[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE COLLEGE]

# Alkylation of Oxindoles

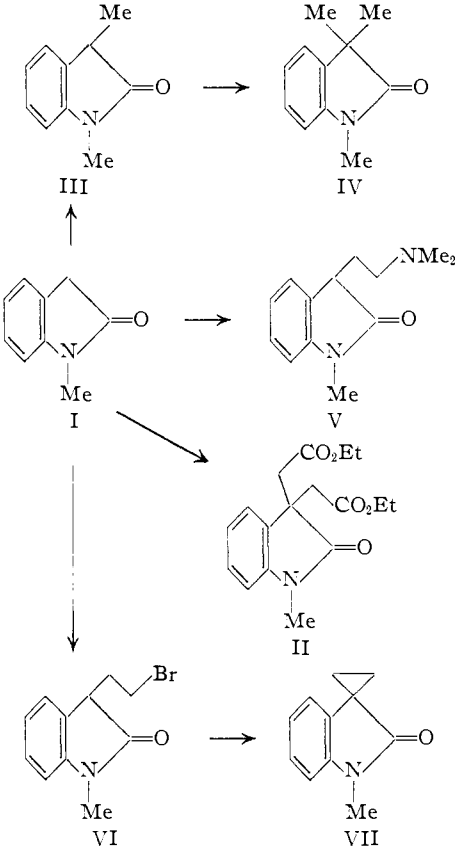
BY ERNEST WENKERT, NABA K. BHATTACHARYYA, THEODORE L. REID AND TRAVIS E. STEVENS

RECEIVED SEPTEMBER 19, 1955

A method for direct C-alkylation of N-methyloxindole is introduced. O-Alkylation procedures and the chemistry of supposedly O-alkylated derivatives of oxindoles are discussed.

Oxindoles are excellent starting materials for the synthesis of indole or oxindole alkaloids. For this purpose a survey of direct C(3)-alkylation methods would appear to be desirable. In the past essentially four procedures have been used to synthesize 3-alkyloxindoles: (1) acylation *via* Claisen condensation with esters, followed by reduction of the 3-acyl compounds[1]; (2) base-induced alkylation of already 1,3-dialkylated compounds[2-5]; (3) Mannich or Michael condensations[4,6,7]; and (4) base-induced C-alkylation of 1-alkyl-3-acyl compounds followed by hydrolysis[2,3] or base-induced O-alkylation of the same systems followed by thermal rearrangement and hydrolysis.[8-10] In two recent reviews on oxindole chemistry[11,12] it was indicated that direct alkylation (with alkyl halides and bases) of 3-unsubstituted N-alkyloxindoles was impossible and that a 3-acyl or 3-alkyl group was necessary for the introduction of another alkyl function. This lack of reactivity, however, is highly doubtful in view of the well-known alkylatability of such analogous systems as 2-indanone[13] and β-tetralone[14] and because of the fact that most recently three actual examples of direct alkylation have been reported: the reactions of N-methyloxindole with (a) chloroacetonitrile[15] and with (b) tetramethylene dibromide,[16] and (c) the ethylene oxide interaction with various oxindoles.[17] Thus a reinspection of direct alkylation of oxindoles became necessary.

A mixture of ethyl bromoacetate and N-methyloxindole (I) in ethanolic sodium ethoxide underwent a rapid exothermic reaction yielding 1-methyl-3,3-dicarbethoxymethyloxindole (II). No monoalkylated product could be isolated regardless of whether a 1:1 or 2:1 molar ratio of ester to oxindole was used. In order to decrease the possibility of dialkylation, all further reactions were carried out in a heterogeneous fashion, *i.e.* by preforming the enolate anion of I with sodium hydride in benzene and mixing its suspension with a benzene solution of the alkyl halide. Methylation of I under these conditions produced 1,3-dimethyloxindole (III), which, in turn, under similar circumstances could be converted to 1,3,3-trimethyloxindole (IV).

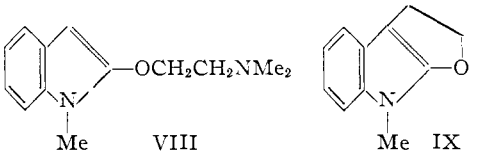



In their search for variously substituted 3-aminoalkyloxindoles Palazzo and Rosnati[7] alkylated N-methyloxindole with β-dimethylaminoethyl chloride under the influence of sodamide in toluene and claimed to have obtained 1-methyl-2-(β-dimethylaminoethoxy)-indole (VIII). This structure was based on an interpretation of the ultraviolet absorption spectrum of the product and a comparison of the melting point of its derivative with that of 1-methyl-3-(β-dimethylaminoethyl)-oxindole (V), the C-alkyl compound, synthesized previously by Julian[3] *via* the acylation of N-methyloxindole with N,N-dimethylglycine ester and reduction of the resulting 3-acyloxindole (*i.e. via* route 1 above).

