad}$ 0.23[34] in a water-saturated butanol system. A sample was recrystallized from water-acetone to give beautiful, colorless crystals melting 90–100°. After being dried in high vacuum at 80° for several hours, then at 110° for 3 hr., the crystals melted at 198° (dec.) with gas evolution starting at 140°. This material contained acetone of crystallization as shown by the acetone C=O at 1698 cm.$^{-1}$ in the infrared and by combustion analyses. The compound also had NH (of $NH_2$—C=N) absorption at 1630 cm.$^{-1}$, C=C and C=N at 1595 and 1475 cm.$^{-1}$, C—OH and C—O—C at 1115 and 1050 cm.$^{-1}$, and broad OH—NH absorption at 3250–3450 cm.$^{-1}$; $[\alpha]_D^{26}$ −75° (0.75% in $H_2O$).

*Anal.* Calcd. for $C_{11}H_{16}N_6O_4 \cdot {}^1/_2C_3H_6O$: C, 46.4; H, 5.83; N, 26.0. Found: C, 45.7; H, 5.78; N, 25.7.

*2-Acetamido-6-amino-9-α-L-rhamnopyranosylpurine* (XVII). *A*. A solution of 516 mg. of blocked nucleoside (XVI) in 5 ml. of hot methyl Cellosolve[38] was quickly cooled in an ice-bath, then treated with 10 ml. of methanol saturated with ammonia at 0°. After standing at 3° for 16 hr. in a stoppered flask, the solution was evaporated to dryness *in vacuo*. The residue was partitioned between 20 ml. each of water and chloroform. The aqueous solution, washed once more with chloroform, was evaporated to dryness *in vacuo* leaving 273 mg (94%) of crystalline product. This compound traveled on paper as a single spot which was purple under ultraviolet light and which had $R_{Ad}$ 0.57.[34]

Recrystallization from water afforded white crystals of a hydrate, m.p. 155–160°; $\nu_{max}^{KBr}$ 3150–3400 cm.$^{-1}$ (broad OH—NH), 1650 cm.$^{-1}$ (inflection, amide C=O), 1635 cm.$^{-1}$ ($NH_2$ of $NH_2$—C=N), 1595 cm.$^{-1}$ (C=C and C=N), 1055, 1112 cm.$^{-1}$ (C—O—); $[\alpha]_D^{26}$ −86° (0.94% in $H_2O$).

(38) Trademark for ethyleneglycol monomethyl ether.

*Anal.* Calcd. for $C_{13}H_{18}N_6O_5 \cdot H_2O$: C, 43.8; H, 5.68; N, 23.6. Found: C, 43.4; H, 5.83; N, 23.0.

*B.* A solution of 510 mg. of XVI in 14 ml. of methanol and 2 ml. of *n*-butylamine was refluxed for 6 hr., then evaporated to dryness *in vacuo* and worked up as in *A*. The water residue was recrystallized from 1 ml. of water by addition of 8 ml. of acetone; yield, 139 mg. (55%) of crystalline product, m.p. 158–160°. This compound has the same infrared spectrum and same $R_{Ad}$ as the product in Part A. The mother liquor was evaporated to dryness *in vacuo*. The glassy residue had an infrared spectrum essentially the same as XX. Examination of this residue by paper chromatography showed that it was mainly XX, but was contaminated with XVII.

*1-α-L-Rhamnopyranosylthymine* (XVIII). Condensation of 1.50 g. of dithyminyl mercury[9] with 3.23 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI), as described for the preparation of XVI, produced 3.63 g. (104%) of crude 1-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl)thymine which could not be crystallized; $\nu_{max}^{KBr}$ 3240 cm.$^{-1}$ (NH), 1730 cm.$^{-1}$ (C=O of benzoate), 1688 cm.$^{-1}$ (non-conj. C=O of ring), 1600, 1490 cm.$^{-1}$ (phenyl). A nitrogen analysis indicated a maximum purity of 54%.

A mixture of 3.60 g of crude 1-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl)thymine, 32 ml. of reagent methanol, and 6 ml. of 1*N* methanolic sodium methoxide was refluxed for 1 hr. The amber solution, acidified with 0.2 ml. of acetic acid, was evaporated to dryness *in vacuo*. The residue was partitioned between water and ether. The aqueous layer was acidified with 3.0 ml. of 1*N* sulfuric acid, then evaporated to dryness *in vacuo*. The residue was triturated with absolute alcohol and filtered. The insoluble solids (344 mg.) were mainly inorganic, and ultraviolet inspection showed the absence of nucleosides. The alcohol filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in acetone and filtered from some insoluble solid (205 mg.). The latter contained little nucleoside as determined by ultraviolet inspection. Evaporation of the acetone solution to dryness *in vacuo* gave 980 mg. (59%) of a glass which had a maximum purity of 85% by ultraviolet analysis. This crude material contained the essential bands in the infrared expected for the nucleoside XVIII.

A mixture of 90 g. of Celite 545[37] and 45 ml. of water saturated with butanol was packed in a 3.1 × 37 cm. column in the usual fashion.[11] A solution of 360 mg. of the above crude 1-α-L-rhamnopyranosylthymine in 1.0 ml. of water saturated with butanol was mixed with 2.0 g. of Celite 545[37] and packed on the column. The column was eluted with butanol saturated with water and 4 ml. fractions were collected. Pigmented material was eluted from 0–80 ml. The major fraction was eluted from 84 ml. to 160 ml. (1 h.b.v.) with a peak at 115 ml. The elutions were followed by ultraviolet inspection of the fractions at 258 mμ.[39] The eluates from 84 ml. to 148 ml. were combined and evaporated to dryness *in vacuo*. A solution of the residue in water was washed several times with chloroform. Evaporation of the aqueous solution to dryness *in vacuo* gave 309 mg. (86% recovery) of a colorless glass. The overall yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (I) was 53%. This compound was chromatographically pure and had $R_{Ad}$ 1.03.[34] The compound had $\lambda_{max}^{H_2O}$ 265 mμ ($a_M$ 9930) and $\nu_{max}^{KBr}$ 3400 cm.$^{-1}$ (broad OH—NH), 1680 cm.$^{-1}$ (non-conj. C=O of ring), 1655 cm.$^{-1}$ (conj. C=O of ring) (inflection), 1090, 1050 (C—O—); $[\alpha]_D^{26}$ −40° (0.82% in $H_2O$). For analysis and ultraviolet spectrum a sample was dried at 80° in high vacuum for several hours.

*Anal.* Calcd. for $C_{11}H_{16}N_2O_6 \cdot {}^1/_2H_2O$: C, 47.0; H, 6.10; N, 9.62. Found: C, 47.1; H, 5.97; N, 9.80.

*1-α-L-Rhamnopyranosylcytosine* (XIX). Condensation of 1.05 g. (3 mmoles) of mercuri-*N*-acetylcytosine[25] with 3.23 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) (6 mmoles) followed by deacylation of the blocked nucleoside with methanolic sodium methoxide (2.8 mmoles) as described for 1-α-L-rhamnopyranosylthymine (XVIII) gave a water-soluble nucleoside fraction. The water solution was evaporated to dryness *in vacuo*. The residue was triturated with absolute alcohol, filtered from sodium sulfate, then evaporated to dryness *in vacuo* leaving 535 mg. of crude nucleoside as a gum.

A 320-mg. sample of this material was purified in a column (3.1 × 35 cm.) made from 90 g. of Celite 545 as described for XVIII. Fractions of 3 ml. size were collected with an automatic volumetric fractionator.[39] The main fraction was eluted between fractions 104 and 150.

The fractions surrounding numbers 106 and 147 were examined by paper chromatography to determine which fractions free of slower and faster moving impurities should be combined for processing. Fractions 106–147 were combined and evaporated to dryness *in vacuo*. The residue was dissolved in water and washed several times with chloroform. Evaporation of the water solution to dryness *in vacuo* left a residue which was evaporated several times *in vacuo* with absolute alcohol to remove water. The nucleoside was chromatographically pure ($R_{Ad}$ 0.39),[34] although analysis showed 13.5% alcohol was present that could not be removed from the glassy product by drying in high vacuum; yield, 105 mg. (21% based on mercuri-*N*-acetylcytosine and corrected for alcohol). The nucleoside had $\lambda_{max}^{pH\ 1}$ 275 mμ ($a_M$ 11,500); $\lambda_{max}^{pH\ 14}$ 268 mμ ($a_M$ 7,900); $\nu_{max}^{KBr}$ 3350 cm.$^{-1}$ (broad OH—NH), 1660 cm.$^{-1}$ (C=O), 1637 cm.$^{-1}$ ($NH_2$ of $NH_2$—C=N), 1600, 1520, 1490 cm.$^{-1}$ (C=C and C=N), 1042, 1085, 1110 (C—O—).

*Anal.* Calcd. for $C_{10}H_{15}N_3O_5$ (+ 13.5% EtOH): C, 47.3; H, 6.85; N, 14.1. Found: C, 46.8; H, 6.63; N, 13.9.

The compound could be further freed of solvent by solution in alcohol and precipitation with ether. After drying at 135° in high vacuum, the product still contained solvent.

*Anal.* Calcd. for $C_{10}H_{15}N_3O_5$: C, 46.7; H, 5.88; N, 16.3. Found: C, 45.7; H, 6.16; N, 15.2.

Treatment of a sample of XIX with sodium nitrite in dilute acetic acid as described for preparation of deoxyuridine[40] caused deamination to 1-α-L-rhamnopyranosyluracil. Examination by paper chromatography showed the presence of only one spot ($R_{Ad}$ 0.77),[34] XIX no longer being present.

*9-α-L-Rhamnopyranosylhypoxanthine* (XXI). To a solution of 300 mg. of 9-α-L-rhamnopyranosyladenine (XI) hydrochloride (adenine free) in 15 ml. of water was added 457 mg. of sodium nitrite. When solution was complete 0.54 ml. of acetic acid was added. After standing for 7 hr., the solution was treated with 270 mg. of sodium nitrite and 0.33 ml. of acetic acid. The solution was allowed to stand an additional 17 hr., then it was evaporated to dryness *in vacuo* (bath 35°). To a solution of the residue in 10 ml. of water was added 0.9 g. of lead acetate. The solution was then treated dropwise with concentrated ammonium hydroxide until no more lead salt precipitated. After several hours the solid was collected on a filter and washed with water. A solution of the lead salt in 15 ml. of 4.5% acetic acid was treated with excess hydrogen sulfide, then allowed to stand for 30 min. The filtered solution was evaporated to dryness *in vacuo*. A solution of the residue in about 10 ml. of water was clarified by filtration through Celite,[37] then evaporated to dryness *in vacuo* leaving 252 mg. of residue. Trituration with acetone gave 220 mg. (83%) of amorphous solid, m.p. 148–153° (dec.). The compound had $\lambda_{max}^{pH\ 1}$ 249 mμ, $\lambda_{max}^{H_2O}$ 249 mμ, $\lambda_{max}^{pH\ 14}$ 254 mμ; $\nu_{max}^{KBr}$ 3380 cm.$^{-1}$ (OH), 1680 cm.$^{-1}$ (conj. C=O of keto form of purine), 1655, 1635, 1590, 1545, 1510 cm.$^{-1}$ (typical complex C=C, C=N of a 6-hydroxypurine), 1080, 1057, 1025 cm.$^{-1}$ (OH and

(39) An automatic volumetric fraction collector with attached ultraviolet absorption meter, purchased from Gilson Medical Electronics, Madison, Wis., was employed.

(40) R. E. Beltz and D. W. Visser, *J. Am. Chem. Soc.* **77**, 736 (1955).

C—O—C); $[\alpha]_D^{25}$ −70° (0.54% in $H_2O$). This material was slightly solvated.

*Anal.* Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.8; H, 5.00; N, 19.9. Found: C, 46.2; H, 5.26; N, 19.3.

Examination by paper chromatography showed that this material traveled as a single spot with $R_{Ad}$ 0.39.[34] There was no spot corresponding to starting material XI, thus demonstrating the efficiency of deamination and lead salt purification.

Attempts to prepare this compound by hydrolysis of 6-chloro-9-α-L-rhamnopyranosylpurine (VIII) with 0.1*N* sodium hydroxide at room temperature or with boiling water containing suspended silver carbonate resulted in rupture of the imidazole ring (cf. Discussion).

*9-α-L-Rhamnopyranosylpurine.* A solution of 400 mg. of crystalline 6-chloro-9-α-L-rhamnopyranosylpurine[11] in 10 ml. of water was stirred with 40 mg. of decolorizing carbon for 15 min., then filtered. To the combined filtrate and washings (20 ml.) were added 56 mg. of magnesium oxide and 136 mg. of 5% palladium-charcoal. The mixture was magnetically stirred with hydrogen at 1 atm. Hydrogen absorption ceased in 28 min. when 0.93 mole-equivalents of gas had been absorbed. The filtered solution was evaporated to dryness *in vacuo*.

A thoroughly mixed preparation of 3.5 ml. of butanol-saturated water and 7 g. of Celite 545[37] was packed in a 1.2 × 15 cm. column.[11] The hydrogenation residue was dissolved in 0.4 ml. of water, mixed with 0.8 g. of Celite 545, and packed on the top of column. Water-saturated butanol was passed through the column until ultraviolet inspection showed no more product was eluted. The product appeared between 10 and 35 ml. The 25 ml. of nucleoside containing eluate was evaporated to dryness *in vacuo*. A solution of the residue in water was washed twice with chloroform, then clarified by filtration through Celite.[37] The aqueous solution was evaporated to dryness *in vacuo* leaving 293 mg. (83%) of a colorless glass which traveled on paper as a single spot ($R_{Ad}$ 0.93, blue-purple in u.v.)[34] and had $\lambda_{max}^{H_2O}$ 261 mμ ($a_M$ 7500) and $\nu_{max}^{KBr}$ 3400 cm.$^{-1}$ (OH), 1600, 1585 cm.$^{-1}$ (C=C and C=N), 1110, 1085, 1060 (C—O—). For analysis and ultraviolet a sample was dried at 80° in high vacuum; the product still contained some water and had $[\alpha]_D^{26}$ −68° (0.39% in $H_2O$).

*Anal.* Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.6; H, 5.30; N, 21.1. Found: C, 49.1; H, 5.15; N, 22.4.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

# Synthesis of Potential Anticancer Agents. VIII.[2] Nucleosides Derived from L-Rhamnofuranose

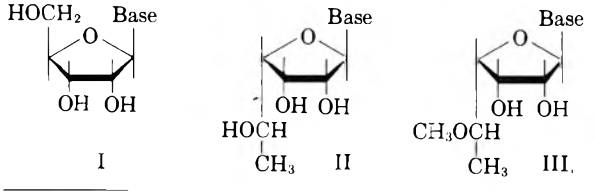
B. R. BAKER* AND KATHLEEN HEWSON

*Received February 11, 1957*

A four-step synthesis of 1,2,3,5-tetra-*O*-benzoyl-L-rhamnofuranose from L-rhamnose has been described. Two new nucleosides derived from L-rhamnofuranose containing adenine or 2,6-diaminopurine, have been synthesized from the tetrabenzoate *via* 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride.

It has been observed that by-product benzoic acid does not interfere with the coupling of a chloromercuri purine with a poly-*O*-benzoyl glycosyl halide. On this basis, a relatively simple synthesis of 9-β-D-xylofuranosyladenine in 47% yield has been found. The latter compound is a valuable nucleoside for further nucleoside transformations.

In the preceding paper of this series[2] the reasons for synthesizing L-rhamnofuranosyl nucleosides were discussed. This paper describes the synthesis of 9-α-L-rhamnofuranosyladenine and 2,6-diamino-9-α-L-rhamnofuranosylpurine (II), potential antagonists of the natural ribofuranosyl nucleosides (I). Since the adenine analog (II) failed to show any anticancer activity against Sarcoma 180 or Adenocarcinoma 755, it is clear that either the configuration at $C_4$ cannot be changed as in II or (less likely) that the extra C-methyl destroys activity.




Only one nucleoside derived from L-rhamnofuranose has been previously described, namely, 7-(5′-*O*-methyl-L-rhamnofuranosyl) theophylline (III).[3] The latter was obtained by condensation of 2,3-di-*O*-acetyl-5-*O*-methyl-L-rhamnofuranosyl bromide with silver theophylline followed by deactylation. Although the anomeric configuration was not assigned, the probability is high that an α-nucleoside with $C_1$-$C_2$-*trans*-configuration was obtained.[2,4,5]

(1) Affiliated with Sloan-Kettering Institute.

(2) This work was supported in part by the C. F. Kettering Foundation. For Paper VII of this series, *cf.* B. R. Baker and K. Hewson, *J. Org. Chem.*, 22, 959 (1957).

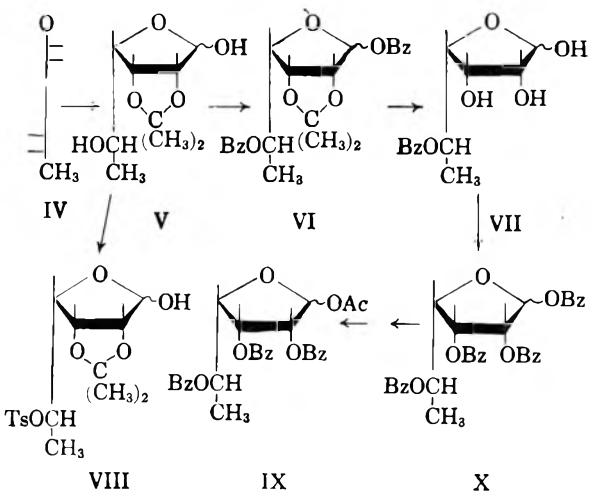
* Present address, Stanford Research Institute, Menlo Park, Calif.

(3) P. A. Levene and J. Compton, *J. Biol. Chem.*, **117**, 37 (1937).

(4) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, 19, 1786 (1954).

(5) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 2396 (1955).

The synthesis of these 9-α-L-rhamnofuranosyl purines required 1-*O*-acetyl(or benzoyl)-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose (IX and X) as a key intermediate. The synthesis started with 2,3-*O*-isopropylidene-L-rhamnofuranose (V) prepared in 73–80% yield by modification of a known procedure.[6] Even though V does not have its 5-hydroxyl group blocked and could be in equilibrium with its pyranose form, Levene and Compton[7] showed that the furanose form was maintained during acylation in pyridine. They observed that tosylation of V with *p*-toluenesulfonyl chloride in pyridine afforded 2,3-*O*-isopropylidene-5-*O*-tosyl-L-rhamnofuranose (VIII) and did not form any appreciable quantity of 2,3-*O*-isopropylidene-4-*O*-tosyl-L-rhamnopyranose. They prepared the latter compound by an alternate unambiguous method and found it to be isomeric with VIII. Thus, benzoylation of 2,3-*O*-isopropylidene-L-rhamnofuranose (V) should lead to 2,3-*O*-isopropylidene-1,5-di-*O*-benzoyl-L-rhamnofuranose (VI). That mainly the furanose (VI) was formed is shown below.




Benzoylation of V in pyridine at about 3° formed the di-*O*-benzoyl derivative (VI) in quantitative yield. Hydrolysis of VI with boiling 70% acetic acid not only removed the *O*-isopropylidene group as expected, but also cleaved most of the 1-benzoate and some of the 5-benzoate to regenerate L-rhamnose. After removal of the dilute acetic acid, the residue was partitioned between 1:1 ethyl acetate–benzene and water, the free L-rhamnose (about 25%) remaining in the aqueous phase. The organic layer was washed with aqueous sodium bicarbonate to remove benzoic acid. Evaporation of the organic phase afforded 5-*O*-benzoyl-L-rhamnofuranose (VII), contaminated with about 20% of innocuous 1,5-di-*O*-benzoyl-L-rhamnofuranose, in 73–78% yield.

At first glance it would appear that the preceding hydrolysis conditions were much too strenuous. However, if less strenuous conditions were used, then unchanged isopropylidene derivative (VI) remained.[8] For example, hydrolysis of VI with 50% acetic acid at the b.p. for 1.5 hr. left 40% of VI still unhydrolyzed. The unchanged isopropylidene derivative (VI) could be removed from the hydrolysis product (VII) by a partition system,[8] but the longer hydrolysis period gave a mixture that is somewhat simpler to separate.

Benzoylation of the 5-*O*-benzoyl-L-rhamnofuranose (VII) with benzoyl chloride in pyridine afforded a 92% yield of tetrabenzoate (X) as a glass suitable for nucleoside synthesis.

Treatment of the tetrabenzoate (X) with hydrogen bromide in acetic acid followed by silver carbonate in aqueous acetone afforded 2,3,5-tri-*O*-benzoyl-L-rhamnofuranose.[9] The latter was reacted with acetic anhydride in pyridine to give 73% 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose (IX) as a sirup suitable for nucleoside synthesis. This material was obtained analytically pure by chromatography on alumina, but the anomers could not be separated and the product was still a glass.

Reaction of the tetrabenzoate (X) with ethereal hydrogen chloride in the usual manner[10] afforded crude 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) contaminated with an equivalent of benzoic acid formed from the 1-benzoate. It has usually been assumed that benzoic acid or acetic acid would be detrimental to a condensation reaction between a poly-*O*-acyl glycosyl halide and a heavy metal salt of a purine since the carboxylic acid, being a stronger acid than a purine, could decompose the purine metal salt and form free purine unavailable for condensation.[10–12] Thus, the acetic acid formed was removed carefully by codistillation with benzene or toluene.[10,11] Since benzoic acid does not codistill appreciably with these solvents, a sugar 1-benzoate was not considered satisfactory for the synthesis of a nucleoside unless the surgar halide was stable enough to water to remove the benzoic acid with aqueous sodium bicarbonate,[12] a procedure which can surely decompose

(6) P. A. Levene and I. E. Muskat, *J. Biol. Chem.*, 106, 761 (1934).

(7) P. A. Levene and J. Compton, *J. Biol. Chem.*, 116, 169 (1936).

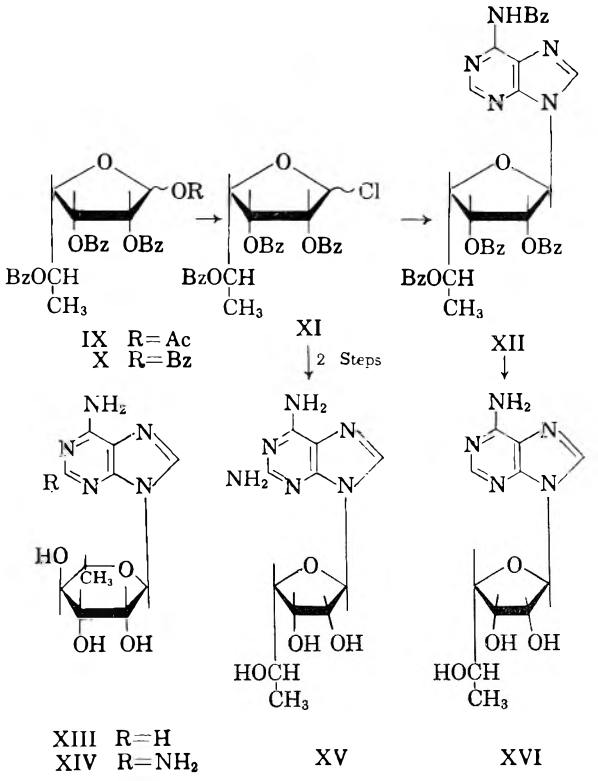
(8) The amount of unchanged VI could be determined readily by distribution of the hydrolysis mixture in the solvent system benzene/hexane/methanol/water:3/7/7/3. The unchanged acetonide (VI) had a distribution coefficient of about 30 in favor of the benzene-hexane layer. The hydrolysis products VII and 1,5-di-*O*-benzoyl-L-rhamnofuranose had distribution coefficients greater than 30 in favor of the methanol-water phase.

(9) H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 75, 2624 (1953), has used this procedure for conversion of α-D-xylofuranose tetrabenzoate to 2,3,5-tri-*O*-benzoyl-D-xylofuranose.

(10) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(11) H. M Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, 77, 18 (1955).

(12) J. J. Fox, N. Jung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, 78, 2117 (1956).




all—or at least part—of the glycosyl halide. This assumption that organic acid cannot be present during a nucleoside coupling reaction has now been proven to be false. Thus, it is no longer necessary to convert a sugar 1-benzoate to the 1-hydroxy or 1-acetate *via* the 1-bromide in order to use a 1-benzoate for nucleoside synthesis.[13]

Condensation of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI), contaminated with the by-product benzoic acid, with chloromercuri-6-benzamidopurine[14] afforded the crude blocked nucleoside (XII). Debenzoylation with methanolic sodium methoxide gave the nucleoside (XVI) isolated *via* its crystalline picrate. Regeneration of the base (XVI) with Dowex 1 ($CO_3$) in the usual manner[2] gave crude XVI free of inorganic material and sugar decomposition products, but contaminated with some pyranosyl nucleoside (XIII)[2] and some adenine.[15] Crystallization from ethanol—methyl ethyl ketone afforded 24% (based on X) of crystalline 9-α-L-rhamnofuranosyladenine (XVI)[17,18] free of adenine and pyranose (XIII)[3] as shown by paper chromatography.[16]

That benzoic acid did not interfere with the nucleoside condensation reaction was shown with another sugar. Thus, 9-β-D-xylofuranosyladenine was prepared in 47% overall yield from α-D-xylofuranose tetrabenzoate[9] *via* the 1-bromide[12] (without removal of the benzoic acid) and chloromercuri-6-benzamidopurine. This yield can be compared with 27% obtained from α-D-xylofuranose tetrabenzoate *via* 2,3,5-tri-*O*-benzoyl-D-xylofuranose[13] and the corresponding chloride where no benzoic acid or acetic acid was present. Since 9-β-D-xylofuranosyladenine is a valuable intermediate for further nucleoside transformations, the 3′,5′-*O*-isopropylidene and the 5′-*O*-trityl derivatives were prepared. Transformations of these blocked nucleosides to possible interesting anticancer agents are currently being investigated.

The fact that the crude 9-α-L-rhamnofuranosyladenine (XVI) was contaminated with some of the corresponding pyranose (XIII) showed that the L-rhamnofuranose tetrabenzoate (X) contained some of the corresponding pyranose tetrabenzoate since ring expansion has not been previously observed to take place during either formation of an *O*-benzoyl glycosyl halide or coupling with a purine. The pyranose tetrabenzoate (X) impurity arose during one or both of two reactions. Benzoylation of 2,3-*O*-isopropylidene-L-rhamnofuranose (V) could give rise to some 1,4-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-rhamnopyranose since the furanose structure of V is not fixed. Secondly, during the acid treatment to remove the isopropylidene group from VI, it is possible for some of the 5-benzoate to have migrated to the 4-hydroxyl group, thus, giving rise to 4-*O*-benzoyl-L-rhamnofuranose.

Condensation of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) (prepared from the tetrabenzoate, X) with chloromercuri-2,6-diacetamidopurine[2] proceeded poorly. After removal of the blocking groups with methanolic sodium methoxide, the crude nucleoside (XV) was isolated as the picrate. Regeneration of the nucleoside from the picrate with Dowex 1 ($CO_3$) and crystallization from water afforded a 4.2% overall yield of pure 2,6-diamino-9-α-L-rhamnofuranosylpurine (XV)[17] which had $R_{Ad}$ 0.38 and was free of the corresponding pyranose (XIV)[2] and 2,6-diaminopurine as shown by paper chromatography.[16]

The synthesis of 2,6-diamino-9-α-L-rhamnofuranosylpurine (XV) from 1-*O*-acetyl-2,3,5-tri-*O*-ben-

(13) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).

(14) J. A. Johnson, Jr., and H. J. Thomas, Southern Research Institute, to be published.

(15) The relative quantities of furanose (XVI), pyranose (XIII), and adenine were readily demonstrated by paper chromatography.[16] The furanose had $R_{Ad}$ 0.79, the pyranose $R_{Ad}$ 0.56, and the adenine $R_{Ad}$ 1.00.

(16) Paper chromatograms were run with water-saturated butanol by the descending procedure on 7 × 17 inch strips of Whatman No. 1 paper with spots 1 inch apart. The spots were located by visual examination with an ultraviolet lamp. Adenine was used as a standard in all cases and was arbitrarily assigned $R_{Ad}$ 1.00. The distances moved by other spots were assigned $R_{Ad}$ values with reference to adenine.

(17) That this nucleoside has a $C_1$-$C_2$-*trans*-configuration, in this case α, is highly probable in view of the rule postulated for the stereochemistry of nucleoside formation.[4,5]

(18) Pure 9-α-L-rhamnofuranosyladenine (XVI) was also prepared in 14% over-all yield from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose *via* 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride and chloromercuri-6-chloropurine.

zoyl-L-rhamnofuranose proceeded in even poorer yield. Finally, the condensation of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) (prepared from either IX or X) with dithyminyl mercury[12] failed completely since after debenzoylation not even 1% yield of 1-α-L-rhamnofuranosylthymine could be detected by paper chromatography.[16] No explanation has been found for these low yields.

## EXPERIMENTAL[16,19]

*2,3-O-Isopropylidene-L-rhamnofuranose* (V). A mixture of 33 g. of L-rhamnose hydrate, 60 g. of anhydrous copper sulfate, 600 ml. of reagent acetone, and 1.2 ml. of 96% sulfuric acid was stirred for 23 hr. in a closed flask. The filtered solution was neutralized with 4.5 ml. of 28% ammonia water, then filtered from ammonium sulfate through a Celite[21] pad. Evaporation of the filtrate to dryness *in vacuo* left a thick colorless sirup which was dissolved in 300 ml. of chloroform. After standing for 2 hr., the chloroform solution was filtered through Celite[21] to remove the last traces of insoluble ammonium sulfate. Evaporation of the chloroform *in vacuo* and distillation of the residue through a short path distillation apparatus afforded 29.5 g. (80%) of product, b.p. 118–120° (0.2 mm.), $\nu_{max}^{film}$ 3400 cm.$^{-1}$ (OH), 1380 cm.$^{-1}$ (C—Me). A similar preparation solidified on standing in a closed tube at 3° for several weeks.

*Anal.* Calcd. for $C_9H_{16}O_5$: C, 52.9; H, 7.84. Found: C, 52.7; H, 7.63.

Other runs afforded 73–80% yields. If the chloroform step was omitted, yields varied from 0–70% and considerable decomposition to a hard polymer sometimes took place during distillation.

Levene and Muskat[6] record b.p. 115° (0.2 mm.) and m.p. 90°, but do not specify the yield.

