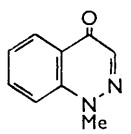
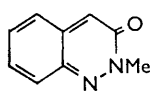
942. *Cinnolines. Part II.*[1] *The Structures of* N-*Methylcinnolones.*

By D. E. Ames and (Miss) H. Z. Kucharska.

Reductions of the compounds previously regarded as 2-methyl-3-cinnolone and 1-methyl-4-cinnolone with lithium aluminium hydride give the same product, which is shown to be 1,2,3,4-tetrahydro-2-methylcinnoline. This indication that both compounds have a 2-methyl group was confirmed by formation of 2-aminoacetophenone on reduction of the supposed 1-methyl-4-cinnolone with zinc and ammonia solution. It is concluded that this compound has a dipolar structure (X), *i.e.*, it is the anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide.

Methylation of 4-hydroxycinnoline with methyl sulphate and alkali or with diazomethane gives compound (X) and a lower-melting product regarded as 1-methyl-4-cinnolone since zinc–acetic acid reduces it to 2-methylaminoacetophenone; lithium aluminium hydride reduces it to 1,2,3,4-tetrahydro-1-methylcinnoline.

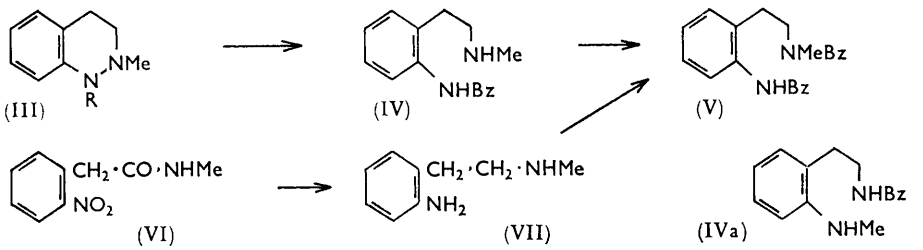
It has been shown [1] that reduction of 3- and 4-hydroxycinnoline with lithium aluminium hydride gives 1,2,3,4-tetrahydrocinnoline (the 4-isomer gives also some cinnoline). This work has now been extended by studying the reduction of the *N*-methylcinnolones, formulated in the literature [2,3] as (I) and (II), which are obtained by the methylation of 4- and 3-hydroxycinnoline, respectively.

(I)   (II)

Reduction of both methylation products with lithium aluminium hydride surprisingly gave the same tetrahydro-*N*-methylcinnoline as an unstable oil, which darkened rapidly but gave satisfactory analytical results and several crystalline derivatives. This amine was shown to be 1,2,3,4-tetrahydro-2-methylcinnoline (III; R = H) by the following reactions. Reduction of the benzoyl derivative (III; R = Bz) with zinc dust and acetic acid gave an amino-amide, assigned structure (IV) rather than the alternative (IVa) because it did not couple with diazotised sulphanilic acid and gave only a pale blue colour with nitrous acid. This conclusion was confirmed by conversion into the dibenzoyl derivative (V). The latter was also prepared by an independent synthesis from *N*-methyl-*o*-nitrophenylacetamide (VI) by catalytic hydrogenation followed by reduction with lithium aluminium hydride to give diamine (VII) and thence the dibenzoyl derivative (V).

[1] Part I is considered to be the paper by Ames and Kucharska, *J.*, 1962, 1509.
[2] Alford and Schofield, *J.*, 1953, 1811.
[3] Schofield and Simpson, *J.*, 1945, 516.

The possibility of ring contraction during the reduction of the *N*-methyl compounds to give *N*-methylaminoindoline (VIII; R = H) was also excluded by preparing the acetyl derivative (VIII; R = Ac) from *N*-aminoindoline by acetylation followed by methylation

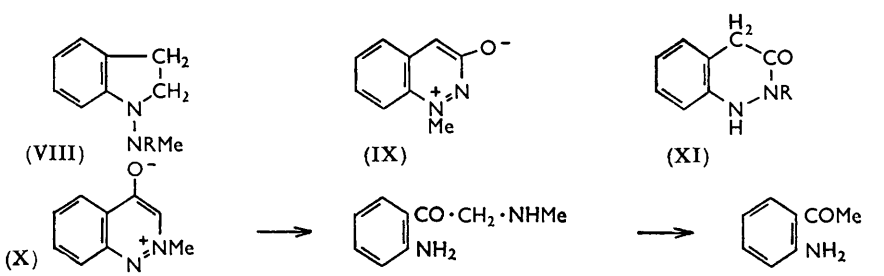


with sodamide and methyl iodide in liquid ammonia. The product was different from the acetyl derivative (III; R = Ac) of 1,2,3,4-tetrahydro-2-methylcinnoline.