(1) P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, THIS JOURNAL, **75**, 5305 (1953), and preceding papers.
(2) P. L. Julian, J. Pikl and D. Boggess, *ibid.*, **56**, 1797 (1934).
(3) P. L. Julian, J. Pikl and F. E. Wantz, *ibid.*, **57**, 2026 (1935).
(4) E. C. Horning and M. W. Rutenberg, *ibid.*, **72**, 3534 (1950).
(5) P. L. Julian and J. Pikl, *ibid.*, **57**, 539, 755 (1935).
(6) P. L. Julian and H. C. Printy, *ibid.*, **75**, 5301 (1953).
(7) G. Palazzo and V. Rosnati, *Gazz. chim. ital.*, **82**, 584 (1952).
(8) P. L. Julian, A. Magnani, J. Pikl and W. J. Karpel, THIS JOURNAL, **70**, 174 (1948).
(9) P. L. Julian and A. Magnani, *ibid.*, **71**, 3207 (1949).
(10) E. Wenkert, A. K. Bose and T. L. Reid, *ibid.*, **75**, 5514 (1953).
(11) P. L. Julian, E. W. Meier and H. C. Printy in R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, Chapter 1, p. 159.
(12) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, Chapter 4, p. 146.
(13) *Cf.* P. Friedländer, W. Herzog and G. v. Vosz, *Ber.*, **55**, 1591 (1922).
(14) *Cf.* M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson and E. A. Bowler, THIS JOURNAL, **72**, 3704 (1950).
(15) Reference 11, p. 171.
(16) B. Witkop and J. B. Patrick, THIS JOURNAL, **75**, 2572 (1953).
(17) F. M. Miller and R. M. Gamson, Abstracts of the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March 29–April 7, 1955, p. 2N.

However, the structural assignment VIII was very much in question because firstly, the ultraviolet spectrum of the compound was not too dissimilar to that of N-substituted oxindoles,[10] secondly, the comparison of melting points was made between that of the *picrolonate* of the liquid product, m.p. 225° dec., and the literature values of the *picrate* of Julian's compound, m.p. 168°, and finally, the experimental conditions in the preparation of the product are those of a C-alkylating type.

Repetition of the above alkylation in the presence of either sodamide in toluene or sodium hydride in benzene resulted in the same product. The ultraviolet and infrared spectra were characteristic of oxindoles: $\lambda_{max}$ 252 m$\mu$ (log $\epsilon$ 3.95); CO(max) 5.82 $\mu$, and the picrates had identical melting points: 155–156°, no depression on admixture. In view of the discrepancy of the latter and that of Julian's picrate, Julian's synthesis of the 3-alkyl compound also had to be repeated. Again the resulting product was identical with the two already on hand. Finally, an authentic sample of the picrate, kindly furnished by Dr. Julian, yielded no mixed melting point depression.[18] It thus appears that the structure of the common alkylation products is V.



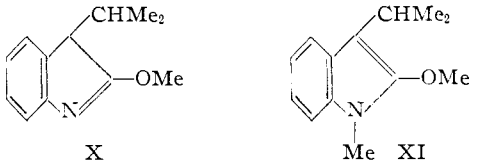

The direct alkylation of N-methyloxindole with ethylene dibromide yielded 1-methyl-3-(β-bromoethyl)-oxindole (VI), a compound which had been synthesized previously by route 4 (*vide supra*): 3-acetylation of N-methyloxindole followed by O-alkylation with β-phenoxyethyl bromide, thermal rearrangement and HBr treatment.[8] Compound VI was needed because of its reported intramolecular O-alkylation with sodium ethoxide yielding the dihydrofuroindole IX. The latter structure was in doubt because formula VII, representing its C-alkyl isomer, could explain equally well the chemical properties of the compound. An inspection of the ultraviolet and infrared absorption spectra of this dehydrobromination product ($\lambda_{max}$ 256 m$\mu$ (log $\epsilon$ 3.8); CO(max) 5.82 $\mu$) indicated clearly that it indeed possessed the spiro structure VII.[19]

(18) Dr. Julian kindly informed the authors that his original m.p. 168° must have been in error since a freshly prepared picrate had a melting point corresponding to the one above.