*1,5-Di-O-benzoyl-2,3-O-isopropylidene-L-rhamnofuranose* (VI). To a stirred solution of 8.6 g. of V in 43 ml. of reagent pyridine cooled in an ice-salt bath was added dropwise 11 ml. of benzoyl chloride at such a rate that the temperature was kept below 12°. After standing in a stoppered flask at 3° for 18 hr., the mixture was diluted with 25 ml. of chloroform and washed with 160 ml. of ice water. The combined chloroform solutions, washed with excess aqueous sodium bicarbonate and dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The residue was dissolved in about 25 ml. of toluene and the evaporation repeated, leaving 20.0 g. (107%) of an amber sirup contaminated with benzoic anhydride. For analysis and infrared, a sample was dried in high vacuum at 80°; $\nu_{max}^{film}$ 1800 cm.$^{-1}$ (C=O of benzoic anhydride), 1735 cm.$^{-1}$ (C=O of benzoate), 1380 cm.$^{-1}$ (C—Me), 1275 cm.$^{-1}$ (C—O—C of benzoate), but only a trace of absorption at 3400 cm.$^{-1}$ (OH). The contaminating benzoic anhydride is removed in the next step.

*Anal.* Calcd. for $C_{23}H_{24}O_7$: C, 67.0; H, 5.83. Found: C, 67.5; H, 5.82.

*5-O-Benzoyl-L-rhamnofuranose* (VII). A solution of 14 g. of VI in 140 ml. of 70% acetic acid was refluxed for 3 hr., then evaporated to dryness *in vacuo*. The residue was partitioned between 75 ml. of 1:1 benzene–ethyl acetate and 50 ml. of water. The aqueous layer, containing about 25% yield of L-rhamnose, was rejected. The organic layer, washed with excess aqueous sodium bicarbonate and dried with magnesium sulfate, was evaporated to dryness *in vacuo;* yield, 6.65 g. (73%) of a glass; $\nu_{max}^{KBr}$ 3400 cm.$^{-1}$ (OH), 1710 cm.$^{-1}$ (C=O), 1265 cm.$^{-1}$ (C—O—C of benzoate). The analysis indicated 18% innocuous contamination with 1,5-di-*O*-benzoyl-L-rhamnofuranose.

*Anal.* Calcd. for $C_{13}H_{16}O_6$: C, 58.3; H, 6.03. Found: C, 59.4; H, 6.19.

In other runs the yields were 73–78%.

*1,2,3,5-Tetra-O-benzoyl-L-rhamnofuranose* (X). To a stirred solution of 6.75 g. of VII in 33 ml. of reagent pyridine cooled in an ice-salt bath was added 11.3 ml. of benzoyl chloride dropwise at such a rate that the temperature was −5 to +5°. After standing overnight at 3° in a closed flask, the mixture was treated with 2 ml. of water, allowed to stand 15 min., then diluted with 33 ml. each of water and chloroform. The separated chloroform layer, washed with excess aqueous sodium bicarbonate and dried with magnesium sulfate, was evaporated to dryness *in vacuo*. The residue was dissolved in about 20 ml. of toluene and the evaporation repeated; weight, 14.2 g. of a glass suitable for further transformations. The yield, corrected for volatile material removable in high vacuum at 80°, was 13.4 g. (92%).

For analysis a 1.4-g. sample was dissolved in ether, filtered, then stirred with excess aqueous sodium bicarbonate for several hours. The ether solution, dried with magnesium sulfate and clarified with Norit, was evaporated to dryness *in vacuo* leaving a clear amber glass. This material was dried in high vacuum at 80° and had $\nu_{max}^{KBr}$ 1735, 1275 cm.$^{-1}$ (benzoate C=O and C—O—C) and no OH at 3400 cm.$^{-1}$.

*Anal.* Calcd. for $C_{34}H_{28}O$ : C, 70.5; H, 4.88. Found: C, 69.7; H, 5.18

*1-O-Acetyl-2,3 5-tri-O-benzoyl-L-rhamnofuranose* (IX). To a solution of 2.30 g. of X in 5 ml. of methylene chloride was added 11.5 ml. of 30% hydrogen bromide in acetic acid. After 30 min. at room temperature, the solution was diluted with 5 ml. of methylene chloride and washed with an equal volume of water. The organic solution, washed thoroughly with excess aqueous sodium bicarbonate (final volume 27 ml.), was added to a mixture of 2.3 g. of silver carbonate, 60 ml. of acetone, and 0.6 ml. of water. After stirring for 30 min., the mixture was treated with Norit and filtered. The combined filtrate and acetone washings were evaporated to dryness *in vacuo* leaving 1.73 g. of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranose as a glass.

A solution of 1.73 g. of the preceding compound in 8.65 ml. of reagent pyridine and 8.65 ml. of acetic anhydride was allowed to stand overnight in a stoppered flask. The solution was diluted with 85 ml. of ice water and extracted 3 times with 10-ml. portions of chloroform. The combined extracts, washed with ice water and excess aqueous sodium bicarbonate, and dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The residue was dissolved in 2 volumes of toluene and the evaporation repeated. A solution of the residue in 10 ml. of ether was filtered through Celite,[21] clarified with Norit, and evaporated to dryness *in vacuo* leaving 1.55 g. (73%) of IX as a glass suitable for further transformations.

*Anal.* Calcd. for $C_{29}H_{26}O_9$: C, 67.2; H, 5.05. Found: C, 66.3; H, 5.53.

For analysis and rotation 1.106 g. was chromatographed with a column containing 60 g. of acid washed alumina.[22] No material was removed from the column with 5:1 or 1:1 hexane-benzene. The material was eluted with benzene, but no separation of the anomers occurred; yield, 0.565 g. of a glass; $\nu_{max}^{KBr}$ 1730 cm.$^{-1}$ (C=O), 1275 cm.$^{-1}$ (benzoate C—O—C), 1210 cm.$^{-1}$ (acetate C—O—C), 700 cm.$^{-1}$ (monosubstituted phenyl) and no absorption at 3400 cm.$^{-1}$

(19) The ultraviolet spectra were determined with a Beckman Model DK-2 spectrophotometer, the infrared spectra with a Perkin-Elmer Model 21 spectrophotometer, and optical rotations with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solution.[20] Melting points were determined in capillary tubes in a stirred oil bath and are uncorrected.

(20) A. S. Keston, Abstracts of 125th Meeting, AMERICAN CHEMICAL SOCIETY, 18C (1955).

(21) An analytical grade product of the Johns-Manville Corp.

(22) Merck and Co., Inc.

(OH); $[\alpha]_D^{27}$ +61° (0.5% in $CHCl_3$). The last traces of benzene could not be removed completely by drying at 80° in high vacuum since extended heating caused the compound to darken.

*Anal.* Calcd. for $C_{29}H_{26}O_9$: C, 67.2; H, 5.05. Found: C, 66.7; H, 5.54.

*6-Benzamido-9-(2′,3′,5′-tri-O-benzoyl-α-L-rhamnofuranosyl)purine* (XII). To a solution of 3.66 g. of crude tetrabenzoate (X) (containing 7% volatile material) in 3.7 ml. of acetyl chloride was added 100 ml. of reagent ether saturated with hydrogen chloride at 5°. The solution was kept in a glass sealed bottle at 3° for 6 days, then evaporated *in vacuo* (bath 40°). The residue was twice dissolved in about 10-ml. portions of reagent benzene and evaporated to dryness *in vacuo*. The residual 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) was dissolved in 40 ml. of xylene and added to an azeotropically dried mixture of 3.32 g. of chloromercuri-6-benzamidopurine,[14] 150 ml. of xylene, and 3.1 g. of Celite.[21] After being refluxed and stirred for 2 hr., the hot mixture was filtered through Celite[21] and the filter cake washed twice with chloroform (about 100 ml.). The xylene solution was evaporated to dryness *in vacuo* and the residue was dissolved in the chloroform washes. Washed successively with 100 ml. of 30% aqueous potassium iodide, water, and excess aqueous sodium bicarbonate, the chloroform solution was dried with magnesium sulfate, then evaporated to dryness *in vacuo;* yield, 4.07 g. of crude blocked nucleoside (XII), obtained as a glass.

*9-α-L-Rhamnofuranosyladenine* (XVI). (*A*). A mixture of 4.1 g. of crude 6-chloro-9-(2′,3′,5′-tri-*O*-benzoyl-α-L-rhamnofuranosyl)purine[23] and 75 ml. of methanol saturated with ammonia (at 0°) was stirred in an ice bath until solution was complete (1 hr.), then allowed to stand in a stoppered flask at 3° for about 18 hr. The solution was then heated in a steel bomb at 100° for 10 hr. The filtered solution was evaporated to dryness *in vacuo* and the residue partitioned between 25 ml. of water and 25 ml. of chloroform. The separated aqueous layer, washed twice more with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 20 ml. of methanol was added 10 ml. of 10% methanolic picric acid. After standing for 1 hr. at 3°, the mixture was filtered and the yellow solid washed with small amounts of ice-cold methanol; weight, 667 mg. of XVI picrate.

Regeneration of the nucleoside from the picrate with Dowex 1 ($CO_3$) in the usual manner[2] gave 325 mg. of glassy residue. This residue was shown by paper chromatography[16] to consist mainly of XVI ($R_{Ad}$ 0.79), contaminated with smaller amounts of 9-α-L-rhamnopyranosyladenine (XIII)[2] ($R_{Ad}$ 0.56) and adenine. The crude product was dissolved in 1 ml. of absolute alcohol. After the addition of 2 ml. of methyl ethyl ketone, during which time crystals began to separate, the mixture was kept at 3° overnight. The mixture was then diluted with 20 ml. more of methyl ethyl ketone, filtered, and the white crystals washed with methyl ethyl ketone; yield, 272 mg. (14% based on IX) of white crystals, m.p. 132–135°. This material was pure and free of pyranose (XIII) and adenine as shown by paper chromatography[16] and had $[\alpha]_D^{27}$ −18° (0.3% in $H_2O$). This compound was solvated with methyl ethyl ketone as shown by the presence of ketone C=O at 1705 cm.$^{-1}$ in the infrared (Nujol mull). The solvate band did not show in a KBr disc but other bands in KBr were 3320 cm.$^{-1}$ (OH), 1660 cm.$^{-1}$ ($NH_2$ of $NH_2$—C=N), 1640 cm.$^{-1}$ (NH), 1605 and 1577 cm.$^{-1}$ (C=C and C=N), 1140, 1065, 1045 cm.$^{-1}$ (C—O—).

*Anal.* Calcd. for $C_{11}H_{15}N_5O_4 \cdot {}^3/_4C_4H_8O_4 \cdot {}^1/_2H_2O$: C, 48.8; H, 6.45; N, 20.3. Found: C, 48.8; H, 6.22; N, 20.7.

This compound could also be crystallized from acetone as a white, crystalline acetone solvate, m.p. 50–135°. Again the presence of the solvate was shown by the presence of ketone C=O absorption at 1705 cm.$^{-1}$ in the infrared (Nujol mull). The ultraviolet absorption also showed a mol. wt. increase of 58 with $\lambda_{max}^{H_2O}$ 258 mμ.

*Anal.* Calcd. for $C_{11}H_{15}N_5O_4 \cdot C_3H_6O$: C, 49.7; H, 6.26; N, 20.6. Found: C, 49.5; H, 6.40; N, 20.4.

(*B*) A mixture of 4.07 g. of crude blocked nucleoside (XII), 30 ml. of methanol, and 4.1 ml. of 1*N* methanolic sodium methoxide was refluxed for 30 min.,[24] then neutralized with acetic acid. The solution was filtered through Celite[21] to remove traces of colloidal mercury, then evaporated to dryness *in vacuo*. The residue was partitioned between about 25 ml. each of water and chloroform. The separated aqueous layer, washed once more with chloroform, was evaporated to dryness *in vacuo*. The residue was dissolved in absolute alcohol, filtered from 200 mg. of inorganic material, and the solution evaporated *in vacuo*. To a solution of the residue in 15 ml. of methanol was added 13 ml. of 10% methanolic picric acid. After standing for 1 hr. at 3°, the mixture was filtered and the picrate washed with small amounts of ice-cold methanol, then with water; yield, 1.32 g.

The free nucleoside was regenerated from the picrate with Dowex 1 ($CO_3$) in the usual manner.[2] The aqueous solution was examined by paper chromatography[16] and was found to contain some adenine and some pyranose nucleoside (XIII), but was mainly the desired furanose nucleoside (XVI). The solution was evaporated to dryness *in vacuo*. Crystallization from 3 ml. of absolute alcohol by addition of 6 ml. of methyl ethyl ketone gave 398 mg. (24% based on X) of white crystals, m.p. 130° (gas). This material traveled as a single spot, identical with preparation A, on paper[16] and was free from adenine and pyranose (XIII). The material had an infrared spectrum identical with preparation A.

Evaporation of the mother liquor left 230 mg. of residue which contained adenine, furanose nucleoside (XVI), and pyranose nucleoside (XIII) as shown by paper chromatography.[16] Over half of the material was the desired furanose (XIII) and probably could be purified by Celite partition chromatography.[2]

*6-Benzamido-9-(2′,3′,5′-tri-O-benzoyl-β-D-xylofuranosyl)-purine.* A warm solution of 3.00 g. of α-D-xylofuranose tetrabenzoate[9] in 6 ml. of ethylene dichloride was quickly cooled to 30° and treated with 15 ml. of 30% hydrogen bromide in acetic acid. After standing at room temperature protected from moisture for 30 min., the solution was evaporated to a sirup *in vacuo* (bath 60–70°). The residue was twice dissolved in 9-ml. portions of xylene and the evaporation *in vacuo* repeated. The residual 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide,[12] contaminated with benzoic acid, was dissolved in 30 ml. of xylene and condensed with 2.55 g. of chloromercuri-6-benzamidopurine[14] as described for XII; weight, 3.72 g. of crude product which was unblocked without further purification. This blocked nucleoside can be obtained as white crystals from benzene, m.p. 105–110° (turbid, clearing at 198°); $\nu_{max}^{KBr}$ 3400 cm.$^{-1}$ (NH), 1718 and 1255 cm.$^{-1}$ (benzoate C=O and C—O—C), 1690 cm.$^{-1}$ (shoulder) (amide C=O), 1510 cm.$^{-1}$ (amide NH); $[\alpha]_D^{27}$ +5.2° (0.8% in $CHCl_3$).

*Anal.* Calcd. for $C_{38}H_{29}N_5O_8$: C, 66.8; H, 4.28; N, 10.3. Found: C, 66.6; H, 4.69; N, 10.2.

*9-β-D-Xylofuranosyladenine.* Debenzoylation of 3.72 g. of crude 6-benzamido-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-xylofuranosyl)purine as described for the preparation of XVI gave a highly insoluble picrate which was washed with methanol until no more brown color was removed from the solid, m.p. 208–214° (dec.). Regeneration with Dowex 1 ($CO_3$), by adding portions of resin and picrate to water at 70–80°, afforded 670 mg. (47% based on α-D-xylofuranose tetra-

(23) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Paper VI of this series, *J. Org. Chem.*, **22**, 954 (1957).

(24) If the *p*H is less than 9 when the solution is spotted on moist indicator paper, then additional sodium methoxide should be added and reflux continued until a total of 30 min. reflux time still gives *p*H greater than 9.

benzoate) of product as a colorless glass ($R_{Ad}$ 0.50) contaminated with about 5% of adenine as shown by paper chromatography.[16]

Similarly, condensation of 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl chloride, prepared from 2,3,5-tri-*O*-benzoyl-D-xylofuranose,[13] with chloromercuri-6-benzamidopurine afforded a 27% yield (based on α-D-xylofuranose tetrabenzoate) of 9-β-D-xylofuranosyladenine contaminated with about 5% adenine.

An alternate, less efficient synthesis of this compound, isolated as a glass, has been previously described.[25] The intermediate picrate had m.p. 210° (dec.).

This nucleoside can be crystallized with considerable loss from ethanol and melts over the range 125–140°. This nucleoside was characterized by the following two derivatives.

*9-(3′,5′-O-Isopropylidene-β-D-xylofuranosyl)adenine.* To a stirred mixture of 338 mg. of amorphous 9-β-D-xylofuranosyladenine, 1.67 g. of anhydrous copper sulfate, and 20 ml. of acetone was added dropwise a solution of 1.0 ml. of mixed alkanesulfonic acid[26] in 8.7 ml. of acetone.[27] After being stirred for 1 hr., the mixture was filtered and the filter cake washed with two 9-ml. portions of acetone. The combined filtrate and washings were added to 67 ml. of 5% aqueous sodium carbonate. The mixture was extracted with chloroform (3 × 8 ml.). Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo* leaving 146 mg. of semicrystalline residue. Recrystallization from ethyl acetate afforded 95 mg. (24%) of product in two crops, m.p. 204–207°; $\nu_{max}^{KBr}$ 3360, 3300, 3160 cm.$^{-1}$ (OH and NH), 1645 cm.$^{-1}$ ($NH_2$ of $NH_2C{=}N$), 1600, 1570 cm.$^{-1}$ (C=N and C=C), 1475 cm.$^{-1}$ (C—Me), 1120, 1090, 1080 cm.$^{-1}$ (C—O—C); $[\alpha]_D^{27}$ −71.6° (0.3% in dimethylformamide).

*Anal.* Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.8; H, 5.58; N, 22.8. Found: C, 51.1; H, 5.85; N, 22.9.

It is probable that the yield could be raised considerably by study of the variables since this reaction was run only once.

*9-(5′-O-Trityl-β-D-xylofuranosyl)adenine.* A solution of 500 mg. of amorphous 9-β-D-xylofuranosyladenine in 4 ml. of reagent pyridine was evaporated *in vacuo* to remove traces of water and alcohol. A solution of the residue and 575 mg. of triphenylmethyl chloride in 4 ml. of reagent pyridine was heated in a bath at 50° for 72 hr., the solution being protected from moisture. The cooled solution was diluted with 15 ml. of chloroform, then 30 ml. of water containing excess sodium bicarbonate. Dried with magnesium sulfate, the chloroform solution was evaporated to dryness leaving 1.033 g. of residue. Crystallization of 946 mg. from 10 ml. of benzene gave 697 mg. (80%) of product, m.p. 180–193°. Further trituration with hot benzene gave 310 mg. (36%) of nearly pure material, m.p. 193–196°. Two more recrystallizations from ethyl acetate–hexane afforded white crystals, m.p. 198–199°; $\nu_{max}^{KBr}$ 3350 cm.$^{-1}$ (OH), 3130 cm.$^{-1}$ (NH), 1635 cm.$^{-1}$ ($NH_2$ of $NH_2C{=}N$), 1080, 1070, 1050 cm.$^{-1}$ (C—O—), 700, 750 cm.$^{-1}$ (monosubstituted phenyl); $[\alpha]_D^{27}$ −24.9° (0.3% in $CHCl_3$).

*Anal.* Calcd. for $C_{29}H_{27}N_5O_4$: C, 68.3; H, 5.34; N, 13.8. Found: C, 67.7; H, 5.39; N, 13.6.

This compound is difficult to purify since the crude product is probably contaminated with N$^6$,5′-dityrityl-9-β-D-xylofuranosyladenine.[28]

*2,6-Diamino-9-α-L-rhamnofuranosylpurine* (XV). Condensation of XI (prepared from 12.0 g. of X) with 9.0 g. of chloromercuri-2,6-diacetamidopurine[2] as described for XII gave 10.4 g. of crude blocked nucleoside. Only 25% of the chloromercuri derivative reacted indicating the reaction proceeded poorly. The crude blocked nucleoside was refluxed with 104 ml. of methanol and 15 ml. of 1*N* methanolic sodium methoxide for 2 hr., then the solution was neutralized with acetic acid. The picrate was isolated as described for the corresponding pyranose (XIV).[2] Regeneration of the nucleoside from the picrate with Dowex 1 ($CO_3$)[2] gave an aqueous solution which contained both the pyranose (XIV) ($R_{Ad}$ 0.24) and the furanose ($R_{Ad}$ 0.41) as shown by paper chromatography.[16] The aqueous solution was evaporated to dryness *in vacuo* and the residue crystallized from 1 ml. of water; yield, 149 mg. (4.2%) of white crystals in two crops, m.p. 190–196° (dec.). Paper chromatography[16] showed this material to be pure with $R_{Ad}$ 0.38. No pyranose ($R_{Ad}$ 0.24) was present. Recrystallization from water gave one of two crystal forms, m.p. 190–196° (dec.) or 270–275° (dec.). Both had identical $R_{Ad}$ values. The material with m.p. 270–275° had $\lambda_{max}^{pH\ 7,14}$ 255 mμ ($a_M$ 9,640), 278 mμ ($a_M$ 10,200); $\lambda_{max}^{pH\ 1}$ 252 mμ ($a_M$ 10,900), 290 mμ ($a_M$ 10,300); $\nu_{max}^{KBr}$ 3400, 3320, 3140 cm.$^{-1}$ (OH, NH), 1650 cm.$^{-1}$ ($NH_2$ or $NH_2C{=}N$), 1630 cm.$^{-1}$ (NH), 1585, 1495 cm.$^{-1}$ (C=C and C=N), 1140, 1095, 1040 (C—O—); $[\alpha]_D^{27}$ −80° (0.03% in 0.1*N* HCl).

*Anal.* Calcd. for $C_{11}H_{16}N_6O_4$: C, 44.6; H, 5.44; N, 28.4. Found: C, 44.5; H, 5.33; N, 27.7.

In other runs, starting with IX or X, the yields were 1.4–5.3%. Attempts to synthesize 1-α-L-rhamnofuranosyl nucleosides of thymine or cytosine were completely unsuccessful starting with either IX or X. The reasons for these low yields remain unknown.

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BIRMINGHAM 5, ALA.

(25) P. Chang and B. Lythgoe, *J. Chem. Soc.*, 407 (1950).

(26) A mixture of methane- and ethanesulfonic acid obtained from the Indoil Co.

(27) A similar procedure has been used for synthesis of 2-methylmercapto-6-dimethylamino-9-(3′,5′-*O*-isopropylidene-β-D-xylofuranosyl)purine.[13]

(28) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **121**, 131 (1937), have observed that tritylation of adenosine gives a mixture of 5′-*O*-trityladenosine and N$^6$,5′-dityryladenosine.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE]

# Reactions of Quaternary Salts of Gramine with Diethyl and Triethyl Phosphite[1]

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The reactions of gramine and certain of its quaternary salts with triethyl phosphite, diethyl phosphite, and sodium diethyl phosphite have been investigated. Triethyl phosphite and sodium diethyl phosphite react smoothly with gramine methiodide and gramine methosulfate to yield diethyl 3-indolylmethylphosphonate.

Two general procedures for the preparation of esters of alkylphosphonic acids involve the phosphorus alkylation by alkyl halides of trialkyl phosphites (Equation 1, A = Cl; Br; I) and of the sodium salts of dialkyl phosphites (Equation 2, A = Cl; Br; I). These procedures are perhaps best known as the Michaelis-Arbuzov and the Michaelis, Becker-Nylen syntheses, respectively, and have been well reviewed by Kosolapoff.[2,3]

$$RA \xrightarrow{P(OR')_3} RPO(OR')_2 + R'A \quad (1)$$

$$RA \xrightarrow{NaPO(OR')_2} RPO(OR')_2 + NaA \quad (2)$$

Classes of compounds other than the alkyl halides may be employed as alkylating agents in these syntheses. Included here, as one type, are reagents bearing a displaceable anionic group other than halogen. For example, Myers, Preis, and Jensen[4] have prepared a series of alkylphosphonates by alkylation of triethyl phosphite and sodium diethyl phosphite with alkyl esters of sulfonic acids (Equations (1) and (2), A = $CH_3SO_2O$; *p*-$CH_3C_6H_4$-$SO_2O$).

Ketone Mannich bases and certain of their derivatives have recently been shown to comprise a different class of reagents for alkylation of trivalent phosphorus esters in procedures analogous to (1) and (2).[5] Ketone Mannich base methiodides, for example, react *via* displacement of the nitrogen function to alkylate the phosphorus atom of triethyl phosphite (Equation 3) and of sodium diethyl phosphite (Equation 4) to produce diethyl γ-ketophosphonates.

$$R'COCH_2CH_2\overset{+}{N}R_2Me\bar{I} \xrightarrow{P(OEt)_3} R'COCH_2CH_2PO(OEt)_2 + Et\overset{+}{N}R_2Me\bar{I} \quad (3)$$

$$R'COCH_2CH_2\overset{+}{N}R_2Me\bar{I} \xrightarrow{NaPO(OEt)_2} R'COCH_2CH_2PO(OEt)_2 + MeNR_2 + NaI \quad (4)$$

Reactions of this type, *i.e.*, the phosphorus alkylation of dialkyl and trialkyl phosphites by amines or quaternary ammonium salts, are of potential wide applicability to the synthesis of a variety of phosphonates since in addition to ketone Mannich bases other classes of amines and of quaternary ammonium salts possess alkylating properties[6] and may serve in such reactions as reagents for phosphorus alkylation. Included among these classes are a number of readily obtainable dialkylaminomethyl derivatives of heterocycles of the general type $ACH_2NR_2$ (A = heterocyclic nucleus) and their quaternary ammonium salts. Gramine (3-dimethylaminomethylindole) and its quaternary derivatives, for example, have found extensive use in the carbon alkylation of a number of species including Grignard reagents, active methylene compounds and cyanide. Similar compounds such as the quaternary salts of 2-dimethylaminomethylpyrrole, 2-dimethylaminomethylfuran and of 2-acetamido-4-methyl-5-dimethylaminomethylthiazole have been employed in the carbon alkylation of active methylene compounds.[7]

To determine the applicability of amines and quaternary salts of this general type as reagents for the phosphorus alkylation of dialkyl and trialkyl phosphites in the synthesis of indolylmethylphosphonates and related compounds [procedures analogous to (3) and (4)], the reactions of gramine, its methiodide, and its methosulfate with triethyl phosphite, diethyl phosphite, and sodium diethyl phosphite were investigated.

Gramine methiodide (I, A = I) and gramine methosulfate (I, A = $CH_3OSO_2O$) were found to react when heated with excess triethyl phosphite to

(1) Supported by a grant from the Graduate Research Committee, University of Illinois Professional Colleges.

(2) G. M. Kosolapoff, *Organophosphorous Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 7.

(3) G. M. Kosolapoff, *Org. Reactions*, **VI**, Chap. 6 (1951).

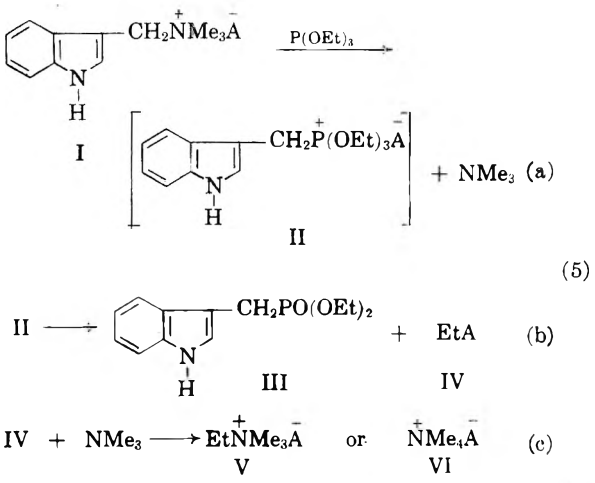
(4) T. C. Myers, S. Preis, and E. V. Jensen, *J. Am. Chem. Soc.*, **76**, 4172 (1954).

(5) T. C. Myers, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 3101 (1955).

(6) For an excellent comprehensive review see J. H. Brewster and E. L. Eliel, *Org. Reactions*, **VII**, Chap. 3 (1953).

(7) See 6 for key references.

give diethyl 3-indolylmethylphosphonate (III) in yields approximating 75%. In analogy to the well-established mechanism operating in reactions between alkyl halides and trialkyl phosphites, these reactions may be postulated to occur as shown in Equation 5.

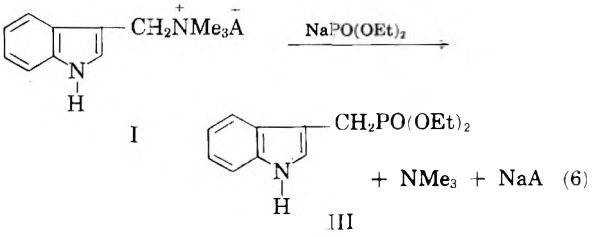



Here is indicated (5,a) the intermediate formation, *via* displacement of trimethylamine, of a quaternary phosphonium salt (II, A = I; $MeOSO_2O$); this salt reacts (5,b) to eliminate a molecule of ethyl iodide (IV, A = I) or of ethyl methyl sulfate (IV, A = $CH_3OSO_2O$) which in turn (5,c) alkylates the trimethyl amine. A 91% yield of trimethylethylammonium iodide (V, A = I) was isolated from the reaction involving gramine methiodide. A mixture of sulfur-containing salts was obtained from the gramine methosulfate reaction from which was isolated in 50% yield a crystalline salt which gave a sulfur analysis corresponding to trimethylethylammonium methosulfate (V, A = $MeOSO_2O$) or to tetramethylammonium ethosulfate (VI, A = $EtOSO_2O$). While our results tend to substantiate the mechanism as written, there is no direct evidence to indicate that the steps occur in the order indicated above and no evidence relating to the type of mechanism operating in the displacement of trimethylamine from the starting quaternary salts.

A crude preparation of gramine methiodide containing bis(3-indolylmethyl)dimethylammonium iodide was found to react smoothly with triethyl phosphite to give III in an over-all yield of 30% based on gramine as compared to a yield of 41% when the pure methiodide was used. Thus the rather laborious procedures for the final purification of the methiodide were of little advantage.

Reactions between gramine methiodide or gramine methosulfate with diethyl hydrogen phosphite under conditions similar to those used with triethyl phosphite produced only high boiling resins from which no diethyl 3-indolylmethylphosphonate could be isolated. Similar results were obtained in a reaction between free gramine and triethyl phosphite.

The reaction in alcohol solution between the sodium salt of diethyl phosphite and the crude preparation of gramine methiodide (I, A = I) just described followed the expected course (Equation 6) to produce diethyl 3-indolylmethylphosphonate (III) in yields from gramine, of 20%. The analogous reaction with gramine methosulfate (I, A = $MeOSO_2O$) produced III in 75% yield (40% based on starting gramine).




Diethyl 3-indolylmethylphosphonate (III) was obtained in each of the above described successful procedures as a crystalline solid of m.p. 61–62°. Its structure was established by elementary analysis and by consideration of its infrared spectrum which showed absorption bands corresponding to the indole nucleus and to the diethylphosphonate grouping.

