attached to a carbon atom of an aromatic nucleus into a formyl group.

To a mixture of 0.05 mole of acetophenone and 6 ml. of concentrated sulfuric acid in 50 ml. of either benzene or nitrobenzene preheated to 60°, 0.05 mole of an alkyl azide is added at such a rate that the reaction temperature maintains itself at 75°. Separation of the layers after dilution with ice-water allows the isolation of benzaldehyde from the benzene layer by distillation. Upon making the aqueous acid layer basic using sodium carbonate and then sodium hydroxide, amines, corresponding to the azides, are isolated by ether extraction. Formaldehyde is detected in the aqueous acid layer as its dimethone derivative by the addition of a methanolic solution of methone.

Four alkyl azides and phenyl azide have been investigated. The best yield (85%) of benzaldehyde is obtained using cyclohexyl azide[2] and good yields (70–80%) are obtained using *n*-butyl,[2] *n*-hexyl[2] or *n*-octyl[3] azides. Phenyl azide[4] is unsuccessful in transforming acetophenone into benzaldehyde. Benzaldehyde, b.p. 35° (2 mm.), $n^{23}D$ 1.5423, was further identified by a mixture m.p. determination (156°) of its phenylhydrazone derivative with a known sample. Apparently the methyl group of acetophenone is transformed into formaldehyde, isolated in 80–85% yield as its dimethone derivative, m.p. and mixture m.p. 191.4°, as an alkyl azide is reduced to an amine. From the corresponding azides, *n*-butyl, *n*-hexyl, *n*-octyl and cyclohexylamines are obtained in yields, respectively, of 60, 65, 52 and 50%. Identification of the amines was indicated by b.p. and confirmed using m.p. determinations of hydrochloride, picrate and chloroplatinate derivatives: *n*-butylamine, b.p. 78° hydrochloride m.p. 195°, picrate m.p. 195°[5]; *n*-hexylamine, b.p. 129–130°, hydrochloride m.p. 219°, chloroplatinate 263–268° dec.[6]; *n*-octylamine, b.p. 175–177°, picrate m.p. 111.5–112.5°[6,7]; cyclohexylamine, b.p. 134°, $n^{20}D$ 1.4371, hydrochloride m.p. 205–207°.[8]

(2) J. H. Boyer, F. C. Canter, J. Hamer and R. K. Putney, THIS JOURNAL, **78**, 325 (1956).
(3) E. Lieber and T. S. Chao, *J. Org. Chem.*, **22**, 238 (1957).
(4) A. Darapsky, *Ber.*, **40**, 3033 (1907).
(5) R. Brown and W. E. Jones, *J. Chem. Soc.*, 781 (1946).
(6) A. Nyssens, *Ing. Chim.*, **18**, 40 (1930).
(7) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 842 (1934).
(8) Guyst, *Bull. soc. chim.*, **47**, 205 (1930).

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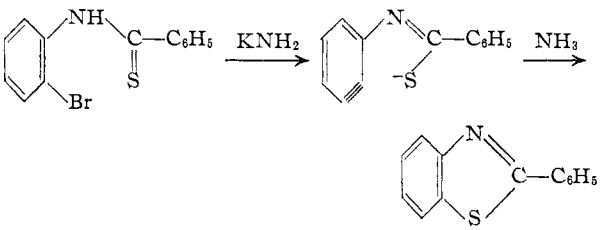
A GENERAL PRINCIPLE FOR THE SYNTHESIS OF HETEROCYCLIC AND HOMOCYCLIC COMPOUNDS[1]

Sir:

We wish to report a new general principle for the synthesis of heterocyclic and homocyclic compounds. This principle involves the creation of an intermediate species which is of the benzyne[2] type and which has a nucleophilic center located so that it can add, intramolecularly, to the "triple bond" of the benzyne structure. This method is illustrated by the conversion of thiobenz-*o*-bromoanilide to 2-phenylbenzothiazole in 90% yield through the action of potassium amide in liquid ammonia



As expected from the mechanism, the same product is obtained from thiobenz-*m*-bromoanilide (in 68% yield).