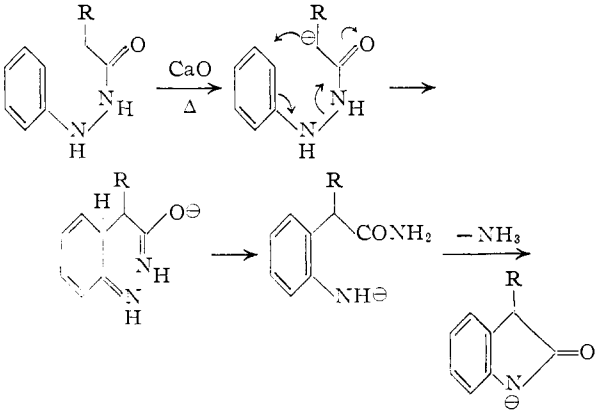
(19) A preliminary report on this phase of the work has already appeared (E. Wenkert and T. L. Reid, *Chemistry and Industry*, 1390 (1953)). A $C_{10}H_9ON$ degradation product common to several oxindole alkaloids, reported therein, was assigned also a spiro structure, the N–H counterpart of VII. This suggestion has been corroborated more recently by a melting point determination on a mixture of authentic 3,3-dimethyleneoxindole and a degradation product kindly furnished by Dr. T. Nozoye of the Itsuu Laboratory, Tokyo, and a similar determination in England on a mixture of samples of Kondo's and Cook's degradation products (H. Kondo, T. Nozoye and M. Tobita, *Ann. Reports Itsuu Lab.*, **5**, 26 (1954)).

Prior to the assignment of the correct formula to the alkaloid degradation product, Kondo, *et al.*, considered among various structures that of 3,4-dimethyleneoxindole but rejected it on the basis of the product's inability to react with ethyl acetate in a Claisen condensation. While this structure could have been dismissed because of its high steric strain, the use of the Claisen condensation as a diagnostic test is misleading because 3-alkyloxindoles would not be expected to undergo this reaction. In like fashion, the inability of 3-methyloxindoles to condense with ethyl oxalate, an experimental result left unexplained by Miller, *et al.*,[17] is also predictable. The Claisen condensation is a reversible reaction, the equilibrium normally being driven in the direction of the most acidic product, which in all these cases unambiguously is the starting material (*cf.* C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 788).

Because of the above structural reassignments it became of interest to reinvestigate other cases of compounds previously assumed to possess a 2-alkoxyindole structure. 3-Isopropyloxindole has been converted to its O-methyl derivative X by the interaction of methyl iodide with its silver salt.[20] While X most probably would exist as its more stable indole isomer, its structure had been distinguished easily from its N- or C-methyl isomers by the fact that it was not identical with synthetic 1-methyl-3-isopropyloxindole and could be hydrolyzed readily in acid solution to its 3-isopropyloxindole precursor. Repeated attempts to duplicate the procedure for the preparation of X were unsuccessful, always yielding merely unreacted starting material. Even various modifications of the process were fruitless although in one run a small amount of a new product, m.p. 126–126.5°, was obtained. Whereas the quantity was insufficient for complete characterization, its lack of N—H and C=O absorption in the infrared as well as the dissimilarity of its ultraviolet absorption spectrum with that of either oxindoles[10] or 3,3-dialkylindolenines[21] might indicate that it was the N,O-dimethylated product XI.




The Brunner reaction, used for the preparation of the above-mentioned 3-isopropyloxindole,[20] was found to give erratic results. In several runs the only isolable product proved to be isovaleranilide. It appears that the lability of the N–N bond in the acylhydrazide, which is responsible for the intramolecular aromatic nucleophilic reaction

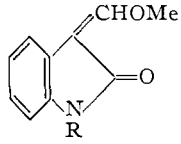



is likewise responsible for a side reaction during which this weak bond is broken. The resulting

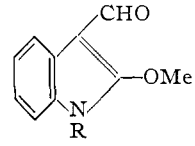
(20) H. Schwarz, *Monatsh.*, **24**, 568 (1903).

(21) M. Tomita, S. Uyeo and R. Yamamoto, *J. Pharm. Soc. Japan*, **64**, 164 (1944).

aniline, probably in form of its anion, then undergoes transamidation with the hydrazide to yield an anilide. Because of the similarity in molecular formula and melting point of isovaleranilide and 3-isopropyloxindole, it became necessary to ascertain whether compound X was perhaps the iminomethyl ether of isovaleranilide. However, the latter, synthesized by a methyl iodide–silver oxide O-alkylation[22] of isovaleranilide proved to be a liquid compound and hence not identical with the previously discussed methylation product.