Attempts to hydrolyze the ester in acid medium were unsuccessful, and resulted in extensive decomposition of the molecule. Hydrolysis by aqueous sodium hydroxide produced the half ester, ethyl hydrogen 3-indolylmethylphosphonate (m.p. 136–137°) in 62% yield.

Diethyl 3-indolylmethylphosphonate and ethyl hydrogen 3-indolylmethylphosphonate are of biological interest as phosphonate analogs of natural metabolites such as tryptophan or heteroauxin (3-indolylmethylacetic acid) which contain the indole nucleus with an acid bearing side chain in the 3-position. They may be of special interest in the latter case since the sulfonic acid analog of heteroauxin (3-indolylmethylsulfonic acid) has been shown to be an inhibitor of heteroauxin.[8] Studies relating to the biological properties of these compounds are in progress.

## EXPERIMENTAL[9]

*Reactants.* Diethyl phosphite and triethyl phosphite, obtained from commercial sources,[10] were redistilled before use.

Gramine was prepared according to the procedure of Snyder, Smith, and Stewart from dimethylamine, formaldehyde, and indole.[11] The preparation of gramine methiodide

(8) T. Wieland, F. Fischer, and F. Moewus, *Ann.*, **561**, 47 (1948).

(9) Analyses were conducted by G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England. All melting points are uncorrected.

(10) The authors are grateful to the Victor Chemical Works and to the Virginia-Carolina Chemical Corp., for generous samples of diethyl and triethyl phosphites.

(11) H. R. Snyder, C. Smith, and J. H. Stewart, *J. Am. Chem. Soc.*, **66**, 200 (1944).

was carried out by the method of Geissman and Armen by treatment of gramine with a large excess of methyl iodide.[12] A crude product of m.p. 154–158° described by these authors was obtained (1.8 g. from 1 g. of gramine) directly from the reaction mixture by trituration with benzene. This product, the "crude gramine methiodide," used directly in some of the reactions described in the following, contained appreciable amounts of bis(3-indolylmethyl)dimethylammonium iodide and tetramethylammonium iodide. A series of recrystallizations of this material from methanol-benzene gave pure gramine methiodide, m.p. 168–169° in 40% (reported 55%) from gramine.

Gramine methosulfate was prepared by the method of Schöpf and Thesing[13]; yield 63%; m.p. 144–145°.

*Reaction of triethyl phosphite with gramine methiodide.* A stirred solution of 524 mg. (1.6 mmoles) of pure gramine methiodide in 1.5 g. (8 mmoles) of triethyl phosphite was heated in an oil bath with careful protection from moisture. At a bath temperature of 130° the methiodide dissolved, and the yellow solution was refluxed at a bath temperature of 160° for 30 min., during which time a clean white precipitate was formed. After cooling, the solid was removed by filtration and washed with dry benzene and then with ethanol. Thus was obtained 310 mg. (91%) of trimethylethylammonium iodide, m.p. 290°.

*Anal.* Calcd. for $C_5H_{14}NI$: I, 59.0. Found: I, 59.6.

The solvents were evaporated from the filtrate at reduced pressure and the residual oil was distilled *in vacuo*. Crude diethyl 3-indolylmethylphosphonate (III) (320 mg., 72%) was collected at 180–200° (0.3 mm.). The viscous distillate solidified on cooling (m.p. 51–55°) and on recrystallization from 30–60° petroleum ether gave 200 mg. of colorless needles, m.p. 61–62°.

*Anal.* Calcd. for $C_{13}H_{18}NO_3P$: C, 58.4; H, 6.7; N, 5.2; P, 11.6. Found: C, 58.2; H, 6.8; N, 5.4; P, 11.2.

The infrared spectrum[14] of this product indicated indole peaks at 773, 1627, and 3190 cm.$^{-1}$ as compared to gramine as a reference compound (peaks at 777, 1623, and 3110 cm.$^{-1}$) as well as the usual phosphonate absorption[15] (peaks at 978, 1060, and 1226 cm.$^{-1}$).

When 7 g. of crude gramine methiodide (see Reactants) was heated with 18 g. of triethyl phosphite, a yellow solution was obtained at a bath temperature of 140°, which was refluxed for an additional 45 min. On cooling, 3.6 g. (77%) of trimethylethylammonium iodide was separated. The filtrate was concentrated at reduced pressure and distillation gave 1.8 g. (30% from gramine) of diethyl 3-indolylmethylphosphonate b.p. 180–200° (0.3 mm.); m.p. 61–62° after recrystallization from 30–60° petroleum ether, undepressed when admixed with a previously analyzed sample.

*Ethyl hydrogen 3-indolylmethylphosphonate.* Diethyl 3-indolylmethylphosphonate (320 mg.) was refluxed with 4 ml. of 5% sodium hydroxide solution for 6 hr. at which time the original two-phase mixture had formed a clear solution. The solution was cooled and neutralized with cold 1:1 hydrochloric acid. The white solid was filtered, washed thoroughly with water, dried and recrystallized from a petroleum ether–acetone mixture to yield 180 mg. (62%) of thread-like colorless crystals, m.p. 136–137°.

*Anal.* Calcd. for $C_{11}H_{14}NO_3P$: C, 55.22; H, 5.86; N, 5.86; P, 12.97; neut. equiv., 239. Found: C, 55.45; H, 6.13; N, 6.20; P, 12.75; neut. equiv., 236.

All attempts at hydrolysis in acid solution resulted in extensive decomposition and no products could be isolated.

*Reaction of triethyl phosphite with gramine methosulfate.* A stirred suspension of 1.5 g. (5 mmoles) of gramine methosulfate in 3.0 g. (50 mmoles) of triethyl phosphite was heated in an oil bath with careful exclusion of moisture. After 30 min. of refluxing at a bath temperature of 170° the solid methosulfate was replaced by a liquid phase. Refluxing was continued for an additional 30 min., the reaction mixture was cooled, and the white precipitate which formed on cooling was filtered and washed with dry benzene to give 810 mg. of a hygroscopic solid. Recrystallization from acetone–absolute ethanol gave 498 mg. (50%) of a crystalline solid which analyzed for ethyltrimethylammonium methosulfate or for tetramethylammonium ethosulfate.

*Anal.* Calcd. for $C_6H_{17}NO_4S$: S, 16.0%. Found: S, 15.9%.

The filtrate and washings were concentrated at reduced pressure and the residual yellow oil was distilled *in vacuo* to give 995 mg. (75%) of diethyl 3-indolylmethylphosphonate; b.p. 200–230° (0.6 mm.); m.p. 55–58°, raised to 61–62° on recrystallization from 30–60° petroleum ether.

*Reaction of triethyl phosphite with free gramine.* No change was observed when a mixture of gramine and a 5 molar excess of triethyl phosphite was stirred at room temperature. On heating to 110° the gramine dissolved and the yellow solution was refluxed for an additional 3 hr. at a bath temperature of 150°. The excess triethyl phosphite was removed under reduced pressure and distillation of the residual resin was attempted. A small amount of a very viscous distillate was collected at 230–250° (0.3 mm.) with the aid of a free flame. No crystalline product could be isolated from this material.

*Reaction of sodium diethyl phosphite with gramine methiodide.* A solution of sodium diethyl phosphite was prepared by addition at room temperature of 1.04 g. (7.5 mmoles) of diethyl phosphite to sodium ethoxide from 170 mg. (7.5 mmoles) of sodium in 21 ml. of absolute ethanol. To this solution there was added 2.6 g. of crude gramine methiodide (from 1.4 g., 7.5 mmoles, of gramine; see Reactants) and the resulting solution was stirred at room temperature. An odor characteristic of trimethylamine was detectable within a few minutes and sodium iodide began to separate after about 1 hr. After 6 hr. the solution was filtered from sodium iodide and concentrated under reduced pressure to a viscous oil. This material was exhaustively extracted with ether, the ether extracts concentrated, and the residual oil distilled *in vacuo* to yield diethyl 3-indolylmethylphosphonate (430 mg., 20% from gramine); b.p. 200–250° (0.6 mm.); m.p. 55–58°, raised to 61–62° after recrystallization from 30–60° petroleum ether, undepressed when admixed with previously described samples.

*Reaction of sodium diethyl phosphite with gramine methosulfate.* Gramine methosulfate, 1.5 g. (5 mmoles), was added to a solution of sodium diethyl phosphite prepared from 695 mg. (5 mmoles) of diethyl phosphite and sodium ethoxide from 11.5 mg. (5 mmoles) of sodium in 12 ml. of absolute ethanol. The mixture warmed spontaneously to about 50° and the resulting solution was stirred at room temperature for 6 hr. The odor of trimethylamine was detectable within a few minutes; no precipitate was formed during the reaction. The solution was concentrated at reduced pressure and the residual oily solid was extracted exhaustively with ether. After evaporation of the ether the product was distilled *in vacuo* to yield 550 mg. (40% from gramine) of diethyl 3-indolylmethylphosphonate; b.p. 180–200° (0.3 mm.); m.p. 57–60°, raised to 61–62° on recrystallization from petroleum ether.

*Reaction of diethyl phosphite with gramine methiodide.* A mixture of gramine methiodide and a 5 molar excess of diethyl phosphite was stirred at room temperature for 4 hr. The slightly cloudy solution was concentrated under reduced pressure to a brown viscous residue. On attempted distillation at 0.3 mm. this material produced a small amount of viscous oil which did not solidify on seeding.

(12) T. A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).

(13) C. Schöpf and J. Thesing, *Angew. Chem.*, **63**, 377 (1951).

(14) The authors are grateful to Dr. James Brader of the Department of Chemistry, University of Illinois, Urbana, for the spectrum analyses and for his interpretations of the different peaks of the product as compared to those of gramine which was the reference compound.

(15) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).

The bulk of the material carbonized in the flask when heated over 200°.

When gramine methiodide was heated for several hours at 100° with excess diethyl phosphite the reaction mixture colored and turned resinous, and carbonization occurred on attempted distillation.

*Reaction of diethyl phosphite with gramine methosulfate.* A suspension of gramine methosulfate in a 5 molar excess of diethyl phosphite was stirred at room temperature for 3 hr. during which time no change was observed. The temperature was raised to 110° to produce a pale yellow solution which was refluxed for 3 hr. On cooling about 60% of the gramine methosulfate reprecipitated and was recovered by filtration. Attempted distillation of the filtrate produced a resinous material which carbonized when heated to 200°.

CHICAGO 12, ILL.

# Notes

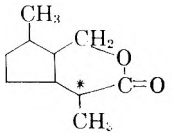
A department for short papers of immediate interest.

## The Interconversion of Nepetalic Acid and Isoiridomyrmecin (Iridolactone)

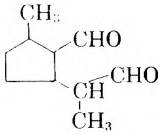
S. M. McElvain and E. J. Eisenbraun

*Received August 6, 1956*

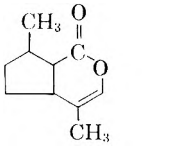
Three compounds that have been isolated from certain *Iridomyrmex* species of ants recently have been shown to bear a remarkable structural and configurational relationship to the nepetalic acids which result from the hydrolysis of nepetalactone (III), the principal constituent of the volatile oil of catnip.[1] Iridomyrmecin was isolated from a species of Argentine ants, *Iridomyrmex humilis* by Pavan[2] and shown by Fusco and collaborators[3] to have the structure I by its oxidation to one (V) of the four nepetalinic acids that have been obtained *via* the corresponding nepetalic acids IV, from nepetalactone (III).[4] The lactone I was epimerized at the asymmetric center* to isoiridomyrmecin (Ia)



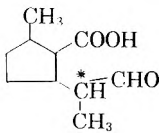
I, m.p. 60–61°
Ia, m.p. 58–59°



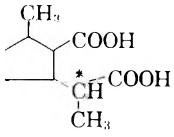
II



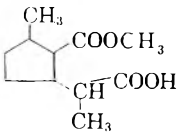
III



IV



V, m.p. 117°
Va, m.p. 85°



VI

by treatment with potassium methoxide. This epimer was converted[5] by oxidation to the nepetalinic acid Va, which had been shown[4] to be an epimer of V at the asymmetric center*.

Iridodial, a dialdehyde isolated from *I. detectus* and *I. conifer*, has been converted by Cavill and coworkers[6] to iridolactone, which previously had been obtained from *I. nitidus*. This lactone was shown to have the structure Ia by oxidation to Va and by comparison with an authentic sample of isoiridomyrmecin (Ia). On the basis of these relationships iridodial was assigned[6] structure II.

One pure nepetalic acid (IV), m.p. 72°, has been obtained from the mixture of two epimeric acids resulting from the hydrolysis of nepetalactone (III). The oxidation of this acid yielded Va and the oxidation of its methyl ester gave the monomethyl ester (VI) of Va.[4] It has now been found that the reduction of VI with a limited amount of lithium aluminum hydride converts VI to a lactone which is identical with isoiridomyrmecin (Ia). Thus the interconversions of compounds isolated from the *Iridomyrmex* species of ants and those obtained from the catnip plant, *Nepeta cataria*, are completed.

### EXPERIMENTAL

*Isoiridomyrmecin* (Ia). To a cooled (−30°) solution of 1.78 g. (0.0084 mole) of methyl nepetalinate (VI),[4] neut. equiv. 212 (calc'd 214), in 30 ml. of tetrahydrofuran, freshly distilled from lithium aluminum hydride, was added over a period of 30 minutes a solution containing 0.0063 mole of lithium aluminum hydride in 17.5 ml. tetrahydrofuran.[7] After stirring for an hour, a few drops of ethyl acetate were added to decompose any excess of the hydride. The solvent was distilled under reduced pressure until foaming was encountered near the end of the distillation; then portions of benzene were added and the distillation continued under reduced pressure to entrain the tetrahydrofuran. When the dry residue was treated with 25 ml. of 20% hydrochloric acid, a distinct odor of lactone was detected. The acidified reaction mixture was thoroughly extracted with ether and with chloroform, and the combined extracts were dried over magnesium sulfate, filtered, and the solvent was distilled at atmospheric pressure. The resulting crude oil, which weighed 1.28 g. (71% yield) crystallized on standing overnight. The crude product was purified by pressing between sheets of filter paper to remove adherent oil and then was sublimed twice at 55° (0.1 mm.) to give isoirido-

(1) S. M. McElvain, R. D. Bright, and P. R. Johnson, *J. Am. Chem. Soc.*, **63**, 1558 (1941).

(2) M. Pavan, *Chimica e industria (Milan)*, **37**, 714 (1955).

(3) R. Fusco, R. Trave, and A. Vercellone, *Chimica e industria (Milan)*, **37**, 251, 958 (1955).

(4) S. M. McElvain and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **77**, 1599 (1955).

(5) Private communication from Professor Fusco.

(6) G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Chemistry & Industry*, 465 (1956).

(7) (a) H. Felkin, *Bull. soc. chim. France*, 347 (1951); (b) *Cf.* also E. L. Eliel, A. W. Burgstahler, D. E. Rivard, and L. Haefele, *J. Am. Chem. Soc.*, **77**, 5092 (1955) for selective reduction of monomethyl phthalates to phthalides.

myrmecin (Ia), m.p. 58–59°, which contained 71.42% C and 9.67% H (calc'd 71.39 and 9.59). The infrared spectrum of Ia was found to be identical with that of authentic isoiridomyrmecin and there was no depression in melting point on admixture of Ia from the two sources.

*Acknowledgment.* The authors are grateful to Professor R. Fusco for generous samples of iridomyrmecin and isoiridomyrmecin.

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## Synthesis of 11β-Acetoxytestosterone Acetate

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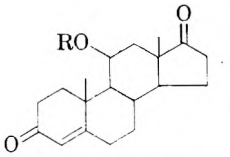
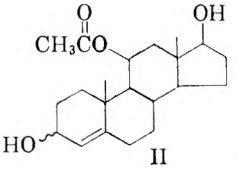
*Received November 5, 1956*

The disappearance of the androgenic and anabolic properties of testosterone upon 11β-hydroxylation[1] led us to examine the effect of esterification of this group. In the case of progesterone, for example, 17α-hydroxylation results in physiological deactivation, whereas the corresponding esters retain activity.[2]

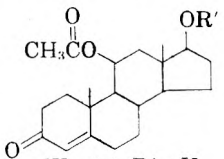
Attempts to prepare 11β-acetoxytestosterone acetate directly from the parent compound[3] were unsuccessful and an indirect route was chosen. Acetylation of 11β-hydroxy-Δ⁴-androstene-3,17-dione[4] (Ia) with special care to reverse the formation of enol acetates, gave the corresponding acetate (Ib). An attempt to perform a selective reduction at C-17 by the method of Norymberski and Woods[5]



I (a) R = H
(b) R = $-\overset{O}{\overset{\|}{C}}CH_3$



II



III (a) R′ = H
(b) R′ = $-\overset{O}{\overset{\|}{C}}CH_3$

failed, as did an attempted reduction with yeast.[6] Reduction with sodium borohydride gave instead the triol acetate II, which crystallized as the hemihydrate. Subsequent oxidation of the allylic hydroxyl group with $MnO_2$[7] gave the desired 11β-acetoxytestosterone (IIIa), which was isolated as the diacetate (IIIb).

In the *levator ani* and seminal vesicle response of castrated rats, compounds Ib, II, and IIIb were essentially inactive.

### EXPERIMENTAL[8]

*11β-Acetoxy-Δ⁴-androstene-3,17-dione* (Ib). 11β-Hydroxy-Δ⁴-androstene-3,17-dione (Ia) (2.00 g.) was suspended in a mixture of 20 ml. of glacial acetic acid and 9 ml. of acetic anhydride, and 200 mg. of *p*-toluenesulfonic acid was added. The resulting suspension was allowed to stand overnight. When almost all of the suspended material had dissolved, the small amount of solid remaining was removed by filtration and the solution was poured slowly onto a slurry of ice. Enough sodium carbonate solution was then added slowly with stirring to adjust to a *p*H of 8 (1.5 hr.) and the oily suspension was stirred for an hour longer. Extraction with ether, followed by washing of the extract with water, drying, and concentration under vacuum, gave a crude solid which was chromatographed on alkaline alumina. The material was placed on the column in benzene and eluted over a broad region (benzene-ether to ether–methylene chloride), combined and crystallized from methylene chloride–ether. There was obtained 1.01 g. of Ib, m.p. 193–194°; $[\alpha]_D$ +179° (diox.); $\lambda_{max}^{MeOH}$ at 239 mμ (ε = 16,000); IR peaks at 5.78, 6.00, and 6.20μ.

*Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22%; H, 8.19%; Found: C, 73.26%; H, 8.10%.

*11β-Acetoxy-Δ⁴-androstene-3ξ,17β-diol* (II). The acetate Ib (1.00 g.) was dissolved in 2 l. of methanol and cooled to 0°. Sodium borohydride (171 mg.) was added, and the solution was allowed to stand 1 hr. at ice temperature. Excess reagent was destroyed with acetic acid and the solution was evaporated to dryness *in vacuo*. The residue was distributed between water and chloroform, and the organic phase was again evaporated to dryness. This latter residue was then chromatographed on neutral alumina (Woelm) by the gradient elution technique, using benzene and 50% benzene–ethyl acetate solutions as the nonpolar and polar eluants, respectively. From the less polar eluates, 403 mg. of II were isolated and crystallized from moist ether,[9] m.p. 107–112°; no selective absorption in the ultraviolet; $[\alpha]_D^{25}$ +70.5°; IR bands at 2.91, 3.01, 3.20, 5.78, 6.02, and 8.00μ.

*Anal.* Calcd. for $C_{21}H_{32}O_4 \cdot {}^1/_2H_2O$: C, 70.55%; H, 9.34%; Found: C, 70.27%; H, 9.18%.

From the more polar eluates, a second material was isolated and crystallized from ether to give 30 mg., having m.p. 168–172°. It was not further investigated.

*11β-Acetoxytestosterone acetate* (IIIb). The triol monoacetate II (600 mg.) was ground to a fine powder, largely

(1) S. C. Lyster, G. H. Lund, and R. O. Stafford, *Endocrinol.*, **58**, 781 (1956).

(2) K. Junkmann, *Arch. exptl. Pathol. Pharmakol.*, **223**, 244 (1954).

(3) M. E. Herr, J. A. Hogg, and R. H. Levin, *J. Am. Chem. Soc.*, **78**, 500 (1956).

(4) T. Reichstein, *Helv. Chim. Acta*, **20**, 978 (1937).

(5) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 1955, 3426.

(6) See, for instance, H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 266 (1953).

(7) F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).

(8) All melting points were taken on a Kofler Block. Rotations were carried out in a 1-dm. tube at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

(9) A few droplets of water actually had to be added to the ether to induce crystallization.

dissolved in 6 ml. of chloroform, and agitated overnight with 1 g. of freshly prepared manganese dioxide. The suspension was diluted with warm chloroform, filtered, washed, and concentrated to dryness. The resulting oil had a strong selective absorption around 240 mμ, but could not be crystallized even after chromatography. Acetylation in the usual manner, however, gave 127 mg. of IIIb, crystallized from hexane, m.p. 144–147°; $\lambda_{max}^{MeOH}$ at 237 mμ ($\epsilon$ = 15,900); $[\alpha]_D^{25}$ +117.8; IR peaks at 5.80, 6.01, 6.18, and 8.08.

*Anal.* Calcd. for $C_{29}H_{32}O_5$: C, 71.10%; H, 8.30%; Found: C, 71.37%; H, 8.32%.

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## Occurrence of Scopoletin in the Genus *Brunfelsia*

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*Received October 25, 1956*

Several *Brunfelsia* species (fam. *Solanaceae*) are widely used as ornamental or medicinal plants in Brazil and other South American countries and the roots of *Brunfelsia Hopeana* (Hook.) Benth. (popular name "Manacá") are listed in the Brazilian Pharmacopoeia. The older literature mentions a number of components but none seems to have been satisfactorily characterized so far. Lascelle-Scott[2] mentions the presence of an alkaloid which he named "francisceine." Lenardson[3] also reported on the alkaloid which he named "manacine." The most extensive paper is by Brandl[4] who worked on manacine and its degradation products. Later Peckolt[5] claimed to have isolated still another alkaloid which he named "brunfelsine." Although analytical data are presented by Brandl, none of the mentioned substances had been obtained in a crystalline state. The only crystalline compound mentioned thus far by Lenardson and Brandl is one which was notable because of its very strong blue fluorescence. Brandl[4] believed it to be aesculetin (6,7-dihydroxycoumarin) based on a color reaction and a combustion analysis.

In our own investigations concerning the possible occurrence of alkaloids in the mentioned plant, we could isolate the same fluorescent compound which, however, was not aesculetin but its methyl ether scopoletin, having been identified by mixture melting point and infrared and ultraviolet spectral comparison with an authentic sample.[6] Scopoletin (6-methoxy-7-hydroxycoumarin) has been found to occur in a number of plants of the *Solanaceae* and other families.[7]

Further investigation showed this compound to be present in other *Brunfelsia* species as well. It could be isolated from the following, all collected in the vicinity of Rio de Janeiro:

*Brunfelsia Hopeana* (Hook.) Benth. (Franciscea uniflora Pohl.).

*Brunfelsia calycina* Benth. var. *macrantha* Bailey (Br. grandiflora Don.).

*Brunfelsia ramosissima* (Pohl.) Benth.

It was also found that the presence of the substance is not limited to the roots, but is general throughout the plants, in roots, stems, twigs, leaves, and flowers. Its remarkable fluorescence allows it to be easily detected hystologically by ultraviolet microscopy.

Isolation of scopoletin was accomplished by first extracting the ground plant material with water and then the aqueous extract continually with chloroform. The crude substance which remained after evaporation of the solvent was then purified by alternate sublimation *in vacuo* and recrystallization from ethanol. The melting point was 204°, the yield in all three species being close to 0.1%.

It is interesting to record that Lenardson, the earliest of the above mentioned investigators, thought that the crystalline compound could possibly be identical with the then recently discovered "gelseminic acid." We know today that "gelseminic acid" is, in fact, scopoletin and Lenardson's assumption was therefore quite correct.

Scopoletin has been found normally to occur only in trace amounts in plants of the family *Solanaceae* (tobacco, potato), but its concentration in the tissues increases significantly as a result of virus infection.[8,9,10] The fact that it is present in relatively high amounts in healthy plants of other genera of the same family suggests a similarity between the metabolism of healthy individuals of one genus with that of diseased individuals of another.

(1) Research Fellow, The Rockefeller Foundation, with Department of Chemistry, Wayne State University, Detroit 2, Mich.

(2) W. Lascelle-Scott, *Jahresber. Pharm.* (*N.F.*), 162 (1887).

(3) R. Lenardson, *Chem. Zentr.*, 11 (1885).

(4) J. Brandl, *Z. Biol.*, **31**, 251 (1895).

(5) Th. Peckolt, *Ber. deut. pharm. Ges.*, **19**, 292 (1909).

(6) We are indebted to Mrs. Dolores J. Phillips, Spectrophotometric Laboratory, Wayne State University, for the infrared and ultraviolet measurements.

(7) R. H. Goodwin, *Ann. Rev. Plant Physiol.*, **4**, 283 (1953).

(8) R. J. Best, *Australian J. Exp. Biol. Med. Sci.*, **14**, 199 (1936); **22**, 251 (1944).

(9) W. A. Andreae, *Can. J. Research*, **26C**, 31 (1948).

(10) S. R. Andreae and W. A. Andreae, *Can. J. Research*, **27C**, 15 (1949).

We wish to thank Mr. José Corrêa Gomes, administrator of the Rio de Janeiro Botanical Garden, for supplying most of the plant material used in this work, and Dr. Leo Marion, National Research Council, Canada, for providing us with an authentic sample of scopoletin from *Gelsemium sempervirens*. We are indebted to the Rockefeller Foundation for a fellowship to one of us (W.B.M.) and to the Conselho Nacional de Pesquisas, Brazil for financial aid. We also extend our thanks to Prof. Carl Djerassi, Chemistry Department, Wayne, State University, for his valuable help and advice.

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## Synthesis and Investigation of Organic Fluorine Compounds. XXII. The Preparation of Newer 2-Fluoroethylurethan Derivatives

GEORGE A. OLÁH, STEVEN J. KUHN, AND GEORGINA KOVÁCS-BRUCKNER

*Received April 30, 1956*

Biologically active fluorinated derivatives have been mentioned by Schrader[1] and Knunyants[2] among the derivatives of 2-fluoroethyl chloroformate. In two preceding papers[3,4] we have described a number of 2-fluoroethylurethan derivatives. Simultaneously with our investigations Sawicki, Ray, and Oliverio[5–7] have also published papers about the preparation of new fluorinated urethans.

The inhibiting action of fluoroacetic acid and 2-fluoroethanol, respectively, on the growth of experimentally produced malignant tumors has already been mentioned by us.[8,9] However, due to the rather high toxicity of both compounds, an attempt was made to find less toxic, biologically active derivatives. It appeared possible that the derivatives of 2-fluoroethylurethan would meet these requirements because their pharmacological tests[10] only show the appearance of toxic symptoms after a longer period of latency.

The compounds were too toxic in the chemotherapeutical experiments,[11] so that no significant effect could be observed. However, in some cases there was a slight but definite therapeutic activity toward cancer and we have therefore continued the preparation of further derivatives in the hope of finding less toxic members of the 2-fluoroethyl series. The new derivatives thus prepared are listed in Table I.

Some of the newly prepared derivatives have a toxicity of over 200 mg./kg./rat. The biological and probable insecticidal activity, which was observed by us in previous investigations,[12] will be reported elsewhere.

TABLE I

PREPARATION AND PROPERTIES OF 2-FLUOROETHYLURETHAN DERIVATIVES

| R—NR′—$COOC_2H_4F$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| R | R′ | B.P., °C. | Mm. | M.P., °C. | Method of preparation | Yield, % | Nitrogen Calcd. | Nitrogen Found |
| $C_2H_5$ | H | 116–117 | 30 | | A | 90 | 13.59 | 13.52 |
| *iso*-$C_3H_7$ | H | 110 | 30 | | A | 91 | 9.40 | 9.28 |
| $C_4H_9$ | H | 126–128 | 10 | | B | 83 | 8.53 | 8.39 |
| *tert*-$C_4H_9$ | H | 100 | 25 | | A | 94 | 8.60 | 8.34 |
| $CH_2$=$CHCH_2$ | H | 98–100 | 5 | | B | 77 | 9.52 | 9.46 |
| $C_6H_{11}$ | H | | | 63 | A | 88 | 7.43 | 7.27 |
| $>CH_2$ | $>CH_2$ | 91–93 | 12 | | B | 90 | 9.78 | 9.77 |
| *o*-$C_2H_5$-$C_6H_4$ | H | | | 81–82 | B | 79 | 6.66 | 6.36 |
| 2-$CH_3$-4-Cl-$C_6H_3$ | H | | | 88–89 | B | 81 | 6.06 | 6.01 |
| 2-$CH_3$-5-Cl-$C_6H_3$ | H | | | 84–85 | B | 77 | 6.06 | 6.00 |
| $C_6H_5$ | $C_6H_5$ | | | 83–84 | C | 69 | 5.40 | 5.33 |
| *p*-$CH_3CO$-$C_6H_4$ | H | | | 153–154 | A | 81 | 6.25 | 6.14 |

(1) G. Schrader, *Die Entwicklung neuer Insektizide auf Grundlage organischer Fluor- und Phosphor-Verbindungen*, 2nd ed., Verlag Chemie, Weinheim, 1952.

(2) I. L. Knunyants, O. V. Kil'disheva, and I. P. Petrov, *J. Gen. Chem., U.S.S.R.*, 19, 101 (1949) [*Chem. Abstr.*, 43, 6163 (1949)].

(3) G. Oláh and A. Pavláth, *Acta Chim. Acad. Sci. Hung.*, 4, 89 (1954) [*Chem. Abstr.*, 49, 6094 (1955)].

(4) G. Oláh, A. Pavláth, and L. Noszkó, *Acta Chim. Acad. Sci. Hung.*, 7, 443 (1955).

(5) E. Sawicki and F. E. Ray, *J. Org. Chem.*, 18, 1561 (1953).

(6) V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, 20, 363 (1955).

(7) V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, 20, 1733 (1955).

(8) C. Sellei, G. Oláh, S. Eckhart, and L. Kapás, *Magyar Orvosi Hetilap*, 93, 756 (1952).

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(10) F. Herr, G. Oláh, and A. Pavláth, *Acta Physiol. Acad. Sci. Hung.*, 6, 105 (1954).

(11) L. Nemeth, G. Oláh, S. Cellei, and B. Kellner, *Arch. Geschwulstforschung*, in press.

(12) G. Oláh and A. Pavláth, *Chem. Tech. (Berlin)*, 7, 204 (1955).