The formation of the compound (III; R = H) from both methylation products could be attributed to migration of the *N*-methyl group of compound (I) during reduction with lithium aluminium hydride or, alternatively, the assignment of structure (I) might be incorrect.

Structures (I) and (II) were originally assigned [2,3] on the basis of the method of preparation and because they were *N*-methyl, not *O*-methyl, derivatives. Curiously, the *N*-methyl derivative of 4-hydroxycinnoline is colourless whereas the 3-isomer is bright yellow. An orange product was also isolated in small yield by Alford and Schofield [2] on methylation of 3-hydroxycinnoline with methyl sulphate and an excess of alkali and was tentatively assigned structure (IX). An analogous dipolar structure (X) for the product from 4-hydroxycinnoline would account for the formation of 1,2,3,4-tetrahydro-2-methylcinnoline on reduction.

Evidence supporting the structure of 2-methyl-3-cinnolone has been reported by Alford and Schofield [2] who showed that reduction with phosphorus and hydriodic acid gave methylamine and oxindole, consistent with the assigned structure (II). Reduction with zinc and ethanolic ammonia, however, gave a dihydro-derivative which they formulated as 1,2,3,4-tetrahydro-2-methyl-3-oxocinnoline (XI; R = Me). Baumgarten, Creger, and Zey [4] have since shown that the analogous compound described by Neber [5] as 1,2,3,4-tetrahydro-3-oxocinnoline (XI; R = H) is 1-amino-oxindole and have pointed out that



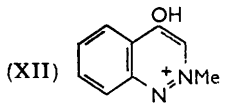
there is no evidence to confirm the assignment of structure (XI; R = Me) to the methyl derivative. We have now confirmed this structure by reduction with lithium aluminium hydride to 1,2,3,4-tetrahydro-2-methylcinnoline.

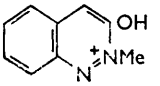
No evidence to confirm structure (I) for the methylation product from 4-hydroxycinnoline has been reported previously. We reduced it with phosphorus and hydriodic acid but isolated only 4-hydroxycinnoline formed by demethylation. Reduction with

[4] Baumgarten, Creger, and Zey, *J. Amer. Chem. Soc.*, 1960, **82**, 3977.
[5] Neber, *Ber.*, 1922, **55**, 826.

zinc dust in aqueous-ethanolic ammonia, however, gave 2-aminoacetophenone presumably by the sequence formulated.

In accordance with the expected ease of reduction of the intermediate α-methylaminoketone, it was found that *N*-methylphenacylamine gave acetophenone under similar conditions, whereas *o*-methylaminoacetophenone was recovered unchanged. This evidence confirms the view that the methylation product has structure (X), *i.e.*, that it is the anhydro-compound of 4-hydroxy-2-methylcinnolinium hydroxide. In the case of 2-methyl-3-





cinnolone, a similar dipolar structure may be regarded as contributing to the resonance. Both *N*-methyl derivatives gave well-defined hydrochlorides which are tentatively regarded as 2-methyl-4- and -3-hydroxycinnolinium chloride, (XII) and (XIII), respectively.

Attempts to synthesise structure (I) unequivocally have so far been unsuccessful and the methylation of 4-hydroxycinnoline with methyl sulphate was therefore re-examined. After compound (X), m. p. 162°, had been removed by crystallisation, the mother-liquors were examined by chromatography and a small amount of another colourless product, m. p. 114°; was isolated. This is regarded as the true 1-methyl-4-cinnolone (I) because reduction with zinc and acetic acid gave *o*-methylaminoacetophenone (reduction with zinc and ammonia solution gave only a dihydro-derivative).

Methylation of 4-hydroxycinnoline with diazomethane was very slow but also gave both 1- and 2-methyl derivatives (contrast the report of Alford and Schofield [2] that methylation was not effected by diazomethane).