XIIa, R = H
b, R = Me




XIIIa, R = H
b, R = Me

In a previous discussion of the O-alkylation of the sodio salt of 1-methyl-3-hydroxymethyleneoxindole with methyl iodide it was pointed out that the accepted structure (XIIIb) of the product required revision to XIIb.[10] A recent report on the diazomethane methylation of the same oxindole claimed the yield of two products, of which one was XIIb,[23] while the same reaction on the des-N-methyl analog was reported to yield only one compound to which structure XIIa was assigned.[24] Repetition of the methylation on both hydroxymethylene compounds yielded a set of two products from each starting material. Elementary analysis, derivative formation and spectral analysis readily permitted the unambiguous assignment of structures XIIa and b, and XIIIa and b to the four compounds. Thus all of them proved analytically to be monomethyl derivatives of their hydroxymethylene precursors. Of the compounds of structure XII the N-methyl compound XIIb was indeed identical with the methyl iodide alkylation product, while XIIa proved to be Horner's product.[24] In close analogy with the properties of compound XIIb, 3-methoxymethyleneoxindole (XIIa) formed a red 2,4-dinitrophenylhydrazone with the concomitant loss of the methoxy group and showed spectral characteristics representative of its chromophore[10] (*cf.* Figs. 1 and 2). On the other hand, compounds of structure XIII, the first authentic examples of 2-alkoxyindoles, possessed distinctly different properties from those above and could be correlated more readily with 3-formylindole. They formed surprisingly black, crystalline 2,4-dinitrophenylhydrazones without the extrusion of any functional groups. They were hydrolyzable back to the hydroxymethyleneoxindoles, as exemplified by the alkaline hydrolysis of specifically XIIIb. Their ultraviolet spectra were most dissimilar to those of variously substituted oxindoles, but quite like the spectrum of 3-formylindole while showing a distinct bathochromic shift attributable to the methoxy group (*cf.* Fig. 1). The double bond region of the infrared spectra showed no absorption below 6.2 $\mu$. The high wave length absorption between 6.2 and 6.4 $\mu$ (*cf.* Fig. 2), much too high for aromatic aldehydes, is indicative of the large extent of ionic character in the carbonyl group, as might be expected from its mesomeric interaction with the $\Delta^{2,3}$-linkage, the indole nitrogen and the 2-methoxy group.

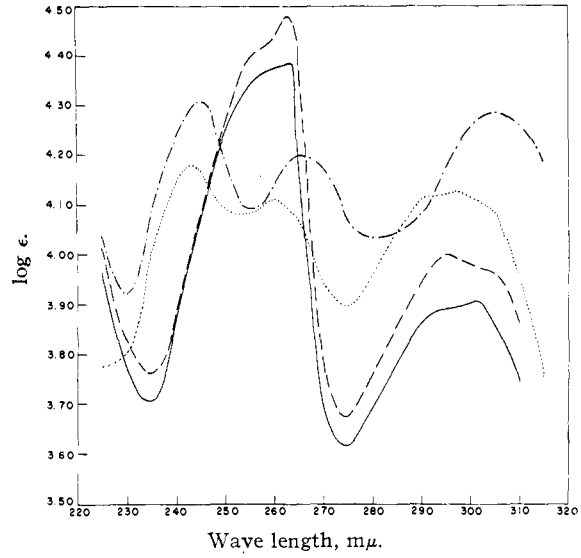



Fig. 1.—Ultraviolet spectra of: ——, 3-hydroxymethyleneoxindole; ------, 3-methoxymethyleneoxindole; ·····, 3-formylindole; -·-·-·, 2-methoxy-3-formylindole. The spectra were run on 95% alcohol solutions on a Beckman DU spectrophotometer.