EXPERIMENTAL

*2-Fluoroethanol* was prepared in 50% yield from ethylene chlorohydrin and potassium fluoride by ultraviolet irradiation as described by Oláh and Pavláth.[13]

*2-Fluoroethyl chloroformate* was prepared in 72% yield by the method of Oláh and Pavláth.[4]

*General procedures for the preparation of the 2-fluoroethylurethan derivatives.* (A). A 0.1-mole portion of the amine was dissolved in 40 ml. of absolute ethyl ether in a three-necked round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a dropping-funnel; then 6.32 g. (0.05 mole) of 2-fluoroethyl chloroformate was slowly dropped on to the ice cooled solution. The stirring was continued for an hour after which time the precipitated amine hydrochloride was filtered. The ether was removed by distillation and the remaining oil was fractionated *in vacuo*. If crystalline the product was recrystallized from hexane.

(B). A 0.1-mole portion of the amine was dissolved in a solution of 4.8 g. (0.12 mole) of sodium hydroxide in 25 ml. of water. The resultant solution was cooled in an ice-water bath and efficiently stirred while 12.65 g. (0.1 mole) of 2-fluoroethyl chloroformate was dropped into the mixture. Stirring was continued without further cooling for 2 hr. The 2-fluoroethylurethan formed was extracted with ether, the ether was evaporated, and the residue was fractionated *in vacuo*. In the case of crystalline products the substances were recrystallized from hexane.

(C). A 0.1-mole portion of the amine was dissolved in 25 ml. of benzene and 6.32 g. (0.05 mole) of 2-fluoroethyl chloroformate was added; the reaction then was continued and worked up as under (A).

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BUDAPEST, XIV, HUNGARIA-KRT. 114

(13) G. Oláh and A. Pavláth, *Acta Chim. Acad. Sci. Hung.*, **3**, 199 (1953) [*Chem. Abstr.*, **48**, 7535 (1954)].

## Synthesis from Thiolacetates. I. Synthesis of Alkanesulfonyl Chlorides[1]

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*Received September 11, 1956*

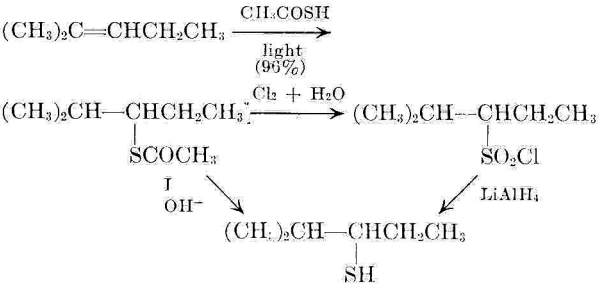
The reaction of thiolacetic acid with olefins has been found to be generally applicable, and to give high yields of thiolacetates.[2] Hydrolysis of these thiolacetates provides an excellent route for the synthesis of thiols.[2] Oxidative chlorination of thiolacetates is utilized herein as a route to the preparation of alkanesulfonyl chlorides from olefins.

Douglass and Johnson included two thiolesters in their general study of the oxidative chlorination of divalent sulfur compounds.[3] They obtained a 71% yield of ethanesulfonyl chloride from ethyl thiolacetate and a mixture of benzyl disulfide, benzyl phenylmethanethiosulfonate, and phenylmethanesulfonyl chloride from benzyl thiolacetate.

In the present study the thiolacetates were prepared in yields of 92–96% from 4-methyl-1-pentene, 2-methyl-2-pentene, and cyclohexene. Oxidative chlorination of these thiolacetates by the method of Douglass and Johnson[3] gave 77%, 62%, and 72% yields of the corresponding sulfonyl chlorides.

The method is, therefore, applicable to the preparation of primary, secondary, and cycloalkanesulfonyl chlorides from the olefins in overall yields of 58–71%. Compounds in which the sulfur atom is attached to a secondary carbon atom appear not to have been subjected to oxidative chlorination of this type before.

The addition of thiolacetic acid to olefins occurs exclusively in an anti-Markownikoff manner,[2b] so the sulfonyl chlorides prepared from them should be of high purity. Their structures should correspond to those of the thiolacetates. However, to make certain that rearrangement does not accompany the oxidative chlorination of thiolacetates to sulfonyl chlorides, the sulfonyl chloride from 1-ethyl-2-methylpropyl thiolacetate (I) was reduced




with lithium aluminum hydride to the thiol. The 2,4-dinitrophenyl sulfide derivative of this thiol was found to be identical with that obtained from the thiol prepared from the original thiolacetate. Since rearrangement is more likely to occur with a secondary thiolacetate having a tertiary hydrogen on an alpha carbon, such as I, than for other types of thiolacetates it seems safe to conclude that rearrangements will not often occur in this reaction.

2-Phenyl-1-propanesulfonyl chloride was prepared by oxidative chlorination of 2-phenylpropyl thiolacetate with the purpose of synthesizing 2-methyl-2,3-dihydrobenzothiophene-1-dioxide from it by ring closure. This is potentially a route to cyclic sulfones of this type from styrenes, but Friedel-Crafts type ring closures were unsuccessful in our hands in this instance.

EXPERIMENTAL[4]

*1-Ethyl-2-methylpropyl thiolacetate* Thiolacetic acid (Eastman Kodak Co., practical grade) was purified by distillation prior to use. One hundred fifty-two and two-tenths

(1) This investigation was carried out as part of American Petroleum Institute Research Project 48B, given in part at the 126th Meeting of the AMERICAN CHEMICAL SOCIETY, New York, N. Y., September 1954 (p 6-O of Abstracts).

(2) (a) The first report of this reaction was B. Holmberg, *Arkiv. Kemi, Mineral Geol.*, **12B**, No. 47, 3 (1938). (b) The literature concerning this reaction, together with numerous further examples, may be found in the Ph.D. dissertation of W. A. Hewett, Northwestern University, August 1955.

(3) I. B. Douglass and T. B. Johnson, *J. Am. Chem. Soc.*, **60**, 1486 (1938).

(4) Microanalyses were by Miss Hilda Beck.

grams (2 moles) of thiolacetic acid was added slowly with stirring to 336.6 g. (4 moles) of 2-methyl-2-pentene (95% mol. % minimum, Phillips Petroleum Co, Special Products Division, Bartlesville, Okla.). The reaction mixture was irradiated during the addition with light from a 100 watt bulb,[5] and irradiation and stirring were continued for 1 hr. after addition of the thiolacetic acid was complete. Distillation of the reaction mixture yielded 308.5 g. (96.2%) of 1-ethyl-2-methylpropyl thiolacetate, b.p. 70° (13 mm.), $n_D^{25}$ 1.4603.

*Anal.* Calcd. for $C_8H_{16}OS$: C, 59.95; H, 10.06. Found: C, 60.46; H, 10.12.

*1-Ethyl-2-methylpropanethiol.* Three hundred five grams (1.92 moles) of 1-ethyl-2-methylpropyl thiolacetate was refluxed for 1 hr. in 2.5 l. of 10% aqueous-alcoholic (50% by volume) potassium hydroxide solution. The solution was neutralized with glacial acetic acid and the non-aqueous phase separated. The aqueous portion was extracted three times with pentane and the pentane extracts were dried over anhydrous magnesium sulfate. The combined non-aqueous phase and pentane extracts were distilled giving 203 g. (90.5%) 1-ethyl-2-methylpentanethiol, b.p. 135°, $n_D^{25}$ 1.4467.

*Anal.* Calcd. for $C_6H_{14}S$: C, 60.95; H, 11.93. Found: C, 61.46; H, 11.75.

The 2,4-dinitrophenyl sulfide derivative of the pure thiol was prepared according to the method of Bost, Turner, and Morton.[6] The sulfide melted at 60–60.5° after crystallization from absolute alcohol.

*Anal.* Calcd. for $C_{12}H_{16}O_4N_2S$: N, 9.85. Found: N, 10.13.

*4-Methyl-1-pentyl thiolacetate.* Starting with 200 g. (2.38 moles) of 4-methyl-1-pentene (95% mol. % minimum, Phillips Petroleum Co., Special Products division, Bartlesville, Okla.) and 121.2 g. (1.59 moles) of thiolacetic acid, 238 g. (93.5%) of 4-methyl-1-pentyl thiolacetate, b.p. 89° (16 mm.), $n_D^{25}$ 1.4575, was obtained by the procedure described above.

*Anal.* Calcd. for $C_8H_{16}OS$: C, 59.95; H, 10.06. Found: C, 60.55; H, 9.56.

*Cyclohexyl thiolacetate.* This compound was prepared in 92.5% yield by the method described above. The boiling point of this compound was 77° (5.8 mm.). Cunneen[7] reported b.p. 90° (14 mm.).

*2-Phenyl-1-propyl thiolacetate.* This compound was prepared in 90% yield by the method described above. The boiling point of this compound was 105–107° (1.8 mm.). Brown, Jones, and Finder[8] reported b.p. 105° (4 mm.).

*1-Ethyl-2-methylpropanesulfonyl chloride.* Twenty grams (0.12 mole) of 1-ethyl-2-methylpropyl thiolacetate, suspended in water, was chlorinated at 0°, and the product processed according to the procedure of Douglass and Johnson.[3] Distillation through a 3-plate Vigreux column yielded 14.8 g. (62%) of 1-ethyl-2-methylpropanesulfonyl chloride, b.p. 70–75° (2 mm.), $n_D^{25}$ 1.4651.

*Anal.* Calcd. for $C_6H_{13}O_2SCl$: C, 39.23; H, 7.13. Found: C, 39.03; H, 6.72.

*Lithium aluminum hydride reduction of 2-methyl-3-pentanesulfonyl chloride.* Nine grams (0.05 mole) of 1-ethyl-2-methylpropanesulfonyl chloride in 25 ml. of dry ether was added slowly with stirring to a slurry of 5.7 g. (0.15 mole) of lithium aluminum hydride in 200 ml. of dry ether. After stirring and heating on the steam bath for an additional 2 hr., the excess lithium aluminum hydride was destroyed by addition of 250 ml. of 10% sulfuric acid. The non-aqueous layer was separated and the aqueous layer was extracted three times with 50 ml. portions of ether. The ether extracts and the non-aqueous layer combined and the ether distilled. Steam distillation of the residue gave 2 g. (30%) of crude 2-methyl-3-pentanethiol. The 2,4-dinitrophenyl sulfide derivative, prepared according to the method of Bost, Turner, and Morton,[6] melted at 60–61° after crystallization from alcohol. The melting point of a mixture with a comparable derivative, prepared from the thiol resulting from hydrolysis of 2-methyl-3-pentyl thiolacetate, was not depressed.

*Other alkanesulfonyl chlorides.* In a manner similar to that described above 17.5 g. (77%) of *4-methyl-1-pentanesulfonyl chloride*, b.p. 84° (2.5 mm.), $n_D^{25}$ 1.4550, was obtained from 20 g. of 4-methyl-1-pentyl thiolacetate.

*Anal.* Calcd. for $C_6H_{13}O_2SCl$: C, 39.23; H, 7.13. Found: C, 38.97, 38.79; H, 6.63, 6.74.

A 72% yield of cyclohexanesulfonyl chloride, b.p. 70° (0.5 mm.), $n_D^{25}$ 1.4958, was obtained from cyclohexyl thiolacetate. Borsche and Lange[9] reported a b.p. of 127–128° (15 mm.), and an anilide melting at 87°. The anilide prepared from our sulfonyl chloride melted at 85–85.5° (uncorr.).

A 54% yield of *2-phenyl-1-propanesulfonyl chloride*, b.p. 126° (2 mm.), was obtained from 2-phenyl-1-propyl thiolacetate.

*Anal.* Calcd. for $C_9H_{11}O_2SCl$: C, 49.42; H, 5.07. Found: C, 50.05, 50.07; H, 4.91, 5.03.

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(5) In most cases visible light is sufficient to initiate the reaction; in some cases, however, peroxides and heating on a water bath or in a bomb are required to increase the yield. Ref. (2) (b) in text.

(6) R. W. Bost, J. O. Turner, and R. D. Morton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

(7) J. I. Cunneen, *J. Chem. Soc.*, 134 (1947).

(8) R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951).

(9) W. Borsche and W. Lange, *Ber.*, **38**, 2767 (1905).

## Conversion of Steroidal Alkaloids, Tomatidine and Solasodine into Dihydrosapogenins

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*Received January 2, 1957*

The elegant work of White[1] on the deamination of aliphatic amines prompted us to apply his method to the deamination of the steroidal alkaloids, tomatidine (I) and solasodine (II).

Accordingly, I and II were converted to their respective *O,N*-diacetyl-22,*N*-dihydro and *O,N*-diacetyl-5,6,22,*N*-tetrahydro derivatives[2] (Ia), (IIa) and treated with nitrogen tetroxide to give the corresponding *N*-nitrosoamides, Ib and IIb. Upon subjecting these crude *N*-nitroso derivatives to thermal deamination and hydrolyzing the resulting diacetates with methanolic alkali, nitrogen free products were obtained. Chromatography on alumina yielded dihydroneotigogenin[3] (Ic) (from tomatidine) and dihydrotigogenin (IIc)(from solasodine) in moderate yields. The deaminated prod-

(1) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008, 6011, 6014 (1955).

(2) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3150 (1956).

(3) The authors are indebted to Dr. Callow of the National Institute for Medical Research, London, for a generous gift of neotigogenin acetate.

ucts agreed[4] in physical properties with authentic specimens.

The dihydrosapogenins (Ic and IIc) were also obtained from the alcohols, *N*-acetyl-22,*N*-dihydrotomatidine (Id) and *N*-acetyl-5,6,22,*N*-tetrahydrosolasodine (IId). In this case the intermediate is apparently the 3-nitrite ester (Ie, IIe) of the respective nitroso derivatives, as shown by their infrared spectra ($\lambda_{max.}^{chlf.}$ No hydroxyl; 5.78, 6.09 and 6.66 $\mu$).

A second component, presumed to be 16,22-epoxycholest-25-en-3$\beta$-ol[1, 5] (III) from infrared absorption data ($\lambda_{max.}^{chlf.}$ 6.05, 11.24 $\mu$, $R_1R_2C = CH_2$) was not obtained in sufficient purity for positive identification.

The sapogenins have previously been converted into steroidal alkaloids[6] and their derivatives[2] but the reverse transformation of steroidal alkaloids into dihydrosapogenins specifically has not hitherto been reported.

## EXPERIMENTAL[7]

*N-Acetyl-N-nitroso-22,N-dihydrotomatidine acetate* (Ib). *O,N*-Diacetyl-22,*N*-dihydrotomatidine (1.07 g.)[2] was dissolved in 15 ml. of carbon tetrachloride, cooled to 0°, and added dropwise, with swirling, to 15 ml. of a carbon tetrachloride solution of nitrogen tetroxide (*ca.* 1.5*M*) at 0° containing 1.5 g. of anhydrous sodium acetate. The anhydrous sodium acetate was previously added to the nitrogen tetroxide solution at −60° and then allowed to warm slowly to 0°. After allowing the reaction mixture to stand at 0° for 15 min., then at room temperature for 20 min., a slurry of ice and water was added to the solution. The organic phase was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. The crude oil (1.1 g.) $\lambda_{max.}^{chlf.}$ 5.79, 6.66 $\mu$, was used for deamination without further purification.

*Dihydroneotigogenin* (Ic). The crude nitroso derivative (Ib) was dissolved in 60 ml. of heptane (b.p. 98.5°) and refluxed gently for 16 hr. The crude, slightly colored oil, recovered after removal of the solvent, was subjected to chromatography on neutral alumina. Elution with benzene-ether (1:1) yielded 520 mg. of oil and further elution with 0.5% methanol in ether gave 273 mg. of another oily fraction.

The above benzene-ether (1:1) eluate was hydrolyzed with 20 ml. of methanolic potassium hydroxide (5%) for 1 hr. After partial concentration and addition of water the precipitate was collected and again subjected to chromatography. The portion eluted with 0.5% methanol in ether gave 155 mg. of dihydroneotigogenin. Recrystallization from acetone-hexane yielded plates, m.p. 170–173°, identical in all respects with an authentic specimen.

*Anal.* Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.35; H, 10.92.

*The dibenzoate*, prepared in the usual manner (benzoyl chloride-pyridine) crystallized from ether-methanol as rods, m.p. 114–116.5°, identical with respect to melting point, mixture melting point, and infrared spectrum with an authentic specimen. The compound seems to crystallize with one-half mole of methanol. For analysis the substance was dried at 110° for 8 hr. in high vacuum.

*Anal.* Calcd. for $C_{41}H_{54}O_5$: C, 78.55; H, 8.68. Found: C, 78.68; H, 8.73.

The early portion of the 0.5% methanol-ether eluate was an oil which failed to crystallize. When this was rechromatographed over alumina and eluted with 0.25% methanol-ether, a small amount of substance, m.p. 68–80°, $\lambda_{max.}^{chlf.}$ 6.06, 11.24 $\mu$, was obtained. Its infrared spectrum somewhat resembled 16,22-epoxycholest-25-en-3$\beta$-ol,[5] (III). It gave a positive tetranitromethane test for double bonds.

*N-Acetyl-N-nitroso-5,6,22,N-tetrahydrosolasodine acetate* (IIb). The compound was prepared in the same manner as Ib. From 320 mg. of IIa, 310 mg. of crude oil was obtained. The infrared spectrum of the compound, $\lambda_{max.}^{chlf.}$ 5.79, 6.66 $\mu$, was similar to that of Ib.

*Dihydrotigogenin* (IIc). The crude nitroso derivative (IIb) (295 mg.) was deaminated in heptane (b.p. 98.5°, 50 ml.) and hydrolyzed in the same way as Ib. The collected crude, dry product weighed 170 mg. One hundred forty milligrams of the above substance was chromatographed over alumina and the fraction (53 mg.) eluted with 0.5% methanol in ether proved to be dihydrotigogenin. Recrystallization from acetone yielded rods of m.p. 168–170.5°. It agreed in properties (melting point, mixture melting point, and infrared spectrum) with authentic dihydrotigogenin.

*Anal.* Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.36; H, 11.17.

*The dibenzoate*, crystallized as plates from ether-methanol, m.p. 112–114.5°, was identical with respect to m.p., mixture m.p., and infrared spectrum with an authentic specimen.

*Anal.* Calcd. for $C_{41}H_{54}O_5$: C, 78.55; H, 8.68. Found: C, 78.31; H, 8.92.

The sample for analysis was dried for 8 hr. at 110° in high vacuum.

The early oily fraction eluted with 0.5% methanol-ether, as in the case of Ic, was rechromatographed on a silica gel column but again no significant progress (m.p. 75–90°) was achieved toward the isolation of the expected unsaturated derivative, III.

*Dihydroneotigogenin from N-acetyl-22,N-dihydrotomatidine*, (Id). To 15 ml. of a carbon tetrachloride solution of nitrogen tetroxide (ca. 1*M*), containing 500 mg. of anhydrous sodium acetate, at 0° was added, dropwise and with swirling, 200 mg. of *N*-acetyl-22,*N*-dihydrotomatidine in 11 ml. of chloroform while cooling the mixture in an ice-bath. After standing for 30 min. at 0°, it was brought to room temperature and allowed to stand for an additional 15 min. Water was added to the mixture and the separated organic phase was washed thoroughly with water. Upon removal of the solvent a partially crystalline slightly yellowish substance (220 mg.) was obtained. A recrystallized sample, m.p. 104–108°, exhibited absorption bands at 5.78, 6.09, and 6.66 $\mu$ in chloroform. This is presumably the 3-nitrite ester, Ie.

When the above crude ester was successively deaminated, hydrolyzed (first with base and then with methanol-hydrochloric acid), and chromatographed as previously described (Ic) dihydroneotigogenin (30 mg.), m.p. 164–167°, was again obtained.

*Dihydrotigogenin from N-acetyl-5,6,22,N-tetrahydrosolasodine*, (IId). The 3-nitrate ester (IIe) was prepared in the same manner as Ic. The compound failed to crystallize. The infrared spectrum was similar to Ie. When the compound was processed in the above manner, dihydrotigogenin was obtained.

(4) It was noticed that Ic and IIc and their benzoates have nearly indistinguishable infrared spectra in chloroform or carbon disulfide. Their spectra in Nujol mulls differ somewhat.

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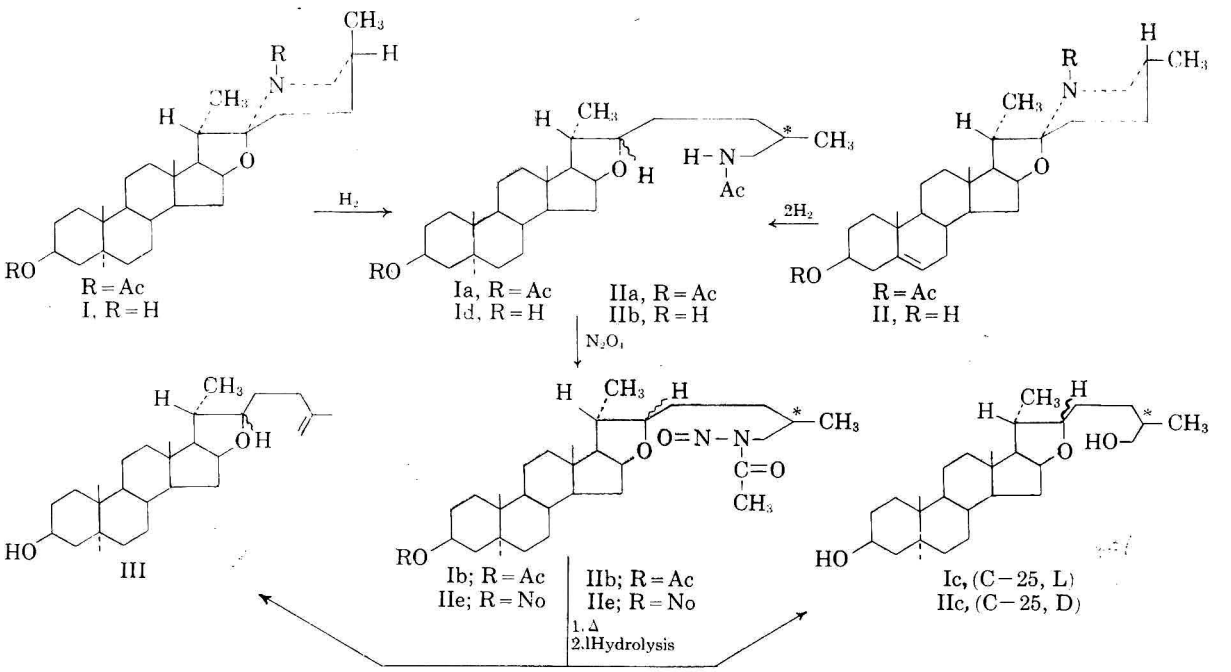
(7) All melting points were taken on the Kofler block and are uncorrected. We are indebted to Dr. W. C. Alford and his associates for the microanalyses and to Mr. H. K. Miller, all of this Institute, for the spectrophotometric measurements.

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## A Convenient Method for Preparation of Quaternary Ammonium Salts

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Three laboratory procedures are generally available for the synthesis of quaternary ammonium salts.[1,2] These methods are: (*a*) neutralization of the free quaternary ammonium base with the acid of the desired anion, *viz.*, $R_4NOH + HX \rightarrow R_4NX + H_2O$, (*b*) metathetical reactions involving the formation of an insoluble compound and the quaternary ammonium salt, *viz.*, $R_4NY + AX \rightarrow AY + R_4NX$, and (*c*) alkylation of amines (the Hofmann reaction), *viz.*, $R_3N + RX \rightarrow R_4NX$.[2-4] The work reported here presents a fourth approach based upon the reaction of equivalent quantities of the free quaternary ammonium base and the ammonium salt of an anion.

The kinship of the quaternary ammonium bases to the alkali metal hydroxides is well known.[5,6] Accordingly, the quaternary ammonium hydroxides will tend to displace the more weakly basic ammonia from aqueous solutions of ammonium salts as per the equation: $R_4NOH + NH_4X \rightarrow R_4NX + H_2O + NH_3$. Because this latter reaction may be driven quantitatively to the right without destruction of the quaternary ammonium ion, a simple, direct means for the preparation of the quaternary ammonium salts of many of the less stable, less familiar acids is made possible. Though the ensuing examples utilize tetraalkylammonium bases, there should be no restrictions preventing the use of other quaternary ammonium bases under suitable experimental conditions.

### EXPERIMENTAL

Aqueous solutions (2–3 wt. %) of tetramethyl- and tetraethylammonium hydroxide were prepared from the commercially available 10 wt. % solutions (Eastman Kodak "White Label" grade). The exact titers of the dilute solutions were obtained by titration with standard 0.1*N* acid to the phenolphthalein end-point. All ammonium salts used were of "Reagent" grade.

*Tetramethylammonium thiocyanate.* To 2.831 g. (0.03106 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.364 g. (0.03106 mole) of ammonium thiocyanate. The solution was boiled down to a volume of 50 ml. three times, the water being replaced after each volume decrease. The mixture was then carefully heated to dryness and placed in an oven for 2 hr. at 100°. Yield: 100% (4.1 g.).

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*Anal.* Calcd. for $(CH_3)_4NSCN$: SCN, 43.90. Found: 43.45, 43.50, 43.62 (by precipitation as silver thiocyanate).

*Tetramethylammonium sulfate.* To 2.754 g. (0.03022 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.997 g. (0.01511 mole) of ammonium sulfate. The solution was boiled and brought to dryness as in preparation (I), whereupon the residue was heated in an oven for 12 hr. at 120° and 6 hr. at 130°. Yield: 92% (3.4 g.).

*Anal.* Calcd. for $[(CH_3)_4N]_2SO_4$: $SO_4$, 39.30. Found: 39.44, 39.47 (by precipitation as barium sulfate).

*Tetramethylammonium bromide.* To 2.661 g. (0.02925 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.865 g. (0.02925 mole) of ammonium bromide. The resulting solution was treated as in preparation (II). Yield: 100% (4.5 g.).

*Anal.* Calcd. for $(CH_3)_4NBr$: Br, 51.88. Found: 51.19, 51.27, 51.28 (by precipitation as silver bromide).

*Tetramethylammonium iodide.* To 2.9651 g. (0.03253 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 4.7157 g. (0.03252 mole) of ammonium iodide which had been previously washed with carbon tetrachloride to remove all traces of free iodine formed as a result of decomposition during prolonged storage. The resulting solution was treated as in preparation (II); yield: 100% (6.5 g.).

*Anal.* Calcd. for $(CH_3)_4NI$: I, 63.12. Found: 62.42, 62.54, 62.64 (by precipitation as silver iodide).

*Tetramethylammonium chromate.* To 3.518 g. (0.03860 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.5 ml. of aqueous 28% ammonia and 2.433 g. (0.00965 mole) of ammonium dichromate. The additional ammonia was needed to bring about conversion of the dichromate ion to the chromate ion. The resulting solution was treated as in preparation (II).

*Anal.* Calcd. for $[(CH_3)_4N]_2CrO_4$: $CrO_4$, 43.89. Found: 43.14, 43.20, 43.41 (by precipitation as barium chromate).

*Tetramethylammonium oxalate.* To 3.170 g. (0.03478 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 2.471 g. (0.01739 mole) of ammonium oxalate monohydrate. The resulting solution was treated as in preparation (II).

*Anal.* Calcd. for $[(CH_3)_4N]_2C_2O_4$: $C_2O_4$, 26.85. Found: 26.40, 26.45, 26.46 (by precipitation as calcium oxalate monohydrate).

*Tetramethylammonium thiosulfate.* To 2.265 g. (0.02484 mole) of tetramethylammonium hydroxide in 125 ml. of water was added 1.841 g. (0.01242 mole) of ammonium thiosulfate. The solution was boiled down twice to 25 ml. with replacement of water, evaporated, and dried for 12 hr. at 105°, and for 4 hr. at 130°; yield 97% (3.1 g.).

*Anal.* Calcd. for $[(CH_3)_4N]_2S_2O_3$: $S_2O_3$, 43.03. Found: 41.97, 42.10, 42.13 (by conversion to sulfate and precipitation as barium sulfate).

*Tetraethylammonium iodide.* To 2.221 g. (0.01508 mole) of tetraethylammonium hydroxide in 125 ml. of water was added 2.186 g. (0.01508 mole) of ammonium iodide. The solution was boiled down twice to 10 ml. with replacement of water, evaporated, and dried for 20 hr. at 85°; yield 100% (3.9 g.).

*Anal.* Calcd. for $(C_2H_5)_4NI$: I, 49.35. Found: 48.84, 48.87, 48.92.

*Tetraethylammonium thiocyanate.* To 2.468 g. (0.01676 mole) of tetraethylammonium hydroxide in 125 ml. of water was added 1.276 g. (0.01676 mole) of ammonium thiocyanate. The resulting solution was treated as in preparation (VII); yield 94% (3.0 g.).

*Anal.* Calcd. for $(C_2H_5)_4NSCN$: SCN, 30.84. Found: 29.83, 29.84, 29.87.

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## Synthesis of Compounds for Chemotherapy of Tuberculosis. VII. Pyridine *N*-Oxides with Sulfur-Containing Groups[1]

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In view of the high activity of thioisonicotinamide in the chemotherapy of experimental tuberculosis in mice,[2] a number of pyridine derivatives containing a —CSNH— moeity were prepared.

Reduction of the pyridine ring eliminated activity; *N*-oxidation reduced activity, and separation from the ring of the —CSNH— group (thioureas and pseudothioureas) eliminated activity as did also the conversion of the group into a ring system (thiazole and thiazolone).

The previously known *N*-oxides of picolinamide,[3,9] thiopicolinamide,[4] nicotinamide,[3] and isonicotinamide,[3] as well as 4-pyridylthiourea,[5] also showed no activity in the same test in which nicotinamide is active.[6] All other compounds prepared were either inactive or less active than thioisonicotinamide.[2]

### EXPERIMENTAL[7]

*Isonicotinonitrile-1-oxide.* Isonicotinamide-1-oxide (147 g.) was heated at reflux for 0.5 hr. with 1500 g. of phosphorus oxychloride. The solution was concentrated to a small volume under vacuum and poured onto cracked ice. The solution was made alkaline with concentrated ammonia and the separated nitrile filtered off. The solution was extracted five times with chloroform using a total of 800 ml. for the extractions. The previously separated solid was extracted at the boiling point with the chloroform extractants and filtered. On cooling, almost pure nitrile separated which could be recrystallized from chloroform or methanol; yield, 85 g., m.p. 229–230°.

