[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, LABORATORY OF ADVANCED RESEARCH, REMINGTON RAND, INC.]

5,6-Dimethylbenzotriazole and its Acyl Derivatives*

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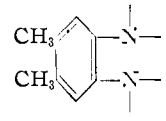
5,6-Dimethylbenzotriazole and several 1-acyl derivatives have been prepared. Absorption spectra of 5,6-dimethylbenzotriazole and its 1-acetyl derivative have been determined. The solvolysis of the 1-acetyl derivative in ethanol and 25% water–75% ethanol has been followed spectroscopically.

The 1,2-dinitrogen-4,5-dimethylbenzene moiety (I) occurs in riboflavin, lyxoflavin, 5,6-dimethyl-

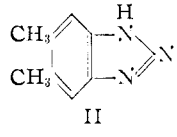


I

benzimidazole and its derivatives.[1] Accordingly, compounds containing this grouping might be expected to possess biological activity, either similar or antagonistic to the function of these naturally occurring substances.

Replacement of an imidazole ring in natural products with the v-triazole ring system has led to demonstrable metabolite antagonism in the case of purines and their analogous v-triazolo(d)pyrimidines.[2] Similarly, a small but definite antagonism to the action of histamine in arterial blood pressure response was brought about by its v-triazole analog.[3]

It was with the thought that the analog of 5,6-dimethylbenzimidazole, 5,6-dimethylbenzotriazole (II), might possess interesting biological activity that its preparation was undertaken. This benzo-



II

triazole has not been previously described; it is likely that the compound was formed when Noelting and Thesmar[4] treated 1,2-diamino-4,5-dimethylbenzene with nitrite in acetic acid solution as a test for an aromatic orthodiamine. These investigators, however, neither isolated, analyzed nor characterized the compound. Synthesis of II was accomplished by diazotization of this diamine according to the above method.

The ultraviolet spectrum of 5,6-dimethylbenzotriazole has absorption maxima at 260 and 285 mμ in absolute alcohol; in chloroform solution the maxima are at 260 and 290 mμ; in 25% water–75% ethanol at 265 and 280 mμ (Fig. 1). The maxima reported in the literature[5] for benzotriazole in alcoholic solution are 254 mμ and 275 or 276 mμ.[6] A bathochromic shift on similar orthodimethyl substitution is seen in the spectra of naphthalene (maxima at 220 and 276 mμ) and 2,3-dimethylnaphthalene (maxima at 227 and 278 mμ).[7]

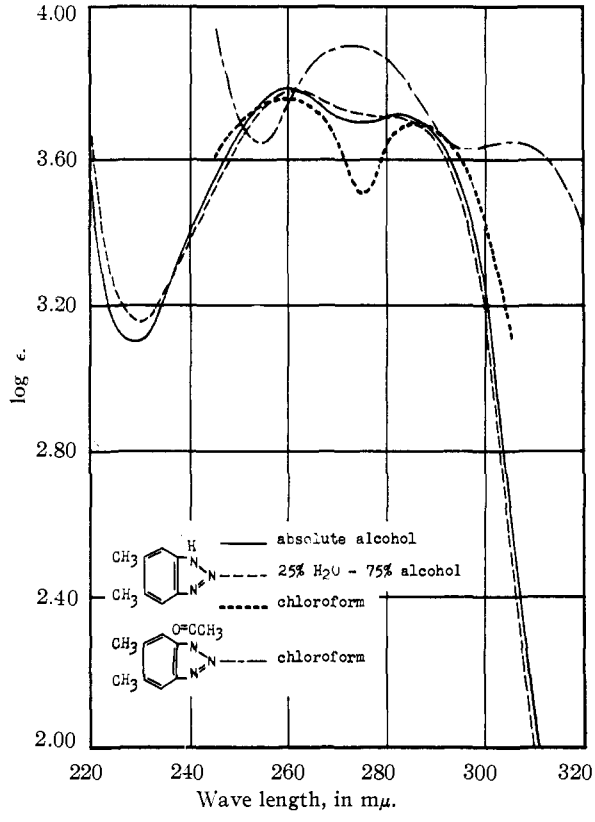


Fig. 1.—Absorption spectra of 5,6-dimethylbenzotriazole and 1-acetyl-5,6-dimethylbenzotriazole.