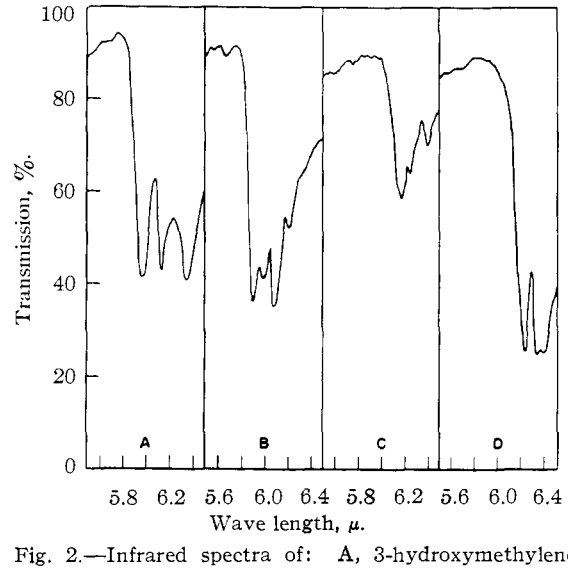
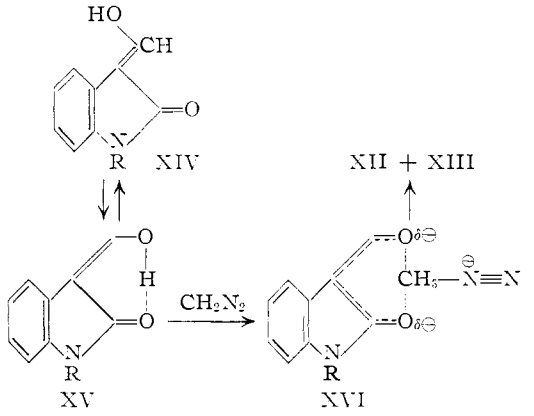



Fig. 2.—Infrared spectra of: A, 3-hydroxymethyleneoxindole; B, 3-methoxymethyleneoxindole; C, 3-formylindole; D, 2-methoxy-3-formylindole.

The reason for the difference of the O-alkylation of 3-hydroxymethyleneoxindoles by diazomethane and by methyl iodide appears to lie in the fact that the reacting species in one case is the enol while in the second it is the enolate anion. In ether solution the enol would be expected to be highly hydrogen-bonded both intermolecularly (XIV) and intramolecularly (XV). If diazomethane were to attack the compound in the latter state, *i.e.* in a configuration wherein the two oxygen atoms are in

(22) *Cf.* G. D. Lander, *J. Chem. Soc.*, 729 (1900).
(23) Reference 11, p. 154.
(24) L. Horner, *Ann.*, **548**, 117 (1941).

close proximity to each other, then the transition complex XVI places the incipient methyl group into juxtaposition with both oxygens, with either of which it can then form the new C–O bond. The enolate anion, however, must possess an *anti* configuration, wherein the negatively charged oxygen atoms are as far removed from each other as possible, and hence the above condition for multiple O-alkylation would not prevail in this case.




**Acknowledgment.**—Financial assistance by the Upjohn Company and the use of the Baird infrared spectrophotometer of the Institute of Atomic Research, Ames, Iowa, are hereby most gratefully acknowledged.

## Experimental[25]

**1-Methyl-3,3-dicarbethoxymethyloxindole.**—(0.068 mole) of N-methyloxindole was added to 100 cc. of a sodium ethoxide solution, prepared from 1.57 g. (0.068 mole) of sodium. After a short while 11.4 g. (0.068 mole) of ethyl bromoacetate was poured into the mixture and the latter shaken. Sodium bromide immediately separated and the mixture became hot. After standing for two hours the reaction mixture was poured into salt solution and extracted three times with chloroform. The latter was washed with salt solution, dried over sodium sulfate and evaporated. The residual red oil then was distilled yielding 3.74 g. of N-methyloxindole at 110–120° (1 mm.) and 10.23 g. of a yellow oil at 170–175° (1 mm.). On trituration of the oily product with petroleum ether it partially crystallized, 4.3 g. of a white solid, m.p. 64–65°, being obtained. Recrystallization from petroleum ether gave white crystals, m.p. 68–69°.

*Anal.* Calcd. for $C_{17}H_{21}O_5N$: C, 63.95; H, 6.58; N, 4.39. Found: C, 64.08; H, 6.78; N, 4.47.

The remaining oil, at first considered to be the monosubstitution product, could not be induced to crystallize, nor was it purifiable by distillation or other means.

In runs involving 2:1 molar ratios of ethyl bromoacetate to N-methyloxindole under conditions analogous to those above a 76% yield of disubstitution product was obtained.