*Anal.* Calcd. for $C_6H_4N_2O$: N, 23.3. Found. N: 22.9.

This compound has been previously reported,[8] with a melting point of 220–221° by preparation from 4-aminopyridine-1-oxide using the Sandmeyer reaction.

*Thioisonicotinamide-1-oxide.* Isonicotinonitrile-1-oxide (30 g.) was dissolved in 300 ml. of a methanol solution containing 30% ammonia by weight. The solution was saturated with hydrogen sulfide gas and on standing 2 days the thioamide separated. The recovered yellow-orange product was recrystallized from hot water; yield, 12 g., m.p. 205–206°.

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*Anal.* Calcd. for $C_6H_6N_2OS$: C, 46.7; H, 3.9. Found: C, 47.0; H, 4.0.

*Thionicotinamide-1-oxide.* Nicotinonitrile-1-oxide was prepared in a 55% yield by treating the nicotinamide-1-oxide with phosphorus oxychloride for 0.5 hr. at reflux. Nicotinonitrile-1-oxide (28 g.) was dissolved in 300 ml. of a methanol solution containing 20% ammonia gas by weight. This solution was saturated with hydrogen sulfide gas and a small quantity of the thioamide separated in 18 hr. The solution was concentrated to a solid and the residue crystallized as a colorless compound from hot water; yield, 14 g., m.p. 161–164°.

*Anal.* Calcd. for $C_6H_6N_2OS$: S, 20.8. Found: S, 20.9.

*Thioisonicctinamide hydrochloride.* Thioisonicotinamide (10 g.) was dissolved in 200 ml. of ethanol and 20 ml. of 9*N* hydrogen chloride in ethanol was added. The orange colored hydrochloride separated and was reerystallized from hot ethanol; yield, 9 g., m.p. 231–232°.

*Anal.* Calcd. for $C_6H_6N_2S{\cdot}HCl$: N, 16.1. Found: N, 16.1.

The hydrochloride exhibited the same order of activity as the free base in tuberculosis of mice.

*Picolinamide-1-oxide.* Picolinamide (70 g.) was heated at 80° for 6 hr. in a solution of 100 g. of pearcetic acid (40%) and 300 ml. of acetic acid. The solution was diluted with 500 ml. of water and concentrated to a solid in vacuum. The colorless solid was recrystallized from methanol; yield, 51 g., m.p. 165–166°.

*Anal.* Calcd. for $C_6H_6N_2O_2$: C, 52.1; H, 4.4; N, 20.3. Found: C, 52.6; H, 4.5; N, 19.8.

The investigation of the picolino-type *N*-oxide gave several anomalies. The reaction of phosphorus pentasulfide and potassium sulfide in pyridine on picolinamide 1-oxide deoxygenated the *N*-oxide and gave only thiopicolinamide.

The reaction of hydrogen peroxide in glacial acetic acid on picolinamide[9] has been reported to give the ammonium salt of picolinic acid 1-oxide. We have verified this reaction although we separated free picolinic acid 1-oxide instead of the salt.

*Picolinonitrile-1-oxide.* A diatomaceous earth (Hyflo, 70 g.) was dried at 110° and mixed with 150 g. of phosphorus pentoxide by shaking in a closed vessel. The dehydrating mixture was added to 500 ml. of sodium dried toluene and 25 g. of dry picolinamide 1-oxide. The mixture was agitated with an efficient stirrer and held at reflux temperature for 4 hr. The gummy mixture was filtered on a dry Hyflo bed. The residue was treated with water and concentrated ammonium hydroxide, and then extracted with chloroform. The chloroform extract was added to the toluene filtrate. The solution of toluene and chloroform was concentrated to a small volume (50 ml.); 20 ml. of chloroform and 20 ml. of ether were then added. On chilling, crystals separated which were recrystallized from ether; yield, 5 g., m.p. 122–123° for which Leonard and Wajngurt[4] report 117–118° by a different method of preparation.

*Anal.* Calcd. for $C_6H_4N_2O$: C, 60.1; H, 3.4. Found: C, 60.6; H, 3.5.

The reaction of boiling phosphorus oxychloride on picolinamide-*N*-oxide rapidly deoxygenated the compound to yield 2-picolinonitrile. In contrast, over 6 hr. of boiling phosphorus oxychloride was required to deoxygenate isonicotinamide-1-oxide to give isonicotinonitrile.

The preparation of picolinonitrile-1-oxide has recently been reported by Leonard and Wajngurt[4] by the direct oxidation of picolinonitrile using aqueous hydrogen peroxide and acetic acid, and from which was also prepared thiopicolinamide-1-oxide (m.p. 145–146°) using hydrogen sulfide and methanolic ammonia.

*4-Pyridylthiourea-1-oxide.* 4-Aminopyridine-1-oxide hydrochloride (20 g.) was treated with 12.5 g. of ammonium thiocyanate in 250 ml. ethanol at reflux temperature for 6 hr. The hot suspension was filtered, concentrated to a solid, and extracted with acetone. A colorless product was obtained by recrystallization from acetone; yield, 20 g., m.p. 126–127°.

*Anal.* Calcd. for $C_6H_7N_3OS$: N, 24.9. Found: N, 24.5.

*2-(3'-Pyridyl)-2-thiopseudourea-1'-oxide hydrobromide.* 3-Bromopyridine-1-oxide hydrochloride (53.5 g.) in 100 ml. water, was neutralized with dilute sodium hydroxide and extracted with chloroform. Concentration of the chloroform gave the free 3-bromopyridine-1-oxide. This material was treated at reflux for 5 hr. in 300 ml. of ethanol with 19 g. of thiourea. On cooling, the colorless product crystallized and was recrystallized from ethanol; yield, 50 g., m.p. 145–147°, for which 142° has recently been reported.[4]

*Anal.* Calcd. for $C_6H_7N_3OS{\cdot}HBr$: N, 16.8. Found. N, 16.5.

This compound could not be decomposed to yield 3-pyridinethiol 1-oxide using sodium hydroxide solution.

*N-Ethylnicotinamide-1-oxide.* *N*-Ethylnicotinamide (60 g.) was treated with 120 g. of 40% peracetic acid in acetic acid at 10–15°. Concentration at 80° to an oil gave a crystalline material on standing at 25° for 48 hr. The colorless product was recrystallized from acetone; yield, 35 g., m.p. 123–124°.

*Anal.* Calcd. for $C_8H_{10}N_2O_2$: N, 16.9. Found: N, 16.9.

*3,5-Dibromopyridine-1-oxide.* 3,5-Dibromopyridine (42 g.), 80 g. 40% peracetic acid in acetic acid and 300 ml. of acetic acid was heated at 80° for 3 hr. and then at 50° for 12 hr. Concentration to a solid and recrystallization from ethanol gave 30 g. of a colorless product; m.p. 143–144°.

*Anal.* Calcd. for $C_5H_3Br_2NO$: N, 5.3. Found: N, 5.5.

*2-(5'-Bromo-3'-pyridyl)-2-thiopseudourea-1'-oxide hydrobromide.* 3,5-Dibromopyridine-1-oxide (20 g.) was treated at reflux for 5 hr. in 300 ml. of ethanol with 15 g. of thiourea. On cooling, the product crystallized and was recrystallized from ethanol; yield, 20 g., m.p. 162–163°.

*Anal.* Calcd. for $C_6H_6BrN_3OS{\cdot}HBr$: N, 12.8. Found: N, 13.0.

*N,N'-methylenebis(thioisonicotinamide) hydrate.* Thioisonicotinamide (25 g.), in 1 l. of water, was treated with 30 ml. of 37% formaldehyde solution. The *p*H was adjusted and maintained at 7.5 using potassium hydroxide solution. After standing 6 hr. the *p*H was adjusted to 7 by formic acid. On cooling to 4°, a yellow product crystallized and was recrystallized from water; yield, 24 g., m.p. 146–147°.

*Anal.* Calcd. for $C_{13}H_{12}N_4S_2{\cdot}H_2O$: C, 51.0; H, 4.5; N, 18.3; $H_2O$, 5.9. Found: C, 51.4; H, 4.3; N, 18.1; $H_2O$, 5.8, 6.0.

This compound was less active than the parent compound in tuberculosis in mice.

The assignment of the linear structure was based on analyses and the fact that infrared analyses gave none of the characteristic absorption bands for the triazine structure which is found in the condensation product, hexahydro-1,3,5-triisonicotinamide-*s*-triazine, from the reaction of isonicotinyl hydrazine[10] with formaldehyde. However, it is interesting to note that picolinyl hydrazine[11] and formaldehyde also gave a linear condensation product, 1,1'-methylenebis(2-picolinylhydrazine)dihydrochloride instead of the triazine.

*4-Cyanopiperidine.* Isonipecotamide (100 g.) in 450 g. of phosphorus oxychloride was refluxed for 2 hr. and concentrated *in vacuo* to a small volume and poured onto ice. The solution was made alkaline with concentrated ammonia and extracted five times using 400 ml. of chloroform for each extraction. Concentration of the chloroform gave an oil, b.p. 100° at 7 mm., $n_D^{23}$ 1.4741; yield, 37 g.

*Anal.* Calcd. for $C_6H_{10}N_2$: N, 25.4. Found: N, 24.8.

4-Cyanopiperidine has been prepared in a 12% yield from isonipecotamide using thionyl chloride.[12]

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*Thioisonipecotamide.* 4-Cyanopiperidine (35 g.) was treated in 300 ml. of 30% ammonia in methanol with hydrogen sulfide gas until saturation. After standing for 48 hr. at 25°, the solution was concentrated to a solid which was recrystallized from water as a very light cream colored compound; yield, 30 g., m.p. 173–174°.

*Anal.* Calcd. for $C_6H_{12}N_2S$: N, 19.4. Found: N, 19.2.

Attempts to convert isonipecotamide to thioisonipecotamide using phosphorus pentasulfide in pyridine failed with or without potassium sulfide as a catalyst In all cases, the ring was dehydrogenated and only thioisonicotinamide was obtained in 25–40% yields.

*5-Methyl-2-(4-pyridyl)-4(5H)-thiazolone hydrobromide.* Thioisonicotinamide (50 g.) and 56 g. of α-bromopropionic acid were heated together in toluene at the boiling point for 6 hr. The excess toluene was decanted and the solid residue dissolved in ethanol and decolorized using activated charcoal. On cooling, a yellow product crystallized which was recrystallized from ethanol; yield, 25 g., m.p. >250°.

*Anal.* Calcd. for $C_9H_8N_2OS \cdot HBr$: C, 39.8; H, 3.3; N, 10.3. Found: C, 40.5; H, 3.5; N, 10.4.

*4-Methyl-2-(4-pyridyl)thiazole hydrochloride.* Thicisonicotinamide (50 g.) was heated at the boiling point in 250 ml. of chloroacetone. The excess chloroacetone was removed *in vacuo* and the residue triturated with ether. The yellow residue was then crystallized from methanol; recrystallization after charcoal decoloration gave a buff yellow material; yield, 11.5 g., m.p. 219–220(dec.).

*Anal.* Calcd. for $C_9H_8N_2S \cdot HCl$: N, 13.1. Found. N, 12.9.

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## Some 3,4,5-Trialkoxybenzoic Acids and Esters

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In a previous report,[1] we described the methods of synthesis and properties of the β-diethylaminoethyl esters of the isomeric trimethoxybenzoic acids. It appeared to be of interest to extend this study by varying the nature of the ether groupings in a representative member of the series. Accordingly, we have prepared the esters of the 3,4,5-trialkoxybenzoic acids which are listed in Table I. The 3,4,5-trialkoxy acids were chosen because of the availability of gallic acid, and because of the relationship of the 3,4,5-trimethoxybenzoate radical to the reserpine molecule.

The 3,4,5-triethoxy-, tri-*n*-propoxy-, and tribenzyloxybenzoic acids were obtained from gallic acid by conventional alkylation procedures. They were converted then to the β-diethylaminoethyl esters by the Horenstein and Pählicke, method.[2]

Difficulties were encountered in attempts to alkylate gallic acid with *n*-butyl and *n*-amyl bromides in the presence of alkali. However, it was possible to convert the trisodium salt of methyl gallate to the corresponding ethers. Hydrolysis of methyl 3,4,5-tri-*n*-butoxybenzoate produced an oil which afforded a small amount of crystalline 3,4,5-tri-*n*-butoxybenzoic acid. Treatment of methyl 3,4,5-tri-*n*-amyloxybenzoate in a similar fashion led to oils which could not be induced to crystallize.

Pharmacological tests[3] have shown that the β-diethylaminoethyl esters of the trimethoxybenzoic acids are relatively impotent in producing local anesthetic action in guinea pigs, whether tested by intradermal administration or topical application to the eye. The corresponding esters of the 3,4,5-triethoxy- and tri-*n*-propoxybenzoic acids apparently do not possess local anesthetic properties. The tribenzyloxy ester is not sufficiently soluble in water to be tested under comparable conditions.

### EXPERIMENTAL[4]

*Materials. 3,4,5-Triethoxybenzoic acid* (m.p. 108–110°; lit.[5] m.p. 110°) was obtained by the ethylation of gallic acid with ethyl sulfate. *3,4,5-Tribenzyloxybenzoic acid* (m.p. 190–191°; lit.[6] m.p. 187°) resulted from the action of benzyl chloride on gallic acid. Treatment of a methyl alcohol of the latter with *n*-propyl bromide and alkali gave 3,4,5-*n*-propoxybenzoic acid; m.p. 89–91° after recrystallization from aqueous alcohol. Esterification of gallic acid by means of methanol, which had been saturated with hydrogen chloride, produced the corresponding ester (m.p. 194–195°; lit.[6] m.p. 198°).

*β-Diethylaminoethyl 3,4,5-trialkoxybenzoate hydrochlorides.* The three amino ester hydrochlorides listed in Table I were prepared according to previously described directions,[1] and were purified by recrystallization from a mixture of absolute ethanol and absolute ether.

*Methyl 3,4,5-tri-n-butoxybenzoate and corresponding acid.* To a solution of 6.9 g. (0.3 g. atom) of sodium in 400 ml. of absolute ethanol was added 18.4 g. (0.1 mole) of methyl gallate and the resulting slurry was heated to reflux. A solution of 54.8 g. (0.4 mole) of *n*-butyl bromide in 50 ml. of alcohol was added dropwise over a period of 1 hr. and the reaction mixture was stirred and heated for an additional 17 hr. Most of the solvent was removed by distillation, 200 ml. of water was added to the residue, and the mixture was extracted with ether. The ether solution was washed several times with dilute sodium hydroxide solution, dried, and concentrated. There was obtained 13 g. (37%) of water which distilled at 190–195°/1 mm.; $n_D^{20}$ 1.4947.

A sample of the ester was hydrolyzed in 10% aqueous alcoholic potassium hydroxide solution. The reaction mixture was acidified, kept cool for several days, and filtered. The resulting solid was recrystallized from aqueous alcohol to give 3,4,5-tri-*n*-butoxybenzoic acid which melted at 68.5–70°.

*Methyl 3,4,5-tri-n-amyloxybenzoate.* A slurry of the trisodium salt of methyl gallate, prepared from 55.2 g. (0.3

(1) N. Rabjohn and A. Mendel, *J. Org. Chem.*, **21**, 218 (1956).

(2) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

(3) The authors are indebted to D. F. Marsh of the McNeil Laboratories for the pharmacological results.

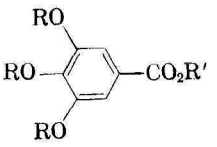
(4) All melting points are uncorrected. The semimicro carbon hydrogen data were obtained by A. M.

(5) W. Will and K. Albrecht, *Ber.*, **17**, 2098 (1884).

(6) C. Schöpf and L. Winterhalder, *Ann.*, **544**, 62 (1940).

TABLE 1

3,4,5-TRIALKOXYBENZOIC ACIDS AND ESTERS,




| Compound | | M.P. or B.P., °C. | Analyses, % | | | |
|---|---|---|---|---|---|---|
| | | | Carbon | | Hydrogen | |
| R | R' | | Calcd. | Found | Calcd. | Found |
| $C_2H_5$ | $C_6H_{15}ClN$[a] | 128–130 | 58.52 | 58.59 | 8.27 | 8.22 |
| $C_6H_5CH_2$ | $C_6H_{15}ClN$[a] | 153–155 | 70.87 | 70.51 | 6.65 | 6.92 |
| *n*-$C_3H_7$ | H | 89–91 | 64.84 | 65.06 | 8.16 | 8.12 |
| *n*-$C_3H_7$ | $C_6H_{15}ClN$[a] | 125–126 | 61.16 | 60.82 | 8.87 | 8.98 |
| *n*-$C_4H_9$ | H | 68.5–70 | 67.43 | 67.45 | 8.94 | 9.01 |
| *n*-$C_4H_9$ | $CH_3$ | 190–195/1 mm. | 68.15 | 68.37 | 9.15 | 9.42 |
| *n*-$C_5H_{11}$ | $CH_3$ | 203–205/1 mm. | 70.01 | 69.71 | 9.71 | 9.58 |

[a] $C_6H_{15}ClN = CH_2CH_2N(C_2H_5)_2 \cdot HCl$.

mole) of the ester and 0.9 mole of sodium ethoxide, in 1 l. of absolute ethanol was stirred and heated to reflux. A solution of 181.2 g. (1.2 moles) of *n*-amyl bromide in 100 ml. of alcohol was added dropwise, and the reaction mixture was heated for 10 hr. It was worked up in a fashion similar to that described in the preceding experiment. Distillation of the residue which remained after concentration of the ether solution yielded 48.5 g. (41%) of the ester; b.p. 203–205°/1 mm., $n_D^{20}$ 1.4971.

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## Isolation of Maltose from Honeydew on Alsike (*Trifolium hybridum*) Seeds[1]

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*Received January 28, 1957*

Recently Northrup King and Company, Minneapolis, drew our attention to the presence of a sticky substance on alsike (*Trifolium hybridum*) seeds harvested in Idaho. The material, a type of honey dew arising from infestation of the plants by aphids, *Therioaphis maculata* (Buckton), was obtained by washing the seeds with water, filtering, and concentrating the brownish yellow filtrate *in vacuo* to a sirup. This sirup reduced Fehling solution and gave a positive Molisch test. Paper chromatographic analysis, using three different solvents; 1-butanol:ethanol:water, (4:1:5);[2] 1-propanol:water azeotrope;[3] ethylacetate : pyridine:water (2.5:1.0:3.5)[4] and *p*-anisidine phosphate spray,[5] revealed the presence of glucose, fructose, maltose, maltotriose, and other more slowly moving components.[6] Inasmuch as the material arose from aphids it was expected that one of the components might be melezitose[7] but none was present. The maltose component was separated by sheet paper chromatography using Whatman No. 3 paper and the above pyridine-ethyl acetate-water solvent in the usual way and extracted from the appropriate segments of the paper with water. Removal of the solvent *in vacuo* produced a colorless sirup which crystallized when dissolved in the minimum quantity of water and treated with ethanol to incipient turbidity. The crystalline product proved to be maltose, melting point and mixed melting point 118–123°, $[\alpha]_D^{22}$ + 126° in water (*c*, 0.5). The maltose was further characterized by reduction with sodium borohydride[8] to maltitol which was tranformed by means of sodium acetate and acetic anhydride into the crystalline nonacetate,[9,10] melting point and mixed melting point 82–83°.

Paper chromatography has shown in other experiments that the honey dew exuded by the leaves of a young peach tree (*Amygdalus sp.*) contained glucose, fructose, and sucrose; that from the leaves of a House Balsam (*Impatiens sultani*) contained

(1) Paper No. 3789 of the Scientific Journal Series, Minnesota Agricultural Experiment Station.

(2) S. M. Partridge, *Nature*, **158**, 270 (1946).

(3) F. Smith and H. C. Srivastava, *J. Am. Chem. Soc.*, **78**, 1404 (1956).

(4) E. F. McFarren, K. Brand, and H. R. Rutkowski, *Anal. Chem.*, **23**, 1146 (1951).

(5) S. Mukherjee and H. C. Srivastava, *Nature*, **169**, 330 (1952).

(6) C. J. P. Wolf and W. H. Ewart, *Arch. Biochem. and Biophys.*, **58**, 365 (1955); R. H. Hackman and Trikojus, *Biochem. J.*, **51**, 653 (1952).

(7) C. S. Hudson and S. F. Sherwood, *J. Am. Chem. Soc.*, **42**, 116 (1920).

(8) M. Abdel-Akher, J. K. Hamilton, and F. Smith, *J. Am. Chem. Soc.*, **73**, 4691 (1951).

(9) M. L. Wolfrom and T. S. Gardner, *J. Am. Chem. Soc.*, **62**, 2553 (1940).

(10) P. Karrer and J. Büchi, *Helv. Chim. Acta*, **20**, 86 (1937).

only sucrose which crystallizes on the plants while the nectar from flowers of the Poinsettia (*Poinsettia sp.*) contained glucose, fructose, and sucrose.

*Acknowledgment.* The authors thank Northrup King and Co., Minneapolis for the alsike clover seeds supplied through the courtesy of Mr. E. Doty.

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## Cation Exchange Resins as Catalysts in the Alkylation of Phenols

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*Received January 28, 1957*

Both anion and cation exchange resins have been widely used as catalysts for reactions such as esterification, hydrolysis, and sucrose inversion[1,2]—reactions which involve only carbon-oxygen bonds. By comparison, reports of the use of resins (particularly cation exchange resins) as catalysts for reactions in which carbon–carbon bonds are formed, are few. Ion exchange resins are reported to catalyze cyanohydrin formation, aldol condensation,[3,4] and the various modifications of the Knoevenagel[5] and Michael[6] condensations. It seemed of interest to investigate other reactions which are normally catalyzed by strong acids, to see whether cation exchange resins could be used in place of the usual Lewis acids.

It has been found that the sulfonic acid type cation exchange resins are excellent catalysts for the alkylation of phenol with olefins such as isobutylene, diisobutylene, and nonene-1.

The resins investigated were Amberlite IR-112 and IR-120, Dowex 50 × 12, and Permutite Q; all were sulfonic acid type resins. The conversion[7] was a little lower when Amberlite IR-112 was used, but all other results were independent of the resin used.

The yields in these alkylations were essentially independent of the concentration of resin.

When phenol was alkylated with isobutylene using a cation resin there was generally no *ortho* isomer in the product.

The presence of water was deleterious, at least in the diisobutylene alkylation reactions, for when the resin was used after only air drying, no reaction occurred. The reaction required an oven-dried resin. Drying of the diisobutylene also increased the yield.

The use of a cation exchange resin as catalyst has the particular advantage over a mineral acid catalyst that at the conclusion of the reaction, a simple filtration of the molten reaction mixture leaves an acid-free solution ready for distillation. There is no chance of acid catalyzed rearrangement during the distillation, and the product is a high purity *p*-alkylphenol. In addition, the use of resins as catalysts eliminates by-products formed by reaction of the mineral acids with the phenol, and by by-products due to polymerization or degradation of the olefin.

Attempts to alkylate xylene and benzene using a resin catalyst were unsuccessful.

### EXPERIMENTAL

*Preparation of resin catalyst.* The resins which are normally purchased in the salt form were converted to the acid form by washing with 5% $H_2SO_4$ until the wash water gave a negative flame test for sodium. The resin was then thoroughly washed with distilled water until the wash water was neutral, air dried for 24 hr., and then heated for 18 hr. in a vacuum oven at 100–120°.

The resin may be washed with acetone and ether, following the air drying, to remove traces of colored organic impurities. This treatment has no effect on the catalytic activity of the resin.

The resins were all commercial materials: Amberlite IR-112 and IR-120, 16 to 50 mesh (Rohm & Haas), Permutite Q, approx. 20 to 60 mesh (Permutite Corp.), and Dowex 50 × 12, 200–400 mesh (Dow Chemical).

*p-tert-Octylphenol*[8] *(p-diisobutylphenol or 1,1,3,3-tetramethylbutylphenol).* A typical preparation is given. Phenol (250 g., 2.6 moles), diisobutylene, (328 g., 219 moles), and 17.5 g. of Amberlite IR-112, prepared as described above, were heated together with vigorous stirring for 24 hr. at 70–75°.

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(1) (a) S. Sussman in *Ion Exchange—Theory and Application,* F. C. Nachod, ed., Academic Press Inc., New York, N. Y., 1949, p. 265. (b) F. C. Nachod, *Ion Exchange Catalysis,* L. Farkas Memorial Volume, A. Farkas, E. P. Wigner, eds., Research Council of Israel, Jerusalem, 1952, p. 188.

(2) (a) R. Kunin and R. J. Meyers, *Ion Exchange Resins,* John Wiley and Sons, New York, N. Y., p. 137, 1950. (b) F. X. McGarvey and R. Kunin in *Ion Exchange Technology,* F. C. Nachod and J. Schubert, eds., Academic Press Inc., New York, N. Y., 1949, p. 265.

(3) C. J. Schmidle and R. C. Mansfield, *Ind. Eng. Chem.,* **44,** 1388 (1952).

(4) P. Mastagli and G. V. Durr, *Bull. soc. chim. France,* 268 (1955); *Chem. Abstr.,* **50,** 1668.

(5) M. J. Astle and W. C. Gergel, *J. Org. Chem.,* **21,** 493 (1956).

(6) E. D. Bergmann and R. Corett, *J. Org. Chem.,* **21,** 107 (1956).

(7) For greater ease in discussing the results of these experiments, the terms "conversion" and "yield" are employed. Percent conversion represents the percent of theoretical value based on the amount of (limiting) starting material charged to the reaction. Percent yield represents the percent of the theoretical value based on the amount of starting material used up (or not recovered) during the reaction.

(8) As used here, *p-tert*-octylphenol refers to the alkyl group 1,1,3,3-tetramethylbutyl-, which results from the alkylation of phenols with diisobutylene (DIB). DIB is a mixture of two isomers, 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene which are assumed to give identical alkylation products.

TABLE I

ALKYLATION OF PHENOL WITH ISOBUTYLENE[a]

| Catalyst | Resin,[b] % | Di-*tert*-Butylphenol, % conv.[c] | *o*-*tert*-Butylphenol, % conv.[c] | *p*-*tert*-Butylphenol, % conv.[c] | *p*-*tert*-Butylphenol, % yield[c] |
|---|---|---|---|---|---|
| Amberlite IR-112 | 6¼ | 0 | 0 | 37 | 98 |
| Permutite Q | 6¼ | 0 | 4 | 51 | 83 |
| Amberlite IR-120 | 6¼ | 0 | 0 | 57 | 87 |
| Dowex 50 × 12 | 6¼ | 0 | 0 | 49 | 77 |

[a] Reactions carried out as described in Experimental. [b] Wt. % based on total charge. [c] See ref. 8.

TABLE II

ALKYLATION OF PHENOL WITH DIISOBUTYLENE IN THE PRESENCE OF AMBERLITE IR-112

| Temp., °C. | Time, Hrs. | Resin,[a] % | *tert*-Butylphenol, % Conv.[b] | *tert*-Octylphenol, % Conv.[b] | *tert*-Octylphenol, % Conv.[b] | |
|---|---|---|---|---|---|---|
| 83 | 3 | 14 | Trace | Trace | Trace | [c] |
| 80 | 2¾ | 14 | 10 | 38 | 63 | [d] |
| 70–5 | 4¼ | 1.4 | 6 | 49 | 100 | [d,e] |
| 70–5 | 8 | 0.4 | 4 | 53 | 97 | [d,e] |
| 70–5 | 24 | 3 | 4 | 73 | 95 | [d,e] |
| 70–5 | 24 | 7 | 3 | 88 | 100 | [d,e] |
| 100–5 | 4¼ | 1.4 | 11 | 65 | 91 | [d,e] |
| 100–10 | 18 | 2 | 14 | 61 | 77 | [d,e] |

[a] Wt. % based on total charge. [b] See ref. 7. [c] Air dried resin used. [d] Heat dried resin. [e] DIB dried.

The resin was then filtered off. The pale yellow filtrate had a set point of 57–60°. On distillation, the following fractions were obtained. b.p. 73–110° (20 mm.), phenol, 63 g.; b.p. 140–153° (20 mm.), *p*-*tert*-octylphenol, 390 g. (73% conversion, 95% yield), colorless liquid which soon crystallized, m.p. 82–83° (lit.[9] b.p.$_{20}$ 163°, m.p. 84°).

*p*-*tert*-*Butylphenol.* In a typical preparation 94 g. (1.0 mole) of phenol and 10 g. of Amberlite IR-120, prepared as described above, were heated at 80° with vigorous stirring as 58.7 g. (0.92 moles) of isobutylene (Atlantic Refining Co.) was passed in beneath the surface of the liquid over a period of 3 hr. The isobutylene was completely absorbed. After the isobutylene had all been added, the temperature was raised to 120° for 4 hr. The resin was filtered off and the colorless filtrate was distilled giving the following fractions: b.p. 175–205°, phenol, 33.5 g.; b.p. 220–228°, *o*- and *p*-*tert*-butylphenol, 1.5 g.; b.p. 230–234°, *p*-*tert*-butylphenol, 73.8 g. (57.5% conversion, 83% yield), m.p. 92° (lit.[9] b.p. 237°, m.p. 100°).

*Nonylphenol.* Phenol (47 g., 0.5 mole), 63 g. (0.5 mole) of nonene-1 and 5 g. of prepared Amberlite IR-112 resin were heated at 100–10° for 24 hr. with vigorous stirring. The resin was removed by filtration and the filtrate distilled giving the following fractions: b.p. 130–160°, nonene-1, 7 g.; b.p. 182–183°, phenol, 10.6 g.; b.p. 297–305°, nonylphenyl, 75.2 g., $n_D^{28}$ 1.5060 (68% conversion, 92% yield).

*Attempted alkylation of xylene.* The reaction was carried out as described under the preparation of *p*-*tert*-butylphenol, except that the isobutylene was fed in more slowly. No absorption of isobutylene occurred, and the xylene was quantitatively recovered.

*Attempted alkylation of benzene.* Benzene (80 g.), 84 g. of propylene tetramer and 5 g. of Amberlite IR-112 were heated at reflux, with stirring for 25 hr. No reaction had occurred for the propylene tetramer was quantitatively recovered on distillation.

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(9) W. A. Pardee and W. Weinrich, *Ind. Eng. Chem.*, **36**, 595 (1944).