The acylation of benzotriazole derivatives has been studied by several investigators[8,9] and has been found to yield acyl derivatives on the 1- or 3-positions of the triazole ring. Since 5,6-dimethylbenzotriazole is symmetrical there is no distinction between the 1 and 3 nitrogen atoms. Except in the as yet unreported instance of acylation in the 2-position, no acyl isomers would be anticipated.[10] This was found to be the case. The acyl derivatives prepared in the present work were obtained by the

* Presented before the Division of Organic Chemistry, American Chemical Society, Atlantic City, Sept. 18, 1952.

(1) G. A. Emerson and K. Folkers, THIS JOURNAL, **73**, 2398, 5383 (1951); N. G. Brink, *et al.*, *ibid.*, **72**, 1866 (1950).

(2) R. O. Roblin, *et al.*, *ibid.*, **67**, 290 (1945); G. W. Kidder and V. C. Dewey, *J. Biol. Chem.*, **179**, 181 (1949).

(3) J. C. Sheehan and C. A. Robinson, THIS JOURNAL, **71**, 1436 (1949).

(4) E. Noelting and G. Thesmar, *Ber.*, **35**, 628 (1902).

(5) H. Specker and H. Gawrosch, *ibid.*, **75B**, 1338 (1942); J. E. Fagel and G. W. Ewing, THIS JOURNAL, **73**, 4360 (1951).

(6) A. K. Macbeth and J. R. Price, *J. Chem. Soc.*, 11 (1936).

(7) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, Spectra No. 195 and 206.

(8) G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, **103**, 1391 (1913).

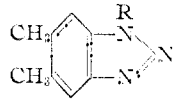
(9) F. Krollpfeiffer, H. Potz and A. Rosenberg, *Ber.*, **71B**, 596 (1938); F. Bell and J. Kenyon, *J. Chem. Soc.*, 954 (1926).

(10) F. R. Benson and W. L. Savell, *Chem. Revs.*, **46**, 61 (1950).

action of the appropriate anhydride or acid chloride in the presence of alkali, and are listed in Table I. To confirm the location of the acyl group, preparation of the acetyl derivative was effected by diazotization of 1-acetylamino-2-amino-4,5-dimethylbenzene. The compound obtained was found by mixed melting point determination and ultraviolet absorption spectra to be identical with that prepared by the direct acetylation of 5,6-dimethylbenzotriazole.

TABLE I

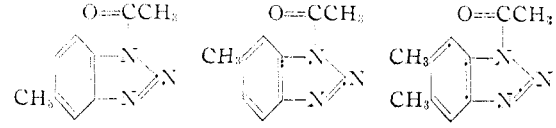
1-ACYL-5,6-DIMETHYLBENZOTRIAZOLES



R	Formula	Yield, %	M.p.,[a] °C.	Nitrogen, %[b] Calcd.	Found
CH_3CO	$C_{10}H_{11}N_3O$	93	99.9	22.2	22.0
C_2H_5OCO	$C_{11}H_{13}N_3O_2$	74	70.5	19.2	19.4
C_6H_5CO	$C_{15}H_{13}N_3O$	82	148.5	16.7	16.6
p-$O_2NC_6H_4CO$	$C_{15}H_{12}N_4O_3$	50	232	18.9	18.8
$C_6H_5SO_2$	$C_{14}H_{13}N_3O_2S$	72	136.9	14.6	14.6

[a] All melting points are corrected. [b] Nitrogen analysis by Dumas method.