**General Procedure for Alkylation.**—The following example illustrates the procedure used for a typical alkylation. A mixture of 0.24 g. (0.01 mole) of sodium hydride and 1.61 g. (0.01 mole) of 1,3-dimethyloxindole in 10 ml. of dry benzene was stirred under nitrogen. After the formation of a white precipitate and the cessation of hydrogen evolution a solution of 1.24 ml. (0.02 mole) of methyl iodide in 5 ml. of dry benzene was added and left standing at room temperature for *ca.* 12 hours. Thereupon the reaction mixture was filtered, the filtrate evaporated to dryness, and the residue distilled under high vacuum yielding 1.3 g. (75%) of a colorless oil which solidified on standing. Recrystallization of the solid from petroleum ether gave white crystals of 1,3,3-trimethyloxindole, m.p. 50–51° (literature[2] m.p. 50°).

N-Methyloxindole and methyl iodide gave a 62% yield of 1,3-dimethyloxindole, m.p. 54–55°, no depression on admixture with an authentic specimen prepared by the procedure of Julian, *et al.*[2]

N-Methyloxindole and β-dimethylaminoethyl chloride yielded 50% of an oil, whose picrate, m.p. 155–156°, gave no depression with that prepared in 45% yield by the Palazzo and Rosnati procedure,[7] with the one obtained in 64% yield by the Julian procedure[3] and with the authentic sample furnished by Dr. Julian.[18]

*Anal.* Calcd. for $C_{19}H_{21}O_8N_5$: C, 51.00; H, 4.73; N, 15.7. Found: C, 51.30, 51.27; H, 4.88, 4.99; N, 15.53.

N-Methyloxindole and ethylene dibromide yielded 60% 1-methyl-3-(β-bromoethyl)-oxindole, m.p. 61–62° (literature[8] m.p. 63°).

**The Brunner Reaction with Isovaleryl Phenylhydrazide.**—The calcium oxide pyrolysis of the hydrazide was carried out by the usual procedure,[20] with the highest yield of 3-isopropyloxindole, m.p. 107–108°, amounting to only 16%. At times when the oxindole was not the product, as high as a 6% yield of isovaleranilide, m.p. 104–105°, could be obtained. The latter was identical in m.p., mixed m.p. and spectra with an authentic sample of anilide, prepared from isovaleryl chloride and aniline, but depressed the m.p. of 3-isopropyloxindole on admixture and yielded spectra different from those of the oxindole.

**Attempted O-Alkylation of 3-Isopropyloxindole.**—The procedure of Schwarz[20] and variations thereof were unsuccessful although the following gave a small measure of success. Equivalent amounts of ethanolic ammonia and ethanolic silver nitrate were added to 0.5 g. (2.9 mmoles) of 3-isopropyloxindole dissolved in absolute alcohol. The voluminous precipitate thus formed was filtered and washed with dry ethanol and ether. The ether-wet solid was transferred to a Parr bomb, excess methyl iodide and dry ether as solvent were added. The closed bomb was then kept immersed in refluxing ethyl acetate for 12 hours. After opening the bomb, filtering the contents and evaporating the filtrate to dryness, the residue was fractionally crystallized from petroleum ether. The major fraction proved to be starting material and only after several recrystallizations of a small amount of mixture, less than 10 mg. of white crystals, m.p. 127–127.5°, could be obtained. While insufficient substance prevented its analysis, its spectrum possessed the following maxima: ultraviolet: 247 mμ (log ε 3.48), 254 mμ (log ε 3.47), major shoulder 293 mμ (log ε 3.15); infrared: 5.75 and 5.80 μ (weak), 6.18 μ (medium) and 6.28 μ (strong).

**Methyl N-Anililiminoisovalerate.**—Isovaleranilide 3.36 g., 0.019 mole) was dissolved in 15 ml. of dry methyl iodide by slowly heating under reflux on a steam-bath, 8.8 g. (0.038 mole) of pure silver oxide was added slowly to the cooled solution and the mixture refluxed for 5 hours. On cooling it was filtered and the residue washed several times with dry ether. When the ether and methyl iodide had been distilled off from the combined filtrate and washings, the remaining oil solidified. It was washed several times with petroleum ether, leaving 1.75 g. of an insoluble white solid which could be identified as starting anilide. After removal of the solvent, the washings were sublimed yielding at 100–105° (2 mm.) 1.15 g. (72%, based on recovered anilide) of a clear colorless liquid, and at 120–125° (2 mm.) 0.1 g. of more starting material. The product could be redistilled, b.p. 82–83° (2 mm.), and showed a 6.03 μ peak in the infrared for the iminoether linkage.

*Anal.* Calcd. for $C_{12}H_{17}ON$: C, 75.4; H, 8.9; N, 7.33. Found: C, 75.21; H, 8.93; N, 7.15.