## Metalation of Phenyl Benzyl Sulfide and Sulfone with *n*-Butyllithium

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The large activating effect of a sulfone group toward metalation at an adjacent C—H bond is well known. Thus Truce and co-workers[2] have demonstrated that diaryl sulfones are metalated readily with *n*-butyllithium at the positions *ortho* to the sulfone group. Gilman and Webb[3] observed the metalation of methyl phenyl sulfone with *n*-butyllithium on the methyl group, and Grignard reagents have been shown to metalate the same position.[4,5]

It was of interest to us to observe the position of metalation of phenyl benzyl sulfone since this molecule contains two different kinds of activated C—H bonds adjacent to the sulfonyl groups. The action of a *n*-butyllithium on an equimolar amount of benzyl phenyl sulfone followed by carbonation and hydrolysis allowed formation of 65% of α-phenylsulfonylphenylacetic acid (I) indicating metalation at the —$CH_2$— group. The structure of the acid from metalation is indicated by comparison of its decarboxylation temperature of 142–

(1) Present address: The Koppers Co., Monaca, Pa.

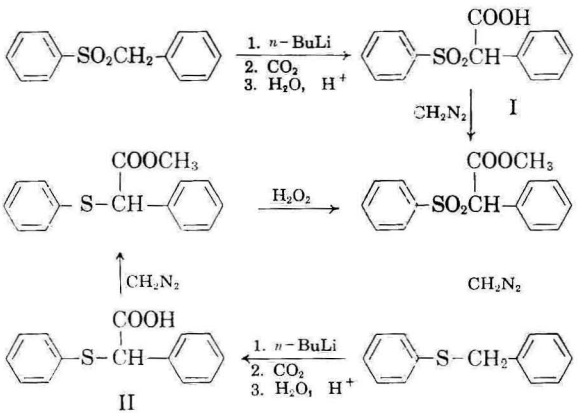
(2) W. E. Truce and M. F. Amos, *J. Am. Chem. Soc.*, **73**, 3013 (1951) and subsequent papers.

(3) H. Gilman and F. J. Webb, *J. Am. Chem. Soc.*, **71**, 4062 (1949).

(4) L. Field, *J. Am. Chem. Soc.*, **74**, 3919 (1952).

(5) W. M. Ziegler and R. Connor, *J. Am. Chem. Soc.*, **62**, 2596 (1940).

143° with the similar value given by Fuchs and Breuer.[6] These latter workers have established the structure of α-phenylsulfonylphenylacetic acid by synthesis. We established that the residue remaining after heating the metalation acid was phenyl benzyl sulfone by the method of mixed melting points. Cohen and Smiles[7] have reported the melting point of the isomeric *o*-benzylsulfonylbenzoic acid as 126–128°. The *m*- and *p*-benzylsulfonylbenzoic acids have apparently never been reported, but it was considered highly unlikely that either of these positions could have been involved in the metalation in view of the very strong tendency of sulfone metalation to occur at the positions adjacent to the sulfone group.




Metalation of phenyl benzyl sulfone with an equivalent amount of methylmagnesium iodide, followed by carbonation, allowed formation of I in 28% yield.

Gilman and Webb[8] have reported the rather unexpected metalation by *n*-butyllithium of methyl phenyl sulfide on the methyl group ("lateral metalation"). We carried out the metalation of phenyl benzyl sulfide with *n*-butyllithium and obtained, subsequent to carbonation and hydrolysis, a 75% yield of α-phenylmercaptophenylacetic acid (II). The melting point of this compound corresponds to that given by Fuchs and Breuer.[6] An attempted oxidation of II to I by hydrogen peroxide in acetic acid caused decarboxylation as well as oxidation and only phenyl benzyl sulfone was isolated. The methyl ester of II, however, was oxidized under the same conditions to the methyl ester of I and comparisons by melting point and mixed melting point were made.

We were unsuccessful in carrying out the metalation of phenyl benzyl sulfide with an equivalent amount of methylmagnesium iodide at 35–40°.

(6) K. Fuchs and F. Breuer, *Monatsh.*, **53**, 438 (1929).

(7) A. Cohen and S. Smiles, *J. Chem. Soc.*, 406 (1930).

(8) H. Gilman and F. J. Webb, *J. Am. Chem. Soc.*, **62**, 987 (1940).

## EXPERIMENTAL[9]

*Phenyl benzyl sulfone.* Phenyl benzyl sulfide was prepared in accordance with the procedure of Shriner, Struck and Jorison[10] and unrecrystallized product, m.p. 39–40°, was used. To a warm solution of crude phenyl benzyl sulfide (from 57 g. or 0.52 mole of thiophenol) in 300 ml. of acetic acid was added slowly with stirring 150 ml. of 30% hydrogen peroxide. External cooling was necessary during the addition, but after the exothermic reaction had subsided, the mixture was heated on the steam bath for 1 hr. A further 75 ml. of 30% hydrogen peroxide was added, and heating on the steam bath continued for another hr. After addition of another 75 ml. of 30% hydrogen peroxide, the reaction mixture was heated to reflux for 1 hr. The resulting solution was added to 300 ml. of cold water. The precipitated colorless crystalline solid was collected by filtration. The weight of product, melting at 148–149°, was 111.3 g., or 92% based on the original amount of thiophenol used. The melting point given by Shriner, Struck, and Jorison[10] for phenyl benzyl sulfone, prepared from sodium benzenesulfinate and benzyl chloride, was 146–146.5°.

*Metalation of phenyl benzyl sulfone with n-butyllithium.* To the well-stirred suspension of 11.6 g. (0.05 mole) of phenyl benzyl sulfone and 100 ml. of dry ether was added slowly at ice-bath temperature an equimolar amount of an ethereal solution of *n*-butyllithium.[11] A nitrogen atmosphere was used. After the addition of *n*-butyllithium was complete, the reaction mixture was stirred for 2 hr. at ice-bath temperature and for 1 hr. after removal of the ice bath. Carbonation of the reaction mixture was accomplished by pouring over a slurry of ether and crushed solid carbon dioxide. After the ether and carbon dioxide had been removed, excess water was added and the resulting mixture was filtered. The residue from filtration was recrystallized from 95% ethanol to give 2.8 g. (24%) of crystalline phenyl benzyl sulfone. The aqueous filtrate was acidified with dilute hydrochloric acid and the colorless crystalline solid which precipitated was collected by filtration. This solid was treated with aqueous sodium carbonate solution, the solution was filtered, the aqueous filtrate was acidified with dilute hydrochloric acid, and the resulting precipitated crystalline solid was collected by filtration. It weighed 9.0 g. (65 per cent) and decomposed at 142–143°. The residue from this decomposition melted at 148–149°. A mixed melting point of this residue with phenyl benzyl sulfone, m.p. 148–149°, was 148–149°. Fuchs and Breuer[6] have reported the same melting point behavior for α-phenylsulfonylphenylacetic acid, whereas Cohen and Smiles[7] have indicated that the melting point of the isomeric *o*-benzylsulfonylbenzoic acid is 126–128°. The *m*- and *p*-benzylsulfonylbenzoic acids have not been reported.

*Anal.* Calcd. for $C_{14}H_{12}O_4S$: C, 60.15; H, 4.35; neut. equiv., 276. Found: C, 60.26; H, 4.54; neut. equiv., 270.

*Metalation of phenyl benzyl sulfone with methylmagnesium iodide.* The Grignard reagent was prepared from 2.0 g. of magnesium, 7.1 g. methyl iodide and 50 ml. of ether. A solution of 11.6 g. (0.05 mole) of phenyl benzyl sulfone in 50 ml. of ether was added. The mixture was stirred at room temperature for 1 hr. and then heated under reflux for 1.5 hr. Carbonation and hydrolysis in the usual manner gave crude acidic product which was dissolved in aqueous sodium carbonate solution, filtered and acidified to give 3.9 g. (28%) of crystalline solid decomposing at 142–143°. The residue from the decomposition melted at 148–149°.

*Methyl α-phenylsulfonylphenylacetate.* A solution of 5.0 g.

(9) Microanalyses are by Galbraith Microanalytical Laboratories of Knoxville, Tenn.

(10) R. L. Shriner, H. C. Struck, and W. J. Jorison, *J. Am. Chem. Soc.*, **52**, 2060 (1930).

(11) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(0.018 mole) of α-phenylsulfonylphenylacetic acid (obtained from the metalation of phenyl benzyl sulfone) in 100 ml. of ether was treated with an excess of an ethereal solution of diazomethane at ice-bath temperature. After the addition of the ethereal solution of diazomethane, the reaction mixture was allowed to stand at room temperature for 1 hr. After the ether and excess diazomethane had been removed by evaporation, the residue was extracted with dilute aqueous sodium carbonate and recrystallized from aqueous methanol. The recrystallized material weighed 4.7 g. (90%) and melted at 109–110°.

*Anal.* Calcd. for $C_{15}H_{14}O_4S$: C, 62.07; H, 4.83. Found: C, 61.88; H, 5.10.

*Metalation of phenyl benzyl sulfide.* Ten grams (0.05 mole) of phenyl benzyl sulfide was dissolved in 150 ml. of dry ether and filtered into the reaction flask which had been previously flushed with nitrogen. To this solution was added slowly with stirring an equimolar amount of *n*-butyllithium in ether. The addition caused an immediate color change and reflux of the ether. After the reflux had somewhat subsided, the reaction mixture was heated at reflux temperature for 5 hr. The reaction mixture was then carbonated by pouring over a slurry of ether and crushed solid carbon dioxide. After the removal of the carbon dioxide, water was added and the aqueous layer was separated, filtered, and acidified with dilute hydrochloric acid. This gave 9.2 g. of solid material melting at 100–102°. After treatment of this solid with dilute aqueous sodium carbonate, filtration, and acidification of the aqueous filtrate, there was obtained 8.8 g. (75%) of solid melting at 102–103°, neutralization equivalent 249. The melting point of this compound corresponds to that reported by Fuchs and Breuer[6] for α-phenylmercaptophenylacetic acid, prepared from α-chlorophenylacetic acid and sodium thiophenolate. The ether layer was dried over anhydrous calcium chloride, filtered, and the ether removed. A yellow oil remained, which on cooling solidified. After recrystallization from methanol, the crystalline solid weighed 1.3 g. (13%) and melted at 41–42°. A mixed melting point with a sample of phenyl benzyl sulfide, melting point 42–43°, was 41–42°.

To 1.6 g. (0.007 mole) of α-phenylmercaptophenylacetic acid in 50 ml. of dry ether was added an excess of an ethereal solution of diazomethane. After the ether and excess diazomethane had been removed, the residue was taken up in 60 ml. of glacial acetic acid and treated with 10 ml. of 35% hydrogen peroxide. The reaction mixture was heated on the steam bath for 1 hr. After the addition of a further 10 ml. of hydrogen peroxide, the reaction mixture was heated to reflux for 0.5 hr. and was then poured into an excess of cold water. The precipitated solid was collected by filtration and recrystallized from aqueous methanol. The recrystallized material weighed 1.3 g. (67%) and melted at 109–110°. A mixture melting point with the methyl ester prepared from α-phenylsulfonylphenylacetic acid, m.p. 109–110°, was 109–110°.

*α-Phenylmercaptophenylacetamide.* One gram (0.004 mole) of α-phenylmercaptophenylacetic acid was heated on the steam bath with 5 ml. of thionyl chloride for 20 min. The reaction mixture was then poured into 20 ml. of ice-cold concentrated ammonia. The precipitated solid was collected by filtration and recrystallized from dilute aqueous ethanol. This gave 0.8 g. (82%) of crystalline solid melting at 174–175°.

*Anal.* Calcd. for $C_{14}H_{13}NOS$: N, 5.76. Found: N, 5.87.

*α-Phenylsulfonylphenylacetamide.* A solution composed of 0.3 g. (0.001 mole) of α-phenylmercaptophenylacetamide, 50 ml. of acetone and 10 ml. of 35% hydrogen peroxide was heated to reflux on the steam bath for 1 hr., after which an additional 10 ml. of 35% hydrogen peroxide was added and the solution was again heated at reflux temperature for 3 hr. The reaction mixture was then poured over an excess of ice and the acetone was removed by evaporation on the steam bath. The colorless solid which precipitated was collected by filtration. It weighed 0.2 g. (65%) and melted at 195–197°. Recrystallization from dilute aqueous ethanol brought the melting point up to 203–204°.

*Anal.* Calcd. for $C_{14}H_{13}NO_2S$: N, 5.41. Found: N, 5.56.

*Hydrazide of α-phenylmercaptophenylacetic acid.* An ethereal solution of 3 g. (0.012 mole) of α-phenylmercaptophenylacetic acid was converted to the methyl ester with diazomethane. The crude ester was converted to the hydrazide, m.p. 85–86°. The yield was 1.1 g. and crystallization was from water.

*Anal.* Calcd. for $C_{14}H_{14}N_2OS$: N, 10.85. Found: N, 10.88.

*Hydrazide of α-phenylsulfonylphenylacetic acid.* A mixture of 0.6 g. (0.002 mole) of methyl α-phenylsulfonylphenylacetate, 100 ml. of absolute ethanol, and 5 ml. of 85% hydrazine hydrate was allowed to stand at room temperature in a stoppered flask for one week. The ethanol was removed by evaporation on the steam bath and the residue was recrystallized from aqueous ethanol. The yield of solid material melting at 182–183° was 0.5 g. (83%).

*Anal.* Calcd. for $C_{14}H_{14}N_2O_3S$: N, 9.66. Found: N, 9.48.

*α-Phenylsulfonylphenylacetamide.* One gram (0.0036 mole) of the acid was converted to the amide, m.p. 278°, with thionyl chloride and ammonia. The yield was 40% and crystallization was from aqueous ethanol.

*Anal.* Calcd. for $C_{14}H_{13}NO_3S$: N, 5.09. Found: N, 5.19.

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## Alkaline Condensation of Phenanthraquinone with Urea

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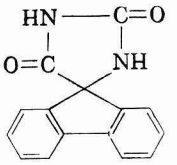
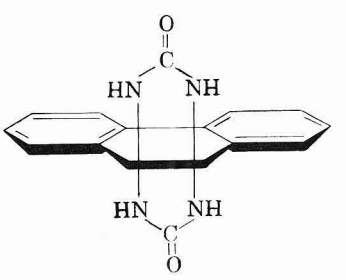
*Received February 12, 1957*

In a previous publication[2] the results of a study of the alkaline condensation of benzil with urea was reported. The products of this reaction were 3a,6a-diphenyl glycoluril, and the rearrangement product 5,5-diphenylhydantoin. The results from a series of 4,4′-disubstituted benzils used in this reaction gave relative migratory aptitudes of *p*-substituted phenyl groups which indicated that the rearrangement involved in the hydantoin formation is closely allied with the benzilic acid rearrangement.

Since phenanthraquinone undergoes the benzilic acid rearrangement,[3] it was supposed that the




I




II

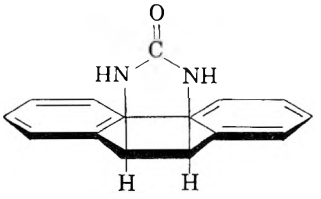
(1) Present address Department of Chemistry, Duke University, Durham, N. C.

(2) W. R. Dunnavant and F. L. James, *J. Am. Chem. Soc.*, **78**, 2740 (1956).

(3) A. von Baeyer and P. Friedländer, *Ber.*, **10**, 126 (1877).

analogous condensation products spiro(fluorene-9,4′-imidazolidine-)2′,5′-dione (I) and 3a,6a-(2,2′-diphenylene) glycoluril (II) might be obtained in the same manner.

It was found, however, that when phenanthraquinone was refluxed for 5 hr. with urea in ethanolic potassium hydroxide, followed by the addition of water, 4,5-diphenylene-4,5-dihydro-2-imidazolone (III) was obtained in 69% yield, but no II.




III

Acidification of the filtrate after the removal of III gave a brown resinous material from which a small amount of I was isolated, which was identified by its melting point, mixed melting point, and infrared spectrum as being identical with an authentic sample of the spiro hydantoin.[4]

The infrared spectrum[5] of I shows a broad band in the NH region at 3200 cm.$^{-1}$ The carbonyl absorptions are characteristic of compounds containing the CONHCO group. These appear as two widely separated bands at 1780 and 1710 cm.$^{-1}$ Compound III shows NH absorption in the 3100 cm.$^{-1}$ region and bands at 1650, 1695, and 1715 cm.$^{-1}$ The 1650 cm.$^{-1}$ band appears in disubstituted ureas and can be assigned to CO absorption.[6] Information is not available to allow full interpretation of the NH absorption in compounds containing the NHCONH group.[6]

In observing the deviation from the expected course of this reaction it is of interest to note that, unlike the benzils with carbonyls in skew positions (not coplanar) previously used in this reaction, the carbonyls of phenanthraquinone must necessarily have *cis*-coplanarity.

### EXPERIMENTAL[7]

*4,5-Diphenylene-4,5-dihydro-2-imidazolone.* A mixture of 6 g. of phenanthraquinone, 4.86 g. of urea, and 3.02 g. of potassium hydroxide in 100 ml. of 95% ethanol was refluxed for 5 hr. The deep brown solution was allowed to cool and was then poured into 300 ml. of ice water. A tar amorphous precipitate was obtained which, after filtering and drying, weighed 4.7 g. (69%). Four recrystallizations from glacial acetic acid (Norit) yielded tiny white needles of III which failed to melt at 400°.

*Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 76.24; H, 5.12; N, 11.85. Found: C, 76.59; H, 5.23; N, 11.73.

*Spiro(fluorene-9,4′-imidazolidine)-2′,5′-dione.* The filtrate from above was acidified with hydrochloric acid and stirred rapidly for 30 min. A brown resinous material was obtained which, after several recrystallizations from glacial acetic acid (Norit) afforded 50 mg. of hard white crystals of I, melting point 350–354° dec. No mixed melting point depression with an authentic sample[4] was observed. The literature reports 352–356° dec.[8]

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(4) The authentic sample of spiro(fluorene-9,4,-imidazolidine)-2,,5,-dione was obtained through the courtesy of Prof. M. S. Newman of The Ohio State University, Columbus, Ohio.

(5) The infrared spectra were obtained as Nujol mulls on a Perkin-Elmer Model 21 Spectrophotometer.

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 191.

(7) The microanalysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(8) M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.* **78**, 2471 (1956).

## Derivatives of Piperazine. XXIX. Salts of *N*-Phenylpiperazine for Utilization in Identification of Organic Acids

C. B. POLLARD AND NARAIN S. GIDWANI

*Received February 15, 1957*

In previous papers[1–3] from this laboratory, certain piperazinium salts were reported for utilization in identification of organic acids. The present paper describes the method of preparation and data concerning 23 new salts of *N*-phenylpiperazine which may be employed for the identification of organic acids. Data for these compounds are shown in Table I.

By the methods employed, the following acids failed to give derivatives which are of practical value in qualitative organic analysis: butyric, iodoacetic, α-bromopropionic, α-bromobutyric, succinic, tartaric, and 4-nitrophthalic. These derivatives showed reasonably sharp melting points which did not change on continued crystallization. However, all analytical determinations gave inconsistent results which did not agree with any reasonable structures.

### EXPERIMENTAL

Salts of the unsubstituted liquid monobasic acids were prepared by mixing equal molar quantities of *N*-phenylpiperazine and the individual acid.

The dibasic acids react in the ratio of two moles of *N*-phenylpiperazine to one of the acid.

Acetone solutions of the solid acids were mixed with *N*-phenylpiperazine to produce the salts.

All of the salts were purified by recrystallization from hot acetone or by washing with hot acetone. In all cases the salts form almost immediately.

(1) C. B. Pollard and D. E. Adelson, *J. Am. Chem. Soc.* **56**, 150 (1934).

(2) C. B. Pollard, D. E. Adelson, and J. P. Bain, *J. Am. Chem. Soc.*, **56**, 1759 (1934).

(3) M. Prigot and C. B. Pollard, *J. Am. Chem. Soc.*, **70**, 2758 (1948).

TABLE I

DATA CONCERNING *N*-PHENYLPIPERAZINIUM SALTS DERIVED FROM VARIOUS ORGANIC ACIDS

| Acids | Yield (%) | Melting Point (°C. corr.) | Nitrogen, % Calcd. | Found | Acids | Yield (%) | Melting Point (°C. corr.) | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|
| *p*-Anisic | 91.0 | 158.3–159.3 | 8.91 | 8.88 | Isovaleric | 70.0 | 78.9–80.4 | 10.59 | 10.25 |
| Cyclohexanebutyric | 92.0 | 87.7–88.6 | 8.42 | 8.29 | Caprylic | 40.0 | 58.4–60.6 | 9.13 | 8.87 |
| Cyclohexaneacetic | 93.0 | 79.4–80.9 | 10.85 | 10.82 | Valeric | 85.5 | 50.5–52.5 | 10.59 | 10.27 |
| Cyclohexanecaproic | 91.0 | 91.6–93.4 | 12.85 | 12.80 | Phenoxyacetic | 97.7 | 117.9–119.0 | 8.92 | 8.84 |
| Cyclohexanevaleric | 90.0 | 67.8–68.9 | 8.12 | 7.95 | Propanoic | 33.0 | 58.9–59.8 | 12.35 | 12.00 |
| Cyclohexanepropionic | 96.0 | 85.2–87.2 | 8.80 | 8.77 | Salicylic | 96.0 | 184.8–185.8 | 9.34 | 9.36 |
| Acetic | 91.0 | 82.0–83.0 | 12.61 | 12.50 | Hendecanoic | 50.0 | 50.5–52.5 | 8.04 | 8.38 |
| Enanthic | 40.0 | 56.1–57.5 | 9.56 | 9.43 | Malonic | 93.5 | 111.8–113.8 | 13.10 | 13.12 |
| Caproic | 35.5 | 65.2–67.3 | 10.05 | 9.85 | Oxalic | 95.0 | 226.7–227.2 | 12.45 | 12.47 |
| Lauric | 89.0 | 60.6–61.5 | 7.74 | 7.74 | Isophthalic | 97.0 | 184.4–185.8 | 11.41 | 11.26 |
| Levulinic | 65.5 | 82.8–84.2 | 10.12 | 10.32 | Phthalic | 98.0 | 188.3–189.9 | 11.41 | 11.25 |
| Formic | 75.5 | 112.6–113.6 | 13.71 | 13.68 | | | | | |

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## Substituted α,α,α-Trifluoroacetophenones, α-Trifluoromethylbenzyl Alcohols, and α-Chloro-α-trifluoromethyltoluenes

RICHARD FUCHS AND GENE J. PARK

*Received February 25, 1957*

As part of a study of substituent effects in nucleophilic displacement reactions at electron-deficient, saturated carbon atoms, a series of five *meta* and *para* substituted α-chloro-α-trifluorotoluenes have been prepared. Three new substituted α,α,α-trifluoroacetophenones were obtained by the reaction of arylmagnesium bromides with trifluoroacetic acid.[1] The ketones were reduced by hydrogen or sodium borohydride to α-trifluoromethylbenzyl alcohols, which were converted to the corresponding chlorides by reaction with thionyl chloride. Preliminary studies indicate a very low reactivity of the chlorides toward the strong nucleophilic reagents iodide, thiosulfate, phenoxide, and butoxide ions, and towards alcoholic silver nitrate. In all cases *p*-methoxy-α-chloro-α-trifluoromethyltoluene was more reactive than the *p*-chloro, *m*-trifluoromethyl, or unsubstituted analogs.

TABLE I

α,α,α-TRIFLUOROACETOPHENONES, $YC_6H_4COCF_3$

| Y | B.p., °C/Mm. | Yield, % | $n_D^{30}$ | Formula | Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| H[a] | 66–67/33 | 67 | 1.4528 | | | | | |
| *p*-$CH_3$[b] | 81–82.5/22 | 66 | 1.4645 | | | | | |
| *p*-$CH_3O$ | 70–70.5/2 | 56 | 1.4944 | $C_9H_7O_2F_3$ | 52.9 | 3.5 | 53.2 | 3.6 |
| *p*-Cl[c] | 84/24 | 56 | 1.4852 | $C_8H_4OClF_3$ | 46.1 | 1.9 | 48.9 | 2.3 |
| *m*-$CF_3$ | 65–67.5/24 | 68 | 1.4100 | $C_9H_4OF_6$ | 44.6 | 1.7 | 44.5 | 1.7 |
| | α-Trifluoromethylbenzyl Alcohols, $YC_6H_4CHOHCF_3$ | | | | | | | |
| H[d] | 53–54.5/2 | 87 | 1.4550 | | | | | |
| *p*-$CH_3$ | 74.5–75/2.5 | 72 | 1.4626[e] | $C_9H_9OF_3$ | 56.8 | 4.8 | 57.3 | 5.0 |
| *p*-$CH_3O$ | 87–88/1 | 91 | 1.4743 | $C_9H_9O_2F_3$ | 52.4 | 4.4 | 52.6 | 4.5 |
| *p*-Cl | 71–73/1.9 | 82 | 1.4785 | $C_8H_6OClF_3$ | 45.6 | 2.9 | 45.7 | 3.1 |
| *m*-$CF_3$ | 95–97/24 | 80 | 1.4133 | $C_9H_6OF_6$ | 44.3 | 2.5 | 44.9 | 3.1 |
| | α-Chloro-α-trifluoromethyltoluenes, $YC_6H_4CHClCF_3$ | | | | | | | |
| H | 70–71/27 | 73 | 1.4540 | $C_8H_6F_3Cl$ | 49.4 | 3.1 | 49.2 | 3.3 |
| *p*-$CH_3$ | 89–90/27 | 66 | 1.4590 | $C_9H_8F_3Cl$ | 51.8 | 3.9 | 52.0 | 4.2 |
| *p*-$CH_3O$ | 57.5–59.5/1 | 73 | 1.4746 | $C_9H_8OClF_3$ | 48.1 | 3.6 | 47.9 | 3.9 |
| *p*-Cl | 95–95.5/24 | 67 | 1.4778 | $C_8H_5Cl_2F_3$ | 41.9 | 2.2 | 41.6 | 2.4 |
| *m*-$CF_3$ | 75.5–76.5/25 | 54 | 1.4128 | $C_9H_5ClF_6$ | 41.1 | 1.9 | 40.9 | 2.2 |

[a] J. H. Simons and E. O. Rambler, *J. Am. Chem. Soc.*, **65**, 389 (1943). [b] J. D. Park, H. A. Brown, and J. R. Lacher, *J. Am. Chem. Soc.*, **73**, 709 (1951). [c] Impure sample. [d] E. T. McBee, O. R. Pierce, and J. F. Higgins, *J. Am. Chem. Soc.*, **74**, 1736 (1952). [e] 25°.

(1) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

EXPERIMENTAL

*α-Trifluoromethylbenzyl alcohols.* α,α,α-Trifluoroacetophenones were prepared by the procedure of Levine,[1] using the Grignard reagent from 1.0 mole of aryl bromide and 0.40 mole of trifluoroacetic acid. Hydrogenation of α,α,α-trifluoroacetophenone at 25 lbs. pressure using platinum oxide catalyst afforded α-trifluoromethylbenzyl alcohol in 48% yield. A better yield was obtained by sodium borohydride reduction in aqueous dioxane, so this procedure was used to prepare all of the substituted alcohols.

*α-Chloro-α-trifluoromethyltoluenes.* The α-trifluoromethylbenzyl alcohols (0.28 mole) were stirred at 150° for 2–3 hr. with 0.29 mole of pyridine and 0.29 mole of thionyl chloride. The reaction mixtures were poured into water, washed with dilute sulfuric acid, water, dilute sodium bicarbonate, and again with water, dried, and distilled.

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## Carbamates and Dimethanesulfonates of Some New Glycols[1]

RICHARD H. WILEY AND HAROLD KRAUS

*Received February 21, 1957*

The inhibitory effect of Myleran, 1,4-butanediol dimethanesulfonate[2] and urethane on the development of various tumors has been noted previously.[3] The availability of a series of previously unknown glycols has prompted our preparation of their dimethanesulfonates and dicarbamates as part of a program on cancer chemotherapy. The glycols were made available through the generosity of the Tennessee Eastman Company. Typical procedures for the preparation of the two types of compounds are given in the experimental section. Data for the preparation and characterization of all samples are given in Tables I and II. Dimethanesulfonates were obtained for all the glycols. Dicarbamates were obtained from most but not all. Available test data from the evaluation of these compounds in tumor retardation studies using Sarcome 180 has thus far disclosed no significant activity in any.[4]

EXPERIMENTAL[5]

*Cyclohexane-1,4-dimethanol dimethanesulfonate.* A solution of 2.8 g. (0.02 mole) of cyclohexane-1,4-dimethanol in 10 ml. of pyridine was cooled to 5–10°. Methanesulfonyl chloride, 5.7 g. (0.05 mole), was added dropwise with stirring. The reaction mixture was poured onto dilute hydrochloric acid and the precipitated product was collected, washed, dried, and recrystallized from benzene-petroleum ether to give 3.3 g. (56%) of the dimethanesulfonate, m.p. 162–163°.

*Cyclohexane-1,4-diol dicarbamate.* A solution of 2.3 g. (0.02 mole) of cyclohexane-1,4-diol in 25 ml. of dry acetone was added dropwise to a solution of 5 g. (0.05 mole) of phosgene in 35 ml. of dry acetone at −10°. The solution was warmed to 10° for 30–60 min., cooled to −20°, and treated with 100 ml. of concentrated ammonium hydroxide. The

TABLE I
GLYCOL DIMETHANESULFONATES

| Glycol | M.P. (°C.) | Yield (%) | Solvent[a] | Analysis: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|
| Cyclohexane-1,2-diol | 136 | 76 | AW | 35.29 | 35.34 | 5.88 | 6.00 |
| Cyclohexane-1,4-diol | 148 | 45 | AW | 35.29 | 35.36 | 5.88 | 6.14 |
| Cyclopentane-1,1-dimethanol | 91 | 81 | AW | 37.76 | 37.86 | 6.29 | 6.37 |
| Cyclohexane-1,1-dimethanol | 54 | 66 | MW | 40.00 | 39.92 | 6.67 | 6.51 |
| Cyclohexane-1,4-dimethanol | 163 | 56 | BP | 40.00 | 39.92 | 6.67 | 6.68 |
| 3-Cyclohexene-1,1-dimethanol | 87 | 100 | AW | 40.27 | 40.30 | 6.04 | 5.97 |
| Norcamphane-2,2-dimethanol | 112 | 80 | AW | 42.31 | 42.24 | 6.41 | 6.71 |
| Norcamphane-2,3-dimethanol | 115 | 36 | MW | 42.31 | 42.27 | 6.41 | 6.46 |
| Norcamphane-2,5-dimethanol | 136 | 49 | MW | 42.31 | 42.40 | 6.41 | 6.46 |
| 2,2′-(1,5-Naphthylenedioxy)-diethanol | 189 | 90 | N | 47.52 | 47.81 | 4.95 | 5.20 |
| Perhydro-1,4-naphthalenediol | 152 | 30 | MW | 44.17 | 44.02 | 6.75 | 6.78 |
| 2,2′-(2,5-Dichloro-*p*-phenylenedioxy)diethanol | 160 | 83 | AW | 34.04 | 34.15 | 3.78 | 3.76 |
| 2,2′-(2,5-Di-*t*-butyl-*p*-phenylenedioxy)diethanol | 175 | 92 | AW | 51.50 | 51.58 | 7.30 | 7.50 |
| 2,2′-(4,4′-Sulfonyldiphenoxy)-diethanol | 134 | 87 | AW | 43.72 | 43.68 | 4.45 | 4.46 |
| 5-Hydroxymethyl-β,β-5-trimethyl-2-*m*-dioxanethanol | 86 | 90 | MW | 40.00 | 39.92 | 6.67 | 6.72 |
| β,β,β′,β′-Tetramethyl-2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-diethanol | 184 | 84 | AW | 44.35 | 44.45 | 6.96 | 7.16 |

[a] Solvent for recrystallization: B, benzene; P, petroleum ether; A, acetone; W, water; M, methanol; N, nitromethane.