The acetyl derivative was readily solvolyzed. When efforts were made to determine its absorption spectrum in absolute alcohol solution, a drift of extinction coefficient was observed which approached the value for 5,6-dimethylbenzotriazole (Fig. 2). Since it was found possible to recrystallize 1-acetyl-5,6-dimethylbenzotriazole from a 25% water–75% alcohol mixture, it was of interest to compare the solvolysis in this solvent with that in absolute ethanol. The presence of water in the solvent results in a slower solvolysis rate for the acetyl compound, the comparable figures after one hour being 19.7% decomposition in pure ethanol and 17.0% in the mixed solvent. After 20 hours the values are 97 and 79%, respectively. When absorption measurements were made in chloroform solution no such drift was noted. The maxima of 1-acetyl-5,6-dimethylbenzotriazole are at 275 and 305 mμ (Fig. 1). It is of interest that a weak maximum has been reported[8] for 1-acetyl-5-methylbenzotriazole at approximately 290–300 mμ and a more definite maximum for 1-acetyl-6-methylbenzotriazole at 265–270 mμ. The spectra of these monomethyl derivatives were determined in absolute alcohol. In view of the solvolysis found in the present study, some doubt must be expressed concerning the absolute accuracy of these maxima. Nevertheless, comparison of the maxima observed for the 5-methyl and the 6-methyl compounds with those of the 5,6-dimethyl derivative suggests that the spectrum of the latter is a combination of that of the two monomethyl derivatives with a slight bathochromic shift.



1-acetyl-5-methylbenzotriazole | 1-acetyl-6-methylbenzotriazole | 1-acetyl-5,6-dimethylbenzotriazole

An important difference should be noted in the behavior of the benzotriazole ring system and the benzimidazole ring system toward benzoyl chloride in the presence of alkali. Whereas 5,6-dimethylbenzimidazole has been reported[11] to be split by this reagent at 0–2°, forming the dibenzoyl derivative of 1,2-diamino-4,5-dimethylbenzene, treatment of 5,6-dimethylbenzotriazole with benzoyl chloride at room temperature and above effected only the formation of 1-benzoyl-5,6-dimethylbenzotriazole. Similar instability of imidazoles[12] and stability of v-triazoles[13] has been described previously.

Bacteriological tests of these compounds showed that *Serratia marcescens* is slightly inhibited by 5,6-dimethylbenzotriazole, the 1-acetyl and the carbethoxy derivative. The 1-carbethoxy compound also effects slight inhibition of *Klebsiella pneumoniae*. Neither *E. coli* nor *Micrococcus pyogenes aureus* is inhibited by any of this series. Investigation of the effect of 5,6-dimethylbenzotriazole on the multiplication of T_2 *E. coli* bacteriophage was kindly made by Dr. J. G. Wooley[14] of the National Institutes of Health. A slight inhibition of this virus was observed which, however, when analyzed statistically gave border-line significance to the data. In tests carried out at the Sloan–Kettering Institute[15] none of the compounds tested (5,6-dimethylbenzotriazole, the acetyl, carbethoxy and benzoyl derivatives) effected significant inhibition of the