Through the action of potassium amide in liquid ammonia, we have also accomplished the synthesis of benzoxazole, phenothiazine, indole and indane ring systems. The examples studied include conversion of benz-*o*-chloroanilide to 2-phenylbenzoxazole (69% yield), of acetoacet-*o*-chloroanilide to 2-hydroxy-3-acetylindole (57%), of 2-amino-2′-bromodiphenyl sulfide to phenothiazine (35%) and of *o*-chlorophenylacetone to indan-2-one (6%). These cases illustrate intramolecular addition of nucleophilic sulfur, oxygen, nitrogen and carbon reagents; the formation of 2-phenylbenzoxazole is of further interest as the first instance of addition of an oxygen reagent to a benzyne derivative in ammonia solution in substantial yield. In these examples the formation of both five- and six-membered rings and of both heterocyclic and homocyclic systems are also illustrated.

To this list of examples should be added the preparation of N-methyl-2,3-dihydroindole (58%) and of N-methyl-1,2,3,4-tetrahydroquinoline (28%) from treatment of appropriate N-methyl-ω-(chlorophenyl)-alkylamines with phenyllithium. These were reported by Huisgen and König[3] without comment on the generality of the method.

One can visualize application of this principle of ring closure to the synthesis of countless heterocyclic and homocyclic systems both known and unknown. We expect that this soon will be recognized as a major method for the synthesis of cyclic compounds.

Some new compounds are involved in the work reported here. Thiobenz-*o*-bromoanilide, m.p. 85–86°, was prepared by thiation[4] of benz-*o*-bromoanilide.[5] (*Anal.* Calcd. for $C_{13}H_{10}BrNS$: Br, 27.35; N, 4.79. Found: Br, 27.50; N, 4.78.) Thiobenz-*m*-bromoanilide, m.p. 106–108°, was similarly prepared. (*Anal.* Found: Br, 27.50; N, 4.78). Condensation of sodium *o*-bromothiophenoxide with *o*-chloronitrobenzene gave 2-nitro-2′-bromodiphenyl sulfide, m.p. 116–117°. (*Anal.*

(1) Research supported in part by the Office of Ordnance Research, U. S. Army.

(2) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, THIS JOURNAL, **78**, 601 (1956).
(3) R. Huisgen and H. König, *Angew. Chem.*, **69**, 268 (1957).
(4) E. Klingsberg and D. Papa, THIS JOURNAL, **73**, 4988 (1951).
(5) F. D. Chattaway and J. M. Wadmore, *J. Chem. Soc.*, **81**, 986 (1902).

Calcd. for $C_{12}H_{18}BrNO_2S$: C, 46.45; H, 2.60. Found: C, 46.41; H, 2.70.) Reduction furnished 2-amino-2′-bromodiphenyl sulfide, m.p. 62–63°. (*Anal.* Calcd. for $C_{12}H_{10}BrNS$: C, 51.44; H, 3.60. Found: C, 51.00; H, 3.63. Hydrochloride, m.p. 132–134°. *Anal.* Calcd. for $C_{12}H_{11}BrClNS$: C, 45.51; H, 3.50. Found: C, 45.57; H, 3.79.) Benz-*o*-chloroanilide[6] and *o*-chlorophenylacetone[7] were made by standard methods. Acetoacet-*o*-chloroanilide was the product of Union Carbide Chemicals Co. Products were identified by mixed melting points with authentic samples or by comparison of melting points of the product and at least one derivative thereof with literature values. The yields reported are not considered to be optimum.

(6) F. D. Chattaway and K. J. P. Orton, *Ber.*, **33**, 2396 (1900).
(7) I. B. Johns and J. M. Birch, THIS JOURNAL, **60**, 919 (1938).

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RECEIVED MARCH 21, 1958

THE SITE OF CLEAVAGE OF *MYO*-INOSITOL BY PURIFIED ENZYMES OF RAT KIDNEY

Sir:

We have reported previously[1] the cleavage and conversion of inositol to glucuronic acid (racemic mixture) by rat kidney extracts. The enzyme preparation has now been purified, and the system that forms D-glucuronate has been obtained free of the one that forms the L-isomer. Resolution was obtained by treatment with calcium phosphate gel which adsorbs only the system that forms the L-isomer. The enzyme system forming the D-isomer was further purified 200-fold. Attempts to elute the adsorbed enzyme from the gel produced inactive preparations. Employing inositol-2-C^{14} [2] as the substrate and incubating separately with either the crude enzyme system or the purified enzyme capable of yielding only the D-isomer, we isolated 8 to 10 mg. of the respective radioactive glucuronic acids. They were converted to their lactones with m.p. of 176–178° for the racemic lactone[1] and 180° for the D-glucuronolactone having an $[\alpha]^{23}D$ +18.6° (*c* 1 in H_2O, *l* = 1 dm.). The radioactive glucuronolactones were diluted fivefold with the respective non-radioactive glucuronolactones and crystallized to a constant specific activity of approximately 1755 c.p.m. per micromole. The distribution of C^{14} within each of the glucuronates was obtained as follows: the uronic acids were reduced with $NaBH_4$ to gulonic acids which were converted to their lactones. The lactone derived from the racemic glucuronate was optically inactive and could not be crystallized. The lactone of the D-isomer had a m.p. of 184–185° and an $[\alpha]^{23}D$ +56° as expected for L-gulonolactone (*c* 1 in H_2O, *l* = 1 dm.). The gulonolactones were titrated with NaOH and were oxidized with HIO_4 to 1 mole of formaldehyde, 1 mole of glyoxylate and 3 moles of formate per mole of gulonolactone. The formaldehyde was isolated as the dimedon derivative, m.p. 191°, in 95% yield. The formic acid was distilled and isolated as the sodium salt in 100% yield. The glyoxylate was obtained in 85% yield and was characterized as described earlier[3] and by its 2,4-dinitrophenylhydrazone, m.p. 192°. Aliquots of these fractions were plated and counted in a gas flow counter. More than 98.5% of the C^{14} of the degraded gulonolactones were recovered in the glyoxylate fraction. The radioactive glyoxylates were further oxidized with HIO_4 to equimolar amounts of CO_2 and formate.[3] This formate contained all the C^{14} of the glyoxylate. These results demonstrate that the C-2 of inositol becomes C-5 of the racemic as well as of the D-glucuronate. Thus, inositol cleavage by the purified enzyme system occurs between C-1 and C-6 to form *exclusively* D-glucuronate. The formation of L-glucuronate may result from cleavage of inositol between C-3 and C-4, assuming that no racemization occurs of a possible intermediate between inositol and D-glucuronate. Further studies are needed to confirm this latter mechanism.

(1) F. C. Charalampous and C. yras, *J. Biol. Chem.*, **228**, 1 (1957).
(2) We are grateful to Dr. Laurens Anderson for a generous gift of inositol-2-C^{14}.
(3) F. C. Charalampous, *J. Biol. Chem.*, **225**, 585 (1957).

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IDENTIFICATION OF CYANOACETIC ACID AS A METABOLITE OF β-AMINOPROPIONITRILE (BAPN) AND OTHER NITRILES[1]

Sir:

The administration of β-aminopropionitrile (BAPN) to rats or rabbits has been shown to result in the formation of a metabolite which could be detected in the urine or blood serum by an orange-pink spot on paper chromatograms developed with diazotized sulfanilic acid.[2] Efforts to isolate the metabolite from ethyl acetate extracts of acidified urine led to the separation of a colorless, crystalline, nitrogenous solid which was very soluble in water, highly acidic, distillable *in vacuo*, and exhibited the characteristic chromatographic behavior.[2] Further examination of this solid showed that it was not pure, but the metabolite was obtained from it in substantially pure form by ion-exchange chromatography on Dowex-1 resin (acetate form) and has now been identified as *cyanoacetic acid*. The isolated substance melted at 67–68°, undepressed by admixture with an authentic sample, and corresponded closely with known cyanoacetic acid in its infrared spectrum and chromatographic behavior on paper. *Anal.* Calcd. for $C_3H_3O_2N$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.33; H, 3.68; N, 15.42.

Cyanoacetic acid was also detected in the urine of rats following administration of 3,3′-iminodipropionitrile,[3,4] ethylene cyanohydrin and valeronitrile. Administered cyanoacetic acid was ex-

(1) Supported in part by grants A538(C8) and A1498 from the National Institutes of Health, U. S. Public Health Service.
(2) J. T. Garbutt, J. J. Lalich, S. H. Lipton and F. M. Strong, *Federation Proc.*, in press.
(3) J. Delay, P. Pichot, J. Thuillier and J. P. Marquiset, *Compt. rend. soc. biol.*, **146**, 533 (1952).
(4) H. A. Hartmann and H. F. Stich, *Science*, **125**, 445 (1957).