(1) The authors wish to acknowledge with appreciation partial support of this research through U. S. Public Health Service Grant C-2457.

(2) This compound is indexed by *Chemical Abstracts* under methanesulfonic acid, tetramethylene ester.

TABLE II

GLYCOL DICARBAMATES

| Glycol | M.P. (°C.) | Yield (%) | Solvent[a] | Analysis Nitrogen Calcd. | Found |
|---|---|---|---|---|---|
| Cyclohexane-1,4-diol | 265 | 50 | N | 13.86 | 13.81 |
| Cyclopentane-1,1-dimethanol | 155 | 33 | CP | 12.96 | 12.99 |
| Norcamphane-2,3-dimethanol | 157 | 54 | CP | 11.56 | 11.36 |
| Norcamphane-2,5-dimethanol | 223 | 45 | WM | 11.56 | 11.22 |
| 2,2′-(1,5-Naphthylenedioxy)diethanol | 265 | 54 | N | 8.38 | 8.29 |
| 2,2′-(2,5-Dichloro-*p*-phenylenedioxy)diethanol | 236 | 94 | H | 7.93 | 7.67 |
| 2,2′-(2,5-Di-*t*-butyl-*p*-phenylenedioxy)diethanol | 178 | 25 | CP | 7.07 | 6.80 |
| 2,2′-(4,4′-Sulfonyldiphenoxy)diethanol | 227 | 25 | N | 6.60 | 6.89 |
| 5-Hydroxymethyl-β,β,5-trimethyl-2-*m*-dioxane-ethanol | 196 | 33 | AW | 9.69 | 9.33 |
| β,β,β′,β′-Tetramethyl-2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-diethanol | 241 | 82 | AW | 7.18 | 7.02 |
| 2,2-Dimethyl-1,5-pentanediol | 155 | 97 | WM | 12.84 | 12.69 |

[a] Solvent for recrystallization: H, acetic acid; N, nitromethane; A, acetone; W, water; C, chloroform; P, petroleum ether M, methanol.

reaction mixture was then warmed to room temperature and poured onto ice to precipitate the product. Recrystallization from nitromethane gave 2.0 g. (50%) of the dicarbamate, m.p. 265°.

*Cyclopentane-1,1-dimethanol dicarbamate.* This compound was prepared by an adaptation of the method previously described.[6] A solution of 2.6 g. (0.02 mole) of cyclopentane-1,1-dimethanol in 25 ml. of chloroform and 5 ml. of pyridine was added to a solution of 5 g. (0.05 mole) of phosgene in 40 ml. of toluene at 0–5°. After warming to room temperature for about 10 hr. the solution was cooled to −78° and treated with liquid ammonia. The mixture was warmed to room temperature. The precipitate was collected and recrystallized from chloroform-petroleum ether to give 1.1 g. (33%) of the dicarbamate, m.p. 154–155°.

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(3) C. C. Stock in J. P. Greenstein and A. Haddow, *Advances in Cancer Chemotherapy*, Vol. II, pp. 446, 459, Academic Press, New York, 1954.

(4) The authors are indebted to Drs. C. C. Stock and D. A. Clarke of the Sloan-Kettering Institute for conducting these tests.

(5) Analyses by Micro Tech Laboratories, Skokie, Ill. All melting points are corrected.

(6) B. Ludwig and E. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

## Preparation and Polymerization of Vinyl Azide

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Vinyl azide, which has been previously described,[1] has been prepared by an improved process. This process is suited for the laboratory preparation of vinyl azide if proper precautions for handling this highly sensitive material are observed. On one occasion a sample in a distilling flask with a ground glass joint detonated when the joint was rotated. Vinyl azide should be handled as a highly sensitive material which is easily detonated. Statements in the literature[1a,2a] that this material is "surprisingly stable" should be regarded as misleading and erroneous.

Some preliminary polymerization studies with vinyl azide have established that a white, apparently infusible solid polymeric product can be obtained by bulk polymerization with peroxide or azo bis initiators. The polymer is highly combustible. Above 70° the azide decomposes with the formation of hydrazoic acid. It has been established that no triazole is present in the higher boiling liquids during the polymerization.

### EXPERIMENTAL

*β-Chloroethyl azide.* One hundred grams of β-chloroethyl *p*-toluenesulfonate was refluxed with a slight excess of sodium azide in the minimum amount of methanol-water mixture necessary to give a homogeneous solution. This solution was prepared by adding methanol to the ester and a half-saturated aqueous solution of sodium azide until a homogeneous solution was obtained. After 24 hr. refluxing the reaction mixture was diluted with water and extracted with ether. The washed and dried ether solution was distilled to give 57–65% yields of β-chloroethyl azide, b.p. *ca.* 45°/25 mm.

*Vinyl azide.* To a hot solution of 100 g. potassium hydroxide in 400 ml. of water and 500 ml. of ethylene glycol was added 52.5 g. of β-chloroethyl azide dropwise. The vinyl azide distilled from the reaction mixture as formed. A short period of reflux after the completion of the addition completed the reaction. The water-vinyl azide mixture in the receiver was freed of water by freezing and decantation. The vinyl azide, b.p. 30°, does not freeze even at −80°. It is obtained in yield of about 20 g. (*ca.* 60%). This amount is probably larger than should be handled by ordinary laboratory procedures, since this amount can cause very severe damage on detonation. Ethanol may be used instead of ethylene glycol, but the separation of pure vinyl azide from the aqueous-alcohol distillate is then much more difficult.

*Vinyl azide polymerization.* All polymerizations were run in nitrogen-filled screw cap vials.

(1) M. O. Forster and S. H. Newman, *J. Chem. Soc.* (*a*) **97**, 2570 (1910); (*b*) **99**, 1278 (1911).

(2) C. E. Schildknecht, *Vinyl and Related Polymers*, John Wiley and Sons, 1952, (*a*) p. 80, (*b*) p. 397.

*Solution:* Solutions of vinyl azide in methanol (about 1 ml. in 3 ml.) containing *ca.* 3 mg. of azobisisobutyronitrile were heated for from 1 to 24 hr. at temperatures of from 50–75° in screw cap vials. The vials were cooled, opened, and the solution evaporated to dryness. The white flakes of polymer were soluble in methanol but insoluble in water. The yields of polymer were under 5%.

*Suspension:* Exploratory attempts to polymerize vinyl azide by suspension techniques in water by the usual techniques gave no polymer.

*Emulsion:* Emulsion polymerizations with a standard recipe[2b] of ammonium persulfate 0.5%, sodium lauryl sulfate 10%, and sodium bisulfite 0.2% in water acidified to *p*H 2 with acetic acid, gave only small yields of polymer at temperatures of from 50 to 75° and times of 1 to 24 hr. The amount of polymer in all cases was very small and did not seem to increase in quantity after the first few hours. The vinyl azide was never completely reacted.

*Bulk:* Bulk polymerizations were run using benzoyl peroxide or azobisisobutyronitrile as initiators in concentrations of 0.1 to 1%. At temperatures of 50–70° yields of less than 5% were obtained. Temperatures over 70° caused decomposition of the vinyl azide as evidenced by brown coloration. This decomposition was very rapid at 100°.

The polymer obtained in the polymerizations listed above was a white, flaky, apparently infusible solid. It burned furiously when held to a flame and decomposed violently when touched with a hot wire. Such combustibility makes carbon-hydrogen analysis impossible. Nitrogen analyses, which are notoriously untrustworthy for polymers, were also not attempted. As a result, no ultimate analytical data are available to characterize the polymer. It is to be noted that polymers obtained in such low yield may very well include fragments from the initiator as a significant portion of their composition.

In all polymerizations a large part of the vinyl azide was converted into higher boiling liquids which were always completely water soluble. No 1,2,3-triazole was ever detected although sensitive methods were used to detect it.

In polymerizations run at temperatures over about 70° ammonium azide crystals formed on the upper wall of the vials. This is a known decomposition product[3] of hydrazoic acid. If vinyl azide cleaves above 70° into hydrazoic acid, the other product would probably be acetylene but that has not been detected.

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(3) L. F. Audrieth, *Chem. Revs.*, **15**, 169 (1934).

## Radioactive Estrogens[1a]

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The recent publication of Hartman *et al.*[1b] prompts us to report a very similar synthesis with radioactive carbon, as well as with tritium.

Ozonolysis of 19-nortestosterone 17-acetate (III) followed by decomposition of the ozonide with hydrogen peroxide gave, in 50% yield, 17β-acetoxy-5-keto-3,5-seco-4-norestrane-3-oic acid.

Lactonization by treatment with acetic anhydride and sodium acetate furnished, in 54% yield, the desired 17β-acetoxy-5-hydroxy-3,5-seco-4-nor-5(10)-estrene-3-oic acid 3,5-lactone.

This enol lactone acetate was added to the equimolar amount of methyl magnesium iodide-$C^{14}$ in ether. The reaction mixture was decompored with dilute hydrochloric acid and after being worked up as usual, the obtained crude product cyclized with hydrochloric acid in acetic acid The reaction product furnished after purification in 47% yield, 19-nortestosterone acetate-4-$C^{14}$ (III).

Attempts to aromatize that compound directly by dehydrogenation[4] with selenium dioxide gave, consistently, a yield below 35%. Dehydrogenation of estra-3,5-diene-3,17β-diole diacetate (I)[2] with selenium dioxide gave however, in very good yield, the desired 17-dihydroequilenin-17β 3,17-diacetate-4-$C^{14}$ (IIb).

Bromination[5] of 19-nortestosterone 17-acetate-4-$C^{14}$ (III) in dry ether with bromine and a few drops of hydrogen bromide in acetic acid gave, crude 2,6-dibromo-19-nortestosterone 17-acetate-4-$C^{14}$, which was dehydrobrominated[6] with lithium chloride in dimethylformamide, giving in 75% yield (calculated on 19-nortestosterone 17-acetate-4-$C^{14}$) the desired estra-1,3,5(10),6-tetraene-3,17β-diol 17-monoacetate-4-$C^{14}$ (IVa), m.p. 247–250°. This tetraene, obtained from a nonradioactive model run, was reacted with tritium and prereduced palladium-on-charcoal to give estradiol 17β-acetate-6,7-*t*.

Estra-1,3,5(10),6-tetraene-3,17β-diol 17-acetate-4-$C^{14}$ (IVa) gave, after reduction[5] with 30% palladium-on-charcoal in ethyl acetate under hydrogen for 3 hr., estradiol 17β-acetate-4-$C^{14}$ (V), in 95% yield. The specific radioactivity of this product and of its starting material (4-$C^{14}$-19-nortestosterone 17-acetate) was identical.

Estra-1,3,5(10),6-tetraene-3,17β-diol 17-acetate-4-$C^{14}$ (IVa) was acetylated[5] with acetic anhydride in pyridine and the resulting 3,17-diacetate (IVb) was dehydrogenated[5] with selenium

(1a) Since this note was submitted S. Kushinsky, Abstracts of 131st Meeting, AMERICAN CHEMICAL SOCIETY, p. 36-O, reported a very similar synthesis.

(1) (b) J. A. Hartman, A. J. Tomasewski, and A. S. Dreiding, *J. Am. Chem. Soc.*, **78**, 5662 (1956).

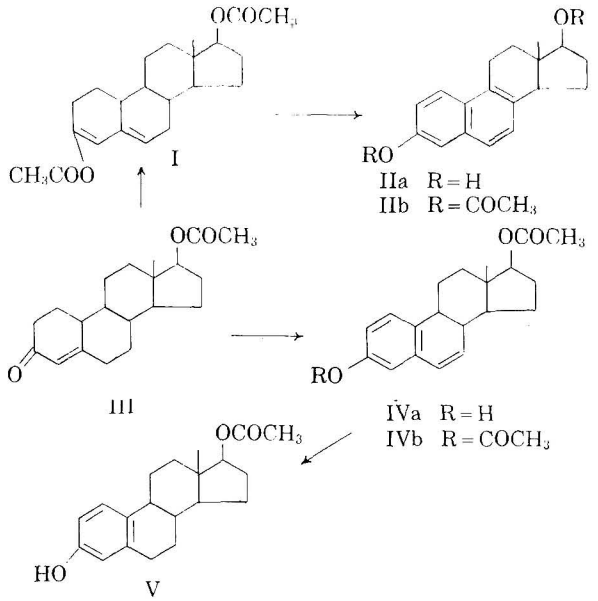
(2) J. A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955).

(3) Compare L. M. Thompson, C. H. Yates, and A. D. Odell, *J. Am. Chem. Soc.*, **76**, 1194 (1954).

(4) Compare H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Org. Chem.*, **21**, 239 (1956); C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(5) Compare C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(6) Compare R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).




dioxide in boiling acetic acid to give 17-dihydroequilenin-17$\beta$ 3,17-diacetate-4-C$^{14}$ (IIb). The crude diacetate afforded after alkaline saponification, followed by chromatography, 17-dihydroequilenin-17$\beta$-4-C$^{14}$ (IIa), in 35% yield. The specific activity was again identical with the activity of 19-nortestosterone acetate-4-C$^{14}$ (III).

## EXPERIMENTAL

Melting points were taken on a Kofler hot stage and are not corrected. The ultraviolet spectra were recorded on a methanol solution with a Cary spectrophotometer model 11 MS. All chromatographic separations, if not indicated otherwise, were made on Davison Silica Gel mesh 100-200. A Packard Tri-Carb liquid scintillation spectrometer was used for radioanalysis.

*19-Nortestosterone acetate-4-C$^{14}$* (III). To a solution of two mmoles of methyl magnesium iodide carbon-14 (4 mc.) in 15 ml. of ether and frozen to $-70°$ was added at once the solution of 637 mgs. (2 mmoles) of 17$\beta$-acetoxy-5-hydroxy-3,5-seco-4-nor-5-estrene-3-oic acid 3,5-lactone in 60 ml. of ether-benzene (1:1), care being taken to exclude all moisture. The mixture was allowed to warm up to 25° in the course of 6 hr.,[7] then decomposed with 2*N* hydrochloric acid and the product taken up in benzene. The benzene layer was washed with dilute sodium carbonate solution, then with water, dried, and evaporated to dryness. The residue was dissolved in 15 ml. of glacial acetic acid, 1.5 ml. of conc. hydrochloric acid added and kept for two days at room temperature in an atmosphere of nitrogen. After removal of the acids *in vacuo* the remaining sirup was dissolved in benzene, washed with sodium bicarbonate solution and with water. The benzene layer was dried, the benzene distilled off, leaving a partially crystalline residue which was chromatographed. The benzene-ether fractions gave after recrystallization from ether-pentane 298 mg. 19-nortestosterone acetate-4-C$^{14}$, m.p. 91–93°, $\lambda_{max}^{MeOH}$ 240 m$\mu$, $\epsilon$ 17700. The specific activity was 2 mc/mM.

*3,17$\beta$-Diacetoxy-estra-3,5-diene-4-C$^{14}$* (I). A solution of 316 mg. (1 mmole containing 1 mc.) of 19-nortestosterone acetate-4-C$^{14}$ in 20 ml. of acetic anhydride-acetyl chloride 3:1 was refluxed under nitrogen for 3 hr. The solvents were evaporated off *in vacuo* and the residue was recrystallized from ethanol to give 300 mg. large plates, m.p. 153–156°,[8] $[\alpha]_D^{25}$ −155° (chf.), $\lambda_{max}^{MeOH}$ 234 m$\mu$, $\epsilon$ 20200, specific activity 1 mc/mM.

*17-Dihydroequilenin 3,17$\beta$-diacetate-4-C$^{14}$* (IIb) *and 17-dihydroequilenin-17$\beta$-4-C$^{14}$* (IIa). Dehydrogenation of 320 mg., 1 mc/mM, of the enol diacetate (I) in 20 ml. of glacial acetic acid with 200 mg. of freshly sublimed selenium dioxide under nitrogen for 15 min. gave 235 mg. impure 17-dihydroequilenin 3,17$\beta$-diacetate-4-C$^{14}$, m.p. 112–119°, which could not be obtained in pure form on repeated recrystallizations, by distillation or chromatography. Reductive hydrolysis with lithium aluminum hydride gave, after purifying on a Hyflow Super Cel column[9] 188 mg. 17-dihydroequilenin-17$\beta$-4-C$^{14}$ with m.p. 238–241°, $[\alpha]_D^{23}$ +53° (dioxane), ultraviolet maxima at 230 m$\mu$ ($\epsilon$ 72000), 271 m$\mu$ ($\epsilon$ 6500), 283 m$\mu$ ($\epsilon$ 7500), 292 m$\mu$ ($\epsilon$ 5000), 328 m$\mu$ (shoulder, $\epsilon$ 2800), 341 m$\mu$ ($\epsilon$ 3900). Specific activity 1 mc/mM.

*Estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-C$^{14}$* (IVa). A solution of 316 mg. (1 mmole, containing 1 mc.) of 19-nortestosterone acetate-4-C$^{14}$ in dry ether was brominated exactly as described by Djerassi *et al.*[5] The crude dibromide gave after dehydrobromination as described by Holysz[6] 235 mg. estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-C$^{14}$, m.p. 247–250°, $[\alpha]_D^{25}$ −201° (chlf.) ultraviolet maxima at 222 m$\mu$ ($\epsilon$ 28000), 262 m$\mu$ ($\epsilon$ 8310), 272 m$\mu$ (shoulder, $\epsilon$ 6300), 203 m$\mu$ ($\epsilon$ 2900).

*Estradiol 17$\beta$-acetate-4-C$^{14}$* (V). A solution of 156 mg. of estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-C$^{14}$, containing 1 mc/mM, was reduced with 20% palladium-on-charcoal.[5] The usual work up gave, after recrystallization from methanol, 132 mg. colorless prisms, m.p. 214–217°, $[\alpha]_D^{24}$ +48° (chlf.), $\lambda_{max}^{MeOH}$ 280 m$\mu$ ($\epsilon$ 2650), specific activity 1 mc/mM.

*Estradiol 17$\beta$-acetate-6,7-t* (V).[10,11] To a suspension of 50 mg. pre-reduced 30% palladium-on-charcoal in 38 ml. ethyl acetate, in which was dissolved 96 mg. of estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17$\beta$-acetate, 16 ml. hydrogen gas containing 1.6 c tritium were added at two atmospheres and the mixture allowed to stand overnight. After 2 hr. shaking 8.3 ml. residual gas was removed, the take-up amounting to 7.7 ml. The catalyst was filtered off, the solvent evaporated and the residue recrystallized from methanol which gave 81 mg. colorless prisms, m.p. 218–219°, $[\alpha]_D^{23}$ +50° (chlf.), $\lambda_{max}^{MeOH}$ 280 m$\mu$ ($\epsilon$ 2700), spec. activity calcd.: 8.0 mc/mg.; found: 7.35 mc/mg. The specific activity remained unchanged after 1 hr. equilibration (refluxed with 7% methanolic sodium hydroxide solution).

*17-Dihydroequilenin-17$\beta$-4-C$^{14}$* (IIa). Acetylation of 316 mgs. of estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-C$^{14}$ (1 mmole containing 1 mc) produced the diacetate, m.p. 150–152°, $\lambda_{max}^{MeOH}$ 263 m$\mu$ ($\epsilon$ 10200).

The selenium dioxide dehydrogenation was carried out exactly as described by Djerassi *et al.*,[5] but the reaction product could not be obtained in pure form by chromatography. Alkaline hydrolysis gave, after chromatography on a Hyflow Super Cel partition column[9] and recrystallization from methanol, 122 mg. 17-dihydroequilenin-17$\beta$-4-C$^{14}$ with m.p. 240–241°, $[\alpha]_D^{24}$ +49° (dioxane), ultraviolet maxima

(7) L. M. Thompson, C. H. Yates, and A. D. Odell, *J. Am. Chem. Soc.*, **76,** 1194 (1954), have already pointed out that the order of addition of Grignard reagent and enol lactone was of no apparent importance.

(8) J. A. Hartman and J. A. Hartman *et al.* (footnotes 1 and 2) give m.p. 170–174°, while the ultraviolet spectrum and the rotation data agree very well.

(9) E. O. Haenny, J. Carol, and D. Banes, *J. Am. Pharm. Assn.*, **42,** 167 (1953).

(10) W. H. Pearlman and M. R. J. Pearlman, *J. Am. Chem. Soc.*, **72,** 5781 (1950) have reported on estrone acetate-6,7-$d_2$.

(11) Thanks are due to New England Nuclear Corp., Boston 18, Mass., for carrying out this reduction.

at 230 mμ (ε 71400), 272 mμ (ε 6500), 283 mμ (ε 7480), 292 mμ (ε 5000), 329 mμ (shoulder, ε 2800), 341 mμ (ε 4000).

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## Attempted Oxygenolysis of Some Halide-$LiAlH_4$ and Nitrile-$LiAlH_4$ Reaction Products

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*Received March 1, 1957*

The literature contains several instances of the reaction of oxygen with hydride reduction complexes to yield hydroxylic products. Thus Hochstein and Brown[1] obtained 1-phenyl-1,3-propanediol (25%) from the reduction of cinnamyl alcohol, Soffer and Katz[2] isolated α-phenyl-β-aminoethanol (7%) from the reduction of phenylacetonitrile, and Cotman[3] reduced polyvinyl chloride to a polyethylene containing approximately one hydroxyl per 25 carbon atoms. In the first two instances these products were taken as evidence for a carbon-metal bond, probably carbon-aluminum. In the last, several alternate explanations were made, of which one assumed the presence of a carbon-lithium bond, and another, the oxidation of aluminohydride ion to an oxyaluminohydride ion which displaced chloride, thus leading to a product which on hydrolysis would yield a secondary hydroxyl group.

In addition, Badger and coworkers obtained the cyclic ether of 4,5-bishydroxymethylphenanthrene from the reduction of 4,5-bisbromomethylphenanthrene.[4] Although an ordinary basic hydrolysis of dibromide to diol cannot be definitely excluded, it seemed possible that the incorporation of oxygen might occur by the reaction of a carbon-metal species with atmospheric oxygen.

$$R{-}Br \xrightarrow{LiAlH_4} R{-}Al\langle \xrightarrow{O_2} R{-}OAl\langle \xrightarrow{HOH} ROH$$

The purpose of this study was to attempt the oxygenolysis of simple halides and nitriles under varying conditions and thus obtain additional information on the role of carbon-metal species in hydride reductions.

Assuming that a reaction of oxygen with a carbon-metal bond occurs, it could conceivably be influenced by many factors in the overall process, such as the nature of the substrate, the molar ratio of hydride and substrate, the manner in which the hydride reaction was performed (with reference to solvent, temperature, and whether by direct or reverse addition[2]), the manner in which oxygen was supplied (concurrent with the hydride-substrate reaction, or following it), as well as by the temperature and time of contact with oxygen. A number of experiments using some of the many possible reaction conditions are summarized in Table I. It can be seen that in no case, except the previously reported run 11, were hydroxylic materials isolated. The products obtained were normal for reductions without attempted oxygenolysis, but yields were considerably lower. The low recoveries were undoubtedly due to the difficulties experienced in extraction of the large quantities of gelatinous, post-hydrolysis reaction mixture.[5] The low yields of expected products can be explained likewise, and by the consumption of hydride by oxygen. Although it is regarded as unlikely that significant amounts of hydroxylic materials could have been present in the reaction mixture, the low recoveries preclude the definite conclusion that no hydroxylic products were formed.

Run 5 was made as a test of Cotman's hypothesis[3] that oxyaluminohydride ions are responsible for the displacement of halide with hydroxyl. Oxygen was passed into the hydride suspension solution at 65° for 4.5 hr., after which benzyl bromide was added and the mixture stirred at 65° for 17 hr. The isolation of toluene and benzyl bromide indicated that the reaction of hydride with oxygen had been incomplete and that little or no reaction occurred between benzyl bromide and the oxidized hydride. The failure to obtain any product other than a 10% yield of phenylacetaldehyde in run 9 can be attributed to the factors of low temperature and concurrent admission of oxygen.

Thus, under the conditions of our experiments, the attempted oxygenolysis of halide-hydride and aliphatic nitrile-hydride reduction complexes were unsuccessful, affording no evidence for a carbon-metal bond in such species. A single test of Cotman's "oxyaluminohydride hypothesis" for the production of hydroxyl during halide-hydride reductions failed to support the hypothesis.

(1) F. A. Hochstein and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3484 (1948).

(2) L. M. Soffer and M. Katz, *J. Am. Chem. Soc.*, **78**, 1705 (1956).

(3) J. D. Cotman, Jr., *J. Am. Chem. Soc.*, **77**, 2790 (1955).

(4) G. M. Badger, J. E. Campbell, J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.*, 2326 (1950). The ether was obtained by sublimation of the actual reduction product which was undoubtedly 4,5-bishydroxymethylphenanthrene. The dehydration of the latter material to the ether was demonstrated by these workers to occur very readily.

(5) Extraction was particularly difficult in the runs where oxygen input was concurrent with the substrate-hydride reaction.

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<br>Benzyl bromide, 42 | — |
| 5 | Benzyl bromide | DA; THF | 1.1 | [h] | (17, 65) | Toluene, 38<br>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<br>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<br>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 Hyarides*, 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

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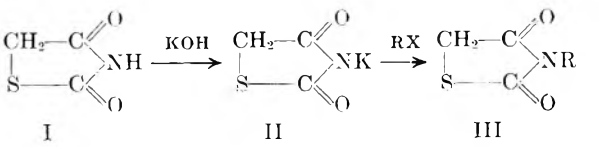
*Received March 4, 1957*

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).




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.

(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 potassium 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.

(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.

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

M. FREDERICK HAWTHORNE

*Received March 6, 1957*

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.

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

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, $\alpha$-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°.

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

NORBERT NEUSS AND HAROLD E. BOAZ

*Received March 12, 1957*

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-

(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 $\mu$ 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).