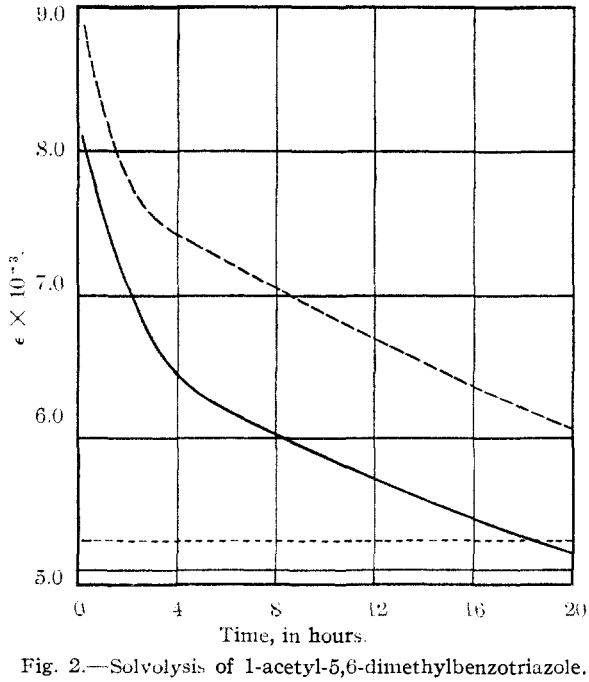


Fig. 2.—Solvolysis of 1-acetyl-5,6-dimethylbenzotriazole. — in absolute ethanol; — — — — in 25% H_2O–75% ethanol, measured at 275 mμ. Lines parallel to the abscissa are values for 5,6-dimethylbenzotriazole at 275 mμ in each solvent.

(11) N. G. Brink and K. Folkers, THIS JOURNAL, **72**, 4442 (1950).
(12) E. Bamberger and B. Berle, *Ann.*, **273**, 342 (1893).
(13) G. Heller, *Ber.*, **40**, 118 (1907).
(14) Private communication.
(15) Anti-tumor tests were conducted by courtesy of Dr. C. Chester Stock.

growth of Sarcoma 180 in mice. All compounds were administered in doses of 500 mg./kg. except the carbethoxy derivative which was tested at 300 mg./kg. Neither Vitamin B_{12} nor anti-B_{12} activity as determined by assay with *Lactobacillus leichmanii* was exhibited by 5,6-dimethylbenzotriazole.[16] This compound was also assayed for riboflavin and anti-riboflavin activity with *Lactobacillus casei*. Growth promotion was not observed in this test; no growth inhibition was found up to a 5,6-dimethylbenzotriazole–riboflavin molar ratio of 7500 to 1.

Experimental

All melting points are corrected for stem exposure.

5,6-Dimethylbenzotriazole.—To a mixture of 5.5 ml. of glacial acetic acid and 14 ml. of water at 5° was added 3.3 g. (about 0.024 mole) of crude 1,2-diamino-4,5-dimethylbenzene.[4] Sodium nitrite (1.7 g., 0.024 mole) in 15 ml. of water was then added rapidly with stirring. The mixture turned dark green in color which soon changed to a light yellow. The temperature, which had risen above 50° was reduced to 10°, and the tan solid was filtered off. The solid was recrystallized once from hot benzene using decolorizing carbon. A second recrystallization from benzene gave white needles which were dried under vacuum; yield 2.0 g. (57% of the theoretical amount).

The compound melts at 157.5°. The following approximate solubilities at room temperature were noted: water, less than 0.001%; carbon tetrachloride and heptane, less than 0.1%; ether, 0.5%; glycerol, 1.8%; dioxane, 4%; ethyl acetate, 7%; acetone, 8%; isopropyl alcohol, 13%; methanol, 14%.

Anal. Calcd. for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.56. Found: C, 65.3; H, 6.4; N, 28.7.

1-Acetylamino-3,4-dimethyl-6-nitrobenzene. (a).—A mixture of 1.0 g. (0.0060 mole) of 3,4-dimethyl-6-nitroaniline[17] with 10 ml. of glacial acetic acid and 0.5 ml. of acetic anhydride was refluxed. After 15 minutes an additional 0.5 ml. of acetic anhydride was added and refluxing continued one-half hour longer. The mixture was poured into ice-water and allowed to stand one hour. The yellow solid which separated was filtered, washed with water, and dried on tile. The product weighed 1.1 g. (88% of the theoretical amount). Recrystallization from heptane afforded bright yellow needles melting at 107.5°. Noelting, *et al.*,[17] report 107°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: N, 13.46. Found: N, 13.3.