Reduction of 1-methyl-4-cinnolone (I) with lithium aluminium hydride gave 1,2,3,4-tetrahydro-1-methylcinnoline, distinct from the 2-isomer already described.

These methylation results indicate the reactive nature of N-2 in the hydroxycinnolines. Simpson and his collaborators [6,7] inferred that the basic centre in cinnoline and substituted cinnolines was probably N-1, but this conclusion depended on the assumption of structures of type (I) for the methylation products from 4-hydroxycinnolines. Atkinson and Taylor,[8] however, obtained evidence that quaternisation in substituted cinnolines could proceed at N-1 and N-2. Further work is being carried out in the hope of correlating the structures of alkyltetrahydrocinnolines with those of the alkylcinnolinium salts.

Experimental

Evaporations were carried out under reduced pressure. Light petroleum refers to the fraction of b. p. 60—80°.

Methylation of 4-Hydroxycinnoline.—(*a*) *With methyl sulphate.* A solution of 4-hydroxycinnoline (5 g.) in 4N-potassium hydroxide (240 c.c.) was stirred at 50° while methyl sulphate (5 c.c.) was added. The mixture was warmed to 70° and after 15 min. more 4N-potassium hydroxide (30 c.c.) was added. Extraction of the solution with chloroform, evaporation, and recrystallisation from benzene gave the anhydro-base of 2-methyl-4-hydroxycinnolinium hydroxide (previously regarded as 1-methyl-4-cinnolone [3]), m. p. 163—165° (1·9 g.). Treatment of the compound with ethanolic hydrogen chloride gave *2-methyl-4-hydroxycinnolinium chloride* as plates, m. p. 230° (decomp.) (from ethanol) (Found: C, 55·2; H, 4·4; N, 14·3; Cl, 18·5. $C_9H_9ClN_2O$ requires C, 54·9; H, 4·6; N, 14·3; Cl, 18·0%).

Chromatography of the mother-liquors in benzene on a 4″ column of alumina gave *1-methyl-4-cinnolone* (0·6 g.), prisms, m. p. 114—116° (from benzene–light petroleum) (Found: C, 67·6; H, 4·8; N, 17·7. $C_9H_8N_2O$ requires C, 67·5; H, 5·0; N, 17·5%). The m. p. was depressed to about 80° on admixture with 4-methoxycinnoline.

[6] Simpson, *J.*, 1947, 1653.
[7] Keneford, Morley, Simpson, and Wright, *J.*, 1950, 1104.
[8] Atkinson and Taylor, *J.*, 1955, 4236.

(*b*) *With diazomethane.* A suspension of 4-hydroxycinnoline (1·8 g.) in methanol (50 c.c.) was treated with diazomethane (from methylnitrosourea, 10 g.) in ether (100 c.c.) at room temperature for 20 hr. The mixture was filtered and evaporated, the residue being extracted repeatedly with benzene [4-hydroxycinnoline(1·1 g.) was recovered from the insoluble fractions]. Chromatography of the benzene solution on alumina gave 1-methyl-4-cinnolone (0·1 g.). In another experiment, the crude product was recrystallised repeatedly from ethyl acetate–light petroleum, to give the anhydro-compound of 2-methyl-4-hydroxycinnolinium hydroxide, m. p. and mixed m. p. 164—165°.

2-Methyl-3-cinnolone.—This compound was prepared as described by Alford and Schofield; [2] no isomer could be isolated. It gave a hydrochloride, presumably *3-hydroxy-2-methylcinnolinium chloride*, yellow plates, m. p. 168° (decomp.) (from ethanol–ether) (Found: C, 54·9; H, 4·5; N, 14·4; Cl, 18·2%).

Reduction of N-*Methyl Derivatives with Lithium Aluminium Hydride.*—(*a*) *2-Methyl-3-cinnolone.* A solution of the cinnolone (6 g.) in benzene (150 c.c.) was added to lithium aluminium hydride (4 g.) in ether (200 c.c.), and the mixture was refluxed for 4 hr. Next day, after addition of 5N-sodium hydroxide (6 c.c.), the mixture was refluxed for 1 hr., cooled, and filtered, the solid being washed with ethyl acetate. The combined filtrates were extracted with 2N-hydrochloric acid; basification and isolation with ethyl acetate gave *1,2,3,4-tetrahydro-2-methylcinnoline* (4·2 g.), b. p. 70—71°/0·2 mm., darkening rapidly in air (Found: C, 72·7; H, 7·7; N, 19·2. $C_9H_{12}N_2$ requires C, 72·9; H, 8·2; N, 18·9%).