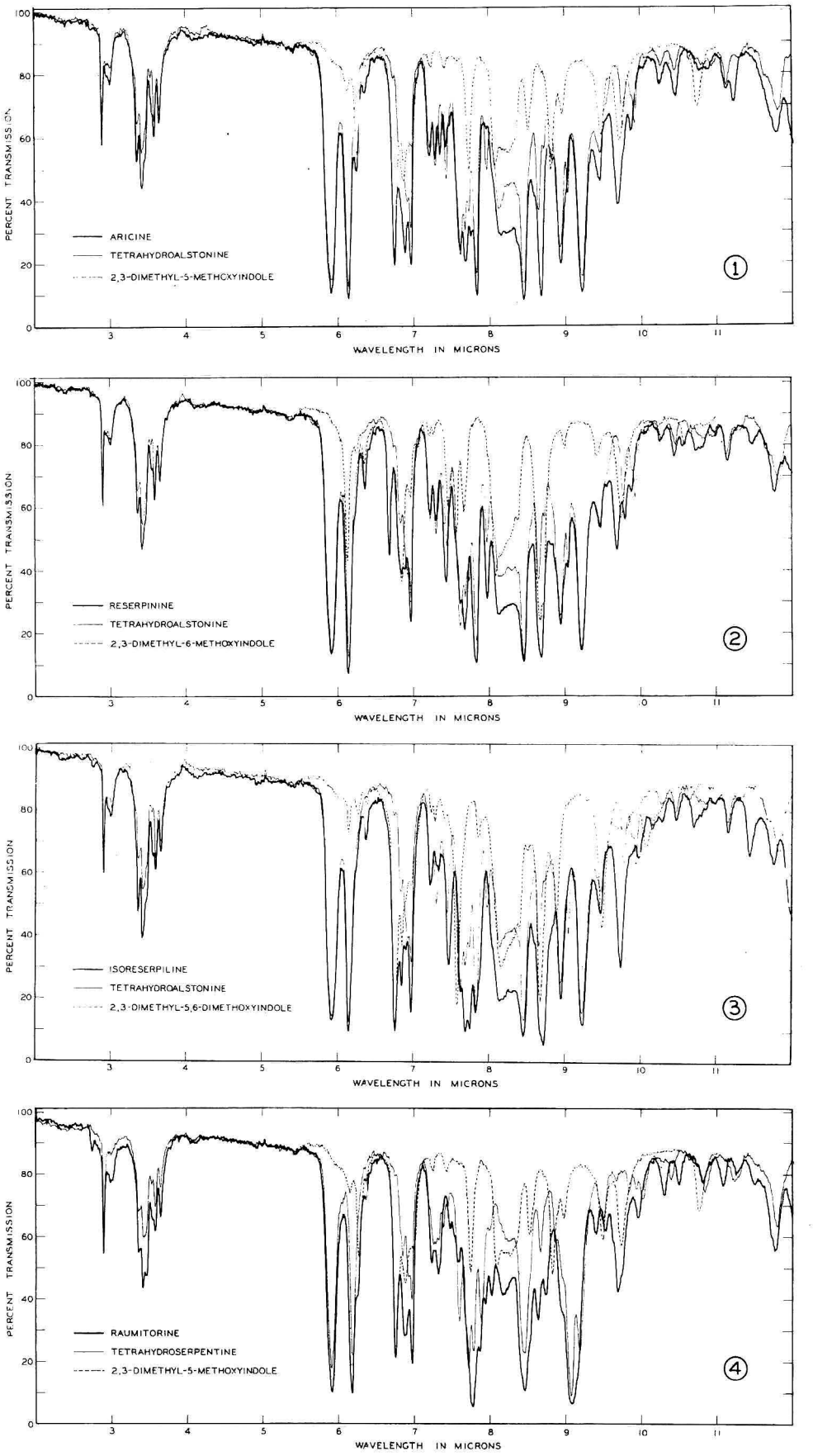
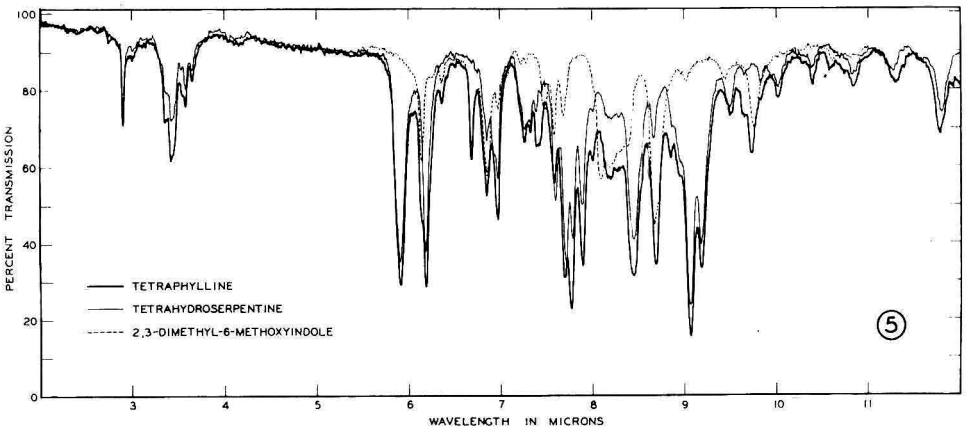
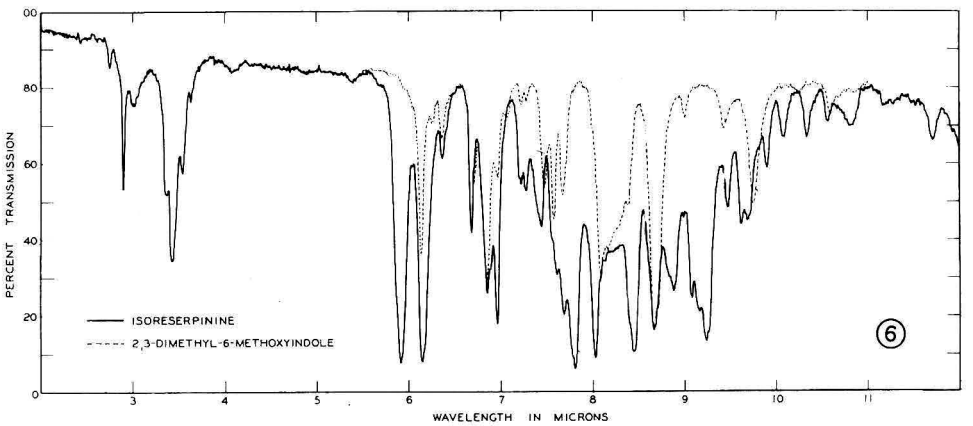
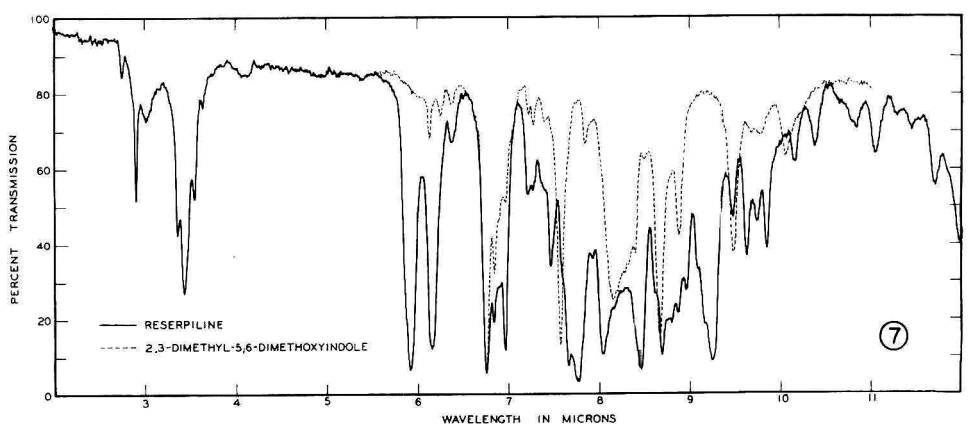
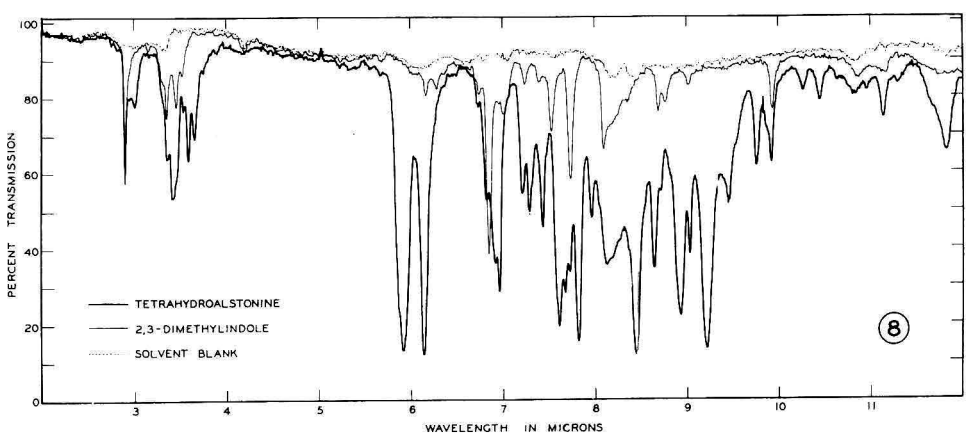



FIG. 1–4. INFRARED SPECTRA OF SOME INDOLE ALKALOIDS.



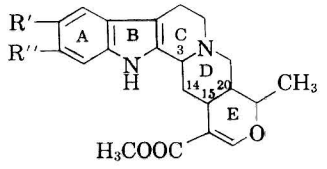




FIGS. 5–8. INFRARED SPECTRA OF SOME INDOLE ALKALOIDS.

phylline (IV),[10] isoreserpinine (V),[7] reserpiline (IX),[11] tetrahydroalstonine (I),[12] and tetrahydroserpentine (II).[4]




R′ = R″ = H; Tetrahydroalstonine (I), Tetrahydroserpentine (II)
R′ = H; R″ = $OCH_3$; Reserpinine (III), Tetraphylline (IV), Isoreserpinine (V)
R′ = $OCH_3$, R″ = H; Aricine (VI), Raumitorine (VII)
R′ = $OCH_3$, R″ = $OCH_3$; Isoreserpiline (VIII), Reserpiline (IX)

The most obvious features of the infrared spectra of methoxy substituted tetrahydroalstonines and their stereoisomers which can be correlated with the structure are the narrow and relatively intense bands in the 6 to 7 $\mu$ region. These bands arise from the peculiar polarization of the indole moiety.[4] Although interaction of the vibrations of this portion of the molecule with those of the conjugated ester vinyl ether in ring *E* of the heteroyohimbane may not be completely absent, it appears to be very small. Likewise there appears from the spectrum as well as from molecular models to be very little if any steric effect of methoxy groups in the 10 and 11 position upon rotational isomerism of the ester or methyl groups in ring *E*. Consequently one can regard in this group of compounds the infrared spectrum to a first approximation as the sum of the spectrum of the corresponding methoxy substituted 2,3-dimethylindole and the spectrum of tetrahydroalstonine or that of the corresponding stereoisomer. (See Fig. 1 to 7)

Deviations from simple summation of spectra between 6 to 7 $\mu$ are hardly observable. In the 7 to 12 $\mu$ region greater differences in wave length and intensity occur, but they raise little doubt as to which of the more intense bands arise from the indole moiety and which ones represent vibrations of the C-D-E ring system including the ester grouping. Examination of the spectrum of 2,3-dimethylindole (Fig. 8) shows that the contribution of the indole portion of tetrahydroalstonine in the 7 to 12 $\mu$ region of the spectrum is relatively small.

All these observations clearly indicate that aricine (VI), reserpinine (III), and isoreserpiline (VIII) are 10-methoxy-, 11-methoxy-, and 10,11-dimethoxytetrahydroalstonine respectively; similarly raumitorine (VII) and tetraphylline (IV) are 10-methoxy- and 11-methoxytetrahydroserpentine. Finally, isoreserpinine (V) and reserpiline (IX) are 11-methoxy- and 10,11-dimethoxy derivatives of a base which is neither tetrahydroalstonine nor tetrahydroserpentine, but resembles tetrahydroalstonine more than tetrahydroserpentine.

The examination of the infrared spectra in carbon disulfide solution of these alkaloids leads also to the conclusion that they can be divided into three groups. (Fig. 9 to 14)

In the first group, including tetrahydroserpentine and tetraphylline, there is a relatively simple ester band[13] at 8.45 $\mu$. (Fig. 9 and 10)

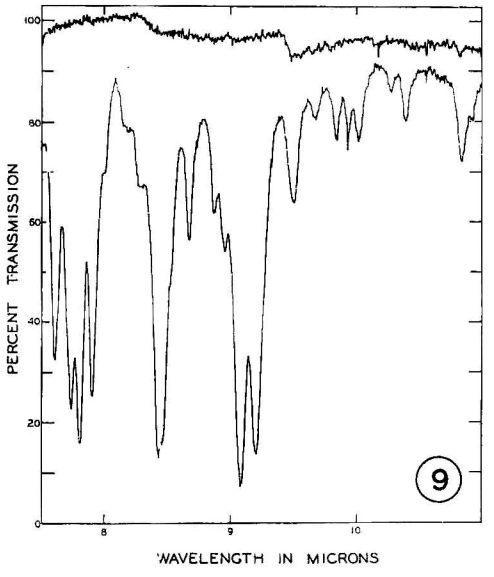
In the second group represented by the spectra of tetrahydroalstonine and reserpinine there appear three distinctly resolved bands at 8.15, 8.32, and 8.45 $\mu$. (Fig. 11 and 12)

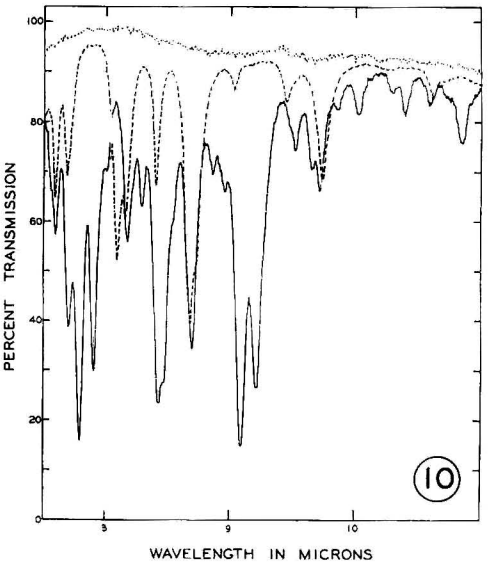
The last group contains reserpiline and isoreserpinine. Instead of the characteristic ester bands mentioned in the first two groups there is a broad band at 8.26 $\mu$ (Fig. 13 and 14). Our attempts to reconstitute the spectra of these two alkaloids by summation of either tetrahydroalstonine or tetrahydroserpentine and the corresponding substituted indole were unsuccessful.[14] However, the superposition of the spectrum of tetraphylline (Fig. 10), reserpinine (Fig. 12), and isoreserpinine (Fig. 14) clearly shows a much greater similarity of the latter compound to reserpinine than to tetraphylline. Actually the bands at 8.32, 8.45, and 9.25 $\mu$ nearly coincide both in wave length and relative intensity in the spectra of these two compounds.[15]

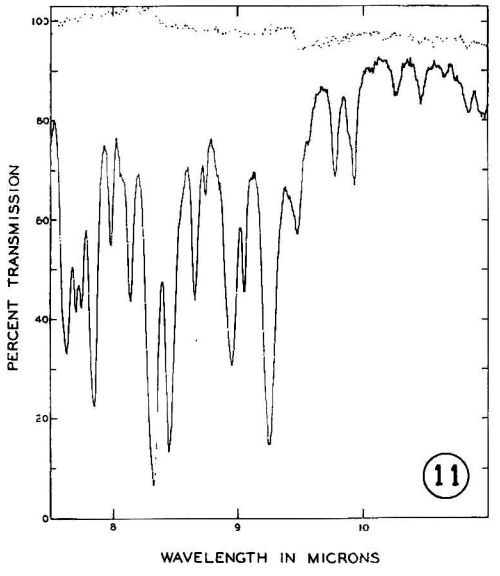
The examination of molecular models (Stuart-Briegleb) of tetrahydroserpentine shows that with a D/E ring junction *cis*, no hindrance to rotation of the carbomethoxy group is evident. Accordingly the infrared spectrum of this alkaloid shows only a small splitting of the ester band. This is in agreement with the findings of Chatterjee *et al.*,[16] who have postulated a *cis* configuration for the D/E ring junction on the basis of the unusual stability to acid of the enol ether linkage of the dihydropyran ring in the ring *E*.

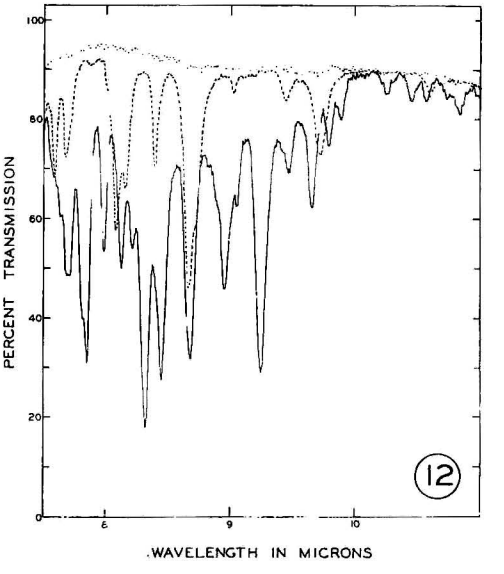
By assembling the molecular model with a *trans* D/E ring junction one observes a restricted rotation of the ester carbonyl hindered by the $C_{(14)}$ methylene hydrogens. As a result the carbon-carbon double bond is in a different plane than the ester carbonyl. In agreement with this configuration the spectrum of tetrahydroalstonine shows a large splitting. Bader has reported the instability of alstonine toward acid and the ease of formation of the 2,4-dinitrophenylhydrazone with a simultaneous fission of the oxygen bridge,[17] and Elderfield

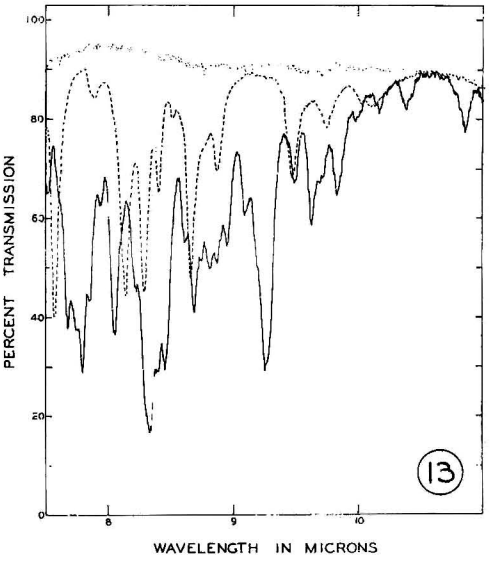
(10) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakrashi, *J. Am. Chem. Soc.*, **79**, 1217 (1957).
(11) Klohs *et al.*, *Chemistry & Industry*, 1264 (1954).
(12) E. Schlittler, H. Schwarz, and F. Bader, *Helv. Chim. Acta*, **35**, 271 (1952).
(13) This band is missing in the spectrum of tetrahydroserpentinol in pyridine solution.
(14) Mayumbine and akuammigine have been reported to be isomeric with tetrahydroalstonine. Unfortunately we were unable to obtain these alkaloids for this study.
(15) Isoreserpinine is a $C_{(3)}$ epimer of reserpinine. We thank Dr. C. Djerassi for this information prior to publication.
(16) A. Chatterjee and S. K. Talapatra, *Science and Culture (India)*, **20**, 568 (1955).
(17) F. E. Bader, *Helv. Chim. Acta*, **36**, 215 (1953).

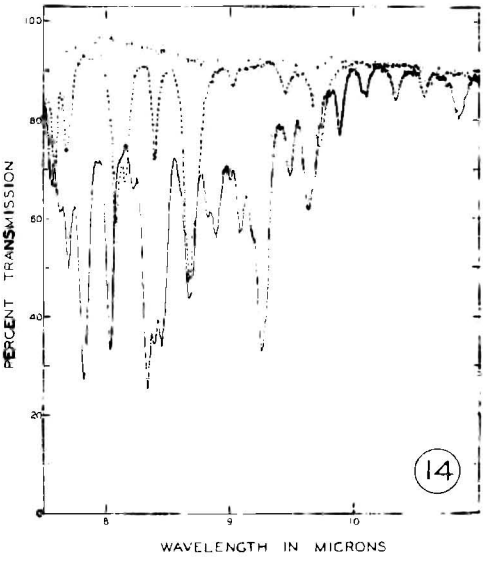



FIGS. 9-14. INFRARED SPECTRA OF: 9, tetrahydroserpentine; 10, tetraphylline; 11, tetrahydroalstonine; 12, reserpinine; 13, reserpiline; 14, isoreserpinene.

has confirmed this instability for tetrahydroalstonine.[18]

The greater acid stability of tetrahydroserpentine as compared to that of tetrahydroalstonine can be attributed to the difference in configuration at the D/E ring junction.[19]

Additional evidence for these configurations of the C/D ring junction in tetrahydroalstonine and tetrahydroserpentine is furnished by the wave lengths of the C=C bands in the infrared spectra in chloroform solution. This band is found at 6.14 $\mu$ in the former and at 6.19 $\mu$ in the latter.

The ultraviolet spectrum also corroborates the C/D ring junction as *cis* for tetrahydroserpentine and *trans* for tetrahydroalstonine. Thus the differential ultraviolet spectrum of tetrahydroalstonine *vs.* yohimbane shows distinctly two bands whereas the corresponding differential spectrum of tetrahydroserpentine has only a simple symmetrical band. (Fig. 15)

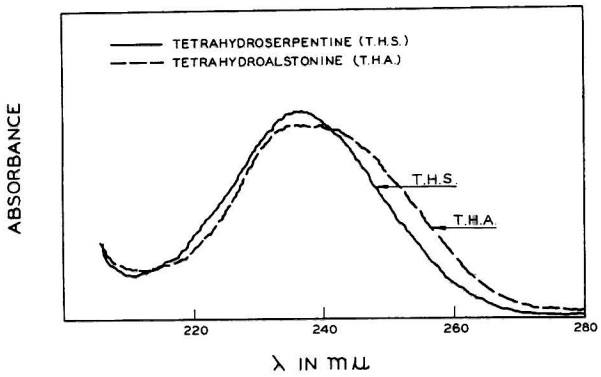
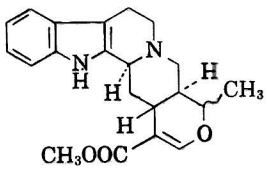


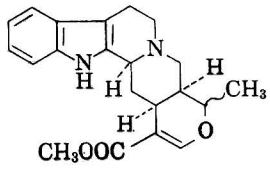

FIG. 15. DIFFERENTIAL U. V. SPECTRUM OF T. H. A. AND T. H. S. VERSUS YOHIMBANE

The configuration at $C_3$ and $C_{15}$ in tetrahydroserpentine has already been proposed as *syn* by Weisenborn.[20] More recently Wenkert[7] has classified various indole alkaloids into *normal* and *allo* products with an $\alpha$-hydrogen at $C_{(3)}$ and *pseudo* or *epiallo* compounds containing a $\beta$-hydrogen at $C_{(3)}$. This assignment was given on the basis of presence or absence of certain bands in the 3.4–3.7 $\mu$ region in chloroform solution. In this classification tetrahydroserpentine and tetrahydroalstonine have an $\alpha$-hydrogen at $C_{(3)}$.

All these data indicate the most probable configuration of tetrahydroalstonine (X) and tetrahydroserpentine (XI) at $C_{(3)}$, $C_{(15)}$, and $C_{(20)}$ and are represented by formulae X and XI, respectively:




X




XI

On the basis of this evidence together with that cited above aricine, reserpinine, and isoreserpiline should be assigned the tetrahydroalstonine and raumitorine and tetraphylline the tetrahydroserpentine configurations.

## EXPERIMENTAL

Spectra in chloroform solution were obtained in 0.11 mm. path; solutes are at concentrations of 0.18–0.2*M*. Spectra in carbon disulfide solution were obtained in 3 mm. path; solutes are at concentrations of 0.003–0.005*M*. All spectra were recorded using Perkin-Elmer, double-beam I.R. spectrophotometer, Model 21.

*Acknowledgment.* We would like to thank Drs. C. Djerassi, M. M. Janot, and A. Hofmann for the samples of some of the alkaloids used in this study.

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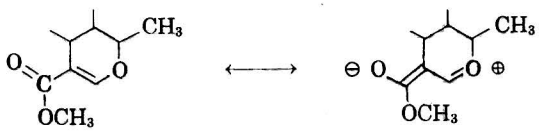
ELI LILLY AND COMPANY
INDIANAPOLIS, INDIANA

(18) We gratefully acknowledge this information from Professor Elderfield (1953).

(19) A system consisting of fused 6-membered rings with a double bond adjacent to a ring juncture has a lower energy when that juncture is *cis* than when it is *trans*. [D. A. H. Taylor, *Chemistry & Industry*, 250 (1954); Andre S. Dreiding, *Chemistry & Industry*, 1419 (1954).] If it is assumed that the disposition of atoms in dihydropyran is not unlike that in cyclohexene, then tetrahydroserpentine (*cis* D/E) should be the more stable. Resonance stabilization of the vinyl ether system will be greater in this alkaloid where the free rotation of the carbomethoxyl group allows complete coplanarity of the carbonyl and ethylenic functions:




We would like to thank Dr. G. B. Kline of these laboratories for this explanation.

(20) F. L. Weisenborn *et al.*, *Chemistry & Industry*, 375 (1954).

## Metal-Catalyzed Condensations of Esters of Acetonedicarboxylic Acid

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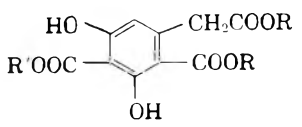
Evidence is presented which suggests that the conversion of dimethyl acetonedicarboxylate (DMADC) to methyl 2,4-dicarbomethoxy-3,5-dihydroxyphenylacetate (I) proceeds through the initial formation of a metal chelate compound. Among the reported reactions of esters of acetonedicarboxylic acid are the self-condensations of these substances to esters of 2,4-dicarboxy-3,5-dihydroxyphenylacetic acid, I, II, III, and IV, under simple experi-

mental conditions.[1-6] With no catalyst, or in the presence of catalytic amounts of sodium, sodium alkoxides, magnesium, magnesium oxide, zinc oxide, ferric oxide, and hydrogen chloride, the reaction has been reported to proceed at temperatures




I R, R′ = $CH_3$
II R = $CH_3$, R′ = H
III R, R′ = $C_2H_5$
IV R = $C_2H_5$, R = H

of 140–180° to give yields of the condensation products up to 60%. Conventional acid and base catalyzed mechanisms have been proposed for these reactions.

In this laboratory no condensation product could be obtained from DMADC alone or in the presence of hydrogen chloride; magnesium metal gave I as reported. From a detailed examination of the literature, it appeared that a metal rather than acid or base might be the prime promoter of this reaction. Indeed, Jerdan felt that the metal was catalytically involved.[4] More recently, Brandstrom has proposed a general hypothesis for the alkylation of tautomeric substances and has emphasized the importance of alkali metal chelate intermediates.[7] Hauser has explained differences in products of condensations catalyzed by $NaNH_2$ and $LiNH_2$ in terms of the stabilities of the metal complexes of the products.[8] The views of these investigators may be extended to the reaction under consideration.

The importance of the metal to the course of this reaction is shown by the data in Table I.

Clearly, I was not formed in the presence of conventional acidic and basic catalysts which contained no metals; nor was it formed with all metallic reagents. However, the reaction proceeded *readily* with *catalytic* amounts of many metals, present either as the preformed metal chelate of DMADC or as a simple organic or inorganic metal compound. The yields of I varied considerably with the catalyst, and there were other unidentified reaction products formed. The amount of a given metal used could change the course of the reaction drastically as is apparent from the early literature.[3,4] The discrepancies of the early literature may be explained on the basis of the general use of soft glass equipment or the presence of metal impurities. When powdered soft glass was used as a catalyst, an appreciable amount of I was formed.

TABLE I

EFFECTIVENESS OF CATALYSTS IN THE CONDENSATION OF DIMETHYL ACETONEDICARBOXYLATE

| Catalyst[a] | Mole % Yield of I |
|---|---|
| None | 0 |
| Hydrogen chloride | 0 |
| *p*-Toluenesulfonic acid | 0 |
| Piperidine | 0 |
| Ammonium acetate | 0 |
| Cupric chloride dihydrate | 0 |
| Copper chelate DMADC[b] | 0 |
| Aluminum chloride hexahydrate | 0 |
| Aluminum acetate basic | 0 |
| Lithium chloride | 3.5 |
| Sodium acetate | 37 |
| Sodium hydroxide | 11 |
| Sodium iodide | 8 |
| Potassium acetate | 6 |
| Magnesium metal | 14 |
| Magnesium oxide | 17 |
| Magnesium chloride hexahydrate | 36 |
| Calcium chloride | 20 |
| Ferric chloride hexahydrate | 14 |
| Cobaltous acetate tetrahydrate | 14 |
| Zinc chloride | 7 |
| Zinc chelate DMADC[c] | 15 |
| Lead acetate trihydrate | 26 |

[a] Catalyst is A.R. and anhydrous unless otherwise noted. [b] Calcd. for $C_{14}H_{18}O_{10}Cu$: C, 41.03; H, 4.43; CuO, 19.4. Found: C, 40.96; H, 4.49; CuO, 19.4. [c] Calcd. for $C_{14}H_{18}O_{10}Zn \cdot 2H_2O$: C, 37.56; H, 4.95; ZnO, 18.18; $H_2O$, 8.05. Found: C, 37.70; H, 5.27; ZnO, 18.2; $H_2O$, 8.32.

The reactions were carried out with about 0.20 mole DMADC and 0.001 mole of catalyst heated at about 145° for 2–24 hr. The reaction mixture was distilled at 50 mm. and 145° until no further distillate came over. The residue was viscous and would crystallize when I had formed; if no I had formed, the undistilled residue remained a mobile liquid. The product was recrystallized from methanol and characterized by melting point (145–146°) and infrared curve.

That the primary step in this self-condensation reaction is probably the formation of a metal chelate compound may be readily illustrated with the reaction involving ferric chloride. Here the immediate deep-red color of the reaction mixture indicates rapid complex formation. With the zinc chelate of DMADC as catalyst the reaction proceeds smoothly. The postulated initial chelation does not exclude complex formation in further steps or the requirement of acid or base in subsequent steps of the reaction. The important fact is that the role of the metal in reactions of this type has been largely overlooked in the past and a reinterpretation of many condensation reactions may be made through the additional consideration of metal chelate formation.

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# Communication TO THE EDITOR

## Ozonolysis of Naphthalene

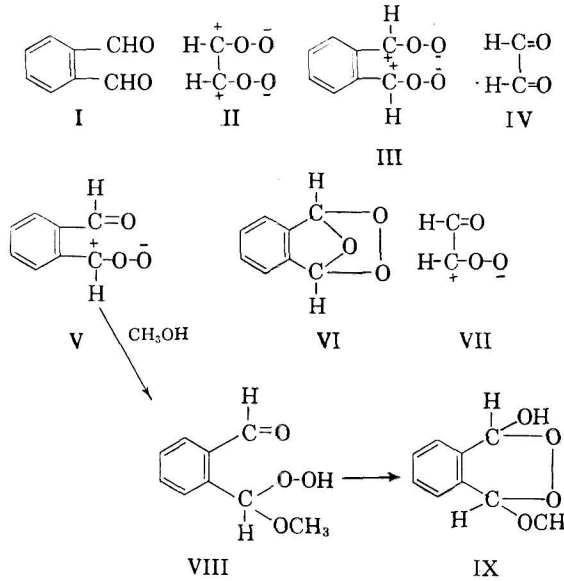
*Sir:*

Harries and Weiss[1] reported the isolation of diozonides of naphthalene and phenanthrene by ozonolyses of these substances in chloroform. It has been shown since then that phenanthrene yields a polymeric monoozonide upon ozonolysis in inert solvents.[2,3] Workers have continued to assume, however, that the ozonide of naphthalene is a diozonide, because two moles of ozone per mole of naphthalene are absorbed.[4-6]

In light of the Criegee mechanism[7] for ozonolysis, one would expect the naphthalene ring to be cleaved at the 1,2 and 3,4 bonds to yield one of the following pairs of fragments: I and II, III and IV, or V and VII. Fragments such as II and VII would be expected to decompose as soon as they are formed.[8] Instead of obtaining a diozonide, therefore, one should obtain one of the following: a monoozonide with two carbons less than in naphthalene (from cyclization of V), a polymer of V, I, or a polymer of III.

Ozonolysis of naphthalene in hexane at −70° resulted in the absorption of 2 molar equivalents of ozone and the precipitation in high yield of a colorless crystalline peroxidic material. The ozonide was too unstable to analyze. If allowed to dry in chunks, it exploded.

Ozonolysis of naphthalene in methanol at −70° (2 molar equivalents of ozone absorbed) followed by partial evaporation and cooling to −70° gave a 94% yield of a colorless crystalline peroxide (m.p. 115–117°; recrystallized from ethyl acetate and hexane, m.p. 126–127°, 85% yield). The material was assigned structure IX because of its elemental analysis (calcd. for $C_9H_{10}O_4$: C, 59.35; H, 5.52; methoxyl, 17.03; mol. wt. 182.17. Found: C, 59.39; H, 5.38; methoxyl, 16.89; mol. wt. 184, 190[9]), its infrared spectrum which showed a hydroxyl but no carbonyl bond, a negative lead tetraacetate test for hydroperoxides,[10] conversion to phthalic acid by acidic hydrogen peroxide and hydrolytic rearrangement under acidic or alkaline conditions to phthaldehydic acid.




The formation of IX obviously is a reaction of zwitterion V, involving cyclization of VIII. One may conclude, therefore, that the ozonide, likewise, was formed from zwitterion V and either was the monomeric monoozonide VI or a polymer of V. We believe it was VI because of its crystalline character and because of its explosiveness. The polymeric ozonide of phenanthrene was not explosive.[2] It has been reported previously that systems such as VI are very unstable.[11]

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