Refluxing 3,4-dimethyl-6-nitroaniline with undiluted acetic anhydride resulted in the formation of pale off-white needles melting at 75°. This material was probably 1,1-diacetylamino-3,4-dimethyl-6-nitrobenzene.

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: N, 11.20. Found: N, 11.4.

(b).—One gram (0.0063 mole) of 3,4-dimethylacetanilide[18] was dissolved in 3.5 g. of concentrated nitric acid which had been cooled in an ice-bath. After 10–15 minutes a yellow solid precipitated. The mixture was allowed to stand at room temperature for two hours, then poured into ice-water. The yellow solid was filtered, washed with water, and dried on tile. The product weighed 1.0 g. (76% of the theoretical amount). Recrystallization from heptane afforded bright yellow needles melting at 108°. A mixed melting point with the product obtained from (a) gave no depression.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: N, 13.46. Found: N, 13.2.

1-Acetylamino-6-amino-3,4-dimethylbenzene.—A weight of 1 g. (0.0048 mole) of 1-acetylamino-3,4-dimethyl-6-nitrobenzene was suspended in a mixture of 50 ml. of water and 1 ml. of acetic acid. The mixture was heated to boiling and 2 g. of iron fillings was added slowly. The cooled mixture was neutralized with sodium carbonate, filtered, and extracted with chloroform. The chloroform was evaporated and the residue recrystallized from water using charcoal; yield 0.2 g. (23% of the theoretical amount) melting at 158.5°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: N, 15.72. Found: N, 15.5.

This method sometimes led to ring closure giving 2,5,6-trimethylbenzimidazole, m.p. 233°.[19]

1-Acetyl-5,6-dimethylbenzotriazole. (a) **From 1-Acetylamino-6-amino-3,4-dimethylbenzene.**—Crude 1-acetylamino-6-amino-3,4-dimethylbenzene (the evaporated chloroform extract from reduction of 2 g. (0.0096 mole) of 1-acetylamino-3,4-dimethyl-6-nitrobenzene as described above) was dissolved in a mixture of 5 ml. of acetic acid and 30 ml. of water. The solution was cooled to 10° and 0.35 g. of sodium nitrite (0.005 mole) in 5 ml. of water added. The mixture turned dark and a solid precipitated. After heating to 50° on the steam-bath, and remaining one hour at room temperature, the mixture was cooled, and solid filtered, washed with water, and dried on tile. The yield of product was 0.6 g. (63% of the theoretical amount based on sodium nitrite used). Recrystallization from 75% ethanol–25% water gave the pure 1-acetylamino-5,6-dimethylbenzotriazole which melted at 99.5°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: N, 22.21. Found: N, 21.8.

(b) **From 5,6-Dimethylbenzotriazole.**—A mixture of 1.0 g. (0.0068 mole) of 5,6-dimethylbenzotriazole and 10 ml. of acetic anhydride was refluxed for 30 minutes. The reaction mixture was then poured on ice and allowed to stand one hour. The white crystals which separated were filtered off, washed with water, and dried on a porous tile; yield 1.2 g. (93%). This solid may be purified further by crystallization from a water–alcohol (1–3) mixture; m.p. 99.9°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: N, 22.21. Found: N, 22.0.

A mixed melting point with the solid obtained from (a) showed no depression.

The following examples will illustrate the procedure used for other acylations of 5,6-dimethylbenzotriazole.

1-Benzoyl-5,6-dimethylbenzotriazole.—A mixture of 1.0 g. of 5,6-dimethylbenzotriazole with 20 ml. of 5% sodium hydroxide solution was stirred while 2 ml. of benzoyl chloride was added in 4 portions about 2 minutes apart. The mixture became warm. After stirring for 30 minutes, the mixture was cooled, and the large lumps broken up After standing one-half hour the mixture was filtered, washed well with water, and dried on a porous tile. The crude product which contained benzoyl chloride and benzoic acid was purified by recrystallization from ethanol.