The *hydrochloride* formed needles, m. p. 185—187° (from ether–ethanol) (Found: C, 58·7; H, 7·0; N, 15·0; Cl, 19·2. $C_9H_{13}ClN_2$ requires C, 58·5; H, 7·1; N, 15·2; Cl, 19·2%). *1-Acetyl-1,2,3,4-tetrahydro-2-methylcinnoline*, prepared by action of pyridine–acetic anhydride at room temperature, formed prisms, m. p. 130—132°, from ethyl acetate–light petroleum (Found: C, 69·2; H, 7·4; N, 14·7. $C_{11}H_{14}N_2O$ requires C, 69·4; H, 7·4; N, 14·7%). *1-Benzoyl-1,2,3,4-tetrahydro-2-methylcinnoline* was obtained by treatment of the amine with benzoyl chloride–pyridine at room temperature and formed rectangular plates, m. p. 155—157°, from ethyl acetate–light petroleum (Found: C, 76·1; H, 6·0; N, 11·4. $C_{16}H_{16}N_2O$ requires C, 76·2; H, 6·4; N, 11·1%). The m. p. of each derivative was undepressed by admixture with a sample prepared from the base prepared as in (*b*).

(*b*) *Anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide.* The compound (7·5 g.) was reduced similarly, to give 1,2,3,4-tetrahydro-2-methylcinnoline (3·1 g.), b. p. 78—79°/0·3 mm. (Found: C, 72·9; H, 7·6; N, 19·3%).

Reduction of 1-Benzoyl-1,2,3,4-tetrahydro-2-methylcinnoline with Zinc and Acetic Acid.—A mixture of the benzoyl derivative (1·7 g.), zinc dust (3·4 g.), acetic acid (50 c.c.), and concentrated hydrochloric acid (2 drops) was heated on a steam-bath for 4 hr. The filtered solution was poured into 2N-sodium hydroxide and extracted with ethyl acetate. Evaporation and recrystallisation from light petroleum (b. p. 80—100°) gave *N-methyl-2-benzamidophenethylamine* (IV) (1·1 g.), prisms, m. p. 67—68° (Found: C, 75·5; H, 7·1; N, 11·2. $C_{16}H_{18}N_2O$ requires C, 75·6; H, 7·1; N, 11·0%).

Benzoylation (Schotten–Baumann) gave *N*-2-(benzamidophenethyl)-*N*-methylbenzamide (V), needles, m. p. 113—115° (from ethyl acetate–light petroleum). The m. p. was undepressed by admixture with an authentic sample (below).

N-*Methyl-o-nitrophenylacetamide.*—*o*-Nitrophenylacetic acid [9] (30 g.) was refluxed for 2 hr. with thionyl chloride (60 c.c.); the excess of thionyl chloride was removed by evaporation at 40°, addition of benzene (100 c.c.), and re-evaporation similarly. The residual oil in ether was added to a stirred, cooled, ethereal solution of methylamine (*ca.* 12 g.). Solid was collected, washed with water, and recrystallised from benzene–chloroform (charcoal), to give the *amide* (23 g.), needles, m. p. 145—147° (Found: C, 55·4; H, 4·9; N, 14·7. $C_9H_{10}N_2O_3$ requires C, 55·7; H, 5·2; N, 14·4%).

N-*Methyl-o-aminophenylacetamide.*—The nitro-amide (3·5 g.) in ethanol (150 c.c.) was hydrogenated in the presence of 10% palladised charcoal (0·5 g.). Evaporation of the filtered solution and recrystallisation from benzene–chloroform–light petroleum gave the *amino-amide* (2·5 g.), m. p. 86—87° (Found: C, 65·9; H, 7·4; N, 16·8. $C_9H_{12}N_2O$ requires C, 65·8; H, 7·4; N, 17·1%).