**3-Hydroxymethyleneoxindole.**—A slurry of 13.3 g. (0.1 mole) of oxindole and 25 ml. of ethyl formate was added with shaking to a warm sodium ethoxide solution, prepared from 3.1 g. of sodium and 50 ml. of absolute ethanol. The mixture set to a solid mass immediately. After standing at room temperature for an hour and then being heated on the steam-bath for 30 minutes the mixture was neutralized with dilute hydrochloric acid and the resulting precipitate filtered. The solid gave a strong $FeCl_3$ test, had a m.p. 207–208° and was sufficiently pure for further reactions. The crude yield amounted to 15.3 g. (96%). Recrystallization from chloroform produced the pure compound, m.p. 212–213° (literature[26] m.p. 213°); ultraviolet spectrum: $\lambda_{max}$ 261 mμ (log ε 4.38), 301 mμ (log ε 3.90).

(25) All melting points are corrected.

(26) P. Friedländer and St. Kielbasinski, *Ber.*, **44**, 3098 (1911), and preceding paper.

Its 2,4-dinitrophenylhydrazone could be prepared by the usual method, yielding red needles, m.p. 271–272°.

*Anal.* Calcd. for $C_{15}H_{11}O_5N_5$: C, 52.78; H, 3.22. Found: C, 52.87; H, 3.54.

**Diazomethane Reaction of (a) 3-Hydroxymethyleneoxindole and (b) 1-Methyl-3-hydroxymethyleneoxindole.**—(a) 4.0 g. of 3-hydroxymethyleneoxindole was added in small portions to 100 ml. of an ether solution of excess diazomethene with shaking. Evolution of nitrogen started immediately, and the mixture was left standing for four hours. The separated solid (m.p. 179–180°) was filtered and shaken with warm chloroform for a few minutes. The residue (m.p. 220–245°) obtained from the suspension after filtration was crystallized several times from 95% ethanol, yielding 0.5 g. of 2-methoxy-3-formylindole, m.p. 252–253°; 0.3 g. more of product could be obtained from the mother liquors, resulting in a total 18% yield.

*Anal.* Calcd. for $C_{10}H_9O_2N$: C, 68.6; H, 5.14; N, 8.00. Found: C, 68.7; H, 5.34; N, 7.95.

Its 2,4-dinitrophenylhydrazone was prepared readily and on recrystallization from a large volume of ethyl acetate, glistening black needles, m.p. 305–306°, were obtained.

*Anal.* Calcd. for $C_{16}H_{13}O_5N_5$: C, 54.1; H, 3.7. Found: C, 54.07; H, 3.74.

The filtrate from the above chloroform solution was concentrated under vacuum and the remaining residue crystallized from 95% ethanol; 0.4 g. (10%) of pure 3-methoxymethylene oxindole, m.p. 191–192° (literature[24] m.p. 189°), was obtained. The 2,4-dinitrophenylhydrazone formation of this compound produced the derivative of its 3-hydroxymethylene precursor, m.p. 271–272° (*vide supra*).

Modification of the diazomethane reaction by varying concentration or solvent never greatly improved the process. The products 2-methoxy-3-formylindole and 3-methoxymethyleneoxindole could be obtained in yields of 10–20% and 10–40%, respectively.

(b) A similar procedure to the above was used for the conversion of 1-methyl-3-hydroxymethyleneoxindole to its two methyl derivatives. As high as 23% of 1-methyl-2-methoxy-3-formylindole, colorless crystals, m.p. 138°, could be isolated.

*Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.83, 69.74; H, 6.14, 6.11; N, 7.44, 7.48.

This could be converted to its 2,4-diuitrophenylhydrazone which on recrystallization from a large volume of ethyl acetate gave black needles, m.p. 283–284°.

*Anal.* Calcd. for $C_{17}H_{15}O_5N_5$: C, 55.28; H, 4.07; N, 18.95. Found: C, 55.18; H, 3.89; N, 19.00.