1-Benzenesulfonyl-5,6-dimethylbenzotriazole.—In 30 ml. of 10% sodium hydroxide there was dissolved 1 g. (0.0068 mole) of 5,6-dimethylbenzotriazole. Two ml. of benzenesulfonyl chloride (about 0.0016 mole) was added with vigorous stirring. After 15 minutes, the aqueous layer was decanted from the oil and treated with 2 ml. of benzenesulfonyl chloride as before. Two further 2-ml. portions of benzenesulfonyl chloride were added in this manner, the oil being removed before the fresh acid chloride was added. The oily residues were combined, washed well with water by decantation and then treated with 20 ml. of ethanol. After cooling the white solid which separated was filtered, washed once with cold ethanol and dried on a porous tile. Two recrystallizations from alcohol gave the desired product.

The absorption spectra were determined with a Model DU Beckman quartz spectrophotometer. In the determination of the absorption spectrum of 5,6-dimethylbenzotriazole the concentration employed for the measurement in chloroform was 1.359×10^{-4} mole/liter; in absolute alcohol 1.291 moles/liter was used, and in 25% water–75% ethanol, 1.532×10^{-4} mole/liter. For 1-acetyl-5,6-dimethylbenzotriazole in chloroform solution a concentration of 1.090×10^{-4} was used for the sample obtained by diazotization (procedure (a) above) and 9.862×10^{-5} mole/liter for that obtained by acetylation of 5,6-dimethylbenzotriazole (procedure (b) above). The curves of the two samples were identical.

In the study of the solvolysis of 1-acetyl-5,6-dimethylbenzotriazole, solutions in absolute ethanol and in 25% water–75% ethanol were used at concentrations of 5.576×10^{-5} and 5.074×10^{-5} mole/liter, respectively. The samples

(16) These tests were performed through the courtesy of Dr. Herman Sokol, Antibiotics Research Division, Heyden Chemical Corp.

(17) Noelting, *et al.*, *Ber.*, **34**, 2251 (1901).

(18) Jacobsen, *ibid.*, **17**, 161 (1884).

(19) G. R. Beaven, *et al.*, *J. Pharm. Pharmacol.*, **1**, 969 (1949).

were kept at room temperature during the period of measurement.

Acknowledgment.—The authors wish to express their appreciation to Dr. Paul D. Sternglanz, Miss Ruth Thompson and Mr. Yao Nan Sheng for the analytical and ultraviolet absorption spectra data, to Mr. D. James Kay for the bacteriological tests, to Mr. Frank Tranner for the riboflavin and antiriboflavin tests, and to Mr. John J. Masterson for assistance in the preparation of these compounds.

SOUTH NORWALK, CONN.

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

The Synthesis of 1,2-Benzo-7,8-(2′,3′-indolo)-tetrahydroquinolizine[1]

BY V. BOEKELHEIDE AND CHU-TSIN LIU

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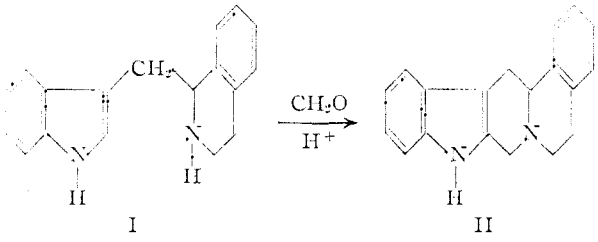
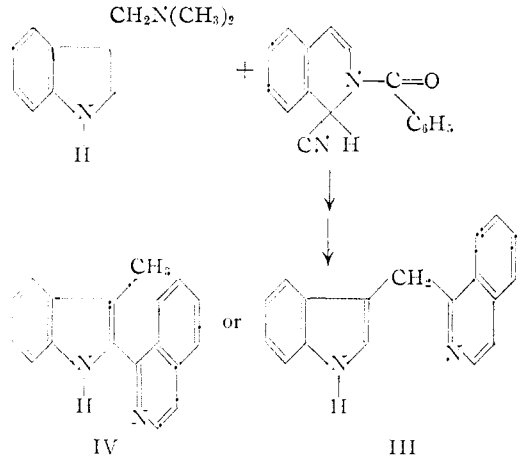
The pentacyclic molecule, 1,2-benzo-7,8-(2′,3′-indolo)-tetrahydroquinolizine (II), has been synthesized by two different methods. Although II was prepared as a model for certain of the calabash curare alkaloids, the quaternary salts of II possess only slight curare activity, indicating that this probably is not the correct type of nucleus for these alkaloids. Unexpectedly, it was found that catalytic hydrogenation of 1-skatylisoquinoline derivatives in acid effects reduction of a benzene ring rather than the pyridine ring.