N-*Methyl-2-aminophenethylamine.*—The preceding amino-amide (2·5 g.) in 1,2-dimethoxyethane (50 c.c.) was added to lithium aluminium hydride (3 g.) in 1,2-dimethoxyethane (150 c.c.),

[9] Wright and Collins, *J. Amer. Chem. Soc.*, 1956, **78**, 221.

and the mixture was refluxed for 3 hr. Ether (200 c.c.) and 5N-sodium hydroxide (5 c.c.) were added successively. Next day, the solid was collected and washed with hot ethyl acetate. Extraction of the combined filtrates with 2N-hydrochloric acid, basification, isolation with ethyl acetate, and distillation gave the *diamine* (VII) (1 g.), b. p. 85°/0·2 mm. (Found: C, 72·2; H, 9·5; N, 18·4. $C_9H_{14}N_2$ requires C, 71·9; H, 9·4; N, 18·6%).

The dibenzoyl derivative (V), prepared by the Schotten–Baumann method, crystallised from light petroleum (b. p. 80—100°) and had m. p. 113—114° (Found: C, 76·9; H, 6·2; N, 8·0%).

1-(N-*Methylacetamido*)*indoline*.—1-Acetamidoindoline [1] (1·5 g.) in tetrahydrofuran (40 c.c.) was added to sodamide (from sodium, 0·45 g.) in liquid ammonia (*ca.* 100 c.c.); after the green solution had been stirred for 2 hr., methyl iodide (3 c.c.) was added dropwise. When the solvent had evaporated, water (100 c.c.) was added and the mixture was extracted with ethyl acetate. Evaporation and recrystallisation from methanol–light petroleum (b. p. 40—60°) afforded 1-(N-*methylacetamido*)*indoline*, prisms, m. p. 72—74° (Found: C, 69·5; H, 7·2; N, 14·7. $C_{11}H_{14}N_2O$ requires C, 69·4; H, 7·4; N, 14·7%).

Reductions of the Anhydro-base of 2-Methyl-4-cinnolinium Hydroxide.—(*a*) *With phosphorus and hydriodic acid*. The compound (2 g.) and red phosphorus (2 g.) were refluxed for 6·5 hr. with 55% hydriodic acid (20 c.c.), and the cooled mixture was filtered and extracted with ether. Evaporation and recrystallisation from 1,2-dimethoxyethane gave 4-hydroxycinnoline, m. p. 226—228°.

(*b*) *With zinc and ammonia solution*. The compound (2 g.), ethanol (40 c.c.), zinc dust (4 g.), and 48% hydrobromic acid (2 drops) were refluxed for 15 min. Aqueous ammonia (30 c.c.; *d* 0·88) was added and the mixture was refluxed for 8 hr. After evaporation of the filtered solution, ethyl acetate was added and the mixture was extracted with 2N-hydrochloric acid. Basification, isolation with ethyl acetate, and distillation yielded *o*-aminoacetophenone, b. p. 82—83°/0·5 mm. The phenylhydrazone, m. p. 104—105°, and the semicarbazone, m. p. 297—298°, showed no m. p. depression on admixture with authentic specimens.

2-*Methylaminoacetophenone*.—2-Toluene-*p*-sulphonamidoacetophenone [10] (20 g.) in ethanol (300 c.c.) containing sodium hydroxide (6·5 g.) and methyl iodide (18 g.) was refluxed for 13 hr. After evaporation the residue was washed with 2N-sodium hydroxide and water and recrystallised from ethanol, to give 2-N-*methyltoluene*-p-*sulphonamidoacetophenone* (11 g.), prisms, m. p. 115—116° (Found: C, 63·5; H, 5·7; N, 4·6. $C_{16}H_{17}NO_3S$ requires C, 63·4; H, 5·7; N, 4·6%). This (4 g.) was refluxed for 15 min. with 70% sulphuric acid (50 c.c.); the mixture was poured on ice, basified with 50% sodium hydroxide solution, and extracted with ether. Distillation gave 2-*methylaminoacetophenone* (2 g.), b. p. 74°/0·3 mm. (Found: C, 72·9; H, 7·3. $C_9H_{11}NO$ requires C, 72·4; H, 7·4%). The *picrate* separated from ethanol and had m. p. 135—136° (decomp.) (Found: C, 47·5; H, 3·9; N, 14·8. $C_{15}H_{14}N_4O_8$ requires C, 47·6; H, 3·7; N, 14·8%).