The yield of 1-methyl-3-methoxymethyleneoxindole, m.p. 134–135°, proved never to be much higher than 10%. The compound was shown to be identical by m.p., mixed m.p. and infrared spectrum with the O-alkylation product of 1-methyl-3-hydroxymethyleneoxindole by methyl iodide.[3,10]

**Hydrolysis of 1-Methyl-2-methoxy-3-formylindole.**—The indole (75 mg.) was dissolved in 10 ml. of 95% slightly warm ethanol and 200 mg. of sodium hydroxide was added thereto with shaking, and water was poured into it until a homogeneous solution was achieved. After standing at room temperature for 50 hours, the solution was added to water and extracted with ether. The aqueous fraction gave a precipitate on acidification with hydrochloric acid, which on filtering, washing with small amounts of ether and alcohol, and drying yielded 50 mg. of a white solid, m.p. 189–190°. This compound gave no depression of melting point on admixture with authentic 1-methyl-3-hydroxymethyleneoxindole, m.p. 190–191°, and also showed an identical infrared spectrum therewith. The ether fraction yielded 15 mg. of a compound, m.p. 120–121°, after washing with water, drying and evaporation of solvent. The latter proved to be crude starting material by inspection of its infrared spectrum and formation of its 2,4-dinitrophenylhydrazone.

AMES, IOWA

---

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE TEST STATION]

# Tetramethylenetrinitramine Trifluoroacetates

BY RUSSELL REED, JR.

RECEIVED JULY 8, 1955

1-Trifluoroacetoxy-2,4,6-trinitro-2,4,6-triazaheptane (III), 1-acetoxy-7-trifluoroacetoxy-2,4,6-trinitro-2,4,6-triazaheptane (IV) and 1,7-bis-trifluoroacetoxy-2,4,6-trinitro-2,4,6-triazaheptane (V) were obtained from the corresponding acetates by treatment with trifluoroacetic acid. V was also prepared from hexamine, nitric acid and trifluoroacetic anhydride. These trifluoroacetate esters reacted readily with alcohols, amines, water, nitric acid, acetic acid and hydrogen chloride as follows: methanol and III, IV or V gave the corresponding methylol derivatives; excess benzylamine degraded III, IV or V to di-(benzylammonium)-methylenedinitramine; aqueous acetone and III, IV or V yielded the theoretical amount of trifluoroacetic acid; nitric acid produced the corresponding nitrate esters; acetic acid gave the corresponding acetates; hydrogen chloride cleaved these trifluoroacetates with the formation of chlorides.

While the acetates 1-acetoxy-2,4,6-trinitro-2,4,6-triazaheptane, $CH_3[N(NO_2)CH_2]_3OCOCH_3$ (I),[1,2] and 1,7-diacetoxy-2,4,6-trinitro-2,4,6-triazaheptane, $CH_3COO[CH_2N(NO_2)]_3CH_2OCOCH_3$ (II),[3–5] are known, the corresponding trifluoroacetates have not been investigated. The acetates are reactive toward both acids and bases, and it was believed that the trifluoroacetates would be even more reactive and thus of value in the synthesis of linear nitramines. These trifluoroacetates were readily prepared by dissolving the acetates in anhydrous trifluoroacetic acid (Table I). Although a solution of the monoacetate I in trifluoroacetic acid at 25° deposited crystals of the ester $CH_3[N(NO_2)CH_2]_3OCOCF_3$ (III), the diacetate II gave the mixed ester $CF_3COO[CH_2N(NO_2)]_3CH_2OCOCH_3$ (IV). However, at 70° both IV and II gave the bis-trifluoroacetate, $CF_3COO[CH_2N(NO_2)]_3CH_2OCOCF_3$ (V).

The bis-trifluoroacetate V was also obtained in good yield by the nitrolysis of hexamine in a mixture of trifluoroacetic acid, trifluoroacetic anhydride and nitric acid at 0°. This reaction was very rapid while the corresponding reaction employing acetic acid–acetic anhydride was much slower and gave at 0° mainly 1,5-endomethylene-3,7-dinitro-1,3,5,7-tetraazacycloöctane (DPT).[6] Higher tem-

(1) F. Chapman, P. G. Owston and D. Woodcock, *J. Chem. Soc.*, 1647 (1949).

(2) R. N. Jones and G. D. Thorn, *Can. J. Res.*, **B27**, 828 (1949).

(3) W. E. Bachmann and J. C. Sheehan, THIS JOURNAL, **71**, 1842 (1949).

(4) W. J. Chute, A. F. MacKay, R. H. Meen, G. S. Meyers and G. F Wright, *Can. J. Res.*, **B27**, 503 (1949).

(5) W. E. Bachmann, W. J. Horton, E. L. Jenner, N. W. MacNaughton and L. B. Scott, THIS JOURNAL, **73**, 2772 (1951).

(6) W. S. Chute, D. C. Downing, A. F. McKay, G. S. Myers and G. F Wright, *Can. J. Res.*, **B27**, 218 (1949).