In a previous communication,[2] we reported on some preliminary studies directed toward the synthesis of 1,2-benzo-7,8-(2′,3′-indolo)-tetrahydroquinolizine (II), a possible model for certain of the calabash curare alkaloids. The final step in the projected synthesis, as previously outlined, involved the cyclization of 1-skatyl-1,2,3,4-tetrahydroisoquinoline (I) with formaldehyde, as shown below. Since no logical explanation could be advanced to explain the failure encountered in attempts to accomplish this reaction, we have reexamined the steps leading to I to see whether the structure assigned might be incorrect.



One of the steps, which appeared open to question, was the alkylation of 1-cyano-1,2-benzoyl-1,2-dihydroisoquinoline with gramine followed by alkaline hydrolysis to produce 1-skatylisoquinoline (III).[2] As Snyder and Eliel have shown in the case of 1-methylgramine,[3] allylic rearrangement can occur in alkylations with gramine derivatives and the possibility existed that our product had structure IV rather than III. That this was not the case was clearly demonstrated when our product was shown to be identical with a sample of 1-skatylisoquinoline prepared independently by the decarboxylation of 1-(2′-carboxyskatyl)-isoquinoline[2] using copper chromite as catalyst.

In view of these results the only step open to question appeared to be the catalytic hydrogenation of 1-skatylisoquinoline. Although Skita has found that the reduction of isoquinoline using platinum in acetic acid leads to 1,2,3,4-tetrahydroisoquinoline[4] and the reduction of 1-skatylisoquinoline would seem to be analogous, it appeared desirable that this be confirmed by reducing 1-skatylisoquinoline in quantity using the older sodium–alcohol procedure.[5] Despite a coincidence in melting points of derivatives of the two samples of reduced amines, it was obvious from a comparison of their infrared spectra that the product obtained by catalytic hydrogenation was different from that resulting from the sodium–alcohol reduction. The latter product showed the properties of a secondary amine and, in keeping with structure I, it readily underwent cyclization with formaldehyde to give the desired base (II) in excellent yield.



When the cyclization of I was attempted using an excess of formaldehyde, the main product of the reaction corresponded to a hydroxymethyl derivative of II. This material showed the properties of a carbinol amine and is assumed to be the result of addition of formaldehyde at the indole nitrogen. In support of this, the hydroxymethyl derivative was easily cleaved by aqueous acid to give back the parent compound, II. When acetaldehyde was substituted for formaldehyde in the cyclization

(1) Aided by a grant from the United Cerebral Palsy Association.

(2) V. Boekelheide and C. Ainsworth, THIS JOURNAL, **72**, 2134 (1950).

(3) H. R. Snyder and E. L. Eliel, *ibid.*, **70**, 1857 (1948).

(4) A. Skita, *Ber.*, **57**, 1977 (1924); *cf.* B. Witkop, THIS JOURNAL, **70**, 2617 (1948).

(5) E. Bamberger and W. Dieckmann, *Ber.*, **26**, 1205 (1893); *cf.* R. Wegler and W. Frank, *ibid.*, **70**, 1279 (1937).