The amino-ketone was recovered after attempted reduction with zinc in aqueous-ethanolic ammonia as described.

Reduction of N-*Methylphenacylamine*.—A mixture of zinc dust (1·5 g.), the amine hydrochloride [11] (0·6 g.), ethanol (25 c.c.), and aqueous ammonia (25 c.c.; *d* 0·88) was refluxed for 6 hr., filtered, and evaporated to half-volume. Isolation with ether gave acetophenone (2,4-dinitrophenylhydrazone, 0·25 g., m. p. and mixed m. p. 240—242°).

Reduction of 1,2,3,4-*Tetrahydro*-2-*methyl*-3-*oxocinnoline*.—The hydro-compound [2] (1 g.) in benzene (50 c.c.) was reduced with lithium aluminium hydride (1 g.) in ether (50 c.c.), and the basic product was isolated in the manner described above. Distillation gave 1,2,3,4-tetrahydro-2-methylcinnoline (0·4 g.), b. p. 73°/0·1 mm. The acetyl derivative had m. p. 130—132°, undepressed on admixture with the specimen described above.

Reduction of 1-*Methyl*-4-*cinnolone*.—(*a*) *With zinc and ammonia solution*. A mixture of the cinnolone (1 g.), zinc dust (3 g.), and ethanol (30 c.c.) containing 48% hydrobromic acid (2 drops) was warmed to 95° and aqueous ammonia (15 c.c.; *d* 0·88) was added gradually. After the mixture had been refluxed for 3 hr., it was filtered, the zinc being washed with ethanol. Evaporation of the combined filtrates and trituration of the residue with light petroleum gave a crude product (0·7 g.), m. p. 94—100°. The *product* (presumably 1,2,3,4-*tetrahydro*-1-*methyl*-4-*oxocinnoline*) formed yellow needles, m. p. 100—102°, from ethyl acetate–light petroleum (Found: C, 65·8; H, 6·2; N, 17·1. $C_9H_{10}N_2O$ requires C, 66·7; H, 6·2; N, 17·3%).

[10] Elson, Gibson, and Johnson, *J.*, 1930, 1131.
[11] Hyde, Browning, and Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2287.

(*b*) *With zinc and acetic acid.* The cinnolone (0·7 g.) in hot acetic acid (10 c.c.) was added to zinc dust (1·5 g.) in acetic acid (20 c.c.) containing 1 drop of concentrated hydrochloric acid. After the mixture had been refluxed for 3 hr., it was filtered and the solid was washed with acetic acid. Basification of the filtrate and isolation with ethyl acetate gave 2-methylaminoacetophenone (0·3 g.), b. p. 69°/0·25 mm. The infrared spectra showed the identity of the product with that already described. The picrate had m. p. and mixed m. p. 136—137°.

(*c*) *With lithium aluminium hydride.* A solution of the cinnolone (2 g.) in benzene (75 c.c.) was added to lithium aluminium hydride (1·5 g.) in ether (75 c.c.), and the mixture was refluxed for 4 hr. After addition of 5N-sodium hydroxide (5 c.c.), the mixture was refluxed for 1 hr. Isolation of the basic product in the manner described, and distillation, gave 1,2,3,4-*tetrahydro*-1-*methylcinnoline* (0·9 g.), b. p. 75—76°/0·3 mm. (Found: C, 72·2; H, 7·9; N, 18·8. $C_9H_{12}N_2$ requires C, 72·9; H, 8·2; N, 18·9%). The *hydrochloride* formed needles, m. p. 160—163° (decomp.), from ethanol–ether (Found: C, 57·9; H, 6·9; N, 15·5; Cl, 19·3. $C_9H_{13}ClN_2$ requires C. 58·5; H, 7·1; N, 15·2; Cl, 19·2%). The *picrate* crystallised from ether–ethanol and had m. p. 118—119° (decomp.) (Found: C, 48·0; H, 4·1; N, 18·1. $C_{15}H_{15}N_5O_7$ requires C, 47·8; H, 4·0; N, 18·6%).

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CHEMISTRY DEPARTMENT, CHELSEA COLLEGE OF SCIENCE AND TECHNOLOGY,
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